



รายงานวิจัยฉบับสมบูรณ์

โครงการ : สนับสนุนการทำวิจัยเชิงสังเคราะห์ร่วมกับ Cochrane
Collaboration และการวิจัยระบาดวิทยาคลินิก

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ผู้วิจัย ศ.น.พ.ภิเศก ลุมพิกานนท์
ภาควิชาสูติศาสตร์และนรีเวชวิทยา
คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น

สนับสนุนโดยสำนักงานกองทุนสนับสนุนการวิจัย

บทคัดย่อ

ความรู้ทางด้านระบาดวิทยาคลินิกจะช่วยให้ นักวิจัยสร้างโครงการวิจัยที่เหมาะสม ดำเนินการวิจัยได้ดีและแปลผลการวิจัยได้ถูกต้อง ซึ่งจะทำให้ผู้วิจัยสามารถตอบคำถามวิจัยต่าง ๆ และนำผลการวิจัยไปใช้ในการดูแลรักษาผู้ป่วยได้อย่างเหมาะสม การดูแลรักษาผู้ป่วยจะต้องเลือกใช้การรักษาพยาบาลที่ได้รับการพิสูจน์โดยการวิจัยที่เชื่อถือได้ว่าให้ผลดีมากกว่าผลเสีย ตามหลักการที่ถูกต้องนักวิชาการไม่สามารถเลือกผลงานวิจัยงานใดงานหนึ่งมาตอบคำถามวิจัยนั้นๆ แต่ควรพิจารณาผลงานวิจัยที่มีคุณภาพดีที่เกี่ยวข้องกับเรื่องนั้น ๆ ทั้งหมด และนำเอาข้อมูลมาสังเคราะห์รวมกันโดยใช้การวิจัยเชิงสังเคราะห์ (Research synthesis) ซึ่งประกอบด้วย ขั้นตอนที่สำคัญ 2 ขั้นตอน ได้แก่ การทบทวนวรรณกรรมอย่างเป็นระบบ (systematic review) และการวิเคราะห์ข้อมูลแบบ meta-analysis การไม่นำผลการวิจัยเชิงสังเคราะห์มาใช้ อาจจะทำให้ผู้ป่วยเสียโอกาสที่จะได้รับการรักษาพยาบาลที่ได้ผลดีหรืออาจจะได้รับการรักษาพยาบาลที่มีผลเสียมากกว่าผลดี อาจจะมีการทำวิจัยที่ไม่จำเป็นเพราะถ้าทำวิจัยเชิงสังเคราะห์โดยใช้งานวิจัยที่มีอยู่ ก็จะได้คำตอบโดยไม่ต้องทำวิจัยแล้ว และทำให้เกิดการใช้ทรัพยากรที่มีอยู่จำกัดอย่างไม่มีประสิทธิภาพ

โครงการนี้มีวัตถุประสงค์เพื่อที่จะผลิตนักวิจัยด้านวิทยาศาสตร์สุขภาพที่มีความสามารถ ทั้งด้าน Clinical epidemiology research และ research synthesis ผลิตงานวิจัยแบบนิพนธ์ต้นฉบับ (Original articles) ที่มีคุณภาพสูงเพื่อตีพิมพ์ในวารสารระดับนานาชาติ และงานวิจัยเชิงสังเคราะห์ เพื่อตีพิมพ์ใน Cochrane Library รวมทั้งดำเนินการให้มีการนำผลงานวิจัยไปใช้อย่างเป็นรูปธรรม

ในระยะเวลา 3 ปีมีนักวิจัยเข้าร่วมในโครงการจำนวน 43 คน จาก 11 สถาบัน มีผลงานตีพิมพ์ใน International journals จำนวน 29 ฉบับ (เป็นงานวิจัย Original articles และบทความใน international peer-reviewed journals จำนวน 17 เรื่อง และงานวิจัยเชิงสังเคราะห์ใน Cochrane Library จำนวน 12 เรื่อง) และมีการตีพิมพ์ Protocols for Cochrane reviews ใน Cochrane Library อีก 9 เรื่อง

Keywords : การวิจัยเชิงสังเคราะห์ การทบทวนวรรณกรรมอย่างเป็นระบบระบาดวิทยาคลินิก
Cochrane library, meta-analysis

Abstract

Knowledge in clinical epidemiology will help researchers in developing appropriate research proposal, conducting research project and interpreting research results correctly. This will allow clinical researchers to answer clinical questions and therefore can provide appropriate healthcare. Healthcare providers should select interventions that have been proven by reliable research that they do more goods than harm. Theoretically, healthcare providers should not base their decision on the research papers that they like. They must search all papers on that topic that are available, critically appraise them and select only those papers with good quality and synthesize the data together. This is the concept of research synthesis which consists of systematic review and meta-analysis as appropriate. Failure to use research synthesis may cause inappropriate use of resources in healthcare and health research. Patients might not receive effective interventions or might receive ineffective or even harmful interventions.

This program aims to produce researchers competent in Clinical epidemiology research and research syntheses, publishing original articles in international peer reviewed journals and research synthesis in Cochrane Library and promote the implementation of research results in healthcare.

During the three-year period there are 43 researchers from eleven institutes involved in the program. There were 29 papers published in international journal (17 original articles and peer-reviewed journals and 12 papers in Cochrane Library). We also published 9 protocols for Cochrane reviews in Cochrane Library.

Keywords : Clinical epidemiology, research synthesis, systematic review, meta-analysis, Cochrane Library.

Executive Summary

1. ความสำคัญและที่มาของปัญหา

ระบบทฤษฎีคลินิกเป็นวิชาพื้นฐานครอบคลุมถึงระเบียบวิธีวิจัยและชีวสถิติ ความรู้ทางด้านระบบทฤษฎีคลินิกจะช่วยให้ นักวิจัยสร้างโครงการวิจัยที่เหมาะสม ดำเนินการวิจัย ได้ดีและแปลผลการวิจัยได้ถูกต้อง ซึ่งจะทำให้ผู้วิจัยสามารถตอบคำถามวิจัยต่าง ๆ และนำ ผลการวิจัยไปใช้ในการดูแลรักษาผู้ป่วยได้อย่างเหมาะสม

ผู้ให้การดูแลรักษาผู้ป่วยจะต้องเลือกใช้การรักษาพยาบาลที่ได้รับการพิสูจน์โดยการวิจัย ที่เชื่อถือได้ว่าให้ผลดีมากกว่า แต่เดิมเป็นที่ยอมรับว่าการวิจัยแบบ randomized controlled trial (RCT) ที่มีขนาดตัวอย่างเพียงพอเป็นการวิจัยที่ดีที่สุดในการจะตอบคำถามวิจัยชนิดนี้ แต่การทำ วิจัยแบบ RCT ต้องการผู้เชี่ยวชาญที่มีความรู้และประสบการณ์ งบประมาณค่อนข้างสูง และใช้ ระยะเวลา นานกว่าจะได้คำตอบและมักจะต้องเป็นการทำวิจัยแบบสหสถาบัน

ตามหลักการที่ถูกต้องนักวิชาการไม่สามารถเลือกผลงานวิจัยงานใดงานหนึ่งมาตอบคำถาม วิจัยนั้นๆ แต่ควรพิจารณาผลงานวิจัยที่มีคุณภาพดีที่เกี่ยวข้องกับเรื่องนั้น ๆ ทั้งหมด และนำเอา ข้อมูลมาสังเคราะห์รวมกันโดยใช้การวิจัยเชิงสังเคราะห์ (Research synthesis) ซึ่งประกอบด้วย ขั้นตอนที่สำคัญ 2 ขั้นตอนได้แก่ การทบทวนวรรณกรรมอย่างเป็นระบบ (systematic review) และ การวิเคราะห์ข้อมูลแบบ meta-analysis เป็นวิธีการที่ใช้สังเคราะห์งานวิจัยตั้งแต่ 2 งานวิจัยขึ้นไป เพื่อสรุปผลหาคำตอบสำหรับคำถามวิจัยแต่ละเรื่อง

ถึงแม้การวิจัยเชิงสังเคราะห์จะไม่ใช่วิธีใหม่แต่ยังมีนักวิชาการไม่มากนักที่เห็น ความสำคัญของการวิจัยแบบนี้ ในการวิจัยทางคลินิกการไม่ทำหรือไม่นำผลการวิจัยเชิงสังเคราะห์ มาใช้อาจจะทำให้เกิดผลเสียที่ร้ายแรงได้ ผู้ป่วยอาจเสียโอกาสที่จะได้รับการรักษาพยาบาลที่ ได้ผลดี หรืออาจจะได้รับการรักษาพยาบาลที่มีผลเสียมากกว่าผลดี อาจจะมีการทำวิจัยที่ไม่จำเป็น เพราะถ้าทำวิจัยเชิงสังเคราะห์โดยใช้งานวิจัยที่มีอยู่ก็จะได้คำตอบโดยไม่ต้องทำวิจัยแล้ว และทำให้ เกิดการใช้ทรัพยากรที่มีอยู่จำกัดอย่างไม่มีประสิทธิภาพ

ในปี พ.ศ. 2544 ได้มีการจัดตั้ง Thai Cochrane Network (TCN) โดยการสนับสนุนของ Department of Reproductive Health and Research, World Health Organization, The UK and Australian Cochrane Centres. TCN เป็นหน่วยงานแรกของ Cochrane Collaboration ในประเทศ ไทยและภูมิภาคเอเชียตะวันออกเฉียงใต้ วัตถุประสงค์ที่สำคัญของ TCN คือสนับสนุนให้มีการใช้ และการทำวิจัยเชิงสังเคราะห์กับ Cochrane Collaboration

2. วัตถุประสงค์

- 2.1 เพื่อผลิตนักวิจัยด้านวิทยาศาสตร์สุขภาพที่มีความสามารถทั้งด้าน clinical epidemiology research และ research synthesis
- 2.2 เพื่อผลิตงานวิจัยแบบนิพนธ์ต้นฉบับ (Original articles) เพื่อตีพิมพ์ในวารสารระดับนานาชาติ และงานวิจัยเชิงสังเคราะห์เพื่อตีพิมพ์ใน Cochrane Library และวารสารนานาชาติอื่น ๆ ตามความเหมาะสม
- 2.3 ดำเนินการให้มีการนำผลงานวิจัยไปใช้อย่างเป็นรูปธรรม

3. ระเบียบวิธีวิจัย

- 3.1 สำหรับการวิจัยแบบนิพนธ์ต้นฉบับ (Original articles) จะใช้ระเบียบวิธีวิจัยและวิธีการทางสถิติที่เหมาะสม
- 3.2 สำหรับการวิจัยเชิงสังเคราะห์จะใช้วิธีการและกลไกของ Cochrane Collaboration

4. ผลการดำเนินงานวิจัย (พ.ศ. 2550-2553)

- 4.1 มีนักวิจัยเข้าร่วมในโครงการจำนวน 43 คน จาก 11 สถาบัน
- 4.2 มีผลงานตีพิมพ์ใน international journals จำนวน 29 papers
 - 4.2.1 ตีพิมพ์ผลงานวิจัย Original articles และบทความใน international peer-reviewed journals จำนวน 17 เรื่อง
 - 4.2.2 ตีพิมพ์ผลงานวิจัยเชิงสังเคราะห์ (Cochrane reviews) ใน Cochrane Library จำนวน 12 เรื่อง
- 4.3 มีการตีพิมพ์ Protocols for Cochrane reviews ใน Cochrane Library จำนวน 9 เรื่อง

เนื้อหางานวิจัย

การวิจัยในโครงการประกอบด้วยส่วนสำคัญ 2 ส่วน ได้แก่

1. การวิจัยด้านระบาดวิทยาคลินิก (Clinical Epidemiology Research)

เป็นการดำเนินการวิจัยเพื่อตอบปัญหาที่เกี่ยวข้องกับการดูแลรักษาผู้ป่วยโดยใช้ระเบียบวิธีวิจัยและสถิติที่เหมาะสมได้แก่

1.1 Tranexamic acid for preventing progressive intracranial haemorrhage in adults with traumatic brain injury: A randomized, double-blinded, placebo controlled trial. (กำลังรอตีพิมพ์)

นอกจากนี้ยังมีงานวิจัยที่ใช้ข้อมูลจากโครงการที่ดำเนินมาก่อนหน้านี้และนำมาวิเคราะห์และตีพิมพ์ในวารสารนานาชาติ ได้แก่

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1.4 Pattanittum P, Ewens MR, **Laopaiboon M**, **Lumbiganon P**, McDonald SJ, Crowther CA, Study Group TS. Use of antenatal corticosteroids prior to preterm birth in four South East Asian countries within the SEA-ORCHID project. BMC Pregnancy Childbirth 2008; 16: 47.

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1.9 **Lumbiganon P**, **Laopaiboon M**, Gulmezoglu AM, Souza JP, Taneepanichskul S, Ruyan P, et al. Method of delivery and pregnancy outcomes in Asia: the WHO global survey on maternal and perinatal health 2007-08. *Lancet* 2010; 375: 490-9.

1.10 Chongsuvivatwong V, Bachtiar H, Chowdhury ME, Fernando S, Suwanrath C, Kor-Anantakul O, Tuan le A, Lim A, **Lumbiganon P**, Manandhar B, Muchtar M, Nahar L, Hieu NT, Fang PX, Prasertcharoensuk W, Radnaabarzar E, Sibuea D, Than KK, Tharnpaisan P, Thach TS, Rowe P. Maternal and fetal mortality and complications associated with cesarean section deliveries in teaching hospitals in Asia. *J Obstet Gynaecol Res* 2010; 36(1): 45-51.

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2. การวิจัยเชิงสังเคราะห์ (Research synthesis) สมาชิกของกลุ่มได้ร่วมทำการวิจัยเชิงสังเคราะห์ร่วมกับ Cochrane Collaboration ตามระเบียบวิธีวิจัยเชิงสังเคราะห์ที่เป็นมาตรฐานตามข้อกำหนดของ Cochrane review groups ต่าง ๆ ได้ดำเนินการวิจัยเรียบเรียงและตีพิมพ์ใน Cochrane Library แล้วจำนวน 12 เรื่อง ได้แก่

2.1 **Suwannachat B, Lumbiganon P, Laopaiboon M.** Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery. Cochrane Database Syst Rev 2008, Issue 3. Art. No.: CD006636.

2.2 **Thanaviratananich S, Laopaiboon M, Vatanasapt P.** Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media. Cochrane Database Syst Rev 2008, Issue 4. Art. No.: CD004975.

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2.6 **Boonmak P, Boonmak S.** Epidural blood patching for preventing and treating post-dural puncture headache. Cochrane Database Syst Rev 2010, Issue 1. Art. No.: CD001791.

2.7 **Perel P, Roberts I, Shakur H, Thinkhamrop B, Phuenpathom N, Yutthakasemsunt S.** Haemostatic drugs for traumatic brain injury. Cochrane Database Syst Rev 2010, Issue 1. Art. No.: CD007877.

2.8 **Ngamjarus C, Pattanittum P, Somboonporn C.** Roselle for hypertension in adults. Cochrane Database Syst Rev 2010, Issue 1. Art. No.: CD007894.

2.9 **Tangjitgamol S, Manusirivithaya S, Laopaiboon M, Lumbiganon P, Bryant A.** Interval debulking surgery for advanced epithelial ovarian cancer. Cochrane Database Syst Rev 2010, Issue 10. Art. No.: CD006014.

2.10 **Krisanaprakornkit T, Ngamjarus C, Witoonchart C, Piyavhatkul N.** Meditation therapies for attention-deficit/hyperactivity disorder (ADHD). Cochrane Database Syst Rev 2010, Issue 6. Art. No.: CD006507.

2.11 **Buppasiri P, Lumbiganon P, Thinkhamrop J, Thinkhamrop B.** Antibiotic prophylaxis for third- and fourth-degree perineal tear during vaginal birth. Cochrane Database Syst Rev 2010, Issue 11. Art. No.: CD005125.

2.12 **Siriwachirachai T, Sangkomkamhang US, Lumbiganon P, Laopaiboon M.** Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections. Cochrane Database Syst Rev 2010, Issue 12. Art. No.: CD007772.

3. ดำเนินการวิจัยเชิงสังเคราะห์ถึงขั้นตอนการตีพิมพ์ Protocol ใน Cochrane Library (เทียบได้กับจัดทำ Research proposal ที่ได้ผ่านการกลั่นกรองและรับรองจาก Cochrane Review Groups ต่าง ๆ แล้วและกำลังทำวิจัยเพื่อให้เป็น Cochrane reviews จำนวน 9 เรื่อง ได้แก่

3.1 **Buppasiri P, Lumbiganon P, Thinkhamrop J, Ngamjarus C.** Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes (Protocol). Cochrane Database Syst Rev 2008, Issue 2. Art. No.: CD007079.

3.2 **Muktabhant B, Lumbiganon P, Ngamjarus C.** Interventions for preventing excessive weight gain during pregnancy (Protocol). Cochrane Database of Syst Rev 2008, Issue 2. Art. No.: CD007145.

3.3 **Khianman B, Pattanittum P, Thinkhamrop J, Lumbiganon P.** Relaxation therapy for preventing and treating preterm labour (Protocol). Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD007426.

3.4 **Khanprakob T, Laopaiboon M, Lumbiganon P, Sangkomkamhang US.** Cyclo-oxygenase (COX) inhibitors for preventing preterm labour (Protocol). Cochrane Database Syst Rev 2009, Issue 2. Art. No.: CD007748.

3.5 **Sangkomkamhang US, Lumbiganon P, Laopaiboon M.** Hepatitis B vaccination during pregnancy for preventing infant infection. Cochrane Database Syst Rev 2009, Issue 3. Art. No.: CD007879.

3.6 **Piromchai P, Thanaviratananich S, Laopaiboon M.** Antibiotics for chronic rhinosinusitis in adults (Protocol). Cochrane Database Syst Rev 2010, Issue 1. Art. No.: CD008233.

3.7 **Sangkomkamhang T, Sangkomkamhang US, Ngamjarus C.** Vitamin K for the prevention and treatment of osteoporosis in post-menopausal women (Protocol). Cochrane Database Syst Rev 2010, Issue 1. Art. No.: CD008329.

3.8 **Khunpradit S, Lumbiganon P, Laopaiboon M.** Admission tests other than cardiotocography for fetal assessment during labour (Protocol). Cochrane Database Syst Rev 2010, Issue 3. Art. No.: CD008410.

3.9 **Tiamklang T, Sumanont S, Foocharoen T, Laopaiboon M.** Double-bundle versus single-bundle reconstruction for anterior cruciate ligament rupture in adults (Protocol). Cochrane Database Syst Rev 2010, Issue 3. Art. No.: CD008413.

Outputs ที่ได้จากโครงการ (2550-2553)

1. ตีพิมพ์ผลงานวิจัย Original articles และบทความใน international peer-reviewed journals จำนวน 17 เรื่อง (กรณาดูรายละเอียดในภาคผนวกที่ 1)
2. ตีพิมพ์ผลงานวิจัยเชิงสังเคราะห์ (Cochrane reviews) ใน Cochrane Library จำนวน 12 เรื่อง (กรณาดูรายละเอียดในภาคผนวกที่ 2)
3. มีนักวิจัยเข้าร่วมในโครงการจำนวน 43 คน จาก 11 สถาบัน (กรณาดูรายละเอียดในภาคผนวกที่ 3)
4. ประเทศไทยมีโครงการวิจัยเชิงสังเคราะห์ที่ทำร่วมกับ Cochrane Collaboration มากขึ้นอย่างรวดเร็วและปัจจุบันเป็นอันดับที่ 3 ใน Asia รองจากจีน และอินเดียเท่านั้น (กรณาดูเอกสารในภาคผนวกที่ 4)
5. ตีพิมพ์ Protocols for Cochrane reviews ใน Cochrane Library จำนวน 9 เรื่อง (กรณาดูรายละเอียดในภาคผนวกที่ 5)
6. งานวิจัยที่ได้ตีพิมพ์ใน international peer-review journals และ Cochrane Library ได้นำไปอ้างอิงในวารสารต่างประเทศ จำนวน 57 ครั้ง (กรณาดูรายละเอียดในภาคผนวกที่ 6)
7. เรียบเรียงหนังสือ การวิจัยเชิงสังเคราะห์ในการดูแลรักษาสุขภาพ (Research Synthesis in Healthcare) จัดพิมพ์เผยแพร่ไปตามห้องสมุดคณะแพทยศาสตร์ทุกแห่ง คณะสาธารณสุขศาสตร์ทุกแห่ง และโรงพยาบาลทั่วไปของกระทรวงสาธารณสุขทุกแห่ง และได้นำขึ้นเว็บไซต์ Thai Cochrane Network ที่ <http://tcn.cochrane.org/recent-update>

ภาคผนวกที่ 1

ตีพิมพ์ผลงานวิจัย Original articles และบทความใน
international peer-reviewed journals จำนวน 17 เรื่อง

Improving the reporting of public health intervention research: advancing TREND and CONSORT

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ABSTRACT

Background Evidence-based public health decision-making depends on high quality and transparent accounts of what interventions are effective, for whom, how and at what cost. Improving the quality of reporting of randomized and non-randomized study designs through the CONSORT and TREND statements has had a marked impact on the quality of study designs. However, public health users of systematic reviews have been concerned with the paucity of synthesized information on context, development and rationale, implementation processes and sustainability factors.

Methods This paper examines the existing reporting frameworks for research against information sought by users of systematic reviews of public health interventions and suggests additional items that should be considered in future recommendations on the reporting of public health interventions.

Results Intervention model, theoretical and ethical considerations, study design choice, integrity of intervention/process evaluation, context, differential effects and inequalities and sustainability are often overlooked in reports of public health interventions.

Conclusion Population health policy makers need synthesized, detailed and high quality *a priori* accounts of effective interventions in order to make better progress in tackling population morbidities and inequalities. Adding simple criteria to reporting standards will significantly improve the quality and usefulness of published evidence and increase its impact on public health program planning.

Keywords public health, primary research, evidence, editorial policies

Introduction

For many years, primary research has been supported by statements or guidelines aimed at improving the quality of reporting. This has resulted in significant improvements in reports of intervention studies, particularly for clinical randomized controlled trials (RCTs). However, there remain many deficiencies in these frameworks for the reporting of complex public health interventions. This has implications for those who conduct systematic reviews of public health interventions, those who conduct implementation evaluations or health systems research and those who use these forms of evidence to inform their decision-making. This paper examines the existing reporting frameworks against information sought by users of systematic reviews of public health interventions, and suggests key additional items that

should be considered in future recommendations on the reporting of public health interventions by researchers and publishers. As the demand for high quality, transparent secondary research increases amongst health care policy makers

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and other end-users it is an auspicious time to address these issues.^{1–3}

Value of CONSORT and TREND in improving the reporting of primary research

The Consolidated Standards of Reporting Trials (CONSORT) statement was first developed in 1996 (and updated in 2001)^{4,5} with the aim of improving the quality of reporting of RCTs. It requires authors of reports and journal articles to follow a checklist of 22 items that should be reported. CONSORT has now been adopted by more than 150 medical, clinical and psychological journals (www.consort-statement.org). The need for an alternate statement to improve the reporting of non-randomized studies was subsequently identified in 2004. This resulted in the development of the Transparent Reporting of Evaluations with Non-randomized Designs (TREND) Statement.⁶ The TREND statement is potentially very important for disciplines such as public health where debate continues about the extent to which RCTs are feasible or appropriate.^{7,8}

A number of other guidelines have also been published to support the systematic review process including QUORUM⁹ (recently renamed PRISMA) (reporting systematic reviews of RCTs), STROBE¹⁰ (reporting of observational studies) and MOOSE¹¹ (reporting systematic reviews of observational studies). The National Knowledge Service in the UK has funded EQUATOR which will act as an umbrella organization to coordinate work with the mutual interest of 'improving the quality of research publications and of research itself'.¹²

CONSORT and TREND were primarily conceived to increase the ability of research consumers to judge the internal validity of published studies, and thereby gain an appreciation of potential sources of bias that may have had some influence on the trial result. Key threats to internal validity that were often hidden in reports of trials were subversion of randomization, blinding and response bias, which are each covered by items in CONSORT. The statement has been associated with improvements in the quality of reporting of primary research: a systematic review conducted in 2006 found that journals using CONSORT had significantly better reporting of method of sequence generation (risk ratio [RR], 1.67; 95% CI, 1.19–2.33), allocation concealment (RR, 1.66; 95% CI, 1.37–2.00) and overall number of CONSORT items than those not using CONSORT (standardized mean difference, 0.83; 95% CI, 0.46–1.19).¹³ CONSORT appeared to have had less effect on items including reporting of participant flow, and blinding of participants or data analysts.¹³ Where studies

compared journals pre- and post-adoption of CONSORT an improvement was found in the description of the method of sequence generation (RR, 2.78; 95% CI, 1.78–4.33), participant flow (RR, 8.06; 95% CI, 4.10–15.83) and total CONSORT items (standardized mean difference, 3.67 items; 95% CI, 2.09–5.25) all improved after the adoption of CONSORT.¹³ This review is currently being updated.¹⁴

However, CONSORT was less concerned with other aspects of the conduct and reporting of intervention studies which can be equally critical to maximize the appropriateness of inferences to be drawn from such research. Within the context of randomized trials of drugs and other well-defined interventions, concerns regarding pre-specification of primary outcomes and planned sub-group analyses have been better addressed through the publication and registration of trial protocols. In the context of more complex interventions, where key concerns are to unpack the 'black box' of the intervention¹⁵ and to make clear assessments about the external validity of the study¹⁶ challenges remain in the reporting of randomized and non-randomized trials and therefore in the interpretation and synthesis of the evidence they provide.

Further, unlike the CONSORT statement which has seen widespread support, the TREND statement appears to be only formally supported by 15 journals. These are primarily in areas of HIV/AIDS, behavioural medicine or psychology, but supporters also include the BMJ and the American Journal of Public Health, which published the statement. It is not known whether other journals informally support TREND or why the uptake has been slower than for CONSORT.

Reporting frameworks can guide primary public health research

Although statements such as CONSORT and TREND have been established to improve the reporting of research, they have also provided researchers with a framework by which to design the primary research itself. Relevant items relate primarily to the mechanics of the scientific conduct of the study; what was implemented and what results occurred and how might these be interpreted. However, although CONSORT and TREND have usefully outlined the key methodological components of randomized and non-randomized trials that need to be reported, additional information is required by users of research to determine generalizability, applicability and transferability. Public health interventions are inherently complex and as such the interpretation of findings is frequently dependent on a range of contextual factors, irrespective of the study design.

The authors of the TREND statement have encouraged feedback on their work and some useful ideas have been subsequently published: Dziewaltowski *et al.*¹⁷ have suggested an increase in focus on factors that impact on external validity. This would include a particular focus on the impact of setting-level factors and intervention staff, skills, intervention costs and long-term outcomes that provide information on whether effects are sustained. Kirkwood⁸ has suggested the authors reflect on the applicability of the items that are based heavily on those outlined in CONSORT and suggests additional guidance for development of interventions, process and confounding variables and evaluation design. Further, one obviously useful modification to the TREND statement, in order to increase its usability by public health, health promotion, practitioners and researchers, would be to expand its focus beyond HIV/AIDS.

In 2001, core information needs required of systematic reviews of public health interventions for public health decision-making were described^{18,19} by users of evidence within global public health policy and programs. The subsequent application of these guidelines in systematic reviews of public health interventions has demonstrated that many sought after dimensions have not been included in either the conduct or reporting of the primary research studies.²⁰ These dimensions have been mapped against the key criteria of CONSORT and TREND to identify the missing components in the existing statements, and used to formulate the suggestions outlined below that are presented in order of the paper section in which they should be reported.

Reporting INTRODUCTION/BACKGROUND

Intervention model and theoretical considerations

Far too often, public health interventions are tested for effectiveness without such a model being established and/or reported, and this leads to poorly specified systematic reviews in which substantially different interventions are lumped together due to similarities in key superficial aspects such as intervention form, setting and/or target health behaviour.¹⁹ Thus, for example, it has been concluded that school based smoking education is ineffective²¹ and should be abandoned, even though there are promising approaches which need to be identified, developed and evaluated.²²

Another area of research where interventions are often complex is health services research, where integrated care pathways can be broken down into critical components.²³ Public health intervention research needs to identify similar ways of describing the intervention-process-outcome

pathway. It is important to have a clear model which sets out how the intervention is intended to bring about change in the intended outcomes, and reports of public health intervention studies should publish such a model as a requirement to allow intelligent consumption and synthesis. In the evaluation field this is known as the logic model.^{24,25} Ideally, the model should distinguish core and peripheral components, and emphasize the relative importance of form and function²⁶ so that the essence of the intervention is captured allowing the integrity of the intervention to be maintained in future implementation.

This section should also provide some detail on the development and piloting of the intervention, and present any theoretical or empirical support for the intervention model and the way it is being operationalized in the intervention. There should also be discussion of potential negative outcomes of the intervention (including the timing and measurement used to assess them²⁷), and any particular ethical concerns that there might be.²⁸

Reporting METHODS

Study design choice

Authors should justify the choice of study design, particularly where the chosen design has been reached as a compromise between the requirements of research rigour and internal validity on the one hand, and the complexity and constraints of the research question and research setting on the other. It may be possible to identify a consistent way of identifying key strengths and weaknesses of the chosen study design, relating particularly to internal validity issues and of describing the justification for accepting design limitations. Key components of study design that should be justified are the research design, operationalization of the design including group allocation and choice of counterfactual, choice of outcome measures and measurement methods.

Reporting RESULTS

Integrity of intervention/process evaluation

The integrity (or fidelity) of the intervention is the degree to which the intervention is implemented as planned.²⁸ Dane and Schneider²⁹ identify aspects of integrity/fidelity as adherence, exposure, quality of delivery, participant responsiveness and program differentiation. All five dimensions should be measured in order to provide a comprehensive picture of intervention integrity.²⁹ CONSORT does not explicitly mention fidelity and while the TREND statement recommends including issues of fidelity in the interpretation

of results, an additional guidance is required to describe how this should be achieved. This is particularly important given that only a limited number of studies disentangle the factors that ensure successful outcomes, characterize the failure to achieve success or attempt to document the steps involved in achieving successful implementation of complex interventions.^{30,31} Process evaluations provide a mechanism to collect and report on intervention fidelity^{15,28} and when reported should include information on the intensity, duration and reach of intervention components, and how these varied by sub-group. Increased access to existing checklists and resources that support the reporting of process evaluations would be beneficial.

Context, differential effects and multi-level processes

The success or failure of a complex public health intervention is often highly dependent on the social, economic and political context in which it is developed and operated.³² Knowing this type of information provides important clues about the applicability and transferability of interventions to other populations or organizational contexts. It also helps to highlight the critical success factors and the elements that are more likely to lead to program failure. Hawe³³ has outlined a range of important contextual information: aspects of the host organization and staff, aspects of the system, characteristics of the target population and inter-organizational networks. These factors should be considered in reporting of public health interventions. Although these data are often collected, they are often then excluded from publications. It would be useful to highlight within publications where this information has been collected but not reported by referring readers to a website or full report.

It is well established through perspectives such as McLeroy's socio-ecological model framework³⁴ and the WHO Ottawa Charter³⁵ that interventions do not work in isolation and require multi-level processes. Effectiveness will vary importantly with reference to context: what works in one setting or population group would not necessarily work in another.^{32,36} Thus reports need to include a description of multi-level processes and a strong set of data to contextualize the study (external validity). They should also report sub-group effects by key demographic and policy factors such as SES, ethnicity and gender so that pooled analysis can be done without needing to obtain original datasets. Counter to established orthodoxy in the analysis and reporting of effectiveness trials, there may be some value in undertaking and reporting sub-group analyses even where there is insufficient statistical power within the study. This would allow pooled analysis of

these sub-group effects to be undertaken in systematic reviews. This is particularly important in considering the differential effect of interventions by socio-economic status to assess the magnitude and direction of the effects of an intervention on health inequalities.^{37,38} Neither CONSORT nor TREND specifically address issues pertaining to inequalities.

Sustainability

Effective public health programs or interventions should attempt to assess the degree to which they would be sustainable beyond the life of the program. In acknowledging this, it is also important to highlight that assessing the sustainability of a program and or its effects is an additional research question requiring supplementary research design development and study conduct. Shediach-Rizkallah and Bone³⁹ present a useful framework to address sustainability. In this framework, the key aspects of program sustainability are defined as maintenance of health benefits from the program, institutionalization of a program within an organization and capacity building in the community. In reporting, authors should consider the economic and political variables, the strength of the organization, the degree to which activities are integrated into existing programs and policies and the degree of community involvement/participation.⁴⁰

Reporting DISCUSSION

Many of the sections above make recommendations for reporting complex public health interventions that should also be considered in the discussion section. We would highlight specifically the opportunity that this section provides for authors to fully discuss limitations of study design and honestly appraise weaknesses. It also allows authors to interpret and discuss any sub-group effects or interactions with context that seem important. As a conclusion to the report, authors should reflect on the original model used and make statements about what worked well and what not so well so that future research or implementation can learn and further develop. An important aspect of this model could include unanticipated effects of the intervention that the investigators became aware of during the course of the study.⁴¹ Although such effects cannot be interpreted in the same way as those outcomes hypothesized and planned for in study design, they are frequently important both for future intervention development and also for the planning of future evaluation studies to capture wider potential harms and benefits, and more broadly scope the potential intervention effects.^{27,42}

Can it possibly fit in journal word limits?

A strength of CONSORT is that it identifies the key elements required in reports of RCTs and as such has assisted authors in producing concise papers that meet the increasingly tight word length requirements of journals.¹⁴ A potential problem for the inclusion of the additional items suggested above is that it will be impossible to adequately report these items without substantial additional text, which traditional printed journals may find difficult to accommodate. Further work will be required to identify efficient, elegant and concise ways of presenting the additional data required, which may, for example, include diagrams of the hypothesized pathway from intervention to intended outcome, or describing the intervention components in a separate text box which does not contribute to overall word length.

Other possibilities may be that online editions of journals offer more space or act as channels to publish supporting documentation covering details of the suggested items. Or more radically, in parallel with established practice in clinical research, there needs to be increased funding and more opportunities for publication of intervention development research, covering phases 1–3 of the MRC Framework⁴³ such that this work is peer-reviewed and published as a precursor to large scale effectiveness studies.

Conclusion

Guidelines for the reporting of public health intervention research are not currently available to the extent to which they are required. Given the need to increasingly understand *what works, for whom, why, when and at what cost*, standards for reporting on public health interventions, aligned with registries and evaluation frameworks,⁴⁴ have the potential to make a significant impact on the capacity to better understand these dimensions for the benefit of public health policy.

The CONSORT and TREND statements have been important in improving the quality of published RCTs and non-randomized evaluations of interventions. This paper has suggested key elements which are additionally needed in the reporting of complex public health interventions. It is hoped that further development of these suggestions will lead to improved conduct and reporting of primary intervention studies, enrichment of systematic reviews of public health interventions and therefore greater support for informed decision-making.

Development of comprehensive guidelines will require the establishment of an international taskforce. A range of practitioners, policy-makers and researchers across different countries and organizational contexts will need to be

members of this taskforce. This will ensure that the guidelines and recommendations meet the needs of public health researchers, practitioners and funders more broadly. If we are to 'improve the quality of research publications and of research itself',¹² then this is a necessary step forward.

New public health relevant Cochrane reviews and protocols from issues 3 and 4, 2007

Reviews

- Abstinence-only programs for HIV infection prevention in high-income countries.
- Diet or exercise, or both, for weight reduction in women after childbirth.
- Home-based support for disadvantaged adult mothers.
- Home-based support for disadvantaged teenage mothers.
- Exercise for improving balance in older people.
- Interventions for the prevention of nutritional rickets in term born children.
- Interventions in the workplace to support breastfeeding for women in employment.
- Interventions to reduce harm from continued tobacco use.
- Parenting interventions for the prevention of unintentional injuries in childhood.
- School-based education programs for the prevention of child sexual abuse.
- Traditional birth attendant training for improving health behaviours and pregnancy outcomes.

Protocols

- Dietary advice in pregnancy for preventing gestational diabetes mellitus.
- Harm reduction interventions to prevent HIV/AIDS transmission in involuntary detainees.
- Indoor residual spraying for preventing malaria.
- Maternity waiting facilities for improving maternal and neonatal outcome in low-resource countries.
- Mobile phone-based interventions for smoking cessation.
- Routine iron supplementation for preventing or treating iron-deficiency anaemia in children in malaria-endemic areas.
- Routine vs. voluntary HIV testing for increasing HIV testing rates.
- Salt fluoridation for preventing dental caries.
- Social norms interventions to reduce alcohol misuse in University or College students.
- Vitamin C for preventing and treating tetanus.
- Zinc supplements for preventing otitis media.

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Reporting the findings of clinical trials: a discussion paper

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Background

When researchers embark on a clinical trial, they make a commitment to conduct the trial and to report the findings in accordance with basic ethical principles. This includes preserving the accuracy of the results and making both positive and negative results publicly available.¹ However, a significant proportion of health-care research remains unpublished and, even when it is published, some researchers do not make all of their results available.² Selective reporting, regardless of the reason for it, leads to an incomplete and potentially biased view of a trial and its results.³

The consequences of publication bias and selective reporting have gained the attention of health-care consumers, the media and politicians. All have recognized the impact that undisclosed results can have on the ability of patients, practitioners and policy-makers to make well-informed decisions about health care. Concern over the underreporting of adverse events, in particular, has increased the demand for more transparent processes for registering clinical trials and reporting their findings. In recent years, trial registration has become increasingly widely accepted and implemented. There are now well-established mechanisms to register trials, assign unique identifiers and make this information publicly available. WHO's International Clinical Trials Registry Platform Search Portal helps bring the data from these registers together, making it much easier to search for the existence of a trial

(available at: <http://www.who.int/trialsearch>).

The value of registration goes far beyond the administrative benefits of having a complete collection of all trials. Trial registers may facilitate recruitment into clinical trials by raising awareness of their existence among potential participants and health-care practitioners. They may also lead to more ethical and successful research by avoiding the unintentional duplication of research already under way elsewhere. From the perspective of this paper, however, the greatest benefit of trial registration is enhanced transparency; that is, making it clear which trials are being conducted so that people can anticipate their results.

The next step to informed decision-making is to make the findings of clinical trials available, since it is knowledge of the findings, rather than of the existence of a trial, that is likely to have the greatest impact on people trying to choose between alternative interventions. The arrival and growth of electronic publishing and the Internet as dissemination tools without page or length restrictions has greatly expanded the ability of people to make findings available and accessible in full. The recognition of the need for reliable evidence to improve health care and to facilitate the synthesis of the results of research into systematic reviews has fuelled the demand for access to the findings of all research, as have the needs of the numerous other stakeholders in clinical research.

A proposed position

The position proposed by the members of the WHO Registry Platform Working Group on the Reporting of Findings of Clinical Trials is that "the findings of all clinical trials must be made publicly available". This paper discusses the principles underlying this position. Our goal is to contribute to the ongoing debate and to foster the collaboration that is necessary to ensure that the findings of clinical trials do not remain hidden from the people who need access to them.

What is a finding?

The language used to discuss the reporting of clinical trials usually focuses on "results" – often taken to mean the numerical results of an analysis for a specific outcome. For example, a summary estimate such as a relative risk. However, the reader or user of research also needs background information that will allow them to correctly interpret the results for specific outcomes. The type and amount of information required will depend on the nature of the audience and how it will use the information received but will have four key elements:

1. Methodological context

The user needs to know what the original plans for the trial were and how it was actually conducted. Some of the original plans will be available if the trial was registered, but more complete

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information should be in the full trial protocol. The actual conduct of the trial might, however, differ from that planned. Such differences may be valid but should be traceable, preferably via a clinical trial registry. The methodological context for a trial might also include information on the primary question that the researchers set out to answer; the hypothesis they were seeking to test; the methods they used to allocate or select participants for the interventions; whether any blinding or masking was done; and a description of the statistical methods planned and used, including a justification of the sample size.

2. Population context

The user needs to consider to whom the results of the trial can be applied. They need to know the characteristics of the population it was initially intended to recruit, as well as the characteristics of the population who were recruited. In reporting their findings, the researchers should therefore refer to the original inclusion and exclusion criteria and provide information on the population that actually took part, describing the extent to which participants left the trial early (with reasons for doing so) and whether interventions were delivered as planned.

3. A result for each outcome

A clinical trial will usually consider several outcomes, each of which might be measured in multiple ways or at multiple time points, and there might be more than one way to analyse each of these measures. The findings should contain the results for every outcome measure and analysis specified in the register entry for the trial, and set out in the protocol or statistical analysis plan. If any of these results are not reported, a reason should be provided for their absence. Any findings from analyses that were not pre-specified should be clearly identified as such.

4. Interpretation

The most contentious aspect of reporting the findings of a clinical trial may be whether the report should include the researchers' opinions and conclusions. It is in this section of a report where the objectivity of the research is confronted by the subjectivity of authors who "use their power as owners of their writing to emphasize one point of view more than another".⁴ Alternatively, linguistic spin is considered by some to be essential to scientific communication, being the opportunity for scientists to speculate and formulate new hypotheses.⁵ Distinguishing opinions and conclusions from advocacy or promotion can be difficult, and it may be preferable to leave the users of the findings to draw their own conclusions and form their own opinions of what the findings of a trial mean for them and their decision-making.

Public availability

Clinical trial results should be available to everyone, regardless of where they live. If the results are not made available within a reasonable period, the reasons for delay and a date by which the findings will be available should be submitted to the relevant clinical trials registry. It should be the responsibility of researchers to produce their findings in a format that can be accessed by potential users, and it should be the responsibility of the user to seek these results. The Internet could provide the main means by which this shared responsibility can be satisfied. Access also needs to be considered in terms of the end user's ability to both view and understand the information obtained.

Historically, access to the results of a trial has usually been achieved through publication in a peer-reviewed journal. This traditional publication model has its limitations, particularly

in an environment where the end users of research information now include health-care policy-makers, consumers, regulators and legislators who want rapid access to high quality information in a "user-friendly" format. In future, researchers may be legally required to make their findings publicly available within a specific timeframe (assuming any legislation created does not have escape clauses built in). In the United States of America, such legislation is already in place (available at: <http://www.fda.gov/oc/initiatives/HR3580.pdf>). This may compromise the ability of researchers to publish trial findings in a peer-reviewed journal. Although some journal editors have acknowledged the changing climate around results registration and reporting (available at: http://www.icmje.org/clin_trial07.pdf), they may have a conflict of interest in that they will probably want the key (and potentially most exciting) messages from a trial to appear first, and perhaps exclusively, in their publication.

Conclusion

People making decisions about health care need access to knowledge derived from the findings of clinical trial research. Following on from WHO's position that all clinical trials must be registered,⁶ it is proposed that the findings of all clinical trials must be made publicly available. This report is the start of a consultation process on how this goal of transparency can be achieved, with the intention that greater accessibility to the findings of all clinical trials will lead to improvements in health and health care. To contribute to the first phase of the consultation, please visit: <http://www.who.int/ictrp/results/consultation> ■

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Use of Evidence-Based Practices in Pregnancy and Childbirth: South East Asia Optimising Reproductive and Child Health in Developing Countries Project

The SEA-ORCHID Study Group*

Abstract

Background: The burden of mortality and morbidity related to pregnancy and childbirth remains concentrated in developing countries. SEA-ORCHID (South East Asia Optimising Reproductive and Child Health In Developing countries) is evaluating whether a multifaceted intervention to strengthen capacity for research synthesis, evidence-based care and knowledge implementation improves adoption of best clinical practice recommendations leading to better health for mothers and babies. In this study we assessed current practices in perinatal health care in four South East Asian countries and determined whether they were aligned with best practice recommendations.

Methodology/Principal Findings: We completed an audit of 9550 medical records of women and their 9665 infants at nine hospitals; two in each of Indonesia, Malaysia and The Philippines, and three in Thailand between January–December 2005. We compared actual clinical practices with best practice recommendations selected from the Cochrane Library and the World Health Organization Reproductive Health Library. Evidence-based components of the active management of the third stage of labour and appropriately treating eclampsia with magnesium sulphate were universally practiced in all hospitals. Appropriate antibiotic prophylaxis for caesarean section, a beneficial form of care, was practiced in less than 5% of cases in most hospitals. Use of the unnecessary practices of enema in labour ranged from 1% to 61% and rates of episiotomy for vaginal birth ranged from 31% to 95%. Other appropriate practices were commonly performed to varying degrees between countries and also between hospitals within the same country.

Conclusions/Significance: Whilst some perinatal health care practices audited were consistent with best available evidence, several were not. We conclude that recording of clinical practices should be an essential step to improve quality of care. Based on these findings, the SEA-ORCHID project team has been developing and implementing interventions aimed at increasing compliance with evidence-based clinical practice recommendations to improve perinatal practice in South East Asia.

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Introduction

The burden of mortality and morbidity related to pregnancy and childbirth remains concentrated in developing countries [1,2]. This disparity continues with rates of neonatal mortality almost 10 times greater in South East Asia than developed regions [3,4]. SEA-ORCHID, a five-year project, is evaluating whether a multifaceted intervention to strengthen capacity for research synthesis, evidence-based care and knowledge implementation improves adoption of best clinical practice recommendations and so leads to better health for mothers and babies [5]. This paper describes empirical evidence of current practices at the beginning of the SEA-ORCHID project for key aspects of maternal and perinatal health care in the participating countries.

Methods

Setting

This audit was conducted in nine hospitals across Indonesia, Malaysia, The Philippines and Thailand, with support from three sites in Australia. Different types of hospital were represented including tertiary referral hospitals (University and regional), provincial hospitals and district hospitals. All were selected as part of the SEA-ORCHID project.

Seven of the hospitals were tertiary referral institutions with regional referrals of women with a high risk pregnancy. Two hospitals were provincial or district institutions. Models of delivery care included a multidisciplinary approach with midwives (including nurses with midwifery qualifications) or obstetric specialists. All hospitals had obstetric specialists and caesarean

section facilities available. Normal vaginal births were conducted by doctors and/or midwives (including nurses with midwifery qualifications) in all hospitals.

The SEA-ORCHID project settings and methods have been published elsewhere. [5]. The project was approved by the local ethics committee of each hospital and by the ethics committee of the administering institution in Australia (University of Sydney).

Procedure

We reviewed the medical records of 9550 women (9665 infants including 111 twins and two sets of triplets) admitted to the labour wards at the nine study hospitals between January–December 2005. The duration of data collection varied according to the number of births per month at the participating hospital. Five hospitals in the sample collected data on a consecutive basis until reaching a total of at least 1000 women. To avoid potential biases associated with short data collection periods, the four largest hospitals sampled cases using various ratios to ensure there was at least a three-month minimum data collection period at each hospital.

Staff at each hospital were trained to prospectively audit medical records using pre-established data extraction forms. We extracted information about current maternal and perinatal practice according to beneficial forms of care and forms of care likely to be ineffective or harmful as suggested in the World Health Organization Reproductive Health Library No.7 [6] and the Cochrane Library [7] (Table 1). The primary caregiver at the birth provided details of the presence of maternal companionship during the labour.

In addition we collected information on maternal characteristics including age, parity, height and weight, and on birth outcomes including gestational age at birth, mode of birth, birth weight, Apgar scores and perinatal mortality.

Completed data extraction forms were sent from the hospitals to the project co-ordinating site in each country for manual data entry by the trained fieldworkers using a secure web-based database. The online form was set-up to minimise transcription errors by performing validation checks to detect discrepancies and missing data. A random sample of between 5 to 10% was independently checked by project staff at one of the Australian support sites to identify data processing errors.

Data analysis

Descriptive analyses were performed across countries and between hospitals within countries. We used STATA software version 8.0 for data analysis [8]. We used frequencies to describe maternal characteristics, maternal and perinatal practices, as well as birth outcomes measured as categorical data. We used means and standard deviations to describe the continuous data variables of maternal age and gestational age at birth.

Results

Maternal characteristics and birth outcomes (Table 2)

For the 9550 mothers (and their 9665 babies) across the nine hospitals in South East Asia, the mean age per hospital ranged from 26 to 31 years. The rate of nulliparity varied, being over 40% in all hospitals of Indonesia, The Philippines and Thailand, and up to 64% in one Thai hospital but only 27% for one Malaysian hospital.

For the 9665 babies, the preterm birth rate (<37 weeks gestation) ranged from 6% to 15%. Overall 30% of all babies were born by caesarean section but the rate varied considerably across the nine hospitals ranging from 12% to 39%. Around a fifth of babies were born by caesarean section in the Malaysian hospitals and over a third in the Thai hospitals. Overall, 18% of babies were of low birth weight (<2500g) with rates ranging from 9% to 20%.

Table 1. Recommended practices in maternal and perinatal health care

Recommended practice	Care practices assessed	Outcome intended to reduce
Beneficial forms of care		
Antibiotics for preterm prelabour rupture of membranes (pPROM) [15]	Use of antibiotics in women with preterm (<37 weeks) prelabour rupture of membranes	Chorioamnionitis; neonatal sepsis
Corticosteroids prior to preterm birth [16]	Use of antenatal corticosteroids in women at risk of preterm birth at <34 weeks gestation	Neonatal death; complications of preterm birth
Continuous support during labour [17]	Family member present with the woman during childbirth	Caesarean section rate
Magnesium sulphate for eclampsia and pre-eclampsia [18,19,20]	Use of magnesium sulphate for women with eclampsia and pre-eclampsia	Maternal death; eclampsia
Management of third stage of labour [21]	Use of uterotonic and controlled cord traction in the third stage of labour	Postpartum haemorrhage; maternal death
- appropriate administration of a prophylactic oxytocic at or after birth of the baby		
- controlled umbilical cord traction to deliver the placenta		
Intraoperative antibiotics during caesarean section [14]	Administration of a single dose of ampicillin or first generation cephalosporin after umbilical cord clamping at caesarean section	Maternal infection
Immunisation for Hepatitis B [22]	Vaccination of babies against Hepatitis B virus	Hepatitis B infection
Forms of care likely to be unnecessary or harmful		
Routine episiotomy [23]	Restrictive use of episiotomy	Perineal injury; maternal infection
Routine shaving* [24]	Avoidance of pubic hair shaving	Maternal infection
Routine enemas* [25]	Avoidance of use of enemas during labour	Maternal infection

*No clear evidence from Cochrane reviews to support or refute use, but identified as practices of importance to research and evaluate
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Table 2. Percent distribution of maternal and infant outcomes across nine hospitals in South East Asia

Countries	Indonesia			Malaysia			The Philippines			Thailand		
	Overall	Tertiary	District	Overall	Tertiary 1	Tertiary 2	Overall	Tertiary 1	Tertiary 2	Overall	Regional	University Provincial
Mothers*	2086	1019	1067	2379	1249	1130	2085	1026	1059	3000	1000	1000
Infants*	2113	1028	1085	2410	1267	1143	2098	1026	1072	3044	1019	1012
Maternal age (years) ^c	30 (5.9)	30 (6.0)	30 (5.7)	30 (6.5)	29 (6.4)	31 (6.5)	27 (6.6)	26 (6.4)	28 (6.8)	27 (6.1)	26 (6.2)	27 (6.3)
Nulliparous [†]	46	46	46	31	36	27	48	55	41	58	64	54
Preterm birth (gestation <37 weeks) [†]	10	14	6	10	10	10	7	6	9	11	15	10
Caesarean section [†]	30	29	31	19	22	17	23	12	33	35	34	34
Low birth weight [†] (<2500 gm)	18	20	16	11	11	11	20	19	20	11	15	9
APGAR Scores <7 at 5 minutes [†]	8	10	6	1	1	1	1	1	2	2	2	2
Perinatal death* Per 1000 total births	35	42	29	12	11	12	4	5	3	16	15	21

Figures are number* and mean (standard deviation)^a or percentage[†] (rounded to the nearest whole number)
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Rates of babies with Apgar scores less than seven at five minutes and perinatal death were highest in the two Indonesian hospitals, compared with rates in the other hospitals. Stillbirths accounted for more than 60% of the perinatal deaths in most hospitals across the countries. There were no maternal deaths prior to discharge reported in any of the hospitals during the audit.

The variation in rates between countries and between hospitals within the same country are likely to be influenced by the sociodemographics and risk status of the populations they care for, and the type of hospital (tertiary, provincial or district).

Beneficial forms of care

The recommended beneficial clinical practices were classified according to periods of pregnancy care: antenatal, intrapartum and postpartum (Table 3). The use of these clinical practices varied markedly across the nine hospitals.

Care practices during the antenatal period to treat pregnancy complications (Table 3). Women with pre-eclampsia represented 4% of the sample; with nearly three-quarters of the women with pre-eclampsia receiving magnesium sulphate. The rate of practice of this intervention varied among the hospitals within Malaysia (range 13% to 44%) and Thailand (range 57% to 82%) but was 100% in both Indonesian hospitals. There were 15 (0.16%) cases of eclampsia. Magnesium sulphate was used in all 15 (100%) of these cases of eclampsia, and in all countries involved in the audit.

Women with preterm prelabour rupture of the membranes (pPROM) received antibiotics 80% of the time. Although this practice was observed in all hospitals, the rates of administration varied across countries (range 62% to 92%) and hospitals (range 44% to 100%). In Indonesia, use was appropriately high whereas variation of the practices was seen among hospitals within each country.

Antenatal corticosteroid administration to women with preterm birth at <34 weeks was infrequently used in most hospitals compared with other clinical practices in the antenatal period. The highest rate of antenatal corticosteroid use was 86% in a regional hospital in Thailand. In the Malaysian hospitals about half the women who gave birth at <34 weeks had been given antenatal corticosteroids. In the Indonesian hospitals this dropped to around 10% and in one tertiary hospital in The Philippines no administration of corticosteroids was recorded. Use of repeat courses of antenatal corticosteroids was less than 15% across all hospitals included in the audit.

Care practices during the intrapartum period (Table 3). Companionship in labour was assessed as to whether the woman had a family member present during childbirth. Rates for family support during labour varied widely, ranging from <1% at a Philippine hospital to 86% at a Malaysian hospital. Among the Malaysian hospitals the rates differed from 32% to 86%. In Thailand the rates of family support during labour were 31% at the university hospital, 44% at the provincial hospital and 83% at the regional hospital.

There were wide variations in the administration of an appropriate prophylactic oxytocic during third stage of labour both between countries and within countries. Rates for the administration of a uterotonic varied from <1% at one Philippine hospital to 98% at the Thai provincial hospital. Among the Thai hospitals rates of the practice were 4%, 76% and 98%. The variation was similar in The Philippines with one hospital giving oxytocics in two-thirds of cases and <1% in the other.

Controlled umbilical cord traction to deliver the placenta was routinely performed in the Indonesian, Malaysian and Philippine

Table 3. Percentage distribution of practices of beneficial forms of care

Care Practices	Indonesia			Malaysia			The Philippines			Thailand		
	Overall	Tertiary	District	Overall	Tertiary	District	Overall	Tertiary 1	Tertiary 2	Overall	Regional	University
<i>Antenatal period</i>												
MgSO ₄ for eclamptic fit	100	100	100	100	100	100	83	100	80	100	100	-
Antibiotic use for pROM	91	88	100	62	83	100	92	99	67	73	91	65
MgSO ₄ for pre-eclampsia	100	100	100	24	44	100	100	91	100	64	57	82
Corticosteroids given to women who gave birth at <34 weeks	9	9	10	55	59	47	15	0	21	73	86	60
<i>Intrapartum period</i>												
Management of the third stage of labour												
Appropriate prophylactic oxytocic given during third stage	26	26	26	5	10	1	27	<1	64	58	4	76
Controlled cord traction to deliver the placenta	100	100	100	100	100	100	98	100	96	56	31	43
Family support during labour	41	38	45	61	86	32	10	<1	19	53	83	31
Appropriate antibiotic use for caesarean section	0	0	0	<1	<1	0	5	0	7	49	72	82
<i>Postpartum period</i>												
Immunisation for Hepatitis B	2	0	3	99	99	99	2	<1	4	99	99	98

pROM: preterm prelabour rupture of membranes, MgSO₄ : Magnesium Sulphate

Figures are percentages (rounded to the nearest whole number)

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hospitals. In Thailand, the rates were below 50% in the regional and tertiary hospitals but 96% in the provincial hospital.

Use of antibiotic prophylaxis for caesarean section in a single dose administered after clamping of the umbilical cord was mostly very low or non-existent across all the hospitals. About a quarter of women who gave birth by caesarean were given appropriate antibiotic prophylaxis (534 out of 2564), over 95% of these women were from two Thai hospitals.

Although antibiotics were often given in other hospitals, the timing of administration was preoperatively or postoperatively, and multiple doses were often prescribed.

Practices during postpartum period (Table 3). Immunising babies against the hepatitis B virus was the only postpartum neonatal care practice assessed in our project. This intervention was only routinely practiced in the Malaysian and Thai hospitals.

Forms of care likely to be ineffective or harmful (Table 4)

Episiotomy was the form of care likely to be harmful which was most frequently practiced across all the hospitals and in all four countries. The overall episiotomy rate for women giving birth vaginally was 65%. Episiotomies were liberally performed in all three hospitals in Thailand, and in only one Malaysian hospital did the rate drop below one-third. Pubic hair shaving, another ineffective and potentially harmful form of care, was commonly practiced in all countries with rates as high as 98% in one Thai hospital. In only one Philippine hospital was this observed as an occasional practice. Use of enemas during labour, an ineffective practice, was occasionally used in four hospitals across all countries and was highest in one Thai (61%) and one Malaysian (44%) hospital.

Discussion

This study describes the rates of use of selected practices of key aspects of perinatal care reported in the medical records of nine hospitals in Indonesia, Malaysia, The Philippines and Thailand. The findings show high rates of compliance for some evidence-based recommendations for perinatal care and wide divergence for others. Practices that were in line with recommendations across most hospitals for the beneficial forms of care were controlled cord traction, one of the components of the active management of the third stage of labour, and treating eclampsia with magnesium sulphate. The unnecessary practice of enema use was appropriately widely avoided. The highest level of divergence from best practice recommendations in most countries was not administering appropriate antibiotic prophylaxis for caesarean section. Liberal use of episiotomy for women having a vaginal birth is not recommended but was often inappropriately practiced across the hospitals in all four countries, demonstrating lack of adoption of the evidence-based recommendation of restrictive episiotomy. Other forms of perinatal care such as pubic hair shaving and the use of enemas during labour varied in rates of compliance across all countries and even between hospitals within the same country.

The principles of evidence-based practice are to encourage health professionals to use practices with proven benefit and eliminate the use of those shown to be ineffective or harmful. Effective implementation of beneficial practices in developing regions [9,10], such as South East Asia, should lead to a reduction in maternal and neonatal mortality and morbidities.

Our findings are consistent with three previous reports of perinatal practice from the Asian and Arab world [11–13]. The first was reported by the Choices and Challenges in Changing Childbirth Research Network [11]. The network documented routine obstetric practices for normal labour and birth in Egypt,

Table 4. Percentage distribution of practices of forms of care likely to be harmful

Care Practices	Indonesia			Malaysia			The Philippines			Thailand		
	Overall	Tertiary	District	Overall	Tertiary 1	Tertiary 2	Overall	Tertiary 1	Tertiary 2	Overall	Regional	University
Episiotomy for vaginal births	54	49	60	47	61	31	64	64	64	91	95	93
Public hair shaving	28	26	29	33	24	42	26	12	40	74	43	79
Enema use	17	17	18	22	2	44	1	<1	3	30	1	29
												61

Figures are percentages (rounded to the nearest whole number).
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Lebanon, Syria and the West Bank, and compared these with evidence-based recommendations. They showed the practices for normal labour were largely not in accordance with the World Health Organization evidence-based classification of practices for normal birth. The second report described facility-based practices for normal labour and birth [12]. Forty-four clinical practices observed in a busy Egyptian teaching hospital were categorised according to World Health Organization Technical Working Group on normal birth classification of normal birth practices. This study concluded that practices for normal labour were largely not consistent with the World Health Organization evidence-based classification of practices for normal births. The third report compared practices of selected childbirth care procedures against evidence-based information and explored user and provider views about each procedure in four hospitals in Shanghai, China [13]. They concluded that obstetric practices of the hospitals studied were not following best available evidence.

There is clear evidence of benefit to perinatal health outcomes with use of appropriate antibiotic prophylaxis for caesarean section, use of antenatal corticosteroids for women at risk of preterm birth and family support during labour. Our findings however, show that these clinical practices were rarely performed in most of the included hospitals, with high rates of variation across the countries. It is likely that there are a range of barriers to all these clinical practices in our study settings, but detailed exploration of these was outside the scope of this initial audit. Although we were not able to interview the care providers or directly observe the clinical practices at the time of this survey, these were planned for a later stage of this project.

Recommendation of use of appropriate antibiotic prophylaxis for caesarean section is defined as administration of a single dose of ampicillin or first generation cephalosporin after umbilical cord clamping of the baby [14]. We found that most non-concordant practices relating to antibiotic prophylaxis for caesarean section arose from giving multiple doses or administering antibiotics pre or post operatively. In some clinical settings multiple doses of antibiotics at pre-operative or post-operative times may be appropriate.

One advantage of our study was that the prospective, sequential collection of data provided accurate information of individual pregnant women and their babies, directly extracted from the medical records of individual pregnant women rather than derived from interviewing health care providers. In addition, the information was extracted prospectively and therefore the findings closely reflect the actual practices of perinatal health care in the nine hospitals of the four South East Asian countries. A limitation of such data collection is that there might be some interventions that were practiced but not well documented in medical records. However, this is likely to be minimal as most information in medical records of the hospitals involved in the study is standardised for the care practices considered.

In summary, few practices of perinatal health care in the nine hospitals within the four South East Asian countries were consistent with best available evidence from Cochrane reviews and the World Health Organization Reproductive Health Library recommendations. At the individual hospitals the audit results were used to evaluate the barriers to adoption of appropriate practices and elimination of inappropriate practices followed by strategies to increase the use of evidence-based practices in perinatal health care. The recording of clinical practices within this audit was a pre-requisite to identifying problems to be addressed.

Based on our findings, the SEA-ORCHID project team developed and implemented interventions that aimed to build

capacity for research conduct, synthesis and translation that would increase compliance with evidence-based clinical practice recommendations and so improve maternal and perinatal care.

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Research article

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Use of antenatal corticosteroids prior to preterm birth in four South East Asian countries within the SEA-ORCHID project

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Abstract

Background: There is strong evidence supporting the use of antenatal corticosteroids in women at risk of preterm birth to promote fetal lung maturation and reduce neonatal mortality and morbidity. This audit aimed to assess the use of antenatal corticosteroids prior to preterm birth in the nine hospitals in four South East Asian countries participating in the South East Asia Optimising Reproductive Health in Developing Countries (SEA-ORCHID) Project.

Method: We reviewed the medical records of 9550 women (9665 infants including 111 twins and two triplets) admitted to the labour wards of nine hospitals in four South East Asian countries during 2005. For women who gave birth before 34 weeks gestation we collected information on women's demographic and pregnancy background, the type, dose and use of corticosteroids, and key birth and infant outcomes.

Results: Administration of antenatal corticosteroids to women who gave birth before 34 weeks gestation varied widely between countries (9% to 73%) and also between hospitals within countries (0% to 86%). Antenatal corticosteroids were most commonly given when women were between 28 and 34 weeks gestation (80%). Overall 6% of women received repeat doses of corticosteroids. Dexamethasone was the only type of antenatal corticosteroid used.

Women receiving antenatal corticosteroids compared with those not given antenatal corticosteroids were less likely to have had a previous pregnancy and to be booked for birth at the hospital and almost three times as likely to have a current multiple pregnancy. Exposed women were less likely to be induced and almost twice as likely to have a caesarean section, a primary postpartum haemorrhage and postpartum pyrexia.

Infants exposed to antenatal corticosteroids compared with infants not exposed were less likely to die. Live born exposed infants were less likely to have Apgar scores of < 7 at five minutes and less likely to have any lung disease.

Conclusion: In this survey the use of antenatal corticosteroids prior to preterm birth varied between countries and hospitals. Evaluation of the enablers and barriers to the uptake of this effective antenatal intervention at individual hospitals is needed.

Background

Infants born preterm are at high risk of neonatal lung disease and associated complications [1]. Respiratory distress syndrome (RDS), a consequence of immature lung development, is the primary cause of early neonatal mortality [2] and contributes to significant immediate [1] and long-term morbidity in survivors [3]. Antenatal corticosteroid treatment for women at risk of very preterm birth before 34 weeks gestation is one of the most effective treatments for the prevention of RDS, reducing neonatal mortality and morbidity [4]. This is of importance for developing countries where resources are scarce and it is often difficult to provide expensive treatments such as neonatal care.

Although evidence of benefit for the use of antenatal corticosteroids has been available for many years [5,6], widespread adoption of this treatment into routine clinical practice was significantly delayed and implementation of their use remained suboptimal in developed countries for many years [7]. There is limited information as to how well this practice has been implemented in developing countries.

Objectives of this review

The aim of this audit was therefore to assess the use of antenatal corticosteroids for women who gave birth at less than 34 weeks gestation in the nine hospitals across four South East Asian countries within the South East Asia Optimising Reproductive Health in Developing Countries (SEA-ORCHID) Project [8]. Information was collated on which women received corticosteroids, their sociodemographics and obstetric history, the type, amount and reason for use of corticosteroids, the birth details and infant health outcomes.

Methods

Setting

Nine hospitals participating in the SEA-ORCHID project in four South East Asian countries namely Indonesia, Malaysia, the Philippines and Thailand were audited [9]. Seven of the nine hospitals were tertiary (university and regional) referral institutions with regional referrals of women with a high risk pregnancy and two hospitals were provincial or district institutions. Delivery care models included obstetric specialists or a multidisciplinary approach with midwives (including nurses with midwifery qualifications). In all hospitals obstetric specialists and caesarean section facilities were available and doctors and/or midwives (including nurses with midwifery qualifications) conducted normal vaginal births.

The SEA-ORCHID project settings and methods have been described elsewhere [8]. The study was approved as an audit by the local ethics committee of each hospital

and the administering institution in Australia. Individual patient consent was not therefore sought.

Procedure

Previously, as part of the SEA-ORCHID baseline data collection we completed a prospective audit of the medical records of 9550 women (9665 infants including 111 twins and two triplets) admitted to the labour wards at the nine participating SEA-ORCHID hospitals during 2005. At five of the participating hospitals medical records were audited on a consecutive basis until a sample of 1000 was reached. To reduce the risk of bias the four largest participating hospitals randomly sampled medical records using various ratios to ensure a sample of 1000 was reached over the three month data collection period.

For this current audit, staff at each hospital were trained to use pre-established data extraction forms to prospectively audit the medical records of the 290 women who gave birth at < 34 weeks regardless of whether they were given antenatal corticosteroids or not (Table 1). Data from each country was sent to Khon Kaen University by post where it was manually entered into a Microsoft Access 2003 database. The database minimised transcription errors by performing validation checks to detect discrepancies and missing data.

Demographic information collected about these women included maternal age, any previous birth ≥ 22 weeks, gestational age at time of last corticosteroid injection, if given, whether the pregnancy was singleton or twins, whether they received public or private care, whether they were booked for birth at the hospital and the main reason they were considered at risk of preterm birth (Table 2).

Health outcomes for all infants exposed to antenatal corticosteroids as well as those who were not were collected including gestational age at birth, birth weight, stillbirth, death prior to discharge, live born babies discharged alive, presence of respiratory distress syndrome, severity of any lung disease, use of oxygen therapy, use and duration of mechanical ventilation (defined as intermittent positive pressure ventilation and/or continuous airways pressure), Apgar scores and length of hospital stay (Table 3).

Maternal health outcomes of all women were collected including use of induction of labour, mode of birth, primary or major postpartum haemorrhage and postpartum pyrexia (Table 4).

Data Analysis

Descriptive statistics assessed the use of antenatal corticosteroids across countries and between hospitals within countries. Difference of means with 95% confidence interval (CI) was used to compare factors measured in

Table 1: Percentage distribution of women who gave birth at < 34 weeks GA and corticosteroid use

Countries	Hospitals	Number of women who gave birth at < 34 weeks n (%)	Antenatal corticosteroids given to women who gave birth at < 34 weeks n (%)
Indonesia	Overall	90 (4)	8 (9)
	Tertiary	69 (7)	6 (9)
	District	21 (2)	2 (10)
Malaysia	Overall	51 (2)	28 (55)
	Tertiary 1	32 (3)	19 (59)
	Tertiary 2	19 (2)	9 (47)
The Philippines	Overall	48 (2)	7 (15)
	Tertiary 1	15 (1)	0 (0)
	Tertiary 2	33 (3)	7 (21)
Thailand	Overall	101 (3)	74 (73)
	Regional	51 (5)	44 (86)
	University	25 (3)	15 (60)
	Provincial	25 (3)	15 (60)

Figures are numbers with percentages rounded to the nearest whole number in brackets.

continuous data, such as maternal age and birth weight, between the two groups. When the data were skewed, difference of medians with 95% CI was used. Independent t-test or Mann-Whitney U test, where appropriate, was used for significant comparison of the two groups and results were shown as p-values. Relative risk (95% CI) and Chi-square tests were used for comparing the factors measured

in categorical data, such as parity and multiple pregnancy between the two groups. The analysis was done using STATA software version 8.0 [10].

Ethics

The SEA-ORCHID project was approved by the local ethics committees of each hospital and by the ethics commit-

Table 2: Characteristics of women receiving/not receiving antenatal corticosteroids with birth 24 to < 34 weeks gestational age

	Antenatal corticosteroids		Comparative statistic [#]	95% CI	p-value
	Received n = 104	Not received n = 148			
Maternal Age* (years)	27.6 (6.8)	28.5 (6.9)	-0.85	-2.59; 0.88	0.34
Parity ‡					
Previous pregnancies ≥ 22 weeks	47 (45)	86 (58)	0.77	0.60; 0.99	0.04
Gestational age at last injection					
< 24 – 27 weeks	20 (19)	-	N/A	N/A	N/A
28 – 31 weeks	42 (40)	-			
32 – < 34 weeks	42 (40)	-			
Multiple pregnancy					
Twins	10 (10)	5 (3)	2.84	1.0; 8.1	0.04
Patient status ‡					
Public	98 (94)	144 (98)	0.96	0.91; 1.01	0.12
Booked for birth at hospital ‡	81 (79)	136 (92)	0.86	0.77; 0.96	0.01
Main reasons for risk of preterm birth					0.01
Preterm labour	42 (40)	36 (24)	-	-	
PPROM	26 (25)	19 (13)	-	-	
Hypertension	18 (17)	18 (12)	-	-	
APH	6 (6)	9 (6)	-	-	
Maternal conditions	4 (4)	6 (4)	-	-	
Multiple pregnancy	2 (2)	2 (1)	-	-	
Fetal concern	1 (1)	8 (5)	-	-	
Other/not recorded	5 (5)	50 (34)	-	-	

Figures are numbers with percentages rounded to the nearest whole number in brackets and with relative risk and 95% confidence intervals as the comparative statistic[#], or *Mean and standard deviation with mean difference between groups and 95% confidence intervals as the comparative statistic[#]. ‡Outcomes not available for a few women

Table 3: Health outcomes for infants exposed to antenatal corticosteroids versus those not exposed

	Antenatal corticosteroids		Comparative statistic [#]	95% CI	p-value
	Exposed	Not exposed			
All babies	n = 114	n = 152			
Gestational age at birth* [‡] (weeks.days)	30.4 (2.6)	29.9 (2.7)	0.47	-0.19; 1.13	0.16
Birth weight* [‡] (kg)	1.62 (0.65)	1.48 (0.63)	0.14	-0.02; 0.29	0.08
Stillbirth	2 (2)	42 (28)	0.06	0.02; 0.25	0.01
All deaths (stillbirths/deaths prior to discharge)	18 (16)	49 (32)	0.49	0.30; 0.79	0.01
Mode of birth					0.01
normal vaginal	59 (52)	99 (65)	1	--	--
vaginal breech	4 (4)	19 (13)	0.39	0.14; 1.11	0.06
operative vaginal birth	2 (2)	2 (1)	1.65	0.24; 11.45	0.63
caesarean section	49 (43)	32 (21)	1.85	1.28; 2.67	0.01
Live born babies	n = 112	n = 111			
Live born babies discharged alive	96 (86)	103 (93)	0.92	0.84; 1.0	0.05
Respiratory distress syndrome ^{‡‡}	59 (60)	54 (57)	1.06	0.83; 1.34	0.64
Severity of lung disease [§]					0.01
none	22 (30)	4 (11)	1	--	--
mild	7 (9)	15 (42)	--	--	--
moderate	27 (37)	6 (17)	--	--	--
severe	18 (24)	11 (30)	--	--	--
Use of oxygen therapy [¶]	50 (50)	55 (57)	0.86	0.66; 1.12	0.27
Use of mechanical ventilation ^{¶¶}	53 (54)	25 (39)	1.38	0.97; 1.98	0.06
Apgar Score < 7 at 1 min [†]	42 (38)	57 (52)	0.73	0.54; 0.98	0.04
Apgar Score < 7 at 5 min [†]	15 (14)	34 (31)	0.44	0.25; 0.75	0.01

Figures are numbers with percentages rounded to the nearest whole number in brackets and with relative risk and 95% confidence intervals as the comparative statistic[#], or *mean and standard deviation with mean difference between groups and 95% confidence intervals as the comparative statistic[#]. [§]Severity of lung disease is defined as none (no oxygen required), mild (Oxygen < 40% FiO₂), moderate (FiO₂ 40–79%), severe (FiO₂ 80% or more). [‡]Values are based on 114 in the Exposed Group and 151 in the Not Exposed Group. ^{‡‡}Values are based on 98 in the Exposed Group and 95 in the Not Exposed Group. [¶]Values are based on 101 in the Exposed group and 96 in the Not Exposed Group. ^{¶¶}P Values are based on 98 in the Exposed Group and 64 in the Not Exposed Group. [†]Values are based on 111 in the Exposed Group and 110 in the Not Exposed Group.

tee of the University of Sydney, the administering institution in Australia.

Results

Corticosteroid administration in South East Asian countries (Table 1)

Antenatal corticosteroids were not frequently administered to women who gave birth at less than 34 weeks gestation at any of the hospitals audited across the four South East Asian countries. Of the 290 women who gave birth at less than 34 weeks gestation presenting to the audited hospitals, 117 (40%) received antenatal corticosteroids.

Thai and Malaysian hospitals showed the highest usage of antenatal corticosteroids for women who gave birth before 34 weeks gestation (73% and 55% respectively). Less than 10% of women who gave birth preterm at Indonesian hospitals were reported to be given antenatal corticosteroids. Hospitals in The Philippines recorded a low rate of antenatal corticosteroid use with one hospital not administering corticosteroids to any women who gave birth preterm.

Table 4: Maternal outcomes for women receiving/not receiving antenatal corticosteroids with birth 24 to < 34 weeks gestational age

	Antenatal corticosteroids		Relative Risk	95% CI	p-value
	Received n = 104	Not received n = 148			
Induction of labour [‡]	3 (3)	11 (23)	0.14	0.04; 0.47	0.01
Primary postpartum haemorrhage (≥ 500 ml) [‡]	27 (26)	22 (15)	1.68	1.02; 2.79	0.04
Major haemorrhage (≥ 1000 ml) [‡]	8 (8)	7 (5)	1.57	0.58; 4.19	0.42
Postpartum pyrexia ≥ 38°C [‡]	9 (9)	2 (1)	6.53	1.44; 29.5	0.01

Figures are numbers with percentages rounded to the nearest whole number in brackets and with relative risk and 95% confidence intervals as the comparative statistic. [‡]Outcomes not available for a few women.

Dexamethasone was the only antenatal corticosteroid used across the nine hospitals. Repeat courses of antenatal corticosteroids were given to 6% of women.

Maternal demographics (Table 2)

Overall, women who gave birth at less than 34 weeks gestational age who received antenatal corticosteroids were similar in age to women who did not receive antenatal corticosteroids (mean maternal age 27.6 years (Standard Deviation (SD) 6.8) and 28.5 years (SD 6.9) respectively). Nearly all women in this audit attended a public hospital throughout their pregnancy. Compared with women who did not receive antenatal corticosteroids, women who did were less likely to have had a previous pregnancy ≥ 22 weeks (RR 0.77, [95%CI 0.60, 0.99], $p = 0.04$), almost three times as likely to have a multiple pregnancy (RR 2.84, [95%CI 1.0, 8.1], $p = 0.04$) and less likely to be booked for birth at the hospital (RR 0.86, [95%CI 0.77, 0.96], $p = 0.01$). For women receiving antenatal corticosteroids, most had their last injection after 28 weeks gestation. Similar numbers of women received their last injection between 28 to 31 weeks and between 32 to < 34 weeks gestation (40% and 40%).

There were significant differences in the distributions of the main reason women were considered at risk of preterm birth between the mothers who were administered corticosteroids and those who did not receive them ($p = 0.01$) (Table 2). More women who received antenatal corticosteroids were in preterm labour, or had preterm prelabour rupture of the membranes or hypertension.

Although health outcomes for the mother and their infants are compared below by whether exposed or not to antenatal corticosteroids, it needs to be remembered these are not randomised groups. Groups may well differ by other factors influencing health outcomes besides the exposure or not to corticosteroids.

Infant health outcomes (Table 3)

Infants exposed to antenatal corticosteroids were born at a similar gestational age and had similar birth weights to infants who were not exposed. The majority of infants in both groups were born between 28 to < 34 weeks (82% and 80% respectively). Infants exposed to antenatal corticosteroids were less likely to be stillborn (RR 0.06, [95%CI 0.02, 0.25], $p = 0.01$) and were less likely to die prior to hospital discharge (stillbirth and death prior to discharge combined, RR 0.49, [95%CI 0.30, 0.79], $p = 0.01$) compared with infants who were not exposed. Live born infants who were not exposed were more likely to be discharged alive than infants who were exposed to antenatal corticosteroids (RR 0.92, [95%CI 0.84, 1.0], $p = 0.05$).

The distribution of severity of any lung disease was significantly different in infants exposed to antenatal corticosteroids with fewer infants having respiratory problems compared with infants who were not exposed ($p = 0.01$). Low Apgar scores (< 7) at 1 minute and 5 minutes were less likely for infants exposed to antenatal corticosteroids compared with infants who were not exposed (RR 0.73, [95%CI 0.54, 0.98], $p = 0.04$ and RR 0.44, [95%CI 0.25, 0.75], $p = 0.01$ respectively).

The risk of respiratory distress syndrome, use of mechanical ventilation and use of oxygen therapy were not statistically different between the two groups of infants.

Maternal health outcomes (Table 4)

Significantly fewer women who received antenatal corticosteroids were induced (RR 0.14, [95%CI 0.04, 0.47], $p = 0.01$) however they were almost twice as likely to have a caesarean section (RR 1.85, [95%CI 1.28, 2.67], $p = 0.01$) compared with women who did not receive antenatal corticosteroids. A primary postpartum haemorrhage (≥ 500 ml) was more likely for women who received antenatal corticosteroids (RR 1.68, [95%CI 1.02, 2.79], $p = 0.04$) and they were over six times more likely to develop a postpartum pyrexia ($\geq 38^\circ\text{C}$) compared with women who did not receive them (RR 6.53, [95%CI 1.44, 29.5], $p = 0.01$).

Discussion

An audit by the SEA-ORCHID group across four South East Asian countries found the use of antenatal corticosteroids to be one of the least performed beneficial interventions in the prenatal period at collaborating hospitals within those countries [9]. We therefore conducted this in depth review of antenatal corticosteroid use prior to preterm birth in women presenting to the nine hospitals in four South East Asian countries to compare sociodemographic factors, obstetric history and birth and infant outcomes between women exposed and non-exposed.

This review reported varying uptake of these guidelines into practice both between the nine hospitals in the four South East Asian countries that were audited and between the countries themselves. Within the countries, there was no obvious relationship between the type of hospital and the implementation of the use of corticosteroids, as use varied between hospitals within some countries and was similar between hospitals in other countries. These findings highlight the need to examine the barriers and enablers to adoption of the use of antenatal corticosteroids among maternal and infant health practitioners at the individual hospitals. Furthermore, it illustrates potential benefit in each hospital developing its own locally relevant clinical practice guideline for antenatal corticosteroid administration so as to encourage standardised best practice.

The results of our review show that women from the nine collaborating hospitals who received antenatal corticosteroids were more likely to be experiencing their first pregnancy and have a multiple pregnancy but were less likely to be booked at the hospital for birth. There remains doubt about the use of antenatal corticosteroids in multiple pregnancies. One study has reported similar risks of death or major morbidity between singleton and multiple infants [11] while other studies suggest that antenatal corticosteroid therapy does not significantly reduce the incidence of respiratory distress syndrome in multiple gestations [12-15]. Further analysis of health outcomes of infants from multiple pregnancies need to be analysed to provide evidence either for or against this practice [4].

Our review showed that in the nine hospitals in the four South East Asian countries audited, over 80% of corticosteroids administered were given when women were over 28 weeks gestation. Gestational age at which antenatal corticosteroids should be given has long been a topic of debate. An earlier systematic review showed limited evidence of benefit if given at less than 28 weeks [16] although the updated systematic review shows respiratory distress syndrome is reduced when corticosteroids are given in multiple doses with the first injection between 26 to 29.9 weeks [4].

The type of antenatal corticosteroid used between countries and between hospitals within countries did not differ, with dexamethasone the only corticosteroid used. It is recognised that the frequency of respiratory distress syndrome is decreased by both betamethasone and dexamethasone [4], although there is still uncertainty concerning which corticosteroid provides better health outcomes [17].

The reason as to only dexamethasone being used in the South East Asian countries audited is most likely due to financial reasons, given that dexamethasone is the less expensive of the two corticosteroids. As a result of this, dexamethasone is often simply the only drug available in these developing countries.

Limited use of repeat steroids was reported for all four South East Asian countries. Evidence for the use of a single course of antenatal corticosteroids for women at risk of preterm birth has been acknowledged and accepted and it has become recommended standard care [7,18,19]. At the time of this audit, evidence regarding the effects of repeat courses of antenatal corticosteroids was still unclear [20].

The published systematic reviews on antenatal corticosteroids papers [4] report positive health outcomes for mothers and infants. The few negative health outcomes seen in

our audit are likely to reflect selection bias due to the use of selective, non randomised groups.

Based on abundant evidence suggesting that antenatal corticosteroids positively influence infant survival for preterm birth, and the audit result of varying uptake of this intervention in the participating hospitals, it is obvious that barriers to uptake of practice, in particular access to evidence-based practice guidelines and recommendations need to be examined at the individual institutions. As part of the SEA-ORCHID project we plan to conduct a survey of evidence-based practice knowledge and clinical change among maternal and infant health practitioners in South-East Asia to explore this issue.

A similar intervention undertaken in Thailand increased the rate of use of antenatal corticosteroids for women who gave birth preterm (< 34 weeks gestation) from a baseline rate of 41% to 73% after evidence became available and was disseminated [21]. Prior to this intervention an increase from 33% to 58% for the rate of antenatal corticosteroid administration in the US was achieved after distribution of information. A further increase to 68% was achieved after further knowledge of evidence distribution [22].

Conclusion

This audit across four South East Asian countries indicates that rates of use of antenatal corticosteroids are varied in the hospitals participating in the SEA-ORCHID project. Antenatal corticosteroids given to women prior to preterm birth had significant health benefits for their babies. The findings of this review highlight an important gap in best practice recommendations that could be improved with relatively low cost and with great benefit to neonatal outcomes in resource poor countries. Barriers to uptake and implementation of evidence-based practice guidelines need to be evaluated and addressed and form part of the ongoing SEA-ORCHID project [8].

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

PL, ML, SM and CC contributed to the design of the study. PP cleaned and analysed the data and all authors contributed to the interpretation of data. ME prepared the first draft of the paper. All authors commented on each draft of the paper.

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Study protocol

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Active management of the third stage of labour without controlled cord traction: a randomized non-inferiority controlled trial

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Abstract

Background: The third stage of labour refers to the period between birth of the baby and complete expulsion of the placenta. Some degree of blood loss occurs after the birth of the baby due to separation of the placenta. This period is a risky period because uterus may not contract well after birth and heavy blood loss can endanger the life of the mother. Active management of the third stage of labour (AMTSL) reduces the occurrence of severe postpartum haemorrhage by approximately 60–70%. Active management consists of several interventions packaged together and the relative contribution of each of the components is unknown. Controlled cord traction is one of those components that require training in manual skill for it to be performed appropriately. If it is possible to dispense with controlled cord traction without losing efficacy it would have major implications for effective management of the third stage of labour at peripheral levels of health care.

Objective: The primary objective is to determine whether the simplified package of oxytocin 10 IU IM/IV is not less effective than the full AMTSL package.

Methods: A hospital-based, multicentre, individually randomized controlled trial is proposed. The hypothesis tested will be a non-inferiority hypothesis. The aim will be to determine whether the

simplified package without CCT, with the advantage of not requiring training to acquire the manual skill to perform this task, is not less effective than the full AMTSL package with regard to reducing blood loss in the third stage of labour.

The simplified package will include uterotonic (oxytocin 10 IU IM) injection after delivery of the baby and cord clamping and cutting at approximately 3 minutes after birth. The full package will include the uterotonic injection (oxytocin 10 IU IM), controlled cord traction following observation of uterine contraction and cord clamping and cutting at approximately 3 minutes after birth. The primary outcome measure is blood loss of 1000 ml or more at one hour and up to two hours for women who continue to bleed after one hour. The secondary outcomes are blood transfusion, the use of additional uterotonics and measure of severe morbidity and maternal death.

We aim to recruit 25,000 women delivering vaginally in health facilities in eight countries within a 12 month recruitment period.

Management: Overall trial management will be from HRP/RHR in Geneva. There will be eight centres located in Argentina, Egypt, India, Kenya, Philippines, South Africa, Thailand and Uganda. There will be an online data entry system managed from HRP/RHR. The trial protocol was developed following a technical consultation with international organizations and leading researchers in the field.

Expected outcomes: The main objective of this trial is to investigate whether a simplified package of third stage management can be recommended without increasing the risk of PPH. By avoiding the need for a manual procedure that requires training, the third stage management can be implemented in a more widespread and cost-effective way around the world even at the most peripheral levels of the health care system. This trial forms part of the programme of work to reduce maternal deaths due to postpartum haemorrhage within the RHR department in collaboration with other research groups and organizations active in the field.

Trial Registration: ACTRN12608000434392

Background

The third stage of labour refers to the period between birth of the baby and complete expulsion of the placenta. Some degree of blood loss occurs after the birth of the baby due to separation of the placenta. This period is a risky period because uterus may not contract well after birth and heavy blood loss can endanger the life of the mother.

The third stage of labour is managed differently around the world. Over the years two management packages, known as 'active management' and 'expectant management' emerged. The primary aim of active management is to reduce postpartum blood loss as a preventive intervention. In active management (AMTSL) a number of interventions are applied in combination while the expectant management represents a more hands-off style with those interventions used in AMTSL withheld. AMTSL has been defined in various ways and current international definition comprises three components: administration of an uterotonic soon after delivery of the baby; controlled cord traction; and uterine massage after delivery of the placenta [1]. Active management of the third stage of labour (AMTSL) reduces the occurrence of severe postpartum haemorrhage by approximately 60–70% [2].

In previous active versus expectant trials the cord was clamped as soon as possible usually within one minute. However, trials of cord clamping timing have shown beneficial effects on newborn haematological indices leading to the recommendation to clamp the cord at around 3 minutes although the effects on the mother are unknown [3].

The WHO PPH Prevention Guidelines published in 2007 recommended AMTSL defined as the use of oxytocin 10 IU IM/IV after birth, cord clamping at around 3 minutes when the uterus contracts and controlled cord traction. There were no recommendations related to the use of uterine massage in this guideline.

Unfortunately, the relative contribution of the components of AMTSL to the overall reduction in blood loss is not clearly known. Understanding the contribution of the components of AMTSL to the overall effect in reducing the incidence of haemorrhage could have major programmatic significance since some components require training while others require an efficient drug procurement and utilization system [4]. At the same time the probability of interaction between AMTSL components should be kept in mind.

These considerations led to a technical consultation of scientists working in the field of postpartum haemorrhage research in December 2007 to discuss work on a research project to evaluate the effects of different components of AMTSL. Such research is important and timely because some components such as the uterotonic and controlled cord traction may not be feasible in all settings and it is worthwhile evaluating a more simple package with fewer components.

Systematic reviews of effects of AMTSL components

Uterotonic

The uterotonic component of AMTSL seems to be important for the reduction in blood loss after delivery [5]. Two trials compared oxytocin to nothing without other active management components practiced [6,7] and one trial compared oxytocin to nothing with other active management components practiced in both groups [8]. Oxytocin used at 5–10 IU seemed to reduce the risk of severe postpartum haemorrhage although the other components were not well described.

Controlled cord traction

Cord traction was introduced into obstetric practice by Brandt (1933) and Andrews (1940) by the so-called Brandt-Andrews maneuver. The aim is to facilitate the delivery of a placenta that is already separated. In 1962 the term *controlled cord traction* (CCT) was introduced which aims to facilitate the separation of the placenta once the uterus contracts [9]. In performing CCT placental separation is not waited and once the uterus contracts the CCT is initiated. The third stage is usually completed in less than 10 minutes when CCT is used.

There is concern by clinicians, based on teachings from their pre-service education that traction on the cord prior to placental separation may lead to maternal complications such as separation of the cord from the placenta and uterine inversion. There is not a large body of direct evidence for or against effects of controlled cord traction in isolation [10].

CCT requires training to acquire this manual skill. Evaluation of CCT component is important because if it does not add any beneficial effects it can be dropped from the AMTSL package with important programmatic implications.

Uterine massage

Uterine massage is used following delivery in various forms. Between delivery of the baby and the placenta a birth attendant will often put his/her hand over the uterus to ensure that there is no undiagnosed twin, to assess if the uterus is contracting and may rub the uterus to stimulate contraction. The Cochrane review on active

versus passive management does not refer to the use of uterine massage as part of AMTSL whereas the FIGO/ICM statement on AMTSL does include uterine massage as part of AMTSL. Evidence that massage contributes to a reduction in blood loss would provide evidence to support the use of this intervention with simple instructions.

The National Institute for Health and Clinical Excellence of the United Kingdom published comprehensive guidelines on intrapartum management on 26 September 2007 <http://www.nice.org.uk/nicemedia/pdf/IPCNICEGuidance.pdf> and has made no reference to uterine massage.

A small pilot trial (n = 200) conducted in Assiut, Egypt, used 'sustained uterine massage' started after delivery applied every 10 minutes and continued for 60 minutes. The findings are promising, since women receiving massage had less blood loss > 500 ml and received less additional uterotonics than women not receiving uterine massage [11]. In the two surveys conducted by Prevention of Postpartum Hemorrhage Initiative (POPHI) massage before placental delivery was practiced in about one third of all deliveries. In the same surveys massage after placental delivery was used in 80–90% of women although it was not possible to observe how long after delivery the massage was continued [12].

Williams Obstetrics states "massage is not employed but the fundus is frequently palpated to make certain that the organ does not become atonic and filled with blood from placental separation". In the United States and some other countries, palpating the uterus and massaging if "soft" for the first few hours after childbirth is considered standard of care [13]. In many countries however, no well-defined massage protocol exists. A systematic review to evaluate the effects of sustained uterine massage from the time of birth of the baby currently contains very little evidence to guide practice [14].

Other interventions

One intervention that has recently been included in AMTSL package is delayed cord clamping. There is evidence that delayed cord clamping increases newborn haematological indices in the short term and also has beneficial effects of reduced intraventricular haemorrhage when applied to preterm infants. However, there is almost no evidence on maternal effects especially whether it increases the blood loss.

Other third stage interventions include squeezing the uterus from the fundus to expel the placenta (Crédé maneuver) [15], placental cord drainage, umbilical vein injection and variations in timing, dose, and route of above discussed components.

Rationale for selecting the experimental intervention

An important aspect of AMTSL components is that one cannot assume that each component has no interaction with others. Such interactions could occur for single, double or triple components. The implication is that even if an intervention may not be (as) effective when individually applied it may have effect together with another component. For example, oxytocin and massage could act synergistically.

The relative importance of all of these uncertainties and the feasibility of evaluating the effects of one or more of the components were discussed in detail at the technical consultation referred above in December 2007. The evaluation of two components namely CCT and uterine massage after placental delivery was given priority. The feasibility of evaluating both interventions in one trial was discussed in detail. Different epidemiological designs such as three-arm and 2×2 factorial design were considered. Evaluating more than one component in a single trial posed particular difficulties. Such difficulties originated from the nature of the intervention(s) (manual procedures being difficult to mask) and the low incidence of the primary outcome measure. The implications of these two factors were resorting to cluster or cross-over cluster designs with added complexity and large sample sizes. At the end of the consultative process evaluation of a package that does not include controlled cord traction was regarded as the highest priority research question among all discussed. The main reason for this conclusion is that currently, the global scale up of AMTSL is limited to those settings where skilled birth attendants are available largely because controlled cord traction (CCT) requires clinical skills training. Considerable training investments are needed to enable health providers to do CCT correctly and safely.

The presence of a skilled birth attendant is essential in every childbirth. Birth attendants are required for not only basic care during the first and second stage of labour but also in the third stage when haemorrhage risk is greatest and also for the immediate care of the newborn. We aim to identify the relative effect of one component that requires manual skill training. In the most peripheral points of the health system the availability of health personnel with skills to implement the full AMTSL package may be more difficult to ensure in some settings. Therefore, evaluation of whether a simplified package without CCT is non-inferior to the full AMTSL package has both clinical and public health importance. The simplified package is also less intrusive for the mother.

If it were possible to demonstrate the non-inferiority of a simplified form of AMTSL, dispensing with CCT, it would greatly reduce programme costs associated with training,

and enable the intervention to be used by lower level providers, especially in out-of-hospital settings.

We therefore put forward the hypothesis that a simplified package comprising oxytocin 10 IU IM/IV (with or without uterine massage) is as effective as the full AMTSL package.

Objective

The primary objective is to determine whether the simplified package of oxytocin 10 IU IM/IV, without CCT, is not less effective than the full AMTSL package with regard to reducing blood loss ≥ 1000 ml in the third stage of labour. The hypothesis will be that of non-inferiority within a margin of 0.45 to 0.50%. If this hypothesis is demonstrated, the simplified package without CCT could be adopted, with the advantage of not requiring training to acquire the manual skill to perform this task.

Study design

This will be a hospital-based, multicentre, individually randomized non-inferiority controlled trial.

Each woman will be randomized to receive either the full (AMTSL) package or the simplified package. The blinding of the intervention will not be possible because the comparison includes a manual procedure.

Interventions

In order to overcome the variations in the actual practice of AMTSL a working definition was discussed and agreed upon during the technical consultation.

Experimental arm: Simplified package

The simplified package will include;

• Uterotonic

Oxytocin 10 IU IM. Oxytocin will be administered as soon as possible after birth preferably within one minute. If a woman has an IV line oxytocin can be administered through the IV line by slow injection.

• Cord clamping

Cord will be clamped following observation of a uterine contraction either manually or visually. For practical purposes this is estimated to be around 1–3 minutes. It is recommended to clamp the cord close to the perineum.

• Placental delivery

Cord traction is omitted. Placenta should be delivered passively by aid of gravity and maternal effort. The caregiver should observe the placental separation and as the placenta delivers it should be held in two hands and gently turned so that the membranes do not tear off.

• Uterine massage

No uterine massage is recommended before placental delivery. After placental delivery the uterus will be rubbed and any clots expressed. For a period of two hours the uterus will be massaged gently until it contracts and this procedure will be repeated every 15 minutes. It is acknowledged that not all centres will be able to implement this component. Each centre will decide before the trial begins whether the uterine massage component will be implemented or not.

Standard intervention arm: Full AMTSL package

The full package will include:

• Uterotonic

Oxytocin 10 IU IM. Oxytocin will be administered as soon as possible after birth preferably within one minute. If a woman has an IV line oxytocin can be administered through the IV line by slow injection.

• Cord clamping

Cord will be clamped following observation of a uterine contraction either manually or visually. For practical purposes this is estimated to be around 1–3 minutes. It is recommended to clamp the cord close to the perineum.

• Placental delivery

Placenta will be delivered by controlled cord traction immediately after cord clamping and cutting. The cord will be gently pulled while applying counter traction to the uterus with the other hand. As the placenta delivers it should be held in two hands and gently turned so that the membranes do not tear off.

• Uterine massage

No uterine massage is recommended before placental delivery. After placental delivery the uterus will be rubbed and any clots expressed. For a period of two hours the uterus will be massaged gently until it contracts and this procedure will be repeated every 15 minutes. It is acknowledged that not all centres will be able to implement this component. Each centre will decide before the trial begins whether the uterine massage component will be implemented or not.

The two intervention packages will differ only in placental delivery technique. If the umbilical cord has been clamped early because of newborn indication cord traction should be applied only after the uterus has contracted as above.

Outcome measures

The primary outcome measure is blood loss of 1000 ml or more at one hour and up to two hours for women who continue to bleed after one hour. Blood collection will be made using the calibrated drape BRASSS-V® and measured

from delivery to one hour following delivery or up to two hours if bleeding continues [16].

Secondary outcomes are;

- blood transfusion,
- the use of additional uterotonics to treat PPH
- blood loss 500 ml or more
- postpartum maternal haemoglobin (in centres where feasible)
- maternal death
- manual removal of placenta,
- additional surgical procedures (e.g. hysterectomy, ligation of vessels)
- composite outcome of maternal death or severe morbidity (admission to intensive care unit, hysterectomy, blood loss of two liters or more, uterine inversion, near miss event as defined in the manual of operations)
- initiation of breastfeeding
- side effects such as nausea and abdominal pain

Once the cord is clamped and cut the drape will be placed under the woman's buttocks and blood loss measurement will begin. The blood loss measurement will continue for one hour regardless of whether the woman is kept in the delivery room or moved elsewhere. If the bleeding continues beyond one hour the blood loss measurement will continue until two hours postpartum.

Side effects will be recorded by the researcher. Any side effect requiring treatment will be regarded as an adverse event and a separate form will be filled.

Serious adverse events will be recorded in special forms and will be returned by the local investigators to the trial coordination unit within 24 hours.

Study population

All women expecting to deliver vaginally at the participating hospitals will be potentially eligible. Women will be approached primarily during antenatal care and early labour for consent for participation except under the following circumstances;

1. Advanced first stage of labour (> 6 cm cervical dilatation)

2. Women who are too distressed to give consent regardless of cervical dilatation or phase of labour. Such evaluation will be made by the clinician in charge of the care of the woman.

3. Minors without a guardian

4. Planned caesarean section

5. If the birth is considered an abortion according to local limits

6. Women with twins or higher order multiple gestations

7. Women who are not capable of giving consent due to other health problems such as obstetric emergencies (e.g. eclampsia) or mental disorder.

Women receive AMTSL regardless of whether they are at high or low-risk for haemorrhage. Therefore all women will be eligible for participation according to the exceptions mentioned above.

Methods

Generation of allocation sequence

The random allocation sequence will be generated centrally at WHO Headquarters using computer generated random numbers. Randomization will be to two groups and stratified by country. Blocking with randomly varying groups of 6–8 will be used to restrict randomization within the strata.

Random allocation technique and allocation concealment

Allocation of the random generated sequence will be by consecutively numbered envelopes. Allocation concealment will be achieved by using sealed opaque envelopes. Allocation will take place during second stage when vaginal delivery is imminent. Once the envelope is opened the name of the woman will be entered on the log file with the envelope number and that woman is enrolled in the trial.

Rationale for the non-inferiority hypothesis and for sample size estimation

The objective of this trial is to show 'non-inferiority' of the simplified package' compared to the full AMTSL package. As such, while superiority would be an added bonus it is not expected and is probably not plausible since the experimental intervention has fewer interventions.

In the conventional superiority trial, the aim is to determine whether one intervention is superior to another, for example, whether uterotonic is superior to nothing. By contrast, in a non-inferiority trial, the aim is to determine whether an alternative intervention with certain advantages

is similar to a gold standard. The full AMTSL package represents the gold standard management strategy for reducing blood loss in the third stage of labour. In order to evaluate the effectiveness of a simplified package with fewer components that package has to be compared to the full package to see whether it is "non-inferior" to the gold standard [17].

Because proof of exact equality is impossible, a pre-stated margin of non-inferiority (Δ) for the difference in effectiveness has to be defined. The choice of the non-inferiority margin can be made using clinical assessment, which is to a certain extent arbitrary, and needs consensus among different stakeholders. A technique which has been proposed [17] to establish the non-inferiority margin is to look at the effect of the gold standard, in this case the full AMTSL, compared with placebo in historical (past) trials, in this case the expectant management. A reasonable criterion is to preserve 80% of the benefit of the full AMTSL package (considered as 100%) over expectant management (considered as 0%). Preserving a higher percentage (say 90%) will push the sample size calculations very high while a smaller percentage (say 50%) may not be considered acceptable.

Estimates of blood loss ≥ 1000 ml (severe PPH – sPPH) with active and passive management were taken from the literature. In addition, unpublished data from several ongoing WHO studies where postpartum blood loss is measured were obtained. Based on those data, a 1.5% risk of blood loss of 1000 ml with full active management was considered realistic and appropriate.

The expectant management sPPH rate was more difficult to estimate because the data was only available from earlier published trials and blood loss estimation methods and the actual expectant management method differed between trials. Values between 3.0 to 4.0% are considered realistic and used for sample size estimations.

Table 1 includes different scenarios for the calculation of sample size, obtained by varying the sPPH rate with expectant management (3.0 to 4.0%) and varying the % retained effect (70% to 80%), assuming a fixed 1.5% sPPH rate for the full AMTSL package. These different scenarios result in different choices of the margin of non-inferiority Δ . The total sample size required for a non-inferiority test at the 2.5% level using a two-sided 95% confidence interval and a power of 80% is shown, as well as the power obtained for fixed sample sizes of 20,000 and 25,000.

A trial of 22,908 women will have 80% power to show non-inferiority of the simplified package within 0.45% of the full AMTSL package sPPH rate (i.e. less than 1.95%

Table 1: Sample size scenarios

Blood loss $\geq$ 1000 ml with full amtsl	Blood loss $\geq$ 1000 ml with Expectant	Estimated impact of Full AMTSL	Proportion (of full AMTSL effect) retained by the simplified package	Δ (Difference to exclude to claim equivalence)	Total N for 80% Power	Power with total N = 20,000	Power with total N = 25,000
1.5	3.0	1.5	0.7	0.45	22,908	75%	83%
1.5	3.5	2.0	0.75	0.50	18,555	83%	90%
1.5	4.0	2.5	0.8	0.50	18,555	83%	90%

sPPH rate), with a level of significance of 2.5% (Table 1, row 1). The estimates from the centres that have expressed interest in participating in the trial indicate that approximately 20,000–25,000 women can be recruited in a 12 months recruitment period. These centres have collaborated with WHO before and have experience in third stage trials.

Type of data and data collection procedure

The trial will be conducted in the labour ward of maternity facilities. All women with anticipated vaginal delivery will be eligible. During the trial period information on the total number of births in the facility will be collected to monitor the recruitment efficiency. Ideally, the participating centres should enroll women 24 hours a day. However, such recruitment may not be possible at all centres.

The main data collection will be during the immediate postpartum period but women will be followed up until discharge from the hospital to record any additional interventions and complications that may occur. Once the bleeding stops and the woman is ready for transfer to the postnatal ward the researcher will fill the data collection form. After discharge the data collection forms will be completed and the form data will be entered on to the online system. The online data entry will be either at the hospital or country level depending on local capacity.

Analysis plan

The main analysis will be on an intention-to-treat principle with comparisons made between the 'simplified' and 'full' AMTSL packages for primary and secondary outcomes. An alternative to the ITT analysis (non-ITT analysis, sometimes called 'per-protocol'), that excludes patients not on their intended treatment and/or those who are not protocol-compliant in any other way could bias the trial in either direction, depending on which patients are thus excluded. In non-inferiority and equivalence trials, performing non-ITT analysis in addition to ITT analysis is desirable as a protection from the increase in type I error risk.

We expect only a small number of protocol deviations because the personnel involved in the study will receive intensive and continuous training and because the trial

will be closely monitored by trial investigators and periodically by a Data Monitoring Committee that will look at protocol deviations. Thus, the decrease in power due to exclusions of protocol deviations will be minimal. Table 1 shows that for the proposed sample size, the power is higher than the usually required 80%.

There may be deviations from the trial protocol if the baby's condition requires urgent action. In such situations the cord may be clamped and cut immediately after birth of the head and if the caregiver is involved in the resuscitation the timing of placental delivery may differ (this could be in either direction). We would expect this deviation to be equally distributed in the two groups. A second type of deviation could occur if a woman who has earlier given consent and randomly allocated to one group withdraws her consent after randomization. The withdrawal of consent after random allocation should be extremely rare since the random allocation will be made when vaginal delivery is imminent. We have looked at earlier trials where expectant management was used (because expectant management omits controlled cord traction) and did not find any suggestion that there was a compliance problem with omission of CCT. Nevertheless, the sample size calculation has a margin of additional power as mentioned in table 2 to ensure that such protocol deviations do not have a negative impact on the conclusions[17]

The actual management of third stage of labour will be recorded in all women to enable the analysis mentioned above.

Comparisons will be expressed as relative risks and risk differences with 95% confidence intervals. The analysis will be stratified by site, and if there is heterogeneity between the sites for any of the results possible causes of heterogeneity will be explored. In the presence of heterogeneity, the results will not be combined in a single summary estimate (or pooled estimate). In the absence of heterogeneity at the 5% level, the results will be combined.

The primary analysis will follow the following scheme for interpretation (Figure 1):[18] If the lower limit of the 95% confidence interval lies to the right of the non-inferiority

Table 2: CONSORT recommendations in the protocol – Checklist for non-inferiority and equivalence trials. Items 1 through 12[17]

Paper section and topic	Item	Descriptor	Reported on section
TITLE & ABSTRACT	1	How participants were allocated to interventions (e.g., "random allocation", "randomized", or "randomly assigned"), <i>specifying that the trial is a non-inferiority or equivalence trial.</i>	Title in cover page. Summary: section 1
INTRODUCTION Background	2	Scientific background and explanation of rationale, <i>including the rationale for using a non-inferiority or equivalence design.</i>	2 and 3. In particular, see 2.1.5, two last paragraphs for rationale for non-inferiority
METHODS Participants	3	Eligibility criteria for participants (<i>detailing whether participants in the non-inferiority or equivalence trial are similar to those in any trial(s) that established efficacy of the reference treatment</i>) and the settings and locations where the data were collected.	4.3 and 4.4.3
Interventions	4	Precise details of the interventions intended for each group <i>detailing whether the reference treatment in the non-inferiority or equivalence trial is identical (or very similar) to that in any trial(s) that established efficacy</i> , and how and when they were actually administered.	4.1
Objectives	5	Specific objectives and hypotheses, <i>including the hypothesis concerning non-inferiority or equivalence.</i>	3
Outcomes	6	Clearly defined primary and secondary outcome measures <i>detailing whether the outcomes in the non-inferiority or equivalence trial are identical (or very similar) to those in any trial(s) that established efficacy of the reference treatment</i> and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors).	4.2
Sample size	7	How sample size was determined <i>detailing whether it was calculated using a non-inferiority or equivalence criterion and specifying the margin of equivalence with the rationale for its choice.</i> When applicable, explanation of any interim analyses and stopping rules (<i>and whether related to a non-inferiority or equivalence hypothesis</i>).	4.4.3
Randomization – Sequence generation	8	Method used to generate the random allocation sequence, including details of any restrictions (e.g., blocking, stratification)	4.4.1
Randomization – Allocation concealment	9	Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	4.4.2
Randomization – Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	4.4.2
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.	4 (last sentence before 3.1)
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s), <i>specifying whether a one or two-sided confidence interval approach was used.</i> Methods for additional analyses, such as subgroup analyses and adjusted analyses.	4.4.3 & 4.5

margin (Δ) the experimental intervention will be declared "inferior" (situation H). Situations A-D indicate non-inferiority with respect to the pre-stated margin Δ . Situations E-G are inconclusive, although E and F are not likely to occur because the trial size guarantees sufficient power. If the results are inconclusive regarding the non-inferiority hypothesis and the whole 95% confidence interval lies to the right of zero (situation G), it will be concluded that the limited package was statistically significantly worse according to a superiority hypothesis.

Interim analysis

A Data Monitoring Committee (DMC) with no direct involvement in the trial will be appointed. The role of the DMC will be to deal with any ethical issues that may arise while the trial is in progress, and to scrutinize an interim analysis. An interim analysis will be conducted to be reviewed by the DMC after the completion of the first 5,000 participants. A second interim analysis will be conducted after 10,000 – 15,000 women are recruited. Interim analyses will be masked to trial investigators but not to DMC members. Reporting and handling of adverse events will be in accordance with the Good Clinical Practice guidelines.

Stopping the trial

The DMC will be asked to give advice regarding stopping the trial if they have proof beyond doubt of an important advantage or disadvantage for one of the treatment groups, and they consider that the results are likely to affect clinical practice. For the main outcome results of the interim analyses, the DMC will base their recommenda-

tion on a superiority hypothesis two-sided stopping rule: if one of the treatments is significantly superior to the other, they will consider to stop the trial. The Haybittle-Peto rule for the α -spending function will be used to determine the level of significance at the two interim analyses and at the final analysis.

Stratified analysis

It is likely that some centres will practice uterine massage and some not. A stratified analysis will be conducted of the primary outcome by the use of uterine massage, to assess the interaction of uterine massage by CCT. However, it is likely that such an analysis will be underpowered. The use of uterine massage will also be considered as a potential confounding variable.

Duration of the project

It is anticipated that the recruitment into the study in the centres can be completed in approximately 12 months. Recruitment will begin around November-December 2008 after trial procedures have been tested and materials have been procured and distributed to the study sites. (Calibrated drape BRASS-V and oxytocin).

Expected outcomes of the study

The main objective of this trial is to investigate whether a simplified package of third stage management can be recommended without increasing the risk of PPH. By avoiding the need for a manual procedure that requires training, the third stage management can be implemented in a more widespread and cost-effective way around the world even at the most peripheral levels of the health care system.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors contributed to the development of the trial protocol and approved the submitted manuscript. AMG is the guarantor of the manuscript

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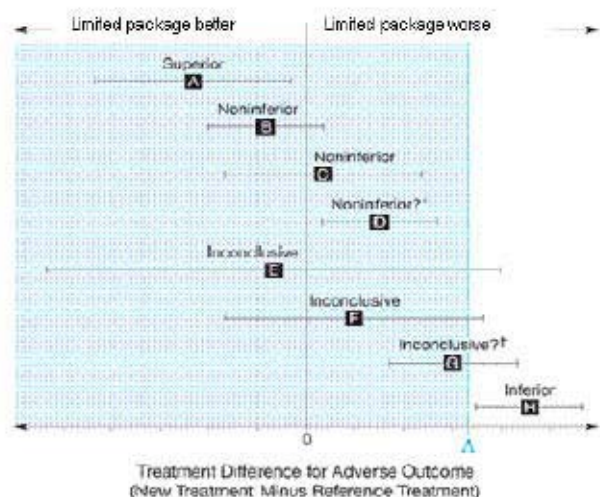


Figure 1
Scheme for the interpretation of the results of the primary analysis.

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Review

Interval debulking surgery for advanced epithelial ovarian cancer: A Cochrane systematic review

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Abstract

Objectives. To assess the effectiveness of interval debulking surgery (IDS) for patients with advanced stage epithelial ovarian cancer (EOC).

Methods. We searched the Cochrane Central Register of Controlled Trials, Medline, EMBASE, and reference lists for randomized controlled trials (RCTs) of advanced stage EOC. The trials had to report survival of women who had primary surgery and had IDS performed between cycles of chemotherapy comparing to survival of women who had conventional treatment (primary debulking surgery and adjuvant chemotherapy). Two review authors independently assessed trial quality and extracted data. Meta-analysis of overall survival (OS) and progression-free survival (PFS) was performed using fixed effects models.

Results. Three RCTs, involving 853 women of whom 781 were evaluated, met the inclusion criteria. OSs were substantial heterogeneity between trials ($I^2=58\%$). Subgroup analysis in two trials, wherein the primary surgery was not performed by the gynecologic oncologists, or was less extensive, showed benefit of IDS: hazard ratio=0.7 (95% confidence interval [CI]: 0.5 to 0.9, $I^2=0\%$). Substantial heterogeneity between two trials for PFS evaluating 702 women was also shown ($I^2=75\%$). Toxic reactions to chemotherapy were similar in both arms (RR=1.3, 95% CI: 0.4 to 3.6). Only one trial reported quality of life, which was generally similar in both treatment arms.

Conclusions. Our review could not conclude whether IDS would improve the survival of women with advanced EOC compared with conventional treatment. IDS appeared to yield benefit only in the patients whose primary surgery was not performed by expert surgeons.

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Keywords: Interval debulking surgery; Advanced epithelial ovarian cancer; Survival

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Introduction

A woman's risk of developing cancer of the ovaries by age 75 years varies between countries, ranging from 0.5% to 1.6% [1]. Primary surgery is the mainstay of treatment for ovarian cancer, followed by adjuvant chemotherapy if indicated. The aim of primary surgery is to remove as much tumor as possible because the amount of residual tumor is one of the most important prognostic factors for survival of women with epithelial ovarian cancer (EOC) [2–4]. An optimal surgery, which is usually defined as a removal of tumors to <1–2 cm, is not always possible especially when the patients have poor medical condition precluding prolonged surgery or when the diseases are extensive. After suboptimal surgery (residual tumors >1–2 cm), induction chemotherapy to reduce tumor size before considering secondary surgery can play an alternative role. In the circumstances when primary debulking surgery is not possible (or not being attempted at all) with only biopsy done for diagnostic purpose, the term neoadjuvant chemotherapy (NAC) is more specifically used to describe the administration of chemotherapy prior to the primary debulking surgery. When a few cycles of chemotherapy are administered with some tumor response, secondary surgery or so called interval debulking surgery (IDS) between the courses of chemotherapy may be possible. The IDS is usually performed after 2 to 4 cycles of chemotherapy because more cycles of chemotherapy could result in the chemotherapy selectively destroying chemotherapy sensitive tumor cells leaving more of the chemotherapy resistant clones.

Many retrospective studies or prospective non-randomized trials reported the beneficial effect of chemotherapy after inoperable advanced EOC or those with gross residual diseases that it may increase the number of patients suitable for secondary surgery (IDS). The rates of optimal resection in IDS after chemotherapy were reported ranging from 77% to 94% [5]–[13]. Other potential benefits of IDS after chemotherapy compared to aggressive primary debulking surgery were also demonstrated, such as, lesser blood loss, lower requirement of intensive care unit admission and duration of hospital stay due to the tumors being smaller [7,11,12]. IDS, by removing the smaller tumor masses induced by chemotherapy, would certainly facilitate the response of any residual tumors to subsequent chemotherapy. The quality of life (QOL) of patients treated with IDS was also reported in one study to be better than those who had conventional treatment (primary debulking surgery followed by a complete and continual cycles of adjuvant chemotherapy) [6].

Unlike the aforementioned advantages of IDS, there is still conflicting evidence regarding its survival benefit in comparison to conventional treatment. Many studies [10,12–17] showed similar survival rates of patients who had IDS after few cycles of chemotherapy and those who had conventional treatment. Only few studies reported significantly longer survival of patients having IDS [8,18], and even fewer studies showed an inferior result of IDS than optimal primary cytoreduction [19]. Of noted, most studies of IDS were non-randomized or retrospective in nature with various character-

istics of the patients and their diseases e.g. extent of residual tumor after primary surgery or IDS, tumor response after induction chemotherapy and prior to IDS, etc. [8,10,18–20]. These factors may lead to conflicting results on the survival benefit of IDS. Even among a few randomized controlled trials (RCTs) [21–23] which evaluated the role of IDS in EOC, their findings did not agree on the benefit of IDS on the patients' survival outcomes. Two trials [21,23] showed similar survival rates of patients between the IDS and conventional treatment, while the other [22] showed significantly longer survival in the IDS group which was still present after a 10-year follow-up [24].

Along with many studies on the role of NAC/IDS, many review articles have also been published. Focusing on the evidenced-based reviews which addressed the specific question whether the advanced EOC patients should have surgery before (conventional treatment) or after few cycles of chemotherapy (NAC/IDS), we could identify only one meta-analytical study [25] and two systematic reviews [26,27]. The meta-analytical study reviewed the role of platinum-based NAC/IDS for advanced EOC, involving 835 patients from 51 studies [25]. The result showed that survival of patients who had NAC/IDS was inferior to those who had primary surgery. However, this review included only phase I–II and retrospective studies. The other systematic review included three RCTs and 32 non-randomized or retrospective studies [26]. The results from these studies were simply described and tabulated according to the survival outcomes of the patients in the NAC/IDS compared to the conventional arm. However, there was no survival meta-analysis. The last systematic review [27], by the Cochrane Collaboration Group, could identify only one RCT [28] which found no significant survival difference of patients who were treated with either treatment. To be noted, the objective of these three systematic reviews was to evaluate if NAC could be used in lieu of primary surgery, rather than the role of repeated surgery or IDS after a primary surgery. We found only one previous meta-analytical study which specifically reviewed the role of IDS in advanced EOC [29]. The authors identified 33 publications and included three RCTs and three historical cohort trials in their review [29]. Homogeneity testing was not statistically significant by the Breslow–Day method. Significant survival benefit from the IDS was identified by the Mantel–Haenszel method with odds ratio of 0.5 ($p=0.02$) [29].

Because of potential intrinsic biases in many retrospective or phase I/II studies, together with conflicting data from the RCTs, a definite conclusion about the advantage of IDS after a suboptimal primary surgery could not be made. We conducted a thorough systematic review focusing only to the high quality data from RCTs to assess the effectiveness and complications of IDS for patients with advanced stage EOC.

Materials and methods

Electronic databases from January 1966 to June 2008 including Medline, EMBASE using Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL), trials registered, and reference lists of journals relevant to the subject

were searched for RCTs involving patients with advanced stage EOC. The patients must have histological confirmed diagnoses from primary surgery which may range from tumor biopsy, tumor removal, or standard surgical staging for EOC.

Eligible RCTs had to compare the survival of patients who were randomized to have IDS performed after 2 to 4 cycles of NAC or induction chemotherapy, followed by further chemotherapy with that of the patients who had only adjuvant chemotherapy without IDS. Phase II study and retrospective analyses or case series were not included.

The keywords used for the literature search included: ovarian cancer or neoplasm, (neoadjuvant or induction or preoperative) chemotherapy, interval debulking or secondary surgery. Two review authors (ST and SM) independently examined all the titles and abstracts retrieved by electronic searching, independently assessed full texts of potentially relevant trials, and extracted data from the eligible trials.

Numbers and characteristics of patients in the included trials, detail of surgical interventions including expertise of surgeons, detail of chemotherapy treatment, and length of follow up were extracted from individual included trials. We abstracted the log hazard ratio (HR) and its variance as data for overall survival (OS) and progression-free survival (PFS). If HRs were adjusted for prognostic factors, these were extracted in preference to unadjusted HRs. We estimated HRs using Parmar's methods [30] from the included trial which reported only Kaplan–Meier survival curves. The data of log HRs of overall death, disease progression and risk ratios of toxic reactions to chemotherapy

were combined using fixed effect model in the RevMan software. Where possible, all data abstracted were those relevant to an intention to treat analysis.

Results

The search identified 134 references whose titles and abstracts were examined. Seventeen studies were potentially relevant to this review. Two studies [31–33] could be readily excluded from the abstracts' data (one of which was presented as abstracts from two proceeding conferences of the American Society Clinical Oncology annual meetings). Full text articles of 15 studies were obtained and were assessed for eligibility. Twelve studies were additionally excluded. We present reasons for individual excluded trial in Table 1 [6–9,28,31,33–40].

Three RCTs met all inclusion criteria and were included in this review involving 853 randomized women [21–23]. They were multicenter trials: one from United Kingdom involved four institutions which were the referral centers for cancer care [21]; one by the European Organisation for Research and Treatment of Cancer (EORTC) involved 14 participating institutions in Europe [22]; and the last one by the Gynecologic Oncology Group (GOG) from the United States involved more than 42 cancer centers [23].

Median lengths of follow-up were reported: 48 months in the trial of Redman [21], 42 months in the EORTC [22] and 47 months in the GOG trials [23]. Although van de Burg et al. from the EORTC trial presented their long term follow-up

Table 1
Characteristics of excluded studies

Study, year [reference]	Type of study	Reason for exclusion
Evdokimova, 1982 [33]	RCT	Patients without ascites were selected to have conventional treatment while those with ascites had either NAC/IDS or conventional treatment.
Liu, 2004 [28]	RCT	NAC given only for 1 cycle via intra-arterial route before IDS in the study arm.
Park Simon, 2006 [34]	RCT	NAC given randomly to the patient for either 2 versus 3 cycles, followed by IDS in both arms.
Kumar, 2007 [31]	RCT	Histopathology of ovarian cancer not required.
Dutta, 2005 [35]	RCT	Preclinical study for proapoptotic and antiapoptotic proteins in ovarian cancer. No survival outcome evaluation.
Fuso, 2006 [36]	Controlled clinical trial	NAC/IDS was selectively assigned to the patients who were judged to be inoperable.
Kuhn, 2001 [8]	Controlled clinical trial	NAC/IDS was selectively assigned to the patients who were in poor general health for primary surgery while the patients who did not agree for IDS or had psychologic reasons were assigned to the control group.
Angioli, 2006 [37]	Controlled clinical trial	NAC/IDS was selectively assigned to the patients who were determined to be inoperable (based on laparoscopic findings).
Giannopoulos, 2006 [7]	Controlled clinical trial	NAC/IDS was selectively assigned to the patients who deemed inoperable from CT scan and initial laparoscopy. Histopathology of ovarian cancer not required.
Lee, 2006 [9]	Controlled clinical trial	NAC/IDS was selectively assigned to the patients who agreed to undergo the protocol. NAC ranged from 3 cycles to 6 cycles. Some patients had secondary surgery which was not an interval setting.
Solomon, 1988 [38]	Prospective study	IDS was selectively performed only in the patients who had not been debulked at primary surgery. Second-look surgery was also performed in patients with clinical complete remission.
Recchia, 2001 [39]	Prospective study	No control group. Histopathologic diagnosis of ovarian cancer was not required.
Chan, 2003 [6]	Prospective study	No control group. Patients were selected by their inoperability based on CT scan without an attempt of primary operation. Histology for a pathologic diagnosis of ovarian cancer was not required.
Ikeba, 2004 [40]	Prospective study	No control group.

Abbreviations: IDS, interval debulking surgery; NAC, neoadjuvant chemotherapy; RCT, randomized controlled trial.

(10 years) as an oral presentation in the European Society of Gynaecological Oncology annual meeting in 2005 [22], sufficient data was not available for meta-analysis.

Some characteristic differences of the patients, their diseases, and interventions among the three trials were observed e.g. the expertise of the primary surgeons; the definitions of optimal debulking from primary surgery, as having residual diseases <2 cm [21] or <1 cm [22,23]; timing of randomization [21–23]; type of chemotherapy in each trial; response rates to induction chemotherapy before the IDS; and etc. Table 2 provided some characteristic descriptions of the included trials.

All three trials reported HRs for OS [21–23] which was calculated either from the initiation date of induction chemotherapy [22], date of randomization after primary surgery and before chemotherapy [21] or after three cycles of

chemotherapy [23]. Both the GOG and the EORTC trials [22,23] reported HRs adjusted for prognostic factors of age, performance status, stage, tumor grade, response to induction chemotherapy, number of lesions, ascites, and size of residual diseases at three time points: after primary surgery, before and after IDS while the Redman trial reported unadjusted HRs. From the three included trials, 853 women were randomized and 781 women (91.5%) were followed up. We found heterogeneity of the HRs of all deaths among the trials ($I^2=58\%$). We explored the sources of heterogeneity by performing subgroup meta-analysis for OS according to expertise of surgeons. In the two trials wherein the primary surgery was performed by general surgeons [21,22], the IDS showed marginally significant survival benefit: hazard ratio comparing the risk of death in the IDS and chemotherapy only

Table 2
Characteristic of included studies

Study, year [reference]	Redman, 1994 [21]	van De Burg, 1995 (EORTC trial) [22]	Rose, 2006 (GOG trial) [23]
Study duration	04/1986–02/1990	03/1987–05/1993	06/1994–01/2001
Timing of randomization	Randomized at entry (after primary surgery)	Randomized after 3 cycles of chemotherapy	Randomized after 3 cycles of chemotherapy
Method of randomization	Random permuted blocks method	Random at Central EORTC data center	Randomly permuted blocks in a blind fashion
Number randomized	86	319	448
Number evaluable	79	278	424
Surgery	Primary surgery must be performed with a maximal attempt to remove tumors. (only 9% were gynecologic oncologists)	Primary surgery were performed in various referring hospitals. (the levels of surgeons not specified)	95% of primary surgery were performed by gynecologic oncologists aiming to remove tumors as much as possible
Participants	Stage II–IV (only resectable stage IV) PS ECOG: at least 2 Histology proven RD>2 cm IDS performed only in patients who had no evidences of PD, and no extraperitoneal tumor>1 cm	Stage IIB–IV Age<75 with performance status WHO: 0–2 Histology proven (central pathologic review) RD>1 cm Randomized only the patients who had no PD and no contraindication to surgery	Stage III–IV ^a Age<75 with performance status ACOG: 0–2 Histology proven (central pathologic review) RD>1 cm Randomized only the patients who had no PD, no extraperitoneal tumor>1 cm, and no medical contraindication
Interventions	Arm 1: IDS after sufficient tumor response in between the 8 cycles of tri-weekly of PC or PAB followed by cyclophosphamide up to 5 cycles Arm 2: No IDS (the same regimen of chemotherapy)	Arm 1: IDS after 3 cycles of tri-weekly PC, followed by 3 more cycles of PC Arm 2: No IDS (the same regimen of chemotherapy).	Arm 1: IDS after 3 cycles of tri-weekly PT, followed by 3 more cycles of PT Arm 2: No IDS (the same regimen of chemotherapy).
Outcomes of interest	OS Peri-operative complications	OS, PFS Peri-operative complications	OS, PFS Adverse effects Quality of life
Response evaluation	PE, imaging studies (CA 125 not used)	PE, imaging studies, and CA 125 (WHO response criteria)	PE, imaging studies, and CA 125 (PD=an increased CA 125>100 U/ml or doubling of the nadir)
Survival evaluation	OS measured from the date of entry (date of randomization)	OS measured from the date of entry (date when chemotherapy begun)	OS and PFS measured from the date of randomization (after 3 cycles of chemotherapy)
Notes	–	Consolidation chemotherapy allowed	Consolidation chemotherapy allowed

Note: All the three trials were multi-center randomized control trials with intention-to-treat analysis.

Abbreviations: ECOG, Eastern Collaborative Oncology Group; PAB, cisplatin/adriamycin/bleomycin; PC, cisplatin/cyclophosphamide; PD, progressive disease; PE, physical examination; PFS, progression-free survival; PS, performance status; PT, paclitaxel/cisplatin; OS, overall survival; RD, residual disease; WHO, World Health Organization.

^a The Gynecologic Oncology Group trial by Rose et al. excluded patients with stage IV diseases after March 1996 when the European Organization for Research and treatment of Cancer trial by van Der Burg et al. reported a greater benefit from secondary surgery after the exclusion of such patients from the analyses.

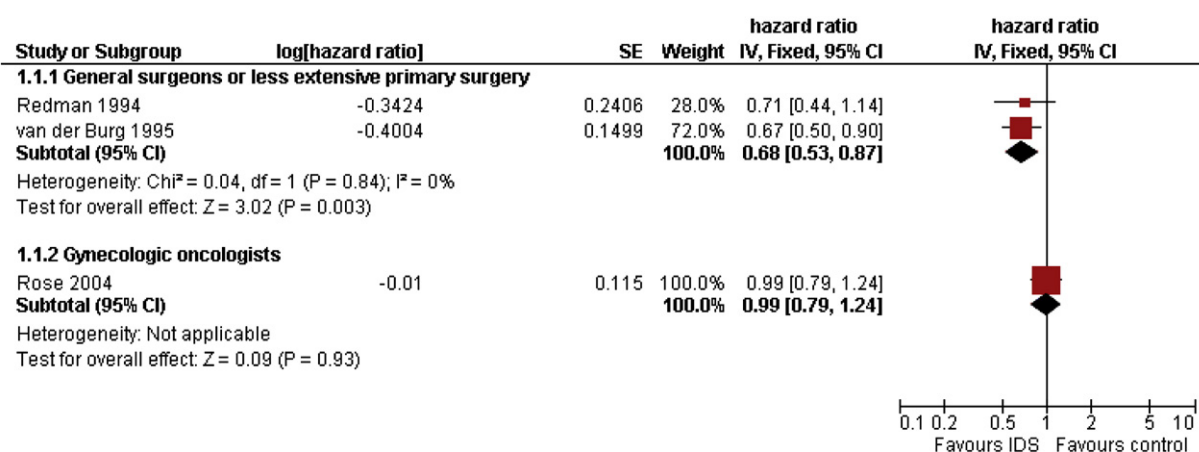


Fig. 1. Overall survival of epithelial ovarian cancer patients who had interval debulking surgery and those who had only chemotherapy after primary surgery according to the expertise of surgeons or the extent of primary surgery.

arms was 0.7 (95% CI: 0.5 to 0.9). Results of subgroup meta-analyses for all deaths are presented in the Fig. 1.

For PFS, only two RCTs [22,23] had available data: one trial reported HR, adjusted for prognostic factors [23] while the other presented Kaplan–Meier disease-free survival curves [22], from which we used Parmar's method to estimate the HR. The two trials were included in the meta-analysis [22,23] involving 767 randomized women of whom 702 were followed up. The HRs comparing the risk of progression-free survival in the IDS with chemotherapy only arms again showed substantial heterogeneity between trials ($I^2 = 75\%$).

Toxic reaction was reported in both treatment groups in the Redman [21] and EORTC [22] trials, and was the only adverse event possible to meta-analyse. The pooled relative risk of toxic reactions to chemotherapy using Mantel–Haenszel methods comparing rates of toxic reactions to chemotherapy in the IDS with chemotherapy-only arms was 1.2 (95% CI: 0.4 to 3.6) (Fig. 2). The GOG trial [23] reported that rates of other adverse events were similar in the two groups, except for a significant higher rate of neurological adverse events in the chemotherapy-alone group (26% versus 16%; $p = 0.01$).

QOL was assessed only in the GOG trial and the results were subsequently reported by Wenzel et al. [41]. The self-reported QOL was assessed in four settings, according to the Functional Assessment of Cancer Therapy-Ovarian (FACT-O), version 2-questionnaire. The evaluations were at baseline before allocation to IDS or chemotherapy only, at the sixth cycle of

chemotherapy, at 6 and 12 months after starting treatment. Completion rates for these questionnaires declined from 90% for the first questionnaire to 83%, 83%, and 80% for the subsequent questionnaires respectively. Nevertheless, lower completion rates were noted in the IDS group compared to chemotherapy only group especially at the second assessment, 77% and 89% respectively ($p < 0.001$). At 6 months after starting treatment, significantly more patients who had only chemotherapy experienced persistent numbness or tingling than those who had IDS, 54% versus 38% ($p = 0.012$). Otherwise, QOL was not significantly different in the two treatment groups at any time point.

Discussion

Our systematic review included three RCTs, which evaluated 781 patients out of 853 randomized. The results provided inconclusive evidence whether IDS improves or worsens the OS and PFS of the patients. Potential reasons for the inconclusive evidence are explored. Firstly, the small number of included studies, evaluating 781 patients, may not have had adequate statistical power to detect a small effect. Furthermore, the studies had different characteristics which may explain the heterogeneity in their results.

A major difference between these trials may be the expertise or the maximal effort to do the primary debulking surgery of the surgeons in the participating institutions of each study.

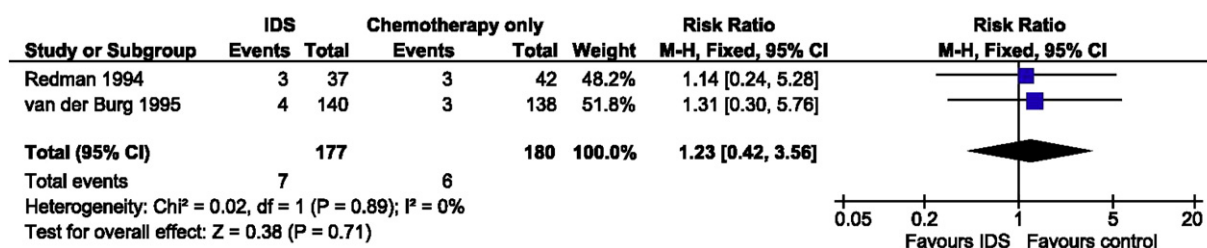


Fig. 2. Toxic reaction to chemotherapy in the epithelial ovarian cancer patients who had interval debulking surgery and those who had only chemotherapy after primary surgery.

Majority or 99% of the operations in the GOG trial were performed by the gynecologic oncologists or fellowship-trained in various cancer centers [23] while the procedures in the Redman trial were performed mostly by general surgeons or gynecologists (only 9% by gynecologic oncologists) in various hospitals [21] or in the EORTC trial in which the primary surgery was performed in various hospitals in Europe wherein the expertise of surgeons was not specified [22] but the maximal effort to perform primary surgery was not attempted in all patients with different extent of debulking surgery [42,43]. Since there is substantial evidence from many retrospective studies that the extent of optimal surgery affects the survival of patients with EOC [2–4], the maximal primary surgical efforts in the optimal surgical setting in the GOG trial might indicate that their primary surgery was sufficient, that another subsequent surgical attempt would not affect the survival further. In comparison to the Redman and EORTC trials [21,22] in which the primary surgery were carried out in suboptimal settings when most of the operations were not performed by gynecologic oncologists [21] or not in the maximal attempt (with less extent of primary debulking surgery) resulting in high proportion of large residual tumors [42,43], so the IDS which were performed after the tumors were down-sized by chemotherapy appeared worthwhile (although significant only in the EORTC trial). Our subgroup meta-analysis confirmed this proposal that IDS had benefit in this particular subgroup of patients. Nevertheless, this should be interpreted with caution because our subgroup analysis was based on only two trials [21,22].

The second difference between these trials was the timing of randomization. Redman was the only trial which randomized the patients into two groups (to have or not to have IDS) at the start of trial [21]. Only 67% of patients in the IDS group of this study actually had it because the other assigned patients had diseases progression or deaths precluding the IDS. While the other two trials of GOG and EORTC randomized only the patients who showed some response to induction chemotherapy [22,23]: this resulted in a high percentage of the patients (approximately 93% in both trials) who were randomized to undergo IDS really had it. This difference may affect the result from each trial, based on the design of an intention to treat analysis in all of these trials.

We also explored the patients or their disease characteristic as the other potential reason for different effects of IDS on survival outcomes. Two trials of Redman and the GOG did not show any advantage of IDS [21,23] while the EORTC demonstrated significant survival improvement with IDS [22]. Redman trial included only 79 patients for analysis of OS, and therefore did not have much influence on the results of the meta-analysis [21]. The difference in outcomes from the GOG [23] and EORTC [22] trials may be due to the different proportions of patients who had poor response to induction chemotherapy: approximately 52% of patients in GOG trial had residual diseases of >1 cm after induction chemotherapy [23] compared to 44% in the EORTC trial [22]. This might be interpreted that the GOG trial had a higher proportion of patients who had more aggressive tumors (who generally had poorer prognosis than

those who showed some response), and so would not have a survival benefit from any treatment, even the optimal IDS. However, this mechanism of tumor aggressiveness and prognosis may not solely explain the ultimate outcome of the patients because the patients in the EORTC trial [22] who had tumor >1 cm after induction chemotherapy but were removed to <1 cm had better survival benefit than any other group of women in the trial. This might suggest that the IDS may play some role in survival improvement.

To emphasize on the importance of the sensitivity or response to chemotherapy before IDS, we would like to point out the findings from the GOG and EORTC trials which showed that the patients whose tumor masses were reduced by chemotherapy to <1 cm before the IDS [22,23] had superior survival than the other groups. This response to chemotherapy might be used as a selective criterion for the patients who are likely to gain survival benefit from IDS.

As we have mentioned in the results, meta-analysis of adverse events was not possible due to different formats of presentation of data in each RCT. The only obvious advantage appears to be fewer neurologic complications in the IDS group than in the chemotherapy only group in the GOG trial [23]. However, this adverse effect may be related to a particular drug and might not be experienced in the other settings using other chemotherapeutic regimens.

For the QOL comparison, which was assessed only in the GOG trial [41], patients in the chemotherapy only arm had a higher rate of neurotoxicity than those in the IDS arm despite a similar total dose of chemotherapy exposures. The authors ascribed this finding to intermission from chemotherapy exposure allowing certain degree of recovery, but it may be a chance finding as 48 tests of possible differences in QOL were made. Although other aspects of QOL were similar in the two groups of patients at every time point of assessment, definitive conclusions cannot be made because a significantly lower proportion of patients in the IDS group completed the questionnaires in the second assessment compared to those in the chemotherapy only group, and it is possible that this lower questionnaire completion rate may be associated with QOL.

Three major studies are ongoing aiming to address the question whether NAC before the surgery could replace the primary surgery before adjuvant chemotherapy in terms of survival comparison [44–46]. The three trials by the Royal College of Obstetrician and Gynaecologist in United Kingdom (CHORUS study) [44], the EORTC in Europe (EORTC 55971 study) [45], and the Japan Clinical Oncology Group in Japan (JCOG 0602) [46] are designed in the same approach that the patients in the NAC arm would have IDS (which is actually the first or primary surgery) before further chemotherapy while the patients in the other arm would have conventional treatment. However, the patients in the conventional arm may also have IDS upon discretion of the physician. Hence, these studies would not be able to answer the actual role of IDS. To directly address the definite role of IDS, future studies should focus on a comparison of current conventional primary surgery with adjuvant chemotherapy versus NAC without any attempt to remove the bulk of tumors (except a biopsy for histologic

diagnosis) followed by IDS (which should be allowed only in this arm) and then by further chemotherapy.

Conclusions

The heterogeneity of the results in our review precludes any definitive suggestion for clinical practice. The choice to perform IDS after chemotherapy must be individualized. Since we found the benefit of IDS in the subgroup of patients whose primary surgery has not been performed under the optimum condition e.g. by the oncologic surgeons or with the maximal surgical effort, we would like to make a comment that the IDS may improve the patient's survival in these settings.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Acknowledgments

This review is modified from the systematic review and meta-analysis of "Interval debulking surgery for advanced epithelial ovarian cancer" first published as a Cochrane Review in The Cochrane Library 2008 issue [47]. The main findings and the core issues are the same as the original Cochrane Review except for some ongoing studies which were additionally reviewed here. Cochrane Reviews are regularly updated as new evidence emerges and in response to comments and criticisms, and The Cochrane Library should be consulted for the most recent version of the Review.

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One-Day Compared With 7-Day Nitrofurantoin for Asymptomatic Bacteriuria in Pregnancy

A Randomized Controlled Trial

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OBJECTIVE: To evaluate whether a 1-day nitrofurantoin regimen is as effective as a 7-day regimen in eradicating asymptomatic bacteriuria during pregnancy.

See related article on page 346.

*For a list of members of the World Health Organization Asymptomatic Bacteriuria trial group who participated in this study, see the Appendix online at <http://links.lww.com/A644>.

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METHODS: A multicenter, double-blind, randomized, placebo controlled noninferiority trial was conducted in antenatal clinics in Thailand, the Philippines, Vietnam, and Argentina. Pregnant women seeking antenatal care between March 2004 and March 2007 who met the inclusion and exclusion criteria were invited to participate in the study. Those who consented were randomly allocated to receive either a 1-day or a 7-day course of 100 mg capsules of nitrofurantoin, which was taken twice daily. The primary outcome was bacteriologic cure on day 14 of treatment.

RESULTS: A total of 1,248 of 24,430 eligible women had asymptomatic bacteriuria, making the overall prevalence of 5.1%. Of these 1,248 women, 778 women were successfully recruited, and 386 and 392 women were randomly allocated to 1-day and 7-day regimens, respectively. *Escherichia coli* was the most common potentially pathogenic bacteria detected, its prevalence approaching 50%. Bacteriologic cure rates at treatment day 14 were 75.7% and 86.2% for 1-day and 7-day regimens, respectively. The cure rate difference was -10.5% (95% confidence interval -16.1% to -4.9%). Mean birth weight and mean gestational age at delivery were significantly lower in the 1-day regimen group. There were fewer adverse effects in the 1-day regimen group, but the differences were not statistically significant.

CONCLUSION: A 1-day regimen of nitrofurantoin is significantly less effective than a 7-day regimen. Women with asymptomatic bacteriuria in pregnancy should receive the standard 7-day regimen.

CLINICAL TRIAL REGISTRATION: ISRCTN, isrctn.org, ISRCTN11966080

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LEVEL OF EVIDENCE: I



The prevalence of asymptomatic bacteriuria in pregnancy ranges from 2–11%, similar to data in nonpregnant populations. However, whereas asymptomatic bacteriuria is relatively benign in nonpregnant populations, 20–30% of culture-positive pregnant women if untreated develop symptomatic disease, often pyelonephritis and its complications.^{1–3} There is also evidence of increases in both low birth weight and preterm delivery and in the subsequent development of preeclampsia if pregnant women with asymptomatic bacteriuria are not treated.⁴ Thus, many authorities recommend screening all pregnant women for asymptomatic bacteriuria and treating those with evidence of infection.⁵ In this respect, antibiotic treatment has been demonstrated to be effective in reducing the risk of subsequent pyelonephritis in women with asymptomatic bacteriuria in pregnancy.⁶ However, achieving this level of care may be elusive, especially in developing nations.

A Cochrane review updated in October 2006 assessed the efficacy of length of treatment on eradicating asymptomatic bacteriuria in pregnancy. The authors concluded that there was insufficient evidence to evaluate whether 1-day therapy with an antibiotic or treatment for a longer duration (traditionally 7 days) had similar efficacy in eradication asymptomatic bacteriuria of pregnancy.⁷

Antibiotics used to treat asymptomatic bacteriuria in pregnancy include ampicillin, amoxicillin, trimethoprim-sulfamethoxazole, cephalexin, and nitrofurantoin. However, resistance of *Escherichia coli* and other uropathogens to ampicillin, trimethoprim-sulfamethoxazole, and first-generation cephalosporins has been steadily increasing, currently approaching 40%.⁸ Fortunately, little or no changes in bacterial resistance to nitrofurantoin have been noted.⁹ We designed a World Health Organization (WHO) multicenter trial to compare whether a 1-day treatment with nitrofurantoin (100 mg twice per day) is as effective as a 7-day regimen (100 mg twice per day) in eradicating asymptomatic bacteriuria during pregnancy.

MATERIALS AND METHODS

A hospital-based, multicenter, double-blind, placebo-controlled, randomized controlled trial was conducted in antenatal clinics in Thailand, the Philippines, Viet Nam, and Argentina. Participating centers were Maharaj Nakorn Chiang Mai Hospital (Chiang Mai University), King Chulalongkorn Memorial Hospital (Chulalongkorn University), Songklanagarind Hospital (Prince of Songkla University) and Srinagarind Hospital (Khon Kaen University) in Thailand; Centro Rosarino de Estudios Perinatales, in Rosario,

Argentina; National Hospital for Obstetrics and Gynecology, Hanoi, in Viet Nam; and Philippines General Hospital (University of the Philippines), Manila, in the Philippines. All these centers are part of the WHO Maternal and Perinatal Research Network, each having extensive trial experience. This network involves centers throughout the world from both developed and developing countries.

Pregnant women seeking antenatal care visits at the participating centers between March 2004 and March 2007 and capable of giving informed consent were recruited at gestational ages between 12 weeks and 32 weeks. Eligibility was asymptomatic bacteriuria with the microorganism sensitive to nitrofurantoin, plus absence of symptoms suggesting urinary tract infection (UTI), no history of treatment for UTI during the current pregnancy, presence of an underlying disease that required continuous steroids and/or antibiotic treatment, antibiotic hypersensitivity, or any hematologic disease including glucose-6-phosphate dehydrogenase (G6PD) deficiency. An additional exclusion criteria required by the Argentinean Center was the ineligibility of women with asymptomatic bacteriuria, due to *Streptococcus* Group B, where a specific antibiotic treatment regimen was required.

Instructions (written and oral) were provided by trained research assistants at each participating center and included how to appropriately collect midstream urine samples into sterile containers. After collection, a microbiologist or a trained research assistant tested the urine sample with Orion Diagnostica's Uricult dipslide (Orion Diagnostica Oy, Espoo, Finland), incubating the dipslide at 35°C to 37°C for 24 hours while the remainder of the sample was refrigerated. Dipslide culture was chosen because it provides results comparable to standard loop inoculation methods.¹⁰ We also evaluated the diagnostic performance of the dipslide, comparing it with urine culture using the data from Argentina, where all pregnant women had standard urine culture performed.¹¹ The dipslide was evaluated by the microbiologist the following day. If the results were positive (100,000 or more colony-forming units per milliliter), the pathologic findings were corroborated by plating a sample from refrigerated urine on both Blood and MacConkey agar plates, the colonies isolated tested for antibiotic susceptibility. These women were then formally diagnosed as having asymptomatic bacteriuria, became eligible for random assignment. All participating microbiologists were trained in the dipslide technique, and their laboratories were routinely audited. Note that glucose-6 phosphate dehydrogenase (G6PD)



deficiency is relatively common in Southeast Asia, particularly in Thailand, where the reported prevalence is 11.1% in male and 5.8% in female cord blood samples.¹²

Recruited women with asymptomatic bacteriuria were screened (Berstein assay) for glucose-6 phosphate dehydrogenase deficiency before receiving any treatment and were excluded from randomization if positive. Before implementing this assay all laboratories were trained and certified for the assay.

Culture-positive women without G6PD deficiency who consented were randomly allocated to receive either 1-day, (intervention group) or 7-day (control group) course of 100-mg capsules of nitrofurantoin to be taken twice daily. Women in the intervention group received a treatment package containing two 100-mg nitrofurantoin capsules for day 1 and 12 of identical placebo, all capsules to be taken, orally, twice daily with food. Women in the control group received an identical treatment package in which all fourteen capsules contained 100-mg nitrofurantoin to be taken twice daily for 7 days. All participants were requested to return to antenatal care clinic 14 days later, at which time a dipslide and regular urine culture were repeated and compliance determined by recording the number of the capsules remaining in the treatment box. Adverse effects, identified through interviews, were recorded on standard forms. Additional therapy, if required, was dictated by the new culture and sensitivity results, treatment continuing until cultures were negative. All participating women received standard antenatal care provided by the clinics, and their clinical courses were monitored until delivery to assess for pyelonephritis, preterm delivery, and low birth weight.

Randomization codes were conducted independently for each study site by the statistical unit at the Department of Reproductive Health and Research, the World Health Organization, Geneva, Switzerland. The random allocation sequence was generated using computer-generated random numbers with randomly varying blocks of 6–8 (SAS software, SAS Institute, Inc., Cary, NC). The random allocation was concealed by using sealed, opaque treatment boxes numbering sequentially using the sequence described above.

The primary maternal outcome was bacteriologic cure after antibiotic treatment, which was assessed by a urine culture 14 days after the initiation of treatment. Secondary outcomes included the incidences of symptomatic UTI, preterm delivery, and adverse effects. The neonatal outcomes were low birth weight and congenital malformations. Pyelonephritis was diagnosed when systemic symptoms or signs such as

fever, chills, nausea, vomiting, and flank pain occurred in the presence of bacteriuria. Symptoms of lower tract infection (ie, frequency and dysuria) might or might not be present.¹³ Preterm delivery was documented when delivery occurred before 37 completed weeks.¹⁴ Low birth weight was defined as birth weight less than 2,500 g.¹⁴

Sample size was calculated for the primary outcome. Considering this trial as an equivalence one, we estimated that regimens would be 80% effective. At 95% confidence level and a power of 90%, an acceptable margin of noninferiority in effectiveness of treatment was 7.5%, for a one-tailed test. The required number of women per treatment group and the number of women to be screened (based on 5% prevalence) were 446 and 17,840, respectively.¹⁵ We chose to use a one-tailed test because we want to confirm that a 1-day regimen of nitrofurantoin is not inferior to the 7-day regimen. A sample size of screening 18,000 pregnant women was planned.

All centers adhered to the standardized trial procedures, including the use of data collection forms. Completed data collection forms from all participating hospitals except CREP, Rosario, Argentina were sent to Khon Kaen University monthly; data entry and audit were performed continuously. All data were entered and cleaned and queries checked immediately with the local investigators. At CREP, data entry and audit were also performed continuously and update databases were sent to Khon Kaen University every three months.

Descriptive statistics were used to describe characteristics of the participants in each arm. The results were reported as intention to treat and with comparisons between 1-day and 7-day regimens of nitrofurantoin treatment. Relative risk (RR) (or cure rate ratio) and risk difference with 95% confidence intervals (CIs) were used to compare the differences of categorical outcomes. Mean differences with 95% CI were used for continuous outcomes. The trial was approved by the Scientific and Ethical Review Group of the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, the WHO Ethics Review Committee and the institutional review boards of the participating centers.

RESULTS

A total of 25,326 women were screened, of whom 24,430 were eligible. There were 1,827 women with positive dipslide for whom urine culture confirmation was sought. Of these women's cultures, 1,248 returned positive, giving the overall prevalence of 5.1%.



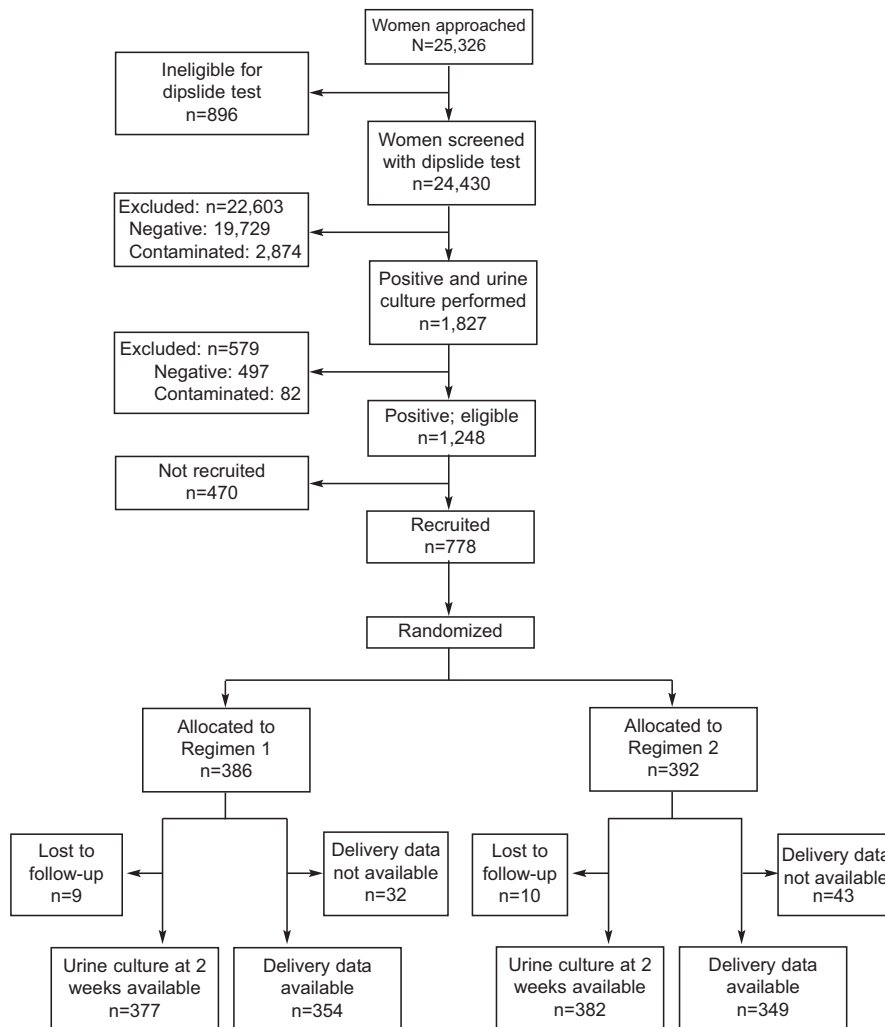


Fig. 1. Trial profile.

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However, only 778 of 1,248 women were recruited into the trial. Main reasons for failure to recruit eligible women included nitrofurantoin resistance (32.2%), loss to follow-up before recruitment could be initiated (22.9%), failure to be in a gestational age range of 12–32 weeks (12.5%), presence of G6PD deficiency or the screening result was unavailable (11.2%), and ineligibility criteria discovered only after the culture had been performed (10.6%). The prevalence of G6PD deficiency among women with positive urine culture was approximately 4%.

We allocated 386 and 392 women to 1-day and 7-day regimens, respectively. Three hundred seventy-seven (97.7%) women in the 1-day regimen group and 382 (97.4%) women in the 7-day regimen group returned for their 2-week follow-up urine culture. Delivery outcomes were available in 354 (91.7%) and 349 (89.0%) women in the 1-day and 7-day regimen group, respectively (Fig. 1).

The sociodemographic characteristics of each group including age, gravidity, and parity were very similar at entry. Compliance was both similar and excellent; 98% of the women in both groups ingested all their tablets (Table 1).

Table 1. Characteristics of Women at Recruitment by Regimen of Nitrofurantoin

Characteristics	1-Day Regimen	7-Day Regimen
Age (y)	386, 27.0 (± 5.9)	392, 26.9 (± 5.7)
School attendance (y)	385, 12 (0–22)	391, 12 (0–19)
Gravidity	386, 2 (1–8)	392, 2 (1–14)
Parity	386, 0 (0–8)	392, 0 (0–11)
Time from enrolment to follow-up (wk)	377, 2 (0–22)	385, 2 (1–15)
Women taking any other medications/supplements	214 (55.4)	205 (52.3)

Data are sample n, (%), mean ($\pm$ standard deviation), or median (range).



Table 2. Causative Agents of Asymptomatic Bacteria Among Pregnant Women With Positive Urine Culture at Recruitment by Treatment Regimen

Microorganisms	1-day Regimen	7-day Regimen
<i>Escherichia coli</i>	47.6 (186)	43.2 (172)
Klebsiella species	4.3 (17)	5.8 (23)
Enterobacter species	5.1 (20)	3.3 (13)
<i>Staphylococcus saprophyticus</i>	12.3 (48)	12.8 (51)
<i>Streptococcus</i> Group B	8.2 (32)	7.0 (28)
Enterococcus species	9.2 (36)	14.3 (57)
<i>Staphylococcus aureus</i>	6.4 (25)	8.0 (32)
<i>Staphylococcus</i> -ve	3.6 (14)	2.8 (11)
<i>Proteus</i>	0.3 (1)	0.3 (1)
Others	3.1 (12)	2.5 (10)
Total*	100.0 (391)	100.0 (398)

Data are % (n).

* Thirteen women had two types of microorganism with colony concentration of 100,000 colony-forming units per milliliter or more.

The causative pathogens for asymptomatic bacteriuria at recruitment in both groups were also similar. *Escherichia coli* was the most common causative bacteria at close to 50%, followed by *Staphylococcus saprophyticus*, *Enterococcus* spp, *Streptococcus* Group B, *Staphylococcus aureus*, *Enterobacter* spp, and *Klebsiella* spp (Table 2). However, when viewing the data, recall that Argentinean women with asymptomatic bacteriuria due to *Streptococcus* Group B were excluded from the trial, because their protocols required all such patients to receive a full 7-day course of antibiotics. After carefully reviewing the data, we realized that the causative bacteria in 23 recruited patients was *Staphylococcus* coagulase negative, which according to the protocol should not be considered as pathogens. Therefore these 23 patients were inappropriately recruited.

Bacteriologic cure rates evaluated at 14 days after treatment were 75.7% and 86.2% for 1-day and 7-day antibiotic treatment regimens, respectively. The cure rate difference was -10.5% (95% CI -16.1% to -4.9%) (Table 3 and Fig. 2) and the cure rate ratio was 0.88 (95% CI 0.82-0.94) (Table 3). Sensitivity analysis, in which all contaminated urine culture

results were assigned as either cure or not cure did not change the cure rate difference or cure rate ratio. Sensitivity analysis performed by excluding 23 inappropriately recruited patients did not change the cure rate difference or cure rate ratio. The 1-day regimen was thus statistically significantly less effective than the standard 7-day regimen. To follow the intention-to-treat principle, we did not exclude these 23 inappropriately recruited patients from the analysis.

During the 2 weeks that followed initiation of treatment, five women in the 1-day and six women in the 7-day group developed symptomatic UTI. The difference was not statistically significant. Similarly, from day 14 through delivery, there were 10 and 12 cases of symptomatic UTI in the 1-day and 7-day regimen groups, respectively. Again, the difference was not statistically significant. Overall, symptomatic UTIs were diagnosed in 15 (5+10) and 18 (6+12) women in the 1-day and 7-day regimen respectively, RR 0.86 (95% CI 0.44-1.67).

Incidences of preterm delivery (11.0% [39 of 353] compared with 8.9% [31 of 349]) and low birth weight (13.2% [48 of 364] compared with 8.0% [28 of 350]) were higher in the 1-day regimen group but the differences were not statistically significant. There was also no statistically significant difference in the risk of congenital malformations (1.4% [5 of 364] compared with 1.1% [4 of 350]) between the two groups. However, mean birth weight and mean gestational age at delivery were statistically significantly lower in the 1-day regimen group, 3,059 g compared with 3,159 g (mean difference -100, 95% CI -181 to -18) and 38.4 weeks compared with 38.7 weeks (mean difference -0.3, 95% CI -0.7 to -.005), respectively (Table 4). There was less nausea, headache, and other adverse effects but more flatulence in the 1-day regimen group, but the differences were not statistically significant (Table 5).

DISCUSSION

These data demonstrate that 1-day nitrofurantoin therapy is significantly less effective than the standard 7-day regimen in achieving bacteriologic cure when

Table 3. Bacteriologic Cure in Pregnant Women at 14 Days After the Initiation of Nitrofurantoin Treatment Between Two Regimens (Excluding Cases With Contamination Results) Adjusted by Centers

Regimen	Sample Women	Bacteriologic Cure [n (%)]	Cure Rate Difference (95% CI)	Cure Rate Ratio (95% CI)
1-day	371	281 (75.7)	-10.5 (-16.1 to -4.9)	0.88 (0.82-0.94)
7-day	370	319 (86.2)	0	1

CI, confidence interval.



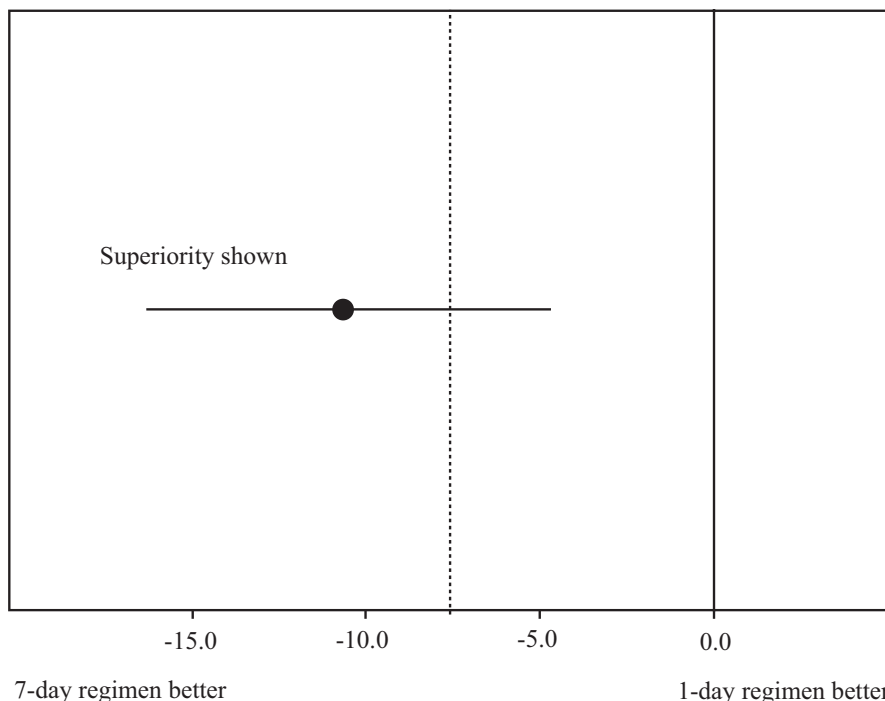


Fig. 2. Bacteriologic cure rate difference (%) with 1-day regimen compared with 7-day regimen. Vertical dotted line represents the margin of clinical equivalence determined a priori. Solid line represents the null effect.

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both approaches were evaluated 14 days after initiating treatment. Patients in the 1-day regimen group also had higher incidences of preterm delivery and low birth weight (not statistically significant), and lower mean birth weight and mean gestational age at delivery (statistically significant). However, the rates of symptomatic UTI were similar in both groups. Interestingly, the rate of clinical UTI was below 5%. Adverse effects were slightly lower in the 1-day regimen group (not statistically significant).

The strength of our findings are underscored by the study design, a multicenter double-blinded placebo-controlled randomized trial. Furthermore, all microbiologists were trained in dipslide technique, the laboratories and data regularly audited to assure high quality, and site visits were performed by WHO officials. There were also two investigators' meetings where trial problems were discussed and resolved. Loss to follow-up

after randomization and the number of contaminated specimens was minimal, the latter problem being also controlled with a sensitivity analysis, where the assumed best (all contaminated negative) or worst (all contaminated positive) did not change the result of primary outcome. All the factors summarized above combine to strengthen the validity of our conclusions.

We could not reach our target sample size of 992 women because we could not recruit 32% of the potential eligible subjects, as already described in the results section. However, we recruited 778 women, which represents 85% of our target sample size, permitting us demonstrate that 1-day nitrofurantoin regimen is significantly less effective than the standard 7-day regimen.

We update the Cochrane review⁷ by incorporating our data into the meta-analysis. Comparing "no cure rate" between 1-day and 4–7 day regimens using the random effects model, adding the data from our

Table 4. Pregnancy Outcomes by Regimen of Nitrofurantoin

Outcome	1-Day Regimen	7-Day Regimen	RR* (95% CI)/Mean Difference (95% CI)
Preterm delivery (GA less than 37 wk) (703 mothers)	39/354 (11.0)	31/349 (8.9)	1.24 (0.79–1.94)
Low birth weight (less than 2,500 g) (714 newborns)	48/364 (13.2)	28/350 (8.0)	1.55 (0.97–2.48)
Congenital malformations (714 newborns)	5/364 (1.4)	4/350 (1.1)	1.20 (0.33–4.44)
Birth weight, g (714 newborns)	3,059 ($\pm$ 582)	3,159 ($\pm$ 523)	–100 (–181 to –18)
Gestational age at delivery, y (703 mothers)	38.4 ($\pm$ 2.6)	38.7 ($\pm$ 2.0)	0.3 (–0.7 to –0.005)

RR, relative risk; CI, confidence interval; GA, gestational age.

Data are n/N (%) or mean ($\pm$ standard deviation) unless otherwise specified.

* Using 7-day regimen as a reference group.



Table 5. Adverse Effects During 14 Days After the Initiation of Treatment by Regimen of Nitrofurantoin

Adverse Effects	1-Day Regimen	7-Day Regimen	RR* (95% CI)
Nausea	23 (6.1)	33 (8.6)	0.72 (0.43–1.20)
Headache	17 (4.5)	22 (5.7)	0.79 (0.43–1.47)
Flatulence	15 (4.0)	9 (2.3)	1.71 (0.76–3.86)
Others	20 (5.3)	26 (6.8)	0.79 (0.45–1.39)
Total	375	385	

RR, relative risk; CI, confidence interval.

Data are n (%) unless otherwise specified.

* Using 7-day regimen as a reference group.

study changes the RR and 95% CI from 1.41 (0.80–2.50) to 1.42 (0.89–2.28). Although the confidence interval is narrower, we cannot conclude from the new meta-analysis that the 4–7 day regimen is significantly more effective than the 1-day regimen. There was significant heterogeneity in these meta-analyses, and unfortunately, only two included studies (Masterton et al¹⁶ 1985 and ours) had adequate allocation concealment, whereas all the other nine studies were classified as inadequate, unclear, or not used. We therefore calculated the pooled RR for these two trials with adequate methodology using a fixed effects model and found that the risk of no cure in the 1-day regimen is significantly higher than the 7-day regimen (RR 2.10, 95% CI 1.44–3.05).

In summary, our trial demonstrates that the 1-day regimen of nitrofurantoin is significantly less effective than the 7-day regimen. Adding these results to the other trial with adequate methodology (Masterton et al¹⁶ 1985 demonstrates that the 1-day regimen is significantly less effective than the 7-day regimen. We therefore conclude that women with asymptomatic bacteriuria in pregnancy should be treated by the standard 7-day regimen of nitrofurantoin, if such treatment is selected, until more data becomes available testing 7-day compared with 3- or 5-day regimens.

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Making stillbirths count, making numbers talk - Issues in data collection for stillbirths

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Abstract

Background: Stillbirths need to count. They constitute the majority of the world's perinatal deaths and yet, they are largely invisible. Simply counting stillbirths is only the first step in analysis and prevention. From a public health perspective, there is a need for information on timing and circumstances of death, associated conditions and underlying causes, and availability and quality of care. This information will guide efforts to prevent stillbirths and improve quality of care.

Discussion: In this report, we assess how different definitions and limits in registration affect data capture, and we discuss the specific challenges of stillbirth registration, with emphasis on implementation. We identify what data need to be captured, we suggest a dataset to cover core needs in registration and analysis of the different categories of stillbirths with causes and quality indicators, and we illustrate the experience in stillbirth registration from different cultural settings. Finally, we point out gaps that need attention in the International Classification of Diseases and review the qualities of alternative systems that have been tested in low- and middle-income settings.

Summary: Obtaining high-quality data will require consistent definitions for stillbirths, systematic population-based registration, better tools for surveys and verbal autopsies, capacity building and training in procedures to identify causes of death, locally adapted quality indicators, improved classification systems, and effective registration and reporting systems.

Background

Why count stillbirths?

The vast majority of stillbirths are preventable, and simple interventions could lead to healthy infants as a rich reward for the resources invested [1-6]. Mothers and families could be spared the emotional burden accompanying pregnancy loss, and societies could gain by reducing a major public health problem.

Being counted is essential. Stillbirths are estimated to account for more than half of the world's perinatal deaths, but only a fraction are registered in any health information system [7]. Stillbirths have been invisible in the World Health Organization (WHO) reports on the global burden of disease [8] and in the United Nations (UN) Millennium Development Goals and Targets. According to the most recent WHO reports on perinatal mortality, 90 countries worldwide lacked any kind of data on stillbirths [7,9]. Improvements in basic registrations of stillbirths are both possible and urgently needed [10]. The "Who Counts?" series in *The Lancet* argued forcefully for the need to build and strengthen civil registration and health information systems globally [11-14]. Systematic and reliable registration of stillbirths is crucial to any health care program planning in this field. Analysis and use of such data provide the fundamentals for accountability and funding. Prioritization of registration and analysis of neonatal deaths in the Millennium Development Goals led to a global effort resulting in significant gains in prevention [15]. Accurately counting stillbirths will similarly provide an opportunity to set specific goals, the first step toward any improvement.

Simply being counted, however, is insufficient for planning, monitoring, and continuously improving efforts to prevent stillbirths. Additional resources and political commitment are needed to improve basic health care services and to overcome limited governance, infrastructure, and workforce. Localities with limited resources are also vulnerable to low-quality health services, where lasting and sustained improvement will likely come through a redesign of health care systems, not through continued funding of current failing systems. In such situations, accessible data are needed on core indicators of quality and availability of care, as well as on the prevalence of underlying causes of these deaths and associated conditions which constitute the framework for understanding stillbirths (Figure 1).

The need for better data is a pressing issue in stillbirth prevention, where there is a significant gap in translating knowledge into proven strategies to reduce fetal mortality [16-20]. Better data on stillbirths are also needed for basic research, which has been neglected. For every 67 publications on unexplained infant death (SIDS) in PubMed, there is only one on the far more prevalent problem of unexplained stillbirths (using the search terms ("unexplained stillbirth*" [All Fields] OR "unexplained fetal death*" [All Fields]) vs. ("Sudden Infant Death" [MeSH] OR "sudden infant death*" [All Fields] OR "SIDS" [All Fields])). This research gap is especially pronounced in low-income countries in which the burden of stillbirths is particularly high. The general lack of data and of research to understand and prevent stillbirths in low-income countries adds to the "10/90 gap"--the fact that less than 10% of research resources address conditions affecting more than 90% of the world's population [21]. Of all publications on stillbirth in PubMed, only about 3% relate to low-income countries (using the search terms (("stillbirth" [MeSH Terms] OR stillbirth* OR "fetal death" [MeSH Terms] OR fetal death*) AND humans [MeSH Terms])) with or without (AND ("developing countries" [MeSH Terms] OR developing countr*)).

Addressing the issue of counting stillbirths is clearly complementary to traditional approaches to perinatal data collection that have prioritized neonatal and maternal deaths. In a continuum of perinatal deaths, data on stillbirths emphasize the earlier phases of pregnancy and bring information that may convey benefits for both maternal and child health. Antepartum and intrapartum stillbirths are strong and direct indicators of quality of prenatal and obstetric care. Also, stillbirth rates, highly correlated to maternal death rates, continue to be a sensitive indicator in less affected communities where maternal deaths are too few to serve as a sensitive indicator [22].

Although counting stillbirths seems simple, it is complex in practice. The incentives for an individual to be counted in civil registration systems are linked to the perceived benefits [11]. For stillbirths, such incentives may not be obvious in communities where few advances in health care are offered. Apparent cultural resistance to registration can be considerable, making data collection problematic if context and culture are not sensitively addressed. In low-income countries, the conduct of even the most well-designed, population-based studies on still-

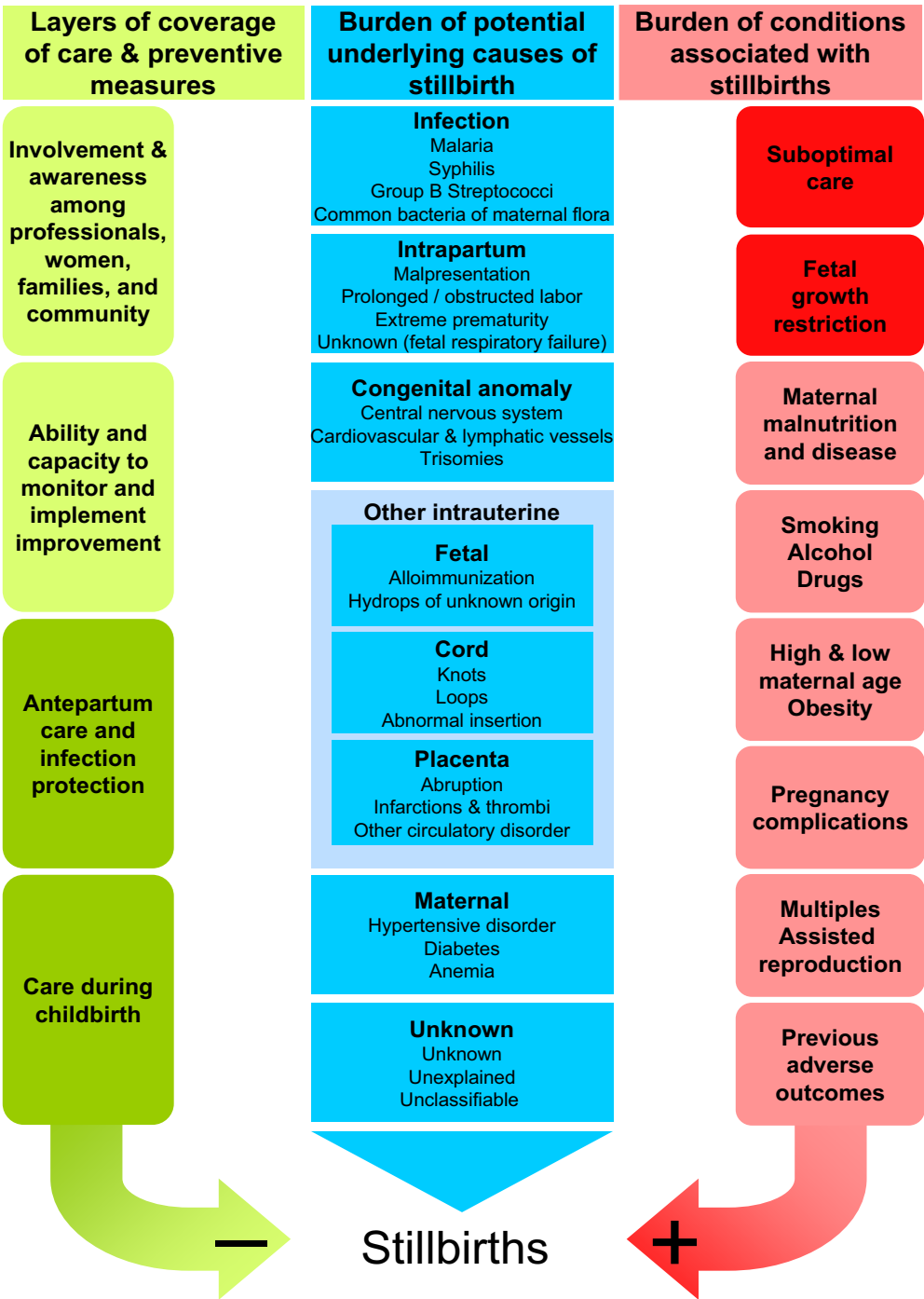


Figure 1
Stillbirth determinants. A framework of the setting and conditions that constitute the data sources needed for the understanding of stillbirth mortality. The classification of significant proportions of underlying causes of death globally is reproduced from CODAC simplified [50].

births weighing more than 1000 g, has been met with difficulties as many stillborn infants are never weighed [10,18].

In this report, we assess how different definitions and limits in registration affect data capture, and we discuss the specific challenges of stillbirth registration, with emphasis on implementation. We identify what data need to be captured, we suggest a dataset to cover core needs in registration and analysis of the different categories of stillbirths with causes and quality indicators, and we illustrate the experience in stillbirth registration from different cultural settings. Finally, we point out gaps that need attention in the International Classification of Diseases (ICD) and review the qualities of alternative systems that have been tested in low- and middle-income settings.

Discussion

International definition and effects on data capture

The WHO/ICD defines stillbirths as the death of a fetus that has reached a birth weight of 500 g, or if birth weight is unavailable, gestational age of 22 weeks or crown-to-heel length of 25 cm (Figure 2) [23]. The WHO also recommends using a higher limit (1000 g/28 weeks/35 cm)

of third-trimester stillbirths for international comparisons [23]. Failure to adhere to WHO definitions and recommendations hampers stillbirth epidemiology. In the USA alone, reporting requirements are determined by individual states, and nine different definitions are used [24]; similar inconsistencies exist in Europe [25]. Reports that include higher rates of early stillbirths typically demonstrate higher rates of congenital anomalies, infections, and placental abruptions, which would suggest a need for different health care planning than in locations that report only third-trimester stillbirths [26-28].

Birth weight, thought to be more reliably reported, takes priority over gestational age in the WHO definition. Most high-resource countries have legislation related to stillbirth registration and reporting, with limitations almost uniformly based on gestational age ranging from 16 to 28 weeks [24,25,29]. In low-resource countries with scarce access to prenatal care and ultrasound dating of pregnancy, the accurate gestational age is seldom known. Differences in technical and cultural understanding of pregnancy duration adds to the problem, as both women and their care providers may count the number and variants of months (calendar, lunar or menstrual cycles) in

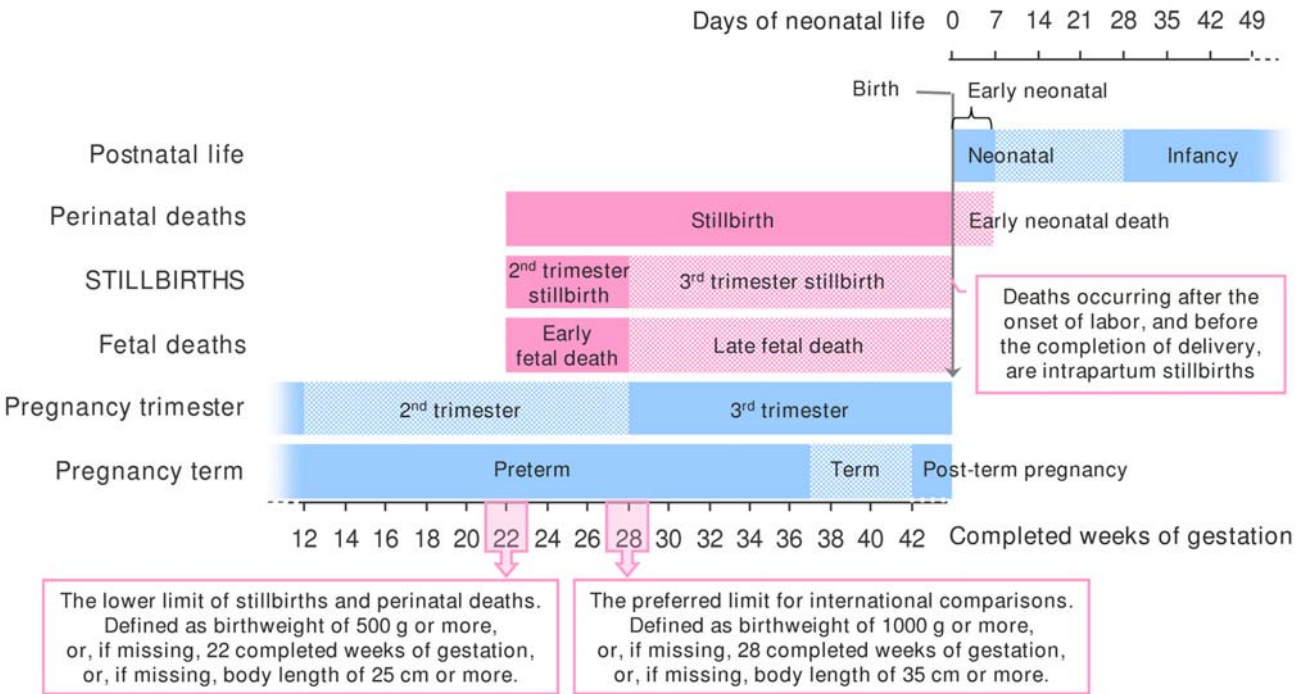


Figure 2
Definition of stillbirth. The definitions of stillbirth used by WHO and ICD in the framework of the continuum of perinatal losses and commonly used definitions of timing of pregnancy and newborn life. Categories of deaths in pink and periods of perinatal life in blue.

various ways [30,31], traditional pregnancy calendars may not add up to 280 days (e.g. the traditional Chinese lunar calendar of ten pregnancy months represents 293 days), and an early spontaneous abortion may not be perceived as the end of a pregnancy but that gestation may be included in the duration of the subsequent pregnancy [32].

Capture by birth weight yields lower stillbirth rates than capture by gestational age (Figure 3); therefore, a high-income country registering stillbirths after 22 weeks and subsequently reporting their numbers according to the 500-g birth weight limit will potentially underreport significantly. If these capture methods are applied to the Norwegian 1997-2007 data (compared with capture by either gestation or weight individually), 4.4% of stillbirths of ≥ 500 g occurring before 22 completed weeks of gestation are lost by the registration limits, and 18.6% of deaths after 22 completed weeks that weigh <500 g at birth are lost by reporting limits. In Australia, while reporting practices may also influence variations seen in reported stillbirth rates, nationally reported rates for 2006 from one agency (Australian Bureau of Statistics, <http://www.ausstats.abs.gov.au>) where birth weight (400 g) takes precedence over gestational age (20 weeks) are 30% lower than those from the other national agency (National Perinatal Statistics Unit, <http://www.npsu.unsw.edu.au>) where birth weight and/or gestation is used (5.2 v 7.4/1000, respectively). The true difference in stillbirth rates between high vs. low income countries is therefore larger than official statistics indicate. This gap will likely be greater in areas with higher rates of intrauterine fetal growth restriction, i.e., in low-resource regions. Underreporting will be an issue when registration

limits are the same as the intended reporting limits. Hence, registrations should aim to document fetal mortality occurring earlier than the limits at which they aim to report for comparative purposes, e.g., 20 weeks/400 g and 26 weeks/750 g, to report accurately at 500 g and 1000 g, respectively [33].

Identification of stillbirths

Beyond the heightened awareness of stillbirths needed to plan vital records or Demographic and Health Surveys to accommodate stillbirth registration in the many countries that lack any data on stillbirths, there are special issues that need to be addressed, providing both challenges and opportunities. An initial challenge is the ability of birth attendants in low-resource areas to identify an infant as stillborn. While the definition of fetal death requires that no heartbeat be present, there is often no ascertainment of such vital signs in settings where no resuscitation is attempted in the live-born but apparently lifeless newborn; such a newborn will be classified as stillborn if he or she does not recover spontaneously [34]. Higher coverage of the diagnostic tools and skills of neonatal resuscitation will improve correct registrations and, more importantly, prevent such apparent stillbirths [34,35].

Registration can only be successful if perceived as beneficial by the population being registered and by those responsible for collecting and reporting events. For the mother and her family, there may be no apparent benefits in terms of civil rights, health care, or other societal advantages normally awarded to mother and infant. In some settings, there are economic disadvantages for parents when a stillbirth is registered (Appendix 4). There is a lack of literature which directly assesses the factors that affect disclosure of stillbirths. However, areas that need attention to enable culturally sensitive data collection may be gleaned from practices in disclosure of pregnancy, the perception of stillbirth and the stillborn, and the context in which women make their health care choices.

In some cultures a new pregnancy is a celebrated event disclosed early in gestation, but a recurrent issue emanating from many low-resource settings is the risk associated with disclosure of pregnancy, which may outweigh perceived benefits. Not only is pregnancy in itself frequently seen as a state of shame and impurity [36], but the pregnant woman may see herself as a prime target for spirit-induced illness, witchcraft and other supernatural forces [37,38]. Such threats to herself and her baby may be perceived as a larger risk than biomedical causes [37], and since seeking health care may increase public exposure and risk, while biomedicine may not help against spirits [37-40], silence and hiding may be the first expressions of prenatal caring in their setting [37]. In the case of a pregnancy loss, disclosure may put both the woman's social

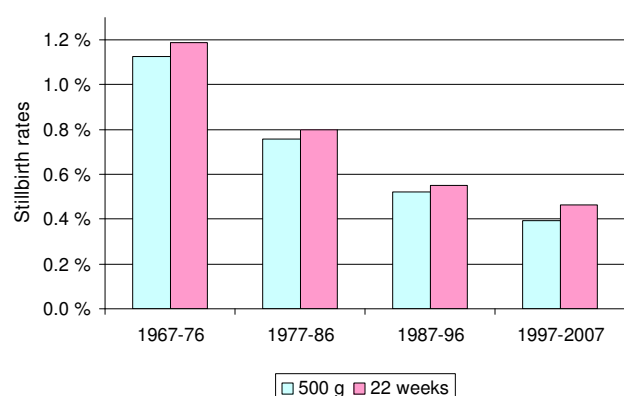


Figure 3
Stillbirth rates by reporting criteria. Norwegian stillbirth rates according to reports based on weight or gestational age. The data include 2.4 million births and 13,100 stillbirths in the Medical Birth Registry of the Norwegian Institute of Public Health.

status and future pregnancies at risk through community judgement of perceived "sins" which may include unfaithfulness, bewitching of her husband, possession by spirits or being a spirit wife of another man, illegal abortion or reproductive incapacity. Such community judgement may result in the women being abandoned or having to pay back the bride price [36,37,41]. Stillbirth is painful in all cultures, and the more problematic emotions are involved, and the less social support and acknowledgement of their loss received, the more complicated their grief [42-44]. Some parents affected by stillbirth receive massive support and recognition of their loss, but in different settings a woman's stillborn child may not be perceived as a significant "entity" and public displays of mourning may be culturally prohibited [36] - making any conversation about her stillbirth difficult. The need to assess the local perceptions of factors facilitating or obstructing stillbirth disclosure, and its ramifications, in planning the methods for data collection in a sensitive, private and confidential manner cannot be overestimated.

For the birth attendant, with first-hand knowledge of the event, there may be barriers to reporting as well. In most communities and for many reasons, health care professionals traditionally tend to underreport adverse events and outcomes, irrespective of whether they are objectively to blame for the event [45,46]. A blame culture with its inherent threat of punishment may result in the health professional's refuse to offer care to pregnancies with known complications, and reluctance to report adverse outcomes [40]. Despite a changing culture from individual blame to a system-approach to adverse events in many health care organizations [47], the health care professional attending births must still be expected to underreport intrapartum deaths unless provided with strong incentives. In communities where most births take place in institutions which provide maternity care, such barriers can potentially be overcome more easily, while they remain a major problem for stillbirths among women in rural areas who give birth at home. The objective lack of health care resources, accessibility and infrastructure, together with subjective maternal views of inadequate quality of care and lack of sensitivity to privacy and social, religious and cultural needs, will continue to prevent a large proportion of births from occurring in institutions in the foreseeable future.

Some of the challenges of capturing data on stillbirths in areas with high birth rates outside birthing institutions may be addressed by ensuring the registration of pregnancies before the perinatal period, if coupled with incentives such as access to antenatal care, allocation to maternity groups, dietary supplements, or other benefits - sufficient to outweigh the perceived risks of disclosing their pregnancy. This strategy will provide the most accurate

denominator, unbiased by maternal or professional barriers, and also provide important opportunities for initial risk assessment and essential preventive measures. With sufficient incentives to register a live-born baby, special focus to document outcomes should be planned for those registered as pregnant but not presenting for birth registration. By registering the mother rather than the infant, pregnancy outcomes lost to follow-up may be captured at subsequent pregnancy registrations, as women experiencing loss have higher rates of renewed pregnancy than those having a live-born child. If health professionals clearly communicate that disclosure of previous stillbirths may aid in preventing recurrence, mothers may also find personal motivation to overcome obstacles in reporting their stillbirth.

Causes and conditions to be captured

Considerable differences in causes and timing of stillbirths exist between populations, and these vary with the stillbirth rates. The setting and epidemiology of causes of death will define the most critical information on stillbirths needed to inform prevention and guide selection of the analyses that will provide the best indicators of improvement.

Longitudinal data from high-resource countries show that the rate of intrapartum stillbirths has fallen with improvements in intrapartum care [48]. Intrapartum death rates are therefore frequently used as an indicator of quality of care. As the rate of intrapartum stillbirths is directly associated with the availability of intrapartum care, a larger proportion of stillbirths occur in the intrapartum period in low- and middle-income than in high-income countries (31% vs. 16% of stillbirths, respectively) [48]. In Western Africa, the intrapartum stillbirth rate was estimated at 15/1000 in 2004 (36% of stillbirths), 50 times higher than the rate in North America of 0.3/1000 (10% of stillbirths) [7,49].

Preventability of intrapartum deaths will depend largely on gestational age, and timing of deaths should be registered both in terms of early versus late gestational deaths and, if known, whether the death occurred antepartum or intrapartum. Neither "intrapartum" nor "intrapartum asphyxia" are underlying causes of death but rather timing and final mechanism, respectively [50]. Such categories alone contain insufficient information to guide targeted improvements in care. When the most basic care is available, a majority of intrapartum deaths are caused by placental, cord, infectious, traumatic, and other specific complications, both in high- and low-resource countries [51-54]. Reports from Pakistan, Palestine, and South Africa all indicate that about one third of cases are linked to suboptimal care [53,55,56]. Characteristics and predisposing risks, such as plurality and maternal size, should

be registered together with events and conditions presenting during the intrapartum period, as should information on the level and quality of care available and received, as indicated in the dataset template.

Irrespective of setting, the largest proportion of stillbirths are antepartum deaths. Although availability of a timely delivery is critically important to prevention, the pregnancy at risk for antepartum death, and the optimal timing of delivery to prevent it, must first be identified through antenatal care. Adverse pregnancy outcome can be most effectively anticipated, prevented, and treated through implementation of adequate antenatal care. Components of this care include counselling and initiation of health-promoting efforts, such as proper nutrition or insecticide-treated mosquito nets, combined with screening, identification, and monitoring of pregnancy risks [3-6].

The reported prevalence of major causes of antepartum deaths will differ between high- and low-resource communities, because of both their true prevalence and the coverage of adequate evaluation to identify and register the cause of death [41]. Adverse antepartum conditions are often complex and can be found in the mother, the fetus, the placenta, and the umbilical cord, and their interactions. On a global scale, syphilis, malaria, and other infections; congenital anomalies; placental abruptions and other placental insufficiencies; and pregnancy-induced hypertension cause most antepartum deaths [2,16,17,20,54,57-63]. Placental pathology, including those cases manifesting clinically as maternal hypertensive disorders, contribute to the underlying cause of death in 6 out of 10 stillbirths in low-income countries [49,64]. In low-resource settings, this condition may more often go untreated and progress to severe preeclampsia or eclampsia and be classified as such. Because of infrequent examinations of the placenta, such cases are likely to be classified as deaths of unknown cause associated with fetal growth restriction or maternal hypertensive disease rather than by the underlying placental cause. While an appreciation of the maternal and fetal conditions associated with placental pathology is important in risk reduction in both high- and low-resource country settings, lack of information about placental pathology still inhibits better understanding of etiology of these deaths.

The relative contribution of congenital anomalies to stillbirth rates in low-resource countries is low because of the high rates of other causes coupled with an under-diagnosis of malformations due to relying on findings from gross external malformations when autopsy and other diagnostic assessments are lacking. In countries with liberal abortion laws, however, the contribution of anomalies is often underestimated as a result of antenatal diagnoses and ter-

minations of pregnancy before the perinatal period. In evaluating mortality rates associated with anomalies in communities with high coverage of prenatal ultrasound and access to medical termination of pregnancy, termination rates must therefore be taken into account [65].

The largest contributors to third-trimester stillbirths of infectious causes in the low-income world are malaria and syphilis [2,63], while typical pathogens in high-income countries are probably mostly missed in low-resource settings because of the specialized tests needed to identify them adequately, as in the case of group-B streptococci, Parvovirus B-19, *Listeria monocytogenes*, and early-gestation infections by common bacteria of maternal intestinal flora. Such undetected infections will also add to the group of antepartum stillbirths of unknown cause. Unknown cause of death may mean two different things in high- and low-income countries. There is a wide gap between unexplained stillbirths despite adequate post-mortem examinations, which represent one fourth of antepartum stillbirths in high-resource settings [66,67], and stillbirths of unknown cause resulting from a lack of information or examinations, which represent up to two thirds of antepartum deaths in communities where either suboptimal testing is performed or causes of death are poorly classified, both in high and low-income settings [68-70]. Addressing the challenges in evaluation of stillbirths of unknown cause, and prevention of unexplained stillbirths, requires that such entities are registered among causes, as discussed later.

Despite such differences, which make direct comparisons across populations difficult, low-resource communities should aspire to register their stillbirths in the same systematic manner as in settings with greater resources. A common classification system is needed to build a common understanding and bridge the knowledge gap. At the same time, it is essential for low-income countries to also collect basic data such as information on timing of death and fetal growth restriction in these same datasets.

Datasets of stillbirths

Data on stillbirths should enable the analysis and monitoring of quality of care and the most prominent specific threats to reproductive health. Relying on "general improvement" of health and health care in the population will be insufficient. Reducing stillbirth rates in Scandinavia from levels currently seen in low-income countries to those seen today has taken more than 100 years [71]. Cause-specific interventions have been shown to be effective in reducing stillbirth rates [1,2,19,72]. The template dataset presented here (Figure 4) has been designed specifically to identify and monitor significant threats to pregnancy health that health care programs can address, both within quality of care and among the most prevalent

causes of death and associated conditions globally. Examples of challenges and opportunities for such data collections are presented in Appendices 1, 2, 3 and 4.

In this template, the main underlying cause of death should be registered, and up to two associated conditions may be added to capture data on the scenario in cases with complex or multiple causes. It includes case details needed to analyze the potential for prevention and to correct for case mix when comparing populations. It also includes some of the basic measures of quality and availability of care, although more detailed information needs to be gathered to monitor specific interventions. In particular, measures of quality of care need to reflect local challenges to be helpful for further improvement [73-75]. National or local guidelines should define what is considered as adequate care versus suboptimal care, depending on which evidence-based interventions that can be provided [3-6], and this dataset segregates deficiencies according to whether suboptimal care was the result of lacking coverage (adequate care not available) or insufficient health care delivery and usage.

Most of the suggested data items are easily observed by a skilled birth attendant in most settings and will be sufficient for classification in main categories of causes of death, as illustrated in Figure 1. A large proportion of stillbirths do, however, occur in settings where the mother has received no antenatal care and gives birth at home with no skilled attendant present. In this situation, a verbal autopsy, taken after the birth, offers a potential source of helpful data. The abolition of pregnant women lacking any maternity health care is already targeted as the primary goal in any preventive strategy against maternal and perinatal deaths. Implementation of basic maternity health care to improve pregnancy outcome is not dependent on knowledge of specific causes of stillbirth within the setting within which it is delivered. Current knowledge is sufficient for remedial action, and the will and ability to change are the only things lacking to mobilize a call to action. Substandard situations must not scale down ambitions for better data collection; rather, the ability to identify causes of death should be scaled up. The template dataset provides the opportunity to register data items as unknown, and the frequency of unknown data should be monitored as a quality indicator together with the rate of stillbirths classified as cause unknown.

The current system for verbal autopsy does seem to provide useful information on the causes of death in most cases, but it still has unsolved issues for stillbirths [76,77]. With the most prevalent causes of death in stillbirths in mind, efforts to improve the value of verbal autopsy should be a priority. Ideally, some level of skilled post-mortem investigation, at least an external macroscopic

examination, should be performed [78]. Birth attendants can be trained to use illustrations on posters to assess the degree of maceration and determine approximately when fetal death occurred, but international standards for verbal autopsy for unattended home deliveries resulting in stillbirth are lacking [79]. Tools to determine pathologies of the placenta for birth attendants in low-resource areas should be developed and tested. The tools would help birth attendants collect basic, but important, information such as placental-fetal birth weight ratio, gross description of placental dimensions and shape and umbilical cord insertion, color and smell indicating infections, detection of clots and sign of abruption, large infarcts, and widespread fibrosis. In settings where autopsies are never performed, protocols that include placental examination often provide valuable data for capturing the cause of death [61,80]. Regrettably, examination of the placenta is often omitted because of lacking resources, training, and protection against contaminated blood, and poor understanding of its clinical importance in identifying the cause of death. Cultural practices may also prevent such examinations, as e.g. in China, Pacific Islands and West Africa, where the placenta may be of high symbolic and spiritual importance, and should be eaten or buried at specific sites.

Although this report focuses on the specific needs to capture data on stillbirths, neonatal conditions and deaths should be included in the same system to ensure a full picture of perinatal mortality, linked to maternal conditions and causes of death. In particular, causes and mechanisms of neonatal deaths within 12-24 hours of life are generally the same as for intrapartum stillbirths [81].

Classification of causes of death and associated conditions

Classification systems for stillbirths may be useful if designed for comparison of communities, for audit of care, and for planning and monitoring prevention and research. Besides the ICD system, there is no international consensus on a classification system for stillbirths. The ICD aims to classify the underlying cause of death, and when not available, the condition most likely to have resulted in death. It is used extensively in low-income countries, for example, to report perinatal mortality to WHO. The ICD system was developed to allow the systematic coding, analysis, interpretation, and comparison of mortality and morbidity, but it is not adapted specifically to stillbirth. Thus, the current ICD-10 does not fully recognize the stillborn infant (with cord, placenta, and membranes) as an individual entity with its own diseases, conditions, and events to be registered separately from the mother. There are limited codes for conditions specific to the perinatal period in the O codes ("pregnancy, childbirth, and puerperium," from the maternal perspective) and P codes ("certain conditions originating in the perina-

Figure 4
Dataset template for stillbirths. A template for the development of data collection forms for datasets of stillbirths.

tal period," from the fetal perspective), where adequate coding for stillbirths should be found. The placental codes in particular are incomplete and can only be used for a few of the placental pathologies affecting pregnancy outcomes. This lack of coding options is further complicated by our incomplete understanding and continued controversy regarding various placental findings and their causality in stillbirths. There is also considerable overlap between O and P codes that may result in confusion for allocation. WHO advocates the accurate use of ICD codes to monitor the quality of registrations of causes of death, but the range of incomplete categories of stillbirths in ICD-10 suggest that for now, other indicators of quality must be defined. The current revision of the ICD system (ICD-11) is expected to be released in 2013.

With these limitations in the ICD system, and with the many different purposes of classification, a number of alternative and mostly mutually incompatible classifications for stillbirths have been designed over the past decades [82]. A classification system should be an information management tool [49,50]. Depending on the purpose (local health care monitoring, planning, or research), different classification systems may be helpful, and a perfect all-purpose system is unthinkable. Although classifications are typically used in low-income countries to identify the main areas of preventive efforts [83,84], none of them has been rigorously tested to determine the effects on stillbirth prevention and rates after implementation. A core classification system for the main categories of causes of death and associated risk factors and conditions in stillbirths, as collected in our proposed dataset template, is nonetheless the starting point. For international comparisons to be meaningful, the most prevalent low-income country-related causes and conditions must be included in the classifications. Most current classifications have been created for high-income countries and implemented in low- and middle-income countries without modifications. Typically, a system for a high-resource setting will not be poised to adequately manage information on, for example, intrapartum deaths or infections such as malaria and syphilis. A base system needs some fundamental elements, and the corresponding characteristics of the few that have been tested in low- and middle-income countries are listed in Table 1.

1) Compatibility with ICD. The aim should be to supplement the ICD system, and to ensure compatibility, a tracking system for stillbirths should adhere to the concepts of capturing the underlying causes. Although additional information, such as the specific identification of potentially preventable associated conditions, may be beneficial, its inclusion should not make the system incompatible with ICD concepts.

2) Expandability of classifications. To be perceived as useful in all settings, the basic categories should allow the simplicity of data collection from verbal autopsies. Yet, these categories should also be expandable to the individual diagnoses registered in high-resource, high-expertise settings to promote consistency across populations and facilitate knowledge transfer. The Causes of Death and Associated Conditions (CODAC) classification is used as one such example for illustration in Figure 5, where the first case could be identified by verbal autopsy as an intrauterine infection with foul-smelling amniotic fluid and maternal fever, and diagnosed in other settings as an ascending *E. coli* infection confirmed by cultures from internal fetal tissues. Second, an obvious congenital anomaly of the head could be subclassified as hydranencephaly in a specialized center for perinatal pathology. Third, a case identified in low-resource settings as a small baby with a rubber-hard placenta with white-gray lesions, can be identified by perinatal pathologists as massive perivillous fibrin depositions. Using expandable classifications, data collection is possible for all, yet none are restricted by a too-simplistic system from preserving more complex information.

3) Capture of intrapartum events. A data system should include categories to distinguish items on antepartum and intrapartum conditions that are targets of preventive efforts in antenatal and intrapartum care, as in the dataset we present here. Specifically, it should not only state that death occurred in the intrapartum period, but also capture the actual intrapartum events. As an example, the Wigglesworth system mainly focuses on timing of death, which is favoured in many low-resource settings because its simplicity allows any birth attendants to use it irrespective of his or her educational level. Yet, in its original version, it did not handle any information other than timing and congenital malformations, and the simplicity of the system does not outweigh the loss of information [84,85]. A classification system without information on intrapartum events will be of little use in one third of stillbirths globally.

4) Capture of placental conditions. The conditions affecting the stillborn infant that are related to the adjoining cord, placenta, and membranes need to be recorded. Of particular importance is managing the information on the placenta, as this is lacking in the current ICD.

5) Ability to differentiate unknown and unexplained events. While infections like syphilis provide direct causes of death as targets for prevention and should be included, the category of "unknown" events in antepartum and intrapartum deaths also provides

Table 1: Classification systems and their characteristics for use in low- and middle-income countries

Systems tested in low- or middle-income countries	Number of categories of stillbirths ^a	Are intrapartum events captured in subcategories?	Does the system aim to capture underlying cause?	Are the main categories consistent with underlying cause?	Resources desirable for use ^b	Does the system separate unknown from unexplained?	Agreement tested (Kappa score or level of agreement)	References
Aberdeen	8-0-0	no	yes	no	B	no	0.35-0.97	[49,84,93-95]
CODAC	10-94-577	yes	yes	yes	B, C	yes	0.65-0.94	[49,50]
CODAC Simplified	10-30	yes	yes	yes	B, C	yes	no	[50]
ICD-10	17-134	yes	yes	yes/no	B	no	no	[23]
Nordic Baltic	13-0-0	no	no	no	A	no	0.85	[84]
Patinson ^c	12-48-0	yes	no	no	B	no	no	[96,97]
PSANZ-PDC	11-52-33	yes/no	yes	yes/no	B, C	yes	0.63-0.90	[49,86]
ReCoDe	9-28-1	yes/no	no	no	B, C	yes	0.51	[49,98]
Tulip	6-24-7	no/yes	yes	yes	B, C	yes	0.74-0.86	[49,87]
Whitfield ^c	12-15-2	no	yes	no	B	no	no	[95,99]
Wigglesworth	5-0-0	no	no	no	A	no	0.25-0.85	[49,84]

^aNumber of main categories followed by subcategories.

^bA = little investigations and no placental examinations necessary; B = some clinical and pathological investigations necessary or desirable; C = placental investigations necessary or desirable (placental conditions included in the classification).

^cModified versions of the Aberdeen classification.

Acronyms: CODAC: Causes of Death and Associated Conditions, PSANZ-PDC: Perinatal Society of Australia and New Zealand Perinatal Death Classification, ReCoDe: Relevant Conditions of Death.

Verbal autopsy	Level I	Level II	Level III
Infection	0 Infection	00 Unspecified or other 02 Malaria 04 Syphilis 05 GBS 06 Common bacteria of maternal flora	• 060 Unspecified • 061 Enterobacter species • 062 Enterococci species • 063 Escherichia coli • 064 Klebsiella species • 065 Mycoplasma species • 066 Staphylococci species • 067 Streptococci species (non-B) • 068 Ureaplasma urealyticum • 069 Other
Intrapartum	2 Intrapartum	20 Unspecified or other 23 Malpresentation 25 Prolonged / obstructed labor 26 Extreme prematurity 29 Unknown (fetal resp. failure)	
Congenital anomaly	3 Congenital anomaly	30 Unspecified or other 31 Central nervous system 32 Cardiovasc. & lymphatic vessels 37 Trisomies	• 310 Unspecified • 311 Anencephaly • 312 Craniorachischisis • 313 Holoprosencephaly • 314 Hydranencephaly • 315 Hydrocephalus • 316 Microcephaly • 319 Other
Other intrauterine	4 Fetal	40 Unspecified or other 43 Alloimmunization 47 Hydrops of unknown origin	
	5 Cord	50 Unspecified or other 51 Knots 52 Loops 53 Abnormal insertion	
	6 Placenta	60 Unspecified or other 63 Abruptio 64 Infarctions & thrombi 65 Other circulatory disorder	• 650 Unspecified • 651 Fetal thrombotic vasculopathy and stem vessel thrombi • 652 Fetal vascular narrowing • 653 Hemorrhagic endovasculitis • 654 Subchorionic fibrin deposition • 655 Perivillous fibrin deposition • 656 Intravillous fibrin deposition • 657 Massive basal plate fibrin dep. ("Maternal floor infarct") • 658 Massive parenchymal fibrin deposition ("Glitterinfarct") • 659 Other
Maternal	7 Maternal	70 Unspecified or other 71 Hypertensive disorder 73 Diabetes 75 Anemia	
Unknown	8 Unknown	80 Unspecified or other 81 Unknown 86 Unexplained 87 Unclassifiable	

Figure 5

Causes of death in stillbirth. Expandable layers of causes of death according to the resources available for evaluations of stillbirths. Select categories of the CODAC classification system [50] used for illustration.

indirect operational causes with opportunity for improvement that should be targeted, as shown in Figure 6. The classification system should enable differentiation between unknown and unexplained causes of death to allow meaningful analysis that takes into account the proportion of items that are unknown in the dataset. Ideally, one would expect unexplained stillbirths to be stillbirths "(...) unexpected by history and in which a thorough autopsy (...), together with gross and histological examination of the umbilical cord, placenta, and membranes, fails to demonstrate an adequate cause of death." [67].

Of the existing classification systems that have been tested in low- or middle-income country settings, only the current versions of the Perinatal Society of Australia and New Zealand Perinatal Death Classification (PSANZ-PDC) [86] and Causes of Death and Associated Conditions CODAC [50] comply with all five of these requirements, although the basic level of the main categories may have to be simplified further to be used with verbal autopsy data only. The summary in the Table 1 would indicate that Tulip [87] requires only the addition of an explicit category for intrapartum events to comply (intrapartum causes are embedded in other categories in Tulip). Tulip is uniquely organized to capture information from a high-

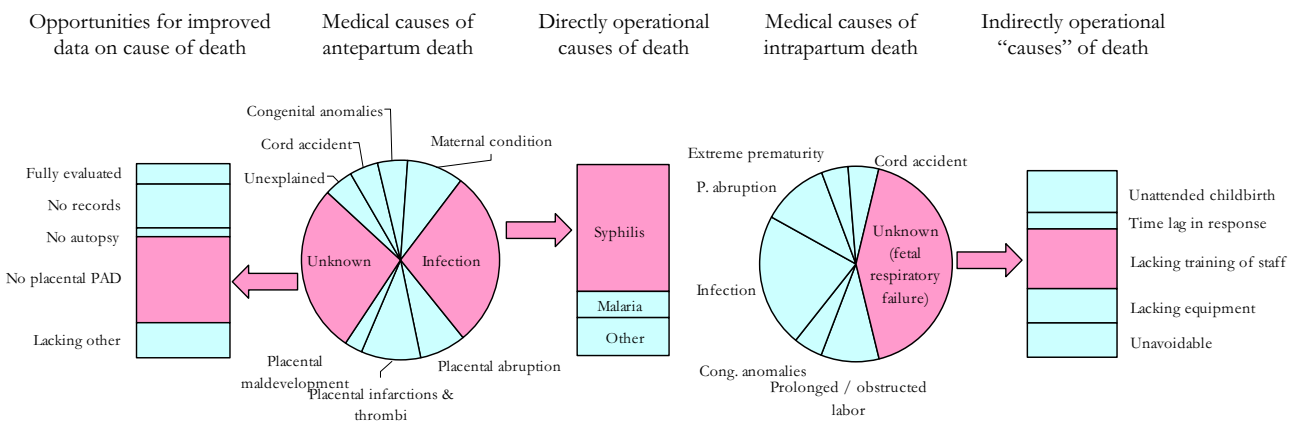


Figure 6
Operational causes of death. Examples of causes of antepartum and intrapartum deaths that may be targeted directly for stillbirth prevention (e.g., syphilis) or indirectly to improve clinical quality of care or ability to capture data for further improvement. PAD: pathological-anatomical diagnosis.

resource, high-expertise setting with focus on the detailed diagnosis of malformations and placental abnormalities [64,87], and it is not intended for use in low- and middle-income country settings.

The two systems that seem to be the best options to supplement ICD, CODAC and PSANZ-PDC, are among the systems in which some clinical, pathological, and placental investigations would be necessary or desirable to ensure consistency in coding (Table 1). This follows from the inclusion of the placenta as an entity to capture. To set lower standards and accept a lack of data on conditions contributing to two thirds of antepartum stillbirths in high-income countries [19,49,64] is not a viable alternative. Use of the more elaborate systems may introduce misclassification in a setting with low resources. For instance, placental and infectious causes may be underdiagnosed, classified instead as unknown causes. However, although the value of placental histopathology and autopsy is undisputed in high-resource countries [88-90], the potential for prevention (for society and for the mother's subsequent pregnancies) associated with elaborate post-mortem testing in low-income countries is unclear, and the minimum level of investigation needed to classify a cause of death as unexplained rather than unknown in low- and middle-income country settings must be defined. For the purpose of data collection from verbal autopsies, categories such as "fetal," "cord," and "placenta," typically found in many classifications, could easily be combined, e.g., into "other intrauterine," as exemplified in Figure 5. The underlying cause of fetal hydrops or location of an intrauterine infection as either

fetal, cord, or placenta will be particularly difficult to decide.

The number of categories per system reflects the amount of information captured by that system (Table 1), but it does not necessarily reflect the applicability of these categories for analyzing stillbirth scenarios in all settings. The ease of use with little information versus more information requiring more resources for investigations must be balanced by the local knowledge of its intended use. Interestingly, testing the ease of use and ability to capture pertinent information on stillbirths in both high- and low-resource settings demonstrated that the complexity of the three systems mentioned previously was not associated with reduced user-friendliness. On the contrary, health professionals coding stillbirths seem to prefer having the opportunity to code exact information rather than registering information in broader and more vague categories [49,50], and all complex systems also have broader categories for comparisons that are detailed in subcategories.

It is time that traditional classifications such as Wigglesworth be celebrated for past achievements and substituted with classification systems that manage the information currently available. Several dozen classification systems exist already. However, some of these systems still require testing, and new systems must be developed specifically to handle verbal autopsy data. Such improvements in data management are essential to informing targeted interventions to prevent stillbirths. As the ultimate goal is stillbirth prevention, future research in the development and use of classification systems should aim to document its usefulness in this respect.

Summary

Scaled-up of coverage of registration of births is needed. Vital registrations and health information systems and other large Demographic and Health Surveys should be adjusted to accommodate registration of stillbirths. Tools for verbal autopsies must be revised to improve capture of causes and events related to stillbirths. The WHO definitions of stillbirth for reporting should be implemented globally, and registrations should capture stillbirths of lower weight and gestation than the intended reporting limits. Pregnancies should be registered before the perinatal period to help overcome the barriers in stillbirth registration and enable prevention efforts in antenatal care. Causes of death in stillbirths must be monitored, and better detection of the most prevalent causes--in particular, infections and placental pathologies--is needed. The ICD system's O and P codes need to be adjusted and supplemented to capture the causes identified. A universal approach to stillbirth classification is optimal and warrants focused attention.

The *BMC Pregnancy and Childbirth* issue on stillbirth prevention illustrates how specific causes of stillbirth can be prevented [3-5,5,6,41,91,92]. None of this will happen without data. Development and evaluation of prevention efforts require registration of all stillbirths, the characteristics of the pregnancies affected, the timing of death, the underlying causes, and the quality and availability of care for each individual. Stillbirths need to count. With careful collection and analysis of these data, the numbers will speak for themselves.

Abbreviations

WHO: World Health Organization; ICD: International Classification of Diseases.

Competing interests

The authors declare that they have no competing interests.

Appendices

Appendix 1 - Success criteria for collection and reporting of stillbirth data

- Consistent use of definitions between institutions
- Systematic approach to capture pregnancies and out-of-hospital stillbirths
- Capacity and training in examinations and testing procedures to identify cause of death
- Easily accessible electronic files for registration
- Training in stillbirth registration and classification

- Dedicated and motivated staff for registrations
- Feedback and other incentives to motivate staff
- Local adaptations of a sustainable system for registering and reporting
- Quality indicators developed for local needs
- Regional or national data collection and analysis

Appendix 2 - Egypt: Assiut University Hospital

The hospital center in Assiut is a tertiary university hospital that receives women from low to middle socioeconomic levels. In 2007, the hospital attended 13,398 deliveries and 6550 antenatal care clients. There is 50%-75% coverage of the care system in the area.

Pregnancies are captured from 22 weeks gestation. The current system can also register stillbirths from 28 weeks gestation (or 1000 g or 35 cm) including intrapartum deaths. Using this definition, the hospital stillbirth rate is 70/1000.

No specific person is responsible for reporting stillbirths in particular. However, systematic reporting on stillbirths is included in the general statistics of the delivery unit, which provides the stillbirth rate. The outcome of pregnancy is reported in the medical file by the attendant obstetrician, but these files are not easily accessed for registrations. Therefore, the hospital is moving towards introducing the recording of labor and delivery data into a computerized database. This move would facilitate data capture and strengthen the quality of data in general and in particular, the quality of reported pregnancies and stillbirths. The main challenge of such a system is sustainability within available resources. Data entry is performed by residents who need to be motivated and to see the usefulness of the work in order to achieve quality in the reporting.

The proposed system of registration could be implemented at the Assiut Hospital. An anticipated challenge would be the necessity to train data collectors in ICD-10. Potential feasible additions to the proposed dataset for monitoring includes collection and laboratory analysis of cord blood to identify blood group incompatibilities, genetic analysis, and photographs to document the findings of macroscopic exams.

Appendix 3 - Thailand: Srinagarind Hospital

Srinagarind is a 1000-bed, urban teaching hospital located in Khon Kaen in the Khon Kaen province of Thai-

land. The hospital provides comprehensive obstetric care. Each year, 2500-3000 women give birth in Srinagarind, and it provides antenatal care to 2500 women. The antenatal care clinic opens weekdays from 9:00 to noon, and the high-risk pregnancy clinic opens from 13:00 to 16:00.

The hospital's strategy is to capture pregnancies from <22 weeks and stillbirths based on the 22-week definition (500 g or 25 cm). With this definition, the stillbirth rate is 7/1000. The stillbirth capturing system identifies intrapartum deaths, which represent 3/1000 births.

Registered nurses register all births (live and stillbirth), and one senior registered nurse is responsible for reporting. There is no lower limit on registration and reporting of live births. Residents are responsible for reporting the monthly statistics in the departmental meeting. Information on all births, including complications, is entered into computer files that can be readily assessed.

The proposed system of registration could be implemented at Srinagarind Hospital, Khon Kaen University. All items are applicable in this setting would be integrated with neonatal death registrations. Additions to the dataset might include the ability to distinguish between vacuum and forceps in assisted vaginal deliveries and separate categories for maternal anemia and pre-eclampsia, preterm labor, and fetal distress.

Appendix 4 - South Africa: East London Hospital Complex

Located in East London, this urban hospital complex is a second-line birthing institution equipped with 1676 beds, of which 60 are gynecology beds and 180 obstetric beds. It receives mainly women from low socioeconomic groups who cannot afford private care. The number of births per year is 13,000-14,000, and the hospital provides antenatal care for the same population. It has high coverage of both antenatal (>80%) and intrapartum (>90%) care. The hospital uses the stillbirth definition ≥ 500 g (weight only, no gestational age or length) for registration, and the stillbirth rate ≥ 1000 g is 23/1000. The intrapartum stillbirth rate is approximately 7/1000.

A significant strength of the hospital's registration program is its participation in the well-structured national Perinatal Problem Identification Program (PPIP, <http://www.ppip.co.za>). Doctors or midwives fill in the individual perinatal death report, while a dedicated statistics nurse registers births and checks that all births recorded in the labor ward are accounted for. Data are submitted monthly to a national PPIP database. PPIP differs from the proposed classification approach in that it does not collect data specifically on intrapartum vs. antepartum

deaths, but on four categories: "stillborn, alive on admission," "fresh stillborn, dead on admission," "stillborn, admission status unknown," and "macerated stillborn." The sum of the three first categories is reported as an approximation of intrapartum death rates.

A weakness of the hospital's current system is the inability to capture deaths outside the hospital in the communities served and, thus, a lack of information on perinatal deaths occurring at home. A second weakness is the use of a manual counting system and not an electronic maternity database. The latter would be a feasible and major opportunity to improve data collection.

In this setting, there are few obstacles to capturing data on stillbirths systematically, and extending registrations to a maternity database remains a question of prioritizing resources in a setting where skilled staff shortage is the main limitation of the health care system. A maternity database would not directly lead to improved capture of stillbirths in home deliveries. Some could be captured with access to death registration data, but some are not reported at all by the families.

A specific disincentive to the registration of stillbirths in South Africa is that registered stillborn babies require a formal burial, which places a large financial burden on the family. Even in the case of in-hospital stillbirths of borderline weight, hospital staff may assist the family to avoid the cost of burial by recording the death as a miscarriage.

Authors' contributions

JFF drafted the manuscript in consultation with SJG. SJG reviewed existing classification systems in the table. AB and MM collected and drafted the experiences on data collection in Appendices 1, 2, 3 and 4. All authors edited drafts of the manuscript and read and approved the final manuscript.

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Method of delivery and pregnancy outcomes in Asia: the WHO global survey on maternal and perinatal health 2007–08

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Summary

Background There has been concern about rising rates of caesarean section worldwide. This Article reports the third phase of the WHO global survey, which aimed to estimate the rate of different methods of delivery and to examine the relation between method of delivery and maternal and perinatal outcomes in selected facilities in Africa and Latin America in 2004–05, and in Asia in 2007–08.

Methods Nine countries participated in the Asia global survey: Cambodia, China, India, Japan, Nepal, Philippines, Sri Lanka, Thailand, and Vietnam. In each country, the capital city and two other regions or provinces were randomly selected. We studied all women admitted for delivery during 3 months in institutions with 6000 or fewer expected deliveries per year and during 2 months in those with more than 6000 deliveries. We gathered data for institutions to obtain a detailed description of the health facility and its resources for obstetric care. We obtained data from women's medical records to summarise obstetric and perinatal events.

Findings We obtained data for 109 101 of 112 152 deliveries reported in 122 recruited facilities (97% coverage), and analysed 107 950 deliveries. The overall rate of caesarean section was 27·3% (n=29 428) and of operative vaginal delivery was 3·2% (n=3465). Risk of maternal mortality and morbidity index (at least one of: maternal mortality, admission to intensive care unit [ICU], blood transfusion, hysterectomy, or internal iliac artery ligation) was increased for operative vaginal delivery (adjusted odds ratio 2·1, 95% CI 1·7–2·6) and all types of caesarean section (anteartum without indication 2·7, 1·4–5·5; anteartum with indication 10·6, 9·3–12·0; intrapartum without indication 14·2, 9·8–20·7; intrapartum with indication 14·5, 13·2–16·0). For breech presentation, caesarean section, either anteartum (0·2, 0·1–0·3) or intrapartum (0·3, 0·2–0·4), was associated with improved perinatal outcomes, but also with increased risk of stay in neonatal ICU (2·0, 1·1–3·6; and 2·1, 1·2–3·7, respectively).

Interpretation To improve maternal and perinatal outcomes, caesarean section should be done only when there is a medical indication.

Funding US Agency for International Development (USAID); UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), WHO, Switzerland; Ministry of Health, Labour and Welfare of Japan; Ministry of Public Health, China; and Indian Council of Medical Research.

Introduction

Several factors, including the increased perception of safety, have contributed to a worldwide increase in rates of caesarean section.¹ In many countries, these rates have reached epidemic proportions, motivating a debate about whether the high rates are appropriate.² Unnecessary caesarean section is a classic example of the mismatch between evidence and practice in obstetrics. This debate also draws attention to the complexities that attempts to change practice entail.^{3,4} On the one hand, some are concerned about possible additional maternal and perinatal morbidity caused by unnecessary caesarean sections. On the other hand, assessment of whether the caesarean section operation poses an intrinsic risk to the mother or the baby is difficult. Ethical and practical constraints prevent assessment of intrinsic risks related to caesarean sections with use of a randomised controlled trial.

In developing countries, improvement of maternal and perinatal health strongly depends on strengthening of health systems.⁵ When resources are scarce, caesarean sections that are not medically indicated could, if done in large numbers, represent a serious resource drain. At the same time as unnecessary overuse of surgical practices is being assessed in some countries, millions of women in other countries who need these procedures do not have access to them, putting their own and their children's lives at risk.⁶

This Article reports the third phase of the WHO global survey project—a study that was implemented in the Americas (2005), Africa (2005), and Asia (2007–08) to alleviate the scarcity of information for planning and assessment of maternal and perinatal health services, specifically, intrapartum care. The survey in Latin America suggested that, at the level of facilities, increasing rates of caesarean section do not necessarily lead to

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improved outcomes and could be associated with harm.⁷ The WHO global survey in Asia aimed to obtain regional estimates of different methods of delivery in facilities, studying the relation between method of delivery and maternal and perinatal outcomes. By undertaking the study in a randomly selected number of health facilities that have not participated in research before, we aimed to develop a network with capacity to collect routine data and participate in collaborative research across countries and regions.

Methods

Study design

Methodological details of the global survey have been published elsewhere.⁸ Briefly, this is a multicountry, facility-based survey that collected data for all delivering women in randomly selected facilities worldwide. WHO subregions, classified by the number of children younger than 5 years and adult mortality rates, were used as a proxy for the burden of maternal and perinatal mortality. A stratified multistage cluster sampling design was used

to obtain a sample of countries and health institutions worldwide. From each subregion, four countries were selected, with probability proportional to population size. When a subregion had fewer than four countries, all countries within that subregion were included. This process resulted in 12 subregions having four countries each, and two subregions having three countries each.⁸ Owing to financial and practical constraints, we could not undertake the survey in developed countries of the region (unless they volunteered to—eg, Japan) and some of the selected countries (eg, Indonesia). Nine Asian countries were included: Cambodia, China, India, Japan, Nepal, Philippines, Sri Lanka, Thailand, and Vietnam. In each country, two regions or provinces, in addition to the capital city, were randomly selected by computer, with probability of selection proportional to their size. Once a province had been selected, we obtained a census of all facilities with more than 1000 births per year and those doing caesarean sections. If there were more than seven facilities, seven were randomly selected by computer, with probability of selection proportional to the number of births per year. If there were fewer than seven facilities, all were selected. In each of the selected institutions, we studied all women admitted for delivery during 3 months in institutions with 6000 or fewer expected deliveries per year and during 2 months in those with more than 6000 expected deliveries per year.

Data collection was started in China in October, 2007, and concluded in the Philippines in May, 2008. We obtained written permission from all ministries of health of the participating countries and the directors of the selected facilities. We obtained data for all individuals from medical records and did not identify participants. The Ethics Review Committee of WHO and of each country independently approved the protocol.

Data collection

We collected data for institutions and for individuals. For institutions, data included characteristics of maternal and perinatal care, including the availability of laboratory tests; anaesthesiology resources; services for intrapartum care, delivery, and care of the newborn baby; and presence or absence of basic emergency medical and obstetric care facilities, intensive care units (ICUs), and human and training resources. We gathered data only once to obtain a detailed description of the health facility and its resources for obstetric care. The hospital coordinator completed a form in consultation with the director or head of obstetrics. For individuals, we obtained data from women's medical records to complete a two-page precoded form, summarising obstetric and perinatal events. Data collected included demographic characteristics, maternal risk, current pregnancy, method of delivery, and outcomes (maternal and perinatal) up to hospital discharge. All women giving birth at the facility during the study period were included. Trained staff reviewed the medical records of all women and their

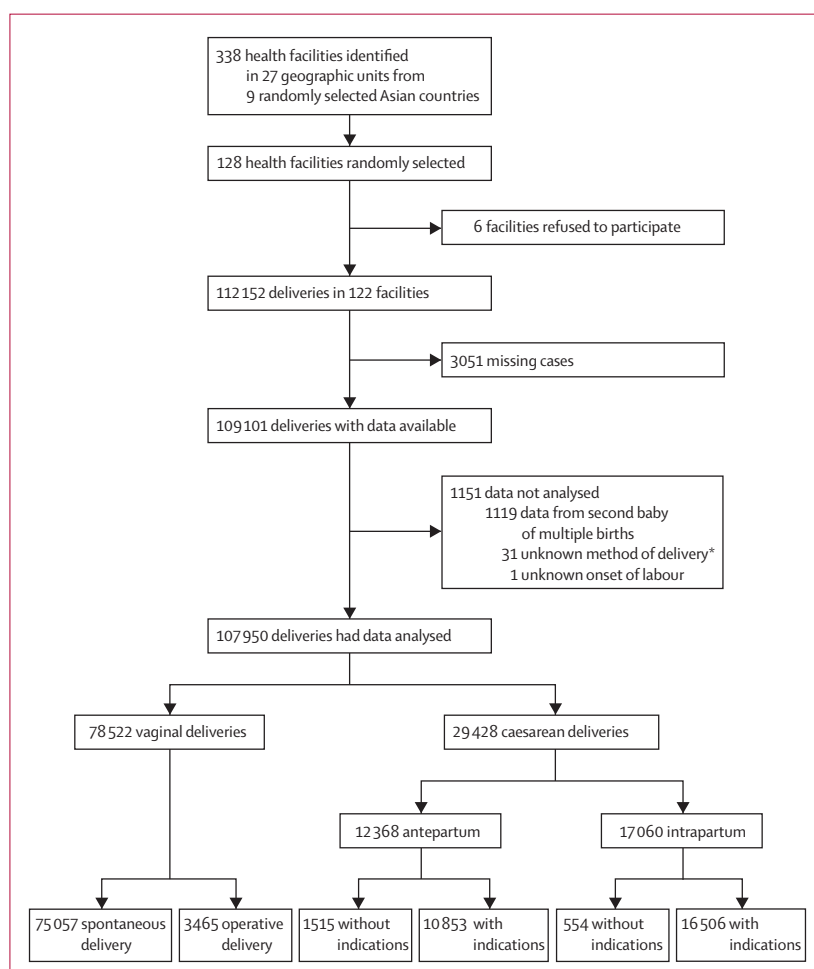


Figure 1: Study profile

*Includes 28 cases of laparotomy for uterus rupture.

	Vaginal delivery		Caesarean section				Total	
	Spontaneous	Operative	Overall	Antepartum without indications	Antepartum with indications	Intrapartum without indications	Intrapartum with indications	
Cambodia	4319 (77.6%)	431 (7.7%)	14.7%	2 (0.04%)	144 (2.6%)	12 (0.2%)	657 (11.8%)	5565 (5.2%)
China	7649 (52.6%)	179 (1.2%)	46.2%	1356 (9.3%)	2855 (19.6%)	341 (2.4%)	2161 (14.9%)	14541 (13.5%)
India	19586 (79.3%)	719 (2.9%)	17.8%	16 (0.1%)	892 (3.6%)	48 (0.2%)	3421 (13.9%)	24682 (22.9%)
Japan	2445 (74.1%)	200 (6.1%)	19.8%	2 (0.1%)	457 (13.9%)	0	196 (5.9%)	3300 (3.1%)
Nepal	6447 (75.9%)	323 (3.8%)	20.3%	3 (0.04%)	522 (6.2%)	5 (0.1%)	1189 (14.0%)	8489 (7.9%)
Philippines	10427 (78.4%)	372 (2.8%)	18.8%	5 (0.04%)	1064 (8.0%)	19 (0.1%)	1408 (10.6%)	13295 (12.3%)
Sri Lanka	9900 (65.9%)	526 (3.5%)	30.6%	83 (0.6%)	3021 (20.1%)	29 (0.2%)	1465 (9.8%)	15024 (13.9%)
Thailand	6007 (61.6%)	420 (4.3%)	34.1%	33 (0.3%)	1309 (13.4%)	15 (0.2%)	1961 (20.1%)	9745 (9.0%)
Vietnam	8277 (62.2%)	295 (2.2%)	35.6%	28 (0.2%)	576 (4.3%)	112 (0.8%)	4021 (30.2%)	13309 (12.3%)
Total	75 057 (69.5%)	3465 (3.2%)	27.3%	1515 (1.4%)	10 853 (10.1%)	554 (0.5%)	16 506 (15.3%)	107 950 (100%)

Table 1: Numbers of women by country and method of delivery

babies before discharge from the hospital, and abstracted data daily to their forms for individual data collection. The hospital coordinator supervised data collection, resolving or clarifying unclear medical notes before forms were sent for data entry. Attending staff updated incomplete records before discharge.

We developed a hospital complexity index, summarising an institution's capacity to provide different levels of care, dependent on its ratings for eight categories: building, general medical care, laboratory, anaesthesiology, screening tests, human resources, basic obstetric services, and continuous medical education. We classified hospitals without any of these services or resources as low level (rating score 0), those that had both essential and optional services and resources as high level (rating score 2), and those that did not have some of the optional services or resources, but had all essentials, as medium level (rating score 1). We judged hospitals with a total score of 9 or less of low complexity, those with scores of between 10 and 12 of medium complexity, and those with scores of 13 or more of high complexity. Criteria for data abstraction were defined in the manual of operations, which was available for staff training and monitoring of data quality, keeping to a minimum the need for judgment and interpretation. The manual contained definitions of all terms used and synonyms of medical and obstetric terms, and described questions and precoded corresponding answers.

Statistical analysis

All data were continuously entered by country data managers or hospital coordinators with a web-based system (MedSciNet AB, Stockholm, Sweden) in collaboration with WHO between October, 2007, and May, 2008. We calculated the survey coverage by comparing the number of delivery forms completed during the study period with the total number of deliveries, as independently recorded in the hospital logbooks. We used frequencies to describe methods of delivery for each country and facility characteristics, and

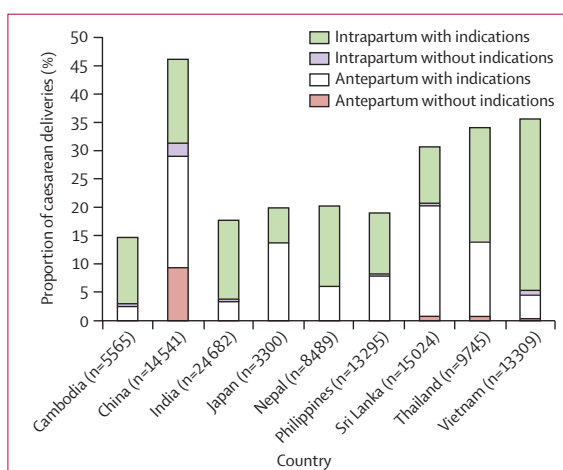


Figure 2: Proportion of caesarean deliveries by four classifications and countries

characteristics of mothers and babies for each group of delivery method. We assessed the association of each maternal outcome of death, admission to ICU, blood transfusion, hysterectomy, and mortality and morbidity index (which was defined as the presence of at least one of: maternal mortality, admission to ICU, blood transfusion, hysterectomy, or internal iliac artery ligation); and perinatal outcomes of perinatal mortality, fetal deaths, neonatal mortality up to hospital discharge, stay in neonatal ICU for 7 days or longer, and perinatal mortality and morbidity index (defined as the presence of perinatal death or stay in neonatal ICU for 7 days or longer), with methods of delivery by use of odds ratios (OR) and 95% CIs.

Univariate analysis was done separately for assessment of the association of methods of delivery and other characteristics of mothers, babies, and facilities individually on each outcome. The crude ORs were always corrected for the clustering effect of the facility. Individual-level and facility-level variables that were significantly associated with the outcome in the univariate

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	Vaginal delivery		Caesarean section				Total (n=107 950)
	Spontaneous (n=75 057)	Operative (n=3465)	Antepartum without indications (n=1515)	Antepartum with indications (n=10 853)	Intrapartum without indications (n=554)	Intrapartum with indications (n=16 506)	
General characteristics							
Marital status (single)	4973 (6.6%)	196 (5.7%)	4 (0.3%)	425 (3.9%)	7 (1.3%)	552 (3.3%)	6157 (5.7%)
Maternal age (years)							
≤16	550 (0.7%)	19 (0.6%)	0	22 (0.2%)	1 (0.2%)	63 (0.4%)	655 (0.6%)
17–34	68 713 (91.6%)	3091 (89.2%)	1378 (91.0%)	8841 (81.5%)	500 (90.3%)	14 772 (89.5%)	97 295 (90.2%)
≥35	5780 (7.7%)	355 (10.2%)	137 (9.0%)	1989 (18.3%)	53 (9.5%)	1667 (10.1%)	9981 (9.3%)
Primigravida	32 479 (43.3%)	1948 (56.2%)	671 (44.3%)	3372 (31.1%)	251 (45.3%)	7743 (46.9%)	46 464 (43.0%)
Last pregnancy							
Last baby birthweight (previous delivery [g])							
<1500	904 (1.2%)	91 (2.6%)	1 (0.1%)	161 (1.5%)	0	93 (0.6%)	1250 (1.2%)
≥1500–2499	9292 (12.3%)	501 (14.5%)	26 (1.7%)	1486 (13.7%)	22 (3.9%)	1654 (10.0%)	12 981 (12.0%)
≥2500–3999	63 900 (85.2%)	2808 (81.1%)	1383 (91.3%)	8664 (79.8%)	510 (92.1%)	14 040 (85.1%)	91 305 (84.6%)
≥4000–4499	873 (1.2%)	56 (1.6%)	95 (6.3%)	457 (4.2%)	21 (3.8%)	621 (3.8%)	2123 (2.0%)
≥4500	69 (0.1%)	6 (0.2%)	9 (0.6%)	83 (0.8%)	1 (0.2%)	87 (0.5%)	255 (0.2%)
Caesarean delivery in the last pregnancy	1034 (1.4%)	127 (3.7%)	43 (2.8%)	3996 (36.8%)	21 (3.8%)	3347 (20.3%)	8568 (7.9%)
Complications during current pregnancy							
Prelabour rupture of membranes	8388 (11.2%)	425 (12.3%)	129 (8.5%)	732 (6.7%)	112 (20.2%)	3100 (18.8%)	12 886 (11.9%)
Pregnancy-induced hypertension	2158 (2.9%)	222 (6.4%)	38 (2.5%)	838 (7.7%)	16 (2.9%)	845 (5.1%)	4117 (3.8%)
Pre-eclampsia	1096 (1.5%)	134 (3.9%)	7 (0.5%)	543 (5.0%)	1 (0.2%)	517 (3.1%)	2298 (2.1%)
Eclampsia	183 (0.2%)	36 (1.0%)	1 (0.1%)	73 (0.7%)	0	96 (0.6%)	389 (0.4%)
Breech or other non-cephalic presentation	805 (1.1%)	725 (20.9%)	0	1637 (15.1%)	0	2172 (13.2%)	5339 (5.0%)
Referred for complication related to pregnancy or delivery	13 719 (18.3%)	698 (20.1%)	100 (6.6%)	2781 (25.6%)	49 (8.8%)	2828 (17.1%)	20 175 (18.7%)
Data are number (% of country total) for method of delivery columns and (% of study total) for total column.							
Table 2: Characteristics of women classified by method of delivery							

Data are number (% of country total) for method of delivery columns and (% of study total) for total column.

Table 2: Characteristics of women classified by method of delivery

analysis ($p < 0.05$) were successively included in a multivariate model. In the multivariate analysis, each model of the outcomes of interest included method of delivery defined in six categories: vaginal spontaneous (reference category); operative vaginal; antepartum caesarean delivery with and without indications; and intrapartum caesarean delivery with and without indications, and the variables found to be significant in the univariate analyses. Variables for both individuals and facilities that did not show significance at the 5% level in the resulting model were then removed one by one until all remaining variables were significant. Gestational age was always included irrespective of statistical significance when we considered perinatal outcomes. For all models fitted, we used generalised linear and latent mixed models (GLLMM) for the multilevel analysis by using procedure GLIMMIX in SAS (version 9.1). The procedure accounted for clustering effects within facilities. The multilevel analysis was also done for perinatal outcomes in subgroups of fetal presentations (cephalic, breech, and others). Risks of maternal and perinatal outcomes associated with method of delivery were presented by adjusted ORs with corresponding 95% CIs.

Role of the funding sources

The sponsors of the study had no role in study design, data collection, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the study profile. In the nine randomly selected Asian countries, we selected 27 geographical units. There were 388 health facilities in these units, of which we randomly selected 128 facilities. Six facilities declined to participate, leaving 122 in the survey. 112 152 deliveries were reported in these 122 facilities during the study period. Our survey collected data for 109 101 deliveries (97% coverage). We checked the data quality by randomly selecting 5% of the records and asking the hospital coordinators to extract the same data from medical records again, and compared these data with the original record. The mean agreement was 92% (range 81–98). We excluded 31 patients with unknown method of delivery, 1119 second babies of multiple births, and one with unknown onset of labour, leaving 107 950 analysable deliveries.

China, India, and the Philippines had the highest numbers of facilities (seven per province), whereas India, Sri Lanka, and China had the highest numbers of deliveries (table 1). 84 (69%) facilities were in urban areas and 104 (85%) were in the public system. Most of the hospitals were secondary or tertiary referral hospitals; however, 83 (68%) had low facility complexity resources. 87 (71%) hospitals had anaesthesiology resources 24 h per day in the facility, and in 75 (62%), financial incentives were offered for undertaking caesarean section. The overall rate of caesarean section of this survey in Asia was 27·3%. China had the highest overall rate followed by Vietnam, Thailand, and Sri Lanka (table 1). China also had the highest rate of caesarean section without indication (11·7%), followed by Vietnam (1·0%), Sri Lanka (0·8%), and Thailand (0·5%; table 1 and figure 2). Since the pattern of caesarean section was substantially different in China from the other countries (figure 2), we undertook a sensitivity analysis for the maternal and newborn outcomes, excluding data from China. We noted no changes to the results (data not shown), and the results are reported for all nine countries together. The commonly reported indications for caesarean section were previous caesarean section (24·2%), cephalopelvic disproportion (22·6%), fetal distress (20·5%), and breech or other abnormal presentation (12·5%).

Table 2 shows characteristics of women by method of delivery. We noted a higher proportion of single marital status and very low birthweight infant (<1500 g) in women who delivered vaginally than in those who delivered by caesarean section. Delivery by caesarean section in the last pregnancy was more common in women who delivered by caesarean section than in those who had vaginal delivery (table 2). The rates of complications during current pregnancy were similar between women who delivered vaginally or by caesarean section (table 2).

For maternal mortality, only operative vaginal delivery had significantly increased risk compared with spontaneous vaginal deliveries (adjusted OR 3·1, 95% CI 1·5–6·5). The risk for antepartum caesarean section without indication could not be estimated because there were no maternal deaths in this group. Operative vaginal delivery and all types of caesarean section had significantly increased risk of admission to ICU compared with spontaneous vaginal delivery (table 3). Operative vaginal delivery, antepartum caesarean section with indications, and intrapartum caesarean section with and without indication had significantly increased risks of blood transfusion compared with spontaneous vaginal delivery (table 3). The risk of hysterectomy was increased in mothers who delivered by operative vaginal delivery, antepartum caesarean section with indications, and intrapartum caesarean section with indications (table 3). We recorded no cases of hysterectomy in women who delivered by antepartum caesarean section without indications and intrapartum caesarean section without indications, so

	n/N (%)	Adjusted OR (95%CI)
Death*		
Spontaneous (reference)	53/75 057 (0·1%)	1
Operative vaginal delivery	9/3465 (0·3%)	3·1 (1·5–6·5)
Antepartum CS without indications	0/1515	..
Antepartum CS with indications	11/10 853 (0·1%)	1·1 (0·5–2·3)
Intrapartum CS without indications	1/554 (0·2%)	4·8 (0·6–36·0)
Intrapartum CS with indications	23/16 506 (0·1%)	1·6 (0·9–2·8)
Admission to ICU†		
Spontaneous (reference)	442/75 057 (0·5%)	1
Operative vaginal delivery	76/3465 (2·0%)	2·4 (1·8–3·3)
Antepartum CS without indications	5/1515 (0·3%)	9·9 (3·8–25·8)
Antepartum CS with indications	391/10 853 (3·6%)	42·8 (34·5–53·1)
Intrapartum CS without indications	35/554 (6·2%)	67·0 (42·0–106·7)
Intrapartum CS with indications	1489/16 506 (9·0%)	55·7 (47·1–65·8)
Blood transfusion‡		
Spontaneous (reference)	785/75 057 (1·0%)	1
Operative vaginal delivery	78/3465 (2·3%)	2·1 (1·6–2·8)
Antepartum CS without indications	3/1515 (0·3%)	0·8 (0·3–2·6)
Antepartum CS with indications	352/10 853 (3·2%)	4·1 (3·4–4·8)
Intrapartum CS without indications	7/554 (1·4%)	3·9 (1·8–8·5)
Intrapartum CS with indications	541/16 506 (3·3%)	4·7 (4·1–5·3)
Hysterectomy§		
Spontaneous (reference)	28/75 057 (0·04%)	1
Operative vaginal delivery	4/3465 (3·3%)	2·8 (0·9–7·9)
Antepartum CS without indications	0/1515	..
Antepartum CS with indications	35/10 853 (0·3%)	6·9 (4·1–11·6)
Intrapartum CS without indications	0/554	..
Intrapartum CS with indications	37/16 506 (0·2%)	5·8 (3·5–9·6)
Maternal mortality and morbidity index¶		
Spontaneous (reference)	1215/75 057 (1·6%)	1
Operative vaginal delivery	146/3465 (4·2%)	2·1 (1·7–2·6)
Antepartum CS without indications	9/1515 (0·6%)	2·7 (1·4–5·5)
Antepartum CS with indications	744/10 853 (6·9%)	10·6 (9·3–12·0)
Intrapartum CS without indications	40/554 (7·2%)	14·2 (9·8–20·7)
Intrapartum CS with indications	1947/16 506 (11·8%)	14·5 (13·2–16·0)

OR=odds ratio. CS=caesarean section. ICU=intensive care unit. *Adjusted for malaria, severe anaemia, other medical disorders, any condition suggesting HIV/AIDS, pre-eclampsia, eclampsia, suspected fetal growth impairment, vaginal bleeding in second half of pregnancy, and referred for complication related to pregnancy or delivery. †Adjusted for maternal age, year of education, birthweight, HIV, chronic hypertension, cardiac/renal diseases, malaria, severe anaemia, other medical disorders, prelabour rupture of membranes, pregnancy-induced hypertension, pre-eclampsia, eclampsia, vaginal bleeding in second half of pregnancy, referred for complication related to pregnancy or delivery, and country. ‡Adjusted for maternal age, year of education, primiparous, birthweight, cervix surgery, chronic respiratory disease, sickle-cell anaemia, severe anaemia, other medical diseases, pregnancy-induced hypertension, pre-eclampsia, eclampsia, vaginal bleeding in second half of pregnancy, referred for complication related to pregnancy or delivery, and country. §Adjusted for chronic hypertension, severe anaemia, and vaginal bleeding in second half of pregnancy. ¶Maternal mortality and morbidity index=death or admission to ICU, blood transfusion, hysterectomy, or internal iliac artery ligation. Adjusted for maternal age, year of education, primiparous, birthweight, history of neonatal death or stillbirth, HIV, chronic hypertension, cardiac/renal diseases, sickle-cell anaemia, severe anaemia, other medical disorders, prelabour rupture of membranes, pregnancy-induced hypertension, pre-eclampsia, eclampsia, vaginal bleeding in second half of pregnancy, any antenatal antibiotic treatment, referred for complication related to pregnancy or delivery, and country.

Table 3: Risk of maternal mortality and morbidity by method of delivery

the risk could not be estimated. Operative vaginal delivery and all types of caesarean section were associated with significantly increased risk of maternal mortality and morbidity index compared with spontaneous vaginal

delivery (table 3). Intrapartum caesarean section (both with and without indications) had higher risk of maternal

mortality and morbidity than did antepartum caesarean section (table 3). Deliveries by all types of caesarean section had significantly increased risks of maternal mortality and morbidities except for perineal tears of third and fourth degree, for which as expected caesarean section had a protective effect compared with vaginal delivery (data not shown).

Risk of perinatal mortality was significantly increased compared with spontaneous vaginal delivery in infants born by operative vaginal delivery and intrapartum caesarean section with indications (table 4). Only infants delivered by antepartum caesarean section with indications had a significantly lower risk of fetal death than those born vaginally, whereas risk of fetal death did not differ significantly for other methods of delivery compared with spontaneous vaginal delivery (table 4). For neonatal mortality up to hospital discharge, infants born by operative vaginal delivery, antepartum caesarean section with indications, and intrapartum caesarean section with indications had significantly increased risk compared with spontaneous vaginal delivery (table 4). We recorded no cases of neonatal mortality up to hospital discharge for women delivering by caesarean section without indication, and the risk compared with spontaneous vaginal delivery could not be estimated.

Infants born by operative vaginal delivery and intrapartum and antepartum caesarean section with indications had significantly increased risk of stay for 7 days or longer in neonatal ICU compared with spontaneous vaginal delivery (table 4). Operative vaginal delivery and antepartum and intrapartum caesarean section with indications had significantly increased risk of perinatal mortality and morbidity index (table 4). For breech and other abnormal presentation, caesarean section with indication, either antepartum or intrapartum, significantly reduced risk of perinatal mortality but had significantly increased risk of stay in neonatal ICU for 7 days or longer (table 5).

Discussion

In the 122 Asian health facilities studied, more than one in four women underwent caesarean section. Facilities in China, Sri Lanka, Vietnam, and Thailand had higher aggregated rates of caesarean section than did those in Cambodia, India, Japan, Nepal, and the Philippines. Operative vaginal delivery and caesarean section were independently associated with increased risk of maternal mortality and morbidity index. Caesarean section without a medical indication was associated with increased risk of maternal mortality and morbidity. Caesarean section for breech presentation was associated with improved perinatal outcomes.

With use of a slightly different analytical approach, this survey confirms the findings of the previous survey undertaken in Latin America.⁹ Together these findings provide strong multiregional support for the recommendation of avoiding unnecessary caesarean

	n/N (%)	Adjusted OR (95%CI)
Perinatal mortality*		
Spontaneous (reference)	1072/75 057 (1.4%)	1
Operative vaginal delivery	126/3465 (3.6%)	1.6 (1.2-2.0)
Antepartum CS without indications	1/1515 (0.1%)	0.3 (0.04-2.3)
Antepartum CS with indications	143/10 853 (1.3%)	1.1 (0.9-1.3)
Intrapartum CS without indications	0/554	..
Intrapartum CS with indications	284/16 506 (1.7%)	1.5 (1.2-1.7)
Fetal death†		
Spontaneous (reference)	673/74 945 (0.9%)	1
Operative vaginal delivery	68/3448 (2.0%)	1.1 (0.8-1.6)
Antepartum CS without indications	1/1515 (0.1%)	0.4 (0.06-3.2)
Antepartum CS with indications	61/10 853 (0.6%)	0.6 (0.5-0.8)
Intrapartum CS without indications	0/554	..
Intrapartum CS with indications	130/16 504 (0.8%)	0.8 (0.6-1.0)
Neonatal mortality up to hospital discharge‡		
Spontaneous (reference)	399/73 726 (0.5%)	1
Operative vaginal delivery	58/3320 (1.8%)	2.5 (1.7-3.7)
Antepartum CS without indications	0/1514	..
Antepartum CS with indications	82/10 767 (0.8%)	1.7 (1.3-2.3)
Intrapartum CS without indications	0/580	..
Intrapartum CS with indications	154/16 319 (1.0%)	2.6 (2.1-3.2)
Stay for ≥7 days in neonatal ICU§		
Spontaneous (reference)	1092/75 057 (1.5%)	1
Operative vaginal delivery	110/3465 (3.2%)	1.9 (1.5-2.4)
Antepartum CS without indications	5/1515 (0.3%)	0.4 (0.2-1.1)
Antepartum CS with indications	458/10 853 (4.2%)	2.4 (2.0-2.8)
Intrapartum CS without indications	5/554 (0.9%)	1.3 (0.5-3.1)
Intrapartum CS with indications	436/16 506 (2.6%)	2.4 (2.1-2.8)
Perinatal mortality and morbidity index¶		
Spontaneous (reference)	2117/75 057 (2.8%)	1
Operative vaginal delivery	232/3465 (6.7%)	1.9 (1.6-2.3)
Antepartum CS without indications	6/1515 (0.4%)	0.4 (0.2-0.9)
Antepartum CS with indications	593/10 853 (5.5%)	1.9 (1.7-2.2)
Intrapartum CS without indications	5/554 (0.9%)	0.9 (0.4-2.3)
Intrapartum CS with indications	707/16 479 (4.3%)	2.1 (1.9-2.3)

OR=odds ratio. CS=caesarean section. ICU=intensive care unit. *Adjusted for year of education, birthweight, history of neonatal death or stillbirth, severe anaemia, pre-eclampsia, eclampsia, vaginal bleeding in second half of pregnancy, breech or other non-cephalic presentation, referred for complication related to pregnancy or delivery, induced labour, country, and gestational age. †Adjusted for year of education, birthweight, sickle-cell anaemia, severe anaemia, eclampsia, suspected fetal growth impairment, vaginal bleeding in second half of pregnancy, breech or other non-cephalic presentation, referred for complication related to pregnancy or delivery, and gestational age. ‡Adjusted for year of education, birthweight, breech or other non-cephalic presentation, referred for complication related to pregnancy or delivery, country, and gestational age. §Adjusted for year of education, birthweight, caesarean delivery, chronic hypertension, condyloma acuminatum, other medical disorders, prelabour rupture of membranes, pregnancy-induced hypertension, pre-eclampsia, eclampsia, suspected fetal growth impairment, vaginal bleeding in second half of pregnancy, any antenatal antibiotic treatment, breech or other non-cephalic presentation, referred for complication related to pregnancy or delivery, induced labour, country, and gestational age. ¶Perinatal mortality and morbidity index=perinatal mortality or stay for 7 or more days in neonatal ICU. Adjusted for year of education, birthweight, history of neonatal death or stillbirth, caesarean delivery, chronic hypertension, chronic respiratory disorders, diabetes mellitus, condyloma acuminatum, other medical disorders, prelabour rupture of membranes, pregnancy-induced hypertension, pre-eclampsia, eclampsia, suspected fetal growth impairment, vaginal bleeding in second half of pregnancy, any antenatal antibiotic treatment, breech or other non-cephalic presentation, referred for complication related to pregnancy or delivery, country, and gestational age.

Table 4: Perinatal outcomes for singleton and first child of multiple births by method of delivery

sections. A randomised controlled trial¹⁰ to assess the benefits and risks of caesarean section might not be a realistic approach in view of the immediate and long-term physical and psychological effects of different methods of delivery on the woman and her baby and the lack of agreement between health professionals. In the absence of a randomised trial, we have to rely on observational studies to elucidate various benefits and risks of this operation. Intrinsic risk associated with the caesarean section operation is not easy to separate from the medical and obstetrical indications that lead to the procedure. In the previous survey, the intrinsic risk was investigated by dividing the method of delivery into three categories: vaginal, elective caesarean section, and intrapartum caesarean section with elective caesarean section as a proxy. We identified six categories as described in the results. Assisted vaginal delivery represents a high-risk situation, and combination of such deliveries with spontaneous vaginal deliveries as the reference group might not be appropriate. Second, we noticed that several births that were recorded as elective had an indication for caesarean section. The group with no medical indication therefore is probably a more appropriate group to assess the intrinsic risk associated with this procedure.

The most important finding of the survey is the increased risk of maternal mortality and severe morbidity, which was analysed as a composite outcome (the maternal mortality and morbidity index), in women who undergo caesarean section with no medical indication. The findings for the individual outcomes that make up the composite outcome suggest that the increased risk is mainly attributable to increased admission to ICU and blood transfusion. Although we acknowledge that both ICU admission and blood transfusion depend on the availability of those services and the potentially differing thresholds for giving blood and for admission of women to ICU or referral to higher levels of care, this outcome is nevertheless important.

Quantification of the risk across facilities and countries might not be appropriate because there will be differences from setting to setting. However, the results show that women receiving the operation are at increased risk of adverse events. We can therefore conclude that women who choose to have caesarean section, and the doctors who recommend the operation with no medical indication, have to make that decision with the understanding of the increased risks. The procedure also costs more than does a vaginal birth. In the UK, each additional vaginal birth instead of caesarean section would save more than £1200.¹¹ The costs include actual direct cost, use of operating theatre facilities, use of anaesthesia, human resources (theatre nurses, anaesthesiologists), and use of postoperative facilities. In low-income countries with an unmet need for caesarean section, the issue of this procedure being a resource drain is even more important than it is in high-income countries. If this operation is limited to medical

	n/N (%)	Adjusted OR (95%CI)
Cephalic presentation		
Perinatal mortality*		
Spontaneous (reference)	914/74 250 (1.2%)	1
Operative vaginal delivery	38/2740 (1.4%)	2.0 (1.4–2.9)
Antepartum CS without indications	1/1515 (0.1%)	0.3 (0.05–2.5)
Antepartum CS with indications	115/9213 (1.3%)	1.3 (1.0–1.7)
Intrapartum CS without indications	0/554	..
Intrapartum CS with indications	206/14 333 (1.4%)	1.9 (1.6–2.2)
Fetal death†		
Spontaneous (reference)	557/74 146 (0.8%)	1
Operative vaginal delivery	21/2737 (0.8%)	1.6 (1.0–2.6)
Antepartum CS without indications	1/1515 (0.1%)	0.5 (0.06–3.5)
Antepartum CS with indications	50/9213 (0.5%)	0.9 (0.6–1.2)
Intrapartum CS without indications	0/554	..
Intrapartum CS with indications	85/14 332 (0.6%)	1.1 (0.8–1.4)
Neonatal mortality up to hospital discharge‡		
Spontaneous (reference)	357/73 111 (0.5%)	1
Operative vaginal delivery	17/2705 (0.6%)	2.5 (1.5–4.4)
Antepartum CS without indications	0/1514	..
Antepartum CS with indications	65/9145 (0.7%)	2.0 (1.4–2.7)
Intrapartum CS without indications	0/554	..
Intrapartum CS with indications	121/14 214 (0.9%)	3.1 (2.4–4.0)
Stay for ≥7 days in neonatal ICU§		
Spontaneous (reference)	1067/74 250 (1.4%)	1
Operative vaginal delivery	72/2740 (2.6%)	2.3 (1.7–3.0)
Antepartum CS without indications	5/1515 (0.3%)	0.4 (0.2–1.1)
Antepartum CS with indications	381/9213 (4.1%)	2.4 (2.0–2.8)
Intrapartum CS without indications	5/554 (0.9%)	1.3 (0.5–3.2)
Intrapartum CS with indications	346/14 333 (2.4%)	2.4 (2.1–2.8)
Perinatal mortality and morbidity index¶		
Spontaneous (reference)	1938/74 250 (2.6%)	1
Operative vaginal delivery	108/2740 (3.9%)	2.2 (1.8–2.8)
Antepartum CS without indications	6/1515 (0.4%)	0.4 (0.2–1.0)
Antepartum CS with indications	489/9213 (5.3%)	2.1 (1.8–2.4)
Intrapartum CS without indications	5/554 (0.9%)	1.0 (0.4–2.4)
Intrapartum CS with indications	541/14 333 (3.8%)	2.3 (2.0–2.5)

(Continues on next page)

indications and unnecessary use is avoided, resources will be used for a need and will not be taken from other parts of the health system.

The situation regarding potential risk of caesarean section is less clear when the woman has medical or obstetric indications for the procedure. We made several statistical adjustments to try to separate the possible effect of caesarean section in the maternal and perinatal outcomes. After all adjustments, women with medical indications for the operation had an increased risk of morbidity and mortality. One possible interpretation is that the increased risk results from the interaction between baseline morbidity and the morbidity specific to caesarean section. Alternatively, the statistical adjustment might have been unable to isolate the effect of the baseline morbidity—ie, the observed increased risk of

	n/N (%)	Adjusted OR (95%CI)
(Continued from previous page)		
Breech and other presentations		
Perinatal mortality		
Spontaneous (reference)	158/805 (19.6%)	1
Operative vaginal delivery	88/725 (12.1%)	0.6 (0.4–0.9)
Antepartum CS with indications	28/1637 (1.7%)	0.2 (0.1–0.3)
Intrapartum CS with indications	78/2172 (3.6%)	0.3 (0.2–0.4)
Fetal death**		
Spontaneous (reference)	116/797 (14.6%)	1
Operative vaginal delivery	47/711 (6.6%)	0.5 (0.3–0.7)
Antepartum CS with indications	11/1637 (0.7%)	0.07 (0.03–0.1)
Intrapartum CS with indications	45/2171 (2.1%)	0.2 (0.1–0.3)
Neonatal mortality up to hospital discharge††		
Spontaneous (reference)	42/613 (6.9%)	1
Operative vaginal delivery	41/615 (6.7%)	1.3 (0.7–2.3)
Antepartum CS with indications	17/1619 (1.1%)	0.4 (0.2–0.9)
Intrapartum CS with indications	33/2104 (1.6%)	0.6 (0.3–1.0)
Stay for ≥7 days in neonatal ICU‡‡		
Spontaneous (reference)	25/805 (3.1%)	1
Operative vaginal delivery	38/725 (5.2%)	1.7 (1.0–3.1)
Antepartum CS with indications	77/1637 (4.7%)	2.0 (1.1–3.6)
Intrapartum CS with indications	90/2172 (4.1%)	2.1 (1.2–3.7)
Perinatal mortality and morbidity index§§		
Spontaneous (reference)	179/805 (22.2%)	1
Operative vaginal delivery	124/725 (17.1%)	0.7 (0.5–1.0)
Antepartum CS with indications	104/1637 (6.4%)	0.4 (0.3–0.6)
Intrapartum CS with indications	166/2172 (7.6%)	0.6 (0.4–0.8)

OR=odds ratio. CS=caesarean section. ICU=intensive care unit. *Adjusted for year of education, birthweight of previous baby, history of neonatal death or stillbirth, severe anaemia, pre-eclampsia, eclampsia, vaginal bleeding in second half of pregnancy, referred for complication related to pregnancy or delivery, induced labour, country, and gestational age. †Adjusted for year of education, birthweight of previous baby, sickle-cell anaemia, severe anaemia, eclampsia, suspected fetal growth impairment, vaginal bleeding in second half of pregnancy, referred for complication related to pregnancy or delivery, incentive for caesarean section, and gestational age. ‡Adjusted for year of education, birthweight of previous baby, referred for complication related to pregnancy or delivery, country, and gestational age. §Adjusted for year of education, birthweight of previous baby, previous caesarean delivery, chronic hypertension, diabetes mellitus, condyloma acuminatum, other medical disorders, prelabour rupture of membranes, pregnancy-induced hypertension, pre-eclampsia, eclampsia, suspected fetal growth impairment, any antenatal antibiotic treatment, referred for complication related to pregnancy or delivery, induced labour, country, and gestational age. ¶Perinatal mortality and morbidity index=perinatal mortality or stay for 7 days or more in neonatal ICU. Adjusted for maternal age, year of education, birthweight, cervix surgery, chronic hypertension, chronic respiratory disorders, diabetes mellitus, severe anaemia, condyloma acuminatum, other medical disorders, prelabour rupture of membranes, pregnancy-induced hypertension, pre-eclampsia, eclampsia, suspected fetal growth impairment, vaginal bleeding in second half of pregnancy, any antenatal antibiotic treatment, referred for complication related to pregnancy or delivery, country, and gestational age. ||Adjusted for fistula, eclampsia, vaginal bleeding in second half of pregnancy, referred for complication related to pregnancy or delivery, country, and gestational age. **Adjusted for sickle-cell anaemia, vaginal bleeding in second half of pregnancy, referred for complication related to pregnancy or delivery, and gestational age. ††Adjusted for referred for complication related to pregnancy or delivery, induced labour, and gestational age. ‡‡Adjusted for condyloma acuminatum, prelabour rupture of membranes, vaginal bleeding in second half of pregnancy, any antenatal antibiotic treatment, country, and gestational age. §§Adjusted for birthweight, fistula, prelabour rupture of membranes, eclampsia, vaginal bleeding in second half of pregnancy, referred for complication related to pregnancy or delivery, induced labour, country, and gestational age.

Table 5: Perinatal outcomes for singleton and first child of multiple births by fetal presentation at delivery and method of delivery

mortality and morbidity could be attributed to the baseline conditions that caused the procedure to be undertaken. We detected a similar relation for assisted vaginal deliveries.

Findings from our survey confirm the protective effect of caesarean section on perinatal mortality for cases of breech or other presentations.¹² This result should be considered as additional evidence for strongly recommending avoidance of vaginal deliveries for breech presentations, while promoting the use of external cephalic version for term breech presentation even if the woman is already in labour.¹³

This study has several strengths. First, it is one of the largest observational studies to address the issue of benefits and harms of caesarean section, complementing the earlier surveys undertaken in Latin America^{7,9} and Africa (unpublished). Second, the random selection of two provinces in addition to the capital province, and then random selection of participating facilities with more than 1000 deliveries per year, ensured avoidance of selection bias. A secondary aim of the project was to strengthen the capacity of a network of health facilities in routine data collection and collaborative research. The random selection process was crucial in working with facilities that had not previously participated in research projects. The high data-extraction quality suggested by the random data checks was very encouraging. In several participating countries, including China and India, data were entered online within facilities, which helped with the resolution of data queries. Afghanistan and Pakistan have been added to this network of facilities in 24 countries where the survey has been undertaken, and these 26 countries will implement the next survey that will focus on maternal and neonatal near miss in the next phase of the project in 2010–11.

Our study has some limitations. First, we had information about mortality and morbidities only until discharge from hospital; some outcomes might therefore have been underestimated, especially for women delivering vaginally who are usually discharged earlier than women having caesarean section. The calculated odds ratio might overestimate the risk of caesarean section. Although we had adjusted for many potential confounding factors, there might be some other factors that we did not have information about and could not adjust for. Second, data were abstracted from the patients' records. We were not able to confirm the absence of some of the risk factors if they had not been recorded. Third, our survey included only hospitals with caesarean facilities having 1000 or more deliveries every year. The results therefore cannot be generalised to smaller facilities. The results, especially rates of caesarean section, should not be regarded as representative rates and outcomes for entire countries or regions.

In view of the strengths and the limitations, our results are corroborated by other observational studies assessing the risks of caesarean section for mothers¹⁴ and infants from different settings.¹⁵ We conclude that caesarean section should be done only when there is a medical indication to improve the outcome for the mother or the baby. Women and their carers who plan to undertake

caesarean section delivery should discuss the potential risks to make an informed decision if they still wish to have a caesarean delivery.

Contributors

PL, ML, AMG, and JPS coordinated the study. EF participated in the preparatory activities, developing the study materials, and site visits. JV was the lead investigator in the first phase of the project undertaken in Latin America and Africa. In the Asia survey, JV supported the preparatory activities such as modifications in the forms, manuals, and training planning. PL, ML, AMG and JPS planned and undertook the analysis and wrote the report with input from all country investigators and GC (regional coordinator of the Latin American survey). KB-T undertook site visits, training, and contributed to the writing of the report. PR, GY, KChu, MR, NDH, RM, KChe, TR, DEA, ST, NS, MF, HTB, VU, and MJVC contributed to study design, data collection, data analysis, data interpretation, and writing of the report. All authors read and approved the final report.

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Conflicts of interest

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Maternal and fetal mortality and complications associated with cesarean section deliveries in teaching hospitals in Asia

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Abstract

Aim: To compare the mortality, morbidity of emergency and elective cesarean section with vaginal delivery among Asian teaching hospitals

Methods: Hospital based prospective study at 12 centers of 9 countries.

Results: 12 591 vaginal deliveries, 3062 elective and 4328 emergency cesarean section were followed up to 5 days postpartum. Maternal deaths (95% CI) per 1000 births among vaginal deliveries being 0.47 (0.17, 1.03) was not significantly different from 0.31 (0.01, 1.73) of elective cesarean section and both rates were significantly lower than 2.87 (1.53, 4.91) per 1000 births of emergency section. The vaginal delivery group had significantly lower incidences of all major complication except significantly higher chance of secondary operations and non-significantly different risk for endometritis. Corresponding neonatal mortality per 1000 deliveries among the three groups were 7 (5.6, 8.6), 2.2 (0.9, 4.6) and 12.4 (9.3, 16.2) ($P < 0.001$). Vaginal delivery also had higher rates of severe asphyxia and palsy than elective cesarean section.

Conclusion: Maternal complications were increased by cesarean delivery but elective section may reduce neonatal complication.

Key words: cesarean section, maternal complications, neonatal complications, neonatal mortality, vaginal delivery.

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Introduction

For more than two decades, the rates of Cesarean Section (CS) have been increasing in both developed and most developing countries despite the World Health Organization's recommendation in 1985 which stated 'There is no justification for any region to have cesarean section rates higher than 10–15%'.¹

Although intended to reduce maternal and fetal morbidity and mortality² rising rates of CS may, however, increase adverse outcomes and place a considerable burden on health services. Adverse outcomes include wound infection, puerperal sepsis, hemorrhage and blood transfusion, anesthesia, pulmonary embolism, intraoperative trauma and fetal injury in the short term and repeat CS in subsequent pregnancies with additional risks of uterine rupture, excess blood loss, difficulties in delivering the neonate, dense adhesions, placenta accrete and hysterectomy.^{3–7} Cesarean section delivery is intended to reduce maternal and fetal mortality and with high birth rates and the limited obstetric health resources of Asian developing countries, such information is needed on its prevalence and complications for policy makers, care providers and the public before any rational guidelines for good clinical practice with regard to CS can be developed.

CS rates have increased over the past two decades and the global rate has been estimated as 15%⁷ and in Australia from less than 20% in 1993 to 29% in 2004.⁸

Similar increases in CS rates have been observed in many developing countries, however, with considerable variation both within and between countries. In South America, Brazil and Chile head the league table where CS accounts for nearly 40% and 42%, respectively, of births.⁹

The average CS rate in Southern and Eastern Asia is 15.9% with China and Hong Kong SAR with the highest estimate rates of 40.5% and 27.4%, respectively.⁷ CS rates in Nepal and Cambodia have been reported as low as 1% which are comparable to a number of other least developed countries in Central Africa. In Thailand, the mean CS rate in 1999 was 24.48 and 22% in the general, private and university hospitals, respectively.¹⁰ In Nepal, between 1997 and 2002, the overall CS rate was 9.4% in a university teaching hospital.¹¹ Rates in a maternity hospital in Mumbai, India increased from 1.9% to 16% between 1957 and 1998 with the greatest increase in the last decade.¹² In a survey of 30 medical colleges and teaching hospitals in India, it was found that the overall rate increased from 21.8% in 1993–1994 to 25.4% in 1998–1999.¹³ CS rates in

the private sector in Madras(Chennai) between 1997 and 1999 have been reported as high as 47%.¹⁴

Apart from the rates quoted in these reviews, there has been little regional information from developing countries in Southern and Eastern Asia on the morbidity, mortality and economic consequences of these rising rates of CS. With high birth rates in most of these countries and limited health resources, such information is needed for policy makers, healthcare providers and the public before decisions can be made on strategies to reduce the rates without compromising maternal and neonatal morbidity and mortality statistics.

With this in mind, the WHO's Special Programme on Research, Development, and Research Training in Human Reproduction initiated a multicenter study involving 12 medical schools and research institutes in nine Southern and Eastern Asian developing countries. The objectives of the study were to compare the mortality, morbidity and the economics of emergency and elective CS with vaginal delivery.

This paper will focus on the morbidity and mortality aspects and a subsequent paper will address the economic issues.

Materials and Methods

Study design

This was a prospective study collecting data from women and their new born infants who were delivered at and residing in proximity to the study hospitals. Data were collected at delivery and on the second and fifth days following delivery. The protocol was approved by the institute's ethical review board of each hospital as well as the Scientific and Ethical Review Group of the World Health Organization Special Programme of Research, Development and Research Training on Human Reproduction. Data were collected during September 2001 to September 2004.

Eligible criteria included all women delivered in the study hospitals, who could be followed up until the fifth day postpartum. Consecutive eligible delivery cases were identified in the labor rooms and postpartum ward by nursing staff and the subjects invited to participate in the study. In cases of elective (planned) CS, informed consent was obtained prior to delivery or as soon as reasonable after delivery. In cases of emergency CS, admission to the study and informed consent was obtained as soon as reasonable after delivery. In subjects with vaginal delivery, informed consent was obtained and admission to the study performed as soon as reasonable after delivery.

Table 1 General statistics of participating centers

County, city	No. Hospitals involved (specialist maternity hospital)	No. Deliveries/year	No. Neonatal beds	No. Obstetricians
Bangladesh, Dhaka	1 (1)	7 500	20	24
China, Chengdu	3 (1)	2 830	17	33
Indonesia, Medan	3 (3)	7 191	65	50
Indonesia, Padang	1 (0)	2 203	54	15
Mongolia, Ulaanbataar	1 (1)	6 119	107	69
Myanmar, Yangon	1 (1)	8 549	250	78
Nepal, Kathmandu	1 (0)	2 679	10	3
Thailand, Hat Yai	1 (0)	2 684	37	22
Thailand, Khon Kaen	1 (0)	3 500	56	22
Sri Lanka, Colombo	1 (1)	5 375	20	4
Vietnam, Hanoi	1 (1)	9 731	60	80
Vietnam, Ho Chi Minh City	1 (1)	25 009	70	70

Case eligibility was confirmed by the principal investigator(s) in each hospital who also reviewed potential cases on a daily basis. For surveillance of complications, a clinical check list on discharge from hospital was used. By this system, all complications of delivery within 48 h were detected at the hospital. Using a similar check list, all CS patients and sample of patients with vaginal deliveries were followed-up at the hospital or at home within five days. A surveillance system was also set up to identify patients who return to the hospital for any reason within six weeks of delivery. In all centers, causes of death and complication were coded using ICD10 and the operative procedures coded with ICD9-CM. This information was checked by the local principal investigators who had attended a series of investigator meeting prior to and during data collection. With the afore-mentioned check list and criteria, important complications were detected and used in statistical analysis.

The sample size calculation was based on using 95% confidence interval and 80% power. Initial assumptions were an estimated rate of 5% of complications in the vaginal delivery group and 10% among the CS group and the proportion of CS cases to be 20%. With these assumptions, 1092 vaginal deliveries, 273 elective and 273 emergency CS are required. However, as the speed of recruitment varied considerably among countries, it was decided to pool all data from all study centers.

Data coding, monitoring and verification were carried out by the local investigators as soon as the form arrives from the interviewers. Computerization of data was carried out using a specific data entry program compiled from EpiInfo version 6.04.¹⁵ The data were transferred and analyzed using R statistical package.¹⁶ Descriptive statistics were used. Chi-squared test and

Table 2 Sample size by centre and mode of delivery sorted by elective CS rate

	Vagina	Elective CS	Emergency CS	Total
Medan	1 013	283	449	1 745
Padang	1 034	274	394	1 702
Hat Yai	1 044	205	336	1 585
Khon Kaen	1 091	270	285	1 646
Hanoi	1 100	270	257	1 627
Hochimin City	1 093	273	360	1 726
Chengdu	1 134	298	360	1 792
Dhakha	1 099	272	367	1 738
Colombo	1 080	292	509	1 881
Yangon	1 214	242	373	1 829
Ulaanbataar	1 057	258	447	1 762
Kathmandu	632	125	191	948
Total	12 591	3062	4328	19 981

Fisher's exact test were used to compute the significant difference among groups of deliveries.

Results

Table 1 shows various characteristics of the study hospitals. All were teaching hospitals with residency training programs or the equivalent. The ratio between neonatal beds and number of deliveries increased among non-maternity university hospitals. In total, there were records of 19 981 subjects recruited who gave birth to 19 740 singletons, 109 pairs of twins and 7 sets of triplets. There were 12 591 vaginal deliveries, 3062 elective and 4328 emergency CS.

Table 2 gives the sample size by centre and by mode of delivery sorted by elective CS rate which was lowest (13%) in Hat Yai and highest in Chengdu (16.6%). Emergency CS rate was lowest (15.8%) in Hanoi and highest in Columbo (27%).

The mean age of the patients undergoing elective CS (29.73 years SD 5.6) was significantly higher than that of the emergency CS group (28.17 SD 5.6 years) and that of the vaginal deliveries (26.71 SD 5.5 years). The youngest patients in the total population were aged 13 and 14 years and the oldest 56 years.

The elective CS group were more likely to have had a previous induced abortion, miscarriage or ectopic pregnancy. Of the 540 women with a previous history of stillbirth, 281 (52%) had a vaginal delivery, 24% an elective and 24% an emergency CS. There was a history of a previous CS in 1527 women of whom 159 had a vaginal delivery (10.4%), 911 (59.7%) an elective CS and the remaining 457 (29.9%) had an emergency CS.

There were 20 maternal deaths occurring in four centers. The maternal mortality rate varied by centre, highest in Hat Yai, Thailand (14.9/1000 births), followed by Medan, Indonesia (14.1/1000), Hanoi, Viet Nam (3.9/1000) and Padang, Indonesia (3.7/1000). Emergency CS was most commonly associated with these rates in these centers. Among the three types of CS, deaths were most common in the emergency group.

The list of main causes of death is shown in Table 3. Eclampsia and other pregnancy induced hypertensive conditions were the most common, contributing 10 of these 20 deaths. Other causes included three deaths from serious infections, recorded as septicemia and puerperal sepsis, one due to postpartum hemorrhage and one due to obstructed labor. Major contributing causes included medical and congenital abnormalities of the mother.

Table 3 Causes of maternal death by ICD code

ICD code	Cause	Frequency
O14.1	Severe pre-eclampsia	3
O15.0	Eclampsia in pregnancy	2
O15.2	Eclampsia in labour	2
O15.2	Postpartum eclampsia	2
A41.8/41.9	Septicemia	2
O85.0	Puerperal sepsis	1
O72.1	Postpartum hemorrhage	1
O71.4	Other obstetric trauma	1
O64.2	Obstructed labour due to malposition and malpresentation	1
O10.1	Pre-existing hypertension complicating pregnancy	1
K76.0	Fatty change of liver	1
K72.9	Hepatic failure	1
O88.1	Amniotic fluid embolism	1
Q21.1	Atrial septal defect	1

In Medan there were five deaths attributed to eclampsia, three to postpartum hemorrhage, two cases of septicemia and postpartum sepsis and one case each of hepatic failure, cardiac failure associated with pre-existing hypertension and gestational hypertension. The five deaths in Hat Yai comprised one case each of amniotic fluid embolism, postpartum hemorrhage, intracerebral hemorrhage, cardiac failure with atrial septal defect and disseminated nocardiosis and AIDS. The deaths in Hanoi and Padang were due to face presentation with obstructed labor and eclampsia, respectively.

The emergency CS group had the highest mortality rate (2.9 per 1000 women), which is statistically higher than the rates among the vaginal delivery and the elective CS groups (0.47 and 0.31 per 1000 women, respectively). The difference between the two latter rates is not statistically significant. None of the maternal deaths was associated with multiple pregnancies.

Maternal complications

Similar to that seen with the maternal mortality rate, there is a consistent ascending order of complications of delivery from vaginal delivery to elective CS and highest at emergency CS as shown in Table 4. These complications include postpartum fever, minor wound infection, peritonitis, urinary problems, hemorrhage needing blood transfusion, hysterectomy, internal iliac artery ligation and anesthetic complications.

Compared to elective CS, emergency CS had a higher rate of major wound problems needing extra hospital stay ($P=0.007$) and secondary operation ($P<0.001$).

Both types of cesarean section had higher rates of postpartum pyrexia than vaginal delivery. Overall, the highest percentages of women with postpartum pyrexia were seen in Kathmandu (10.5% of women), Ho Chi Minh City (8.0%), Yangon (6.4%) and Medan (6.1%). Postpartum urinary tract infections or symptoms were more common in the CS groups and highest in Kathmandu (38.4% of women), Khon Kaen (28.3%) and Dakha (24.1%). Blood transfusion was more commonly reported in the emergency CS group than the elective CS women. In Medan, 7.8% of the women undergoing elective CS and 24.5% of the emergency CS group were transfused and in Padang the corresponding figures were 2.2 and 13.3%.

Internal iliac artery ligation was exclusively performed in both types of CS with more or less equal rates.

Table 4 Maternal complication rates (per 1000 deliveries with 95% CI) among vaginal delivery, elective and emergency CS

	Vaginal delivery	Elective CS	Emergency CS	<i>P</i> value*
Maternal death	0.47 (0.17, 1.03)†	0.31 (0.01, 1.73)†	2.87 (1.53, 4.91)	<0.001
Fever	5.7 (4.5, 7.2)	16.7 (12.4, 21.8)†	18 (14.3, 22.4)†	<0.001
Minor wound infection	21.9 (19.4, 24.6)	84.9 (75.3, 95.4)	116 (106.6, 125.9)	<0.001
Peritonitis	0.2 (0, 0.6)	2.6 (1.1, 5.1)†	4.6 (2.8, 7.1)†	<0.001
Urinary problem	26.1 (23.3, 29)	54.9 (47.1, 63.5)	71.4 (63.9, 79.5)	<0.001
Hemorrhage	13.7 (11.7, 15.8)	21.2 (16.4, 27)	63.5 (56.4, 71.2)	<0.001
Hysterectomy	1.7 (1.1, 2.6)†	3.3 (1.6, 6)†‡	7.2 (4.9, 10.2)‡	<0.001
Internal iliac artery ligation	0 (0, 0.3)	2.9 (1.3, 5.6)†	2.5 (1.3, 4.5)†	<0.001
Anesthetic complication	0 (0, 0.3)	22.5 (17.6, 28.4)†	25.9 (21.4, 31.1)†	<0.001
Major wound infection	3.7 (2.7, 5)†	2 (0.7, 4.3)†	6.5 (4.3, 9.3)	0.007
Second operation	37.7 (34.5, 41.2)	1.3 (0.4, 3.3)†	1.6 (0.7, 3.3)†	<0.001
Endometritis	0.6 (0.2, 1.1)	0.3 (0, 1.8)	1.4 (0.5, 3)	0.143

*Chi-squared test or Fisher's exact test (when >20% of expected value were <5). †,‡Different groups having the same superscript are not significantly different from each other if the overall *P* value is <0.05.

Table 5 Neonatal complication rates (per 1000 deliveries with 95% CI) among vaginal delivery, elective and emergency CS

	Vaginal	Elective CS	Emergency CS	Fisher's exact test <i>P</i> value
Dead	7 (5.6, 8.6)	2.2 (0.9, 4.6)	12.4 (9.3, 16.2)	<0.001
Moderate asphyxia	10.9 (9.2, 12.9)	17.9 (13.5, 23.1)†	25.3 (20.8, 30.5)†	<0.001
Severe asphyxia	4.3 (3.2, 5.6)	1.3 (0.3, 3.3)	8 (5.5, 11.1)	<0.001
Jaundice needing therapy	19 (16.7, 21.6)†	22 (17.2, 27.8)†	30.6 (25.6, 36.2)	<0.001
Anemia needing transfusion	1 (0.5, 1.7)	1 (0.2, 2.8)	1.4 (0.5, 3.1)	0.663
Fracture	0.5 (0.2, 1)	0.6 (0.1, 2.3)	0.2 (0, 1.3)	0.71
Palsy	1.3 (0.7, 2.1)	0.3 (0, 1.8)	0.9 (0.3, 2.4)	0.356
Internal organ damage	0.2 (0, 0.6)	1.3 (0.3, 3.3)†	2.1 (1, 4)†	<0.001
Intracranial hemorrhage	1 (0.5, 1.7)	0 (0, 1.2)	0.7 (0.1, 2.1)	0.25

†Different groups having the same superscript are not significantly different from each other if the overall *P* value is <0.05.

Major wound infections were most commonly seen in the emergency CS group with the highest rates seen in Ho Chi Minh City (6.6% of women), Yangon (5.0%) and Medan (2.6%). On the other hand, second operations were most commonly needed among vaginal delivery group. Endometritis rates were however, not significantly different among different modes of delivery (*P* = 0.142).

Neonatal deaths and complications

There were 163 stillbirths: 149 were singleton, 6 were first and 8 were second twins. The stillbirth rates (SBR) per 1000 births varied from 26.1 in Padang, 18.7 in Medan, 11.5 in Kathmandu, 9.7 in Yangon, 9.5 in Dakha, 6.4 in Columbo, 4.2 in Hanoi, 3.9 in Ulanbatar, 3.1 in Hat Yai, 1.6 in Khon Kaen, 1.1 in Chengdu, and 0 in Hochimin City. This rate was highest in the emergency CS group (12.6%) followed by the vaginal delivery group (7.7%) and lowest in the elective CS group (2.1%) (Chi-squared test, *P* < 0.001).

The number of early neonatal deaths (NND) was 147 (7.4 per 1000 live births), 131 singletons and 7 first and 9 second twins. In all centers except Khon Kaen, Hanoi, Chengdu and Ulanbatar, the rates were highest in emergency CS group. Centers with high neonatal death rates after adjusted for distribution of mode of delivery were Padang and Medan with the rates of 15.0 and 11.8 per 1000 live births, respectively. Centers with early NND rate below 2 per 1000 live birth were Hat Yai, Khon Kaen and Hanoi. Other centers had this rate between these to extreme groups. The different rates among centers were statistically significant (*P* < 0.001).

From the first row of Table 5, it can be seen that death and complication rates in the fetal and neonatal cohort were different from maternal complication rates. Elective CS has lowest early neonatal mortality rate (2.2/1000 births), significantly lower than those in the vaginal delivery (7.0) and the emergency CS group (12.4). Having vaginal delivery group as reference and with adjustment for centre, odds ratio was

0.31 (95% CI = 0.14, 0.67) for elective CS and 1.68 (95% CI = 1.19, 2.37) for emergency CS.

Of important neonatal complications, significantly lowest rates observed in the vaginal group were moderate asphyxia (Apgar score at 5 min of lower than 7 and greater than 4), jaundice needing therapy and internal organ damage. Neonatal complications with the lowest rate in the elective CS was severe asphyxia (Apgar score at 5 min of 4 or lower). The rates for anemia needing transfusion, fracture, palsy and intracranial hemorrhage were not significantly different among groups.

Discussion

This study confirms that in a large number of teaching hospitals in South and East Asia, the rate of various maternal complications generally increases from vaginal delivery to elective and emergency cesarean deliveries. On the fetal side, elective CS demonstrated its benefits by having the lowest early neonatal complication rates followed by vaginal and emergency cesarean delivery.

The findings of high rates of complications have been reported from previous studies, principally in developed countries³⁻⁹ and country and region-specific rates are described by Bertran *et al.*⁷ Most of them have been retrospective medical record reviews where the assessment was confined to time of discharge from the hospital and the definitions of specific types of complication varied from one study to another. Moreover, very few had a comparison group of vaginal deliveries.

However, direct comparisons between CS rates found in our study and those estimated from Demographic and Health Surveys (DHS) are not particularly useful as the DHS used retrospective questionnaires and the study data in this paper are derived from a prospective study in a tertiary care teaching hospital environment.

Eclampsia was the most common cause of maternal death in this study with six cases and a further three cases of maternal death associated with severe pre-eclampsia, suggesting inadequate management of pregnancy-induced hypertension, compared to other classic causes of death such as hemorrhage and infection. The study hospitals were mainly referral centers often with seriously complicated cases. In the community, the range of causes would probably be different.

The overall still birth rate in this study of 7.9/1000 births is much lower than that quoted for South-central Asia (33/1000 births) and 15/1000 births for South-

eastern Asia by WHO.¹⁷ With the exception of the two Indonesian centers in our study, the SBR results are also lower than those cited by WHO for individual Asian countries. The WHO data were compiled from DHS and national surveys and were not confined to tertiary care facilities as in our study and therefore are not strictly comparable.

The relationship between mode of delivery and the outcomes however, should be interpreted with caution. Selection of the mode was not randomly assigned by indication. Emergency cesarean delivery is generally considered as a life saving obstetric procedure and patients who had indications for this procedure would have already been at risk compared to elective cesarean and vaginal delivery and thus prone to higher complication rate.

Elective cesarean delivery is usually performed under controlled conditions. Although indications for elective cesarean delivery may predispose the patients to subsequent complications, with better prepared conditions, the level of predisposition would be lower than in the emergency situation.

From our data, cesarean deliveries, regardless of whether elective or emergency, introduce excess risk of various types such as anesthetic complications, major wound infections and hemorrhage. On one hand, our data suggest that various procedures in cesarean deliveries did exert significant additional risk to the women. This excess risk was not balanced by the reduction in the number of less serious complication specific to vaginal deliveries such as perineal wound infections and secondary operation. On the other hand, the relationship between emergency CS and the complications could be confounded by indication. In other words, a higher risk woman who tended to have bad delivery outcome might be more likely to undergo emergency CS. Moreover, in certain cases, the relationship could even be reverse causal. For example, excessive bleeding might dictate the need for emergency CS. Therefore, the data must be interpreted with caution.

The overall findings on the fetal and neonatal aspects were different from the maternal side in that there were relatively low fetal complication rates observed in the elective cesarean delivery group. Since this procedure is usually indicated in certain high risk pregnancies, had elective section not been carried out, more complications would be expected among the vaginal and emergency cesarean delivery groups.

In conclusion, cesarean deliveries can increase maternal complications significantly. It should be restricted to the high risk patients. Elective section,

when properly chosen, can reduce maternal complication from emergency section and save the fetus and neonate from complications.

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Screening and treating asymptomatic bacteriuria in pregnancy

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Purpose of review

Asymptomatic bacteriuria (ASB) in pregnancy, if left undiagnosed and appropriately treated can lead to acute pyelonephritis in mothers and low birth weight in infants. Urine culture is the gold standard for diagnosing ASB. Unfortunately, urine culture is limitedly available. The present review aims at evaluating performance of various screening tests and effectiveness of antibiotic regimens for ASB.

Recent findings

Positive dipstick test is very likely to have a definitive diagnosis of ASB, whereas a negative result effectively rules out ASB. Available evidences regarding the performance of urine dipstick are still conflicting, it is currently not appropriate to recommend urine dipstick for screening ASB in pregnancy. Choice of antibiotics should be guided by antimicrobial susceptibility testing whenever possible. Nitrofurantoin seems to be antibiotic of choice for ASB in pregnancy. Seven-day regimen of antibiotics gives a better microbiological cure rate but no difference in important clinical outcomes compared with 1-day regimen.

Summary

Dipstick culture is a promising screening test for ASB. Pregnant women with ASB should be treated with 7-day regimen of antibiotics, although 1-day regimen might be appropriate in some settings. More research is needed for identifying appropriate screening tests for ASB.

Keywords

asymptomatic bacteriuria, pregnancy, screening, treatment

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Introduction

Asymptomatic bacteriuria (ASB) is generally defined as the presence of significant bacteriuria without symptoms. The US Preventive Services Task Force (USPSTF) recommends screening for ASB with urine culture in pregnant women at 12–16 weeks gestation or at the first prenatal visit, if later [1]. Unfortunately, urine culture is not widely available. Some more simple methods have been used for screening ASB [2]. A *Cochrane* review shows that antibiotic treatment for ASB in pregnancy is effective in reducing the risk of pyelonephritis and low birth weight [3]. The present review aims at evaluating the screening and treatment of ASB in pregnancy.

Definition of asymptomatic bacteriuria

ASB is defined as the presence of significant bacteriuria without the symptoms of an acute urinary tract infection (UTI). Significant bacteriuria is the presence of two consecutive clear-voided urine specimens both yielding positive cultures of the same uropathogen more than 10^5 colony-forming units (cfu)/ml of urine [4].

Epidemiology of asymptomatic bacteriuria in pregnancy

Recent studies reported the prevalence of ASB in pregnancy to be 2.5–15% [2*,5,6*]. *Escherichia coli* was the most common potentially pathogenic bacteria detected [2*,5,6*]. Risk factors of ASB in pregnancy include history of previous UTI, low socioeconomic status [7] and lower education [8]. A *Cochrane* review showed that antibiotic treatment was effective in clearing ASB [risk ratio (RR) 0.25, 95% confidence interval (CI) 0.14–0.48] and reducing incidence of pyelonephritis (RR 0.23, 95% CI 0.13–0.41). Antibiotic treatment also reduced the incidence of low birth weight (RR 0.66, 95% CI 0.49–0.89) but a difference in preterm delivery was not seen [9].

Diagnosis of asymptomatic bacteriuria in pregnancy

An important issue in the diagnosis of ASB is differentiating contamination from significant bacteriuria.

Urine culture

The original criterion for clinically significant ASB, positive cultures of the same uropathogen more than

10^5 cfu/ml of urine on two consecutive clean-catch specimens, has a 95% probability that the pregnant woman has true bacteriuria. The detection of more than 10^5 cfu/ml in single-voided midstream urine is accepted as a more practical and adequate option, although there is only an 80% probability the woman has true bacteriuria [10]. Urine culture is still the gold standard and the test of choice for detecting ASB. It is time-consuming, 24–48 h to obtain result, and also requires a microbiology laboratory with qualified staff. It is therefore not possible for urine culture to be a universal screening test for all levels of healthcare centers, especially in developing countries where only limited laboratory facilities and experienced staff are available [11].

Many screening tests for ASB are available. The tests include urine Gram stain, microscopic urinalysis, urine dipsticks, dipslide urine cultures, bioluminescence assay, etc. An ideal screening test should be simple, rapid, sensitive, specific and not too expensive so that it can be implemented in all settings. The decision about the test to screen ASB in pregnancy is a balance between the performance of the test and cost of screening.

Dipslide culture

The dipslide, a rapid screening test, is simpler to perform and can be applied as an office screening test. The device consists of a plastic paddle coated on both sides with agar media, one side for the detection of Gram-negative organisms (coated with MacConkey agar) and the other side supports the growth of all organisms (coated with cysteine-lactose-electrolyte-deficient agar). The dipslide is inoculated by dipping the agar-coated slides into the urine specimen, enough to wet both agar surfaces and incubated for 18–24 h at 35°C. The colony counts of the Uricult (Lifesign LLC, Somerset, New Jersey, USA) are determined using a color chart. This method cannot identify the specific species of bacteria isolated. Once significant growth is detected, standard urine cultures have to be done for species identification [12]. The test results can be read directly by physicians or paramedical personnel without waiting for laboratory responses. There is also the potential advantage of directly culturing a freshly voided urine sample, eliminating the risk of potential overgrowth of commensal flora during transport to the laboratory [13]. In this respect, it is well known that leaving urine specimens at room temperature for a prolonged period of time may modify the final counts of microorganisms. A proven accurate dipslide test would be of greater value where delays between the clinics and the laboratory are either unavoidable, unpredictable, or both, and where facilities for refrigeration are unavailable [14]. In addition, it could contribute to reducing the costs of testing women for ASB and would be very suitable for settings in which healthcare resources in terms of laboratory and trained personnel are limited [13].

There are studies evaluating the diagnostic performance of dipslide test as a more feasible alternative test to urine culture [2*, 15–17]. A recent published study of diagnostic tests confirmed the ability of dipslide tests in screening ASB during pregnancy. The prevalence of ASB was 15%, and *E. coli* was the most prevalent organism. The authors found that the dipslide had high accuracy; the likelihood ratio for a positive dipslide test was 225 (95% CI 113–449), increasing the probability of ASB to 98%. Conversely, the likelihood ratio for a negative dipslide test was 0.02 (95% CI 0.01–0.05), reducing the probability of bacteriuria to less than 1%. In addition the tests had advantages regarding their use. They concluded that dipslide should be considered as valid alternative to the standard culture. The conclusions also suggested that a pregnant woman with a positive dipslide test is very likely to have a definitive diagnosis of ASB, whereas a negative result effectively rules out the presence of bacteriuria [2*]. However, this was an ancillary study within a trial comparing single-day with 7-day therapy in treating ASB [6*]. The authors suggest having further research in more pragmatic conditions before recommending the dipslide as an office-screening test [2*].

Urine dipstick

Urine dipstick tests with individual and combination components mainly of leukocyte esterase and nitrite are the other potential tests for rapid diagnosis of ASB during pregnancy. The tests are easy to perform and do not need a laboratory or trained laboratory personnel. The results of the dipstick test are instant whereas the standard culture takes 24–48 h for definitive diagnosis. There are reports evaluating the performance of urine dipstick for rapid diagnosis of ASB [18–23]. The results of these primary studies are conflicting.

In Garingalo-Molina's systematic review [24], five studies using urine dipsticks showed generally low sensitivity, variable specificity, positive predictive and negative predictive values (NPVs). None recommended the tests as sufficient screening method. However, a more recent meta-analysis of the accuracy of the urine dipstick to rule out a urine infection also included studies of pregnant women [25]. Ten studies in pregnancy with both symptomatic bacteriuria and ASB were included in the subgroup analyses of diagnostic performance of nitrites on urine dipsticks. The accuracy of nitrites was concluded high in pregnant women with a diagnostic odds ratio (95% CI) of 165 (73–372) and that a negative test for both leukocyte esterase and nitrites could rule out UTIs in asymptomatic pregnant women. Positive results, however, need confirmation. If positive results are proven, it will be useful in follow-up of patients after treatment of UTI. This is useful in poor resource settings especially in the third world where there is lack of trained personnel and equipment for urine culture [25]. As available

evidences are still conflicting, it is not appropriate to recommend urine dipstick as a screening test for ASB in pregnancy.

Other tests

Performance of the other rapid screening tests, that is, urine Gram stain, microscopic urinalysis, bioluminescence assays, etc. for detecting ASB in pregnant women were also reported in various settings [26–30]. A report from India evaluating Gram's staining of uncentrifuged urine, pus cell count, compared against urine culture. Gram's stain of the uncentrifuged urine had a sensitivity and NPV of 85.1% and 98.8%, respectively. Pus cell count was the least sensitive [26]. Performance of enhanced urinalysis (uncentrifuged urine white blood cell count/ml plus Gram stain) in detecting ASB in obstetric patients was evaluated by a study from Turkey. Clean-catch midstream urine specimens were collected from 250 consecutive asymptomatic pregnant women, a prevalence of ASB was 4%. The sensitivity and specificity of enhanced urinalysis were found to be 50.0 and 96.7%, respectively [31]. Simple urinalysis and urine culture were performed on 774 pregnant women in Thailand. Simple urinalysis had a sensitivity of 18.4, a specificity of 97.2%, 45.7% positive predictive value, 90.4% NPV and 88.4% accuracy in detecting ASB. The authors concluded that because of its low sensitivity and the possible consequences of ASB, simple urinalysis should not be used as a screening test for ASB in pregnancy [32]. An evaluation of bioluminescence assay compared with standard culture as a screening test for the detection of ASB in pregnancy was conducted in 1000 pregnant women in Austria. Bioluminescence screening had 93% sensitivity, 78% specificity and 99% predictive accuracy for negative results. The authors concluded that bioluminescence assay was an effective, time-saving and labor-saving but questionably cost-effective method for the detection of bacteriuria in pregnancy [30]. Evidences from these reports do not support their uses in screening ASB in pregnancy. However, some of these tests are still widely used because they are easy to perform and produce results rapidly.

Treatment of asymptomatic bacteriuria in pregnancy

Many antenatal guidelines include routine screening and treatment for ASB in pregnancy as recommended by American College of Obstetrics and Gynecology (ACOG), Infectious Diseases Society of America (IDSA) and USPSTF [33–35].

Rationale for treatment of asymptomatic bacteriuria in pregnancy

A recent *Cochrane* review showed that antibiotic treatment was effective in clearing ASB (RR 0.25, 95% CI 0.14–0.48) and reducing the incidence of pyelonephritis (RR 0.23, 95% CI 0.13–0.41). Antibiotic treatment also reduced the incidence of low birth weight (RR 0.66, 95% CI 0.49–0.89) but a reduction in preterm delivery was not observed (RR 0.37; 95% CI 0.10–1.36) [9].

Selection of antibiotics

The most common pathogen in ASB in pregnant women is *E. coli*. Other common uropathogens include *Klebsiella pneumoniae*, *Proteus mirabilis*, *Streptococcus* group B, *Enterococcus* and *Staphylococcus saprophyticus* [2*,6*]. Various antibiotics are available for the treatment of ASB in pregnancy as summarized in Table 1. Commonly used antibiotics are ampicillin (pivampicillin), amoxicillin, trimethoprim, sulfonamide and nitrofurantoin [36]. Antibiotics chosen for the treatment of ASB should have high efficacy, low resistance rate and good maternal and fetal outcomes. As *E. coli* is the most common pathogen in ASB in pregnancy, empirical antimicrobial agent for initial treatment should be considered. Unfortunately, up to 40% of isolated *E. coli* are resistant to ampicillin and sulfonamides [37]. Ampicillin and sulfonamides are therefore not recommended for empirical treatment in areas where *E. coli* resistance is common. Nitrofurantoin has a relatively low level of resistance among community-acquired uropathogens due to its multiple mechanisms of action. However, nitrofurantoin may cause hemolysis in glucose-6-phosphate dehydrogenase deficient patients and should be used with caution especially in high

Table 1 Common antibiotics for asymptomatic bacteriuria in pregnancy

Type of antibiotics	Advantages and disadvantages
1. Amoxicillin	No evidence of teratogenic effect High resistance rates
2. Cephalosporin	No evidence of teratogenic effect Not active against <i>Enterococcus</i> spp.
3. Nitrofurantoin	No evidence of teratogenic effect, few or no changes in bacterial resistance rates, covers <i>E. coli</i> and <i>Enterococcus faecalis</i> but not active against <i>Proteus</i> and <i>Pseudomonas</i> spp., may cause hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency
4. Trimethoprim-sulfamethoxazole	High resistance rates, trimethoprim is associated with neural tube and other birth defects when using in the first trimester, sulfonamides should be avoided after 32 weeks' gestation as it could cause severe jaundice leading to kernicterus, acute hemolytic anemia in newborns with G6PD deficiency
5. Fosfomycin	Single dose therapy is as effective as multiple doses of other antibiotics, low incidence of resistance <i>E. coli</i> , does not cover <i>S. saprophyticus</i> , there is limited experience for using in pregnancy

prevalence areas [38]. Cephalosporin is another alternative if there is bacterial resistance to first line drugs. Cephalexin is an oral cephalosporin that is most widely used in pregnancy [39]. However, cephalosporin is not effective for *Enterococcus* spp. [40]. Fosfomycin, a derivative of phosphonic acid, can also be used to treat lower UTI. A randomized trial comparing single dose of fosfomycin with 7–10 day course of nitrofurantoin, norfloxacin, co-trimoxazole found no differences of effectiveness in treating uncomplicated lower UTI [41]. However, caution is advocated as there is limited experience for using in pregnancy [36]. The choice of antibiotics should be guided by antimicrobial susceptibility testing whenever possible, but this decision is becoming more difficult because of increasing rates of antimicrobial resistance to commonly prescribed antibiotics.

Duration of treatment

A *Cochrane* systematic review of duration of treatment for ASB during pregnancy that was updated in 2006 found that the 4–7 day regimen is not more effective than 1-day or single dose regimen in term of bacteriological cure rate. A recent WHO multicenter randomized noninferiority trial reported that 1-day regimen of nitrofurantoin is significantly less effective than a 7-day regimen in treating women with ASB [6^{*}]. The bacteriological cure rates for 7-day and 1-day regimen were 86.2 and 75.7% respectively. The cure rate difference was 10.5% (95% CI 16.1, 4.9%). Mean birth weight and mean gestational age at delivery were statistically significantly lower in the 1-day regimen group (3159g compared with 3059g; mean difference 100; 95% CI 181, 18 and 38.7 weeks compared with 38.4 weeks; mean difference 0.3; 95% CI 0.7 and 0.05, respectively). However, there is no difference between 7-day and 1-day regimen for the outcomes of symptomatic UTI, preterm delivery, adverse effects and low birth weight. This marginal but statistically significant improvement in bacteriological cure with the 7-day regimen was debated to be balanced against the advantages of the 1-day regimen. As the 1-day regimen was not associated with increased adverse perinatal outcomes, it may be considered to be as effective as the 7-day regimen. In situations when compliance and cost are problematic, a 1-day antibiotic treatment could be beneficial, although a 7-day regimen is preferable if feasible [42]. However, in developing countries where urine culture is usually very limited and follow-up urine culture after treatment until negative is not practical we may need the most effective regimen with acceptable adverse effects at affordable cost of 7-day regimen of nitrofurantoin [43].

Conclusion

ASB is quite common in pregnancy. All pregnant women should be routinely screened and appropriately treated for ASB. Urine culture is currently the gold standard for

detecting ASB during pregnancy. Dipslide culture is a promising alternative as a screening test for ASB. Pregnant women with ASB should be treated with 7-day regimen of antibiotics wherever possible, although 1-day regimen might be appropriate in some settings. More research is needed for identifying appropriate screening tests for ASB.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 186).

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Misoprostol as an adjunct to standard uterotonics for treatment of post-partum haemorrhage: a multicentre, double-blind randomised trial

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Summary

Background Post-partum haemorrhage is a leading cause of global maternal morbidity and mortality. Misoprostol, a prostaglandin analogue with uterotonic activity, is an attractive option for treatment because it is stable, active orally, and inexpensive. We aimed to assess the effectiveness of misoprostol as an adjunct to standard uterotonics compared with standard uterotonics alone for treatment of post-partum haemorrhage.

Methods Women delivering vaginally who had clinically diagnosed post-partum haemorrhage due to uterine atony were enrolled from participating hospitals in Argentina, Egypt, South Africa, Thailand, and Vietnam between July, 2005, and August, 2008. Computer-generated randomisation was used to assign women to receive 600 µg misoprostol or matching placebo sublingually; both groups were also given routine injectable uterotonics. Allocation was concealed by distribution of sealed and sequentially numbered treatment packs in the order that women were enrolled. Providers and women were masked to treatment assignment. The primary outcome was blood loss of 500 mL or more within 60 min after randomisation. Analysis was by intention to treat. This study is registered, number ISRCTN34455240.

Findings 1422 women were assigned to receive misoprostol (n=705) or placebo (n=717). The proportion of women with blood loss of 500 mL or more within 60 min was similar between the misoprostol group (100 [14%]) and the placebo group (100 [14%]; relative risk 1.02, 95% CI 0.79–1.32). In the first 60 min, an increased proportion of women on misoprostol versus placebo, had shivering (455/704 [65%] vs 230/717 [32%]; 2.01, 1.79–2.27) and body temperature of 38°C or higher (303/704 [43%] vs 107/717 [15%]; 2.88, 2.37–2.50).

Interpretation Findings from this study do not support clinical use of 600 µg sublingual misoprostol in addition to standard injectable uterotonics for treatment of post-partum haemorrhage.

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Introduction

Haemorrhage is the leading cause of maternal mortality in low-resource settings:¹ an estimated 125 000 deaths are due to post-partum haemorrhage every year.² Maternal death from haemorrhage is rare in high-resource settings, suggesting that medical interventions for haemorrhage contribute substantially to survival. Conventional treatment of post-partum haemorrhage relies heavily on hospital-based interventions. However, post-partum haemorrhage is largely unpredictable,³ and can lead to death within hours. Simple treatment methods are needed for implementation at all levels of care.

Misoprostol is a prostaglandin E1 analogue that is widely marketed in tablet form, and is registered for use in the prevention and treatment of peptic ulcer disease. It is thermostable, can be taken orally, and is fairly inexpensive. Although misoprostol is less effective than oxytocin for prevention of post-partum haemorrhage,⁴ it has been promoted widely for the ease with which the drug can be taken,⁵ and the positive results from a trial of misoprostol administration by rural birth attendants in India.⁶ Concerns about misuse⁷ and side-effects⁸ have

emerged, and misoprostol use for labour induction seems to increase post-partum blood loss.⁹

Clinical use of misoprostol for post-partum haemorrhage is based on weak evidence.^{10,11} At the start of our study, three randomised trials of misoprostol for treatment of post-partum haemorrhage had been published.^{12–14} Lokugamage and colleagues¹² reported that 800 µg rectal misoprostol stopped post-partum haemorrhage significantly more effectively than did combined intramuscular syntometrine and intravenous syntocinon. However, in that trial treatment allocation was unblinded and the outcome was subjective assessment of clinical response, so investigator bias could have favoured the misoprostol group. Hofmeyr¹³ and Walraven¹⁴ and their colleagues did double-blind trials and showed reduced blood loss with misoprostol compared with placebo, both in combination with standard uterotonics, but the differences were not significant. In a meta-analysis of the results of these trials, misoprostol significantly reduced the primary outcome of additional blood loss of 500 mL or more (relative risk 0.57, 95% CI 0.34–0.96).¹⁵ However, in a systematic review, Mousa and Alfrevic¹⁶ concluded that evidence for any advantage from

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addition of misoprostol to standard uterotonic treatment was insufficient, and called for more safety data on misoprostol as adjunctive treatment for post-partum haemorrhage.¹⁶ The main side-effects of misoprostol are shivering and pyrexia, which are dose-dependent.^{11,17}

We aimed to establish whether further blood loss could be reduced with the addition of 600 µg misoprostol sublingually to standard uterotonic treatment (mostly oxytocin) in women with post-partum haemorrhage that was suspected to be caused by uterine atony in vaginal delivery. Findings from pharmacokinetic data show that sublingual administration results in the most rapid absorption, and the highest serum concentrations and bioavailability.^{18,19} Reduced blood loss with this simple, inexpensive adjunctive treatment for post-partum haemorrhage could have major public health implications. Conversely, demonstration of lack of efficacy would provide evidence to help avoid further use of an ineffective and potentially harmful drug.

Methods

Participants

All women delivering vaginally were eligible to participate in the study if they had clinically diagnosed post-partum haemorrhage that was suspected to be due to uterine atony, and they needed additional uterotonics. Participants were enrolled from hospitals in Argentina, Egypt, South Africa, Thailand, and Vietnam between July, 2005, and August, 2008. Women were not eligible for the trial if: delivery was by caesarean section; misoprostol could not be given sublingually; any severe allergic or bleeding disorders (eg, haemophilia) were recorded; temperature was higher than 38.5°C; the delivery was defined as a miscarriage according to local gestational age limits; or the placenta was not delivered.

Women were provided with information about the trial during antenatal care. At admission for delivery, women were approached to participate in the trial and invited to give informed consent; all women provided written consent. The trial was approved by the ethics committees of the participating centres and by the Scientific and Ethical Review Group for the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction. The findings are reported in accordance with the revised CONSORT guidelines.²⁰

Randomisation and masking

A computer-generated randomisation sequence was derived centrally by Gynuity Health Projects (New York, NY, USA), and was stratified by country. Within the strata women were individually allocated by block randomisation (varying blocks of six and eight) to receive 600 µg misoprostol sublingually (three tablets of 200 µg; GyMiso, HRA Pharma, Paris, France) or matching placebo; both groups received standard uterotonics. The standard uteronic was in most cases 10 IU oxytocin given

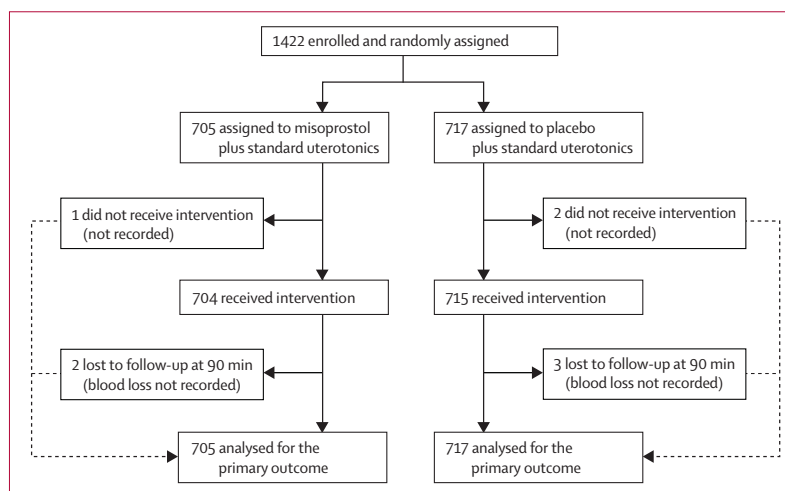


Figure 1: Trial profile

	Misoprostol (n=705)	Placebo (n=717)
Age (years)	26 (5.6)	26 (6.0)
Nulliparous	287 (41%)	290 (40%)
Type of uterotonic given during active management of third stage of labour		
Oxytocin	688 (98%)	701 (98%)
Ergometrine	44 (6%)	49 (7%)
Prostaglandins	8 (1%)	6 (1%)
Any uterotonic taken before study drug	645 (91%)	647 (90%)
Birthweight of neonate (g)	3148 (589)	3164 (557)

Data are mean (SD) or number (%).

Table 1: Baseline characteristics of participants

intramuscularly or by slow intravenous injection. The use of uterine massage was not consistent. The randomisation code was not shown to any participating trial centre or member of the study team until the trial was closed.

Treatment boxes were identical in appearance for both groups, and placebo tablets were identical in shape, colour, weight, feel, and taste to misoprostol tablets. To conceal allocation, treatment boxes were sealed and numbered sequentially according to the randomisation sequence, and distributed in the order that women were judged to be eligible and were enrolled in the study. After diagnosis of post-partum haemorrhage, standard uterotonics were given immediately as per standard practice at participating hospitals. Participants were then randomly allocated to treatment by the health provider, and received the study drug as soon as possible after standard uterotonics. Both providers and participants were masked to treatment allocation.

Procedures

The primary outcome was measured blood loss of 500 mL or more within 60 min after randomisation. Secondary outcomes were: need for blood transfusion; haemoglobin concentration of less than 80 g/L within 24 h post partum

	Misoprostol (n=705)	Placebo (n=717)	Relative risk (95% CI)
Primary outcome			
Blood loss of ≥ 500 mL within 60 min after randomisation	100 (14%)	100 (14%)	1.02 (0.79 to 1.32)
Secondary outcomes			
Blood transfusion after randomisation	103 (15%)	117 (16%)	0.89 (0.70 to 1.14)
Haemoglobin concentration of < 80 g/L within 24 h post partum or need for blood transfusion*	121 (18%)	139 (20%)	0.89 (0.72 to 1.11)
Blood loss after randomisation			
Within 60 min (mL)	200 (100–306)	200 (100–340)	0 (0 to 0)†
≥ 1000 mL	9 (1%)	9 (1%)	1.02 (0.41 to 2.55)
Within 90 min (mL)‡	250 (120–440)	250 (120–450)	0 (–40 to 20)†
≥ 500 mL	149 (21%)	162 (23%)	0.93 (0.77 to 1.14)
≥ 1000 mL	17 (2%)	22 (3%)	0.78 (0.42 to 1.47)
Any uterotonic after randomisation	188 (27%)	203 (28%)	0.94 (0.79 to 1.11)
Maternal death	2 ($< 1\%$)	0	NA
Severe morbidity§	8 (1%)	10 (1%)	0.81 (0.32 to 2.00)

Data are number (%) or median (IQR), unless otherwise indicated. NA=not applicable. *Data were recorded for 691 patients receiving misoprostol and 710 patients receiving placebo; outcomes could not be measured in remaining patients. †These data are median difference (95% CI). ‡Data were recorded for 703 patients receiving misoprostol and 714 patients receiving placebo; outcomes could not be measured in remaining patients. §Defined as hysterectomy or admission to a maternal intensive care unit.

Table 2: Primary and secondary outcomes

or need for blood transfusion; median blood loss at 60 min and 90 min after randomisation; blood loss of 500 mL or more within 90 min after randomisation; blood loss of 1000 mL or more within 60 min and 90 min after randomisation; need for any additional uterotonic; maternal death; severe morbidity (hysterectomy or admission to a maternal intensive care unit); side-effects (shivering, pyrexia, diarrhoea, vomiting, or nausea) within 60 min and 90 min after randomisation; and need for any other interventions. Unless otherwise specified, all secondary outcomes were recorded from randomisation up until discharge. Providers assessed side-effects by direct observation or questioning of participants, and every woman with a side-effect was asked to classify the side-effect as mild, moderate, or severe. Any side-effect needing treatment was recorded as severe. Body temperature was assessed with standard thermometers that were routinely used in every hospital.

The trial adhered to the methods used for blood loss measurement in the WHO trial of misoprostol for the prevention of post-partum haemorrhage.⁴ Blood collection started immediately after the study drug was given. A fresh, non-absorbent sheet was placed under the buttocks of the woman. A low-profile plastic fracture bedpan was positioned below the woman's perineum to collect all subsequent blood lost for 90 min. The blood in the bedpan plus any spilled blood from the non-absorbent sheet or blood-soaked gauze swabs, or both, was transferred to a jar and the volume was measured. At the centre in Egypt, blood was collected into a calibrated plastic sheet that was placed below the woman immediately after she took the

study drug, and the volume was measured accordingly. Measures of blood loss were recorded at 60 min and 90 min after randomisation. If bleeding did not stop, providers continued to provide standard care for post-partum haemorrhage according to local protocol. Thus the only addition to routine care was use of the study drug.

Baseline characteristics, blood loss at 60 min and 90 min after randomisation, side-effects and all other interventions were obtained and recorded on paper forms by trained study staff at the time of the delivery; data were reviewed by the principal investigator at each hospital. All data entry forms were stored at the participating hospital. Data were entered locally into a centralised online database developed by the Geneva Foundation for Medical Education and Research, Switzerland. All data were available for viewing by designated study monitors throughout the trial. Regular monitoring continued throughout the trial period to ensure protocol adherence and reliable data recording and data entry.

The data safety and monitoring board convened twice to review the data. After 400 women had been recruited, the first meeting took place to review the rate of side-effects with 600 µg misoprostol, and to confirm that the trial had an adequate sample size. After 700 women had been recruited, the second meeting took place to assess treatment effectiveness. The trial investigators were advised to continue with recruitment after both interim analyses.

Statistical analysis

On the basis of a systematic review of previous trials,¹¹ we estimated that additional blood loss of 500 mL or more would occur in about 16% of women on placebo. Therefore, 691 women per group would be needed to detect a reduction to 10% in women receiving misoprostol (relative risk reduction of 37%) at a 5% significance level (two-sided test) with 90% power, so the trial size was set at 1400 women.

All analyses were by intention to treat. Comparisons between treatment groups for baseline characteristics were done to ensure comparability between study groups and to identify any possible confounding factors. Categorical outcomes are presented as percentages and were compared between treatment groups with relative risks (95% CI). Continuous outcomes were not distributed normally, so these data are presented as median (IQR) values; treatment groups were compared from the difference in median values, and 95% CIs were derived with a bootstrap procedure. Stratified analyses were done with the Cochran-Mantel-Haenszel statistic. Homogeneity tests (Breslow-Day) were done to assess the association between outcomes and treatment across participating countries. The number needed to harm (95% CI) was calculated for side-effects if a significant difference was recorded. All statistical analyses were done with SAS (version 9.2), and we judged *p* values of less than 0.05 to be significant.

This study is registered, number ISRCTN34455240.

Role of the funding source

The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the trial data and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 1422 women were enrolled and randomly assigned to receive 600 µg misoprostol sublingually plus standard uterotonics (n=705 participants), or placebo plus standard uterotonics (n=717). Baseline characteristics were similar for participants allocated to each study group (table 1).

Analysis of the primary outcome showed no significant difference in the proportion of women with measured blood loss of 500 mL or more within 60 min after randomisation between the misoprostol and placebo groups (table 2). This result was consistent across the five trial centres (data not shown). Stratified analysis to account for any potential differences between nulliparous and multiparous women did not detect any differences between the treatment groups (data not shown). Stratification by labour induction with and without misoprostol was not done because no participants were induced with misoprostol. Stratified analyses by country did not differ from the previously presented results.

We recorded no significant difference between treatment groups in secondary effectiveness outcomes of: blood loss of 1000 mL or more within 60 min and 90 min after randomisation; blood loss of 500 mL or more within 90 min after randomisation; median blood loss at 60 min; and haemoglobin concentration of less than 80 g/L within 24 h post partum or need for blood transfusion before discharge as requested on the basis of the health provider's clinical judgment (table 2). Additional uterotonics to stop bleeding and avoid the need for blood transfusion after randomisation were given with similar frequency to women allocated to misoprostol and placebo (table 2).

Within 60 min and 90 min after randomisation, shivering was the most common side-effect and was strongly associated with misoprostol (table 3). Furthermore, severe shivering occurred in more women on misoprostol than on placebo. Misoprostol use was also associated with an increased proportion of women who had a temperature of 38°C or higher within 60 min and 90 min after randomisation, a temperature of 40°C or higher within 60 min and 90 min after randomisation, or vomited within 60 min or 90 min after randomisation. Reports of diarrhoea and nausea were infrequent, and differences between the treatment groups were not clinically or statistically significant. Numbers needed to harm suggested that for every three women treated with misoprostol plus standard uterotonics, one additional episode of shivering would be recorded compared with use of standard uterotonics alone. Similarly, for every 35 women treated with misoprostol

	Misoprostol (n=704)*	Placebo (n=717)	Relative risk (95% CI)	Number needed to harm (95% CI)†
Within 60 min after randomisation				
Shivering				
Any	455 (65%)	230 (32%)	2.01 (1.79–2.27)	3.1 (2.7–3.6)
Severe	80 (11%)	7 (1%)	11.64 (5.41–25.03)	9.6 (7.8–12.6)
Temperature				
≥38°C	303 (43%)	107 (15%)	2.88 (2.37–2.50)	3.6 (3.1–4.2)
≥40°C	18 (3%)	3 (<1%)	6.11 (1.81–20.65)	46.7 (29.4–113.6)
Diarrhoea				
Any	2 (<1%)	3 (<1%)	0.68 (0.11–4.05)	..
Severe	0	0	NA	NA
Vomiting				
Any	36 (5%)	16 (2%)	2.30 (1.28–4.09)	34.7 (20.7–107.5)
Severe	2 (<1%)	2 (<1%)	1.02 (0.14–7.21)	..
Nausea				
Any	45 (6%)	35 (5%)	1.31 (0.85–2.01)	..
Severe	2 (<1%)	1 (<1%)	2.04 (0.18–22.41)	..
Within 90 min after randomisation				
Shivering				
Any	514 (73%)	252 (35%)	2.08 (1.86–2.32)	2.6 (2.3–3.0)
Severe	95 (13%)	13 (2%)	7.44 (4.21–13.16)	8.6 (6.9–11.1)
Temperature‡				
≥38°C	406 (58%)	137 (19%)	3.00 (2.55–3.53)	2.6 (2.3–3.0)
≥40°C	48 (7%)	3 (<1%)	16.21 (5.07–51.78)	15.6 (11.6–22.3)
Diarrhoea				
Any	6 (1%)	5 (1%)	1.22 (0.37–3.99)	..
Severe	0	0	NA	NA
Vomiting				
Any	45 (6%)	25 (3%)	1.83 (1.14–2.96)	34.4 (19.6–153.8)
Severe	2 (<1%)	2 (<1%)	1.02 (0.14–7.21)	..
Nausea				
Any	60 (9%)	49 (7%)	1.25 (0.87–1.79)	..
Severe	2 (<1%)	1 (<1%)	2.04 (0.18–22.41)	..

Data are number (%), unless otherwise indicated. ..=data unavailable because of uncertainty between benefit and harm. NA=not applicable. *Blood loss alone was recorded for one patient randomly allocated to misoprostol, and so data are supplied for 704 patients. †Misoprostol plus standard uterotonics versus placebo plus standard uterotonics. ‡Data were recorded for 702 patients receiving misoprostol and 711 patients receiving placebo; outcomes could not be measured in remaining patients.

Table 3: Side-effects

plus standard uterotonics, one additional episode of vomiting would be expected compared with use of standard uterotonics alone (table 3).

18 women had severe maternal morbidity, which was defined as hysterectomy or admission to a maternal intensive care unit (table 2). Two women died, both in the misoprostol group (table 2). One woman was diagnosed with severe post-partum haemorrhage that was unresponsive to treatment, and she died of disseminated intravascular coagulopathy on the day of delivery. The other woman was diagnosed with post-partum haemorrhage that was suspected to be due to uterine atony. She received a blood transfusion and a laparotomy was done under general anaesthesia, at which time a spiral tear of the left lateral wall of the uterus was

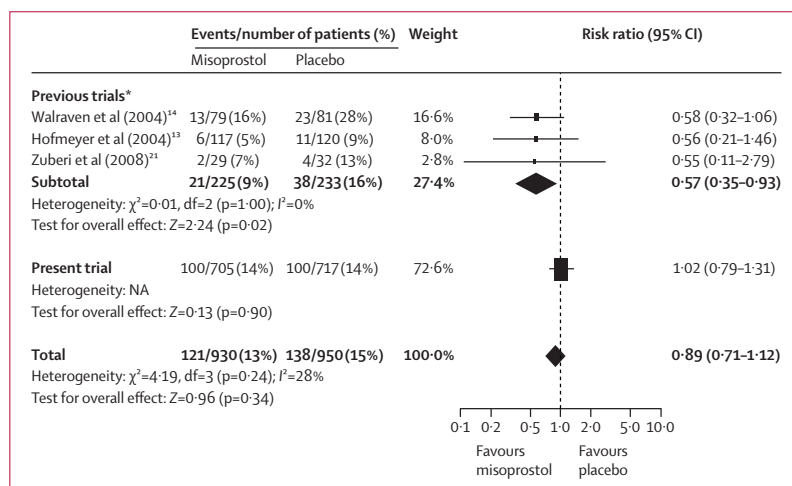


Figure 2: Meta-analysis of blood loss of 500 mL or more within 60 min after randomisation in trials of misoprostol as an adjunct to standard uterotonics for treatment of post-partum haemorrhage
NA=not applicable. *Misoprostol doses were: 400 µg sublingually and 200 µg orally;¹⁴ 400 µg sublingually, 200 µg orally, and 400 µg rectally;¹³ and 600 µg sublingually.²¹

identified and repaired, and the uterine artery was ligated. She was admitted to the intensive care unit for postoperative ventilation, circulatory support, and further blood transfusions, but died the next day from multiorgan failure. The final diagnosis was ruptured uterus and not uterine atony.

Discussion

The results of this large trial show no benefit of misoprostol in addition to standard injectable uterotonics for the treatment of post-partum haemorrhage. Moreover, misoprostol use was associated with shivering, body temperature of 38°C or higher, and vomiting.

Three randomised trials have studied use of misoprostol plus uterotonics versus uterotonics alone for treatment of post-partum haemorrhage: two were published before our study was planned,^{13,14} and one was published while our trial was underway.²¹ Meta-analysis of these three trials found a reduction of 40–50% in blood loss of 500 mL or more in women on misoprostol versus those on placebo (figure 2). The dose and route of administration of misoprostol differed between the three trials, but these differences are unlikely to account for variations in outcome. Variations could possibly be the result of chance since the studies have small sample sizes, and could be compounded by publication bias from other small trials with less optimistic results that have not been published.²² In total, the three trials enrolled 458 women, whereas a major strength of our study is the large sample size (1422 women from five countries) and statistical power. Meta-analysis of the three previous trials and our trial shows a pooled risk ratio of 0.89 for blood loss with misoprostol versus placebo (figure 2). These results underscore the importance of adequately powered large trials since the pooled results of several small trials can

suggest a promising beneficial effect that is not necessarily real.

This trial is limited by several factors. First, post-partum haemorrhage that was suspected to be due to uterine atony was clinically diagnosed and subject to error. Because our trial was pragmatic, misoprostol was given in clinical situations in which it would be used in routine practice had it been shown to be effective. Second, side-effects such as shivering, nausea, vomiting, and diarrhoea were recorded on the basis of women's reports or health-care providers' observations. Last, we were not able to assess the reduction in haemoglobin concentrations after delivery because haemoglobin concentration was not routinely measured before delivery at participating sites. Therefore, the haemoglobin concentration was measured 24 h after delivery only. However, randomisation produced similar study groups for all measured variables, so we do not expect that mean haemoglobin concentrations would have differed between the groups.

Misoprostol is an effective myometrial stimulant post partum, according to findings from physiological studies.^{23,24} It is slightly more effective than oxytocin for induction of labour, but is accompanied by undesirable side-effects, such as uterine hyperstimulation.^{25,26} The absence of effectiveness of misoprostol for treatment of post-partum haemorrhage was an unforeseen result, but is consistent with the unexpected finding that oxytocin is more effective for prevention of post-partum haemorrhage than is misoprostol.⁴ However, the standard uterotonics used in the trial could have caused maximum stimulation of the myometrium such that no further uterotonic effect could be achieved. The trial does not exclude the possibility that misoprostol could be effective in the treatment of post-partum haemorrhage in settings where standard uterotonics are not available. Indeed, findings from two double-blind randomised trials of 40 IU intravenous oxytocin versus 800 µg sublingual misoprostol for primary post-partum haemorrhage have shown that misoprostol is a suitable alternative treatment for post-partum haemorrhage.^{27,28}

The occurrence of two maternal deaths in the misoprostol group is probably a chance finding. As reported in previous trials,^{13,14,21} shivering and pyrexia, both associated with prostaglandin use, were significantly more common in women on misoprostol than in those on placebo. One of the 18 women in the misoprostol group who had temperatures of 40°C or more had delirium. Vomiting also occurred in a significantly higher proportion of women on misoprostol than in those on placebo. In view of the dose-relation of side-effects with misoprostol, future research should use the lowest dose of misoprostol that is judged likely to be effective.

The findings of this trial do not support the use of misoprostol in addition to other conventional uterotonics for the treatment of atonic post-partum haemorrhage. Any further research on misoprostol should focus on the

possible effectiveness of misoprostol in settings where standard uterotonics are not available.

Contributors

MW, JB, GJH, GC, HA-A, PL, NTNN, and BW conceived and designed the study. All authors participated in the trial implementation. DW was responsible for data analysis, and MW, JB, GJH, GC, HA-A, PL, NTNN, DW, and BW interpreted the data. MW, JB, and GJH drafted the report with input and editing from all authors.

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Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

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STUDY PROTOCOL

Open Access

A cluster randomized controlled trial to evaluate the effectiveness of the clinically integrated RHL evidence -based medicine course

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Abstract

Background and objectives: Evidence-based health care requires clinicians to engage with use of evidence in decision-making at the workplace. A learner-centred, problem-based course that integrates e-learning in the clinical setting has been developed for application in obstetrics and gynaecology units. The course content uses the WHO reproductive health library (RHL) as the resource for systematic reviews. This project aims to evaluate a clinically integrated teaching programme for incorporation of evidence provided through the WHO RHL. The hypothesis is that the RHL-EBM (clinically integrated e-learning) course will improve participants' knowledge, skills and attitudes, as well as institutional practice and educational environment, as compared to the use of standard postgraduate educational resources for EBM teaching that are not clinically integrated.

Methods: The study will be a multicentre, cluster randomized controlled trial, carried out in seven countries (Argentina, Brazil, Democratic Republic of Congo, India, Philippines, South Africa, Thailand), involving 50-60 obstetrics and gynaecology teaching units. The trial will be carried out on postgraduate trainees in the first two years of their training. In the intervention group, trainees will receive the RHL-EBM course. The course consists of five modules, each comprising self-directed e-learning components and clinically related activities, assignments and assessments, coordinated between the facilitator and the postgraduate trainee. The course will take about 12 weeks, with assessments taking place pre-course and 4 weeks post-course. In the control group, trainees will receive electronic, self-directed EBM-teaching materials. All data collection will be online.

The primary outcome measures are gain in EBM knowledge, change in attitudes towards EBM and competencies in EBM measured by multiple choice questions (MCQs) and a skills-assessing questionnaire administered electronically. These questions have been developed by using questions from validated questionnaires and adapting them to the current course. Secondary outcome measure will be educational environment towards EBM which will be assessed by a specifically developed questionnaire.

Expected outcomes: The trial will determine whether the RHL EBM (clinically integrated e-learning) course will increase knowledge, skills and attitudes towards EBM and improve the educational environment as compared to standard teaching that is not clinically integrated. If effective, the RHL-EBM course can be implemented in teaching institutions worldwide in both, low-and middle income countries as well as industrialized settings. The results will have a broader impact than just EBM training because if the approach is successful then the same educational strategy can be used to target other priority clinical and methodological areas.

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Background

Research is constantly increasing medical knowledge. For this increased knowledge to be useful in improving the health of populations it should be added to the existing knowledge pool, critically evaluated for validity and implemented by health care professionals. In recent years it is increasingly recognized that improvements in knowledge and skills of health care personnel and improvements in health care outcomes is best accomplished by employing evidence-based medicine (EBM) as part of everyday work. EBM promotes health care decisions based on the current best (valid and relevant) evidence. To achieve this, EBM curricula need to inculcate amongst learners the skills to gain, assess, apply, integrate and communicate new scientific knowledge into clinical decision-making. There is much debate about the effectiveness of various EBM teaching and learning methods and outcomes. Computer-based learning has been shown to be as effective as face-to face, lecture based sessions in improving knowledge [1,2]. There is a lack of consensus, however, as to what methods constitute the best educational practice: a practice that results not only in improvement of basic educational outcomes, such as knowledge and appraisal skills but also in attitudes and behaviour, which, ultimately leads to improved practice [3,4].

Empirical and theoretical evidence suggests that there is a hierarchy of teaching and learning activities in terms of their educational effectiveness: Level 1, interactive and clinically integrated activities; Level 2(a), interactive but classroom based activities; Level 2(b), didactic but clinically integrated activities; and Level 3, didactic, classroom or standalone teaching [3]. Workshop-based teaching, probably one of the most common forms of postgraduate teaching, can at best achieve level 2. Workshops can be interactive but it is the provision of clinically integrated activities that seem to have more sustained effects and have advantages over workshop-based programmes. Such programmes are few and variable in their quality.

A clinically integrated EBM course for teaching postgraduates was developed by the European Union-EBM Unity Project, a consortium of eleven European partners within the framework of Leonardo da Vinci vocational programme of the European Union <http://ebm-unity.pc.unicatt.it/> [5]. This course is learner-centred, problem-based and has integrated e-learning with clinical activities in the workplace. When successfully implemented, the course is designed to provide just-in-time learning through on-the-job-training, with the potential for teaching and learning to directly impact on practice and workplace environment. The course was formally piloted for feasibility in five European countries, in different medical specialties and different languages and tested

in a cluster randomized controlled trial in two countries with promising results [6,7]. However, the generic nature of this course makes application in specific clinical specialties tedious. There is a need to develop specialty-specific courses and to further evaluate this approach rigorously in appropriate settings.

The World Health Organization has published the *WHO Reproductive Health Library* (RHL), an evidence-based specialist library in sexual and reproductive health since 1997. RHL is disseminated extensively in low and middle-income countries to approximately 15,000 users every year. RHL contents are Cochrane systematic reviews in high priority topics mainly in maternal and perinatal health and fertility regulation complemented by commentaries, practical guidance documents and educational videos on techniques to implement effective practices.

In addition, a course on *Evidence-based Decision-making in Reproductive Health* including RHL content has been developed in past years as part of capacity strengthening efforts. This course includes six powerpoint presentations on evidence-based decision-making and a manual with the presentations. Several workshops have been conducted using these materials in the past seven years.

The EU-EBM Unity Project materials were revised to adapt into a sexual and reproductive health context and include RHL as a resource. The revision has made this innovative approach to postgraduate teaching suitable for implementation at obstetrics and gynaecology departments in low and middle-income countries that collaborate with HRP/RHR. As mentioned above, the promising nature of the approach and the relatively weak evidence base to recommend it widely is the principal reason behind the development of this protocol to conduct a RCT to evaluate its effects on various relevant outcomes.

Educational activities within a clinical environment primarily aim to improve the knowledge, attitudes and skills of clinical staff that will lead to improved health care practices and health outcomes of the patients. Given the multitude of educational activities that come in various formats (i.e. didactic, interactive, face-to-face, electronic (1)) it should be an implicit aim of these activities that they result in creating an environment that is more conducive to in-service learning in addition to their more immediate objectives. The context in which these educational activities and learning by staff and students take place is defined as the 'educational environment'. A single educational project may not cause major changes in the educational environment and many other factors related to health system functioning and cultural characteristics may play a role in making the environment more educationally-friendly or not. Nevertheless, measuring the educational environment is important both as an end-point

as well as an explanatory factor for evaluating educational interventions.

Rationale for this trial

Evidence-based reproductive health care requires clinicians to engage with use of evidence in decision-making. To genuinely get involved, healthcare professionals need to effectively incorporate contemporaneous research-based information in the clinical setting. The proposed research project represents part of a continued programme of activities at HRP/RHR aimed at improving the quality of care and capacity-strengthening for evidence-based decision-making in low and middle-income countries. Such research is timely and important because health care workers in many under-resourced settings face difficulties in providing good quality care, keeping their knowledge up-to-date and having the skills to interpret and implement this knowledge. If effective, the clinically integrated e-learning approach can be scaled up without major investment at teaching institutions worldwide. The studies available to date have been exclusively conducted in developed countries. Before engaging in large scale implementation the benefits of this integrated approach should be demonstrated through rigorous research in relevant settings. The hypothesis is that the proposed RHL-EBM integrated e-learning course (experimental group) will improve participants' knowledge, skills and attitude, as well as institutional practice and educational environment, as compared to the use of standard postgraduate educational resources for EBM teaching.

Previous similar studies

We identified a systematic review including 23 studies comparing standalone with clinically integrated teaching in postgraduate teaching in EBM [8]. Most studies reported on knowledge, fewer on skills, (i.e. critical appraisal skills) attitudes and behaviour towards EBM. None of the studies evaluated health outcomes. Results showed that both standalone and clinically integrated courses can improve knowledge. Clinically integrated courses also improved skills, attitudes and behaviour towards EBM. However, the studies included used different teaching methods and assessment tools, and no study compared directly standalone with integrated approach. While the evidence of the review looks promising, more robust evaluation is needed comparing standalone with clinically integrated teaching.

A recent systematic review assessed the effectiveness of EBM teaching on knowledge, skills and attitude/behaviour regarding EBM [9] in postgraduates. The review included 24 studies of different designs, all studies were conducted in developed countries, and most had small sample size and provided little detail about assessment tools and actual intervention. These weaknesses point

towards a need for appropriate sized randomized controlled trials and trans-culturally adapted measurement instruments.

Objectives

The main objective is to evaluate whether the RHL-EBM course is effective in improving knowledge, skills and competencies as compared to passive dissemination of resource materials. A secondary objective is to validate an EBM educational environment tool.

Methods

General

A cluster randomized design is proposed. Such a design is more appropriate for this intervention since the intervention will be implemented at the teaching unit level and the outcome assessments will be measured similarly at the institutional level. In addition, individual randomization can invalidate such an intervention due to contamination [10], whereby control participants have access to and use experimental intervention to enhance their learning if they are working in the same environment.

Participants

Participants are training institutions in obstetrics and gynaecology in the participating countries. Hospitals belonging to the same training institution will form the cluster. Principal investigators from each country will determine the number of potentially eligible training units/clusters in their countries by contacting the head of the specialist training unit and the local authorities (if required). A baseline survey of staffing levels and current postgraduate teaching programmes has been conducted to determine the number of units that can meet eligibility criteria.

Inclusion criteria

Training units that can provide at least four junior residents/registrar (postgraduate trainees) who have not yet been exposed to structured, formal EBM training and who will be available for the duration of the trial will be eligible. Brief descriptive characteristics of each participating junior postgraduate trainee will be collected.

Each institution needs to identify a 'facilitator' who will be able to work with the participants during the trial period. The facilitator will be someone working in the same department with the participants but will be a senior staff member preferably a specialist in obstetrics and gynaecology who is knowledgeable about basic EBM principles.

Recruitment and allocation

The training institutions (clusters) identified by the principal investigators and fulfilling the inclusion criteria will be asked to participate in the trial. The random allocation

Table 1: Intervention 1: WHO RHL EBM clinically integrated e-learning course

Description of the intervention	A course developed in a collaborative project involving 8 international partners. This course is based on the <i>Leonardo da Vinci - Community Vocational Training Action Programme</i> initiated and supported by the European Commission. http://ebm-unity.pc.unicatt.it .
Aim	To familiarise course participants with evidence based medicine (EBM) basics to help incorporate evidence from systematic reviews into practice.
Target participants	Trainee doctors.
Learning objectives	Upon the completion of the course, participants should be competently able to: •generate structured questions arising from clinical problems in practice •search relevant literature, identifying systematic reviews wherever possible •assess the quality (validity) of systematic reviews and primary research included within them •assess the applicability of research findings in clinical practice •identify possible barriers when implementing the output from above activities into clinical practice and apply strategies to overcome them.
Reading/ Learning Resource	A study guide outlining the course and providing learning exercises/assignments and E-learning sessions. 5 modules provide learning materials for undertaking the exercises in the study guide: - Module 1: Asking clinical questions - Module 2: Searching the evidence - Module 3: Critical appraisal of systematic reviews - Module 4: Applicability of the evidence to the patient - Module 5: Implementation of evidence into practice The WHO Reproductive Health Library CD-ROM/ internet version
Learning/ teaching methods	Participant initiated (supported by a facilitator) teaching and learning in a clinical setting Clinical facilitator will guide participants in a clinical setting: •Identifying learning opportunities in a clinical setting •Directing appropriate use of learning resources •Providing feedback on learning exercises/ assignments Participants will pursue independent study using the study guide and e-learning modules directed/ facilitated by the facilitator and will undertake summative assessments.
Student Directed Learning	2 - 3 hours - e-learning.

Table 1: Intervention 1: WHO RHL EBM clinically integrated e-learning course (Continued)

Contact time	20 hours - total including assignments, feedback, and assessments.
Assessments	Feedback on assignments Multiple choice questions to test knowledge Questionnaire to test attitudes OSCE to test competencies Questionnaire on educational environment (EBMEEM).

scheme will be generated at HRP/RHR using computer-generated random numbers. Each cluster will be allocated to either of two groups: RHL-EBM course (intervention 1) or passive dissemination of EBM teaching materials (intervention 2). Due to the nature of the intervention and design it will not be possible to blind the research teams or the participants of their allocated group. However, the participants will only be informed about an educational programme evaluation and will not be told which groups are compared. The individual trainees will receive similar information on a written information sheet.

Interventions

The project aims to evaluate the effects of the experimental intervention (RHL-EBM clinically integrated e-learning course) over passive dissemination of resources that have very similar content and the same learning objectives. It is acknowledged that other EBM teaching activities can also take place independently at the participating institutions. Information on those activities will be recorded systematically. The contents and presentation of both intervention courses were refined and finalized at two meetings of the steering committee that includes experts in research methodology, medical education and obstetrics and gynaecology.

Intervention 1: RHL-EBM Course

The RHL-EBM clinically integrated e-learning course will be the experimental intervention. The course content has been developed following well established guidelines when planning a curriculum [11]. The Course is described in detail in Tables 1 and 2. Briefly, the teaching takes place in the clinical environment and the postgraduate trainee obtains the theoretical knowledge from the interactive e-learning materials, completes assignments and interacts with her/his facilitator throughout the process.

Descriptive information about facilitators' position in the unit, professional qualification and possible EBM teaching activities will be collected. There should be one facilitator per group of 5 to 10 postgraduate trainees. At each training institution one facilitator will be responsi-

Table 2: Details about the activities (intervention)

1. E-learning sessions	The web-based e-learning tools are structured as short <u>sessions</u> (one or more per module) that each can be completed in 15-25 minutes by the participant. These sessions are aimed to give a basic understanding about the concepts involved in each module. Multiple choice questions for self-assessment will be incorporated in the e-sessions.
2. Learning/teaching in a clinical setting	This part is guided by a facilitator during the wardround and includes identification of learning opportunities in a clinical setting. Participants will, by using practical examples, apply the concepts of evidence-based medicine in a real clinical case scenario and be able to discuss with the facilitator and their colleagues.
3. Formative assessment (assignments, OSCE)	The participant needs to complete formative assignments which consist of MCQs, assignments for each module and questionnaires (attitude, educational environment) and OSCEs at the end of the course. After having studied each module, completed assignments need to be sent to the tutor who will provide feedback, which will serve as discussion background between participant and facilitator. The facilitator will decide when the assignment has been completed successfully. OSCEs will need to be completed at the end of the course.
4. Summative assessment	Participants are assessed at the end the course by multiple choice questions (MCQs) which have to be completed pre-course and four weeks after the end of the course. A questionnaire to assess participants' attitudes towards EBM and a questionnaire to assess the educational environment will be taken pre-course (at baseline) and at the end of the course. This will not count towards the participant's overall assessment. Participants will be provided with a password to gain access to the online MCQs. For this, a suitable place at the learner's department or institute providing internet access should be identified. The test has to be taken in presence of the tutor or a person designated by the tutor and the use of additional materials is not allowed. Once the pre-course MCQs have been completed, the participant will have access to the online e-sessions and related materials. Assignments need to be completed for each module before moving on to the next module. Assessment (MCQs for all five modules) will need to be completed at the beginning of the course and at the end.

ble for trial related activities. Facilitators will interact with the participants providing feedback on their assignments, and facilitate discussions during ward rounds/discussions and journal clubs. Facilitators will receive a handbook that will help them to guide the participant.

Intervention 2: Self-directed learning (Passive dissemination of EBM teaching materials)

The RHL-EBM Course will be compared to passively disseminated EBM resources from the WHO RHL workshop-based course that has the same learning objectives. The materials include 6 PowerPoint presentations. The content of the presentations are similar to the content of the RHL-EBM Course. It is detailed described in Table 3. The PowerPoint presentations focus on:

- formulating clinical answerable questions;
- searching effectively for evidence using tools such as the Reproductive Health Library and the Cochrane Library;
- critically appraise clinical evidence for its validity and applicability;
- understanding basic effect measures such as Relative Risk and Numbers Needed to Treat.

The basic differences between experimental (intervention 1) and control (intervention 2) groups are outlined in Table 4.

Outcome measures

The primary outcome measures are:

Gain in EBM knowledge measured by multiple choice questions (MCQs) that have been shown to have face/content validity in relation to course objectives and discrimination capacity in previous studies. Multiple choice questions have been developed by using questions from validated questionnaires and adapting them to the current course [4,12,13].

Change in attitudes towards EBM and competencies in EBM. Attitudes towards EBM will be measured by a validated questionnaire. Previously validated questions to assess attitudes towards EBM will be used [4].

Skills competence in applying EBM principles will be measured by *Objective Structured Clinical Examination* (OSCE). The OSCE is a well established way to assess clinical competency. In this case, EBM-skills related questions following the OSCE structure will be developed for completion electronically.

As a secondary outcome measure, we will assess the educational environment towards EBM by using a questionnaire (EBMEEM). The EBMEEM development is based on previously validated environment measurement tools in different clinical settings [14,15]. The trial will also serve to validate the tool in a larger setting. Trial participants will complete the questionnaire at the beginning and at the end of the course. Only data from the first

Table 3: Intervention 2: Self-directed learning (Passive dissemination of RHL-EBM documents)

Description of the intervention	A course developed by WHO RHR in collaboration with South African Cochrane Centre. This course is implemented either through workshops or simple dissemination of course materials.
Aim	To familiarise course participants with evidence based medicine (EBM) basics to help incorporate evidence from systematic reviews into practice.
Target participants	Trainee doctors.
Learning objectives	Upon the completion of the course, participants should be competently able to: •generate structured questions arising from clinical problems in practice •search relevant literature, identifying systematic reviews wherever possible •assess the quality (validity) of systematic reviews and primary research included within them •assess the applicability of research findings in clinical practice
Reading/Learning Resource	6 Powerpoint presentations WHO Reproductive Health Library CD-ROM/internet version
Learning/teaching methods	Participant initiated learning using electronic resources provided
Student Directed Learning	e-learning (approximately 10 hours learning time)
Contact time	No structured planned contact time. Participants will have access to the online powerpoint presentations for 8 weeks after they have completed the baseline assessment.
Assessments	Multiple choice questions to test knowledge Questionnaire to test attitudes OSCE to test competencies Questionnaire on educational environment (EBMEEM).

completion (baseline) will be used for validation purposes. Data from the second administration at the end of the course will be analysed after determining the items to be included in the validated instrument. Items remaining in the validated instrument will be used to generate baseline scores for the educational environment and to monitor and compare any possible changes at the end of the trial.

Development of the EBMEEM tool

Using the format of previously developed tools the content of the RHL-EBM Course were adapted and included in a draft instrument that yielded 63 Likert-scale items. The items were organized around certain themes namely, learning opportunities; own learning (EBM competence); availability of leaning resources; teachers and teaching (EBM specific); supervision and support; EBM practice (EM atmosphere); and general atmosphere. After several iterations of pilot-testing involving postgraduate trainees in a number of countries and the Steering Committee, the draft instrument to be validated and used in outcome assesment was agreed upon.

Process outcomes such as the experience of the facilitators and the postgraduate trainees will be evaluated through interviews.

Follow-up procedure

The intervention period will be 8-12 weeks. Currently, follow-up beyond the trial period is not planned mainly due to financial constraints. If funds are available a one-year assessment of the EBM educational environment will be considered.

Data management

Data will be collected in the centres using an online data management system developed by the Geneva Foundation for Medical Education and Research (GFMER). Data management will be based at the GFMER, Geneva, Switzerland supervised and monitored by HRP/RHR and Birmingham University.

Data collection will be at baseline (before the intervention), and after completion of the intervention. Data will be recorded by online completion of data forms (MCQs) and questionnaires (attitude, educational environment).

Data entry will be monitored on a day-to-day basis and any problems with logins, missing data and queries will be resolved promptly. The system allows data export to common statistical packages for analysis. It has been agreed that the data files will be exported to an Excel file to be analyzed by the trial statistician in the Statistics and Informatics Services Team at the HRP/RHR.

Analysis plan

Since the random allocation is by teaching units and the inferences will be made at this level, the analysis at the teaching unit will be the unit of analysis.

Table 4: Intervention and control group

	Experimental group	Control group
Before	Introduction and consent MCQs M1-M5 Attitude questionnaire Educational environment measurement tool	Introduction and consent MCQs M1-M5 Attitude questionnaire Educational environment measurement tool
Implement interventions	•RHL EBM course over maximum 8 weeks (5 modules, completion of assignments for each module/week) •Current local teaching	•RHL and workshop-based course materials handed out to each participant •Current local teaching
Assessment	•MCQs: 3-4 weeks after the end of the course •Attitudes: questionnaire 3-4 weeks after the end of the course •Competencies: OSCE 4 weeks after the end of the course •Educational environment: 4 weeks after the end of the course	•MCQs: 12 weeks after baseline assessment •Attitudes: 12 weeks after baseline assessment •Competencies: OSCE 12 weeks after baseline assessment •Educational environment: 12 weeks after baseline assessment

At each participating unit the postgraduate trainees will use the online system to enter their personal data and access the assessment questions (all) and the e-learning modules of the course (either intervention or control materials). The postgraduate trainees will complete the relevant sections at baseline and at the end of the trial period.

Analysis plan for primary outcomes

A score for each individual by dividing the number of points obtained in a test by the maximal number of points that can be obtained will be computed. A summary measure will be obtained for each teaching unit as the mean score for all the individuals taking the test in that unit at baseline (pre-) and post-evaluation phase.

We will compare the knowledge (main outcome) between intervention and control units using analysis of covariance, with pre-test score as a baseline covariate and terms for the stratum and for the group in the model. A 95% confidence interval will be calculated for the difference in knowledge between intervention and control, based on the error term from the analysis of covariance.

We will also compute the change in knowledge as the difference between the post- and the pre-test scores for each individual. A summary measure of the gain in knowledge for each teaching unit will be computed as the mean gain in knowledge. We will compare the gain in knowledge between intervention and control units using analysis of variance, with terms for the stratum and for the group in the model. A 95% confidence interval will be calculated for the difference in gain in knowledge between intervention and control, based on the error term from the analysis of variance.

It is anticipated that in some countries there will be existing formal or informal postgraduate training activities on EBM. These will be reported in the survey of EBM activities that will be conducted before the trial. If data permits a stratified analysis based on the presence or absence of additional basic EBM courses will be conducted. However, it is acknowledged that the study may be underpowered to provide a definitive answer according to the two strata.

Number of subjects and statistical power

There is limited information regarding baseline EBM knowledge and possible knowledge gains and practice changes following implementation of such courses [16]. The evaluation of the pilot course developed within the Leonardo da Vinci pilot project provided some data that were used in the sample size calculation [6,7]. In the pilot evaluation only electronic modules were evaluated as a before and after analysis: For sample size calculations, the standard deviation (SD) for the average gain in knowledge (%) estimated from teaching units/modules means in different countries as SD = 7.9% (likely to be an overestimate) was taken. To allow for random variation of this estimate, a range of SD between 5% and 15% was considered. The power achieved with a total of 60 teaching units to detect a difference in gain of 10% (relative to the maximum score) between two groups in a two-sided test of 5% level, assuming SD = 10%, is 97%. If SD = 12%, the power is 90%. If SD = 14%, the power is 80%. Seven countries: Argentina (4 institutions), Brazil (20), Democratic Republic of Congo (4), India (10), Philippines (10), South Africa (6), Thailand (10) will participate in the trial whose duration is estimated in one year.

Main problems anticipated

Identification of facilitators in the experimental intervention units: The principal investigator will use her/his judgement on the selection of the facilitators and provide training if appropriate. However, the whole philosophy of the Course is for the facilitators to guide the students in the clinical setting and monitor their progress in the process. The facilitators do not need to be EBM experts but rather respected clinicians that could be seen as role models or opinion leaders within their settings.

Internet connectivity

Although all settings will have access to internet for data entry and course content (RHL-EBM) our initial contacts suggest that there may be connectivity problems in some settings like Congo DRC and South Africa. In these settings close monitoring by principal investigators will be required to ensure that emerging problems are solved rapidly.

Existing EBM courses

It is possible that in some of the teaching units there may be other postgraduate teaching activities such as workshops or scientific conferences. It is not possible to control these activities occurring in each setting. The survey conducted before the trial will give information on the scope of the activities likely to exist in each setting. There are two possible protective mechanisms against these activities becoming a threat to the validity of trial results. First, random allocation should ensure that such activities are equally distributed in both groups. Second, stratified analysis based on the presence and absence of existing courses is planned as a secondary analysis.

Expected outcomes of the study

If effective, the RHL-EBM Course will provide an educational intervention that can be scaled up in low and middle-income countries in both teaching and non-teaching institutions. As such it will form a core component to improve quality of care. Discussions with national and international professional organizations to implement the course with formal certification can be performed.

Improvements on knowledge gain, attitudes and skills are important for providing good quality care. Any potential improvement in educational environment will have a major impact on the quality of inservice training not only in resource-poor settings. An original EBM Educational Environment Measurement Tool will be available for all academic or nonacademic settings.

Trial results will be published in a peer-reviewed journal. The results will be disseminated to the participating centres through meetings of the research team with participants at the end of the study. The results will also be

presented and disseminated through the WHO website and the WHO reproductive Health Library (RHL).

Ethics and informed consent

The trial interventions are implemented at the institutional level. Therefore, the primary point at which permission is sought is at the institutional level. Receiving permission from the institution does not constitute a consent on behalf of the participants. It constitutes an administrative agreement between the PI and the institution. A permission sheet will be presented to the person responsible for the institution to be signed. We anticipate that in most cases this person will be the academic head of the obstetrics and gynaecology department.

The facilitators/focal persons and the postgraduate trainees will be informed that one or more educational programme(s) are being evaluated but with no further details. After random allocation each unit will be informed about the activities they should follow including completion of MCQs and other online assessments. We plan to seek consent from individuals within the participating institutions. Individuals will not be identified in the questionnaire. If *intervention 1* is shown to be beneficial in the primary endpoints then it will be provided to all *intervention 2* institutions.

The study protocol was ethically approved by WHO and will also be approved in each participating country.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

RK, KSK and AMG had the original idea for the study and drafted the first version of the research protocol. It was then discussed with all other authors in two meetings in Geneva and the correspondent inputs were added to the protocol. All have read and agreed with the final version of the current study protocol.

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Building capacity for evidence generation, synthesis and implementation to improve the care of mothers and babies in South East Asia: methods and design of the SEA-ORCHID Project using a logical framework approach

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Abstract

Background: Rates of maternal and perinatal mortality remain high in developing countries despite the existence of effective interventions. Efforts to strengthen evidence-based approaches to improve health in these settings are partly hindered by restricted access to the best available evidence, limited training in evidence-based practice and concerns about the relevance of existing evidence. South East Asia - Optimising Reproductive and Child Health in Developing Countries (SEA-ORCHID) was a five-year project that aimed to determine whether a multifaceted intervention designed to strengthen the capacity for research synthesis, evidence-based care and knowledge implementation improved clinical practice and led to better health outcomes for mothers and babies. This paper describes the development and design of the SEA-ORCHID intervention plan using a logical framework approach.

Methods: SEA-ORCHID used a before-and-after design to evaluate the impact of a multifaceted tailored intervention at nine sites across Thailand, Malaysia, Philippines and Indonesia, supported by three centres in Australia. We used a logical framework approach to systematically prepare and summarise the project plan in a clear and logical way. The development and design of the SEA-ORCHID project was based around the three components of a logical framework (problem analysis, project plan and evaluation strategy).

Results: The SEA-ORCHID logical framework defined the project's goal and purpose (*To improve the health of mothers and babies in South East Asia* and *To improve clinical practice in reproductive health in South East Asia*), and outlined a series of project objectives and activities designed to achieve these. The logical framework also established outcome and process measures appropriate to each level of the project plan, and guided project work in each of the participating countries and hospitals.

Conclusions: Development of a logical framework in the SEA-ORCHID project enabled a reasoned, logical approach to the project design that ensured the project activities would achieve the desired outcomes and that the evaluation plan would assess both the process and outcome of the project. The logical framework was also valuable over the course of the project to facilitate communication, assess progress and build a shared understanding of the project activities, purpose and goal.

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Background

Poor health and pregnancy care leads to over half a million maternal deaths and almost eight million perinatal deaths each year. For every woman who dies, about 20 more suffer injuries, infection and disabilities [1]. The burden of death and injury falls disproportionately on low and middle income countries, as is indicated by the lifetime risk of maternal death in South East Asia which is one in 130 compared to one in 7,300 in developed regions [2]. Importantly, much of this burden could be prevented if interventions which have been demonstrated by research to be effective and feasible were implemented at scale [3].

Implementation of the results of research into practice has been identified by the WHO as the most significant challenge to health care [4]. An overview of approaches to bridging the gap between research and practice has highlighted the lack of primary research about what interventions are effective in increasing use of research in health care in low-income settings [5]. In part this reflects the low priority afforded to health services research in these settings [6]. This is a concern given that increasing the generation and use of research in health care are essential steps in improving health systems and achieving better health, particularly in low-income settings [7-9].

Ensuring access to scientifically valid and up-to-date information is a prerequisite to use of research in guiding health care, or 'evidence-based practice'. In spite of the profusion of health information available in print and electronic media (and several international initiatives to promote access), healthcare workers in low-income settings are still disadvantaged when it comes to accessing reliable information on effective care [10,11]. Organisational, financial and technical barriers to accessing research (including lack of computers and internet access, limited scientific literacy, lack of availability of research, inappropriate format of research publications, etc.) and concerns about relevance to local settings are compounded by a lack of skills among practitioners and other stakeholders to appraise and interpret research findings [12].

The South East Asia - Optimising Reproductive and Child Health in Developing Countries (SEA-ORCHID) project aimed to address some of these issues. This five-year project (2004-08) was funded through the International Collaborative Research Grants Scheme, a partnership between the UK-based Wellcome Trust and Australia's National Health and Medical Research Council. The scheme was designed to foster collaborative research between countries in South East Asia and Australia by funding research into major health issues affecting developing countries and developing research capacity.

The objective of SEA-ORCHID was to evaluate whether a intervention designed to strengthen the capacity for research generation, synthesis, and use, improved perinatal practice and led to better health outcomes for mothers and babies.

The SEA-ORCHID study protocol reporting the overall research design and project plan has been published previously [13]. The protocol outlined the core groups targeted by the intervention and key intervention activities. Planning and designing the intervention was undertaken in two stages: development of a project-wide logical framework before the intervention phase; and a site-specific action research-based operationalisation of this framework undertaken during the intervention phase. In this paper, we describe the methods and results of the first stage.

Methods

The SEA-ORCHID project was a pragmatic study that used an uncontrolled before-and-after design to evaluate the impact of a multifaceted tailored educational intervention, implemented within an action research framework (Figure 1). The intervention consisted of a wide range of components and strategies, based on sound educational principles, tailored to meet the needs, priorities and resources of each of the participating hospitals.

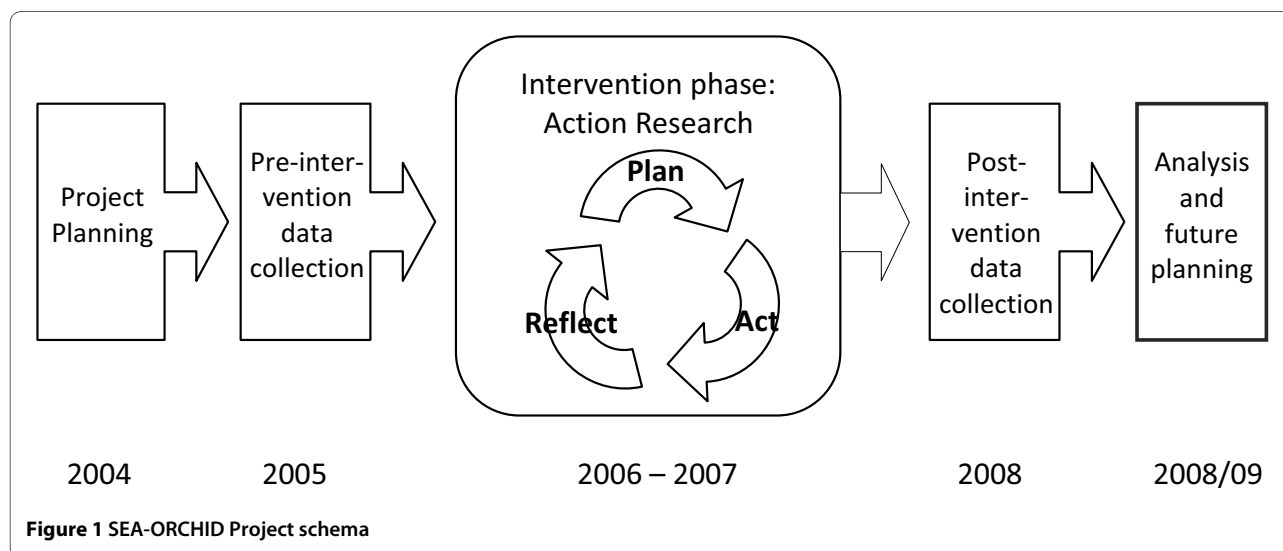
The project was approved by the ethics committee relevant to each participating hospital and by the ethics committee of the administering institution in Australia (University of Sydney).

Logical Framework Approach

In complex projects that have broad goals, a logical framework approach can help summarise and describe the multiple strands of the project clearly and systematically, and clarify the core goals, broad objectives, activities and expected outcomes [14]. There are three main components of a logical framework: project rationale (analysis of main problems and their causes); project plan (goal, objectives, activities, outputs) and evaluation and measurement strategy. The logical framework tool helps develop and demonstrate the *logic* of the project in two dimensions. The first, vertical dimension, is whether the activities of the project are likely to achieve the objectives and whether these objectives are likely to achieve the broader goals. The second, horizontal dimension, is whether the evaluation plan will measure the project's progress (process measures) and whether the progress of the project will in turn address the identified problems (outcome measures).

Development of the logical framework

The SEA-ORCHID project coordinator (SM) and one of the Australian-based project staff (CC) managed the



development of the logical framework, drawing on information from several sources, along with contributions from members of the SEA-ORCHID team.

Information sources

The information sources used to develop the logical framework included the study protocol [13], a brief survey of perceived current practice, and in-depth discussions at investigator and project meetings (to capture the experiences and perspectives of the local decision-makers). The study protocol set the parameters of the project in terms of its overall aims and design.

At the start of the project planning phase, the SE Asian investigators completed an informal survey of current practice which provided a snap shot of the extent to which care was in line with research (as perceived by the investigators who were senior clinicians working in the participating sites) at different levels within the hospital system in each country (tertiary, regional, provincial and district). The survey also collected data on any complementary research activities that might inform or affect the intervention design, such as participation in the *WHO Reproductive Health Library* cluster randomised trial [15] (Additional file 1: SEA-ORCHID survey).

Discussions at the early investigator meetings were pivotal in articulating the key issues and beginning the process of translating these into objectives linked to activities. At the first full meeting of all the investigators and Australian-based educators in Adelaide in March 2005, several general principles were agreed with respect to intervention planning:

- sustainability and capacity-building should underpin all intervention strategies;
- interdisciplinary teamwork, including both clinical and non-clinical staff, such as librarians and biostatisticians, should be encouraged;

- SEA-ORCHID project baseline data on clinical practices should be used wherever possible to determine local priorities.

During the same meeting, each SE Asian investigator summarised the current situation at the project hospitals in their country in terms of awareness, acceptance and use of research in practice; outlined particular barriers and enablers that could affect the intervention; and suggested activities they considered priorities.

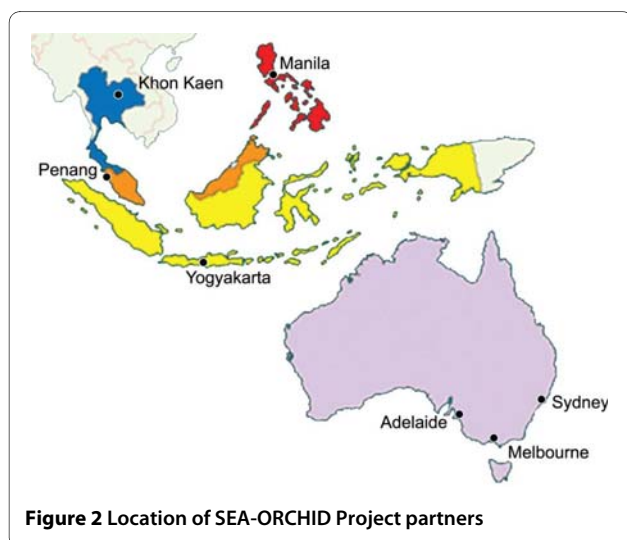
The information from these three sources served as the raw material for the logical framework.

Contributors

The logical framework was developed with input from the seven chief investigators (one from each of the SE Asian countries, and three from Australia), the two project coordinators (from Australia and Thailand) and the Australian project staff.

The SE Asian investigators were senior obstetricians or neonatologists responsible for co-ordinating the project and determining both local and national priorities within the overall framework of the project.

The selection of investigators was determined on the basis of existing partnerships and networks within SE Asia and Australia (Figure 2). Professional links have been fostered over many years through regular meetings of Federation of Asia and Oceania Perinatal Societies and the Perinatal Society of Australia and New Zealand. The participating centres and their respective investigators in Thailand (Khon Kaen University, Khon Kaen), The Philippines (University of the Philippines, Manila) and Indonesia (Gadjah Mada University, Yogyakarta) collaborate on studies initiated by the World Health Organization and are also linked through INCLEN (International Clinical Epidemiology Network) and the Global Network for Perinatal and Reproductive Health. In Thailand, Khon



Kaen University also serves as the co-ordinating base of the Thai Cochrane Network. The participating centre in Malaysia (initially at Ipoh Hospital and then Penang Medical College) is the focal point for initiatives to support and develop Cochrane activity.

The three Australian investigators were from centres that have strong links with The Cochrane Collaboration and international research networks for maternal and perinatal health. The Australian Research Centre for Health of Women and Babies (ARCH) at the University of Adelaide <http://www.health.adelaide.edu.au/og/research/arch.html> comprises several research divisions. The research synthesis division, where the regional co-ordi-

nating unit for the Cochrane Pregnancy and Childbirth Group is based, also includes the ARCTURUS Clinical Trials division and the national coordinating office for the WOMBAT Collaboration <http://www.wombatcollaboration.net> and promotes and supports high quality randomised trials in maternal and perinatal health.

The Centre for Perinatal Health Services Research at the University of Sydney aims to improve the process and outcome of care for mothers and infants in New South Wales, nationally and internationally, through research and education promoting evidence-based practice <http://www.psn.org.au/>. The Centre is also the regional co-ordinating base for the Cochrane Neonatal Group. The third Australian site was at Monash University and houses the Australasian Cochrane Centre <http://www.cochrane.org.au/>, which is responsible for training and supporting review authors and fostering the development of Cochrane activity in Australasia and South East Asia.

The nine study sites (hospitals) were purposively selected to include tertiary referral hospitals (University and regional), provincial hospitals and district hospitals. All were public hospitals and ranged in size from a district hospital in Indonesia with 100 births a month to a tertiary referral hospital in the Philippines with up to 2500 births a month (Table 1). We selected hospitals in which the SEA-ORCHID team members were actively involved in providing clinical services to ensure that the project would be locally owned and that project development, implementation and evaluation would be participatory. The participatory approach to designing the intervention plan did not extend to formal engagement

Table 1: Hospitals in the SEA-ORCHID Project

Country	Hospital site	Type of hospital	Average births per month (in 2005)
Indonesia	Dr Sardjito Hospital, Yogyakarta	Tertiary	100
	Sleman District Hospital, Yogyakarta	District	100
Malaysia	Ipoh Hospital, Ipoh	Tertiary	750
	Kelantan Hospital, Kota Bharu	Tertiary	650
Philippines	Philippine General Hospital, Manila	Tertiary	500
	Jose Fabella Hospital, Manila	Tertiary	2500
Thailand	Srinagarind Hospital, Khon Kaen	Tertiary	200
	Khon Kaen Hospital, Khon Kaen	Regional	300
	Kalasin Hospital, Kalasin	Provincial	350

with local decision-makers or community members who were not actively involved in SEA-ORCHID.

Development process

Development of the logical framework included establishing a project rationale by defining and unpacking the central problem - the problem analysis - and developing a project goal that captured the overarching aim of the project in addressing the central problem.

The project planning component of the process sought to generate a range of possible activities and outputs designed to meet the objectives underpinning the project's overall aim. The third component of the logical framework - evaluation and measurement - outlined the process measures designed to monitor the project's progress and the outcome measures designed to assess whether the project was meeting its goal and purpose.

Refining the logical framework was a four-month, iterative process with drafts circulated among the project teams for feedback and comments. The final version of the logical framework was approved in June 2005.

Results

Project rationale

The starting point for the problem analysis (Figure 3) was the less than optimal reproductive health outcomes in South East Asia, as reflected by high maternal and perinatal mortality. The direct causes of maternal mortality were understood to be unsafe abortions, bleeding, infections, hypertension and obstructed labour; and of perina-

tal mortality were understood to be low birth weight, asphyxia and infection. In response to this, the overarching goal developed for the SEA-ORCHID project was 'To improve the health of mothers and babies in South East Asia'.

Three issues were identified as underlying the central problem of poor reproductive outcomes. These were:

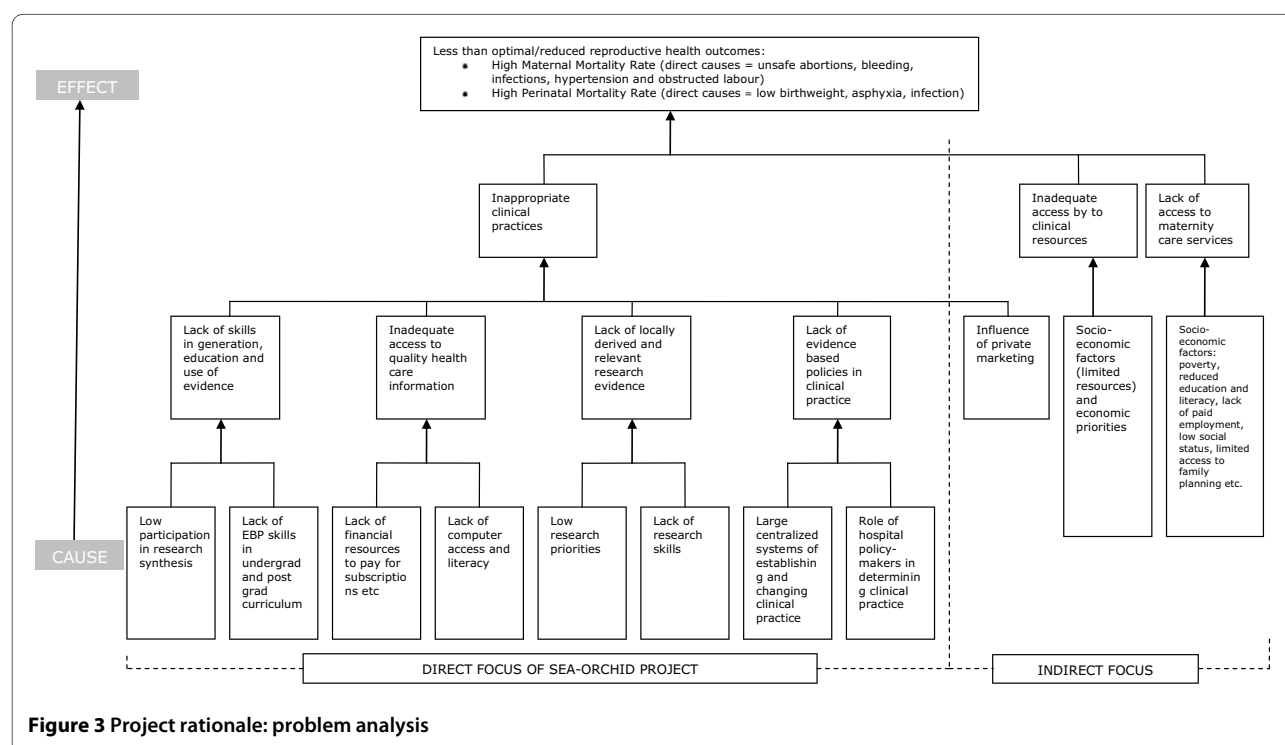
1. Inappropriate clinical practices
2. Inadequate access to clinical resources
3. Lack of access to maternity care services

Since SEA-ORCHID was not a multi-million dollar international aid project, our focus was on the first of these. The purpose of the SEA-ORCHID project was thus defined as 'To improve clinical practice in reproductive health in South East Asia'.

The problem analysis outlined several reasons why clinical practice was not always in line with the results of research. These included a lack of skills in generating and using evidence; inadequate access to reliable healthcare information; lack of locally derived and relevant research evidence; and lack of evidence-based policies and clinical practice guidelines (Figure 3).

These reasons were determined to have several underlying causes:

- low participation in research synthesis
- lack of evidence-based practice training in medical and nursing curricula
- lack of financial resources to pay for subscriptions, etc
- lack of computer access and literacy



- low priority given to research
- lack of research skills
- large centralized systems of establishing and changing clinical practice
- role of hospital policy-makers in determining clinical practice.

Project Planning

In the project planning phase, project objectives were developed to address these underlying causes (Figure 4). The objectives of the SEA-ORCHID project were:

1. to build capacity in research synthesis
2. to increase capacity and skills for evidence-based practice
3. to demonstrate effective implementation strategies for evidence-based practice change
4. to improve access to quality healthcare information
5. to increase locally derived and relevant research activity
6. to increase evidence-based policy making
7. to influence the broader socio-economic and health policy environment.

In relation to the first objective '*To build capacity in research synthesis*', proposed activities included training in systematic reviews and guideline development, developing structures to sustain research synthesis activity in

the longer term, and facilitating recognition of systematic reviews as a valid form of academic research.

Activities linked to the second objective '*To increase capacity and skills for evidence-based practise*' included developing curriculum materials, training educators and users of evidence, and working towards the integration of EBP within existing curricula.

In relation to the third objective '*To demonstrate effective implementation strategies for evidence-based practice change*', activities focused on assessing barriers and educational needs, promulgating adult learning principles, monitoring clinical practice and disseminating findings, and developing collaborative implementation strategies.

The fourth objective '*To improve access to quality healthcare information*' gave rise to activities that included pursuing consortia with medical schools or colleges, promoting access to various professional groups, and developing a longer term strategy to secure national provision to *The Cochrane Library*.

The fifth objective '*To increase locally derived and relevant research activity*' included activities aimed at identifying local research needs and appropriate questions for systematic reviews, facilitating and mentoring those involved in research synthesis, and incorporating research skills into training programs.

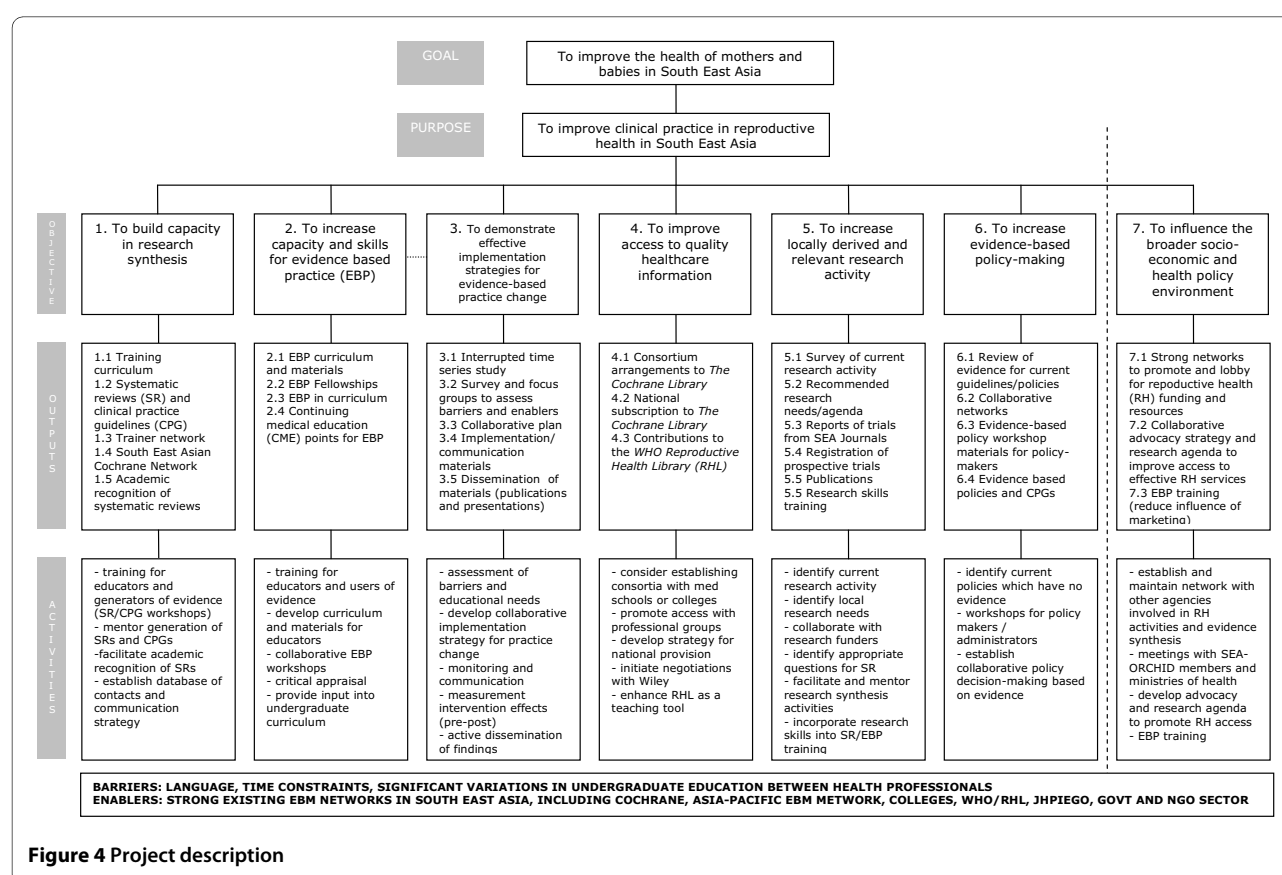


Figure 4 Project description

Activities in relation to objective six '*To increase evidence-based policy making*' included identifying evidence gaps and organising workshops for policy makers.

The final objective '*To influence the broader socio-economic and health policy environment*' was concerned with activities around advocacy and awareness raising, and collaborating with other agencies.

These broad objectives and activity descriptions were used by the project teams in each country and site to develop and implement detailed project plans reflecting local priorities, needs and resources. Descriptions of the specific activities undertaken at each participating hospital are available at <http://www.seaorchid.org>.

Evaluation and measurement

Outcome Measures

To establish whether the project met its goal of improving health for mothers and babies and its purpose of improving perinatal clinical practice, primary outcome measures were designed to evaluate change in maternal and neonatal health outcomes and 15 key evidence-based clinical practices. At each of the participating hospitals we collected data on 1000 births before and after the project intervention to determine changes in health outcomes and practices (Figure 5). Specific outcome measures were also established to evaluate each of the project objectives.

These secondary outcome measures are provided in Table 2.

Process measures

Assessment of the progress of the project was done through face-to-face project meetings, teleconferences and regular reporting. Project meetings involving team members from all SEA-ORCHID sites were held every nine months to provide an opportunity for sharing successes, brainstorming approaches to overcoming barriers, encouraging networking across nodes and refining the planned activities for the next period of the intervention phase. Between project meetings, the Australian educators initiated regular two-monthly teleconferences with each of the project nodes to ensure progress was on track, provide support and resources, and help with any problems or issues that arose. The project investigators also had regular teleconferences. SEA-ORCHID team members reported every two months on the activities undertaken at their hospital by completing activity statements which were then uploaded to the SEA-ORCHID website <http://www.seaorchid.org> to give a cumulative summary of all activities undertaken during the project.

Discussion

There are many different program logic models and frameworks used for planning and evaluating programs.

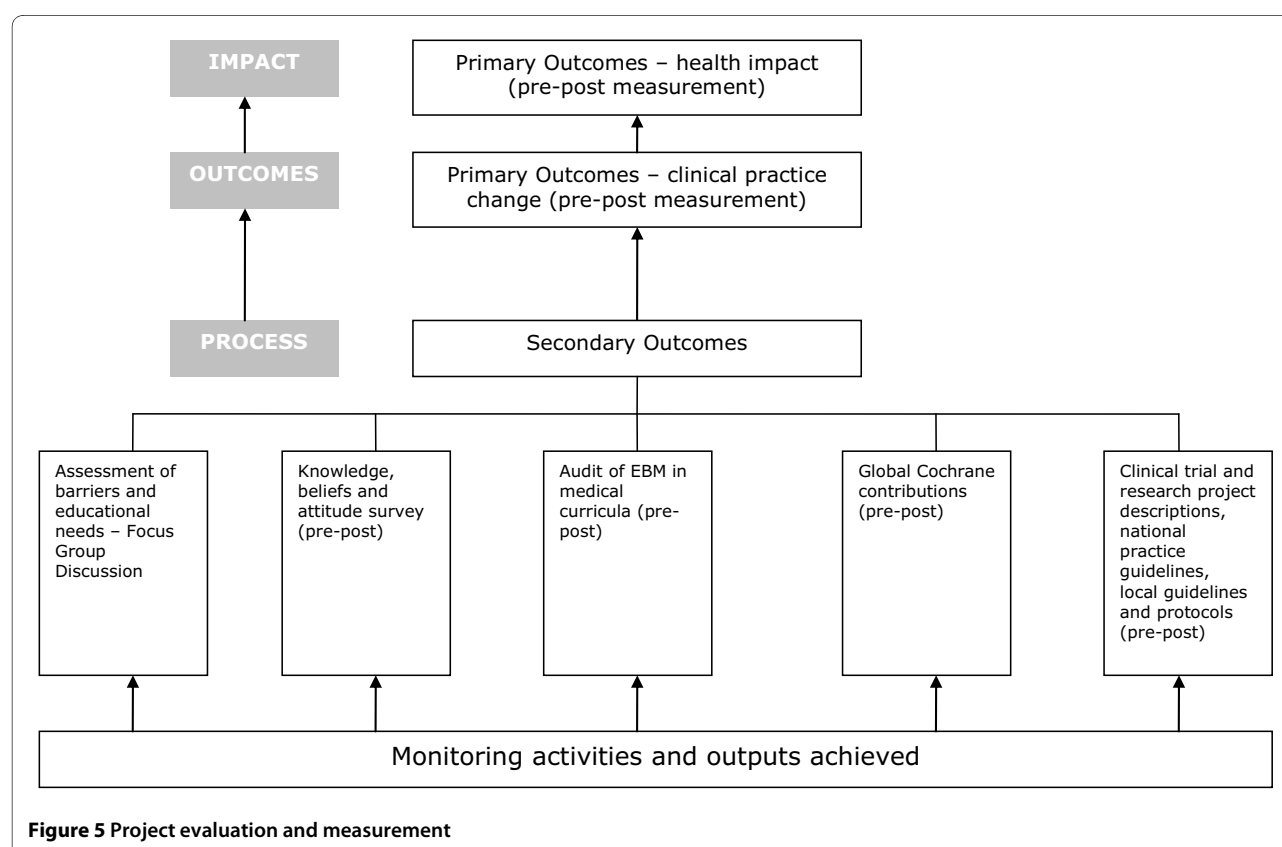


Table 2: Objectives and related outcome measures of the SEA-ORCHID Project

Project Objective	Outcome measures
To build capacity in research synthesis	SR and CPG workshops conducted SRs and CPGs produced SR trainers on database Participants in Cochrane Collaboration Branches of Australasian Cochrane Centre in SE Asia Academic sites recognising SRs in SE Asia
To increase capacity and skills for evidence-based practice	Training materials developed EBP sessions undertaken and number of participants EBP fellowships EBP in curricula pre- and post-intervention Nodes with documented recognition of CME points Persons receiving CME points for EBP training
To demonstrate effective implementation strategies for evidence-based practice change	Pre- and post-intervention measurement of primary and secondary outcomes Qualitative assessment of barriers and enablers to EBP Knowledge, beliefs and attitudes to EBP Program logic framework with input and consensus from all project partners Process evaluation of project implementation Description of collaboration and communication strategies Publication describing current practice
To improve access to quality healthcare information	<i>Cochrane Library</i> usage statistics National subscriptions to <i>Cochrane Library</i> RHL contributions
To increase locally derived and relevant research activity	Research activities Reports of trials identified and submitted to the Cochrane Central Register of Controlled Trials Research trials registered Papers published Training sessions conducted Participants attending training sessions
To increase evidence-based policy making	Description of networking arrangements and communication strategy and members Collaborative activities Workshops conducted Participants attending workshops EB policies and CPGs

Table 2: Objectives and related outcome measures of the SEA-ORCHID Project (Continued)

To influence the broader socio-economic and health policy environment	Documented advocacy strategies
	Advocacy and lobbying networks and activities
	Responses and outcomes to advocacy activities
Systematic Review (SR), Clinical Practice Guidelines (CPG), Evidence-Based Practice (EBP), Continuing Medical Education (CME), WHO Reproductive Health Library (RHL)	

Despite differences in approach, they share a common purpose which is to describe the rationale behind a program and to clarify the relationships between monitoring and evaluation and the project activities. In development projects, logical frameworks are the predominant program logic method used and are particularly important as communication tools in projects that cover diverse countries, cultures and languages [16]. The purpose of using a logical framework in the SEA-ORCHID project was to:

- assess whether the project activities were addressing perceived needs;
- clarify the expected cause-and-effect relationships between the project activities and expected outcomes;
- predict the extent to which the planned outcome measures were likely to evaluate the impact of the project activities; and
- assist project workers to reach a consensus about realistic goals and outcomes of the project.

The logical framework became the core tool that guided the overall intervention strategy and was taken by each site and used as the basis for devising a tailored suite of activities that was implemented within an action research framework during the two-year intervention phase (2006-07). Over the course of the project the logical framework was a powerful tool for facilitating communication within and between sites, and for maintaining a shared understanding of the purpose and progress of a complicated, multilayered intervention.

There are several limitations of the logical framework approach for projects of this nature. Firstly, the linear model does not always do justice to the complex multifaceted influences, dynamic interactions, cultural differences and unforeseen consequences that are part of everyday reality. Therefore they need to be used flexibly and adapted as projects evolve. Secondly, the logical framework only represents the consensus of the individuals involved in developing it. However, they can be used to clarify the assumptions on which project plans are made and allow incoming members of the project to check whether these assumptions are relevant to their local context. Finally, the logical framework approach in

this instance had to be adapted to meet the realities of planning a project intervention within the constraints of a research grant. Under ideal conditions, projects are planned systematically by looking first at the problem, then developing goals and objectives, and finally devising an accompanying evaluation plan [17]. In SEA-ORCHID, the broad issue of building capacity for evidence-based practice and the pre- and post-intervention evaluation strategy was defined first and the specific goals and objectives defined subsequently within the requirements of a research protocol.

Experts in healthcare improvement emphasise the crucial importance of acquiring a good understanding of the problem, the target group, its setting and obstacles to change [5]. Logic models, such as the logical framework, value participatory processes in project planning as a means of achieving this understanding. SEA-ORCHID is an international collaborative project that aims to improve health outcomes for mothers and babies in South East Asia by strengthening capacity for generating, synthesising and implementing evidence. The logical framework approach is an established project design method that is based on a systematic analysis of the problem or situation and an exploration of possible solutions. For SEA-ORCHID, the use of a project-wide logical framework has provided a mechanism for further developing site-specific intervention plans. Overall, this approach is both robust and flexible and appropriate for real-world research into change processes.

Conclusions

The process of developing a logical framework in the SEA-ORCHID project was valuable because it enabled a reasoned, logical approach to the project design that ensured the project activities would achieve the desired outcomes and that the evaluation plan would assess both the process and outcome of the project. The logical framework was also valuable over the course of the project to facilitate communication, provide a reference for assessment of progress and build a shared understanding of the project activities, purpose and goal.

Additional material

Additional file 1 SEA-ORCHID survey.

Abbreviations

EBP: Evidence-based practice; SE Asia: South East Asia; SEA-ORCHID: South East Asia - Optimising Reproductive and Child Health in, Developing Countries; WHO: World Health Organization

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

DH-S, PL, SG and CAC conceived the SEA-ORCHID study. SM and CC devised and refined the logical framework based on contributions from the investigators. SM wrote the initial draft of the manuscript which TT revised. All investigators and Australian educators were involved in developing the design of the project, critically revising the manuscript for intellectual content and have given final approval of the version to be published.

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CLINICAL ARTICLE

Influence of training in the use and generation of evidence on episiotomy practice and perineal trauma

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ABSTRACT

Objective: To examine episiotomy practices before and after a multi-component intervention designed to support the use and generation of research evidence in maternal and neonatal health care. **Methods:** Set in 9 centers across 4 Southeast Asian countries, a retrospective survey was performed for 12 recommended pregnancy/childbirth practices and 13 outcomes of women in each center before and after intervention. Qualitative interviews were conducted to assess staff awareness and experience in evidence-based practice. **Results:** There were significant decreases in the rate of episiotomy, from 64.1% to 60.1% (risk difference [RD] −4.0; 95% confidence interval [CI], −5.8 to −2.2) for all women and from 92.2% to 80.7% (RD −11.5; 95% CI, −13.4 to −9.6) for nulliparous women. Severe trauma decreased from 3.9% to 1.9% (RD −2.0; 95% CI, −2.7 to −1.4) for all women and from 6.7% to 3.0% (RD −3.7; 95% CI, −4.9 to −2.5) for nulliparous women. The frequency of intact perineum increased from 12.4% to 15.6% (RD 3.2; 95% CI, 1.9–4.6) for all women and from 1.7% to 8.0% (RD 6.3; 95% CI, 5.0–7.5) for nulliparous women. **Conclusion:** An intervention based on understanding and using the best available evidence can result in significant improvements in care and health outcomes.

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1. Introduction

Despite being a form of trauma, episiotomy is one of the most common surgical procedures performed on women [1]. High episiotomy rates, some close to 100%, have been reported in North America and Asia [2,3].

Three Cochrane Systematic Reviews provide evidence regarding the practice of episiotomy—comparing restrictive and routine episiotomy [4], suturing techniques [5], and suturing materials [6]. Restrictive episiotomy reduces by approximately 30% severe perineal trauma, need for suturing, and healing complications, without any increase in pain, dyspareunia, or urinary incontinence—despite an almost doubling of the risk of anterior perineal trauma. The benefit of a restrictive practice outweighs the potential harm [4]. If perineal repair is required, a continuous suture results in less pain than does interrupted suturing, although the technique is more difficult [5];

furthermore, the use of synthetic absorbable suture material causes less pain but is more likely to require removal [6].

According to Pakenham-Walsh et al. [7], “providing access to reliable health information for workers in developing countries is potentially the single most cost-effective and achievable strategy for sustainable improvement in health care.” Turning evidence into practice is a complex process; strategies found to be effective include the use of local opinion leaders [8], educational outreach [9], and audit and feedback [10].

The aim of the present study was to examine episiotomy practices used for women undergoing normal vaginal delivery at term in Southeast Asia before and after a multi-component intervention designed to support the use and generation of research evidence in maternal and neonatal health care.

2. Materials and methods

The study was part of the South East Asia Optimising Reproductive and Child Health in Developing Countries (SEA-ORCHID; <http://www.seaorchid.org>) project. The SEA-ORCHID project was designed to

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answer the question “can the health of mothers and babies in Thailand, Indonesia, Philippines, and Malaysia be improved by increasing capacity for the synthesis of research, implementation of effective interventions, and identification of gaps in knowledge needing further research in those countries?”

The present study was undertaken in 9 centers (Khon Kaen University, Khon Kaen Hospital, and Kalasin Hospital in Thailand; Universiti Sains Malaysia and Hospital Raja Permaisuri Bainun Ipoh in Malaysia; Philippines General Hospital and Jose Fabella Hospital in the Philippines; and Dr Sardjito Hospital and Sleman District Hospital in Indonesia) across 4 Southeast Asian countries, with support from 3 Australian Universities (University of Sydney, University of Adelaide, and Monash University). There were 3 main phases to the SEA-ORCHID project, the details and methods for which have been described previously [11]. Briefly, in the first (pre-intervention) phase, primary data were obtained via an audit of 12 areas of recommended practice (including restrictive episiotomy) and 13 health outcomes in pregnancy, childbirth, and neonatal care (including intact perineum). Secondary data were obtained by examining staff knowledge of evidence-based practice, access to evidence, research activity, guideline development, systematic review activity, and undergraduate teaching in evidence-based practice. The second phase comprised an educational intervention, and in the third phase the audit was repeated.

The intervention was tailored to meet the specific needs of each site. It focused on evidence users (clinicians and policy makers), generators (systematic review, guideline development, and improving research infrastructure), and educators (teachers and trainers).

Two or 3 clinical educators from each country, usually mid-career and selected for their ability to act as opinion leaders, underwent a period of training in Australia and then carried out site-specific activities to support building capacity in evidence-based practice tailored to perceived need. Training included interactive evidence-based practice workshops, and some centers used poster displays of evidence, periodic audit, and feedback of rates. All categories of staff were involved. In addition, training was provided on systematic reviewing, guideline development, and input into undergraduate curricula. The academic exchanges consisted of 1–2-month fellowships to the Australian centers for 23 Southeast Asian participants, and teaching tours provided by Australian educators and investigators. The centers did not include specific training on episiotomy, and direct orders to stop or reduce the frequency with which this procedure was performed were not given. Some centers carried out specific training on protecting the perineum without episiotomy, in addition to continuous suturing technique.

The primary audit of 1000 deliveries in each center recorded whether episiotomy was performed, the type of suture material and suture technique used for repair, and the degree of perineal trauma. All women who had a normal vaginal delivery at term were included. Data were extracted from medical records by trained data collectors using a specially designed format, then manually entered into a secure web-based database. Pre-intervention data were collected between April 1 and October 31, 2005, and post-intervention data were obtained between January 1 and June 30, 2008.

Perineal trauma was defined as trauma of the perineum during childbirth that required stitches. Vaginal and perineal tears were classified as follows: first-degree tears involved the vaginal mucosa and connective tissue; second-degree tears included the underlying muscles; third-degree tears involved complete transection of the anal sphincter (confirmed by clinical observation/examination); and fourth-degree tears involved the rectal mucosa. Third- or fourth-degree trauma was classified as severe. Episiotomy was defined as surgical enlargement of the vagina via perineal incision during delivery. The technique of skin closure was classified as either continuous (simple, non-locking, continuous subcuticular sutures) or interrupted (interrupted transcutaneous sutures).

Qualitative data were collected via in-depth interviews conducted during the final 9 months of the intervention (from July 1, 2007, to

February 28, 2008). The interviews were based on a pre-specified protocol and were designed to explore the interviewees' awareness of and experience in undertaking evidence-based practice, carrying out research, and developing guidelines. Two members of the Australian team with experience in qualitative methods and practice change conducted semi-structured face-to-face interviews with maternity and neonatal clinicians at each participating hospital. At each hospital, 2 junior and 2 senior doctors, and 2 junior and 2 senior nurses/midwives were interviewed. In Indonesia and Thailand, interpreters were used during the interviews.

All interviews were audio recorded, transcribed, and anonymized; data were analyzed in emerging themes using NVivo (QSR International, Melbourne, Australia).

Rates were given as percentages, and the difference pre- and post-intervention was described as a risk difference (RD) and a 95% confidence interval (CI) of the RD. This was done for all women and for nulliparous women. Data for each country were pooled and the RD for intact perineum was adjusted for maternal age and parity. $P < 0.05$ was considered to be statistically significant.

The SEA-ORCHID project was approved by the ethics committee at the project administration center, University of Sydney, and at each participating center. Informed written consent was obtained before the interviews were conducted.

3. Results

Data were available for 11 016 women who underwent vaginal delivery at term. The baseline characteristics of women and infants were similar pre- and post-intervention, except for those of nulliparous women in both of the Malaysian centers (Table 1).

Five centers reported a significant decrease in the rate of episiotomy post-intervention, 2 reported no change, and 2 reported a significant increase. The initial rate of episiotomy across all centers was 64.1%, and this decreased to 60.1% post-intervention (RD -4.0; 95% CI, -5.8 to -2.2). For nulliparous women, there was a decrease in 6 centers, with the overall rate decreasing from 92.2% to 80.7% (RD -11.5; 95% CI, -13.4 to -9.6) (Table 2).

There was a significant increase in the rate of intact perineum in 4 centers, a trend toward significance in 2 centers, and an decrease in 1 centre—resulting in an overall increase from 12.4% to 15.6% (RD 3.2; 95% CI, 1.9–4.6) for all women and from 1.7% to 8.0% (RD 6.3; 95% CI, 5.0–7.5) for nulliparous women. In 1 center, there was a significant decrease in the overall rate of intact perineum, but an increase among nulliparous women (Table 2). When data were pooled for each country, Thailand and the Philippines showed an improvement in the rate of intact perineum; however, the improvement remained significant only for the Philippines after adjustment for parity and maternal age (Table 3).

The pre-intervention rate of severe trauma ranged from 0.0% to 36.9% across the 9 centers. Overall, the rate decreased from 3.9% to 1.9% (RD -2.0; 95% CI, -2.7 to -1.4) for all women. This reduction was greatest for nulliparous women: 6.7%–3.0% (RD -3.7; -4.9 to -2.5). The rate of severe trauma also decreased for women with and women without episiotomy, with a greater reduction in the latter group (Table 4).

The rate of use of continuous sutures was more than 90% both pre- and post-intervention in 4 centers. Three centers reported a significant decrease in the use of continuous suture, and only 1 experienced a significant increase. The remaining center reported a non-significant increase. Overall, the use of continuous sutures decreased from 71.5% to 63.6% (Table 5).

Chromic catgut was the most common suture material used for perineal repair. Polyglycolic acid was used in 60 (1.2%) of the 5070 pre-intervention births and 429 (9.8%) of the 4358 post-intervention births (Table 5). A change to polyglycolic acid was implemented in 6 centers, 2 of which achieved a significant increase.

Table 1
Characteristics of women and infants for all full-term normal births in pre- and post-intervention surveys.^{a,b}

Table 2

Surgical episiotomy rate pre- and post-intervention by center expressed as a percentage of full-term normal births.

Center	Births pre-intervention ^a	Births post-intervention ^a	Episiotomy pre-intervention, %	Episiotomy post-intervention, %	Risk difference (95% confidence interval) ^b	P value ^c
Thailand (all)	1568	1482	91.8	84.1	−7.7(−10.0 to −5.4)	<0.01
Center 1	505	504	95.8	82.9	−12.9(−16.6 to −9.2)	<0.01
Center 2	536	477	92.9	97.3	4.4 (1.8–7.0)	<0.01
Center 3	527	501	86.7	72.9	−14.1(−18.9 to −9.2)	<0.01
Philippines (all)	1274	1237	63.7	62.2	−1.5(−5.3 to 2.3)	0.44
Center 1	777	763	63.6	55.8	−7.8(−12.6 to −2.9)	<0.01
Center 2	497	474	64	72.6	8.6 (2.8–14.4)	<0.01
Malaysia (all)	1700	1403	46	39.3	−6.6(−10.1 to −3.2)	<0.01
Center 1	881	679	60.6	51.1	−9.5(−14.5 to −4.6)	<0.01
Center 2	819	724	30.3	28.3	−2.0(−6.5 to 2.6)	0.40
Indonesia (all)	1146	1016	53.5	51.2	−2.3(−6.5 to 1.9)	0.28
Center 1	546	476	45.2	38.4	−6.8(−12.8 to −0.8)	0.03
Center 2	600	540	61	62.4	1.4(−4.2 to 7.1)	0.63
Total sample	5688	5138	64.1	60.1	−4.0(−5.8 to −2.2)	<0.01

^a Full-term normal birth.^b Figures may not add up owing to rounding.^c Proportion Z test for 2 independent samples.

In total, 75 individual, 25 pair, and 11 group interviews were conducted. Episiotomy was mentioned in 50 interviews, distributed equally across countries. In some hospitals, clinicians reported that practice regarding episiotomy had changed substantially as a result of the project: “Like the episiotomy. I think last time we did routinely do it but, after the introduction of the SEA-ORCHID, now we selectively practice this.”

Several clinicians in other hospitals indicated that they were aware that there was evidence that episiotomy should be undertaken selectively rather than routinely, but that it was still being carried out routinely in their hospitals. One frequently reported reason for routine episiotomy was fear of tearing. Some nurses and junior doctors were concerned about the response of senior doctors if significant tearing occurred when episiotomy was not performed. Episiotomies were preferred to tears because they were easier to repair: “Maybe they are not [relying] on the evidence, because sometimes when we give birth without episiotomy the wound, the vagina, is teared [sic] and it's difficult to repair; that is a bad experience for them.” There was also an increase in difficulties associated with suturing tears following other practice changes such as reducing perineal shaving.

The need for preparation of the perineum (e.g. through perineal massage) was mentioned frequently, and it was suggested by some

clinicians that research into selective episiotomy was applicable to other populations in which women underwent appropriate perineal preparation. The applicability of research into episiotomy in different populations was also questioned for other reasons: “For example, episiotomy because the size of the vagina is different between [local women] and foreigners.”

The need to train junior staff in episiotomy technique was another reported barrier to change in several hospitals: “This hospital is a referral and teaching hospital, so the residents study here...so the episiotomy, they need to do it so [they] know by themselves how to stitch the patients. That's why it is difficult to eradicate episiotomy.”

Several interviewees noted that a lack of time led some clinicians to perform episiotomies unnecessarily: “Sometimes they are impatient. Because you must have patience to wait for patients to deliver normally vaginally, she needs to take time. They want to fasten [sic] the delivery.”

In several hospitals, another barrier to change was the use of outdated protocols still recommending routine episiotomy. Three approaches were suggested as being particularly helpful in terms of changing practice regarding episiotomy. In 2 hospitals at which clinicians believed there had been a successful change in practice, staff had undertaken research projects to investigate the impact of moving from routine to selective episiotomy at the hospital. This was felt to be

Table 3

Rate of intact perineum for full-term normal births for all women and nulliparous women.

Center	Nulliparous				Total sample				
	Pre-intervention, %	Post-intervention, %	RD (95% CI)	P value ^a	Pre-intervention, %	Post-intervention, %	RD (95% CI)	P value (unadjusted) ^a	Adjusted RD (95% CI) ^b
Thailand (all)							2.0 (0.8–3.3)	<0.01	1.3 (−0.8 to 3.3)
Center 1	0.6	2.6	2.0 (0.01–4.0)	<0.05	1.6	4.4	2.8 (0.7–4.9)	<0.01	
Center 2	0.8	0.4	−0.4 (−1.7 to 1.0)	0.60	0.6	0.2	−0.4 (−1.1 to 0.4)	0.38	
Center 3	2.3	2.5	0.2 (−2.3 to 2.6)	0.88	4.2	7.6	3.4 (0.5–6.3)	0.02	
Philippines (all)							12.5 (8.9–16.1)	<0.01	14.8 (2.5–27.1)
Center 1	4.9	30.8	26.0 (21.0–30.9)	<0.01	29.6	38.9	9.4 (4.4–14.3)	<0.01	
Center 2	0.0	9.2	9.2 (5.2–13.3)	<0.01	6.1	23.5	17.3 (12.8–21.8)	<0.01	
Malaysia (all)							−1.1 (−3.8 to 1.6)	0.43	0.5 (−2.8 to 3.8)
Center 1	0.0	1.1	1.1 (−0.4 to 2.5)	0.08	9.3	11.8	2.5 (−0.6 to 5.6)	0.11	
Center 2	1.5	5.7	4.2 (0.6–7.7)	0.03	28.2	22.5	−5.7(−10.0 to −1.4)	0.01	
Indonesia (all)							0.8 (−1.8 to 3.4)	0.54	1.4 (−1.9 to 4.6)
Center 1	1.8	3.6	1.8 (−1.2 to 4.8)	0.25	11.7	13.4	1.7 (−2.4 to 5.8)	0.41	
Center 2	2.2	1.1	−1.1 (−3.2 to 1.0)	0.32	8.1	8.1	0.04 (−3.1 to 3.2)	0.98	
Total	1.7	8.0	6.3 (5.0–7.5)	<0.01	12.4	15.6	3.2 (1.9–4.6)	<0.01	

Abbreviations: CI, confidence interval; RD, risk difference.

^a Proportion Z test for 2 independent samples.^b Adjusted RD for whole-country outcomes only (adjusted for parity and maternal age).

Table 4

Rate of severe trauma pre- and post-intervention for full-term normal births in all women, nulliparous women, and those with and without episiotomy.^a

Item	Pre-intervention	Post-intervention	RD (95% CI)	P value ^b
With and without episiotomy	213 (3.9)	96 (1.9)	−2.0(−2.7 to −1.4)	<0.01
All women	n = 5433	n = 5034		
With and without episiotomy	163 (6.7)	71 (3.0)	−3.7(−4.9 to −2.5)	<0.01
Nulliparous	n = 2418	n = 2337		
Without episiotomy	27 (1.4)	5 (0.2)	−1.1(−1.7 to −0.6)	<0.01
All women	n = 1972	n = 2043		
With episiotomy	186 (5.4)	91 (3.0)	−2.3(−3.3 to −1.4)	<0.01
All women	n = 3461	n = 2991		

^a Values given as number (percentage) unless otherwise indicated.

^b Proportion Z test for 2 independent samples.

important in demonstrating that the results of research conducted elsewhere also applied locally.

Changes in financial incentive were also noted as being effective at modifying episiotomy practice: “[Before] if you put...‘vaginal delivery’, that may not be compensated. But, if you put maybe ‘episiotomy and repair,’ it will be compensated. So now they don’t compensate [episiotomy] anymore...you can only provide normal delivery and you will be compensated.”

Finally, several clinicians mentioned the value of visits to other hospitals, undertaken by themselves or colleagues, to witness firsthand that selective episiotomy was safe.

4. Discussion

In the present study, a multi-component intervention centered around understanding and using the best available evidence resulted in significant improvements in restrictive episiotomy practice and an increase in the rate of intact perineum in both parous and nulliparous women undergoing vaginal delivery at term.

Before the intervention, episiotomy rates were high in 8 of the 9 centers, and across all centers almost all nulliparous women underwent episiotomy. Following the intervention, although significant reductions were achieved, rates were still high. In a survey of Canadian hospitals practicing restricted episiotomy, the median rates reported were 62% for nulliparous and 40% for multiparous women [12]. In 1989, 39% of women undergoing vaginal delivery in the USA underwent episiotomy [1], compared with 28%–83% in the present study. It was gratifying that all centers reporting a decrease in the rate of episiotomy experienced an increase in the rate of intact perineum, which was associated with an overall reduction in the rate of severe trauma among both the women who underwent episiotomy and those who did not. Although the 2.9% increase in the rate of intact perineum (9.2% for nulliparous women) corresponded to thousands of women in Southeast Asia experiencing childbirth without the pain and complications of episiotomy, there are still many more women who could benefit from this intervention. Similarly, although this improve-

ment translated into less use of resources and health practitioner's time, further reductions are possible.

The fact that each center designed and implemented their intervention could explain the wide variation in RD pre- and post-intervention. The intervention focused on the skills needed to understand and implement evidence, resulting in a varied emphasis on specific practices depending on perceived needs. This could also be the reason why some centers reported no decrease or even an increase in episiotomy rate. In addition, it might explain why the overall decrease in episiotomy rate (from 64.1% to 60.1%) was modest. However, the advantage of this approach is that centers now have the skills to identify and implement new evidence. An unexpected benefit was that episiotomy rate was included as a national indicator in the Quality Improvement Programme of Malaysia. Thus, Malaysia could expect a decrease in episiotomy rate nationwide.

The intervention period was 2.5 years, and some changes may take longer to implement: for example, changes to midwifery and undergraduate medical curricula/subsequent graduation of students taught the new curricula. Furthermore, teachers of restrictive episiotomy practice also require initial training on conducting a normal birth without perineal trauma. This was evidenced by the fact that data collection at 1 of the centers at which there was an increase in episiotomy rate coincided with the entry of new residents trained in routine episiotomy. In addition to differences in intervention, differences in the enthusiasm of key staff could contribute to the wide variation seen between centers.

Several centers attempted to change from catgut to synthetic suture material, but the associated cost prohibited implementation in most centers. In 1 country, it was discussed at national level and a decision was made that it was too expensive to implement. In 2 countries, patients had to pay for the suture material themselves; despite this, 2 centers reported a significant change (data not shown).

The interviews identified a range of barriers to restrictive episiotomy practice. These included fear of tearing, difficulty in repairing tears compared with cuts, lack of perineal preparation, applicability of research carried out in a different population, lack of time, and need to train junior staff. Fear of tearing and difficulty associated with repair were reasons for episiotomy originally being introduced. The applicability of evidence between different populations is a valid concern, and it is reasonable to query whether there could be anatomic differences in perineal structure among Southeast Asian women that might affect applicability. Higher rates of episiotomy and perineal trauma have been reported for Asian women than for non-Asian women [13–16]. One center had successfully implemented restricted episiotomy practice pre-intervention. During the study, most centers were able to implement a restrictive practice without an increase in severe trauma and, in fact, many experienced a decrease. The results show that evidence for restricted episiotomy can be applied beneficially to Southeast Asian populations.

In conclusion, an intervention to increase the use and generation of evidence can result in significant improvements in episiotomy practice and a reduction in the rate of perineal trauma among women. The model could be adapted to improve the uptake of evidence-based practice in other centers and in other disciplines.

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Table 5

Suture material and technique used for skin closure at all centers for full-term normal births.^a

Item	Pre-intervention (n = 5070)	Post-intervention (n = 4358)
Polyglycolic acid	60 (1.2)	429 (9.8)
Continuous suture	3624 (72)	2775 (64.0)
Continuous suture using polyglycolic acid	57 (1.1)	208 (4.8)

^a Values given as number (percentage) unless otherwise indicated.

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Conflict of interest

The authors have no conflicts of interest.

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Air vs Perfluoropropane Gas in Pneumatic Retinopexy

A Randomized Noninferiority Trial

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Objective: To evaluate whether air is as effective as perfluoropropane gas in treating rhegmatogenous retinal detachment by pneumatic retinopexy.

Methods: In a double-blind, randomized, clinically controlled noninferiority trial, eligible patients were randomized into 2 treatment groups by using block randomization and treated by pneumatic retinopexy using filtered air or perfluoropropane gas.

Main Outcome Measures: Retinal reattachment rate and final visual recovery.

Results: One hundred twenty-six patients were recruited. Half (63 patients) were assigned to receive filtered air during pneumatic retinopexy and half received perfluoropropane gas. The single-procedure reattachment rate was higher for the perfluoropropane gas group (73.0% [46 patients]) than for the air group (60.3% [38]), but the difference was not statistically significant (risk difference, -12.7%; 95% confidence interval, -29.0% to 3.6%). The final reattachment rate after additional pneu-

matic retinopexy and/or surgical procedures was 92.1% (58) in the air group and 96.8% (61) in the perfluoropropane gas group. This result showed an equivalent effect on the final reattachment rate (risk difference, -4.7%; 95% confidence interval, -12.7% to 3.2%). Final visual acuity did not differ significantly between groups.

Conclusion: Pneumatic retinopexy using filtered air is associated with a nonsignificantly lower initial reattachment rate than using perfluoropropane gas but results in an equivalent final reattachment rate and final visual recovery.

Application to Clinical Practice: Air is an acceptable alternative to perfluoropropane gas when treating rhegmatogenous retinal detachment by pneumatic retinopexy.

Trial Registration: clinicaltrials.gov Identifier: NCT00120445

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PNEUMATIC RETINOPEXY IS A commonly used technique to repair rhegmatogenous retinal detachment (RRD). In this procedure, a gas bubble is injected into the vitreous cavity and placed over the retinal break by manipulating the patient's head position. The break is closed, and retinopexy seals the break.^{1,2} Subretinal fluid is then reabsorbed by the retinal pigment epithelium. This technique has several potential advantages in the management of uncomplicated RRD. It has been shown that pneumatic retinopexy involves less tissue manipulation, has less morbidity, and has better functional visual results compared with scleral buckling and vitrectomy.³⁻¹¹ Some researchers used air instead of expansile gas in an attempt to minimize vitreous disturbance and reported satisfactory results. Carim¹² demonstrated

that using air in pneumatic retinopexy was successful in selected cases. Yospaiboon and Sajjapong¹³ also reported satisfactory results using filtered air in this procedure, particularly in patients with phakic eyes. The reattachment rate and visual recovery were comparable to those when using expansile gas.

To the best of our knowledge, no clinical trial has compared air and expansile gas in pneumatic retinopexy. We hypothesized that both air and expansile gas are similarly effective as agents in pneumatic retinopexy. Perfluoropropane (C₃F₈) gas is expensive, and, in settings where C₃F₈ gas is not available or affordable, such as developing countries or remote areas, air would be a reasonable alternative. Therefore, we conducted a double-blind, randomized, controlled study to evaluate whether air is as effective as C₃F₈ gas in treating RRD by pneumatic retinopexy. We

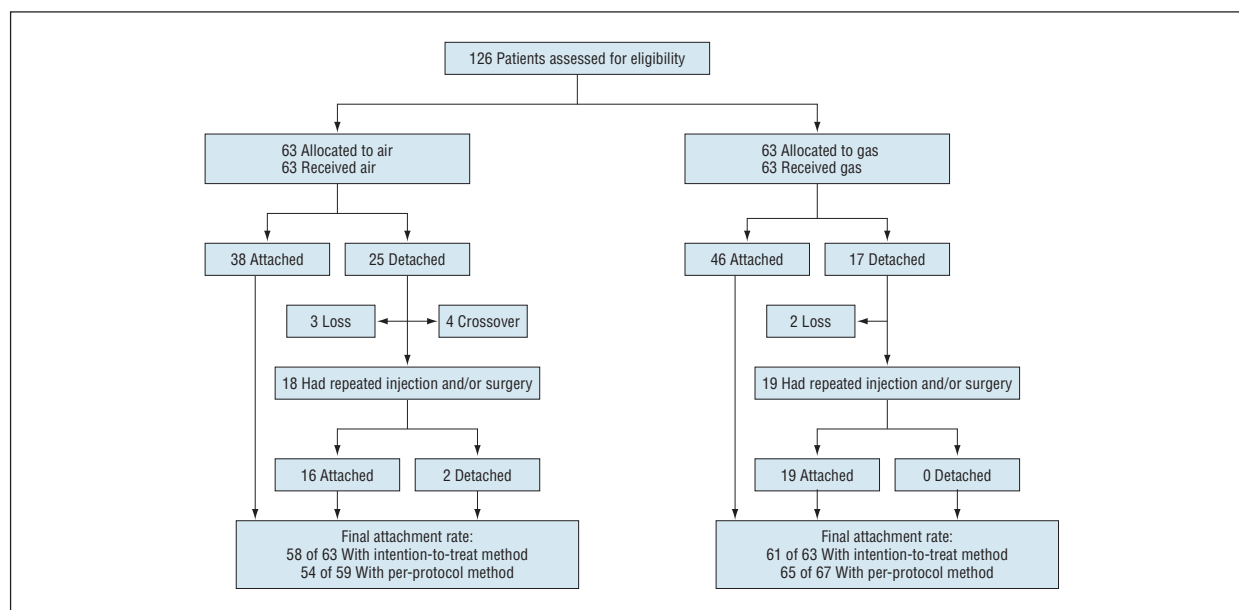


Figure 1. Study flowchart.

selected C_3F_8 gas because it was commonly used for pneumatic retinopexy at our hospital.

METHODS

A hospital-based, double-blind, randomized, clinically controlled noninferiority trial was conducted in a vitreoretinal center at Srinagarind Hospital, Khon Kaen University, in Thailand. This trial followed the tenets of the Declaration of Helsinki and was approved by the Khon Kaen University Ethics Committee for Human Research. All patients with RRD who visited the center between April 1, 2004, and October 31, 2008, were recruited. The eligibility criteria were having a superior retinal break between the 8-o'clock and 4-o'clock positions, having a single retinal break not larger than 2.5 clock hours, having multiple breaks not more than 3 clock hours away, having no or minimal proliferative vitreoretinopathy (PVR), being able to physically and mentally cooperate in postoperative head positioning, having at least 12 weeks of follow-up, and being capable of giving informed consent. Patients were excluded if they had only 1 eye or had ocular media opacities, advanced glaucoma, aphakia, pseudophakia, or a history of previous ocular surgical procedures. Recruited patients were allocated into 2 groups by block randomization with varying block size. Patients were treated by pneumatic retinopexy using filtered air or C_3F_8 gas (**Figure 1**).

One surgical nurse (S.P.) prepared air and C_3F_8 gas for intravitreal injection. An insulin syringe was connected to a filter (Millipore; Bausch & Lomb Inc, Rochester, New York) that had the capacity to filter bacteria at a level of $0.22\ \mu m$,¹⁴ and 0.3 mL of filtered air or C_3F_8 gas was drawn into the syringe. Syringes were then coded A or B for use in the treatment of patients in the air or C_3F_8 gas group, respectively. The allocation sequence was generated using computer-generated random numbers with randomly varying block size (SAS statistical software; SAS Institute Inc, Cary, North Carolina). The random allocation sequence was concealed in a sealed opaque envelope, numbered sequentially, and kept by the surgical nurse, who was the only one who knew which code was for air or C_3F_8 gas. The researchers and patients did not know the code, and unblinding was done at the end of the study.

The primary outcomes for both groups were the retinal reattachment rate and the final visual recovery. The retinal reattachment rate was calculated from the number of patients who had an attached retina after surgery divided by the total number of patients treated. The final visual recovery was the difference between the preoperative and postoperative best-corrected visual acuity that improved by 1 or more lines on a Snellen acuity chart was classified as "improved"; postoperative best-corrected visual acuity that decreased by 1 or more lines was classified as "worse."

We considered this an equivalence trial; thus, a formula by Jones et al¹⁵ was used for sample size calculation. We estimated that both groups would have a 90% final reattachment rate. At a 95% confidence level and a power of 80%, an acceptable margin of noninferiority in effectiveness of treatment was 15% for a 1-tailed test. The required number of patients per treatment group was calculated to be 63. For a 1-tailed test, equivalence is declared if the lower 1-sided confidence limit exceeds the defined level. We chose to use the 1-sided test in this study because we wanted to confirm that pneumatic retinopexy using air is not inferior to the procedure using C_3F_8 gas. Equivalence and superiority were both regarded as positive outcomes.

Descriptive statistics were used for the patients' demographic characteristics and clinical findings. Intention-to-treat and per-protocol methods were used to analyze the results and the comparisons between air and C_3F_8 gas. The reattachment rate, final visual recovery, and risk difference with 95% confidence intervals (CIs) were used to compare the differences for categorical outcomes.

RESULTS

A total of 126 patients with RRD were recruited into the trial. We allocated 63 patients to the air group and another 63 patients to the C_3F_8 gas group (**Figure 1**). The demographic characteristics of the patients in each group, including age and sex, and the associated conditions, such as myopia and history of trauma, were similar at study entry. The clinical findings in each group, including the duration of symptoms, type and number of retinal breaks,

Table 1. Demographic Characteristics and Clinical Findings

Characteristic	No. (%) of Patients	
	Air Group (n=63)	C ₃ F ₈ Gas Group (n=63)
Age, mean (SD) [range], y	54.1 (11.3) [28-76]	52.6 (13.5) [16-72]
Sex		
Female	21 (33.3)	20 (31.8)
Male	42 (66.7)	43 (68.2)
Associated conditions		
Myopia	6 (9.5)	5 (7.9)
Trauma	5 (7.9)	3 (4.8)
Duration of symptoms, mean (SD), wk	3.8 (4.0)	4.2 (5.8)
No. of retinal breaks, mean (SD)	1.4 (0.7)	1.4 (1.0)
Extent of detachment, No. of quadrants		
1	7 (11.1)	7 (11.1)
2	22 (34.9)	34 (54.0)
3	24 (38.1)	15 (23.8)
Total detachment, PVR grade ^a	10 (15.9)	7 (11.1)
A	41 (65.1)	41 (65.1)
B	21 (33.3)	21 (33.3)
C1	1 (1.6)	1 (1.6)

Abbreviations: C₃F₈, perfluoropropane; PVR, proliferative vitreoretinopathy.^aGrading of PVR is explained in Tornambe et al.¹⁶**Table 2. Pneumatic Retinopexy and Surgical Procedures**

	No. (%) of Patients	
	Air Group (n=63)	C ₃ F ₈ Gas Group (n=63)
Pneumatic retinopexy, No. of injections ^a		
Single	38 (60.3)	46 (73.0)
Multiple	25 (39.7)	17 (27.0)
Complications	12 (19.1)	13 (20.6)
New or missed break	3 (4.8)	8 (12.7)
Subretinal gas	4 (6.3)	1 (1.6)
Glaucoma	0	2 (3.2)
Epithelial defect	2 (3.2)	0
Other	3 (4.8)	2 (3.2)
Surgical procedures	24 (38.1)	20 (31.8)
Pars plana vitrectomy	19 (30.2)	12 (19.1)
Scleral buckling	1 (1.6)	6 (9.5)
Combined procedure	4 (6.3)	2 (3.2)
Follow-up, range, wk	6-228	6-190

Abbreviation: C₃F₈, perfluoropropane.^a*P* < .001.

extent of the detached retina, and grading of PVR, were also similar (**Table 1**). The interventions, including pneumatic retinopexy and other surgical procedures, are given in **Table 2**. Patients in the air group needed statistically significantly more injections (*P* < .001) than did those in the C₃F₈ gas group.

In this study, the initial reattachment rate for the air group was 71.4% (5 of 7 patients) for those with a retinal detachment extending 1 quadrant, 63.6% (14 of 22) for those with a retinal detachment extending 2 quadrants, 66.7% (16 of 24) for those with a retinal detachment extending 3 quadrants, and 30.0% (3 of 10) for those

Table 3. Reattachment Rate and Final Visual Recovery

	No. (%) of Patients		Risk Difference (95% CI)
	Air Group (n=63)	C ₃ F ₈ Gas Group (n=63)	
Reattachment rate			
Initial	38 (60.3)	46 (73.0)	-12.7 (-29.0 to 3.6)
Final	58 (92.1)	61 (96.8)	-4.7 (-12.7 to 3.2)
Final visual recovery			
Improved	33 (52.4)	36 (57.1)	-4.8 (-2.2 to 12.6)
Stable	23 (36.5)	18 (28.6)	7.9 (-8.4 to 24.2)
Worse	7 (11.1)	9 (14.3)	-3.2 (-14.8 to 8.4)

Abbreviations: C₃F₈, perfluoropropane; CI, confidence interval.

with total detachment. The initial reattachment rate for the C₃F₈ gas group was 85.7% (6 of 7 patients) for those with a retinal detachment extending 1 quadrant, 67.6% (23 of 34) for those with a retinal detachment extending 2 quadrants, 66.7% (10 of 15) for those with a retinal detachment extending 3 quadrants, and 100% (7 of 7) for those with total detachment.

The incidence rate of complications was 19.0% (12 of 63 patients) in the air group and 20.6% (13 of 63) in the C₃F₈ gas group (**Table 2**). There was no statistically significant difference in the number of complications from pneumatic retinopexy between the groups. Of interest, the incidence of new or missed breaks was 4.8% (3 patients) in the air group and 12.7% (8 patients) in the C₃F₈ gas group.

After the initial procedure, 4 patients in the air group in whom the reattachment failed were treated with C₃F₈ gas. Following the intention-to-treat principle, we did not exclude these 4 patients who crossed over from the analysis. Three patients in the air group and 2 in the C₃F₈ gas group were lost to follow-up. We assumed that they left the study because of an unsatisfactory result, and we included these patients in the group with detached retinas during analysis. Retinal reattachment rates evaluated after a single procedure were 38 of 63 patients (60.3%) in the air group and 46 of 63 (73.0%) in the C₃F₈ gas group (**Table 3**). The difference in initial reattachment rates was -12.7% (95% CI, -29.0% to 3.6%), which was not statistically significant (**Figure 2**). The final reattachment rates after repeated pneumatic retinopexy and/or additional surgical procedures were 92.1% (58 of 63 patients) in the air group and 96.8% (61 of 63) in C₃F₈ gas group. The difference in final reattachment rates was -4.7% (95% CI, -12.7% to 3.2%), indicating an equivalent effect of air and C₃F₈ gas on the final reattachment rate.

Although the intention-to-treat method can preserve the value of the randomization, substantial discontinuation or crossover between treatments will cause it to underestimate the magnitude of the treatment effect. Therefore, using intention-to-treat analysis might make the groups more similar and increase the likelihood that the treatments will be equivalent. We also used the per-protocol method to analyze our data. The final reattachment rates after repeated pneumatic retinopexy and/or surgical procedures were 91.5% (54 of 59 patients) in the air group and 97.0% (65 of 67) in the C₃F₈ gas group.

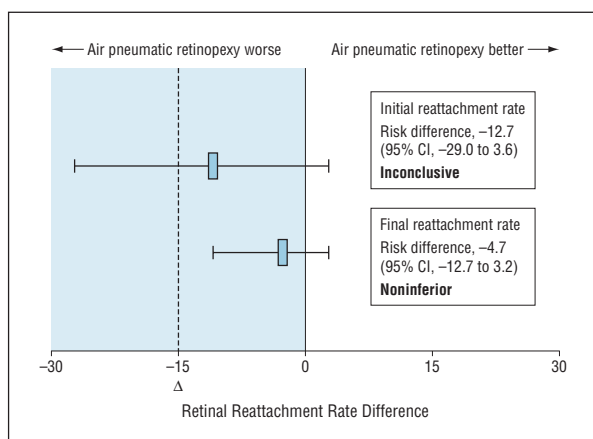


Figure 2. Retinal reattachment rate difference, determined by subtracting the perfluoropropane treatment reattachment rate from the air treatment reattachment rate. The vertical dotted line represents the margin of clinical equivalence; the vertical solid line, the null effect; and the error bars, 2-sided 95% confidence intervals (CIs). The shaded area indicates the zone of inferiority. For the initial reattachment rate difference (upper bar), the 95% CI includes Δ (which indicates the acceptable margin of noninferiority in effectiveness of treatment) and zero, and the difference is nonsignificant but the result regarding noninferiority is inconclusive. For the final reattachment rate difference (lower bar), the 95% CI extends to the right of Δ and includes zero, and the air treatment is noninferior but not shown to be superior.

The difference in final reattachment rates was -5.5% , which was similar to the result from the intention-to-treat analysis. This similarity indicates that pneumatic retinopexy using air is noninferior but not superior to retinopexy using C_3F_8 gas. In other words, there was an equivalent effect on the final reattachment rate. Final visual acuity results were slightly better in the C_3F_8 group compared with the air group, but the difference was not statistically significant ($P = .61$) (Table 3).

COMMENT

The results of this study demonstrate that final visual acuity and reattachment rates after pneumatic retinopexy for RRD were similar when using filtered air or C_3F_8 gas. This finding agrees well with previous studies.^{3,16,17} In a collaborative study of 100 cases, Hilton and coworkers³ demonstrated a reattachment rate of 78% after a single pneumatic retinopexy using C_3F_8 gas, with subsequent procedures resulting in a final reattachment rate of 98%.

Partial vitreal gas filling induces both biochemical and structural alterations and might predispose the eye to PVR, epimacular membrane, and new or missed break formation. From the previous reports, PVR was 5.2%, epimacular membrane was 2% to 4%, and new or missed retinal break formation was 11.7%.¹⁸ Therefore, some researchers used air in an attempt to minimize vitreous disturbance and reported satisfactory results. In 1990, the idea of using nonexpanding gas of short duration in pneumatic retinopexy was first introduced by Carim.¹² He used variable amounts of air (up to 1.0 mL) and had a reattachment rate of 75%. Three years later, Sebag and Tang¹⁹ performed pneumatic retinopexy using 0.8 mL of filtered air, with a reattachment rate of 87% (39 of 45 patients) after a single intravitreal injection. In that case series, paracentesis of the anterior chamber was performed

in all patients. Yospaiboon and Sajjapong¹³ also demonstrated a reattachment rate of 75% following a single injection of 0.3 mL of air for pneumatic retinopexy, with a final reattachment rate of 90% after subsequent procedures. The reattachment rate in phakic eyes was 88% following a single air injection and 94% after subsequent procedures. They concluded that pneumatic retinopexy with air can be performed in selected cases of phakic retinal detachment with a success rate that is comparable to that of the procedure using expansile gases.

Two gas properties, surface tension and buoyancy, play roles in the mechanism of pneumatic retinopexy. A gas bubble occludes the retinal break, permitting the retinal pigment epithelium to remove subretinal fluid, and then presses the retina against the retinal pigment epithelium, sheltering the edge of the break from eddy currents until a chorioretinal scar is formed, sealing the break. Generally, mild chorioretinal adhesion after laser photocoagulation occurs within 24 hours, moderate adhesion in 5 to 7 days, and strong adhesion in 10 to 14 days. Because moderate chorioretinal adhesion was noted 5 to 7 days after retinopexy, the air bubble, with a half-life of 24 to 48 hours and a duration of 5 to 6 days, also has these 2 properties and remains in the eye long enough to carry out its task.

Although some retinal surgeons use pneumatic retinopexy for small or limited detachments only, we routinely attempt the procedure in all patients with RRD—even those with total detachments—as long as they meet the eligibility criteria. Our clinical experience is that pneumatic retinopexy works well.

Reattachment failure occurs for 2 main reasons: (1) persistent vitreous traction on the break such that the buoyancy of the bubble fails to close the break and (2) development of new or sequential breaks, presumably secondary to vitreous traction that is promoted by a bubble. In this study, the incidence of new or missed breaks in the C_3F_8 gas group (12.7%) was comparable to that reported in previous studies (11.7%).¹⁸ The C_3F_8 gas group had a much higher rate of new or missed breaks (compared with 4.8% for the air group), which may be attributed to a greater vitreous traction effect caused by the progressive expansile gas.

As we noted, reattachments in 3 patients in the air group and 8 in the C_3F_8 gas group failed because of a new or missed break. The remaining failures (22 in the air group and 9 in the C_3F_8 gas group) were attributed to too much residual vitreous traction, which allowed the break to flatten or caused a reopening despite chorioretinal adhesion.

Our study is the first, to our knowledge, to directly compare air and C_3F_8 gas in a double-blind, randomized, controlled trial. Furthermore, the number of patients who were lost to follow-up after randomization was minimal. However, we controlled this problem with a sensitivity analysis in which the assumed best (all attached) or worst (all detached) did not change the result of the primary outcome. All these factors strengthen the validity of our conclusions.

The one limitation of this study was the blinding. Although the patients, those administering the intervention, and those assessing the outcomes were unaware of the group assignment, the assessor could determine that

air had been administered because it was reabsorbed faster than expansile gas. The assessor, therefore, might have had selection bias for repeated injections. The crossover also might have biased the study toward equivalency. In those cases, we used both intention-to-treat and per-protocol methods for analysis. The similar results increase the confidence in our conclusions.

In summary, pneumatic retinopexy using air is associated with a nonsignificantly lower initial reattachment rate than is pneumatic retinopexy using C₃F₈ gas but results in an equivalent final reattachment rate and final visual recovery. We recommend using either filtered air or C₃F₈ when treating RRD by pneumatic retinopexy.

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100 Years Ago in the Archives

In the various discussions which have taken place, from time to time, as to the advantages and disadvantages of this operation, it has been contended, by the opponents of the operation for the extraction of the cataract in the capsule, that one of the chief objections to this operation is the frequency of the escape of vitreous. This being the only complication which is at all frequent, and the one which is most commonly met with beginners in this operation, I inquired from Major Smith on my arrival in Jullundur in 1906 if any series of cases had ever been published, in which the after-effects of escape of vitreous in this operation were given.

Reference: Lister AEJ. The after-effects of escape of the vitreous during the operation of extraction of cataract in the capsule, by Smith's operation. *Arch Ophthalmol*. 1910;39:1.

RESEARCH ARTICLE

Open Access

Caesarean section without medical indications is associated with an increased risk of adverse short-term maternal outcomes: the 2004-2008 WHO Global Survey on Maternal and Perinatal Health

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Abstract

Background: There is worldwide debate about the appropriateness of caesarean sections performed without medical indications. In this analysis, we aim to further investigate the relationship between caesarean section without medical indication and severe maternal outcomes.

Methods: This is a multicountry, facility-based survey that used a stratified multistage cluster sampling design to obtain a sample of countries and health institutions worldwide. A total of 24 countries and 373 health facilities participated in this study. Data collection took place during 2004 and 2005 in Africa and the Americas and during 2007 and 2008 in Asia. All women giving birth at the facility during the study period were included and had their medical records reviewed before discharge from the hospital. Univariate and multilevel analysis were performed to study the association between each group's mode of delivery and the severe maternal and perinatal outcome.

Results: A total of 286,565 deliveries were analysed. The overall caesarean section rate was 25.7% and a total of 1.0 percent of all deliveries were caesarean sections without medical indications, either due to maternal request or in the absence of other recorded indications. Compared to spontaneous vaginal delivery, all other modes of delivery presented an association with the increased risk of death, admission to ICU, blood transfusion and hysterectomy, including antepartum caesarean section without medical indications (Adjusted Odds Ratio (Adj OR), 5.93, 95% Confidence Interval (95% CI), 3.88 to 9.05) and intrapartum caesarean section without medical indications (Adj OR, 14.29, 95% CI, 10.91 to 18.72). In addition, this association is stronger in Africa, compared to Asia and Latin America.

Conclusions: Caesarean sections were associated with an intrinsic risk of increased severe maternal outcomes. We conclude that caesarean sections should be performed when a clear benefit is anticipated, a benefit that might compensate for the higher costs and additional risks associated with this operation.

Background

Caesarean sections performed appropriately and following an appropriate medical indication are potentially life-saving procedures. In this context, the provision of timely and safe caesarean sections in high maternal mortality countries is a major challenge faced by local health systems [1]. At the same time, in many settings,

women are increasingly undergoing caesarean sections without any medical indication which may contribute to the worldwide secular trend towards higher rates of caesarean sections [2,3]. Over the last two decades, there has been a debate about the appropriateness of caesarean sections performed due to maternal request or following the indication of health care professionals but without a clear medical reason for this surgical procedure. Safety, costs, women's rights and wishes, maternal and professional satisfaction have been elements of this debate [4-10].

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One factor that certainly favoured the liberalization of caesarean section in clinical practice has been the perception of caesarean section as a generally safe procedure, despite the increased costs associated with it. However, the assessment of the intrinsic risk of caesarean sections is complicated by substantial limitations in the existing medical literature [11,12]. Strong evidence would be provided by a well-designed randomized controlled trial, in which healthy women without co-existing medical conditions would be allocated to either intention to deliver by elective caesarean section or expectant management [13]. Obviously, ethical constraints prevent such a trial. In other designs, the scientific community has been struggling with indirectness, imprecision due to sample size limitations and paucity of data, or difficulties in disentangling confounders and effect modifiers in order to establish clear associations between caesarean sections and the occurrence of severe maternal outcomes.

In this context, the World Health Organization Global Survey on Maternal and Perinatal Health (WHOGS) provides evidence on the relationship between mode of delivery and maternal and perinatal outcomes. The WHOGS is a large cross-sectional study conducted in 24 countries around the world between 2004 and 2008. The project has been implemented in three continental steps, and each continental analysis has shown an association between caesarean section and an increased risk of adverse maternal outcomes [5-7,14,15]. In the present three continental analyses we aimed to further investigate the relationship between caesarean section and severe maternal outcomes; more specifically, we wanted to assess the intrinsic risk of caesarean sections with a special focus on those without medical indication.

Methods

Study design

Methodological details of the global survey have been published elsewhere [14]. Briefly, this is a multicountry, facility-based survey that collected data for all delivering women in randomly selected facilities from randomly selected countries. A stratified multistage cluster sampling design was used to obtain a sample from countries and health institutions worldwide. Countries in the WHO regions were further grouped according to adult and under-five infant mortality. From each of these sub regions, four countries were selected, with probability proportional to population size. A total of 54 countries were selected, but owing to financial and practical constraints, the study was implemented in the selected countries of three continents: Africa, the Americas and Asia. For the same reasons, developed countries were excluded (unless they volunteered to participate with their own funds, for example, Japan). Few other countries

(for example, the Democratic People's Republic of Korea, Ethiopia, Haiti, Indonesia) could not participate due to country refusal, security issues or other reasons. A total of 24 countries took part in the study. In each country, two regions or provinces, in addition to the capital city, were randomly selected with probability of selection proportional to their size. Once a province had been selected, we obtained a census of all facilities within the province with more than 1,000 births per year and those reported as able to perform caesarean sections. If there were more than seven facilities, seven were randomly selected with probability of selection proportional to the number of births per year. If there were fewer than seven facilities, all were selected. In each of the selected institutions, we studied all women admitted for delivery during three months in institutions with 6,000 or fewer expected deliveries per year and during two months in those with more than 6,000 expected deliveries per year.

Data collection took place during 2004 and 2005 in Africa and the Americas and during 2007 and 2008 in Asia. We obtained written permission from all ministries of health of the participating countries and the directors of the selected facilities. We obtained data for all individuals from medical records and participants were not identified. The Ethics Review Committee of WHO and of each country independently approved the protocol.

Data collection

Data were collected for institutions and for individuals. For institutions, the hospital coordinator completed a form in consultation with the director or head of obstetrics. Data included characteristics of maternal and perinatal care, including the availability of laboratory tests; anesthesiology resources; services for intrapartum care, delivery, and care of the newborn baby; and presence or absence of basic emergency medical and obstetric care facilities, intensive care units (ICUs), and human and training resources. For individuals, data were obtained from women's medical records to complete a two-page form. Individual data included demographic characteristics, maternal risk, current pregnancy, method of delivery, and outcomes (maternal and perinatal) up to hospital discharge. All women giving birth at the facility during the study period were included. Trained staff reviewed medical records of all women and their babies before discharge from the hospital, and abstracted data daily to their forms for individual data collection. The hospital coordinator supervised data collection, resolving or clarifying unclear medical notes before forms were sent for data entry. Attending staff updated incomplete records before discharge. Criteria for data abstraction were defined in the manuals of operations, which were available for staff training and monitoring of data quality, keeping to a minimum the need for judgment and

interpretation. The manual contained definitions of all terms used and synonyms of medical and obstetric terms, and described questions and corresponding answers. Shortly after collection, data were entered at the country, provincial or facility level in a web-based system (MedSciNet AB, Stockholm, Sweden).

Statistical analysis

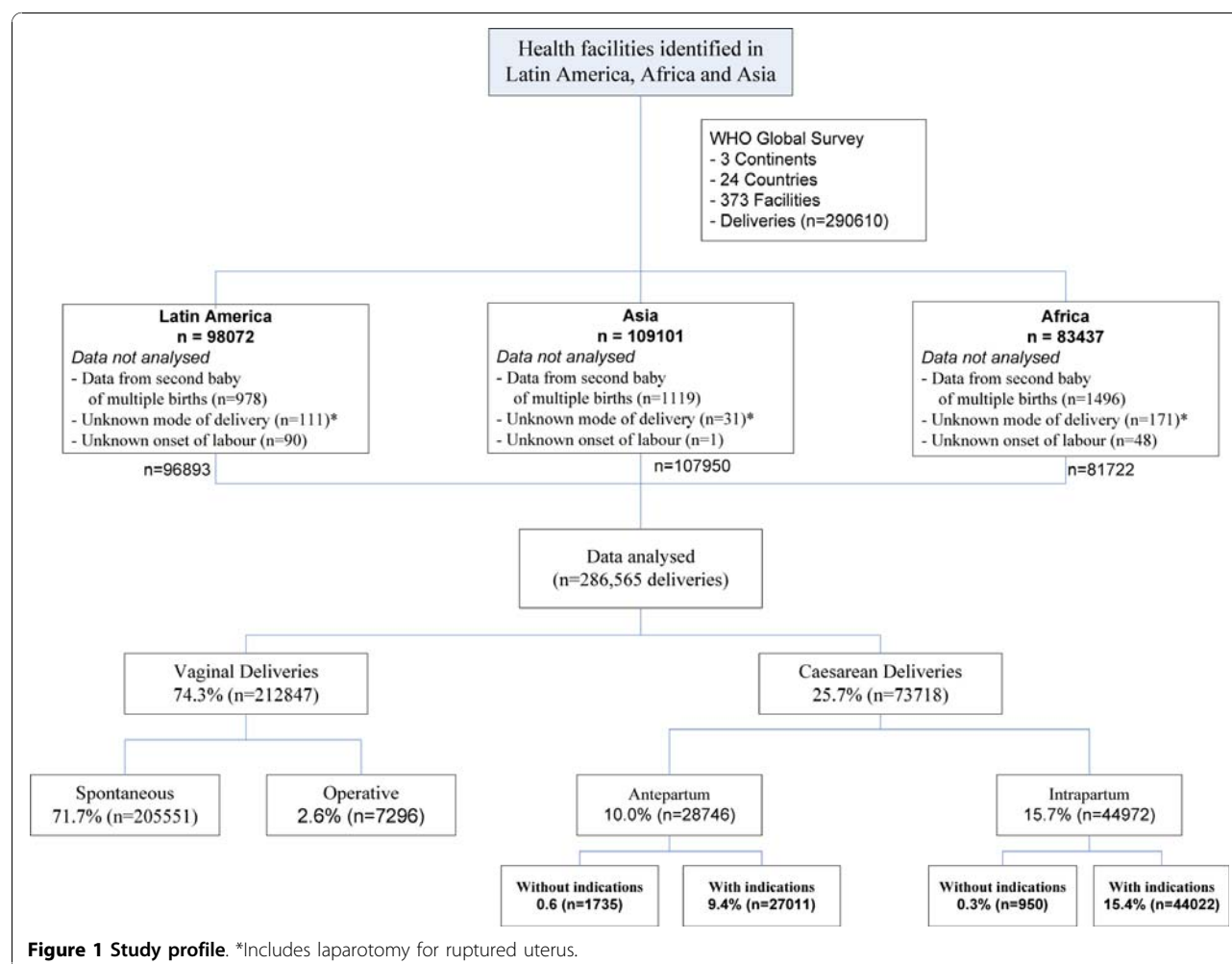
In this three-continent analysis, the continental databases were merged into a global database. Then, frequencies were used to describe modes of delivery for each country and facility characteristics as well as characteristics of mothers and babies for each group's mode of delivery (including caesarean section without medical indication). The main outcome was severe maternal outcome, defined as the occurrence of any of the following conditions: death, admission to ICU, blood transfusion or hysterectomy within the seven days following birth. The severe perinatal outcomes considered were fetal death, neonatal mortality up to hospital discharge limited to the first week of life, and stay of more than or equal to seven days in the neonatal intensive care unit. Univariate analysis followed by generalized linear and latent mixed models (GLLAMM) for multilevel analysis was performed to study the association between each group's mode of delivery and the severe maternal and perinatal outcome using the GLIMMIX procedure in SAS (version 9.1 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina, USA). This procedure was intended to account for clustering effects within facilities and the analysis was adjusted for possible confounding factors and effect modifiers, including individual and institutional characteristics. Among the institutional characteristics, a hospital complexity index was used to assess the hospital capacity in terms of providing essential health services, emergency obstetric care and human resources. This hospital complexity index was used in previous Global Survey analysis and was detailed elsewhere [14]. Risks of maternal and perinatal outcomes associated with modes of delivery (including caesarean section without medical indications) were presented by adjusted Odds Ratios (Adj OR) with corresponding 95% Confidence Intervals (95% CI). Heterogeneity between countries was explored through simple regional stratification and adjusted country-based forest plots. Two subgroup analyses were conducted, one excluding all women with morbidities, complications, multiple pregnancies, breech presentations and previous caesarean sections and another of neonates with breech presentation.

Results

A total of 24 countries and 373 health facilities participated in the WHO Global Survey on Maternal and Perinatal Health, collecting information on 290,610

deliveries. The study was implemented in seven African countries (131 health facilities, 83,437 participants), eight Latin American countries (120 health facilities, 98,072 participants) and nine Asian countries (122 facilities, 109,101 participants). Most of the facilities were located in urban areas ($n = 275$) and of low complexity ($n = 280$). Data from the second or high order baby in multiple pregnancies and from participants with unknown mode of delivery or unknown onset of labour were not analysed, resulting in 286,565 participants included in the present analysis. Figure 1 presents the study profile, while Table 1 shows the total number of deliveries and facilities by country, and percentages of deliveries by mode and country. African countries had the highest rates of spontaneous vaginal delivery while Asian countries tended to have higher rates of operative vaginal delivery. The overall caesarean section rate was 25.7% and the Chinese health facilities had the highest caesarean section rates (average for Chinese health facilities: 46.2%). A total of 1.0 percent of all deliveries had caesarean sections without medical indications, either due to maternal request or in the absence of other recorded indications. In 23 out of 24 countries, the overall proportion of women delivering by caesarean section without medical indication ranged from 0.01 to 2.10%. In the Chinese institutions participating in this survey this figure was exceptionally higher at 11.6%. A total of 63% of all caesarean sections without medical indications were performed in Chinese health facilities ($n = 1,689/2,685$ caesarean sections without medical indications; 11.6% of all deliveries in China). Table 2 presents characteristics of women by mode of delivery. Women delivering by caesarean section antepartum without medical indications had some distinctive features: a higher proportion of married women, fewer adolescents, more educated and more primiparous women, and less frequent antecedent of low birth weight and fetal and neonatal death in a previous pregnancy. A proportion of women having caesarean sections without a medical indication had some other comorbidities, which, nevertheless, were not considered as the indication for the caesarean section.

Table 3 presents the risk of severe maternal outcomes by mode of delivery. Overall, the prevalence of severe maternal outcomes was 37 cases/1,000 deliveries. In addition, compared to spontaneous vaginal delivery, all other modes of delivery presented an association with increased risk of death, admission to ICU, blood transfusion and hysterectomy, including antepartum caesarean section without medical indications (Adjusted Odds Ratio (Adj OR), 5.93, 95% Confidence Interval (95% CI), 3.88 to 9.05) and intrapartum caesarean section without medical indications (Adj OR, 14.29, 95% CI, 10.91 to 18.72). Table 4 presents the stratification of the



combined severe maternal outcomes by region, showing that in all regions there was a trend towards an increased risk associated with caesarean sections without indication. This association is stronger in Africa, compared to Asia and Latin America. The adjusted country level analysis and the resulting country-based forest plots were limited by the low frequency of severe maternal outcomes: in various countries the outcome data (adjusted OR) became zero or non estimable after adjustment for the factors listed at the footnote of Table 3. Overall, the results at the country-level were more imprecise but a trend towards an increased risk has been observed with no country presenting statistically significant results favoring caesarean section. In the subgroup of women without any recorded morbidity including multiple pregnancies, breech presentations and previous caesarean sections, caesarean sections without indications were compared to spontaneous vaginal births. A total of 1,412 women having caesarean sections were compared to 118,742 women having a spontaneous vaginal delivery:

26 women having caesarean sections and 879 women having vaginal deliveries presented severe maternal outcomes (OR = 2.52; 95% CI 1.70 to 3.73).

Table 5 presents the relationship between mode of delivery and severe perinatal outcome. Compared to spontaneous vaginal delivery, operative vaginal delivery, antepartum caesarean section with indications and any intrapartum caesarean section were associated with an increased risk of severe perinatal outcomes. In the subgroup of neonates with breech presentation, caesarean delivery was associated with a reduced risk of severe perinatal outcome (antepartum caesarean section, adj OR = 0.64, 95% CI 0.51 to 0.80; intrapartum caesarean section, adj OR = 0.80, 95% CI 0.66 to 0.97; data not shown in tables).

Discussion

In this paper, the intrinsic risk of caesarean sections was assessed. Caesarean sections were associated with an intrinsic risk for short-term severe maternal outcomes.

Table 1 Total number of deliveries and facilities by country, and the percentages of deliveries by mode and country

	Vaginal Delivery		Caesarean section without indications		Caesarean section with indications		Total deliveries	Total facilities
	Spontaneous	Operative	Antepartum	Intrapartum	Antepartum	Intrapartum		
	%	%	%	%	%	%	n	n
Africa								
Algeria	80.5	5.9	0.04	0.1	5.9	7.5	15,578	18
Angola	97.7	0.8	0.1	0.02	1.0	0.5	6,322	20
D.R. Congo	84.8	2.3	0.1	0.1	1.4	11.4	8,804	21
Kenya	82.9	1.5	0.1	0.5	3.2	11.8	19,968	20
Niger	91.5	3.2	0.02	0.2	0.4	4.8	8,275	11
Nigeria	81.1	4.4	0.1	0.3	3.6	10.5	8,939	21
Uganda	85.4	1.2	0.1	0.3	2.1	10.9	13,836	20
Americas								
Argentina	62.1	2.8	0.2	0.1	17.8	17.0	10,689	14
Brazil	68.5	2.0	0.3	0.2	15.4	13.6	15,129	19
Cuba	61.7	2.7	0.02	0.1	16.6	18.8	12,642	17
Ecuador	59.2	0.5	0.1	0.6	7.8	31.8	12,414	18
Mexico	60.4	1.9	0.1	0.1	15.8	21.8	20,883	21
Nicaragua	69.1	0.1	0.1	0.2	7.7	22.8	5,636	8
Paraguay	57.3	0.8	1.2	0.9	18.1	21.7	3,460	17
Peru	65.4	0.6	0.01	0.0	13.2	20.8	16,040	17
Asia								
Cambodia	77.6	7.7	0.04	0.2	2.6	11.8	5,565	5
China	52.6	1.2	9.3	2.3	19.7	14.9	14,541	21
India	79.4	2.9	0.1	0.2	3.6	13.8	24,682	20
Japan	74.1	6.1	0.1	0.0	13.9	5.9	3,300	10
Nepal	76.0	3.8	0.04	0.1	6.2	14.0	8,489	8
Philippines	78.4	2.8	0.04	0.1	8.0	10.3	13,295	6
Sri Lanka	65.9	3.5	0.5	0.2	20.2	9.8	15,024	14
Thailand	61.6	4.3	0.3	0.1	13.4	20.2	9,745	12
Vietnam	62.2	2.2	0.2	0.8	4.3	30.2	13,309	15
Total	71.7	2.6	0.6	0.3	9.4	15.4	286,565	373

Overall, this risk was higher in African countries than in Asia or Latin America. These findings corroborate the previous WHO Global Survey continental-level analyses [5-7,15] and also provide further evidence for cautioning physicians and patients about issues related with caesarean sections with no medical indications.

Over the years, it has been noted in the medical literature that the interaction between the maternal underlying condition and the caesarean section operation complicates the assessment of caesarean section intrinsic risk. In order to address this issue, we tried to account for the contribution of the medical conditions leading to the operation, other risk factors, confounders and effect modifiers through multilevel statistical modeling. The

results of this statistical adjustment (presented in Table 3) show a substantial positive association between caesarean section and severe maternal outcomes. Similar methods were used in the previous continental analysis for Asia and it is reassuring to find a consistent trend in the two other continents. Furthering this approach, we conducted a subgroup analysis including only women with no identifiable medical risk factors: the caesarean section operation was found to increase the risk of severe maternal outcomes. Stratifying the assessment at continent and country level, similar findings were found. Operative vaginal delivery was also found to be associated with an increased risk of severe maternal outcomes suggesting that these interventions should be

Table 2 Selected maternal characteristics and mode of delivery (%)

	Vaginal delivery		Caesarean section without indications		Caesarean section with indications		Total
	Spontaneous	Operative	Antepartum	Intrapartum	Antepartum	Intrapartum	
	N = 205,551	N = 7,296	N = 1,735	N = 950	N = 27,011	N = 44,022	N = 286,565
Marital status (single)	13.5	9.3	2.7	6.0	11.8	10.7	12.7
Maternal age							
≤16 years	2.5	2	0.1	1.9	1.4	2.4	2.3
16 to 35	87.8	85.7	89.4	85.9	80.1	86	86.8
≥35	9.7	12.3	10.6	12.3	18.5	11.6	10.9
Years of education							
<7	30.9	28.4	11.4	20.5	18.4	24.7	28.6
7 to 12	57.1	54.9	59.0	56.1	59.4	57.6	57.4
>12	12	16.7	29.7	23.4	22.2	17.7	14.1
Primiparous	41.2	57.3	73.3	58.8	37.6	49.7	42.8
Previous pregnancy							
Low birth weight	10.0	14.1	3.1	5.4	14.9	10.1	10.5
Fetal or neonatal death	2.0	2.4	1.6	3.6	2.6	2.6	2.1
Caesarean delivery in the last pregnancy	2	5.9	6.7	11.9	39.3	23.5	9
Current pregnancy							
Induced labour	9.9	15.4	0.0	13.9	0.0	13.9	9.7
Prelabour rupture of membranes	9.4	13.2	8.4	16.0	8.7	15.3	10.3
Pregnancy induced hypertension	2.8	5.3	2.9	3.2	8.5	5.5	3.8
Pre-eclampsia	1.6	3.2	1.3	1.3	8.9	4.8	2.8
Eclampsia	0.2	0.8	0.1	0.3	1	0.6	0.4
Chronic hypertension	0.6	1	0.2	0.2	2.4	1.2	0.8
Vaginal bleeding in second half of pregnancy	0.9	1.2	0.6	0.9	3.6	2	1.3
Suspected fetal growth impairment	0.8	1	0.3	0.7	2.5	1	1
Breech or other non-cephalic presentation	1	25.1	0	0	14.7	12.6	4.7
Referred for complication related to pregnancy	18.8	23.9	9.1	14.2	34	28.8	21.8
HIV	0.8	0.5	0.5	1.4	1	0.9	0.8
Cardiac/Renal diseases	0.3	1	0.5	0.5	1.1	0.5	0.5
Chronic respiratory conditions	0.5	0.7	0.3	0.2	1	0.6	0.6
Diabetes mellitus	0.4	0.7	1.5	0.3	2.6	1	0.7
Malaria	3.3	2.7	0.2	1.3	0.4	1.1	2.6
Sickle cell anaemia	0.3	0.1	0.0	0.3	0.5	0.4	0.3
Severe anaemia	0.5	0.8	0.1	0.5	0.8	0.5	0.6
Pyelonephritis or urinary infection	5.9	4.4	0.6	5.4	8.4	8.6	6.5
Other medical conditions	5.3	5.3	10.2	5.7	12.6	8.2	6.5

performed very carefully by trained providers and only when necessary.

Severe maternal outcomes are relatively rare conditions during pregnancy and childbirth. This factor may contribute to the misperception of safety related to caesarean section and lead to the overuse of the procedure. The relatively low frequency of severe outcomes also makes their appropriate assessment more complex, requiring large databases. The present analysis and findings were possible due to key features of the WHO

Global Survey on Maternal and Perinatal Health project. In this project, standard methods were used across 373 hospitals around the world, generating a consistent and large database, containing a considerable number of severe maternal outcomes, including maternal deaths, intensive care unit admission, blood transfusion and hysterectomy. Another unique feature of the database was the concurrent data collection in all participating health facilities in each region thus ensuring that clinical practice in the various settings was captured during the

Table 3 The relationship between mode of delivery and severe maternal outcomes (that is, death, admission to ICU, blood transfusion, hysterectomy)

Maternal outcomes	n/N (%)	Adjusted OR [95%CI]
Death*		
Spontaneous (reference)	196/205,551 (0.10)	1
Operative	34/7,296 (0.47)	2.9 (1.84 to 4.56)
Antepartum without indications	0/1,735(0)	Not estimated
Intrapartum without indications	2/950(0.21)	3.21 (0.78 to 13.2)
Antepartum with indications	36/27,011(0.13)	1.51 (0.97 to 2.33)
Intrapartum with indications	74/44,022(0.17)	1.7 (1.24 to 2.33)
Admission to ICU**		
Spontaneous (reference)	1,189/205,551 (0.58)	1
Operative	172/7,296 (2.36)	2.27 (1.89 to 2.73)
Antepartum without indications	22/1,735(1.27)	30.75 (18.12 to 52.17)
Intrapartum without indications	67/950(7.05)	58.85 (41.46 to 83.52)
Antepartum with indications	1,741/27,011 (6.45)	63.4 (56.32 to 71.36)
Intrapartum with indications	3,457/44,022 (7.85)	51.3 (46.56 to 56.59)
Blood transfusion†		
Spontaneous (reference)	1,940/205,303 (0.94)	1
Operative	198/7,287 (2.72)	2.11 (1.79 to 2.48)
Antepartum without indications	9/1,735(0.52)	1.79 (0.91 to 3.52)
Intrapartum without indications	18/950(1.89)	3.7 (2.24 to 6.1)
Antepartum with indications	892/26,967(3.31)	3.75 (3.39 to 4.14)
Intrapartum with indications	1,475/43,928 (3.36)	3.85 (3.55 to 4.16)
Hysterectomy††		
Spontaneous (reference)	82/205,299 (0.04)	1
Operative	11/7,278 (0.15)	3.38 (1.73 to 6.59)
Antepartum without indications	0/1,733(0)	Not estimated
Intrapartum without indications	4/949(0.42)	13.53 (4.79 to 38.2)
Antepartum with indications	100/26,916(0.37)	6.11 (4.38 to 8.52)
Intrapartum with indications	118/43,889(0.27)	6.68 (4.91 to 9.09)
Severe Maternal Outcomes†††		
Spontaneous (reference)	3,147/205,551 (1.53)	1
Operative	346/7,296 (4.74)	1.84 (1.62 to 2.1)
Antepartum without indications	28/1,735(1.61)	5.93 (3.88 to 9.05)
Intrapartum without indications	86/950(9.05)	14.29 (10.91 to 18.72)

Table 3 The relationship between mode of delivery and severe maternal outcomes (that is, death, admission to ICU, blood transfusion, hysterectomy) (Continued)

Antepartum with indications	2,452/27011 (9.08)	13.28 (12.3 to 14.34)
Intrapartum with indications	4,523/44,022 (10.27)	12.05 (11.33 to 12.82)

*Total number of years attended school, birth weight, Pregnancy induced hypertension or preeclampsia or eclampsia or chronic hypertension, suspected fetal growth impairment, vaginal bleeding in second half of pregnancy, Breech or other non-cephalic presentation, referred for complication related to pregnancy or delivery, induced labour, HIV positive, Any other medical complication during pregnancy (excluding chronic hypertension) and incentive for caesarean section (no missing data for this outcome).

**Maternal age, total number of years attended school, birth weight, prelabour rupture of membranes, pregnancy induced hypertension or preeclampsia or eclampsia or chronic hypertension, vaginal bleeding in second half of pregnancy, Referred for complication related to pregnancy or delivery, induced labour, HIV positive, any other medical complication during pregnancy (excluding chronic hypertension), incentive for caesarean section and country (no missing data for this outcome).

†Maternal age, total number of years attended school, primiparaous, birth weight, neonatal death or stillbirth, pregnancy induced hypertension or preeclampsia or eclampsia or chronic hypertension, vaginal bleeding in second half of pregnancy, any antenatal antibiotic treatment, referred for complication related to pregnancy or delivery, induced labour, hiv positive, any other medical complication during pregnancy (excluding chronic hypertension), incentive for caesarean section and country (395 participants with missing data for this outcome).

†† Maternal age, Primiparaous, birth weight, vaginal bleeding in second half of pregnancy, referred for complication related to pregnancy or delivery, any other medical complication during pregnancy (excluding chronic hypertension), country and incentive for caesarean section (501 participants with missing data for this outcome).

†††Maternal age, total number of years attended school, birth weight, neonatal death or stillbirth, prelabour rupture of membranes, pregnancy induced hypertension or preeclampsia or eclampsia or chronic hypertension, vaginal bleeding in the second half of pregnancy, any antenatal antibiotic treatment, breech or other non-cephalic presentation, referred for complication related to pregnancy or delivery, induced labour, hiv positive, any other medical complication during pregnancy (excluding chronic hypertension), country and incentive for caesarean section (data available for at least one of the included outcomes for all participants).

Table 4 Relationship between mode of delivery and severe maternal outcomes by continent

Severe Maternal Outcomes	No (%)	Adjusted OR [95% CI]
Africa †		
Spontaneous (reference)	1011/69,364 (1.46)	1 to
Operative	151/2,298 (6.57)	2.58 (2.12-3.15)
Antepartum without indications	14/63(22.22)	71.29 (32.06 to 158.55)
Intrapartum without indications	36/202(17.82)	40.67 (24.56-67.33)
Antepartum with indications	960/2,399 (40.02)	88.61 (74.88 to 104.86)
Intrapartum with indications	1,942/7,396 (26.26)	54.26 (47.81 to 61.59)
Americas††		
Spontaneous (reference)	946/61130 (1.55)	1
Operative	50/1533 (3.26)	2.2 (1.62 to 2.99)

Table 4 Relationship between mode of delivery and severe maternal outcomes by continent (Continued)

Antepartum without indications	6/157(3.82)	1.94 (0.77 to 4.9)
Intrapartum without indications	10/194(5.15)	4 (2.05 to 7.82)
Antepartum with indications	803/13759(5.84)	3.04 (2.71 to 3.41)
Intrapartum with indications	640/20120(3.18)	1.91 (1.71 to 2.13)
Asia^{†††}		
Spontaneous (reference)	1190/75057 (1.59)	1
Operative	145/3465 (4.18)	1.91 (1.56 to 2.35)
Antepartum without indications	8/1515(0.53)	2.14 (1.04 to 4.43)
Intrapartum without indications	40/554(7.22)	12.86 (8.83 to 18.73)
Antepartum with indications	689/10853(6.35)	8.09 (7.12 to 9.18)
Intrapartum with indications	1941/16506 (11.76)	11.61 (10.56 to 12.76)

†Maternal age, Total number of years attended school, Primiparaous, Birth weight, Neonatal death or stillbirth, Caesarean section at last pregnancy, Pregnancy induced hypertension or preeclampsia or eclampsia or chronic hypertension, Suspected fetal growth impairment, Vaginal bleeding in 2nd half of pregnancy, Referred for complication related to pregnancy or delivery, Any other medical complication during pregnancy (excluding chronic hypertension), Country, Incentive for caesarean section.

††Birth weight, Prelabour rupture of membranes, Pregnancy induced hypertension or preeclampsia or eclampsia or chronic hypertension, Vaginal bleeding in 2nd half of pregnancy, Any antenatal antibiotic treatment, Referred for complication related to pregnancy or delivery, Induced labour, HIVPOS, Any other medical complication during pregnancy (excluding chronic hypertension) and Incentive for caesarean section.

††† Maternal age, Total number of years attended school, Primiparous, Birth weight, Neonatal death or stillbirth, Prelabour rupture of membranes, Pregnancy induced hypertension or preeclampsia or eclampsia or chronic hypertension, Vaginal bleeding in 2nd half of pregnancy, Breech or other non-cephalic presentation, Referred for complication related to pregnancy or delivery, HIVPOS, Any other medical complication during pregnancy (excluding chronic hypertension), Country and Complexity of index.

(Differently from the previous Asian specific analysis [7], the severe maternal outcomes included in this analysis are: death, admission to ICU, blood transfusion and hysterectomy).

same period. Quality features of the study also ensured that nearly all deliveries in each health facility during the study period were recorded.

Nevertheless, we should acknowledge some weaknesses of this study. The first one is the study design. This is a cross-sectional study, which *per se* makes this evaluation unable to establish causal relationships between caesarean sections and the maternal outcomes. However, considering the existing constraints in terms of using other designs, we consider this a fair approach to the question. Another point is that our findings may not be country or continent representative; our sample was based on a random selection of countries, regions within countries and health facilities. Doing so, we

simply aimed at avoiding other selection biases, and tried to be inclusive as much as possible, considering the available resources we had. Another issue that should be considered is the disproportionately higher contribution of Chinese health facilities to the group of women undergoing caesarean sections without medical indications. The “country” variable was included in the statistical model used to adjust the findings, reducing both the clustering effect and the role of an individual country’s contribution to the results. On the other hand, in the assessment of caesarean sections with indications, the Chinese facilities’ contribution was not especially prominent and the findings were similar.

The low frequency of events makes the absolute risk associated with caesarean sections low, but even this low risk is substantially higher when compared to spontaneous vaginal deliveries. From the population perspective and considering the frequency with which the procedure is practiced, these findings may be relevant for avoiding the occurrence of severe maternal outcomes, especially in those settings where avoidable caesarean sections are more prevalent.

In this context, one could speculate about the relationship of these findings with the underlying health system and the implication of these results to developed countries. The higher intrinsic risk of caesarean sections observed in Africa compared to Asia and Latin America and the lower intrinsic risk in Latin America compared to Asia could suggest some ecological relationship between the strength of health system, urbanization, facility-based care and development status with the safety of surgical procedures including caesarean section. Data from Japan, the only developed country that took part in the study, could clarify that, but the low number of severe maternal outcomes actually prevented a conclusive assessment by country. Nevertheless, the above mentioned ecological relationship could suggest that in developed settings the intrinsic risk of caesarean sections would be lower compared to less developed settings.

Conclusion

We conclude that caesarean sections should be performed when a clear benefit is anticipated, a benefit that might compensate for the higher costs and additional risks in the context of the specific setting where the operation is taking place. This additional risk should be considered by health care professionals and patients when deciding the mode of delivery. In the end, the main challenge related to caesarean sections is making the best use of this procedure, which is certainly an important resource for the reduction of maternal mortality, but of which overuse may be associated with an increased risk of severe maternal outcomes.

Table 5 Perinatal outcomes among singleton and first child of multiple births by mode of delivery

Perinatal outcomes	n/N (%)	Adjusted OR [95%CI]
Perinatal mortality[†]		
Spontaneous (reference)	3218/205551(1.57)	1
Operative	415/7296(5.69)	3.16 (2.76 to 3.61)
Antepartum without indications	6/1735(0.35)	0.72 (0.26 to 1.97)
Intrapartum without indications	16/950(1.68)	2.41 (1.39 to 4.2)
Antepartum with indications	534/27011(1.98)	1.3 (1.15 to 1.47)
Intrapartum with indications	1081/44022(2.46)	2.01 (1.84 to 2.19)
Fetal death^{††}		
Spontaneous (reference)	1981/205551 (0.96)	1
Operative	291/7296 (3.99)	3.25 (2.79 to 3.79)
Antepartum without indications	3/1735(0.17)	0.48 (0.12 to 1.98)
Intrapartum without indications	11/950(1.16)	2.3 (1.2 to 4.4)
Antepartum with indications	248/27011 (0.92)	0.92 (0.78 to 1.09)
Intrapartum with indications	577/44022 (1.31)	1.6 (1.43 to 1.79)
Early neonatal deaths up to hospital discharge[‡]		
Spontaneous (reference)	1237/203570 (0.61)	1
Operative	124/7005 (1.82)	2.76 (2.19 to 3.47)
Antepartum without indications	3/1732(0.17)	0.88 (0.21 to 3.62)
Intrapartum without indications	5/939(0.53)	2.01 (0.8 to 5.06)
Antepartum with indications	286/26477(1.08)	1.68 (1.42 to 1.98)
Intrapartum with indications	504/43445(1.16)	2.2 (1.94 to 2.5)
Stay for ≥7 days in neonatal intensive care unit^{‡‡}		
Spontaneous (reference)	2704/205551(1.32)	1
Operative	203/7296(2.78)	1.57 (1.31 to 1.88)
Antepartum without indications	17/1735(0.98)	1.18 (0.7 to 1.99)
Intrapartum without indications	16/950(1.68)	2.09 (1.21 to 3.6)
Antepartum with indications	1466/27011(5.43)	2.63 (2.4 to 2.89)
Intrapartum with indications	1625/44022(3.69)	2.77 (2.55 to 3)
Severe perinatal outcome^{‡‡‡}		
Spontaneous (reference)	5820/205551 (2.83)	1
Operative	613/7296 (8.4)	2.33 (2.07 to 2.62)
Antepartum without indications	22/1735(1.27)	1 (0.61 to 1.62)
Intrapartum without indications	32/950(3.37)	2.48 (1.66 to 3.69)
Antepartum with indications	1968/27011(7.29)	2.05 (1.9 to 2.22)
Intrapartum with indications	2656/44022(6.03)	2.42 (2.27 to 2.58)

[†] Maternal age, Total number of years attended school, birth weight, Neonatal death or stillbirth, Pregnancy induced hypertension or preeclampsia or eclampsia or chronic hypertension, Vaginal bleeding in 2nd half of pregnancy, Any antenatal antibiotic treatment, Referred for complication related to pregnancy or delivery, Induced labour, Any other medical complication during pregnancy (excluding chronic hypertension), country and gestational age.

^{††} Maternal age, Total number of years attended school, birth weight, Neonatal death or stillbirth, Pregnancy induced hypertension or preeclampsia or eclampsia or chronic hypertension, Vaginal bleeding in 2nd half of pregnancy, Referred for complication related to pregnancy or delivery, Any other medical complication during pregnancy (excluding chronic hypertension) and gestational age.

[‡] Total number of years attended school, birth weight, Neonatal death or stillbirth, Vaginal bleeding in 2nd half of pregnancy, Referred for complication related to pregnancy or delivery, Induced labour, country and gestational age.

^{‡‡} Maternal age, Total number of years attended school, Primigravida, birth weight, Neonatal death or stillbirth, Caesarean section at last pregnancy, Prelabour rupture of membranes, Pregnancy induced hypertension or preeclampsia or eclampsia or chronic hypertension, Suspected fetal growth impairment, Any antenatal antibiotic treatment, Breech or other non-cephalic presentation, Referred for complication related to pregnancy or delivery, Induced labour, Any other medical complication during pregnancy (excluding chronic hypertension), country, complexity of index and gestational age.

^{‡‡‡} Maternal age, Total number of years attended school, birth weight, Neonatal death or stillbirth, Caesarean section at last pregnancy, Prelabour rupture of membranes, Pregnancy induced hypertension or preeclampsia or eclampsia or chronic hypertension, Suspected fetal growth impairment, Vaginal bleeding in 2nd half of pregnancy, Breech or other non-cephalic presentation, Referred for complication related to pregnancy or delivery, Induced labour, Any other medical complication during pregnancy (excluding chronic hypertension), country, complexity of index and gestational age.

Abbreviations

95% CI: 95% Confidence Interval; Adj OR: Adjusted Odds Ratio; GLIMMIX: procedure for generalized linear mixed models; GLLAMM: generalized linear and latent mixed models; HRP: UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction; ICU: Intensive Care Unit; OR: Odds Ratio; UNDP: United Nations Development Programme; UNFPA: United Nations Population Fund; USAID: United States Agency for International Development; WHO: World Health Organization; WHOGS: World Health Organization Global Survey on Maternal and Perinatal Health.

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Authors' contributions

JPS, AMG, PL and ML conceived this analysis of the WHO Global Survey on Maternal and Newborn Health database. ML carried out the statistical analysis. JPS drafted the manuscript and AMG, PL, ML, GC, BF and PR provided important input on it. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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ภาคผนวกที่ 2

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Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery (Review)

Suwannachat B, Lumbiganon P, Laopaiboon M



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[Intervention review]

Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery

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ABSTRACT

Background

Vacuum extraction is a common technique of assisted vaginal delivery. Traditionally, it has been recommended that the pressure is increased slowly in a stepwise procedure; some have advocated rapid increases in pressure.

Objectives

To assess the efficacy and safety of rapid versus stepwise negative pressure application for assisted vaginal delivery by vacuum extraction.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (March 2008).

Selection criteria

Randomized controlled trials and quasi-randomized controlled trials of rapid compared with stepwise increase in negative pressure application of vacuum extraction.

Data collection and analysis

Two authors independently assessed trial quality and extracted data.

Main results

One trial of 94 women was included. Duration of vacuum procedure was reduced in rapid application group (mean difference -6.10 minutes, 95% confidence interval -8.83 to -3.37). There were no significant differences in detachment rate, degree of perineal tears, Apgar score less than seven at one and five minutes, umbilical venous pH less than 7.2, scalp laceration greater than a quarter, cephalhematoma and number of tractions.

Authors' conclusions

Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery (Review)
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The rapid negative pressure application for vacuum assisted vaginal birth reduces the duration of the procedure whilst there is no evidence of differences in maternal and neonatal outcome. Due to a small number of participants in the single included trial, the evidence is limited and either policy may be employed until further controlled trials provide conclusive evidence of benefit from one or other method.

PLAIN LANGUAGE SUMMARY

Applying negative pressure rapidly or in steps for vacuum extraction assisted vaginal delivery

Assisted vaginal delivery is an important part of obstetric care. Indications for its use include prolonged second stage of labour, actual or potential fetal compromise or distress and to shorten labour. The established method is to grasp the fetal head with obstetric forceps and turn and position the head to facilitate the descent and birth of the infant. A vacuum extractor is becoming the method of choice as it is less likely to injure the mother although failure of attempted vacuum extraction may occur more often than with forceps. The vacuum extractor is contraindicated with face, brow or breech presentation and if the gestational age of the fetus is less than 34 weeks because of the risk of damage to the scalp (cephalhematoma) and intracranial bleeding.

The pressure for vacuum extraction can be increased in a stepwise procedure, to ensure attachment, or more rapidly. Rapid application would address the concern that vacuum extraction is too slow to be used when rapid delivery is required. Potential adverse effects of rapid application include detachment of the cup and injury of the infants scalp and blood vessels. Only one good quality randomised controlled trial involving 94 women was identified. Rapid negative pressure application for vacuum assisted vaginal birth reduced the duration of the procedure without any evidence of differences in outcomes for the mother or infant. Rapid application reduced procedure time by some six minutes (range 8.8 to 3.4 minutes). Rate of detachment of the cup, degree of perineal tears, low Apgar scores, acidic umbilical cord venous blood, damage to the scalp and number of tractions were not clearly different with rapid and stepwise negative pressure application for vacuum extraction assisted vaginal delivery. The small number of participants in the single included trial means that the evidence is limited.

BACKGROUND

Historically, obstetricians sought a method to assist vaginal delivery, to grasp the fetal head in order to turn and manipulate its position, and facilitate its descent and delivery. Assisted vaginal delivery has become an integral part of obstetric care; the obstetric forceps was the primary instrument used in assisting vaginal delivery. However, more recently, forceps have been overtaken in popularity in some countries by the vacuum extractor (Bofill 1996). In the United Kingdom, there has been an increasing use of vacuum extraction compared with forceps extraction (O'Connell 2000; Patel 2004). The acceptance of the vacuum device as a safe alternative to forceps was delayed in the USA as compared to European countries, but as of 1992, the rate of vacuum delivery surpassed the rate of forceps delivery in the USA (Mikovsky 2001). Rates of vacuum extraction vary around 10% in the Middle East and Canada (Cargill 2004; Shihadeh 2001), 6% in Australia (Laws 2005) and 8% in the USA (Kozak 2002).

Vacuum extraction is fast becoming the method of choice for many assisted vaginal deliveries. Current evidence suggests that when assisted vaginal delivery is required, the vacuum extraction should often be chosen first; principally because it is significantly less likely to injure the mother (Chalmers 1989; Johanson 1999), though failure of attempted vacuum extraction will occur more

often than failed forceps delivery (Johanson 1999).

Indications for vacuum assisted delivery include prolonged second stage of labour, suspicion of actual or potential fetal compromise, and to shorten the second stage of labour for maternal benefit (ACOG 2000). The vacuum extractor is contraindicated with face, brow or breech presentation. It has been suggested that it should not be used at gestations of less than 34 weeks because of the risk of cephalhematoma and intracranial haemorrhage (RCOG 2005; Vacca 1999).

There is a traditional recommendation that, for vacuum cup application, the operator should gradually increase negative pressure at 0.2 kg/cm² every two minutes, to reach 0.8 kg/cm² over 8 to 10 minutes. Theoretically, this process would allow the vacuum to be firmly attached to the fetal head, thus decreasing the chance of vacuum extraction failure (Malmstrom 1965). However, some experts suggest that this is both unnecessary and wastes time (Wider 1967). More recently, it has been suggested that there is no significant difference in the traction force developed between stepwise and rapid application of the vacuum (Svenningsen 1987). Since adequate chignon forms within one to two minutes of creating the vacuum and traction may be commenced after one minute without compromising efficiency and safety (Guardino 1962; Lim 1997; Wider 1967). It has been proposed that, for the soft cups,

negative pressure could be increased to 0.8 kg/cm² in as little as one minute (Kuit 1993). Potential adverse effects of rapid application of vacuum extraction include cup detachment and injury of the fetal scalp and blood vessels.

The perception that vacuum extraction is too slow to be used when rapid delivery is required (e.g. severe fetal distress) may not, therefore, be supportable. In some countries, most obstetricians still use the stepwise negative pressure application, in the belief that this prevents cup detachment. We systematically evaluated whether there are any differences in efficacy and safety in rapid versus stepwise negative pressure application for vacuum assisted vaginal delivery.

Readers may wish to refer to the following Cochrane systematic review for further information on vacuum extraction for assisted vaginal deliveries: 'Vacuum extraction versus forceps for assisted vaginal delivery' (Johanson 1999). This review is currently being updated.

OBJECTIVES

To assess efficacy and safety of rapid versus stepwise negative pressure application for assisted vaginal delivery by vacuum extraction.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials and quasi-randomized controlled trials.

Types of participants

Women undergoing vacuum extraction assisted vaginal delivery.

Types of interventions

Rapid (within two minutes) versus stepwise (as defined by trialists) negative pressure application for vacuum extraction assisted vaginal delivery.

Types of outcome measures

Primary outcomes

(1) Maternal

1. Success or failure rate of vacuum procedure
2. Detachment rate
3. Duration of vacuum extraction procedure

4. Birth passage injury including degree of perineal tears, cervical and uterine tears
5. Actual mode of delivery

(2) Fetal

1. Birth asphyxia (according to trialists' definition)
2. Fetal injury including scalp abrasions or lacerations, caput succedaneum, cephalhematoma, subgaleal hemorrhage, intracranial injury (rely on trialists' definition)
3. Hyperbilirubinemia

Secondary outcomes

(1) Maternal

1. Perineal pain after delivery
2. Perineal wound infection
3. Rectovaginal fistula
4. Postpartum haemorrhage

(2) Fetal

1. Retinal hemorrhage
2. Breastfeeding failure
3. Perinatal death

(3) Obstetrician satisfaction

(4) Maternal satisfaction

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Groups Trials Register by contacting the Trials Search Co-ordinator (March 2008).

The Cochrane Pregnancy and Childbirth Groups Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#). Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Two authors assessed for inclusion all potential studies we identified as a result of the search strategy. There were no disagreements.

Assessment of methodological quality of included studies

Two authors assessed the validity of the identified study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005). We have described the methods used for generation of the randomization sequence in the 'Characteristics of included studies' table.

(1) Selection bias (allocation concealment)

We assigned a quality score using the following criteria:

- (A) adequate concealment of allocation: such as telephone randomization, consecutively-numbered, sealed opaque envelopes;
- (B) unclear whether adequate concealment of allocation: such as list or table used, sealed envelopes or study does not report any concealment approach;
- (C) inadequate concealment of allocation: such as open list of random-number tables, use of case record numbers, dates of birth or days of the week.

(2) Attrition bias (loss of participants, e.g. discharge very soon after birth, withdrawals, dropouts, protocol deviations)

We assessed completeness to follow up using the following criteria:

- (A) less than 5% loss of participants;
- (B) 5% to 9.9% loss of participants;
- (C) 10% to 19.9% loss of participants;
- (D) more than 20% loss of participants.

(3) Detection bias (blinding of outcome assessment)

We assessed detection bias using the following criteria:

- (A) adequate blinding explanation: such as investigators measured birth passage injury among the women without awareness of the interventions they received;
- (B) unclear blinding explanation: such as investigators measured birth passage injury among the women similarly;
- (C) inadequate blinding explanation: such as birth passage injury was measured from the women in both groups.

The one identified and included trial scored an A when rating selection bias and detection bias.

Data extraction and management

We used the Cochrane Pregnancy and Childbirth Group's data extraction form template to extract data. Two review authors extracted the data using the agreed form. There were no discrepancies. We used the Review Manager software (RevMan 2003) to enter data.

Data analysis

We carried out statistical analysis using RevMan 2003. Where relevant, we reported birth passage injury, postpartum haemorrhage, birth asphyxia, fetal injury and other binary outcomes using risk ratio with 95% confidence intervals.

If we had identified more than one trial or if we identify other trials in future updates, we will use the methods we prespecified in the published protocol - see Appendix 1.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

We identified two studies as potentially eligible for inclusion in this review. We excluded one study because it was neither a randomized controlled trial nor a quasi-randomized controlled trials (Svenningsen 1987) - see table of 'Characteristics of excluded studies'. A single trial of 94 women met the selection criteria (Lim 1997) - see table of 'Characteristics of included studies' for full details.

Risk of bias in included studies

The one included study was of good quality. Women eligible for the study were randomized to rapid and stepwise method application by using sealed envelopes in blocks of 10. The outcome variables were recorded by the obstetrician one hour after birth between the third and the fifth day after birth; a physical examination of the infant was performed by a paediatrician who paid attention to possible neonatal morbidity associated with ventouse extraction procedures. The paediatrician was not aware of the manner in which the vacuum had been applied. This implies that there could have been outcome assessment bias on the part of the obstetrician. Follow-up data were available on 73 children. In 21 cases, the parents did not return with their child to the outpatient clinic: 10 in the rapid group and 11 in the stepwise group.

Effects of interventions

In the group of women who received rapid method of vacuum application, there was a significant reduction in the duration of the vacuum extraction procedure (mean difference -6.10 minutes, 95% confidence interval -8.83 to -3.37). There were no significant differences in detachment rate, degree of perineal tears, Apgar score less than seven at one and five minutes, umbilical cord venous blood pH less than 7.2, scalp laceration more than a quarter of the surface, cephalhematoma and number of tractions.

DISCUSSION

The policy of rapid negative pressure application for vacuum assisted vaginal birth seems to reduce the duration of the procedure by about six minutes and that can be useful when rapid delivery is required, whilst no increase in cup detachment, or other maternal and neonatal adverse outcomes. The results should be interpreted with caution due to the paucity of evidence.

AUTHORS' CONCLUSIONS

Implications for practice

The rapid negative pressure application for vacuum assisted vaginal birth may be suitable for use, especially if rapid delivery is required.

Implications for research

There is insufficient evidence from this review to guide clinical practice to use rapid negative pressure application method due to a dearth of trials. Whilst many obstetricians already practice in this way, more research is needed to assess the safety of rapid application for vacuum assisted vaginal delivery.

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As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team) and the Group's Statistical Adviser.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Lim 1997

Methods	Randomized controlled trial using sealed envelopes in blocks of 10. No pretrial sample size given.
Participants	94 women eligible for the study were those with an uncomplicated singleton pregnancy of more than 37 weeks of gestation, with a cephalic presentation. Instrumental vaginal delivery was indicated due to prolonged second stage of labour (defined as at least 1 hour of active expulsive efforts) without signs of fetal distress. 8% of eligible women were excluded.
Interventions	Ventouse extraction procedures were performed by application to the fetal head of a metal cup

Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery (Review)

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Lim 1997 (Continued)

(Malmstrom, 50 mm) connected to an automatic electric pump (Egnell compact 5, Ameda, Cary, Illinois, USA). The conventional stepwise method consisted of 4 incremental steps of 0-2 kg/cm² every 2 min to obtain a final negative pressure of 0-8 kg/cm². In the rapid method the negative pressure of 0-8 kg/cm² was applied in 1 step. When the final pressure had been achieved, traction was undertaken during uterine contractions and maternal expulsive efforts. If there was detachment of the ventouse cup, it was applied again to the fetal head in the manner indicated by the initial randomization.

Outcomes	Duration of the complete procedure, The number of detachment of the cup, Apgar scores at 1 min and 5 min, and acid-base status of venous cord blood, superficial scalp lesions, cephalhematomas and clinical jaundice, serum bilirubin concentration, Scalp lesions were scored according to the extent of the fetal scalp involved: < 1/4, 1/4 to 3/4 or > 3/4 of the surface. The neurological condition of the child was determined by the Sarnat score, including crying, irritability and feeding problems, and a physical neurological examination. The Sarnat score runs from 0 (normal) to 4 (severe neurological damage).
Notes	Follow-up data were available on 73 children. In 21 cases the parents did not return with their child to the outpatient clinic: 10 in the rapid group and 11 in the stepwise group. Sarnat score < 0 was not prespecified in the protocol for this review. There was no low Sarnat score in either group so RR would not be calculated.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment??	Yes	A - Adequate
min: minutes		
RR: risk ratio		

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Svenningsen 1987	This study was not a clinical trial.

DATA AND ANALYSES

Comparison 1. Rapid versus stepwise negative pressure application

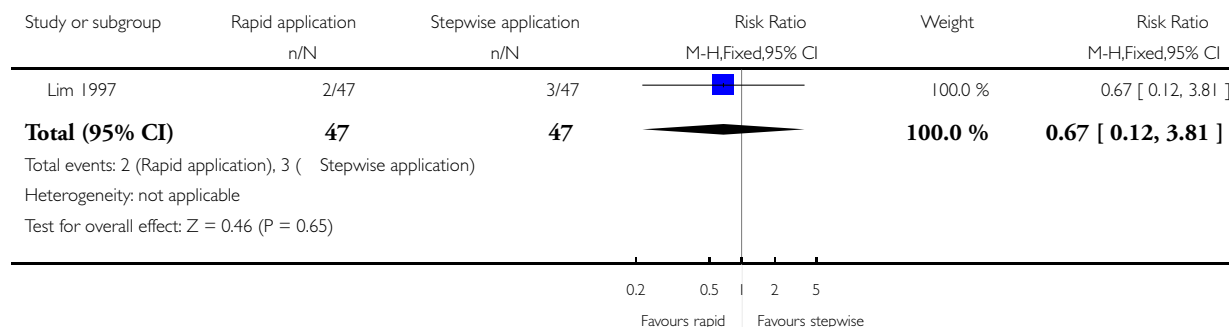
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Success/failure rate of vacuum procedure			Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Detachment rate	1	94	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.12, 3.81]
3 Duration of vacuum extraction procedure	1	94	Mean Difference (IV, Fixed, 95% CI)	-6.10 [-8.83, -3.37]
4 Second degree of perineal tears	1	94	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.24, 2.09]
5 Third degree of perineal tears	1	94	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.06, 15.52]
6 Apgar score < 7 after 1 minute	1	94	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.22, 1.77]
7 Apgar score < 7 after 5 minutes	1	94	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.06, 15.52]
8 Umbilical venous pH < 7.2	1	94	Risk Ratio (M-H, Fixed, 95% CI)	2.01 [0.19, 21.31]
9 Scalp laceration > 1/4	1	73	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.18, 3.03]
10 Cephalhematoma	1	73	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.35, 4.17]
11 Number of traction	1	94	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.55, 0.75]
12 Subgaleal hemorrhage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13 Intracranial injury	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14 Hyperbilirubinemia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15 Perineal pain after delivery	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16 Perineal wound infection	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
17 Rectovaginal fistula	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18 Postpartum haemorrhage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
19 Retinal hemorrhage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
20 Breastfeeding failure	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
21 Perinatal death	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
22 Obstetrician satisfaction	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
23 Maternal satisfaction	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 1.2. Comparison 1 Rapid versus stepwise negative pressure application, Outcome 2 Detachment rate.

Review: Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery

Comparison: 1 Rapid versus stepwise negative pressure application

Outcome: 2 Detachment rate

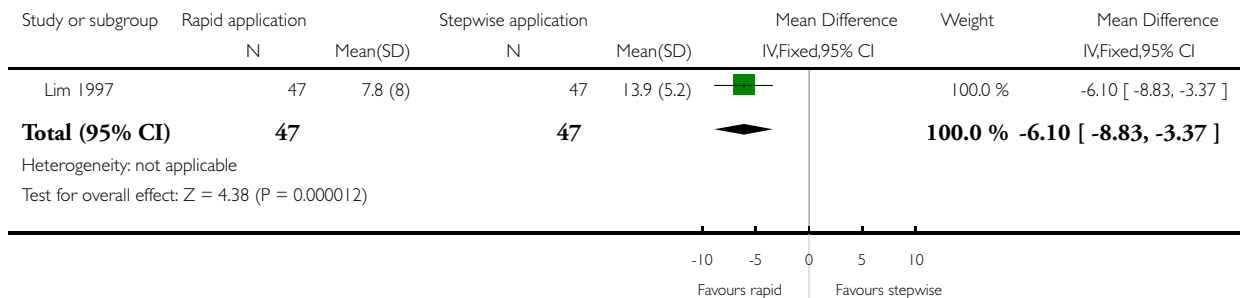


Analysis 1.3. Comparison 1 Rapid versus stepwise negative pressure application, Outcome 3 Duration of vacuum extraction procedure.

Review: Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery

Comparison: 1 Rapid versus stepwise negative pressure application

Outcome: 3 Duration of vacuum extraction procedure

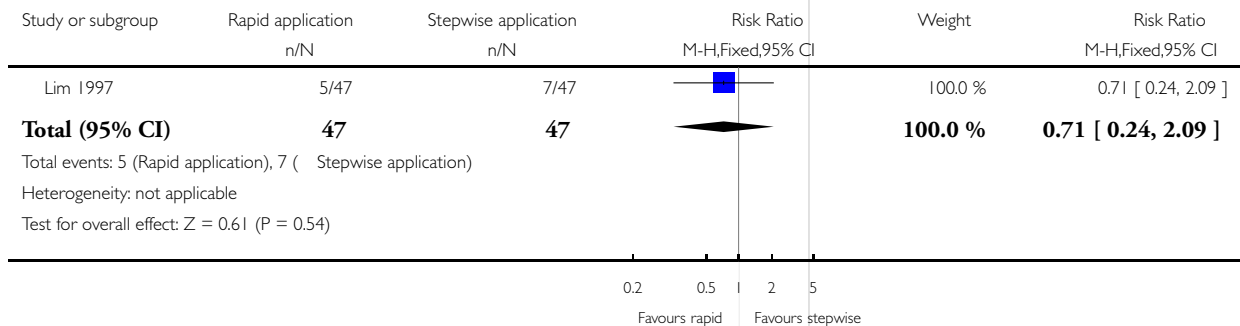


Analysis 1.4. Comparison 1 Rapid versus stepwise negative pressure application, Outcome 4 Second degree of perineal tears.

Review: Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery

Comparison: 1 Rapid versus stepwise negative pressure application

Outcome: 4 Second degree of perineal tears

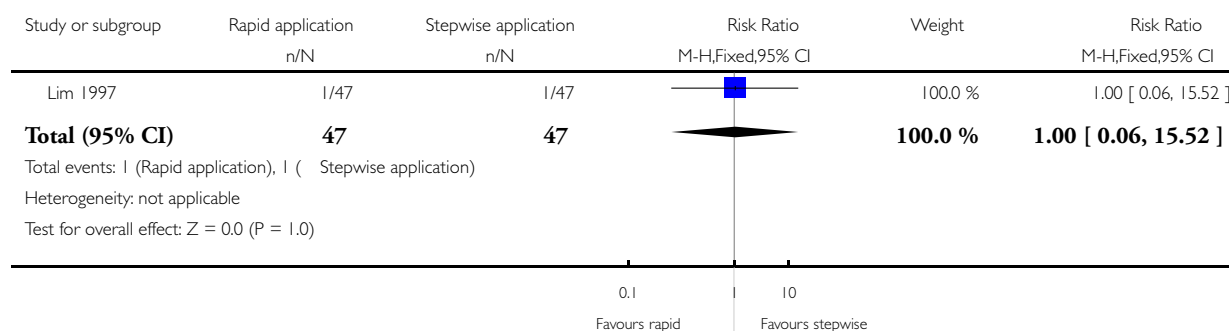


Analysis 1.5. Comparison 1 Rapid versus stepwise negative pressure application, Outcome 5 Third degree of perineal tears.

Review: Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery

Comparison: 1 Rapid versus stepwise negative pressure application

Outcome: 5 Third degree of perineal tears

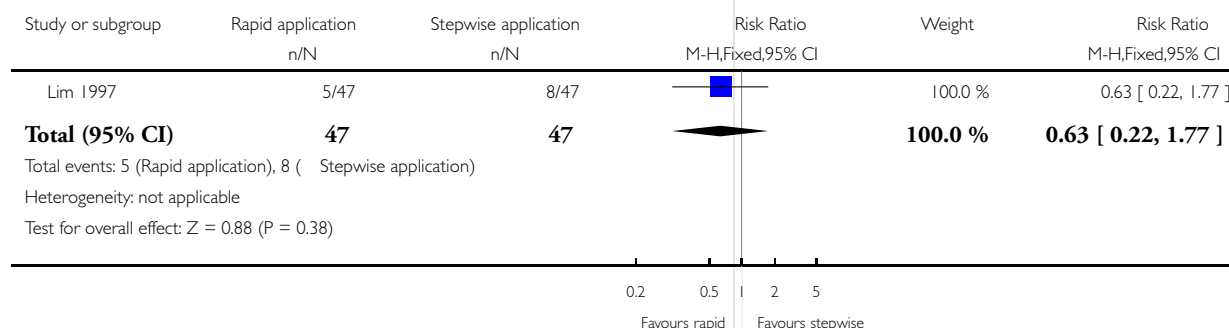


Analysis 1.6. Comparison 1 Rapid versus stepwise negative pressure application, Outcome 6 Apgar score < 7 after 1 minute.

Review: Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery

Comparison: 1 Rapid versus stepwise negative pressure application

Outcome: 6 Apgar score < 7 after 1 minute

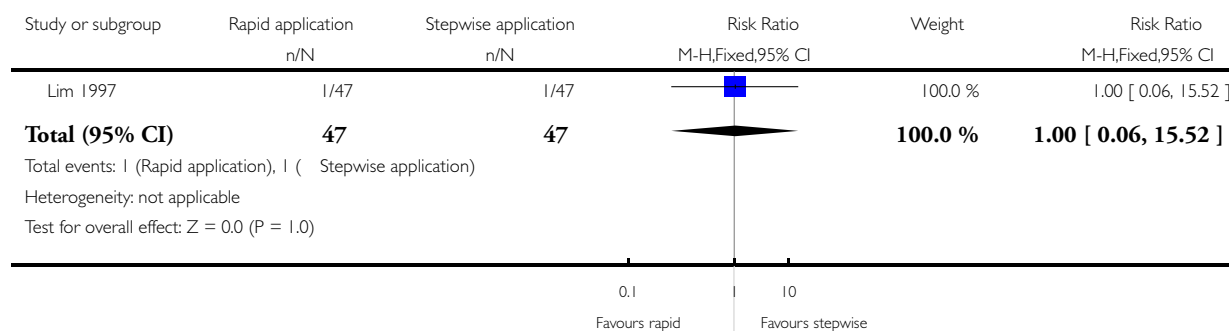


Analysis 1.7. Comparison 1 Rapid versus stepwise negative pressure application, Outcome 7 Apgar score < 7 after 5 minutes.

Review: Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery

Comparison: 1 Rapid versus stepwise negative pressure application

Outcome: 7 Apgar score < 7 after 5 minutes

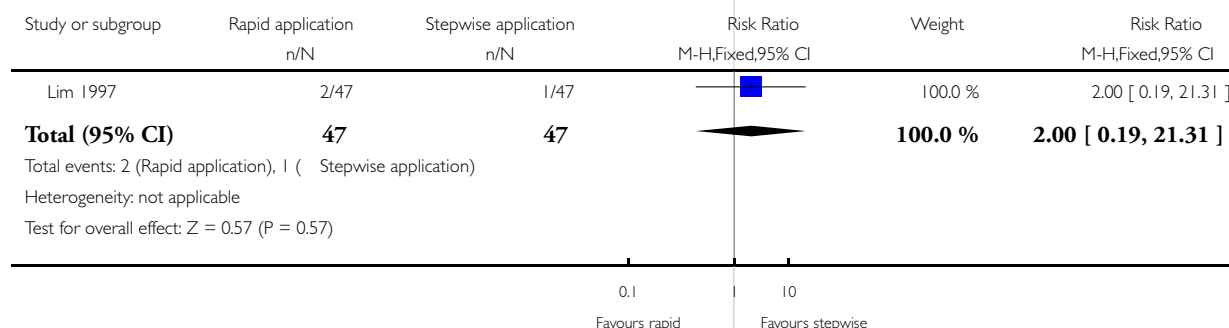


Analysis 1.8. Comparison 1 Rapid versus stepwise negative pressure application, Outcome 8 Umbilical venous pH < 7.2.

Review: Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery

Comparison: 1 Rapid versus stepwise negative pressure application

Outcome: 8 Umbilical venous pH < 7.2

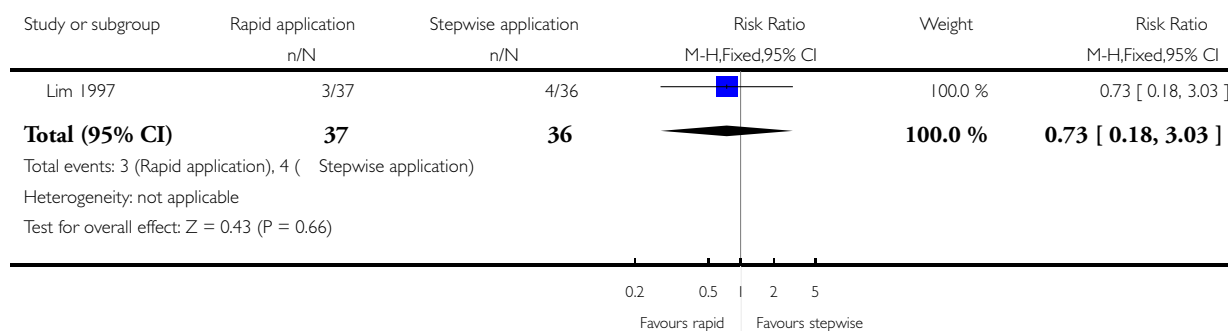


Analysis I.9. Comparison I Rapid versus stepwise negative pressure application, Outcome 9 Scalp laceration > 1/4.

Review: Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery

Comparison: I Rapid versus stepwise negative pressure application

Outcome: 9 Scalp laceration > 1/4

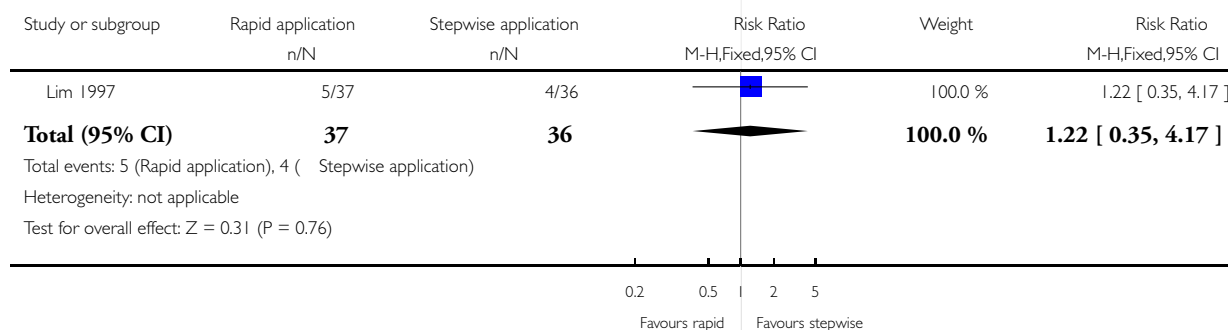


Analysis I.10. Comparison I Rapid versus stepwise negative pressure application, Outcome 10 Cephalhematoma.

Review: Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery

Comparison: I Rapid versus stepwise negative pressure application

Outcome: 10 Cephalhematoma

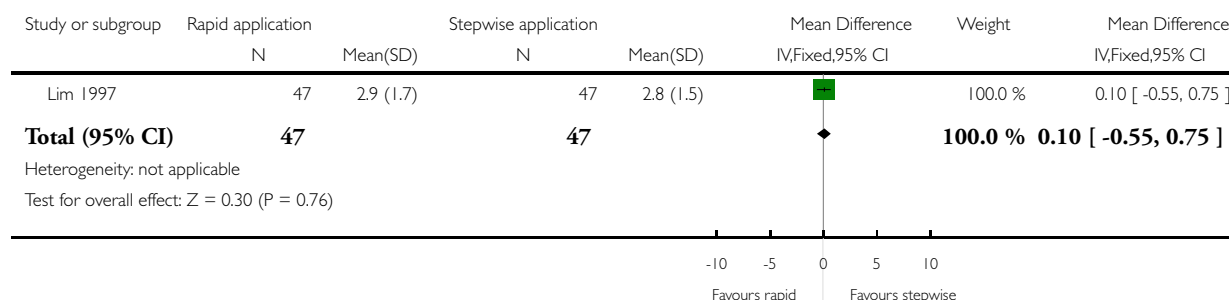


Analysis 1.11. Comparison 1 Rapid versus stepwise negative pressure application, Outcome 11 Number of traction.

Review: Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery

Comparison: 1 Rapid versus stepwise negative pressure application

Outcome: 11 Number of traction



APPENDICES

Appendix 1. Methods to be used if other studies identified

We will use the mean difference to combine trials that measure the same outcome, but use different methods. If there is evidence of skewness, this will be reported.

We will assess heterogeneity by visual forest plots of the outcomes' data among trials and by using the I-squared statistic (Higgins 2005) with 95% confidence interval. If we find statistical heterogeneity among the trials, inconsistent forest plots and I-square exceeding 50%, we will look for an explanation using subgroup analysis. The analysis will be conducted where sufficient data are available according to the following specified factors including type of vacuum extraction procedure (ACOG 2000), type of cup, parity, gestation, indication of delivery, with or without epidural anesthesia. If trials in individual subgroups of the potential factors are thought to be comparable by interaction test as described by Deeks 2001, we will use a random-effects meta-analysis for estimating an overall summary. Alternatively, we will use fixed-effect meta-analysis for combining data.

Where sufficient trials are included, we will consider publication bias using funnel plots of between-treatment effect and its precision of individual trials, and Egger's test (Egger 1997). If we find asymmetry funnel plots with statistical publication bias, we will further examine the effect of the bias on the meta-analysis conclusion using sensitivity analysis.

We will carry out sensitivity analyses to explore the effect of trial quality and, where appropriate, cluster-randomized trials on the meta-analysis conclusion. The trial quality will involve analysis based on high-quality trials. Trials of poor quality will be excluded in the analysis (those rating B, C, or D) in order to assess for any substantive difference to the overall result.

WHAT'S NEW

Last assessed as up-to-date: 30 March 2008

Date	Event	Description
29 April 2008	Amended	Converted to new review format

HISTORY

Protocol first published: Issue 3, 2007

Review first published: Issue 3, 2008

CONTRIBUTIONS OF AUTHORS

B Suwannachat (BS) initiated the topic. BS, P Lumbiganon and M Laopaiboon drafted the protocol. All review authors approved the final version of the protocol.

BS drafted the first version of the review. All review authors approved the final version of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Kalasin Hospital, Ministry of Public Health, Thailand.
- Faculty of Medicine, Khon Kaen University, Thailand.
- Faculty of Public Health, Khon Kaen University, Thailand.

External sources

- Thailand Research Fund, Senior research scholar, Thailand.
- Thailand Cochrane Network, Thailand.

Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media (Review)

Thanaviratananich S, Laopaiboon M, Vatanasapt P



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[Intervention Review]

Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media

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ABSTRACT

Background

Acute otitis media (AOM) is a common problem in children, for which the antibiotic amoxicillin, with or without clavulanate, is frequently prescribed.

Objectives

To compare the effectiveness of one or two daily doses with three or four daily doses of amoxicillin, with or without clavulanate, for the treatment of AOM in children.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2008, issue 1), which contains the Acute Respiratory Infections (ARI) Group's Specialized Register; MEDLINE (January 1950 to March 2008); EMBASE (1974 to March 2008); the Science Citation Index (2001 to March 2008); and NLM Gateway (HSRProj) (March 2008).

Selection criteria

We included studies if they met the following criteria: randomized controlled trials (RCTs) of children aged 12 years or younger with AOM, diagnosed by the following explicit criteria: acute ear pain (otalgia) and inflamed ear drum (confirmed by positive tympanocentesis or tympanogram of type B or C).

Data collection and analysis

We extracted data on treatment outcomes from individual trials. We assessed quality based on selection bias, performance bias, attrition bias and sample size calculation. The quality grading was defined as low risk of bias, moderate risk of bias or high risk of bias. The results were summarized as risk ratio (RR) and 95% confidence intervals (CI).

Main results

We included six studies with 1601 children in the review. Although the clinical cure rates at the end of therapy and at the follow-up periods of each study were shown to be comparable between the two groups, we did not perform pooled data analysis because of moderate to high risk of biases in the included studies. Most of the children were aged 2 months to 12 years. None of the studies had any consistently significant results either for benefit or harm. The outcomes were assessed at the end of therapy (often 10 days) and this may have been too late to measure any differences.

Authors' conclusions

This review showed insufficient evidence to judge whether once or twice daily doses of amoxicillin, with or without clavulanate, were comparable with three or four daily doses for the treatment of AOM. The evidence appears to be biased and therefore no firm conclusions can be drawn.

PLAIN LANGUAGE SUMMARY

Once or twice daily doses compared with three or four daily doses of amoxicillin, with or without clavulanate, for the treatment of acute otitis media in children

Acute otitis media is very common disease in children and may cause pain and hearing loss. Amoxicillin, with or without clavulanate, is the most commonly used antibiotic for the treatment of acute otitis media. Currently one or two daily doses are increasingly used, in preference to three or four times daily doses, to aid compliance. We could not claim that the different dosage schedules have the same effectiveness, as the included studies were biased. To study whether both dosing schedules have the same effectiveness, a good quality equivalence trial is necessary.

BACKGROUND

Description of the condition

Acute otitis media (AOM) is one of the most common diseases in children. During the first six months of life about 48% of infants have one episode of AOM or otitis media with effusion (OME) and about 20% have two or more episodes (Daly 1999). The peak incidence of AOM occurs between 6 and 12 months of age. It has been found that by the end of the first year of life 62.4% of infants have had one or more episodes of AOM and 17.3% have had three or more episodes (Teele 1989). The risk of developing another episode within one month after the onset of the primary infection is estimated at 35% (Carlin 1987).

The common bacterial pathogens of AOM are *Streptococcal pneumoniae* (*S. pneumoniae*), *Haemophilus influenzae* (*H. influenzae*) and *Moraxella catarrhalis* (*M. catarrhalis*) (Jacobs 1998). These bacteria are becoming increasingly resistant to antibiotics (Barnett 1995; Faden 1994; Henderson 1988; Johnson 1996; Kaplan 1995). Systematic reviews have demonstrated that in uncompli-

cated AOM, about 15 children must be treated with antibiotics to prevent one child having some pain after two days (Glasziou 2004) and about eight children must receive antibiotics to avoid one clinical failure (Rosenfeld 2001). A recent study demonstrated that antibiotics seemed to have most benefit in children younger than two years of age with bilateral AOM, and in children with both AOM and otorrhea (Rovers 2006). However, the emergence of multiple-drug resistant strains, particularly *S. pneumoniae*, complicates the management of AOM and increases the risk of treatment failure. Antibiotics are frequently used for AOM in the US (Froom 1997; Glasziou 2004), where it is the most frequent disease that antibiotics are used to treat in outpatients departments (McCaig 1995). In contrast, the national Dutch guidelines recommend that children be treated for symptoms but do not receive antibiotics unless fever or pain persists (Froom 1997).

Description of the intervention

Due to growing bacterial resistance, the Center for Disease Control and the American Academy of Pediatrics promotes the judicious use of antibiotics in the treatment of AOM. Antibiotic therapy remains an appropriate treatment option for most children with AOM because spontaneous cure rates are lower in complicated AOM and AOM secondary to *S. pneumoniae* infection. When amoxicillin, the treatment of choice in AOM, is not effective or not tolerated in children, an alternative antibiotic such as amoxicillin/clavulanate, or second- and third-generation cephalosporins, which can cover beta-lactamase producing bacteria, should be considered (Pichichero 2003).

The effectiveness of antibiotics does not depend solely on their antimicrobial activity against the suspected pathogens, but also on characteristics such as dosage, appropriate dosing intervals, tolerability and palatability, which promote compliance and adherence. A convenient once- or twice-daily dosing schedule increases the likelihood of compliance with a full course of therapy (Leibovitz 2003). The traditional dosing interval for prescribing amoxicillin, with or without clavulanate, is every six to eight hours. These dosing intervals may result in poor compliance especially for children at school or daycare centers, which necessitates the involvement and co-operation of a third person.

How the intervention might work

The length of time that antibiotic serum levels are above the Minimal Inhibitory Concentration (MIC), or time above the MIC, has been demonstrated to be a major determinant in predicting successful clinical outcomes for beta-lactam antimicrobial agents (Cars 1997; Drusano 1997). This finding denotes that the dosing frequency of beta-lactam antimicrobial agents could be reduced by increasing the dose, in order to maximize time above the MIC. An increased dose, instead of three times daily dosing, will enhance compliance (Grob 1992; Urquhart 1992). However, these studies relate to conditions other than otitis media.

Why it is important to do this review

In recent years, an increased dosing interval of amoxicillin, with or without clavulanate, has been more frequently used to treat AOM (AAPS 2004). It is therefore reasonable to assess clinical trials comparing the effectiveness of reduced dosing intervals (one or two daily doses) with traditional dosing intervals (three or four daily doses) of amoxicillin, with or without clavulanate, for the treatment of AOM in children.

OBJECTIVES

To compare the effectiveness of one or two daily doses with three or four daily doses of amoxicillin, with or without clavulanate, for the treatment of AOM in children.

To compare the complication rates and adverse reactions.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) comparing two different dosing intervals of the same intervention, amoxicillin, with or without clavulanate.

Types of participants

Patients aged 12 years or younger, with AOM diagnosed by acute ear pain (otalgia) and an inflamed ear drum (confirmed by positive tympanocentesis or tympanogram of type B or C). (A tympanogram is the print-out of an impedance bridge showing the stiffness or the compliance of the middle ear structures as it varies with changes in pressure within the external ear canal. A type B tympanogram suggests fluid in the middle ear; type C suggests that the pressure within the middle ear is below atmospheric pressure).

Types of interventions

Once or twice daily doses compared with three or four daily doses of amoxicillin, with or without clavulanate.

Types of outcome measures

Primary outcomes

Clinical cure rate at the end of antibiotic therapy (days 7 to 14), in terms of resolution of otalgia, resolution of fever, and bacteriological cure rate, if data are provided.

Secondary outcomes

1. Clinical cure rate during therapy (days two to three), in terms of resolution of otalgia and resolution of fever.
2. Clinical cure rate post-treatment (one to three months), in terms of resolution of middle ear effusion, as determined by tympanometry, assessed only in those who do not have recurrences of AOM after completion of therapy.
3. AOM complications: recurrent AOM (after completion of therapy), acute mastoiditis.

4. Adverse reactions to medication.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2008, issue 1) which contains the Acute Respiratory Infection (ARI) Group's Specialized Register; MEDLINE (January 1950 to March 2008); EMBASE (1974 to March 2008); the Science Citation Index (2001 to March 2008); and NLM Gateway (HSRProj) (March 2008).

The following terms were combined with the Cochrane highly sensitive search strategy for identifying randomized trials in MEDLINE (Lefebvre 2008), run over CENTRAL and MEDLINE and adapted for the other electronic databases.

MEDLINE (OVID)

- 1 exp Otitis Media/
- 2 Otitis Media, Suppurative/
- 3 otitis media.tw.
- 4 AOM.tw.
- 5 1 or 2 or 3 or 4
- 6 exp Amoxicillin/
- 7 amoxicillin.mp.
- 8 amoxycillin.mp.
- 9 6 or 7 or 8
- 10 (singl* or one or once or two or twice).tw.
- 11 ("q.d." or "qd" or "o.d." or "od" or "b.d." or "bd").tw.
- 12 (three or thrice or four).tw.
- 13 ("t.d.s." or "tds" or "q.i.d." or "qid").tw.
- 14 10 or 11
- 15 12 or 13
- 16 14 and 15
- 17 5 and 9 and 16
- 18 randomized controlled trial.pt.
- 19 controlled clinical trial.pt.
- 20 randomized.ab.
- 21 placebo.ab.
- 22 drug therapy.fs.
- 23 randomly.ab.
- 24 trial.ab.
- 25 groups.ab.
- 26 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
- 27 humans.sh.
- 28 26 and 27
- 29 17 and 28

See [Appendix 1](#) for the EMBASE search strategy; [Appendix 2](#) for the Science Citation Index search strategy; and [Appendix 3](#) for

the NLM Gateway search strategy. We applied no language or publication restrictions.

Searching other resources

We checked the reference lists of identified clinical trials and any relevant reviews or meta-analyses. We contacted major pharmaceutical companies that manufacture antibiotics and relevant experts in the field for additional trial information. We contacted the first author of relevant trials if any questions arose.

Data collection and analysis

Selection of studies

Two review authors (ST, PV) retrieved titles and abstracts from the literature search for checking against the inclusion/exclusion criteria and recorded data on a pre-designed screening form. The same review authors independently screened results for each title/abstract and disagreements were resolved by a third review author. If the title or the abstract were unclear then we requested the full text articles.

Data extraction and management

Two review authors (ST, PV) independently reviewed each article and completed data extraction forms. We resolved disagreements through group discussion.

Assessment of risk of bias in included studies

The criteria for the assessment of study quality were 1) random allocation concealment; 2) blinding; 3) follow up and 4) sample size calculation. We graded risk of bias as A (low risk: plausible bias unlikely to seriously alter the result); B (moderate risk: plausible bias that raises some doubt about the result); and C (high risk: plausible bias that seriously weakens confidence in the result).

We assessed the methodological quality of the selected trials using the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2006). The methods used for the generation of the randomization sequence were described for each trial.

1. Selection bias (randomization and allocation concealment).

We assessed the possibility of selection bias for each trial, using the following criteria:

- a. adequate concealment of allocation (such as telephone randomization, consecutively-numbered, sealed opaque envelopes);
- b. unclear whether adequate concealment of allocation (such as list or table used, sealed envelopes, or study did not report any concealment approach);

c. inadequate concealment of allocation (such as open list of random-number tables, use of case record numbers, dates of birth or days of the week, or did not adequately describe the details of concealment of allocation);

d. did not use concealment of allocation.

2. Performance bias (blinding of participants, researchers and outcome assessment).

We assessed performance bias for each trial, using the following criteria:

a. blinding of participants:

yes: patients did not know which intervention they received or placebos were used;

no: patients knew which intervention they received;

unclear: no information;

b. blinding of outcome assessment:

yes: investigators measured the primary outcome among the patients without awareness of the interventions they received or placebos were used);

no: the primary outcome was measured without blinding of the outcome assessors;

unclear: no information or the study did not describe how outcome assessors were blinded.

3. Attrition bias (loss of participants, for example, withdrawals, drop-outs, protocol deviations) (Laupattarakasem 2008):

a. less than 5% loss of participants;

b. 5% to 9.9% loss of participants;

c. 10% to 19.9% loss of participants;

d. more than 20% loss of participants.

4. Sample size calculation:

a. adequate explanation of sample size calculation (all information related to sample size calculation was available);

b. unclear whether the sample size was calculated or no available information;

c. inadequate explanation of sample size calculation (some information related to sample size calculation was available);

d. not calculated.

Low risk of bias was defined as those receiving an 'A' rating for selection bias, attrition bias and sample size calculation, and 'yes' for blinding of participants and outcome assessment.

Moderate risk of bias was defined as those receiving at least one 'B' or 'C' rating for selection bias, attrition bias, sample size calculation, or 'unclear' for blinding of participants or outcome assessment.

High risk of bias was defined as those receiving at least one 'D' or 'no rating' for selection bias, attrition bias, sample size calculation, and blinding of participants or outcome assessment.

Assessment of heterogeneity

When important heterogeneity was suspected from the Chi² test for heterogeneity (at 10%), or from visual inspection of the results, we investigated this by looking for differences in clinical

and methodological factors between the trials. When concern about heterogeneity persisted, we considered using a random-effects model. We calculated the I² statistic to estimate the degree of heterogeneity.

Assessment of reporting biases

We examined publication bias by using funnel plots (Light 1984). When asymmetry was observed, we used the Trim and Fill method to assess the effect of this asymmetry on the conclusions (Duval 2000). When meta-analysis was inappropriate, we drew conclusions from the trials' descriptive elements, methodological quality, the number of trials with consistent findings, the plausibility of the results, the strength of the associations in the primary trials, as well as consensus among the authors. However, we did not produce the funnel plots because there were only six studies.

Data synthesis

Where appropriate, we will perform meta-analyses to pool trial data using Review Manager (RevMan) 5.0 (RevMan 2008) software. The meta-analysis method will be dependent upon the nature of the outcomes. For categorical data (for example, proportion of participants with cure), we will relate the numbers reporting an outcome to the numbers at risk in each group, to derive a risk ratio (RR) and 95% confidence interval (CI). We will show continuous differences between groups in the meta-analysis (for example, pain relief on a visual analogue scale) as a mean difference (MD) and 95% CI. As a general rule, a fixed-effect model will be used for calculations of summary estimates and their 95% CI.

Subgroup analysis and investigation of heterogeneity

We were unable to assess heterogeneity between trials as no trials were combined. We will assess heterogeneity in future updates if appropriate. If we identify high levels of heterogeneity among trials (exceeding 50%) it will be explored by pre-specified subgroup analyses.

Subgroup analyses will be performed and heterogeneity will be investigated on the basis of types of interventions (i.e. amoxicillin alone, amoxicillin with clavulanate) and dosage.

Sensitivity analysis

If there are sufficient trials in future updates, we will carry out sensitivity analyses to explore the effect of trial quality on the review's conclusions. Analysis of trial quality will be based on allocation concealment. Trials with clearly inadequate allocation concealment will be excluded to assess differences on the overall result.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

The MEDLINE search retrieved 162 studies. However, there were only six studies relevant to the objectives of this review ([Behre 1997](#); [Damrikarnlert 2000](#); [Hoberman 1997](#); [Jacobsson 1993](#); [Murph 1993](#); [Principi 1986](#)). Among the 229 results retrieved by the EMBASE search, six relevant studies were found ([Behre 1997](#); [Damrikarnlert 2000](#); [Hoberman 1997](#); [Jacobsson 1993](#); [Murph 1993](#); [Principi 1986](#)). No study was retrieved by searching the Science Citation Index and HSRProj. Six studies was found in health services research meetings abstract but only one was relevant to the review objectives ([Damrikarnlert 2000](#)). Six out of 172 studies were retrieved from the CENTRAL search ([Behre 1997](#); [Damrikarnlert 2000](#); [Hoberman 1997](#); [Jacobsson 1993](#); [Murph 1993](#); [Principi 1986](#)).

Included studies

We included five studies involving 1601 children ([Behre 1997](#); [Damrikarnlert 2000](#); [Hoberman 1997](#); [Murph 1993](#); [Principi 1986](#)).

Four studies were supported by pharmaceutical funding ([Behre 1997](#); [Damrikarnlert 2000](#); [Hoberman 1997](#); [Principi 1986](#)). Two trials compared amoxicillin without clavulanate ([Murph 1993](#); [Principi 1986](#)) used one and two times daily versus three times daily, while three studies compared the effectiveness of amoxicillin/clavulanate two times versus three times daily ([Behre 1997](#); [Damrikarnlert 2000](#); [Hoberman 1997](#)). Treatment duration was 10 days in four trials ([Behre 1997](#); [Hoberman 1997](#); [Murph 1993](#); [Principi 1986](#)) and 7 to 10 days in one trial ([Damrikarnlert 2000](#)).

Excluded studies

We excluded the study by Jacobsson ([Jacobsson 1993](#)) because it included only recurrent AOM cases or cases that were not responsive to amoxicillin/penicillin or cefaclor, which differed from other studies. In addition, the total daily dosage for amoxicillin was quite low (20 to 33.2 mg/kg/day).

Risk of bias in included studies

The detailed risk of biases and quality of each study is shown in [Table 1](#). We found no study with low risk of bias among the five included trials. Two studies had a moderate risk of bias ([Damrikarnlert 2000](#); [Murph 1993](#)) while the other three studies had a high risk of bias ([Behre 1997](#); [Hoberman 1997](#); [Principi 1986](#)).

Table 1. Quality assessment for individual trial

Trial	Randomisation process	Allocation concealment	Blinded investigators	Blinded patients	Blinded assessors	Drop-outs	Sample size calculation	Overall quality
Behre 1997	Unclear	No (D)	No	No	Unclear	4.8% to 8.2% (B)	A	High risk
Damrikarnlert 2000	Clear	Unclear (B)	No	No	Unclear	11% to 10.7% (C)	A	Moderate risk
Hoberman 1997	Unclear	No (D)	Unclear	No	Unclear	5.2% to 5.6% (B)	A	High risk
Murph 1993	Clear	Unclear (B)	Yes	Yes	Yes	7.7% (B)	B	Moderate risk
Principi 1986	Unclear	No (D)	No	No	Unclear	0% (A)	D	High risk

Allocation

All five studies claimed that they were randomized clinical trials but only two clearly mentioned the method of randomization. One was by a computer generation method (Damrikarnlert 2000) and the other was by generating a table of random numbers (Murph 1993). Three studies did not describe the method of allocation concealment (Behre 1997; Hoberman 1997; Principi 1986) while two studies did not clearly mention allocation concealment (Damrikarnlert 2000; Murph 1993).

Blinding

There was only one study that had a placebo control and the investigator, participants and assessors were blinded to this (Murph 1993). Three studies did not describe the process of blinding the investigators and participants and the blinding of the assessors was not clearly described (Behre 1997; Damrikarnlert 2000; Principi 1986). The study by Hoberman showed an unclear process for blinding the investigators and assessors and there was no evidence of blinding of the patient (Hoberman 1997).

Incomplete outcome data

There was one study with no drop-outs (Principi 1986). Three studies had less than 10% drop-outs (Behre 1997; Hoberman 1997; Murph 1993) and one study had more than 10% drop-outs (Damrikarnlert 2000).

Selective reporting

Four trials assessed the primary outcome at the end of treatment (Behre 1997; Damrikarnlert 2000; Murph 1993; Principi 1986), while Hoberman 1997 assessed the primary outcome at the follow-up visit, days 32 to 38. Thus we used the secondary outcome (clinical response at days 12 to 14) by Hoberman as the primary outcome in this review and vice versa. The secondary outcome of clinical cure was assessed at days 28 (Behre 1997), days 38 to 42 (Damrikarnlert 2000), days 32 to 38 (Hoberman 1997), and days 30, 60 and 90 (Principi 1986), while Murph (Murph 1993) assessed this outcome only at the end of therapy, on days 10 to 14. Other secondary outcomes assessed were adverse events and compliance rates (Behre 1997; Damrikarnlert 2000; Hoberman 1997), recurrence rate (Hoberman 1997), persistent middle ear effusion without signs and symptoms of infection at day 15, recurrence rate and persistence of OME at days 30, 60 and 90, and adverse events (without showing compliance rates) (Principi 1986). The secondary outcomes in Murph 1993 were resolved AOM with middle ear effusion (MEE) at days 10 to 14 and compliance rates. Two trials did not mention whether the analysis was performed based on an intention-to-treat principle or not (Murph 1993; Principi 1986). Two trials were based on intention-to-treat results only (Behre 1997; Damrikarnlert 2000), and only one trial (Hoberman 1997) reported results of the analysis both on an intention-to-treat and per-protocol principle.

Other potential sources of bias

There was no sample size calculation in one study (Principi 1986). Although the rest of the included studies demonstrated sample size calculation, there were no data for estimated cure rate or improvement rate in the study by Murph (Murph 1993).

Effects of interventions

Clinical cure rates at the end of treatment were reported in all trials. However, clinical cure rates at days 28 to 42 were reported only in three trials (Behre 1997; Damrikarnlert 2000; Hoberman 1997). All three of these trials had a moderate risk of bias. There were only two trials that reported the overall event rates (Behre 1997; Damrikarnlert 2000) and four trials reported the compliance rates (Behre 1997; Damrikarnlert 2000; Hoberman 1997; Murph 1993). Since all studies were of moderate (Damrikarnlert 2000; Murph 1993) to high risk (Principi 1986; Behre 1997; Murph 1993) of bias, we did not perform pooled data analysis. Instead, each study was displayed in forest plots (Analysis 1.1; Analysis 1.2; Analysis 1.3; Analysis 1.4; Analysis 1.5; Analysis 1.6; Analysis 1.7; Analysis 1.8). No microbiological studies of middle ear fluid were performed.

Clinical cure at the end of therapy

Five studies involving 1601 participants compared one or two daily doses of amoxicillin, with or without clavulanate, with three daily doses. However, as previously mentioned, we did not perform pooled data meta-analysis.

Clinical cure at follow up (days 28 to 42)

Three trials reported the outcome at days 28 to 42, which showed no difference in clinical cure rate (Behre 1997; Damrikarnlert 2000; Hoberman 1997). However, all of these trials had a moderate risk of bias (grade C).

Adverse events

Two trials reported overall adverse events (Behre 1997; Damrikarnlert 2000) and included 440 and 438 participants in the one or two daily doses and three daily dose groups, respectively. Two trials reported diarrhea events (Behre 1997; Hoberman 1997). Skin adverse events were reported in one trial (Hoberman 1997). Adverse events in each trial were no different between the two dosages of amoxicillin.

Compliance rate

Compliance rates were reported in four trials (Behre 1997; Damrikarnlert 2000; Hoberman 1997; Murph 1993). Only the study by Murph showed that there was a higher compliance in the three times daily dosages of amoxicillin group than in the reduced dosage group, which, due to the small sample size, could have occurred by chance.

Persistent middle ear effusion at follow-up visits

Only one trial reported the persistence of middle ear effusion ([Principi 1986](#)), and showed no statistically significant difference between the two groups at days 30, 60 and 90 with RR 0.93 (95% CI 0.73 to 1.19), 0.98 (95% CI 0.71 to 1.35) and 0.82 (0.54 to 1.25) respectively. This study, however, had a high risk of bias (grade D).

DISCUSSION

Acute otitis media (AOM) is one of the most common infections for which antibacterial agents are prescribed for children in the US ([Rovers 2004](#)). The diagnosis and management of AOM has a significant impact on the health of children, the cost of providing health care, and the use of antibiotics. Although there has been much discussion surrounding the treatment of uncomplicated AOM using antibiotics or observation, antibiotics are still widely used. The first line antibiotic of choice for AOM is amoxicillin, with or without clavulanate ([AAPS 2004](#)). The effectiveness of antibiotics does not depend solely on their antimicrobial activity against the suspected pathogens, but also on factors such as dosage, appropriate dosing intervals, tolerability and palatability. One or two daily doses of oral antibiotics have a higher compliance rate than doses taken three times daily ([Kardas 2007](#); [Pechere 2007](#)).

Summary of main results

This review identified five RCTs reporting clinical outcomes in children treated with one or two daily doses of amoxicillin, with or without clavulanate, compared to three daily doses. No trial used four daily doses. None of the studies reported a clearly significant outcome for benefits or harms. Due to moderate ([Damrikarnlert 2000](#); [Murph 1993](#)) to high risk ([Principi 1986](#); [Behre 1997](#); [Hoberman 1997](#)) of biases among these studies, we did not perform pooled data analysis. The findings did not show statistical difference in the effectiveness of the two different dosages of amoxicillin, with or without clavulanate. We cannot, however, draw conclusions without valid data from good quality studies.

Overall completeness and applicability of evidence

The included studies all showed moderate to high risk of biases, therefore there was not sufficient evidence to demonstrate the effectiveness of one or two daily dosages compared with three or four daily doses of amoxicillin, with or without clavulanate, for the treatment of AOM. This review did not show sufficient evidence that one or two times daily doses of amoxicillin, with or without

clavulanate, had an equal effectiveness as three or four times daily doses for the treatment of AOM.

Quality of the evidence

Moderate to high risk of biases.

Potential biases in the review process

No.

Agreements and disagreements with other studies or reviews

There have been no other published studies or reviews comparing the two dosages of amoxicillin, with or without clavulanate, for the treatment of AOM.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence appears to be biased and therefore we can draw no firm conclusions.

Implications for research

The information provided in the included studies is of limited value due to major problems in the studies, in particular the lack of microbiological data, the lack of stratification of patients in relation to disease severity and prior patient history of AOM, and the inappropriate age range of included patients. More than 90% of AOM cases occur in patients less than two years of age, however, in all of the included studies the age ranges were between two months and 12 years, with few cases less than two years of age. A good quality equivalence or non-inferiority trial should be performed to see whether the treatments are either equally effective or whether a lower dosage scheme is as effective as a higher dosage scheme. Children less than two years of age should also be included in the study and a microbiological study of middle ear fluid should be performed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Behre 1997

Methods	Multicenter, randomized, single-blinded (observer-blinded) controlled trial conducted in 26 centers in Germany, Belgium, Switzerland, the UK and Eire AOM was defined by the visual appearance of the ear drum or presence of middle ear effusion on otoscopy, and the presence of 2 of the following symptoms: ear pain, ear discharge, hearing loss, fever, lethargy, irritability, anorexia, vomiting or diarrhea Analysis was performed based on the intention-to-treat and per protocol principle, however only the intention-to-treat analysis was shown	
Participants	463 AOM children aged 2 to 12 years (231 and 232 children in the 2 and 3 times daily groups, respectively)	
Interventions	10 days with amoxicillin/clavulanate (70/10 mg/kg/day and 60/15 mg/kg/day for the 2 and 3 times daily groups, respectively)	
Outcomes	Primary outcome Clinical cure at days 10 to 17, defined as complete or partial resolution (212/231 (91.8%) versus 210/232 (90.5%) for the 2 and 3 times daily groups, respectively) Secondary outcomes 1. Clinical cure at day 28 (185/231 versus 180/232 in the 2 and 3 times daily groups, respectively) 2. Adverse events (111/231 and 94/232 children in the 2 and 3 times daily groups, respectively) 3. Compliance rate (at least 80%) (192/231 and 269/232 in the 2 and 3 times daily groups, respectively)	
Notes	Supported by SmithKline Beecham Pharmaceuticals Although 34 and 44 children were noted to withdraw from the study, the total number of children at the end of therapy and follow-up visit were the same as at the entry High risk of bias	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	The authors did not describe the method of randomization and allocation concealment

Damrikarnlert 2000

Methods	Multicenter, randomized, single-blinded (observer-blinded) trial conducted at 18 centers in Argentina, Brazil, Costa Rica, India, Kenya, Mexico, Morocco, Nigeria, Thailand and Turkey between August 1996 and March 1998 Block of 6 randomization was performed using SAS software. Although analyses using the intention-to-treat and per-protocol principle were planned, only the intention-to-treat principle analysis was shown	
Participants	415 AOM children aged 2 months to 12 years (209 and 206 children in the 2 and 3 times daily groups, respectively). However, 199 and 187 patients were analyzed for primary outcome	

Interventions	7 to 10 days (depending on national prescribing practice) with amoxicillin/clavulanate 45/6.4 mg/kg/day and 40/10 mg/kg/day (2 versus 3 times daily groups, respectively)	
Outcomes	Primary outcome Clinical success at days 7 to 12 (187/199 (94%) versus 175/187 (94.1%) in the 2 and 3 times daily groups, respectively) Secondary outcome 1. Successful clinical response at days 38 to 42 (153/174 (87.9%) versus 168/180 (93.3%) in the 2 and 3 times daily groups, respectively) 2. Adverse events (25/209 (12%) versus 37/206 (18%) in the 2 and 3 times daily groups, respectively) 3. Compliance rate (at least 80%) (173/209 and 173/206 in the 2 and 3 times daily groups, respectively)	
Notes	Supported by Smithkline Beecham Pharmaceuticals. There were many details which were not inappropriate: 1. The definitions of intention-to-treat (ITT) principle and per-protocol for analysis were not appropriate. The ITT principle should be defined as outcome analysis based on the group which was randomized at entry, while the per-protocol analysis should be according to the treatment received in each group 2. 415 patients were randomized to treatment: 209 versus 206 in the 2 and 3 times daily group. Thirty-six patients of 209 (17.2%) and 40 of 206 patients (19.4%) in the 2 and 3 times daily groups, respectively, withdrew during the study. However, the total patients in Table 2 showed that the total number at the end of therapy (days 7 to 12) was 199 and 187 in the 2 and 3 times daily groups, respectively. Table 4 demonstrated that at the end of therapy (days 7 to 12) and follow-up visit (days 38 to 42) the total patients in the 2 times daily group were 198 and 180 respectively, while the total patients in the 3 times daily group were 186 and 174, respectively. This meant that the total patients in Table 2 and 4 did not match the withdrawal rate 3. 54/209 patients (25.8%) and 74/206 patients (35.9%) were excluded from the per-protocol populations because of poor compliance and failure to return for the end of therapy visit within the specified time window Moderate risk of bias	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	The authors stated that following enrolment, study medication was dispensed by the pharmacist or study nurse who instructed the patient's parent or guardian in its administration

Hoberman 1997

Methods	Multicenter, randomized, non-placebo controlled trial conducted at four university-affiliated hospitals and 20 private practices in the US and Canada between January and July 1994 AOM was defined as either presence of purulent otorrhea for less than 24 hours or evidence of middle ear effusion in addition to at least one indicator of acute middle ear inflammation Investigators were blinded to treatment assignments and patients, parents and guardians were asked not to discuss medications or duration of treatment with investigators
Participants	575 children aged 2 months to 12 years were included (287 and 288 in the 2 and 3 times daily groups, respectively)
Interventions	10 days of amoxicillin/clavulanate 40/10 mg/kg/day 2 times daily versus 45/6.4 mg/kg/day 3 times daily
Outcomes	Primary outcome 1. Recurrence (completely resolved or improved, but recurred or worsened thereafter) at days 32 to 38 (51/287 (17.8%), 34/288 (11.8%). Intention-to-treat principle) Secondary outcomes 1. Clinical cure (completely/improved symptoms and signs of AOM at days 12 to 14) (241/287 (84%) versus 229/288 (79.5%). (Intention-to-treat principle) 2. Adverse events: diaper rash (23/287 (8%) versus 30/288 (10.4%)); vomiting (29/287 (10.1%) versus 31/288 (10.8%)); diarrhea (15/287 (5.2%) versus 20/288 (7%)) 3. Compliance rate (257/287(89.5%) versus 246/288 (85.4%))
Notes	Supported by SmithKline Beecham Pharmaceuticals High risk of bias

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	The authors did not mention the methods of randomization and allocation concealment

Murph 1993

Methods	Double-blind, placebo-controlled study. A table of random numbers was used to generate a randomized sequence AOM was defined as evidence on otoscopic assessment of an inflamed tympanic membrane and presence of middle ear effusion
Participants	77 AOM children, aged 7 months to 12 years old, recruited from the Pediatric Child Health Clinic of the University of Iowa Hospitals and Clinics 10/77 (7.7%) children could not be evaluated because failed to return for follow up or withdrew from the study; 33 and 34 children in the once and 3 times daily groups, respectively, were left for the analysis
Interventions	10 days of amoxicillin 40 mg/kg/day once versus 3 times daily
Outcomes	Primary outcome Resolved AOM with or without MEE (27/33 (82%) and 23/24 (68%) for once and 3 times daily) assessed

Murph 1993 (Continued)

	at days 10 to 14 Secondary outcome 1. Resolved AOM with MEE present at days 10 to 14 (13/33 (39%) versus 8/34 (24%)) 2. Compliance rate (at least 80%): 100% for both groups	
Notes	No pharmaceutical industry support Intention-to-treat principle analysis was not mentioned Moderate risk of bias	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	A table of random numbers was used to assign children to one of the two treatment groups but allocation concealment was not clearly mentioned

Principi 1986

Methods	Randomized controlled study conducted in the outpatient ward of the Pediatric Department IV of the University of Milan between October 1984 and 1985 AOM was defined on clinical data (fever or otalgia or both), otoscopic finding of ear drum, and presence of ear effusion shown by tympanograms. Children with spontaneously perforated ear drums were also included only if the ear had been draining for no longer than 12 hours
Participants	55 AOM children in each treatment group (total 110), aged 6 months to 12 years
Interventions	10 days of amoxicillin 60 mg/kg/day 2 or 3 times daily
Outcomes	Primary outcome Clinical cure (normalization of clinical or relief of acute signs and symptoms of AOM) assessed at day 15 (49/55 (89.1%) versus 51/55 (92.7%) for 2 and 3 times daily groups, respectively) Secondary outcome 1. Persistent middle ear effusion without signs and symptoms of infection at day 15 (41/55 (74.5%) versus 40/55 (72.7%)) 2. Clinical cure at days 30, 60 and 90 (cure at day 30, 44/49 (89.8%) versus 51/51 (100%); at day 60, 42/46 (91.3%) versus 49/50 (98%), and at day 90, 42/46 (91.3%) versus 48/49 (98%)) 3. Persistence of otitis media with effusion (at day 30 (34/49 versus 38/51); at day 60 (28/46 versus 31/50); and at day 90 (20/46 versus 26/49))
Notes	Supported in part by a Farmitalia-Carlo Erba SpA Milano grant Intention-to-treat principle analysis was not mentioned Clinical evaluation at 30 days was stated to be performed in all the children who had entered the study (55 children in each group), however only 49 and 51 in the 2 and 3 times daily groups were analyzed High risk of bias
Risk of bias	

Principi 1986 *(Continued)*

Item	Authors' judgement	Description
Allocation concealment?	No	No randomization process and allocation concealment methods were mentioned

AOM: acute otitis media

MEE: middle ear effusion

Characteristics of excluded studies *[ordered by study ID]*

Jacobsson 1993	1. Included only recurrence or cases that were not responsive to amoxicillin/penicillin or cefaclor, which was different from other studies 2. The total daily dosage for amoxicillin was quite low (20 to 33.2 mg/kg/day)

DATA AND ANALYSES

Comparison 1. Once or twice daily versus thrice daily

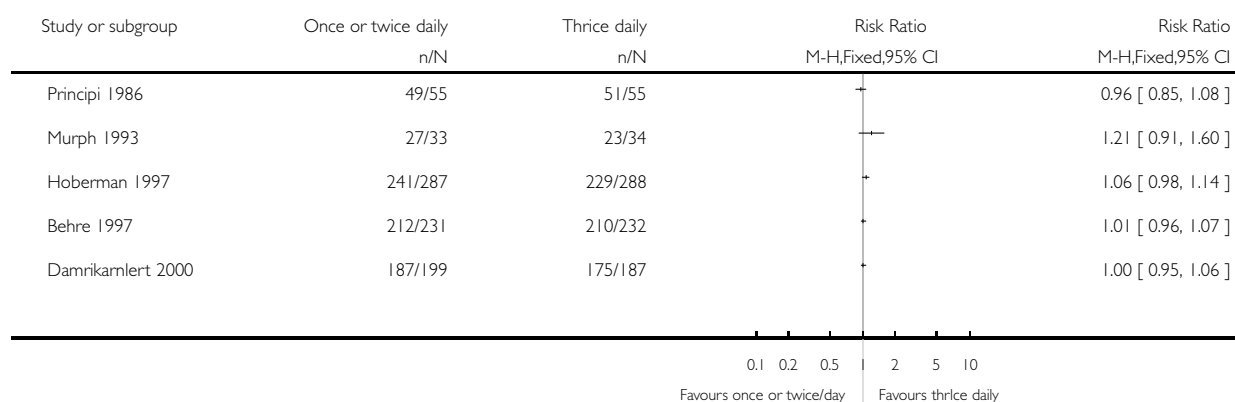
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical cure at the end of therapy	5		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Clinical cure at follow up (days 28 to 42)	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Overall adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Specific adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Diarrhea	2		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2 Skin adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Compliance rate	4		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Persistent middle ear effusion at follow-up visit (day 30)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Persistent middle ear effusion at follow-up visit (day 60)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Persistent middle ear effusion at follow-up visit (day 90)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Once or twice daily versus thrice daily, Outcome 1 Clinical cure at the end of therapy.

Review: Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media

Comparison: 1 Once or twice daily versus thrice daily

Outcome: 1 Clinical cure at the end of therapy

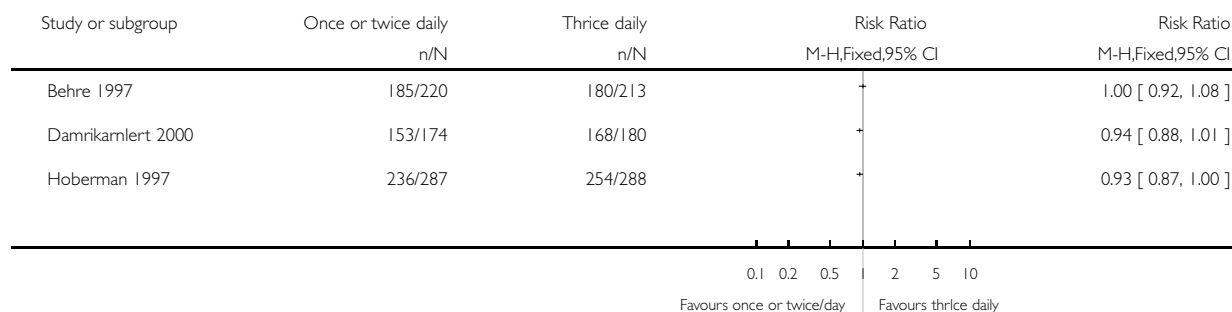


Analysis 1.2. Comparison 1 Once or twice daily versus thrice daily, Outcome 2 Clinical cure at follow up (days 28 to 42).

Review: Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media

Comparison: 1 Once or twice daily versus thrice daily

Outcome: 2 Clinical cure at follow up (days 28 to 42)

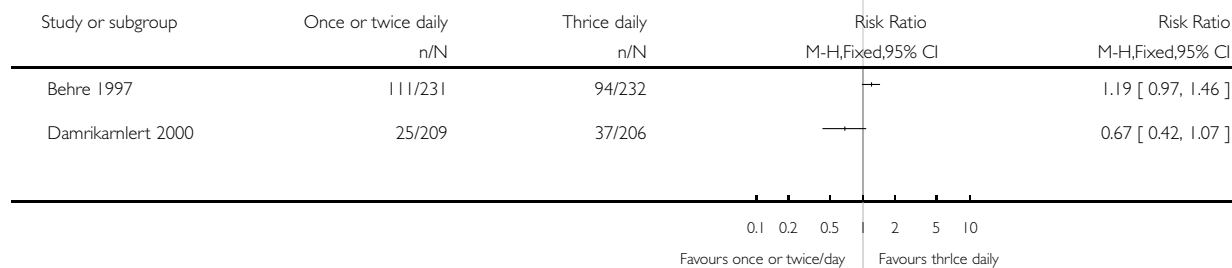


Analysis 1.3. Comparison 1 Once or twice daily versus thrice daily, Outcome 3 Overall adverse events.

Review: Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media

Comparison: 1 Once or twice daily versus thrice daily

Outcome: 3 Overall adverse events

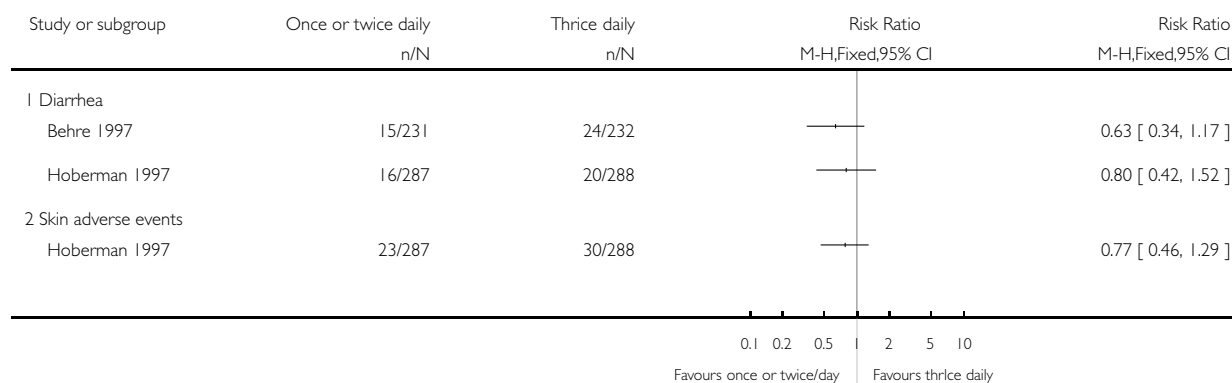


Analysis 1.4. Comparison 1 Once or twice daily versus thrice daily, Outcome 4 Specific adverse events.

Review: Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media

Comparison: 1 Once or twice daily versus thrice daily

Outcome: 4 Specific adverse events

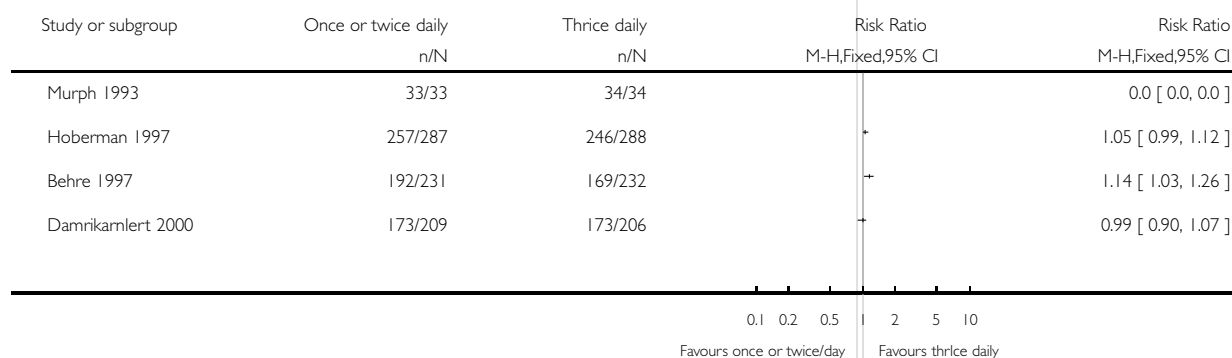


Analysis 1.5. Comparison 1 Once or twice daily versus thrice daily, Outcome 5 Compliance rate.

Review: Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media

Comparison: 1 Once or twice daily versus thrice daily

Outcome: 5 Compliance rate

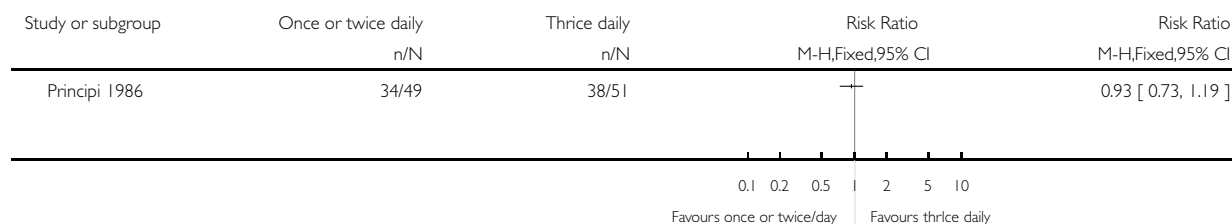


Analysis 1.6. Comparison 1 Once or twice daily versus thrice daily, Outcome 6 Persistent middle ear effusion at follow-up visit (day 30).

Review: Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media

Comparison: 1 Once or twice daily versus thrice daily

Outcome: 6 Persistent middle ear effusion at follow-up visit (day 30)

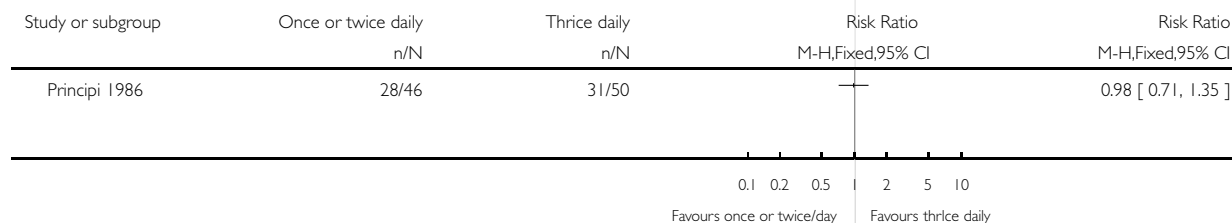


Analysis 1.7. Comparison 1 Once or twice daily versus thrice daily, Outcome 7 Persistent middle ear effusion at follow-up visit (day 60).

Review: Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media

Comparison: 1 Once or twice daily versus thrice daily

Outcome: 7 Persistent middle ear effusion at follow-up visit (day 60)

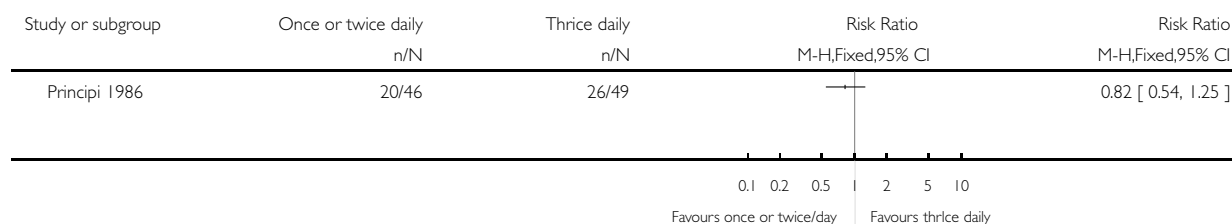


Analysis 1.8. Comparison 1 Once or twice daily versus thrice daily, Outcome 8 Persistent middle ear effusion at follow-up visit (day 90).

Review: Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media

Comparison: 1 Once or twice daily versus thrice daily

Outcome: 8 Persistent middle ear effusion at follow-up visit (day 90)



APPENDICES

Appendix 1. EMBASE search strategy

- #1. 'otitis media'/exp AND [embase]/lim
- #2. 'acute otitis media'/exp AND [embase]/lim
- #3. 'acute suppurative otitis media'/exp AND [embase]/lim
- #4. 'otitis media':ti,ab AND [embase]/lim
- #5. 'aom':ti,ab AND [embase]/lim
- #6. 'asom':ab,ti AND [embase]/lim
- #7. #1 OR #2 OR #3 OR #4 OR #5 OR #6
- #8. 'amoxicillin'/exp AND [embase]/lim
- #9. 'amoxicillin plus clavulanic acid'/exp AND [embase]/lim
- #10. amoxicillin:ti,ab AND [embase]/lim
- #11. amoxycillin:ab,ti AND [embase]/lim
- #12. #8 OR #9 OR #10 OR #11
- #13. (singl*:ti,ab OR one:ti,ab OR once:ti,ab OR two:ti,ab OR twice:ti,ab) AND [embase]/lim
- #14. ('q.d.':ti,ab OR 'qd':ti,ab OR 'o.d.':ti,ab OR 'od.':ti,ab OR 'b.d.':ti,ab OR 'bd':ti,ab) AND [embase]/lim
- #15. (three:ti,ab OR thrice:ti,ab OR four:ti,ab) AND [embase]/lim
- #16. ('t.d.s.':ti,ab OR 'tds':ti,ab OR 'q.i.d.':ti,ab OR 'qid':ti,ab) AND [embase]/lim
- #17. #13 OR #14
- #18. #15 OR #16
- #19. #17 AND #18
- #20. #7 AND #12 AND #19
- #21. 'randomized controlled trial'/exp AND [embase]/lim
- #22. 'controlled study'/exp AND [embase]/lim
- #23. 'single blind procedure'/exp AND [embase]/lim
- #24. 'double blind procedure'/exp AND [embase]/lim
- #25. 'phase 3 clinical trial'/exp AND [embase]/lim
- #26. random*:ab,ti AND [embase]/lim
- #27. placebo*:ti,ab AND [embase]/lim
- #28. 'clinical trial':it AND [embase]/lim
- #29. 'randomized controlled trial':it AND [embase]/lim
- #30. (singl*:ti,ab OR doubl*:ti,ab OR tripl*:ti,ab OR trebl*:ti,ab) AND (blind*:ti,ab OR mask*:ti,ab) AND [embase]/lim

#31. 'controlled clinical trial':ti,ab AND [embase]/lim
 #32. 'controlled clinical trials':ti,ab AND [embase]/lim
 #33. #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR # 31 OR #32
 #34. ('nonhuman'/exp OR 'animals'/exp) NOT 'human'/exp AND [embase]/lim
 #35. #33 NOT #34
 #36. #20 AND #35

Appendix 2. Science Citation Index search strategy

Science Citation Index searched by ISI Web of Knowledge (<http://apps.isiknowledge.com>)

#1 TI = "otitis media"
 #2 TI = amoxicillin
 #3 TI=amoxycillin
 #4 #2 OR #3
 #5 TI = once
 #6 TI = one
 #7 TI = singl*
 #8 TI = two
 #9 TI = twice
 #10 #5 OR #6 OR #7 OR #8 OR #9
 #11 TI = three
 #12 TI=thrice
 #13 TI=four
 #14 #11 OR #12 OR #13
 #15 #10 AND #14
 #16 #1 AND #4 AND 15

Appendix 3. NLM Gateway search strategy

We used the terms ("otitis media" AND (amoxycillin OR amoxicillin) AND (one OR once OR two OR twice OR singl*) AND (thrice OR three OR four) to search NLM Gateway.

WHAT'S NEW

Last assessed as up-to-date: 17 March 2008.

21 January 2010	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 4, 2004

Review first published: Issue 4, 2008

8 May 2009	Amended	Contact details updated.
18 March 2008	New search has been performed	Searches conducted.
12 March 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Sanguansak Thanaviratananich (ST) was responsible for conceiving, designing and co-ordinating the protocol, developing the search strategy, assessing the quality of studies, entering text into RevMan and writing the review.

Patravoot Vatanasapt (PV) was responsible for designing and co-ordinating the review, assessing the quality of the studies and providing general advice on the review.

Malinee Laopaiboon (ML) was responsible for entering text into RevMan and providing general advice on the statistical analysis and the review generally.

DECLARATIONS OF INTEREST

No conflict of interest known.

SOURCES OF SUPPORT

Internal sources

- Faculty of Medicine, Khon Kaen, Thailand.

External sources

- Thai Cochrane Network, Thailand.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Amoxicillin [*administration & dosage]; Anti-Bacterial Agents [*administration & dosage]; Clavulanic Acid [*administration & dosage]; Drug Administration Schedule; Drug Therapy, Combination; Otitis Media [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Child; Humans

Paracervical local anaesthesia for cervical dilatation and uterine intervention (Review)

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[Intervention Review]

Paracervical local anaesthesia for cervical dilatation and uterine intervention

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ABSTRACT

Background

Cervical dilatation and uterine intervention can be performed under sedation, local or general anaesthesia for obstetrics and gynaecological conditions. Many gynaecologists use paracervical local anaesthesia (PLA) but its effectiveness is unclear.

Objectives

To determine the effectiveness and safety of paracervical anaesthesia for cervical dilatation and uterine intervention when compared with no treatment, placebo, other methods of regional anaesthesia, systemic sedation and analgesia, or general anaesthesia (GA).

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2006, Issue 1), MEDLINE (1966 to January 2006), EMBASE (1980 to January 2006) and reference lists of articles.

Selection criteria

We included randomized or controlled clinical studies involving cervical dilatation and uterine intervention for obstetric and gynaecological conditions.

Data collection and analysis

Two authors independently evaluated studies, extracted data, checked and entered data into Review Manager.

Main results

We included 17 studies involving 1855 participants. No study of PLA versus GA met our criteria; eight studies compared PLA versus placebo. Injection of local anaesthetic was slightly less painful than injection of saline placebo, a reduction of 0.87 points (95% CI 0.14 to 1.60) on a 10-point pain scale. Compared to placebo, PLA reduced abdominal pain during uterine intervention equivalent to two or three points on a 10-point pain scale and reduced the risk of severe pain (RR 0.16, 95% CI 0.06 to 0.74). There was no

evidence that PLA reduced pain after the uterine intervention and little evidence for any effect on postoperative back or shoulder pain. Pain reduction by PLA was not confirmed in four studies that compared PLA with no treatment. Three studies compared PLA with uterosacral block; intracervical block; and intrauterine topical anaesthesia. Two of these studies showed no significant difference in pain during the procedure. Compared to intrauterine instillation, PLA slightly reduced severe pain (from 8.3 to 7.6, on a 10-point pain scale), which may be negligible. This benefit appeared to be greater for women who required cervical dilatation. Two studies compared PLA with sedation. There were no statistically significant differences in pain during or after the procedure, postoperative analgesia requirement, adverse effects, patient satisfaction, and the operator's perception of analgesia.

Authors' conclusions

No technique provided reliable pain control in the 17 included studies. Some studies reported that women experienced severe pain (mean scores of 7 to 9 out of 10) during uterine intervention, irrespective of the analgesic technique used. We concluded that the available evidence fails to show whether paracervical block is inferior, equivalent or superior to alternative analgesic techniques, in terms of efficacy and safety, for women undergoing uterine interventions.

PLAIN LANGUAGE SUMMARY

Paracervical local anaesthesia for cervical dilatation and uterine interventions

Paracervical block involves injection of local anaesthetic around the cervix to numb nearby nerves. Cervical dilatation and uterine interventions (such as hysteroscopies, endometrial biopsies, fractional curettage, and suction terminations) can be performed without any analgesia or anaesthesia; with regional anaesthetic injections as with paracervical block; using oral or intravenous analgesics and sedatives; or under general anaesthesia. Many gynaecologists use paracervical block for uterine intervention but it is unclear how effective and safe this method is. We included 17 studies involving 1855 women undergoing uterine interventions who were randomly allocated to paracervical block or an alternative. We found that women had less pain during uterine intervention with paracervical block than with placebo injection (saline or water). However, in most studies this reduction was small. We did not find any evidence that paracervical block reduces residual pain after the procedure. Four studies that compared paracervical block with no treatment (not even a placebo injection) did not find any differences in level of pain experienced by women having hysteroscopies, evacuation of retained products of conception, and suction terminations. We found insufficient evidence to determine any differences in pain experienced by women having paracervical block compared to alternative regional anaesthetic methods, or the use of systemic analgesics and sedatives. Information on any important side effects was insufficient to determine if these are more common with paracervical block than with other methods of analgesia.

BACKGROUND

Indications for cervical dilatation and uterine intervention include abnormal uterine bleeding that does not respond to medical treatment, postmenopausal bleeding, and abortion. General anaesthesia (GA) provides adequate operating conditions for cervical dilatation and uterine intervention. However, there are some situations when GA is hazardous, for example when the patient is in a poor medical condition or when no anaesthesiologist is available. Paracervical local anaesthesia (PLA) offers an alternative to GA for cervical dilatation and uterine intervention in these women. Injection of local anaesthetic around the cervix, at the 'three and

nine o'clock' positions, anaesthetizes the second to fourth sacral nerve roots as they pass through Frankenhauser's plexus at a depth of 2 to 4 mm (Piyamongkol 1998). The advantages of PLA compared to GA are that it does not require general anaesthetic equipment nor the personnel trained to give GA. However, paracervical local anaesthetic should be administered by trained staff and resuscitation facilities should be available. Many gynaecologists use PLA for cervical dilatation and uterine intervention and its effectiveness is unclear. Premenopausal and postmenopausal as well as pregnant and non-pregnant women have different cervical conditions in terms of their anatomy and physiology. In this review we

compared the effectiveness and safety of PLA for cervical dilatation and uterine interventions versus no treatment, placebo, other methods of regional anaesthesia, sedation and systemic analgesia, and general anaesthesia.

OBJECTIVES

The objectives of this review were to determine the effectiveness and safety of PLA for cervical dilatation and uterine intervention versus no treatment, placebo, other methods of regional anaesthesia, sedation and systemic analgesia, and general anaesthesia.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled studies in which allocation was randomized or pseudo-randomized (alternate days, weeks, odd and even hospital numbers). We excluded concurrent cohort and observational studies.

Types of participants

We included women of any age who underwent cervical dilatation and uterine intervention for any indication.

Types of interventions

We Included studies in which at least one group had paracervical block. The comparison interventions were: placebo; no treatment; other regional anaesthesia; sedation and systemic analgesia. We did not compare one type of local anaesthetic with another.

Types of outcome measures

We included pain, adverse effects and patient satisfaction.

Primary outcomes

1. Pain during or after cervical dilatation and uterine intervention measured as categorical data, continuous data (for example on a visual analogue scale), or the requirement for additional analgesia;
2. adverse effects (such as nausea, vomiting, hypotension).

Secondary outcomes

1. Patient satisfaction (as defined by the study authors).

Search methods for identification of studies

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; [Appendix 1](#)), (*The Cochrane Library* 2006, Issue 1), MEDLINE on Silver Platter (1966 to January 2006; [Appendix 2](#)), EMBASE (January 1980 to January 2006; [Appendix 3](#)), and reference lists of articles.

We combined our search strategies with the Cochrane highly sensitive search strategy for randomized controlled studies phase one and two as contained in the Cochrane Handbook for Systematic Reviews of Interventions ([Higgins 2005](#)).

We searched for ongoing and recently published studies at www.controlled-studies.com.

We did not apply any language restrictions.

Data collection and analysis

Eligibility

We did not blind the names of the study authors, institutions, or journal of publication. Two authors (TT and US) independently evaluated the eligibility of studies from their title, abstract, and the full paper. We analysed the results of the randomized controlled studies that we had selected and graded their methodological quality for: concealment of allocation; blinding of the intervention administered; completeness of follow up; and blinding of outcome assessment. We used the Cochrane method for stratifying qualitative aspects of each study: 'A' for adequate; 'B' for unclear; 'C' for inadequate; and 'D' for not used ([Higgins 2005](#)). We resolved any disagreements through discussion. The third author (PL) evaluated disputed studies to obtain a consensus.

Data extraction

We used the standard methods of the Cochrane Anaesthesia Review Group. Two authors (TT and US) scrutinized all the titles and abstracts for their suitability and independently extracted data. One author (TT) checked the data and entered them into [Review Manager 5.0](#). We contacted the authors of any study that had missing data.

Statistical analyses

Where appropriate we analysed pooled data using [Review Manager 5.0](#) (RevMan). The method of meta-analysis was dependent on the nature of the outcomes. For categorical data (for example proportion of participants with an event) we related the number reporting an event to the number at risk in each group to derive a

relative risk (RR) and 95% confidence interval (CI). We pooled continuous differences between groups in the meta-analysis (for example pain relief on a visual analogue scale) as mean differences (MD) or standardized mean differences (SMD), as appropriate, with their 95% CI. As a general rule we used a fixed-effect model for calculation of summary estimates. When we suspected important heterogeneity, determined by visual inspection or the I^2 statistic for heterogeneity (Higgins 2003), we investigated differences in clinical and methodological factors between studies. We performed a sensitivity analysis for assessing the effect of quality of studies on the conclusions. We assessed the clinical significance of statistically significant differences between the groups. When meta-analysis was inappropriate we drew conclusions from the descriptive elements of the studies; methodological quality; number of studies with consistent findings; plausibility of the results; and the strength of the associations in the primary studies as well as consensus among authors.

We anticipated that we would conduct meta-analyses for the following comparisons.

1. Paracervical local anaesthesia versus placebo.
2. Paracervical local anaesthesia versus no anaesthesia.
3. Paracervical local anaesthesia versus other methods of regional anaesthesia.
4. Paracervical local anaesthesia versus systemic analgesia.
5. Paracervical local anaesthesia versus general anaesthesia.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#).

We identified 1110 studies with our initial search strategies of which 97 had relevant titles and abstracts. We excluded 78 studies (see [Characteristics of excluded studies](#)). Titles and abstracts were unclear in three studies and we put them into studies awaiting assessment (Chaudhuri 1980; Regina 1987; Sen 1980). We identified 17 relevant studies with a total of 1855 women that were published in full. We included three studies of paracervical local anaesthesia versus sedation and systemic analgesia (Buppasiri 2005; Guida 2003; Mola 1996); eight studies versus placebo (Chanrachakul 2001; Chatfield 1970; Cicinelli 1998; Egziabher 2002; Glantz 2001; Lau 1999; Miller 1996; Titapant 2003); three studies versus other regional techniques (Finikiotis 1992; Kan 2004; Yazaci 2003); and four studies versus no anaesthesia (Carroll 2005; Gómez 2004; Kan 2004; Vercellini 1994). We did not find any studies of paracervical block versus general anaesthesia that met our inclusion criteria (see [Characteristics of included studies](#)).

Risk of bias in included studies

We graded allocation concealment as adequate in six studies (Carroll 2005; Cicinelli 1998; Glantz 2001; Gómez 2004; Lau 1999; Mola 1996); unclear in six studies (Buppasiri 2005; Chanrachakul 2001; Chatfield 1970; Miller 1996; Titapant 2003; Yazaci 2003); and inadequate in five studies (Egziabher 2002; Finikiotis 1992; Guida 2003; Kan 2004; Vercellini 1994). Seven of 17 studies reported adequately blinding women to their allocated intervention (Chanrachakul 2001; Chatfield 1970; Cicinelli 1998; Egziabher 2002; Glantz 2001; Lau 1999; Miller 1996). Four studies reported adequately blinding treatment providers to the allocated intervention (Chanrachakul 2001; Chatfield 1970; Glantz 2001; Lau 1999); and five studies reported adequately blinding the outcome assessors to the allocated intervention (Chanrachakul 2001; Chatfield 1970; Cicinelli 1998; Glantz 2001; Lau 1999). Three of these (Chatfield 1970; Cicinelli 1998; Glantz 2001) blinded assessors to outcomes other than abdominal pain. All studies completed follow up for all women.

Effects of interventions

We included 17 studies involving 1855 women. Studies compared paracervical block versus: placebo, no treatment, other types of regional anaesthesia, and systemic analgesia (and sedation). Outcomes included pain, adverse effects and patient satisfaction.

Paracervical local anaesthesia versus placebo

(Analysis 1.1 to Analysis 1.10)

Eight studies compared paracervical block with placebo (Chanrachakul 2001; Chatfield 1970; Cicinelli 1998; Egziabher 2002; Glantz 2001; Lau 1999; Miller 1996; Titapant 2003). Uterine interventions included hysteroscopy, endometrial biopsy, fractional curettage, and vacuum aspiration. The local anaesthetics used were lidocaine, chloroprocaine, and xylocaine (see [Characteristics of included studies](#) for details).

Pain during the procedure

Paracervical injection of local anaesthetic was 0.87 points (95% CI 0.14 to 1.60) less painful than injection of saline placebo on a 10-point pain scale (from about 4.5 with placebo to about 3.6 with PLA where a score of 0 means 'no pain' and a score of 10 means 'worst pain') (Analysis 1.1). In two studies (Lau 1999; Miller 1996) there was no evidence that paracervical block reduced pain during cervical dilatation (Analysis 1.2). Compared to placebo, paracervical block reduced pain during uterine interventions (endometrial biopsy, fractional curettage, suction evacuation, or aspiration) by the equivalent of two or three points on a 10-point pain scale (standardized mean difference (SMD) (Analysis 1.3). In two studies (Chatfield 1970; Egziabher 2002) paracervical block

reduced the risk of severe pain during uterine intervention (RR 0.16, 95% CI 0.06 to 0.74) but not the risk of any pain ([Analysis 1.4](#)). [Chanrachakul 2001](#) reported that paracervical block significantly reduced the median pain score during fractional curettage, from 6.0 to 4.0 (statement unsupported by a P value).

Postoperative pain

We did not find any evidence that paracervical block reliably reduced postoperative pain when compared to placebo injection ([Analysis 1.5](#); [Analysis 1.6](#); [Analysis 1.10](#)). In one study ([Egziabher 2002](#)) paracervical block did not reduce the summated risk of intraoperative and postoperative backache ([Analysis 1.9](#)). Paracervical block did not reduce the risk of shoulder pain at any time ([Analysis 1.9](#)).

Adverse effects

Paracervical block did not change the risk of sweating, nausea or vomiting ([Analysis 1.10](#)). In one study ([Lau 1999](#)) the risk of hypotension after paracervical block was greater than after placebo injection (RR 3.06, 95% CI 1.21 to 7.78). Three women out of 27 injected with lidocaine reported symptoms consistent with toxicity (tingling lips, dizziness) in [Miller 1996](#).

Paracervical local anaesthesia versus no anaesthesia

([Analysis 2.1](#) to [Analysis 2.2](#))

Four studies compared paracervical block versus no treatment ([Carroll 2005](#); [Gómez 2004](#); [Kan 2004](#); [Vercellini 1994](#)). In two studies women had hysteroscopies ([Carroll 2005](#); [Vercellini 1994](#)) and in two studies women had suction termination or evacuation of incomplete miscarriages ([Gómez 2004](#); [Kan 2004](#)).

Pain during the procedure and postoperative pain

[Kan 2004](#) found no evidence that paracervical block reduced median pain scores during or after suction termination under sedation when compared to no block. There was no evidence for significant differences in pain during hysteroscopy and endometrial biopsy in [Vercellini 1994](#) ([Analysis 2.1](#)). [Carroll 2005](#) reported no differences in pain scores measured immediately after hysteroscopy and 5 and 10 minutes later ([Analysis 2.2](#)). [Gómez 2004](#) reported no difference in intraoperative pain as recalled 10 minutes after the procedure.

Adverse effects

No study found evidence for differences in the risks of adverse effects.

Patient satisfaction

[Kan 2004](#) did not find evidence for differences in patient satisfaction.

Paracervical local anaesthesia versus other regional anaesthesia

([Analysis 3.4](#) to [Analysis 3.3](#))

Three studies ([Finikiotis 1992](#); [Kan 2004](#); [Yazaci 2003](#)) compared paracervical block to other local anaesthetic techniques: uterosacral block ([Finikiotis 1992](#)), intracervical block ([Kan 2004](#)), and intrauterine topical analgesia ([Yazaci 2003](#)).

Pain during the procedure

In one study ([Finikiotis 1992](#)) paracervical block did not reduce the risk of pain during hysteroscopy compared to uterosacral block (RR severe pain 0.17, 95% CI 0.42 to 3.27; RR moderate to severe pain 1.22, 95% CI 0.80 to 1.85). Paracervical block did not change median pain scores compared to intracervical block measured during or after suction termination under sedation ([Kan 2004](#)). [Yazaci 2003](#) reported that women in both groups experienced severe pain during endometrial biopsy; the paracervical block group (mean pain score 76.3 out of 100) experienced slightly less pain than the intrauterine local anaesthetic instillation group (mean pain score 83.2 out of 100) ([Analysis 3.1](#)).

Postoperative pain

Postoperative pain was slightly less in the paracervical group in [Yazaci 2003](#) ([Analysis 3.2](#)), mean difference (out of 100) 4.63 (95% CI 0.24 to 9.02).

Adverse effects

[Yazaci 2003](#) did not find any difference in the risk of a vasovagal reaction ([Analysis 3.3](#)).

Paracervical local anaesthesia versus systemic analgesia

([Analysis 4.1](#) to [Analysis 4.7](#))

Three studies compared paracervical block with systemic analgesics and sedatives: mefenamic acid ([Buppasiri 2005](#)); fentanyl and midazolam ([Guida 2003](#)); and pethidine and diazepam ([Mola 1996](#)). [Buppasiri 2005](#) studied women undergoing fractional curettage, [Guida 2003](#) studied women undergoing hysteroscopy, and [Mola 1996](#) studied women having bi-manual removal of retained placenta.

Pain during uterine intervention and postoperative pain

There was no evidence that paracervical block reduced median pain scores during or after uterine intervention when compared to mefenamic acid (Buppasiri 2005), or pethidine and diazepam (Mola 1996). There were no consistent differences in intraoperative and postoperative pain scores between paracervical block and treatment with midazolam and fentanyl in Guida 2003 (Analysis 4.1 to Analysis 4.3). Mola 1996 found no differences between paracervical block and combined analgesia and sedation in the risk of intraoperative pain identified by the women (Analysis 4.2) or the operator's perception of women's pain (Analysis 4.7).

Adverse effects

Guida 2003 reported no evidence for a difference in the risk of pallor, hypotension, or nausea and vomiting. Buppasiri 2005 reported no evidence for a difference in the risk of dizziness (Analysis 4.5).

Patient satisfaction

Guida 2003 reported no evidence for a difference in the risk of dissatisfaction (Analysis 4.6).

Paracervical local anaesthesia versus general anaesthesia

We did not find any eligible studies for this comparison. We found no studies that compared the effectiveness of paracervical block in premenopausal and postmenopausal women or in gynaecological and obstetric indications.

DISCUSSION

Summary of main results

Seventeen included studies compared paracervical block and other anaesthetic and analgesic methods for women undergoing uterine interventions in terms of effectiveness in pain control, adverse effects and patient satisfaction. Some studies had co-interventions (amnesic sedation or opioids), given to both intervention and control groups, however we found no differences in pain control in these studies. Premedications such as opioid are given to allay the patient's apprehension on entering an operating theatre and being placed in the lithotomy position. In these studies, where the premedication was given to both groups, analgesics were omitted to avoid confusion in pain assessment. We anticipated that a clinically significant difference in the need for pain relief or the risk of adverse events would be a 50% difference, but we did not find any

differences in effectiveness and safety between paracervical block and placebo or other anaesthetic and analgesic methods.

Overall completeness and applicability of evidence

We included 17 relevant studies involving 1855 women. Although we had planned to include five comparisons the available studies allowed only four. Eight included studies, with 754 women, compared paracervical block with placebo. Four studies (584 women), three studies (365 women), and three studies (283 women) compared paracervical block with no anaesthesia, other regional anaesthesia methods, and systemic analgesia, respectively. All 17 studies measured pain as an outcome. Six studies had information on adverse effects, two studies reported patient satisfaction, and two studies reported on postoperative analgesic requirements. The women included in this review were undergoing both obstetric (dilatation curettage, manual placenta removal, manual vacuum aspiration) and gynaecologic (hysteroscopy, fractional curettage, endometrial biopsy or ablation) interventions. The studies in this review included sufficient numbers of women, who received either paracervical block or other anaesthetic or analgesic methods, involved both obstetric and gynaecologic interventions and evaluated all major outcomes.

Quality of the evidence

Only 7 of the 17 included studies had adequate random allocation concealment but we could not perform sensitivity analyses to evaluate the robustness of the result. This was because we had more than one comparison and each comparison had a limited number of included studies. Only 7 of 17 included studies reported using some form of blinding. In conclusion, less than half of the included studies had adequate quality in terms of randomised allocation concealment and blinding.

Potential biases in the review process

We strictly followed the search strategies recommended by the Cochrane Anaesthesia Review Group (CARG). We searched all recommended databases and had access to all the potential studies identified except the three awaiting assessment (Chaudhuri 1980; Regina 1987; Sen 1980). We will add these awaiting studies in an update of the review. Since we used the recommended review process described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005), any bias in the review should be minimal.

AUTHORS' CONCLUSIONS

Implications for practice

All of the techniques used in the 17 included studies failed to reliably prevent pain in conscious women having uterine interventions. The available evidence does not show if paracervical block is inferior, equivalent, or superior to the alternative analgesic techniques, either in terms of efficacy or safety.

Implications for research

Our systematic review showed that pain experienced by women having uterine interventions is inadequately controlled by paracervical block. The findings of the 17 included studies suggest that the other methods that were compared with paracervical block (local anaesthetic methods, sedation and systemic analgesics) also inadequately control the pain. Researchers should conduct systematic reviews of these other methods to confirm or refute this finding. The design of any future randomized controlled trials of techniques for controlling pain in women having uterine interventions without general anaesthesia should take into account the results of such systematic reviews.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Buppasiri 2005

Methods	Randomized controlled trial	
Participants	87 women, 40 years and over, undergoing outpatient fractional curettage for abnormal uterine bleeding (44 in PLA group and 43 in analgesia group). The authors excluded women with peptic ulcer, a known sensitivity to non-steroidal anti-inflammatory drugs, taking medications with known interactions with non-steroidal anti-inflammatories, who were sensitive to lignocaine, or unable to provide informed consent.	
Interventions	1. PLA: 2% lignocaine 5 ml injected into the lateral fornix at 3 and 9 o'clock at a depth of between 3 and 5 mm. Fractional curettage was performed 5 min after the paracervical injection. 2. Analgesic: mefenamic acid 500 mg orally two hours before the procedure.	
Outcomes	Pain was evaluated using a 10 cm visual analogue scale: Before the procedure 2. During endocervical curettage 3. Endometrial curettage 4. Immediately after curettage 5. 30 minutes after completing the procedure. Adverse effects: 1. Dizziness.	
Notes	Three women in each group could not tolerate the pain and needed intravenous pethidine.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	Randomly allocated

Carroll 2005

Methods	Randomized controlled trial	
Participants	58 women undergoing endometrial biopsy (27 in PLA and 31 in no anaesthesia group). Women were excluded for the following reasons: allergy to lidocaine, allergy to ibuprofen, refusal to participate, additional procedure (e.g. loop electrosurgical excision procedure, colposcopy etc), or inability to speak English.	
Interventions	1. PLA: 10 ml of 1% lidocaine injected paracervically at 2, 4, 8, and 10 o'clock positions and waited 3 to 5 minutes before biopsy (Pipelle biopsy). 2. No anaesthesia.	
Outcomes	Pain immediately before the procedure, immediately after the procedure, at 5 minutes, and at 10 minutes.	

Carroll 2005 (Continued)

Notes	We were unable to perform a subgroup analysis comparing cervical dilatation versus no cervical dilatation because results were not reported by intervention.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	Opaque sealed envelopes

Chanrachakul 2001

Methods	Randomized controlled trial	
Participants	140 women who underwent fractional curettage (70 in each of paracervical and saline groups). The exclusion criterion was an allergic reaction to lidocaine.	
Interventions	1. PLA: 1% lidocaine hydrochloride. 2. Placebo: 0.9% sodium chloride. Injection was with a 23-gauge spinal needle at 3 and 9 o'clock of the cervicovaginal reflection.	
Outcomes	Pain during and after the procedure.	
Notes	Using the visual analogue scale, each patient made four assessments of intensity of pain: 1. Pain immediately after insertion of the speculum and was for intensity of pain during insertion of the speculum 2. Immediately after curettage and was for intensity of pain during curettage 3. Intensity of pain immediately after curettage 4. 30 minutes after curettage for intensity of pain at that time. The repeated injection was limited to 10 ml of 1% lidocaine. No patient asked for lidocaine during the procedure or asked to leave the study.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Chatfield 1970

Methods	Randomized controlled trial	
Participants	100 consecutive women with an incomplete abortion; uterine size varied from 8 to 16 weeks and in the majority the cervix was open and required no further dilatation for the evacuation procedure (50 in each: PLA and placebo group).	

Chatfield 1970 (Continued)

Interventions	1. PLA: 0.25% bupivacaine with 1:400,000 adrenaline, 5 ml. 2. Normal saline, 5 ml. Injected through the vaginal wall of each lateral fornix, approximately 1 cm from the cervix and at eight and four o'clock, half-an-hour prior to evacuation.	
Outcomes	Patient's impression of discomfort during evacuation.	
Notes	“Promazine 25 mg and promethazine 25 mg given after the block to allay the patient's natural apprehension on entering an operating theatre and being placed in the lithotomy position awake. Analgesics were omitted from the premedication to avoid confusion in the assessment of the efficacy of the anaesthetic. The discomfort was recorded as being none, slight, moderate or severe.”	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	Random selection

Cicinelli 1998

Methods	Randomized controlled trial	
Participants	72 postmenopausal women undergoing diagnostic hysteroscopy and endometrial biopsy for uterine bleeding. All women had been amenorrhoeic and free of oestrogen replacement for at least one year.	
Interventions	1. PLA: 10 ml of 1.5% mepivacaine. 2. Placebo: 10 ml of saline. Injected at the junction of the cervix and vagina at the 4 and 8 o'clock position.	
Outcomes	Pain Vasovagal reactions.	
Notes	Visual analogue scale contained a 20-cm scale for the patient to record responses as follows: 0 cm, no pain; 5 cm, low pain; 10 cm, moderate pain; 15 cm, severe pain; and 20 cm, excruciating pain.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	"Sealed envelopes containing computer-generated block randomization numbers"

Egziabher 2002

Methods	Randomized controlled trial	
Participants	142 women with incomplete abortion underwent manual vacuum aspiration. Inclusion criteria: less than 16 weeks of gestation. Exclusion criteria: evidence of infections, blood pressure more than 140/90 mm Hg, diabetes, cardiac diseases, severe anaemia, cervix less than 1.5-2 cm dilated, allergy to lidocaine, respiratory distress and acute pelvic inflammatory disease.	
Interventions	1. PLA: 1% lidocaine. 2. Placebo: sterile water. Injected about 2 ml of lidocaine or placebo just under the epithelium not deeper than 2-3 mm at 3 and 9 o'clock.	
Outcomes	Pain Side effects: abdominal pain, shoulder tip pain, and backache.	
Notes	We analysed data during and after the procedure only, not data before the procedure.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	“Selected women using random tables”

Finikiotis 1992

Methods	Controlled clinical trial	
Participants	120 women who were referred from general practitioners and other gynaecologists for the investigation of a variety of gynaecological complaints and underwent outpatient hysteroscopy.	
Interventions	1. PLA: 16-20 ml of 1% lidocaine using a paracervical block after a small amount (<0.5 ml) was injected into the anterior lip of the cervix for placement of a tenaculum. 2. USB: 2ml of 2% lidocaine with 1:80,000 adrenaline into each uterosacral ligament. A small amount (<0.5 ml) was injected into the anterior lip of the cervix which was then grasped with a tenaculum.	
Outcomes	Pain.	
Notes	We used the cut-off point at 0-3.3 = no pain and 3.4 to 10 = pain.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	Randomized by odd or even unit numbers

Glantz 2001

Methods	Randomized controlled trial
Participants	79 pregnant women at least 18 years old, between 7 and 12 weeks' gestation, undergoing elective termination of pregnancy by mechanical aspiration. Women were excluded if they had significant medical complications that put them at risk for complications in the clinic setting, or if they had a history or sensitivity to local anaesthetic.
Interventions	1. PLA: 10 ml of 1% chlorprocaine. 2. Placebo: 10 ml of saline. Group A: 3-5-7-9 o'clock (5-2-2-5 ml, 1% chlorprocaine) Group B: 4-8 o'clock (7-7 ml, 1% chlorprocaine) Group C: 3-5-7-9 o'clock (5-2-2-5 ml, normal saline) Group D: 4-8 o'clock (7-7 ml, normal saline). The day before the procedure, a nurse practitioner inserted one laminaria into the cervical canal, women took 600 mg of ibuprofen 1 hour before aspiration. The laminaria were removed on the day of the termination procedure.
Outcomes	Pain immediately following paracervical block administration, after aspiration, and arrival in the recovery room.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	"Ordered opaque sealed envelopes"

Guida 2003

Methods	Randomized controlled trial
Participants	166 women with surgically treatable lesions associated with infertility or abnormal uterine bleeding (82 in the PLA group and 84 in the SA group). Exclusion criteria were menopausal women (FSH > 40 mIU/ml, 17 beta-estradiol < 20 pg/ml), and/or pregnancy (positive beta-hCG test), and a history of anaesthetic or surgical complications.
Interventions	1. PLA: 10 ml of 1% mepivacaine hydrochloride injected with 22-gauge spinal needle at four sites (3, 5, 7 and 9 o'clock positions) at the junction of the cervix and vagina. 2. SA: 0.5 mg of atropine, 0.25 mg of fentanyl, followed by an intravenous slow injection of 2.0 mg of midazolam.
Outcomes	Pain. Adverse effect: 1. Pallor or hypotension 2. Nausea and vomiting. Patient satisfaction.
Notes	

Guida 2003 (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	"Women randomized into two groups using a computer-generated list in blocks of two"

Gómez 2004

Methods	Randomized controlled trial	
Participants	215 women who were at 12 weeks of gestation or less with incomplete abortion (107 in no anaesthesia group and 108 in paracervical group). Women with active infections, severe illness, psychiatric disorders, or allergies to lidocaine were excluded.	
Interventions	1. PLA: Psychological support and paracervical block using 1.0% lidocaine 5 ml injected slowly to a depth of 0.5 cm in the cervix-vaginal joint at 4 or 5 or 7 or 8 o'clock positions. 2. Placebo: Psychological support but no paracervical block.	
Outcomes	Intraoperative pain. Changes in the level of pain: before and during the procedure. The need to suspend the procedure or administer anaesthetics medicaments or parenteral sedatives; the need for other parenteral analgesics. Existence of intraoperative and postoperative complications.	
Notes	We analysed pain and administered anaesthetic medicaments or parenteral sedatives.	

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	"Sealed sequential opaque envelopes"

Kan 2004

Methods	Randomized controlled trial	
Participants	134 women attending for suction termination of pregnancy under local anaesthesia: age over 16 years, normal general and gynaecological examination, up to 12-weeks gestation on the day of recruitment and size of the uterus on pelvic examination compatible with estimated duration of pregnancy. Exclusions: Allergy to lidocaine, history of severe respiratory or cardiac disease, severe and recurrent liver disease, myasthenia gravis, psychiatric conditions requiring medication, contraindications to prostaglandins use.	
Interventions	1. PLA: 10 ml of 1% lidocaine injected at the vaginal vault. 2. Intracervical: 10 ml of 1% lidocaine injected at the cervix 2.5 cm beneath the mucosa. 3. No local injection. All women received conscious sedation 2 mg midazolam and 25 mcg fentanyl.	

Kan 2004 (Continued)

Outcomes	Pain before the operation, just after the operation, and 1 hour after suction evacuation Need for additional analgesia. Adverse effects. Patients' satisfaction.	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	A nurse used an open randomized allocation list

Lau 1999

Methods	Randomized controlled trial	
Participants	99 women undergoing outpatient hysteroscopy and endometrial biopsy for abnormal uterine bleeding.	
Interventions	1. PLA: 10 ml of 2% lidocaine. 2. Placebo: 10 ml of normal saline. Paracervical block was performed using a 22-gauge spinal needle and the solution was given at 3, 5, 7, and 9 o'clock of the paracervical region in divided doses.	
Outcomes	Pain felt at different stages of the procedure. Vasovagal reaction.	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	Number put inside sealed envelope.

Miller 1996

Methods	Randomized controlled trial	
Participants	52 women presenting for pregnancy termination (27 in PLA group and 25 in placebo group). Exclusion criteria: did not speak English, allergy to lidocaine, had used cocaine within 24 hours, or were greater than 14 weeks' gestation as estimated by ultrasound measurements.	
Interventions	1. PLA: 20 ml of 1% lidocaine. 2. Placebo: 20 ml of 0.9% sodium chloride. * I.V. 50 microgram fentanyl given before procedure if requested.	

Miller 1996 (Continued)

Outcomes	Pain: after speculum placement, after cervical canal dilation and/or insertion of the cannula, after aspiration, and then 30 minutes after the procedure. Vasovagal reactions.	
Notes	Block was repeated on request by one woman who found dilatation painful.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	“All study syringes were made up at the beginning of each clinic session and labelled with random five-digit numbers. Syringes were then mixed in a draw and withdraw one at a time”

Mola 1996

from 1990

Methods	Randomized controlled trial	
Participants	30 women undergoing bi-manual removal of retained placentas.	
Interventions	1. PLA: women 40-59 kg received 20 ml, 60-79 kg received 32 ml and weighing > 79 kg received 40 ml of 0.5% lidocaine, respectively [these women received premedication - see notes]. 2. Diazepam and pethidine group: women 40-59 kg received pethidine 50 mg and diazepam 5 mg, women 60-79 kg received pethidine 75 mg and diazepam 7.5 mg, and weighing > 79 kg received pethidine 100 mg and diazepam 10 mg, respectively.	
Outcomes	Patients' perception of pain experienced during the procedure. The operator's perception of the patients' pain and the difficulty of the placental removal. Immediate and late complications.	
Notes	Both groups were premedicated with intravenous pethidine 0.5 mg/kg and diazepam 1 mg/10 kg between 30 and 60 minutes before the procedure.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	"Sealed envelopes"

Titapant 2003

Methods	Randomized controlled trial	
Participants	70 women with unknown cause of abnormal vaginal bleeding who underwent fractional curettage (35 in PLA group and 35 in placebo group). All women were healthy, except for their bleeding, did not have diabetes mellitus or hypertension. Women who had abnormal coagulation or a history of chronic pelvic pain were excluded.	

Titapant 2003 (Continued)

Interventions	1. PLA: 1% xylocaine without adrenaline. 2. Placebo group: normal saline. Infiltrated around cervix just before the procedure was performed.	
Outcomes	Pain during the procedure and 30 minutes afterwards.	
Notes	No explanation of what pain scale was - what was the smallest and largest possible numerical values and what did they mean? We analysed pain during endometrial curettage only, not during endocervical curettage.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	“Randomly allocated to two groups”

Vercellini 1994

Methods	Randomized controlled trial	
Participants	177 women with excessive uterine bleeding for at least 3 months. Excluded: pregnancy, menopausal (FSH >29 mIU/mL), genital infections, previous cervical surgery or hysteroscopies, severe cardiac disease, sensitivity to local anaesthetic.	
Interventions	1. PLA: 10 ml of 1% mepivacaine hydrochloride solution injected with a 22-gauge spinal needle at four sites at 3, 5, 7, and 9 o'clock positions at the junction of the cervix and vagina. 2. No anaesthesia.	
Outcomes	Lower abdominal and pelvic pain at hysterectomy and endometrial biopsy.	
Notes		
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	No	"A randomization list was used to allocate subjects"

Yazaci 2003

Methods	Randomized controlled trial	
Participants	114 woman undergoing endometrial biopsy for abnormal uterine bleeding . All women were multiparous without history of allergy to lidocaine or any other medication. Women suspected to be pregnant were excluded.	

Yazaci 2003 (Continued)

Interventions	Women were randomly assigned into four groups: Group A (Placebo group): intrauterine instillation of 2 ml of 0.9% saline solution Group B: intrauterine instillation of 2ml of 20 mg/ml lidocaine hydrochloride Group C: paracervical injection of 1% lidocaine (volume unclear) Group D: intrauterine instillation of 2ml of 20 mg/ml lidocaine hydrochloride and paracervical injection of 1% lidocaine (volume unclear).	
Outcomes	Pain: during the application of the anaesthetic; during cervical dilation; during endometrial biopsy; 15 minutes after the procedure. Adverse effects.	
Notes	We compared PLA alone (group B) with intrauterine instillation of lidocaine (group C). We also analysed data comparing with and without cervical dilatation among groups.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	“Women were randomly assigned”

PLA = Paracervical local anaesthesia

GA = General anaesthesia

SA = Systemic analgesia

D & C = Dilatation and curettage

GA = General anaesthesia

CVS = Cardiovascular system

RS = Respiratory system

ml = millilitre

mg = milligram

mcg = microgram

i.v. = intravenous

kg = kilogram

sec = second

USB = Uterosacral block

Characteristics of excluded studies [ordered by study ID]

Agostini 2003	The intervention of this study was performed using neither anaesthesia nor analgesia.
Amyot-Legault 1981	This study was not a randomized controlled study.
Bain 2001	The intervention for this study was intracervical not paracervical block.

(Continued)

Baskett 1974	This study was excluded because a comparison between different strengths of bupivacaine. No direct comparison between procedures.
Bradley 1995	The intervention of this study was performed under neither anaesthesia nor analgesia
Broadbent 1992	The intervention for this study was intracervical not paracervical block
Canni 2001	All women received paracervical block. No comparison between paracervical block and other anaesthesia but evaluated the role of periorificial infiltration of local anaesthetic.
Cetin 1997	All women received paracervical block and assessed the effect of deep or regular injection of local anaesthetics.
Chen 1994	This study was excluded because the intervention was not cervical dilatation and a uterine intervention
Coker 1968	This study is case series, no comparison group.
Duggan 1999	All women tested all-in-one paracervical block and intravenous sedation. No direct comparison between procedures.
Duncan 2005	The intervention of this study was not cervical dilatation and uterine intervention but colposcopically directed biopsy and anaesthetic or placebo was injected into the biopsy site and treatment with coagulator, not paracervical block.
Edelman 2004	All women received paracervical block and compared between intrauterine lidocaine and saline infusion to study the effects on perceived patient pain.
Esteve 2002	The intervention for this study is intracervical not paracervical block.
Fernandez 1997	This study was not a randomized controlled study.
Ferry 1994	This study was not a randomized controlled study.
Formiga-Filho 1974	This study was a case series, no comparison group.
Gad 1967	This study was not a randomized controlled study.
Grimes 1979	This study was excluded because no clinically relevant outcomes (pain or nausea and vomiting) were reported. There were only operative complications (uterine haemorrhage, uterine perforation, intra-abdominal haemorrhage, cervical injury, fever, blood transfusion, cervical suture, laparotomy, hysterotomy or hysterectomy) shown.
Guasch 2005	This study was excluded because no clinically relevant outcomes were reported and the objective of the study was to compare the prolactin and stress hormone response to surgical stimulus under various anaesthetic techniques.
Gudgeon 1968	This study was excluded because comparison between different strengths of bupivacaine. No direct comparison between procedures.

(Continued)

Harper 1994	This study was excluded because the intervention was not cervical dilatation and uterine intervention with comparison between paracervical and intracervical block.
Harper 1998	This study was excluded because the intervention was not cervical dilatation and uterine intervention.
Hasham 1993	This study was excluded because performed paracervical block following ablation of the endometrium.
Hedberg 1966	This study was a case series, no comparison group.
Jensen 1984	This study was excluded because the intervention was in the first stage of labour without uterine intervention.
Johnson 1989	This study was excluded because the intervention was not cervical dilatation and uterine intervention.
Johnson 1996	This study was excluded because the intervention was not cervical dilatation and uterine intervention.
Kamat 1979	This study compared paracervical and pericervical block. No direct comparison between paracervical block and other anaesthesia.
Kaya 2004	All women tested all-in-one paracervical block and intravenous sedation. No direct comparison between procedures.
Kun 1999	The intervention for this study was intracervical not paracervical block.
Lee 1986	This study was excluded because the intervention was not cervical dilatation and uterine intervention.
Lee 1998	This study was excluded because the intervention was not cervical dilatation and uterine intervention.
Lewis 1971	This study was not a randomized controlled clinical study.
Littlepage 1969	This study was not a randomized controlled clinical study.
Longhi 1996	This study was excluded because a non-randomized controlled study and all women received paracervical and pudendal block.
Mackay 1985	This study was excluded because no clinically relevant outcomes (pain, nausea and vomiting) were reported. There were only operative complication (uterine haemorrhage, uterine perforation, intra-abdominal haemorrhage, cervical injury, fever, blood transfusion, cervical suture, laparotomy, hysterotomy or reported (fever, blood transfusion, unintended abdominal surgery, retained products of conception, postoperative haemorrhage, repeat curettage).
Makris 2001	The procedure in this study was performed without any kind of anaesthesia.
Mckenzie 1978	All women received paracervical block using modified jet injector compare with standard syringe and needle technique. No comparison between paracervical block and other anaesthesia.
Mercorio 2002	The intervention for this study was intracervical not paracervical block.

(Continued)

Moller 1978	This study was excluded because no clinically relevant outcomes (pain, nausea and vomiting) were reported.
Nielsen 1975	All women tested all-in-one paracervical block and intravenous sedation. No direct comparison between procedures.
Nielsen 1988	This study had many different co-interventions in each group, not comparing PLA alone with other anaesthesia.
O'Neal 2003	This study was excluded because the intervention was not cervical dilatation and uterine intervention.
Owalabi 2005	The intervention for this study not paracervical block alone but combined intracervical block.
Oyama 2003	The intervention of this study was not cervical dilatation and uterine intervention but colposcopically directed biopsy and lidocaine was injected into the biopsy site, not paracervical block.
Peretz 1982	This study was not a randomized controlled study.
Peters 1978	This study was excluded because a comparison between intracervical and paracervical block.
Phair 2002	All women received paracervical block and assessed the effect on pain of waiting between injection and procedure.
Picton 1968	This study was excluded because a comparison between different strengths of bupivacaine. No direct comparison between procedures.
Prest 1976	This study was not a randomized controlled study.
Raeder 1992	This study had many different co-interventions in each group, not comparing PLA alone with other anaesthesia.
Ragab 1978	This study was excluded because no clinically relevant outcomes.
Rattanachaiyanont	All women received paracervical block and compared between intrauterine lidocaine and saline infusion to study the effectiveness of intrauterine anaesthesia for pain relief.
Readman 2004	This study was a review, not a randomized controlled study.
Reguer Noriega 1973	This study was a case series, no comparison group.
Rogstad 1992	This study was excluded because the intervention was not cervical dilatation and uterine intervention.
Rotchell 1976	This study was a case series, no comparison group.
Ruoss 1968	This study was excluded because a comparison between different strengths of bupivacaine. No direct comparison between procedures.
Sammarco 1993	This study was excluded because the intervention was not cervical dilatation and uterine intervention

(Continued)

Sandmire 1974	This study was not a randomized controlled study.
Santonja 1974	This study was a case series, no comparison group.
Scott 1968	This study was excluded because a comparison between different strengths of bupivacaine. No direct comparison between procedures.
Shapiro 1975	All women tested all-in-one paracervical block and other sedation or stereophonic headphones. No direct comparison between procedures.
Stefanidis 1998	This study was excluded because the intervention was not cervical dilatation and uterine intervention.
Strausz 1971	This study was not a randomized controlled study.
Stuart 1993	This study was excluded because the intervention was not cervical dilatation and uterine intervention.
Teramo 1975	This study was excluded because a comparison between different strengths of etidocaine. No direct comparison between procedures.
Thonneau 1998	This study was not a randomized controlled study and no clinically relevant outcomes.
Toth 2000	This study was not a randomized controlled study.
Van Praagh 1967	This study was not a randomized controlled study.
Walden 1973	This study was not a randomized controlled study.
Wallage 2003	The intervention for the study not paracervical block alone but combined with intracervical block.
Whitehouse 1968	This study was excluded because a comparison between different strengths of bupivacaine. No direct comparison between procedures.
Wiebe 2005	All women tested all-in-one paracervical block and intravenous sedation. No direct comparison between procedures.
Willdeck 1975	This study was excluded because no direct comparison between the procedure but compared different strengths of etidocaine.
Winkler 1997	This study was excluded because no clinically relevant outcomes.
Wong 2002	All women received paracervical block and conscious sedation. No comparison between paracervical block but evaluated the role of conscious sedation.

Characteristics of studies awaiting assessment *[ordered by study ID]***Chaudhuri 1980**

Methods	not yet assessed
Participants	not yet assessed
Interventions	not yet assessed
Outcomes	not yet assessed
Notes	

Regina 1987

Methods	not yet assessed
Participants	not yet assessed
Interventions	not yet assessed
Outcomes	not yet assessed
Notes	

Sen 1980

Methods	not yet assessed
Participants	not yet assessed
Interventions	not yet assessed
Outcomes	not yet assessed
Notes	

DATA AND ANALYSES

Comparison 1. Paracervical versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on paracervical injection	2	178	Mean Difference (IV, Random, 95% CI)	-0.87 [-1.60, -0.14]
2 Pain dilating cervix	2	151	Std. Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.57, 0.07]
3 Pain during uterine intervention	5		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Pain when the uterus is distended by carbon dioxide	1		Std. Mean Difference (IV, Random, 95% CI)	Not estimable
3.2 hysteroscopy	1		Std. Mean Difference (IV, Random, 95% CI)	Not estimable
3.3 Endometrial biopsy	2		Std. Mean Difference (IV, Random, 95% CI)	Not estimable
3.4 Uterine curettage	1		Std. Mean Difference (IV, Random, 95% CI)	Not estimable
3.5 Suction evacuation or aspiration	2		Std. Mean Difference (IV, Random, 95% CI)	Not estimable
4 Pain during uterine intervention	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Risk of any pain	2	242	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.54, 1.34]
4.2 Risk of severe pain	2	242	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.04, 0.74]
5 Postoperative pain	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Immediately after the procedure	3	223	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.92, 0.24]
5.2 15 minutes after the procedure	1	72	Std. Mean Difference (IV, Random, 95% CI)	-0.94 [-1.43, -0.45]
5.3 30 minutes after the procedure	3	221	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.29, 0.35]
6 Postoperative abdominal pain	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 Immediately after surgery	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.2 30 minutes after surgery	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
7 Postoperative abdominal pain	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1 Immediately after surgery	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
7.2 30 minutes after surgery	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
8 Back pain	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1 During procedure	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.2 15 minutes after procedure	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.3 30 minutes after procedure	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
9 Shoulder pain	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 During the procedure	2	144	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.39]
9.2 After the procedure	2	241	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.51, 3.49]
10 Adverse effects	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Nausea/vomiting	3	429	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.02, 2.80]
10.2 Sweating	1	142	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.70, 1.67]
10.3 Hypotension	2	171	Risk Ratio (M-H, Random, 95% CI)	3.06 [1.21, 7.78]

Comparison 2. Paracervical versus no anaesthesia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain during uterine intervention	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 Hysteroscopy	1		Mean Difference (IV, Random, 95% CI)	Not estimable
1.2 Endometrial biopsy	1		Mean Difference (IV, Random, 95% CI)	Not estimable
2 Postoperative pain at different times	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Immediately after the procedure	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.2 5 minutes after the procedure	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.3 10 minutes after the procedure	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable

Comparison 3. Paracervical block versus other regional anaesthesia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain during anaesthetic application	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Pain during uterine intervention: continuous	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Endometrial biopsy	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3 Postoperative pain at different time: continuous	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 15 minutes after the procedure	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
4 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 vasovagal reactions	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable

Comparison 4. Paracervical versus systemic analgesia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain during uterine intervention	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 hysteroscopic electrosurgery	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2 Pain during uterine intervention	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Postoperative pain	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 at 15 minutes	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.2 at 1 hour	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable

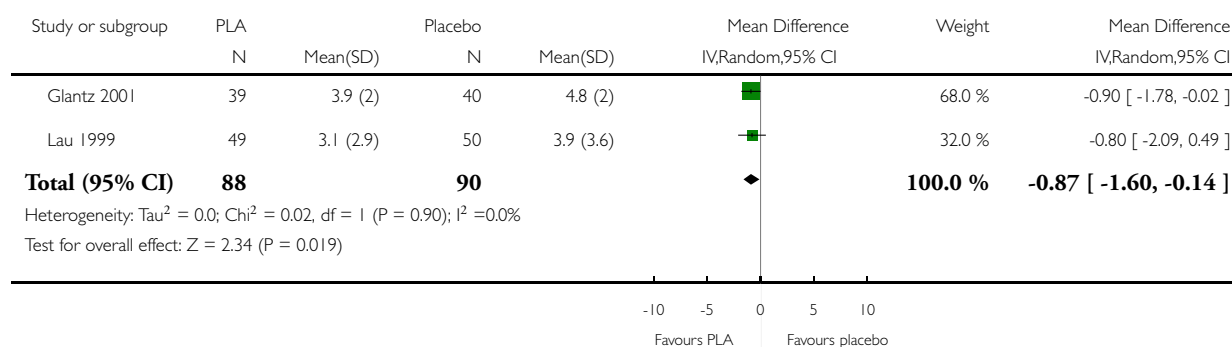
3.3 at 24 hours	1	Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.4 at 3 days	1	Mean Difference (IV, Fixed, 95% CI)	Not estimable
4 Requirement for postoperative analgesics	1	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Adverse effects	2	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Pallor or hypotension	1	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5.2 Nausea and vomiting	1	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5.3 Dizziness	1	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6 Patient satisfaction	1	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Operator's perception of the analgesia	1	Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Paracervical versus placebo, Outcome 1 Pain on paracervical injection.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 1 Paracervical versus placebo

Outcome: 1 Pain on paracervical injection

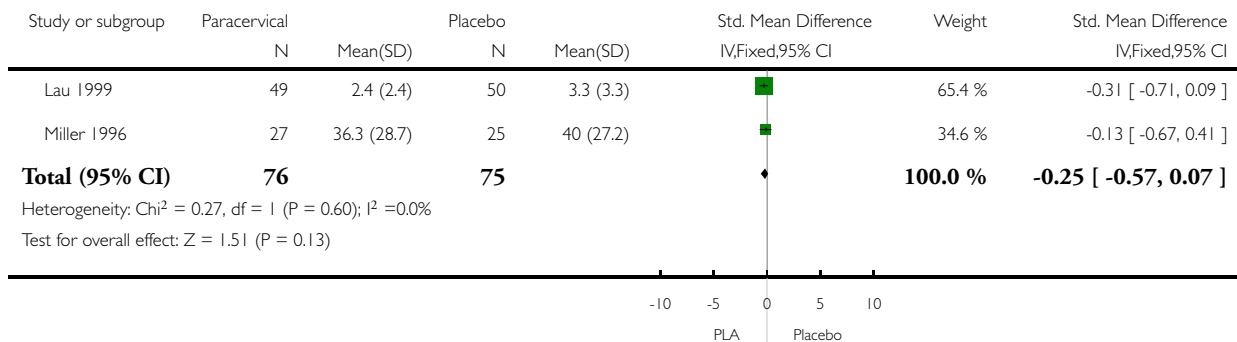


Analysis 1.2. Comparison 1 Paracervical versus placebo, Outcome 2 Pain dilating cervix.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 1 Paracervical versus placebo

Outcome: 2 Pain dilating cervix

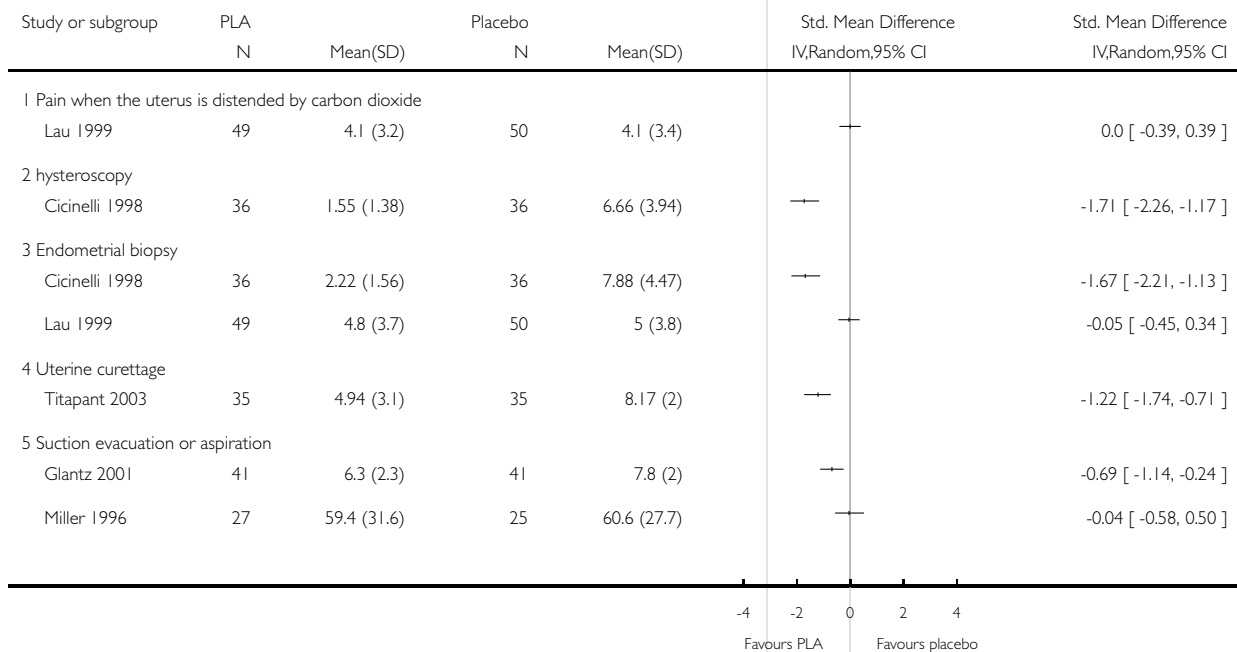


Analysis 1.3. Comparison 1 Paracervical versus placebo, Outcome 3 Pain during uterine intervention.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 1 Paracervical versus placebo

Outcome: 3 Pain during uterine intervention

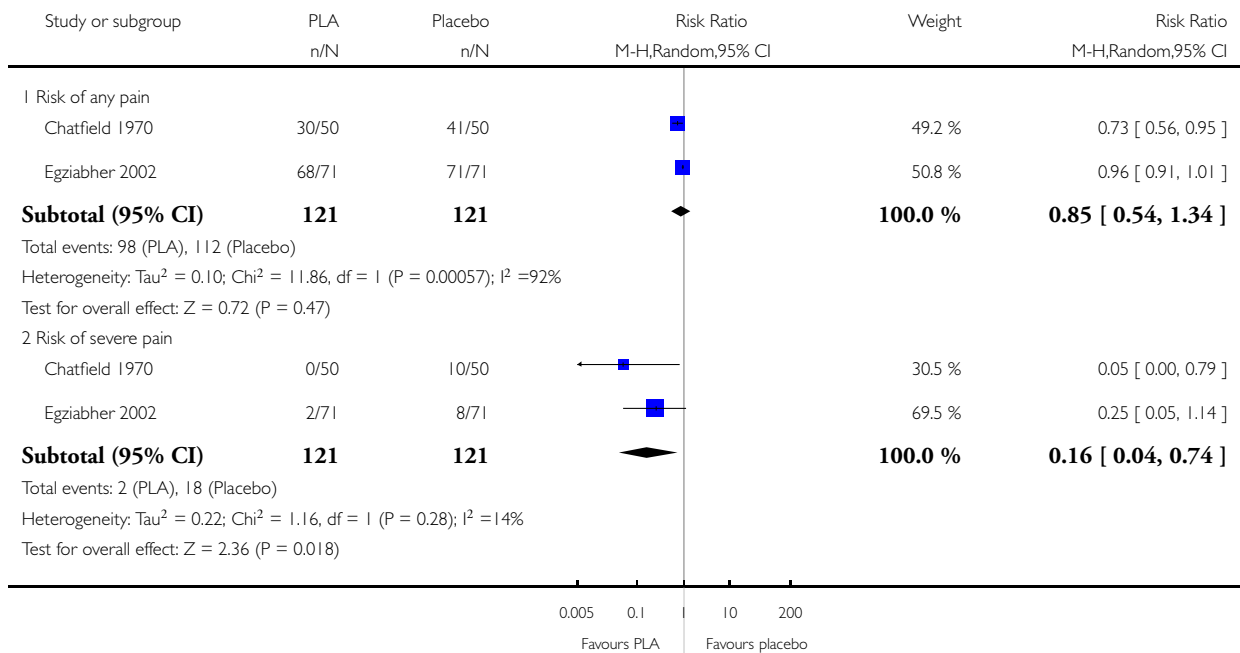


Analysis 1.4. Comparison 1 Paracervical versus placebo, Outcome 4 Pain during uterine intervention.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 1 Paracervical versus placebo

Outcome: 4 Pain during uterine intervention

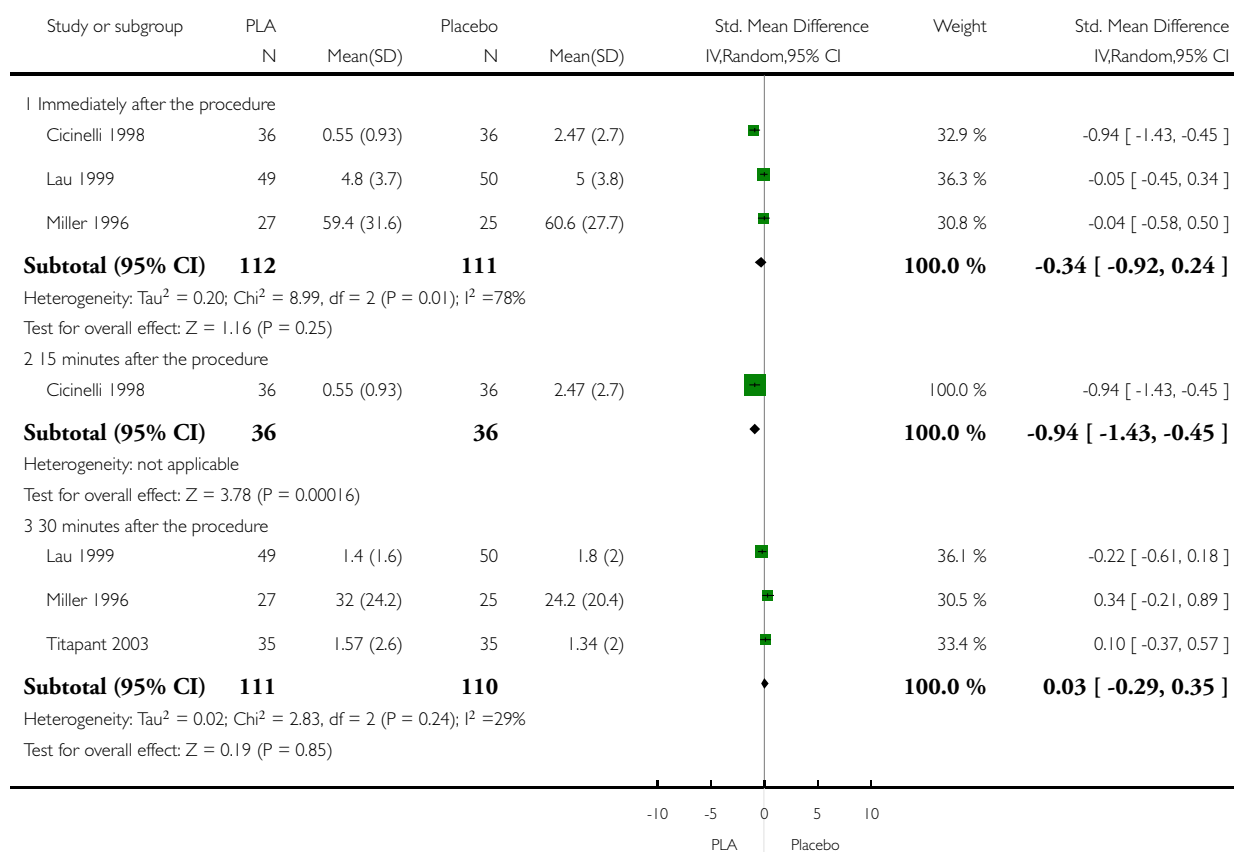


Analysis 1.5. Comparison 1 Paracervical versus placebo, Outcome 5 Postoperative pain.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 1 Paracervical versus placebo

Outcome: 5 Postoperative pain

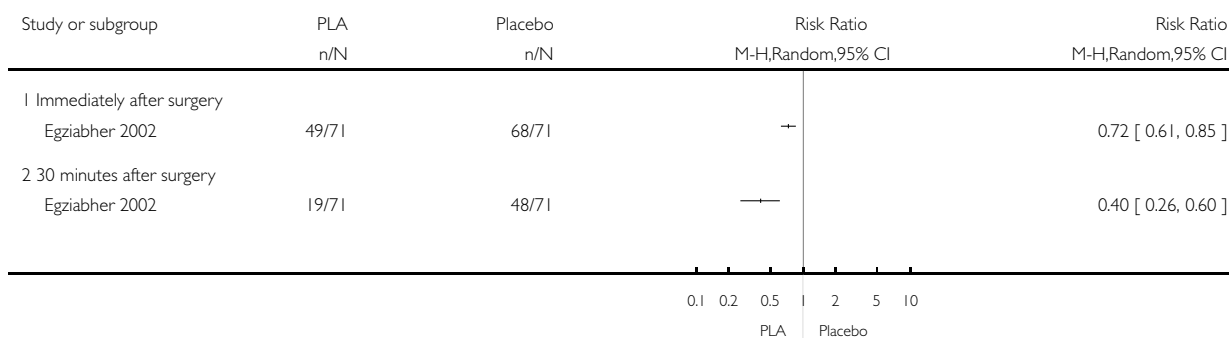


Analysis 1.6. Comparison 1 Paracervical versus placebo, Outcome 6 Postoperative abdominal pain.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 1 Paracervical versus placebo

Outcome: 6 Postoperative abdominal pain

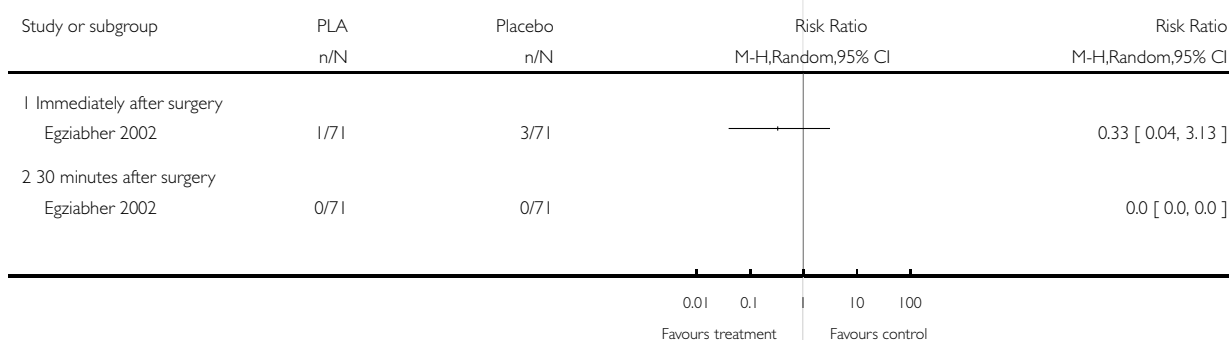


Analysis 1.7. Comparison 1 Paracervical versus placebo, Outcome 7 Postoperative abdominal pain.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 1 Paracervical versus placebo

Outcome: 7 Postoperative abdominal pain

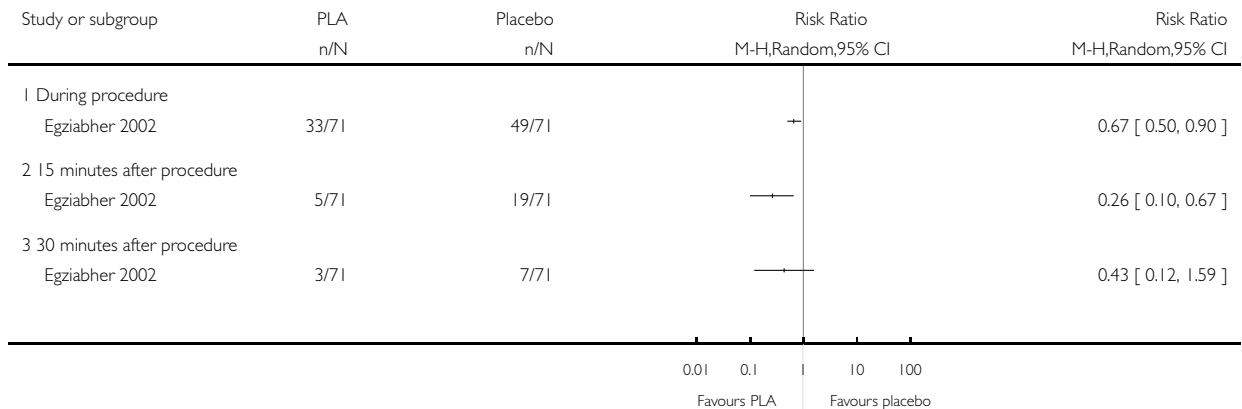


Analysis 1.8. Comparison 1 Paracervical versus placebo, Outcome 8 Back pain.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 1 Paracervical versus placebo

Outcome: 8 Back pain

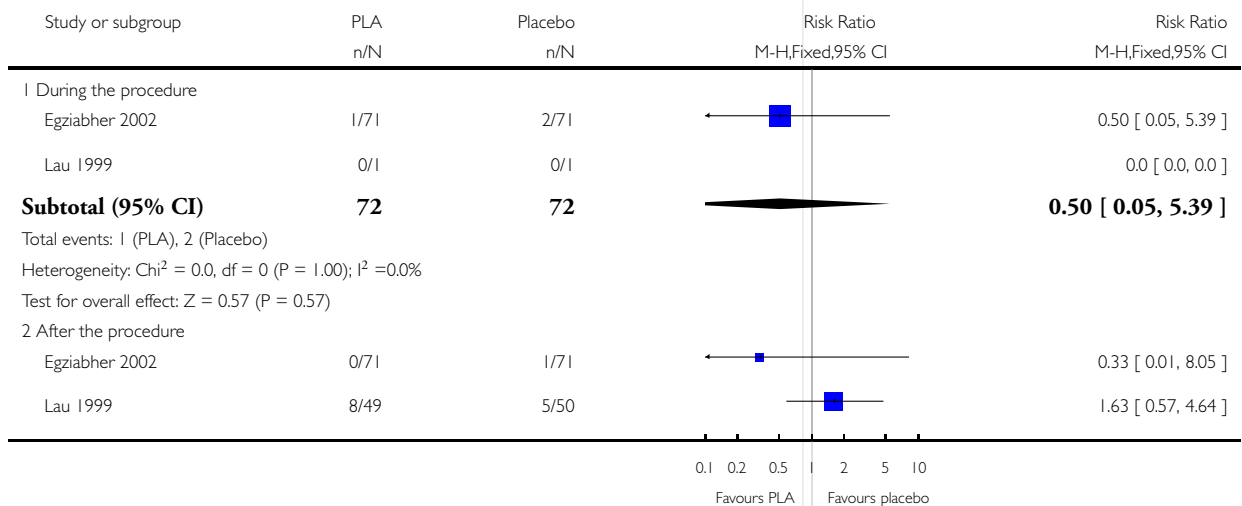


Analysis 1.9. Comparison 1 Paracervical versus placebo, Outcome 9 Shoulder pain.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

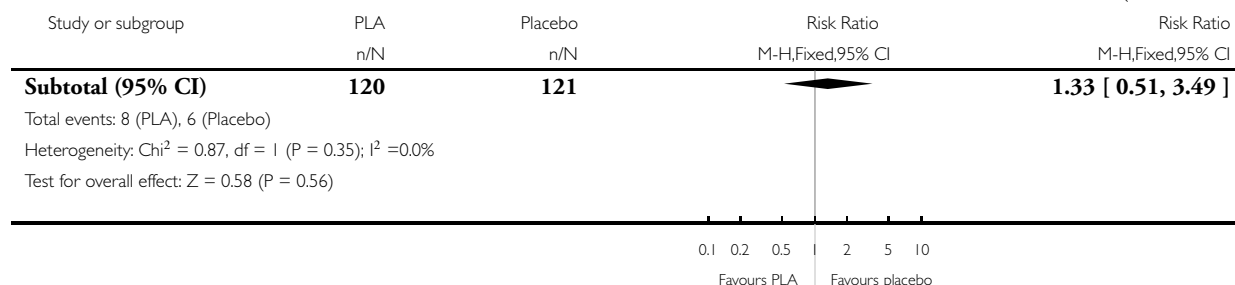
Comparison: 1 Paracervical versus placebo

Outcome: 9 Shoulder pain



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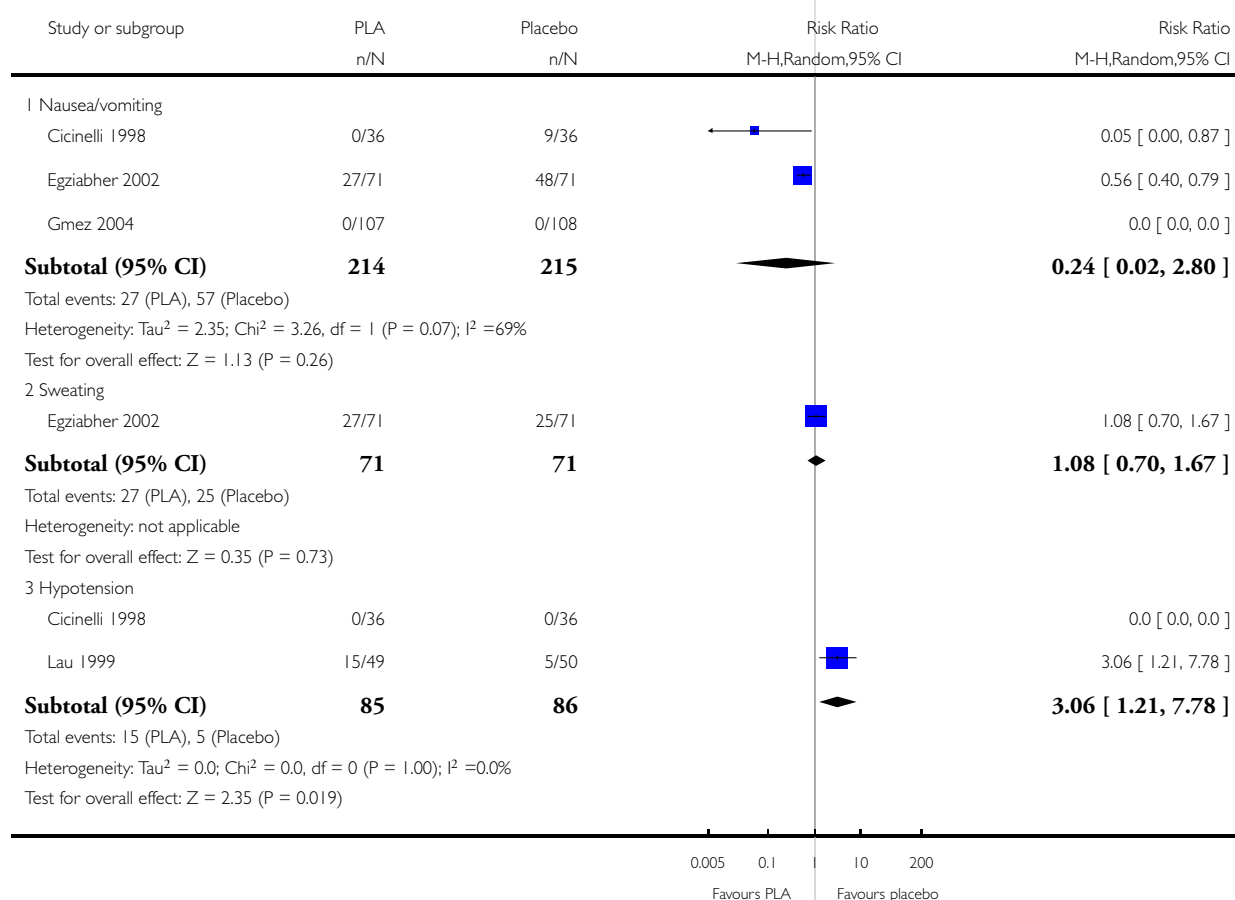


Analysis 1.10. Comparison 1 Paracervical versus placebo, Outcome 10 Adverse effects.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 1 Paracervical versus placebo

Outcome: 10 Adverse effects

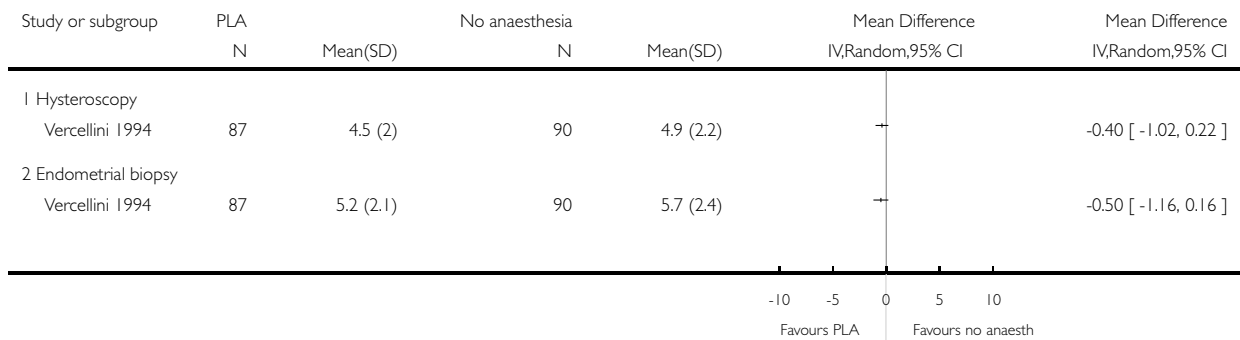


Analysis 2.1. Comparison 2 Paracervical versus no anaesthesia, Outcome 1 Pain during uterine intervention.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 2 Paracervical versus no anaesthesia

Outcome: 1 Pain during uterine intervention

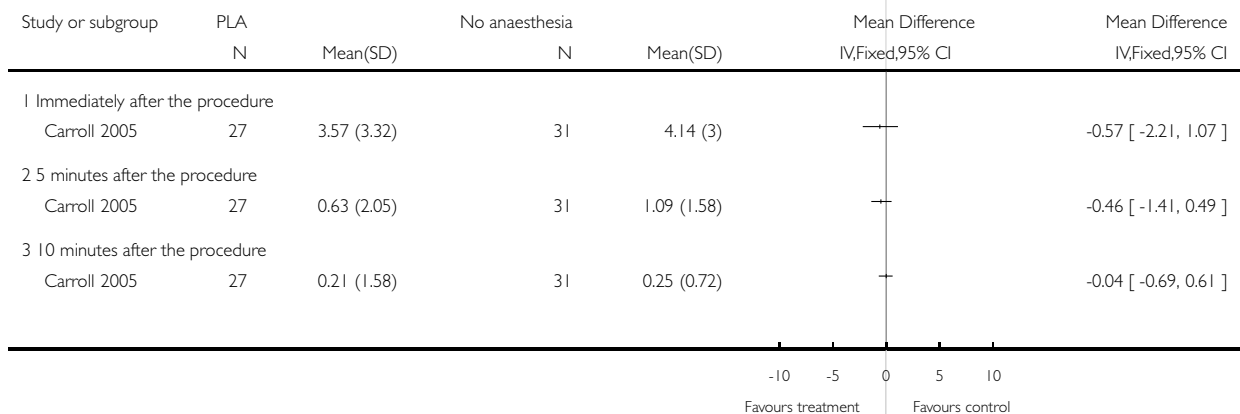


Analysis 2.2. Comparison 2 Paracervical versus no anaesthesia, Outcome 2 Postoperative pain at different times.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 2 Paracervical versus no anaesthesia

Outcome: 2 Postoperative pain at different times

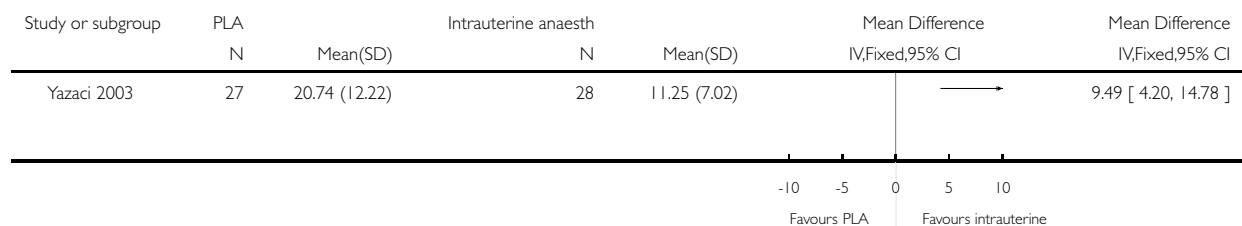


Analysis 3.1. Comparison 3 Paracervical block versus other regional anaesthesia, Outcome 1 Pain during anaesthetic application.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 3 Paracervical block versus other regional anaesthesia

Outcome: 1 Pain during anaesthetic application

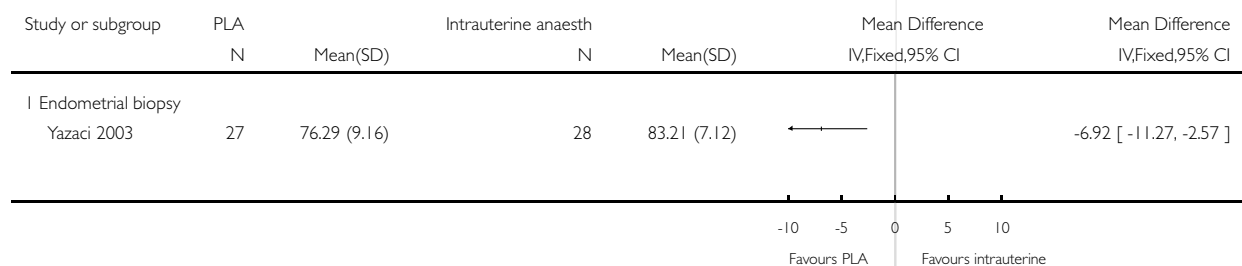


Analysis 3.2. Comparison 3 Paracervical block versus other regional anaesthesia, Outcome 2 Pain during uterine intervention: continuous.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 3 Paracervical block versus other regional anaesthesia

Outcome: 2 Pain during uterine intervention: continuous

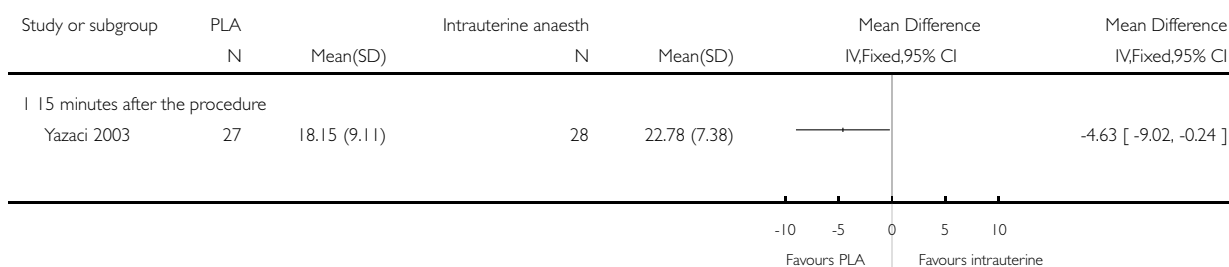


Analysis 3.3. Comparison 3 Paracervical block versus other regional anaesthesia, Outcome 3 Postoperative pain at different time: continuous.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 3 Paracervical block versus other regional anaesthesia

Outcome: 3 Postoperative pain at different time: continuous

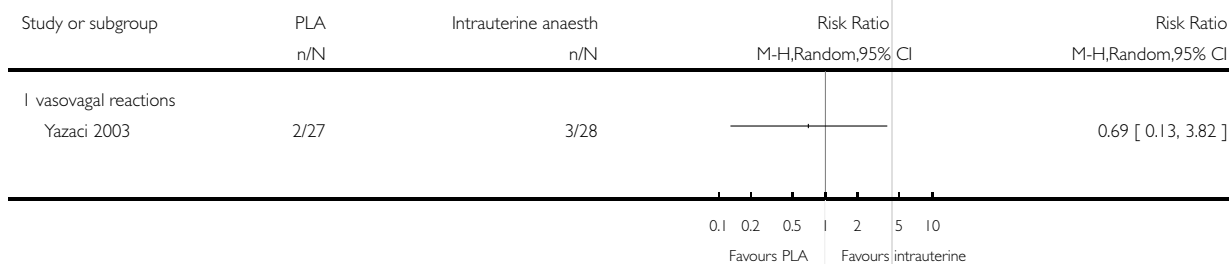


Analysis 3.4. Comparison 3 Paracervical block versus other regional anaesthesia, Outcome 4 Adverse effects.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 3 Paracervical block versus other regional anaesthesia

Outcome: 4 Adverse effects

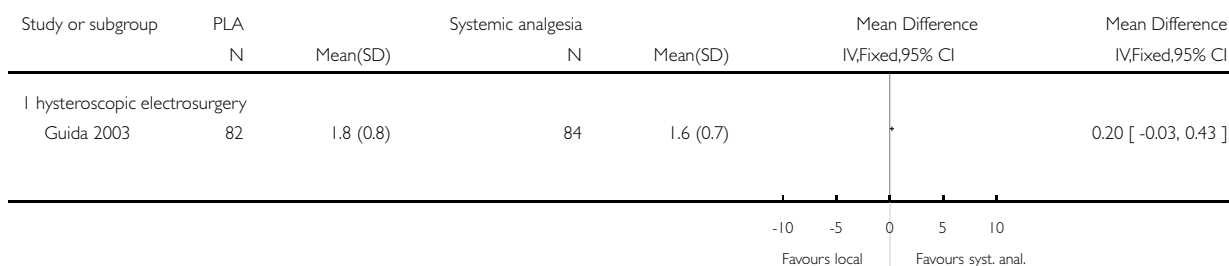


Analysis 4.1. Comparison 4 Paracervical versus systemic analgesia, Outcome 1 Pain during uterine intervention.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 4 Paracervical versus systemic analgesia

Outcome: 1 Pain during uterine intervention

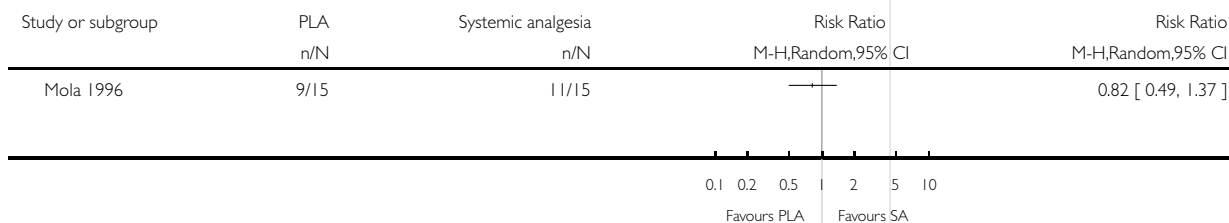


Analysis 4.2. Comparison 4 Paracervical versus systemic analgesia, Outcome 2 Pain during uterine intervention.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 4 Paracervical versus systemic analgesia

Outcome: 2 Pain during uterine intervention

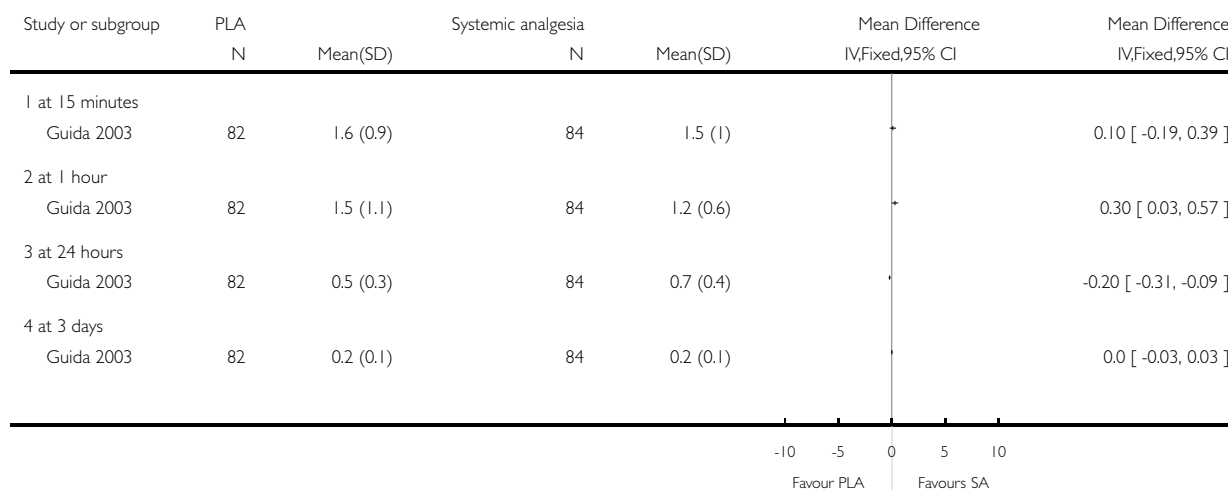


Analysis 4.3. Comparison 4 Paracervical versus systemic analgesia, Outcome 3 Postoperative pain.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 4 Paracervical versus systemic analgesia

Outcome: 3 Postoperative pain

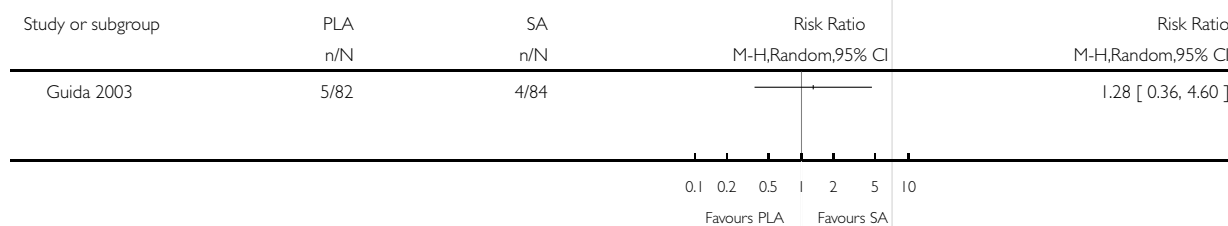


Analysis 4.4. Comparison 4 Paracervical versus systemic analgesia, Outcome 4 Requirement for postoperative analgesics.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 4 Paracervical versus systemic analgesia

Outcome: 4 Requirement for postoperative analgesics

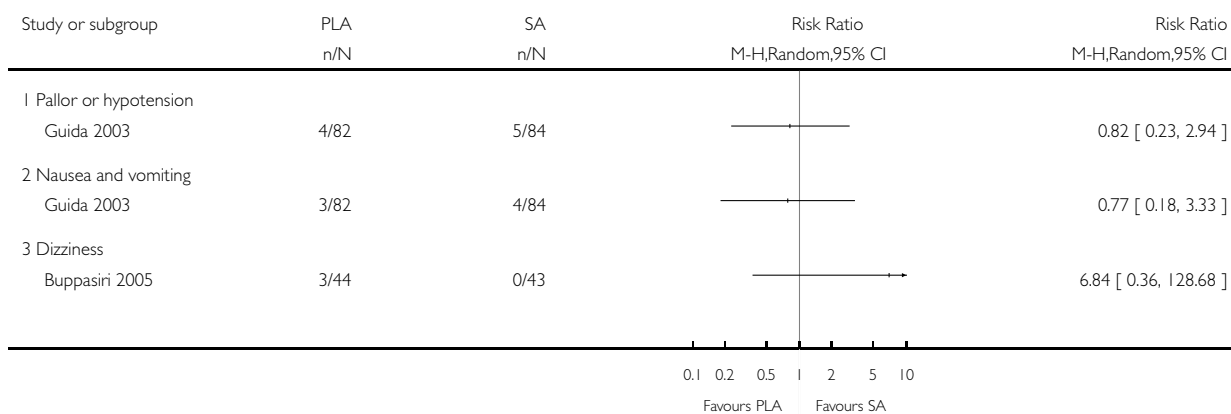


Analysis 4.5. Comparison 4 Paracervical versus systemic analgesia, Outcome 5 Adverse effects.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 4 Paracervical versus systemic analgesia

Outcome: 5 Adverse effects

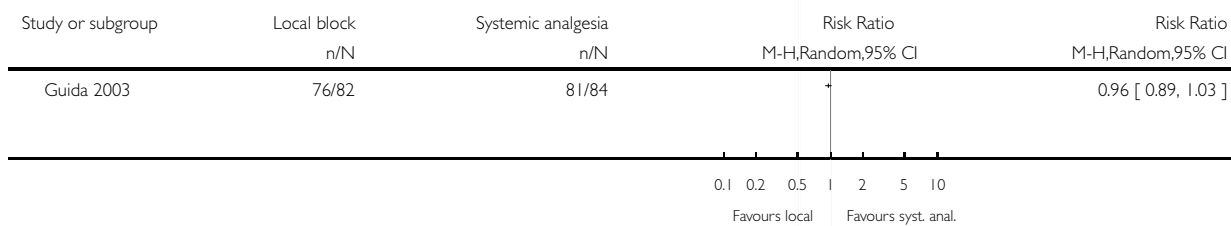


Analysis 4.6. Comparison 4 Paracervical versus systemic analgesia, Outcome 6 Patient satisfaction.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 4 Paracervical versus systemic analgesia

Outcome: 6 Patient satisfaction

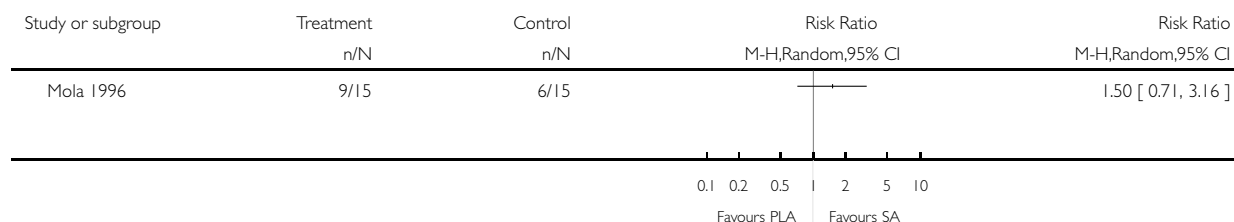


Analysis 4.7. Comparison 4 Paracervical versus systemic analgesia, Outcome 7 Operator's perception of the analgesia.

Review: Paracervical local anaesthesia for cervical dilatation and uterine intervention

Comparison: 4 Paracervical versus systemic analgesia

Outcome: 7 Operator's perception of the analgesia



APPENDICES

Appendix I. CENTRAL search strategy (The Cochrane Library Issue I, 2006)

Number	Search strategy
#1	paracerv*
#2	(paracerv* near (local next anesth*))
#3	(paracervical next block next anesth*)
#4	((paracerv* near block*) or (nerv* near block*))
#5	(lidocain* or lignocain* or bupivacain* or marcain* or levobupivacain* or prilocain* or chlorprocain* or procain* or xylocain* or ropivacain* or tetracain* or amethocain* or mepivacain*)
#6	(#1 or #2 or #3 or #4 or #5)
#7	((obstet* near intervent*)or (gyne* near interven*))
#8	(cervic* near dilat*)
#9	dilat*
#10	(uter* near intervent*)
#11	DILATATION AND CURETTAGE:ME

(Continued)

#12	curett*
#13	(uter* near curett*)
#14	((vacuum and curett*) or (vacuum next extract*) or (vacuum next aspirat*))
#15	(#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14)
#16	(#6 and #15)
#17	PAIN POSTOPERATIVE:ME
#18	POSTOPERATIVE NAUSEA AND VOMITING:ME
#19	(postoperative* near complicat*)
#20	(postoperativ* near pain)
#21	((postoperativ* near nausea) or (postoperativ* near vomit*))
#22	PATIENT SATISFACTION:ME
#23	(patient* near satisfact*)
#24	ABORTION INDUCED:ME
#25	HYPOTENSION ORTHOSTATIC:ME
#26	(#17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25)
#27	(#16 and #26)

Appendix 2. MEDLINE search strategy (1966 to January 2006)

Number	Search strategy
#1	paracerv*
#2	(paracerv* near (local next anesth*))
#3	(paracervical next block next anesth*)
#4	((paracerv* near block*) or (nerv* near block*))

(Continued)

#5	(lidocain* or lignocain* or bupivacain* or marcain* or levobupivacain* or prilocain* or chlorprocain* or procain* or xylocain* or ropivacain* or tetracain* or amethocain* or mepivacain*)
#6	(#1 or #2 or #3 or #4 or #5)
#7	((obstet* near intervent*)or (gyne* near interven*))
#8	(cervic* near dilat*)
#9	dilat*
#10	(uter* near intervent*)
#11	DILATATION AND CURETTAGE:ME
#12	curett*
#13	(uter* near curett*)
#14	((vacuum and curett*) or (vacuum next extract*) or (vacuum next aspirat*))
#15	(#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14)
#16	(#6 and #15)
#17	PAIN POSTOPERATIVE:ME
#18	POSTOPERATIVE NAUSEA AND VOMITING:ME
#19	(postoperative* near complicat*)
#20	(postoperativ* near pain)
#21	((postoperativ* near nausea) or (postoperativ* near vomit*))
#22	PATIENT SATISFACTION:ME
#23	(patient* near satisfact*)
#24	ABORTION INDUCED:ME
#25	HYPOTENSION ORTHOSTATIC:ME
#26	(#17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25)
#27	(#16 and #26)

Appendix 3. EMBASE search strategy (1980 to January 2006)

Number	Search strategy
#1	PARACERV*
#2	Paracerv* near (local an?esth*)
#3	paracervical block an?esth*
#4	explode paracervical-block / all subheadings
#5	explode nerve-block/all subheadings
#6	(paracerv* near block*) or (nerv* near block*)
#7	explode local-anesthetic-agent/all subheadings
#8	explode local-anesthesia/all subheadings
#9	LIDOCAIN* or LIGNOCAIN* or BUPIVACAIN* or MARCAIN* or LEVOBUPIVACAIN* or PRILOCAIN* or CHLORPROCAIN* or PROCAIN* or XYLOCAIN* or ROPIVACAIN* or TETRACAIN* or AMETHOCAIN* or MEPIVACAIN*(56634 records)
#10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#11	(obstet* near intervent*)or (gyn?e* near interven*)
#12	explode uterine-cervix-dilatation/all subheadings
#13	explode obstetric-operation/all subheadings
#14	cervic* near dilat*
#15	dilat*
#16	uter* near intervent*
#17	explode curettage/all subheadings
#18	curett*
#19	uter* near curett*
#20	(vacuum and curett*)or(vacuum extract*) or (vacuum aspirat*)

(Continued)

#21	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
#22	#10 and #21
#23	explode postoperative complication/all subheadings
#24	post?operative* near complicat*
#25	explode postoperative pain/ all subheadings
#26	post?operativ* near pain
#27	(explode postoperative nausea/ all subheadings) or (explode postoperative vomiting/ all subheadings)
#28	explode postoperative nausea / all subheadings and vomiting
#29	(post?operativ* near nausea) or (post?operativ* near vomit*)
#30	explode patient satisfaction/all subheadings
#31	patient* near satisfact*
#32	explode induced hypotension/all subheadings
#33	explode hypotension/all subheadings
#34	#23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33
#35	#22 and #34

WHAT'S NEW

Last assessed as up-to-date: 30 January 2006.

7 January 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 2004

Review first published: Issue 1, 2009

CONTRIBUTIONS OF AUTHORS

Conceiving the review: Thumwadee Tangsiriwatthana (TT)

Co-ordinating the review: Ussanee Swadpanich (US)

Undertaking manual searches: TT and US

Screening search results: TT and US

Organizing retrieval of papers: TT

Screening retrieved papers against inclusion criteria: TT, US and Pisake Lumbiganon (PL)

Appraising quality of papers: TT and US

Abstracting data from papers: TT and US

Writing to authors of papers for additional information: TT

Providing additional data about papers: TT

Obtaining and screening data on unpublished studies: TT and US

Data management for the review: TT

Entering data into Review Manager ([Review Manager 5.0](#)): TT

RevMan statistical data: Malinee Laopaiboon (ML)

Other statistical analysis not using RevMan: ML

Double entry of data: (data entered by person one: TT; data entered by person two: US)

Interpretation of data: TT, US and PL

Statistical inferences: ML

Writing the review: TT, US, PL and ML

Securing funding for the review: PL

Performing previous work that was the foundation of the present study: PL

Guarantor for the review (one author): PL

Persons responsible for reading and checking review before submission: TT, US, PL and ML

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Medical Education Centre, Khon Kaen Regional Hospital, Thailand.
- Khon Kaen University, Thailand.

External sources

- Thai Cochrane Network, Thailand.
- Thailand Research Fund (Senior Research Scholar), Thailand.
- Cochrane Anaesthesia Review Group (CARG), Denmark.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed some search strategies from the published protocol for higher sensitivity. See [Appendix 1](#), [Appendix 2](#) and [Appendix 3](#).

INDEX TERMS

Medical Subject Headings (MeSH)

Anesthesia, Local [adverse effects; *methods]; Anesthetics, Local [administration & dosage; adverse effects]; Biopsy [adverse effects]; Dilatation and Curettage [*adverse effects]; Endometrium [pathology]; Hysteroscopy [adverse effects]; Nerve Block [*methods]; Pain [*prevention & control]; Pain, Postoperative [prevention & control]; Randomized Controlled Trials as Topic; Uterus [*surgery]

MeSH check words

Female; Humans; Pregnancy

Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes (Review)

Laopaiboon M, Lumbiganon P, Martis R, Vatanasapt P, Somjaivong B



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[Intervention Review]

Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

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ABSTRACT

Background

Evidence on the benefits of music during caesarean section under regional anaesthesia to improve clinical and psychological outcomes for mothers and infants has not been established.

Objectives

To evaluate the effectiveness of music during caesarean section under regional anaesthesia for improving clinical and psychological outcomes for mothers and infants.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 September 2008).

Selection criteria

We included randomised controlled trials comparing music added to standard care during caesarean section under regional anaesthesia to standard care alone.

Data collection and analysis

Two review authors, Malinee Laopaiboon and Ruth Martis, independently assessed eligibility, risk of bias in included trials and extracted data. We analysed continuous outcomes using a mean difference (MD) with a 95% confidence interval (CI).

Main results

One trial involving 76 women who planned to have their babies delivered by caesarean section met the inclusion criteria, but data were available for only 64 women. This trial was of low quality with unclear allocation concealment and only a few main clinical outcomes reported for the women. The trial did not report any infant outcomes. It appears that music added to standard care during caesarean

section under regional anaesthesia had some impact on pulse rate at the end of maternal contact with the neonate in the intra-operative period (MD -7.50 fewer beats per minute, 95% CI -14.08 to -0.92) and after completion of skin suture for the caesarean section (MD -7.37 fewer beats per minute, 95% CI -13.37 to -1.37). There was also an improvement in the birth satisfaction score (maximum possible score of 35) (MD of 3.38, 95%CI 1.59 to 5.17). Effects on other outcomes were either not significant or not reported in the one included trial.

Authors' conclusions

The findings indicate that music during planned caesarean section under regional anaesthesia may improve pulse rate and birth satisfaction score. However, the magnitude of these benefits is small and the methodological quality of the one included trial is questionable. Therefore, the clinical significance of music is unclear. More research is needed to investigate the effects of music during caesarean section under regional anaesthesia on both maternal and infant outcomes, in various ethnic pregnant women, and with adequate sample sizes.

PLAIN LANGUAGE SUMMARY

Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Caesarean section is a surgical procedure for delivering a baby. It involves making surgical incisions into the mother's abdominal wall and uterus. These operations are performed if there is a serious medical concern for the mother or baby. Caesarean sections are generally done with regional anaesthesia, either a spinal or epidural block with anaesthetic injected into the area around the spine in the lower back, which makes the mother feel numb from the waist down. Women have increased risks associated with anaesthesia and surgery, and the baby may be more likely to be admitted to a neonatal unit or separated from the mother.

Women having a caesarean section under regional anaesthesia are often highly anxious during the operation and may feel some discomfort. Listening to relaxing music of the woman's choice may lead to better outcomes and less need for treatment.

The review findings indicate that listening to music during planned caesarean section under regional anaesthesia may improve pulse rates and birth satisfaction scores, although the effect sizes were not large enough to indicate a clinically beneficial effect. The review authors identified one controlled trial that randomly assigned 76 women who listened to their preferred music through earphones, or to standard care, but data were available for only 64 women. The music was provided from the beginning of anaesthesia to the end of surgery. The women's heart rates were reduced by some seven beats/minute when measured at the end of contact with the newborn during the intra-operative period and after the surgeon had completed skin suture. Birth satisfaction scores were increased by a mean of 3.4 points on a 35-point scale when women listened to music. Respiration rates were no different for the two groups and neither were levels of anxiety, which decreased at the end of contact with the newborn and again after closing the skin, with no clear difference with or without music. The trial was from Taiwan and reporting of trial methodology was poor.

BACKGROUND

Caesarean section is a surgical procedure for delivering a baby through incisions made on the mother's abdominal wall and uterus. Caesarean section is performed for emergency conditions, for example, for fetal distress and cephalopelvic disproportion. It is also electively performed for non-emergencies, e.g. previous caesarean section, breech presentation. Pregnant mothers undergoing caesarean section often experience anxiety in anticipation of the event that may be unfamiliar, uncomfortable or have undesirable results. This anxiety can increase the risk of psychological and physiological complications and delays in postoperative recovery (Good 1996; Mok 2003). This anxiety, however, could be reduced

by various means including support by their surgeons, nurses and, possibly, music in the operative rooms.

There is evidence to suggest that there are increased maternal risks associated with surgery, including anaesthetic risks, surgical complications, increased blood loss, need for transfusion, and pulmonary embolism (Kelleher 1994). Women may also experience restrictions in their daily activities (Chippington 2004) and experience breastfeeding difficulties (Francome 1993). Caesarean section may also increase the chances of women experiencing problems in subsequent pregnancies related to uterine scarring (Hemminki 1996). Furthermore, new, unexpected, long-term risks of caesarean section continue to be reported; these include abnor-

mal placentation (Wu 2005), ectopic pregnancy, haemorrhage and hysterectomy following uterine evacuation, latex allergy, implantation endometriosis, adenomyosis and increased hospital readmission (Bewley 2002). Caesarean section has also been associated with emotional difficulties (Clement 2001) for the woman, including postpartum depression and negative feelings about the experience of childbirth (Minkoff 2003). Suggested increased risks for babies delivered by caesarean section include increased rates of admission to neonatal units and separation of the mother and neonate (Treffers 1993), iatrogenic prematurity (Wagner 2000), laceration (Smith 1997), increased neonatal respiratory problems (Madar 1999) and stillbirth if the mother has previously had a caesarean section (Smith 2003).

Music is an intentional auditory stimulus with organised elements including melody, rhythm, harmony, timbre, form, and style. Repetitive listening allows the listener to identify and predict sounds (Standley 2002). Thus, repeated exposure may enhance clinical effects (Kemper 2005). An observational study (Good 2000) found that musical choices were related to cultural background of patients admitted to hospitals. Music was found to enhance well being in a randomised crossover trial (McCrary 1998). Other studies report that music reduced stress and distracted adult hospital patients from unpleasant symptoms (in a systematic review of RCTs by Evans 2002 and also in a quasi-experimental study by Shertzer 2001). Although there are wide variations in individual preferences, music appears to exert direct physiologic effects through the autonomic nervous system. For example, one randomised trial in which outcomes were measured repeatedly (White 1999) and two quasi-intervention studies (Umemura 1998; Urakawa 2005) report that listening to classical music may increase the heart rate variability, whereas listening to noise or rock music may decrease heart rate variability (reflecting greater stress) in healthy subjects. Music has also been found to have indirect effects by modifying caregiver behaviour. A randomised controlled trial (RCT) (Lepage 2001) and two quasi-intervention studies (Haun 2001; Yung 2002) found that music effectively reduced anxiety and improved the mood of medical and surgical patients, patients in intensive care units and patients undergoing procedures. Music is a low-cost intervention that may reduce surgical, procedural, acute, and chronic pain. However, the findings are from many studies that have methodological problems, such as small sample sizes, lack of randomisation, and lack of control for patient anaesthesia (Kemper 2005). Furthermore, a systematic review of RCTs on music for pain relief (Cepeda 2006) found that the beneficial effect of music on pain intensity levels and opioid requirements was unclear.

Other studies have found that music improved the quality of life for patients receiving palliative care (Hilliard 2003), enhancing a sense of comfort and relaxation according to results from a pre and post study (Burns 2001) and two RCTs (Cassileth 2003; Smith 2001). A quasi-intervention study (Allen 1994) and another RCT

(Bittman 2003) show that providing music to caregivers may be a cost-effective and enjoyable strategy to improve empathy, compassion, and relationship-centred care while not increasing errors or interfering with the technical aspects of care.

Music's ability to slow respiratory rates and decrease the stress response appears to be beneficial during labour. It has been reported that music shortened labour in an observational study (Winokur 1984). Even when the course of labour does not speed up when music is utilised, the perceived length of labour decreases, as shown in a quasi-intervention study (Clark 1981). A review by McKinney 1990 and a self-controlled experiment by Hanser 1983 have both found that when music is played, pain is decreased.

The efficacy of music for premature infants was reported in a nonsystematic review of literature by Standley 2002, and their findings suggest that music is clinically useful for the care of this group. One cohort study describes the use of medical resonant music as preoperative preparation for caesarean section. Music is thought to influence cortical dynamics and through it subcortical and vegetative areas of the nervous system (Wein 1997). Such influence is thought to cause an integration and synchronisation of different activity systems within the human body, strengthening psycho-physiological defences and improving health conditions (Gerasimovich 1995; Gerasimovich 1999). Compared with a control group of women who received sedatives for preoperative preparation, the intervention group receiving Medical Resonance Therapy music (MRT-music) had lower cortisol levels and noted better sleep and less need for analgesics postoperatively (Sidorenko 2000).

Most caesarean sections are performed under epidural or spinal block where the pregnant woman is anaesthetised from the waist down. However, there is often some degree of discomfort for the woman before the baby is born, when the uterus is manipulated. Music may be useful during caesarean section under regional anaesthesia in terms of improving outcomes for the mother and baby but thus far there has not been a systematic review on this topic.

OBJECTIVES

To assess the effectiveness of music during caesarean section under regional anaesthesia for improving clinical and psychological outcomes for mothers and infants.

METHODS

Criteria for considering studies for this review

Types of studies

All identified published, unpublished and ongoing RCTs and quasi-RCTs for inclusion. The randomised units could be individual or clustered (e.g. hospitals).

Types of participants

Pregnant women scheduled to receive caesarean sections under regional anaesthesia.

Types of interventions

The addition of any type of music to routine care compared with routine care alone during caesarean section.

Types of outcome measures

Primary outcomes

For mothers

1. Pain intensity (self-report measured with the visual analogue scale during and after caesarean section)
2. Analgesic requirement during and after caesarean section
3. Anxiety during and after caesarean section as defined by investigators
4. Maternal death
5. Clinical outcomes
 - 5.1 Blood pressure
 - 5.2 Pulse haemoglobin oxygen saturation (SpO₂)
 - 5.3 Respiratory rates
 - 5.4 Heart rate and its variability
 - 5.5 Blood loss
 - 5.6 Immediate postoperative complications

For infants

6. Apgar scores at one and five minutes
7. Birth asphyxia
8. Infant death

Secondary outcomes

For mothers

1. Maternal satisfaction
2. Injury from surgical procedures such as urinary bladder injury, vessel injury, etc
3. Skin to skin contact between mother and infant during or after caesarean section
4. Breastfeeding initiation and duration

For infants

5. Injury from surgical procedures such as cut wound, etc
6. Physical and psychological development of infants as defined by investigators

Search methods for identification of studies

Electronic searches

We contacted the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (30 September 2008).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors, Malinee Laopaiboon (ML) and Ruth Martis (RM), independently assessed for inclusion all potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion with the third review author, Pisake Lumbiganon (PL).

Assessment of methodological quality of included studies

Malinee Laopaiboon (ML) and Ruth Martis (RM) independently assessed risk of bias for the included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2008](#)).

1) Sequence generation (checking for possible selection bias)

We described for the included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- yes, low risk of bias (any truly random process e.g. random number table; computer random number generator);
- no, high risk of bias (any non random process e.g. odd or even date of birth); or
- unclear.

2) Allocation concealment (checking for possible selection bias)

We described for the included study the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- yes, low risk of bias (e.g. consecutively numbered sealed opaque envelopes);
- no, high risk of bias (open random allocation; unsealed or non-opaque envelopes); or
- unclear.

3) Blinding (checking for assessment bias)

It was not feasible to blind clinicians and participants to the music. We only assessed blinding for outcome assessors:

- yes, low risk of bias;
- no, high risk of bias; or
- unclear for outcome assessors.

4) Incomplete outcome data (checking for possible attrition bias)

We describe for the included study, and for each outcome, the completeness of data including attrition and exclusions from the analysis. We addressed whether attrition and exclusions were reported, the numbers included in the analysis compared with the total randomised participants, reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes.

We assessed methods as:

- yes, low risk of bias;
- no, high risk of bias; or
- unclear.

5) Selective reporting bias

We described the possibility of selective outcome reporting bias.

We assessed the methods as:

- yes, low risk of bias (where it was clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- no, high risk of bias (where not all the study's pre-specified outcomes were reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported incompletely and so could not be used; study failed to include results of a key outcome that were expected to be reported); or
- unclear.

6) Other sources of bias

We described any important concerns about other possible sources of bias in the one included study.

We assessed whether it was free of other problems that could put it at risk of bias:

- yes, low risk of bias;
- no, high risk of bias; or
- unclear.

We made explicit judgements about whether the included study was at high risk of bias, low risk of bias or unclear risk of bias according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008).

Data extraction and management

We designed a form, based on the Cochrane Pregnancy and Childbirth Group's template, to extract data. ML and RM extracted the data using the agreed form. We resolved discrepancies through discussion. We used the Review Manager software (RevMan 2008) to double enter all the data or a sub sample.

We did not contact authors of the original report as we had sufficient information.

Data analysis

This review included one trial. We have provided full methods of data analysis for future updates of this review in [Appendix 1](#).

Measures of treatment effect

We carried out statistical analysis using Review Manager software (RevMan 2008). We have reported continuous outcomes such as maternal blood pressure, pain and infant Apgar scores as mean differences with 95% confidence intervals (CI) if the outcomes are measured in the same way among trials.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

The search strategy identified two potentially relevant studies. We excluded one ([Reza 2007](#)) because the caesarean section was done under general anaesthesia (see '[Characteristics of excluded studies](#)').

We included one RCT in this review ([Chang 2005](#)). For more information see '[Characteristics of included studies](#)'. The trial was undertaken in a medical centre in southern Taiwan between June and October 2002, and evaluated the effects of music on women's clinical and psychological measures, such as anxiety and satisfaction during caesarean section. Seventy-six women, scheduled to deliver their babies by caesarean section, were eligible following initial assessment and allocation. Thirty-eight women were each randomly assigned to either the intervention (music added to standard care) or the control group (standard care alone). Consent to receive music was given after random allocation. There were six women in the intervention group who declined participation for various reasons: two lost interest; two received sedative/nitrous oxide; one had a newborn with imperforate anus; and one had failure of local anaesthesia. Six women participating in the control group dropped out for the following reasons: two had an emergency caesarean section; and four received sedative/nitrous oxide. In total, 64 randomised women were studied, with 32 each in

the intervention and control groups. For the intervention group, women received standard care plus listening to music through earphones using a compact disc player. Women chose their preferred music from either western classical, new age or Chinese religious music. Music listening started from the beginning of anaesthesia to the end of surgery, and lasted at least 30 minutes. Mean listening time was 87.59 minutes (SD 13.01). For the control group, women received standard care without music. The trial reported the women's self-assessed anxiety (measured using the Visual Analogue Scale for Anxiety (VASA), which consists of a 10 cm horizontal line with the descriptors 'no anxiety' at the left extent and 'worst possible anxiety' at the right extent ([Gift 1989](#))). Clinical measures reported by [Chang 2005](#) include: pulse haemoglobin oxygen saturation (SpO₂ (%)); finger temperature (° F); respiration rate (per minute); pulse rates (beats/minute); systolic blood pressure (mmHg); and diastolic blood pressure (mmHg).

Data was collected at three points: in the operation room prior to anaesthesia and caesarean section (pre-test); at the end of maternal contact with the neonate in the intra-operation period (post-test I); and after completion of skin suture for the caesarean section (post-test II). The trial also reported the women's birth satisfaction, as assessed by the Satisfaction of Caesarean Delivery Scale (SCDS) and measured at the post-test II period only. The SCDS was designed specifically for the study; for more information about this instrument see [Characteristics of included studies](#). The baseline characteristics of the two groups are given in [Table 1](#).

Table 1. Outcomes measured at pre-test

Outcomes	Intervention	Control
	Mean (SD)	Mean (SD)
SpO ₂ (%)	99.22 (0.94)	98.88 (1.41)
Respiration rate (per minute)	22.72 (2.25)	23.34 (2.66)
Pulse rate (beats/minute)	86.69 (13.65)	90.25 (10.65)
Systolic blood pressure (mm Hg)	131.72 (18.03)	126.16 (15.90)
Diastolic blood pressure (mm Hg)	80.34 (15.85)	77.00 (12.86)
Anxiety (VASA) scores	6.80 (3.05)	5.54 (3.42)

Risk of bias in included studies

The one included trial was assessed as having 'unclear' information in five domains of risk of bias: sequence generation; allocation concealment; blinding; free selective reporting; and free other risk of bias. Women eligible for inclusion were sequentially recruited and then randomly allocated to the intervention or control groups.

It was not feasible to blind the participants and clinicians to music. Outcome assessors for VASA scores and birth satisfaction were not blinded because the outcomes were self assessed by the participants themselves. However, the trial does not report on blinding of outcome assessors for clinical outcomes. The analysis was not done on an intention-to-treat basis because 12 patients (six in the intervention group and six in the control group) were excluded

after randomisation. Outcomes were measured from a total of 64 women: 32 women in the intervention group and 32 women in the control group. Selective outcome reporting cannot be ruled out because the trial protocol was not available to compare the planned outcomes with those reported.

Effects of interventions

One trial (Chang 2005) of 64 women (32 for music group and 32 for control group) evaluated the effects of music on women's clinical outcomes, anxiety and satisfaction during caesarean section.

Primary outcomes

The clinical outcomes of SpO₂, respiration rate, pulse rates, systolic and diastolic blood pressure, and VASA anxiety score were presented as means and standard deviations (SD) for the intervention and control groups at two time points after the intervention. Mean difference (MD) percentages of SpO₂ were 0.03 (95% CI -0.27 to 0.33) at the end of maternal contact with the neonate in the intra-operation period and -0.31 (95% CI -0.75 to 0.13) after completion of skin suture for the caesarean section (See Analysis 1.1; Analysis 1.2).

Small, non-significant changes in respiration rates for both groups were seen at the two post-test points. MD were not statistically significant, -0.82 (95% CI -1.70 to 0.06), at the end of maternal contact with the neonate in the intra-operation period and -0.53 (95% CI -1.27 to 0.21) after completion of skin suture for the caesarean section (See Analysis 1.3; Analysis 1.4).

Reductions in pulse rates at the two post-test periods were larger in the intervention group compared to the control group. MD were statistically significant, -7.50 (95% CI -14.08 to -0.92) at the end of maternal contact with the neonate in the intra-operation period and -7.37 (95% CI -13.37 to -1.37) after completion of skin suture for the caesarean section (See Analysis 1.5; Analysis 1.6).

No changes in systolic blood pressure were seen at the two post-test periods for the women in the intervention group compared with those in the control group. MDs of systolic blood pressures were not statistically significant, -1.66 mmHg (95% CI -7.30 to 3.98), at the end of maternal contact with the neonate in the intra-operation period and 0.90 mmHg (95% CI -5.76 to 7.56) after completion of skin suture for the caesarean section (See Analysis 1.7; Analysis 1.8).

There were no significant changes in the patterns of diastolic blood pressure in women in the intervention and the control groups, at the end of maternal contact with the neonate in the intra-operation period (MD -1.36; 95% CI -7.88 to 5.16) or after completion of skin suture for the caesarean section (MD -0.09; 95% CI -5.00 to 4.82) (See Analysis 1.9; Analysis 1.10).

Chang 2005 reports that the mean anxiety (VASA) scores were decreased ($P < 0.01$) between pre- and post-test in both the intervention and control groups. At both time points (post-test I and II) there was no evidence of a statistically significant difference between groups (Analysis 1.12; Analysis 1.13)

Secondary outcomes

Birth satisfaction scores were statistically significantly higher in the intervention group compared with the control group (MD 3.38, 95% CI 1.59 to 5.17) (See Analysis 1.11).

DISCUSSION

This review aimed to assess the effectiveness of music during caesarean section under regional anaesthesia for improving clinical and psychological outcomes for mothers and infants.

We included only one trial (Chang 2005) involving 64 of 78 randomised women. Outcomes included SpO₂, respiration rates, pulse rates, systolic and diastolic blood pressure, and VASA anxiety score as primary outcomes and birth satisfaction as a secondary outcome. There were no statistically significant differences between the intervention and control groups for most outcomes. There were statistically significant differences between the intervention and control groups for pulse rates and birth satisfaction. However, the effect sizes were small and may not suggest a clinically beneficial effect of music. Although the mean VASA scores were lower in the intervention group than in the control group at the two post-test periods, the data are skewed, so statistically significant differences cannot be ruled out.

The included trial may be of limited generalisability to clinical practice. The trial was conducted in Taiwan, with data from only 64 women available for inclusion in the final analysis. Three types of music (Western classical, new age and Chinese religious) might have different effects on outcomes. The number of women choosing each type of music was not available. We, therefore, cannot rule out differential effects on maternal outcomes resulting from the type of music. The maternal outcomes were limited to anxiety, some clinical outcomes and birth satisfaction. No infant outcomes were reported. The reporting of trial methodology was poor and there was no information available in relation to randomisation methods and allocation concealment. In this included study it was not possible to blind the assessors, as it would have been obvious which women were in the receiving music therapy (the intervention group) because they were wearing earphones connected to a compact disc player. In addition, risk of attrition bias (drop-out) was possible since 12 patients were excluded after randomisation. These factors limit the methodological strength of the evidence.

AUTHORS' CONCLUSIONS

Implications for practice

The findings of this review indicate that music during caesarean section under regional anaesthesia may have positive effects on pulse rates and birth satisfaction of mothers. However, the poor

methodological quality of the one included study makes it impossible to draw any firm conclusions about the effectiveness of music during caesarean section under regional anaesthesia for improving maternal and infant outcomes.

Implications for research

More research is needed in order to evaluate the effects of music during caesarean section under regional anaesthesia. Future RCTs with good methodology, in terms of randomisation methods, concealment, and blinded outcome assessors, should be undertaken involving different types of music, adequate sample sizes, and pregnant women from a variety of different ethnic groups.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Chang 2005

Methods	RCT, reported only sequentially recruited eligible women which were then randomly allocated to intervention and control groups. Blinding: assessment of some outcomes, i.e. anxiety and birth satisfaction were not blinded. Description of withdrawals: yes, 12 women (six in the intervention and six in the control) dropped out after randomisation for various reasons. Intention-to-treat analysis: no.
Participants	76 women scheduled to receive caesarean section between June and October 2002 at a medical centre in southern Taiwan. Participants were married, aged 20-40 years, term pregnancies and planned to undergo caesarean births, underwent spinal or epidural anaesthesia, and having singleton babies with Apgar scores ≥ 7 at 5 minutes. Number of women randomised: 76, but only 64 (32 for the intervention (music) group and 32 for the control group) received interventions for the following reasons: Intervention group: 6 declined to participate (2 lost interest, 2 received sedative/nitrous oxide, 1 had a newborn with imperforate anus and 1 had failure of local anaesthesia). Control group: 6 dropped out (2 had emergency caesarean section and 4 received sedative/nitrous oxide).
Interventions	Intervention group: standard care plus at least 30 minutes listening to music through earphones via a compact disc player. Participants chose the music they preferred: either Western classical, new age, or Chinese religious music. Music listening started at the beginning of anaesthesia until the end of surgery. The researcher accompanied participant into theatre and stayed to obtain data. Control group: received standard care and no music. The researcher accompanied participant into theatre and stayed to obtain data.
Outcomes	Primary: anxiety in VASA consisting of a 10 cm horizontal line with the descriptors 'no anxiety' at the left and 'worst possible anxiety' at the right. clinical outcomes: SpO₂, temperature of finger, respiration rate, pulse rates, systolic blood pressure, diastolic blood pressure, all measured by standard tests without the assessor's knowledge. Secondary: birth satisfaction: women's satisfaction of caesarean section delivery scale (SCDS) designed for the study. The SCDS was composed of seven items, including the woman's perceived health status, the perceived health status of the baby, the maintenance of physical function, the maintenance of physical comfort, seeking safe passage for herself, ego orientation, and birth atmosphere.

Chang 2005 (Continued)

	Items are scored on a Likert-type scale of 1 to 5, representing 1, extremely dissatisfied; 2, not satisfied; 3,uncertain; 4, satisfied; and 5, extremely satisfied. Data were collected at three points: pre-test: at the operation room prior to anaesthesia and caesarean section; post-test I: upon the end of maternal contact with the neonate in the intra-operation period; post-test II: after completion of skin suture for the caesarean section. Data on birth satisfaction were collected only at the post-test II period.	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No description.
Allocation concealment?	Unclear	Reported as “sequentially recruited eligible women then randomly allocated to intervention and control”.
Blinding? All outcomes	Unclear	Not feasible to blind participants and clinicians. No information given regarding the assessors for clinical outcomes. Self assessment by participants for VASA scores and birth satisfaction but were recorded to data sheets by the researcher.
Incomplete outcome data addressed? All outcomes	Yes	Outcomes were able to be measured in the total 64 women being received intervention (32) and control (32).
Free of selective reporting?	Unclear	The trial protocol was not available to compare the planned outcomes with reported outcomes.
Free of other bias?	Unclear	No other information given in the paper.

SpO₂: pulse haemoglobin oxygen saturation

VASA: Visual Analogue Scale for Anxiety

Characteristics of excluded studies *[ordered by study ID]*

Reza 2007	Caesarean section was done under general anaesthesia, which does not comply with our inclusion criteria of caesarean sections under regional anaesthesia.

DATA AND ANALYSES

Comparison 1. Music added to standard care (intervention) versus standard care alone (control)

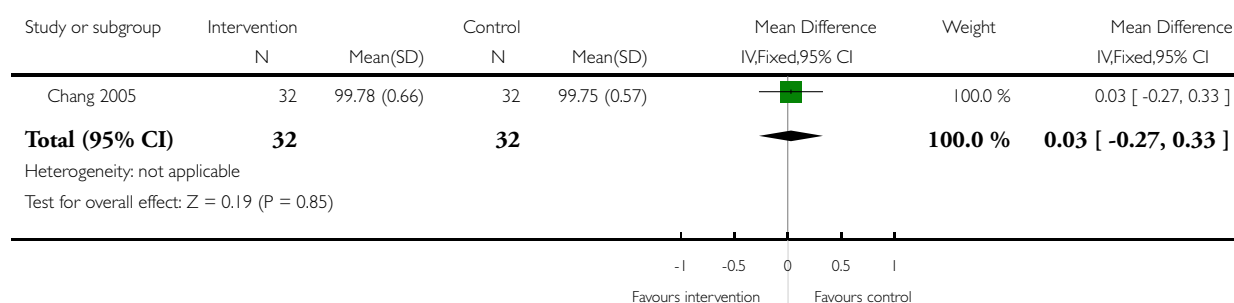
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SpO ₂ at post-test I	1	64	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.27, 0.33]
2 SpO ₂ at post-test II	1	64	Mean Difference (IV, Fixed, 95% CI)	-0.31 [-0.75, 0.13]
3 Respiration rate at post-test I	1	64	Mean Difference (IV, Fixed, 95% CI)	-0.82 [-1.70, 0.06]
4 Respiration rate at post-test II	1	64	Mean Difference (IV, Fixed, 95% CI)	-0.53 [-1.27, 0.21]
5 Pulse rate at post-test I	1	64	Mean Difference (IV, Fixed, 95% CI)	-7.5 [-14.08, -0.92]
6 Pulse rate at post-test II	1	64	Mean Difference (IV, Fixed, 95% CI)	-7.37 [-13.37, -1.37]
7 Systolic blood pressure at post-test I	1	64	Mean Difference (IV, Fixed, 95% CI)	-1.66 [-7.30, 3.98]
8 Systolic blood pressure at post-test-II	1	64	Mean Difference (IV, Fixed, 95% CI)	0.90 [-5.76, 7.56]
9 Diastolic blood pressure at post-test I	1	64	Mean Difference (IV, Fixed, 95% CI)	-1.36 [-7.88, 5.16]
10 Diastolic blood pressure at post-test II	1	64	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-3.00, 4.82]
11 Birth satisfaction at post-test II	1	64	Mean Difference (IV, Fixed, 95% CI)	3.38 [1.59, 5.17]
12 Anxiety (VASA) score post-test I	1	64	Mean Difference (IV, Fixed, 95% CI)	-1.11 [-2.49, 0.27]
13 Anxiety (VASA) score post-test II	1	64	Mean Difference (IV, Fixed, 95% CI)	-0.78 [-1.90, 0.34]

Analysis 1.1. Comparison 1 Music added to standard care (intervention) versus standard care alone (control), Outcome 1 SpO₂ at post-test I.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: 1 Music added to standard care (intervention) versus standard care alone (control)

Outcome: 1 SpO₂ at post-test I

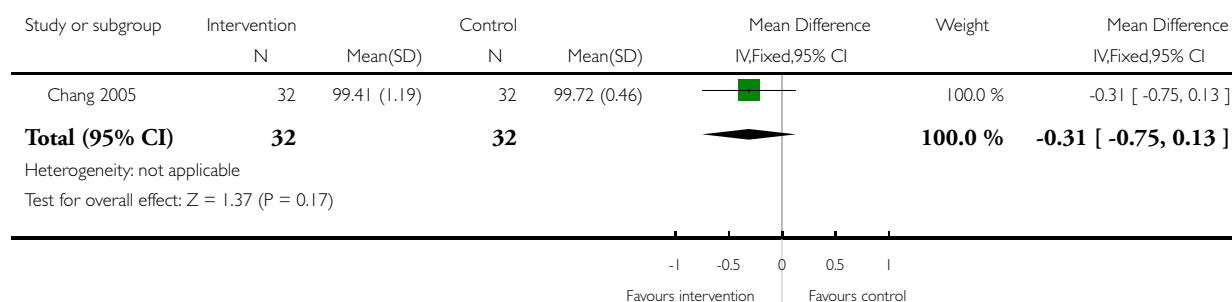


Analysis 1.2. Comparison 1 Music added to standard care (intervention) versus standard care alone (control), Outcome 2 SpO₂ at post-test II.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: 1 Music added to standard care (intervention) versus standard care alone (control)

Outcome: 2 SpO₂ at post-test II

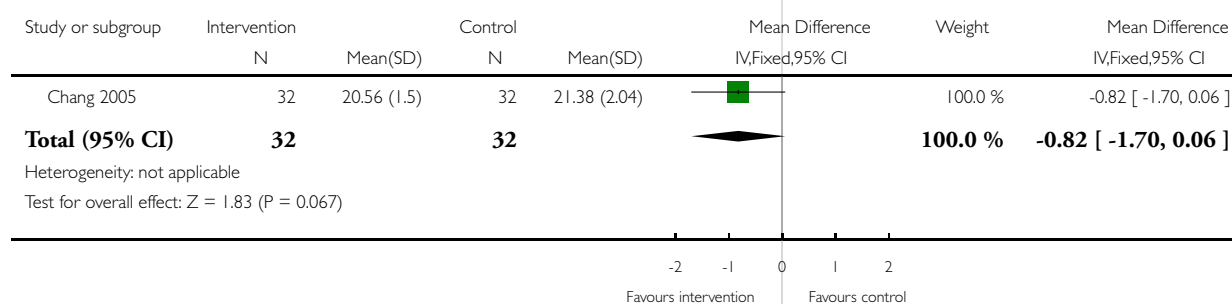


Analysis 1.3. Comparison 1 Music added to standard care (intervention) versus standard care alone (control), Outcome 3 Respiration rate at post-test I.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: 1 Music added to standard care (intervention) versus standard care alone (control)

Outcome: 3 Respiration rate at post-test I

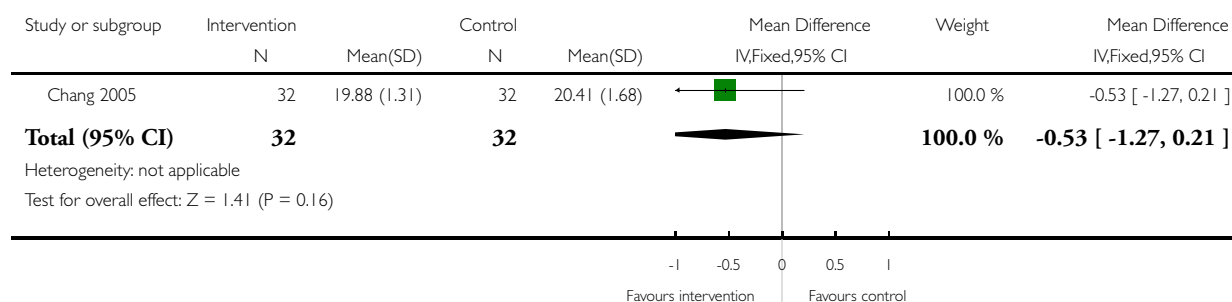


Analysis 1.4. Comparison I Music added to standard care (intervention) versus standard care alone (control), Outcome 4 Respiration rate at post-test II.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: I Music added to standard care (intervention) versus standard care alone (control)

Outcome: 4 Respiration rate at post-test II

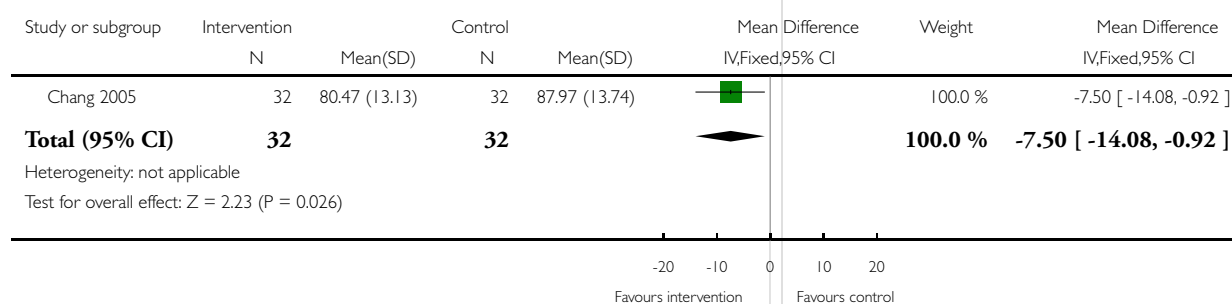


Analysis 1.5. Comparison I Music added to standard care (intervention) versus standard care alone (control), Outcome 5 Pulse rate at post-test I.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: I Music added to standard care (intervention) versus standard care alone (control)

Outcome: 5 Pulse rate at post-test I

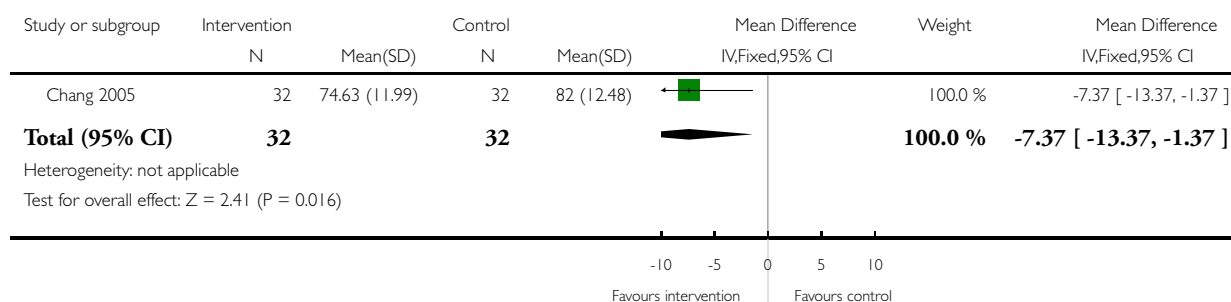


Analysis 1.6. Comparison 1 Music added to standard care (intervention) versus standard care alone (control), Outcome 6 Pulse rate at post-test II.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: 1 Music added to standard care (intervention) versus standard care alone (control)

Outcome: 6 Pulse rate at post-test II

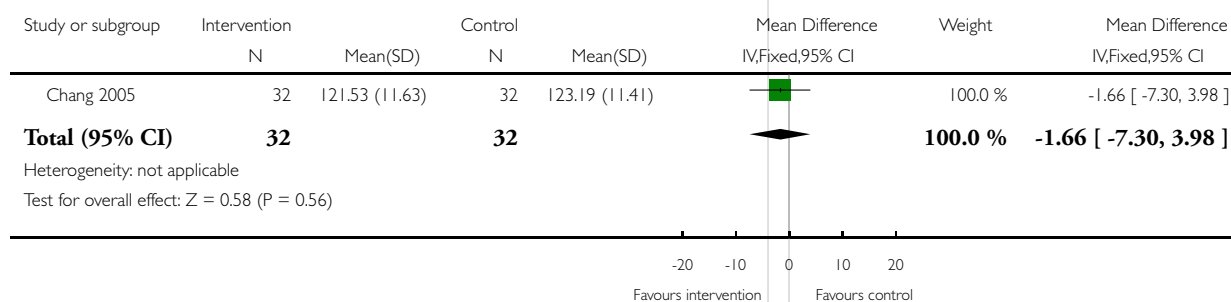


Analysis 1.7. Comparison 1 Music added to standard care (intervention) versus standard care alone (control), Outcome 7 Systolic blood pressure at post-test I.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: 1 Music added to standard care (intervention) versus standard care alone (control)

Outcome: 7 Systolic blood pressure at post-test I

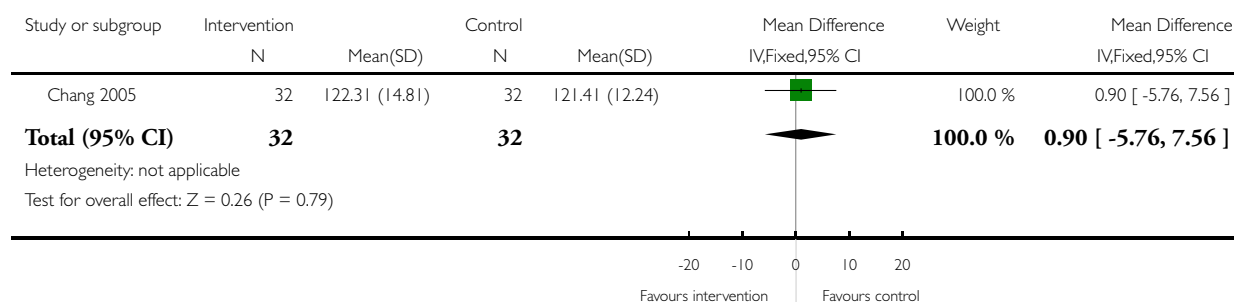


Analysis 1.8. Comparison 1 Music added to standard care (intervention) versus standard care alone (control), Outcome 8 Systolic blood pressure at post-test-II.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: 1 Music added to standard care (intervention) versus standard care alone (control)

Outcome: 8 Systolic blood pressure at post-test-II

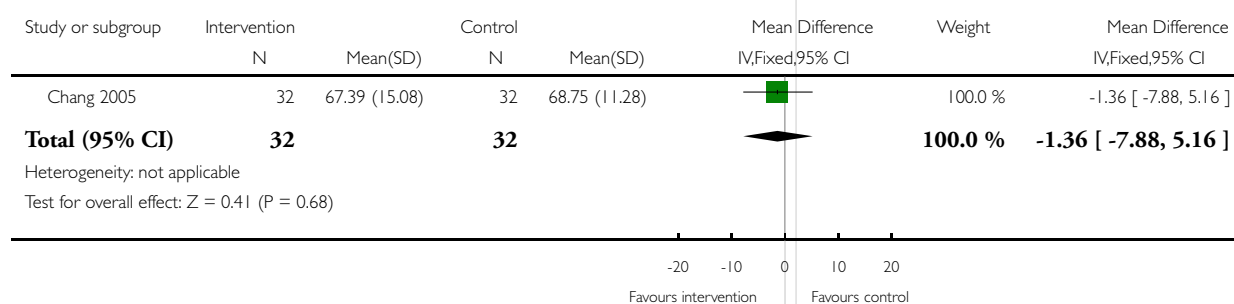


Analysis 1.9. Comparison 1 Music added to standard care (intervention) versus standard care alone (control), Outcome 9 Diastolic blood pressure at post-test I.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: 1 Music added to standard care (intervention) versus standard care alone (control)

Outcome: 9 Diastolic blood pressure at post-test I

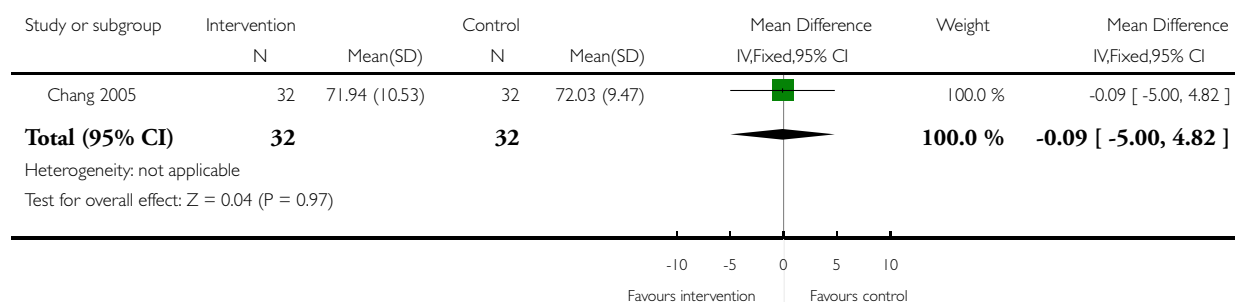


Analysis 1.10. Comparison 1 Music added to standard care (intervention) versus standard care alone (control), Outcome 10 Diastolic blood pressure at post-test II.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: 1 Music added to standard care (intervention) versus standard care alone (control)

Outcome: 10 Diastolic blood pressure at post-test II

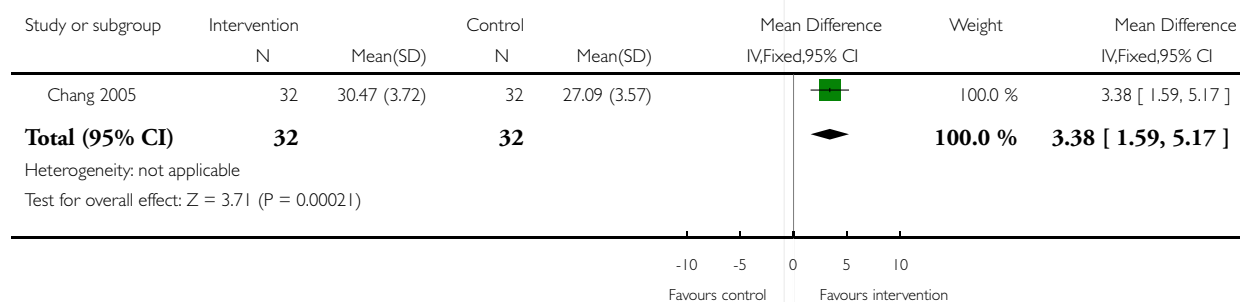


Analysis 1.11. Comparison 1 Music added to standard care (intervention) versus standard care alone (control), Outcome 11 Birth satisfaction at post-test II.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: 1 Music added to standard care (intervention) versus standard care alone (control)

Outcome: 11 Birth satisfaction at post-test II

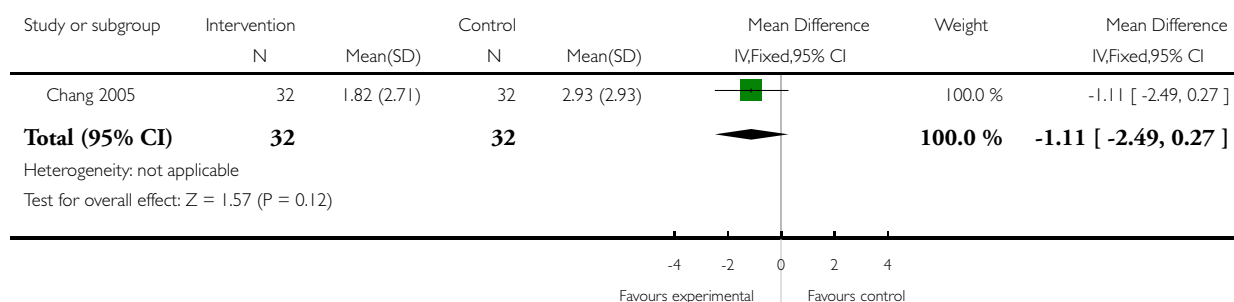


Analysis 1.12. Comparison I Music added to standard care (intervention) versus standard care alone (control), Outcome 12 Anxiety (VASA) score post-test I.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: I Music added to standard care (intervention) versus standard care alone (control)

Outcome: 12 Anxiety (VASA) score post-test I

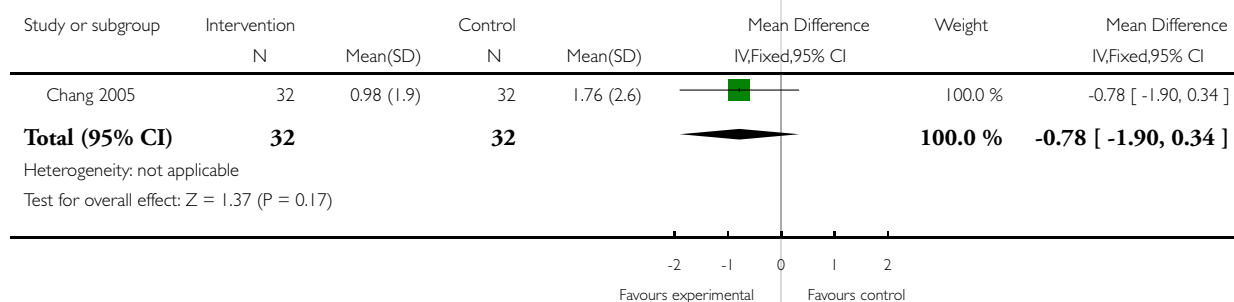


Analysis 1.13. Comparison I Music added to standard care (intervention) versus standard care alone (control), Outcome 13 Anxiety (VASA) score post-test II.

Review: Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes

Comparison: I Music added to standard care (intervention) versus standard care alone (control)

Outcome: 13 Anxiety (VASA) score post-test II



APPENDICES

Appendix I. Methods for data analysis in subsequent updates of this review

Data analysis

Measures of treatment effect

In subsequent updates of this review we plan to use standardised mean difference to combine trials measuring the same outcome, but using different methods. For dichotomous data we will use relative risk with 95% confidence intervals (CI) and the corresponding number needed to treat. For continuous data we will use mean differences with 95% confidence intervals (CI) if the outcomes are measured in the same way among trials.

Assessment of heterogeneity

We will assess heterogeneity using the I^2 statistic (Higgins 2003). If we identify high levels of heterogeneity among the trials (exceeding 50%), we will explore it by prespecified subgroup analysis.

Subgroup analyses

We will conduct subgroup analyses classifying for potential sources of heterogeneity including ethnic groups (i.e. Caucasian, African, Latino, and Asian), types of music (i.e. mother's or investigator's preference and genre), methods of music delivery (via loud speakers or headphone), elective versus emergency caesarean section, and primary versus multiple caesarean section, where sufficient data are available. If trials in individual subgroups of the potential factor are thought to be heterogeneous by interaction test as described by Deeks 2001, we will not estimate an overall summary but present each specific subgroup effect size.

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually randomised trials. We will adjust their sample sizes according to the methods described in Gates 2005, using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources are used, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisations unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisations unit and perform a separate meta-analysis. Therefore, the meta-analysis will be performed in two parts as well.

Dealing with missing data

We will analyse data on all participants with available data in the group to which they are allocated, regardless of whether or not they received the allocated intervention. If in the original reports participants are not analysed in the group to which they were randomised, and there is sufficient information in the trial report, we will attempt to restore them to the correct group. In addition, other strategies are planned for handling of missing data. If possible, we will contact the trial authors for requesting missing data. Imputation of missing data following with sensitivity analysis will be performed for considering the impact of missing data on robustness of the results.

Assessment of publication bias

We will consider publication bias using funnel plots of between-treatment effect and its precision on individual trials, and Egger's test (Egger 1997). If we find asymmetrical funnel plots with statistical publication bias, we will further examine the effect of the bias on the meta-analysis conclusion using sensitivity analyses.

Sensitivity analyses

We will carry out sensitivity analyses to explore the effect of trial quality and, where appropriate, cluster-randomised trials, on the review's conclusions. The trial quality will involve an analysis based on concealment of allocation. Trials with clearly inadequate allocation of

concealment will be excluded in order to assess for any substantive difference on the overall result. For the clustering effect, we will perform a sensitivity analysis to see what the effect of different values of the ICC on the results of the analysis would be.

HISTORY

Protocol first published: Issue 1, 2008

Review first published: Issue 2, 2009

14 April 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Malinee Laopaiboon (ML) drafted the protocol and is guarantor for the review. ML, Pisake Lumbiganon (PL), Ruth Martis (RM), Patravoot Vatanasapt (PV) and Bussaba Somjaivong (BS) helped to develop and finalise the protocol. ML, RM and PL selected trial and extracted data. ML did the data analysis. ML and PL drafted the review. RM drafted the plain language summary. ML, PL, RM, PV and BS reviewed drafts and finalised the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Faculty of Public Health, Khon Kaen University, Thailand.
- Faculty of Medicine, Khon Kaen University, Thailand.
- Faculty of Nursing, Khon Kaen University, Thailand.
- Discipline of Obstetrics and Gynaecology, The University of Adelaide, Australia.

External sources

- Thailand Research Fund (Senior Research Scholar), Thailand.
- SEA-ORCHID project, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have updated our methodology for 'Assessment of methodological quality' in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* [Higgins 2008](#).

Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones (Review)

Srisubat A, Potisat S, Lojanapiwat B, Setthawong V, Laopaiboon M



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Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones (Review)

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[Intervention Review]

Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones

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ABSTRACT

Background

Stones in the urinary tract are a common medical problem in the general population. At present, the great expansion in minimally invasive techniques has led to the decrease in open surgery. Extracorporeal shock wave lithotripsy (ESWL) has been introduced as an alternative approach which disintegrates stones in the kidney and upper urinary tract through the use of shock waves. Nevertheless, as there are limitations with the success rate in ESWL, other minimally invasive modalities for kidney stones such as percutaneous nephrolithotomy (PCNL) and retrograde intrarenal surgery (RIRS) are also widely applied.

Objectives

To evaluate the effectiveness and complications of ESWL compared with PCNL or RIRS for managing kidney stones.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL in *The Cochrane Library*), MEDLINE, EMBASE and reference lists of articles without language restriction.

Selection criteria

Randomised controlled trials (RCTs) assessing the use of ESWL compared to PCNL or RIRS for kidney stone management.

Data collection and analysis

Two authors independently assessed all the studies for inclusion. Statistical analyses were performed using the random effects model and the results expressed as risk ratio (RR) for dichotomous outcomes or mean difference (MD) for continuous data with 95% confidence intervals (CI).

Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones (Review)

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Main results

Three studies (214 patients) were included, however results could not be pooled. Two RCTs compared ESWL to PCNL. The success rate at three months for lower pole kidney stones was statistically higher for PCNL (RR 0.39, 95% CI 0.27 to 0.56). Re-treatment (RR 1.81, 95% CI 0.66 to 4.99) and using auxiliary procedures (RR 9.06, 95% CI 1.20 to 68.64) after PCNL were less compared to ESWL. The efficiency quotient (EQ) in PCNL was higher than ESWL. Hospital stay (MD -3.30 days, 95% CI -5.45 to -1.15), duration of treatment (MD -36.00 minutes, 95% CI -54.10 to -17.90) and complications were less for ESWL. One RCT compared ESWL versus RIRS for lower pole kidney stones. The success rate was not significantly different at the end of the third month (RR 0.91, 95% CI 0.64 to 1.30).

Authors' conclusions

Results from three small studies, with low methodological quality, indicated ESWL is less effective for lower pole kidney stones than PCNL but not significantly different from RIRS. Hospital stay and duration of treatment was less with ESWL. More RCTs are required to investigate the effectiveness and complications of ESWL for kidney stones compared to PCNL or RIRS.

PLAIN LANGUAGE SUMMARY

Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones

Stones in the urinary tract are a common medical problem. Fifty per cent of patients with previous urinary stones have a recurrence within 10 years. Kidney stones can cause pain, blood in the urine, infection, decreased kidney function and kidney failure. The treatment is to remove the stones from kidney. Extracorporeal shock wave lithotripsy (ESWL) disintegrates stones using shock waves and is a minimally invasive technique. Other minimally invasive methods (percutaneous nephrolithotomy (PCNL)) and retrograde intrarenal surgery (RIRS)) are widely used for kidney stones management because ESWL had limited success rate. This review aimed to compare the effectiveness and complications between ESWL and stones removing using the nephroscopy through the skin at kidney level (PCNL) or ureteroscope through the bladder and ureter to the kidney (RIRS). Three small randomised studies (214 patients) were included. Two studies compared ESWL with PCNL and one study compared ESWL with RIRS. Patients with lower pole kidney stones who undergo PCNL have a higher success rate than ESWL whereas RIRS was not significantly different from ESWL. However, ESWL patients spent less time in hospital and the duration of treatment was shorter.

BACKGROUND

Urolithiasis (stones in the urinary tract) is a common medical problem with a prevalence of approximately 2% to 3% in the general population. Fifty per cent of patients with previous urinary stones have a recurrence within 10 years (Portis 2001). Additionally, the overall probability of forming kidney stones varies according to age, gender, race, geographic location, climate, occupation. Men are more commonly found to have urinary stones than women (2-3:1), and Caucasians have the highest incidence of upper urinary tract stones compared with Asians, Hispanics and African Americans (Pearle 2007). Kidney stones can also cause serious morbidity, pain, haematuria, infection, decreased kidney function and kidney failure.

At present, the great expansion in minimally invasive techniques has led to the decrease in open surgery. Extracorporeal shock wave lithotripsy (ESWL) has been introduced as an alternative approach and disintegrates stones in the kidney and upper urinary tract through the use of shock waves. However, there are several factors which will affect the choice of treatment for kidney stones including the size, location, and stone composition. For small stones with a maximum diameter of 20 mm or a surface area of 300 mm², ESWL had been established as the standard procedure due to it being non-invasive, having a low rate of complications, and no need for anaesthesia (Tiselius 2006). The overall stone-free rate of ESWL has been reported as 66% (stones 20 mm or less) and 49%

(stones more than 20 mm) (Obek 2001). The stone-free rates at three months for stones are 86% to 89% (renal pelvis), 71% to 83% (upper calyx), 73% to 84% (middle calyx) and 37% to 68% (lower calyx) (Albala 2001; Coz 2000; Maggio 1992; Obek 2001; Turna 2007). Lower caliceal stones have a lower clearance rate after ESWL and the stone size for treatment in this location is generally limited to 10 mm (Albala 2001; Tiselius 2006). The success rate for lower pole stones based on stone size are; 63% to 74% (1-10 mm), 23% to 56% (11-20 mm) and 14% to 33% (21-30 mm) (Albala 2001; Alken 2003). The success rate of ESWL also depends on stone composition. ESWL for uric acid and calcium oxalate dihydrate stones results in a better coefficient of fragmentation than those composed of calcium oxalate monohydrate and cystine. The success rates between these two groups were shown to be 38% to 81% and 60% to 63% respectively (Tiselius 2006).

Currently, the contraindications for ESWL treatment are restricted to pregnancy, severe skeletal malformations, severe obesity, urinary tract obstruction distal to the stone, and aortic and/or renal artery aneurysms. Moreover, ESWL should not be carried out in patients with uncontrolled blood coagulation, uncontrolled hypertension or uncontrolled urinary tract infection (Tiselius 2006). Despite its widespread use for the treatment of stones, ESWL can cause trauma to the kidney. The complications of ESWL are steinstrasse (obstruction due to fragments becoming lodged in the ureter), haematoma, infection, sepsis, hypertension and diabetes mellitus (Krambeck 2006; Riedler 2003).

Due to the limitations of the success rate and the complications of ESWL, other minimal invasive modalities for kidney stones such as percutaneous nephrolithotomy (PCNL) and retrograde intrarenal surgery (RIRS) are widely used. PCNL is indicated for patients with large kidney and upper ureteral stones. The main advantage of PCNL is the higher success rate for these larger stones (May 1998; Netto 1991) as it is not dependent on the stone burden or composition (Tiselius 2006). Pearle 2007 reported that for patients with stones smaller than 10 mm, 100% of patients treated with PCNL were stone-free, compared to 63% for those treated with ESWL. For those patients with stones 11-20 mm, 93% treated with PCNL were stone-free, compared to only 23% of those treated with ESWL. For patients with stones 21-30 mm, 86% treated with PCNL were stone-free, compared to 14% for those treated with ESWL. However, PCNL is more invasive and has a higher associated morbidity than ESWL (Cass 1996; Havel 1998).

With the advance of endourologic technology, RIRS is considered as the second line therapy in the treatment of the ESWL-resistant lower pole stones and for patients with co-morbidities. RIRS management of the kidney stone is a reasonable alternative to ESWL or PCNL in patients with low volume stones (Auge 2001; Chung 2006; Grasso 1999; Holland 2006; Kourambas 2000; Preminger 2006; Stav 2003).

OBJECTIVES

This review aimed to assess the effectiveness and complications of ESWL for kidney stones compared with PCNL or RIRS.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at the outcomes between ESWL and PCNL or RIRS. The first period of randomised cross-over studies were also to be included.

Types of participants

Inclusion criteria

Patients with kidney stones treated using ESWL compared to PCNL or RIRS.

Exclusion criteria

Pregnant women and children with kidney stones were excluded.

Types of interventions

Any patient with kidney stones treated with ESWL compared to PCNL or RIRS.

Types of outcome measures

Primary outcomes

- Success rate: Stone-free, clinically insignificant residual fragments (CIRF) (residual fragment < 4 mm)
- Re-treatment rate
- Auxiliary procedures
- Efficiency quotient (EQ)

Secondary outcomes

- Mean procedural or operating time
- Mean hospital stay
- Complications after treatment

Search methods for identification of studies

Electronic searches

1. The Cochrane Renal Groups specialised register and the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*. CENTRAL and the Renal Groups specialised register contain the handsearched results of conference proceedings from general and speciality meetings. This is an ongoing activity across the Cochrane Collaboration and is both retrospective and prospective ([Master List 2009](#)). Therefore we did not specifically search conference proceedings. Please refer to The Cochrane Renal Review Group's Module in *The Cochrane Library* for the most up-to-date list of conference proceedings ([Renal Group 2009](#)).

2. MEDLINE (from 1966) using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs ([Dickersin 1994](#)) with the a specific search strategy developed with input from the Cochrane Renal Groups Trial Search Co-ordinator.

3. EMBASE (from 1980) using a search strategy adapted from that developed for the Cochrane Collaboration for the identification of RCTs ([Lefebvre 1996](#)) with a specific search strategy developed with input from the Cochrane Renal Groups Trial Search Co-ordinator.

See [Appendix 1](#) for search terms used.

Searching other resources

1. Reference lists of nephrology textbooks, review articles and relevant studies.

2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The review was undertaken by five authors (AS, SP, BL, VS, ML). The search strategy described was used to obtain titles and abstracts of studies that were potentially relevant to the review. The titles and abstracts were screened independently by AS, SP and VS, who discarded studies that were not applicable, however studies

and reviews that may have included relevant data or information on studies were retained initially. Authors BL and VS (who are Urologists) independently assessed retrieved abstracts and the full text of these studies to identify studies which satisfied the inclusion criteria.

Data extraction and management

Data extraction was carried out independently by the same authors using standard data extraction forms. Studies reported in non-English language journals were planned to be translated before assessment but we did not find any non-English language articles. Where more than one publication of one study existed, reports were to be grouped together and the most recent or most complete dataset was to be used. Any discrepancy between published versions was to be highlighted. Disagreements were resolved by discussion. Data entry and analysis was performed by ML.

Assessment of risk of bias in included studies

The quality of studies to be included was assessed independently by AS and SP without blinding to authorship or journal using the checklist developed by the Cochrane Renal Group. Discrepancies were resolved by discussion. The items assessed were:

- Sequence generation
- Allocation concealment
- Blinding (patients, investigators, outcome and data assessors)
- Completeness of follow-up
- Selective reporting.

See [Appendix 2](#) for criteria used.

Measures of treatment effect

The mean procedural or operating time and mean hospital stay were assessed using mean difference (MD) with 95% confidence intervals (CI). The risk ratio (RR) with 95% CI was used to assess the success of treatment (stone-free rate, CIRF), re-treatment, and use of auxiliary procedures. The outcomes between studies could not be compared as they used different criteria for measurement. Likewise, due to the difficulty of comparing the complications, we chose to describe the outcomes of each study.

Dealing with missing data

Participants were to be analysed according to the group to which they were randomised, regardless of whether or not they received the allocated intervention, but we could not restore them to the correct group and analyse because information of the missing data in the study reports were not clear.

Assessment of heterogeneity

We could not evaluate the similarity between ESWL and other modalities effect sizes in the included studies because of different study criteria. Therefore, the I^2 statistic ([Higgins 2003](#)) and subgroup analyses were not undertaken.

Assessment of reporting biases

We could not use funnel plots of between-treatment effect and its precision on individual studies for publication bias due to insufficient studies.

Subgroup analysis and investigation of heterogeneity

Initially we planned to conduct subgroup analyses for kidney stone sizes (< 10 mm, 10-20 mm, > 20 mm) and/or stone location (renal pelvis, upper pole, middle pole, and lower pole) and for different comparison interventions of ESWL with PCNL or RIRS but could not because of insufficient data.

Sensitivity analysis

Sensitivity analyses were not conducted to explore the effect of study quality as there were too few studies and different criteria used for measuring outcomes.

RESULTS

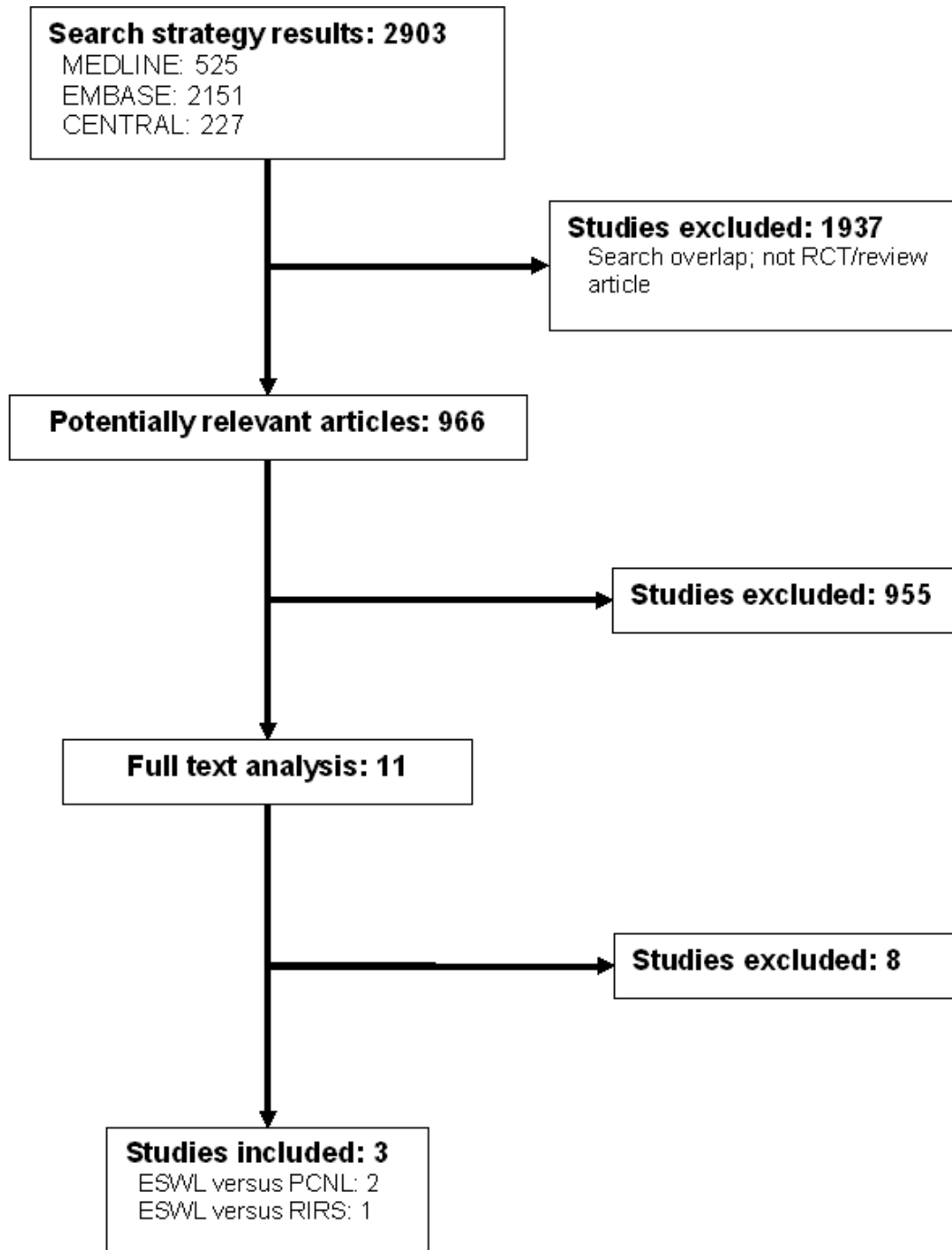
Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

The search for studies retrieved 2903 reports and after initial screening we identified 996 potentially relevant titles. Further screening via abstract review identified 11 potentially relevant studies. We retrieved the full-text articles for further evaluation. Eight articles were excluded, six were not RCTs, one was a time series and the other was an editorial comment. Three studies (214 patients) fulfilled our inclusion criteria ([Albala 2001](#); [Carlsson 1992](#); [Pearle 2005](#)). Two were from the USA ([Albala 2001](#); [Pearle 2005](#)) and one from Sweden ([Carlsson 1992](#)). See [Figure 1](#) for study selection procedure.

Figure 1. Flow chart of study selection procedure



Included studies

Two studies compared ESWL and PCNL (Albala 2001; Carlsson 1992) and one compared ESWL and ureteroscopy for lower pole kidney stones (RIRS) (Pearle 2005).

Albala 2001 compared ESWL with PCNL for symptomatic lower pole kidney stones 30 mm or less. This study was supported by a grant from Microvasive. A total of 160 patients aged over 18 were initially randomised however 32 patients were excluded post-randomisation but pre-intervention (withdrew after randomisation (21); stones moved away or passed before surgery (7); violated study protocol (4)). Sixty were enrolled in the ESWL group and 68 in the PCNL group. The mean stone size was 14.43 mm in the ESWL group and 13.59 mm in the PCNL group. Stratified randomisation according to stone sizes of 1-10, 11-20, and 21-30 mm was performed. For ESWL, all lithotriptors were used according to recognised standards. Stone fragments with diameters 3 mm or less were defined as successful ESWL treatment. Most PCNL were performed using a single stage procedure and one centre used a two stage technique. The initial outcome measurements were assessed by the end of the third month. They were stone-free status using nephrotomograms, re-treatment, auxiliary procedures, complications, stone burden, stone composition, quality of life, EQ, and hospital stay.

Carlsson 1992 compared ESWL with PCNL for medium-sized kidney stones (4-30 mm in diameter). Fifty five consecutive patients from one single hospital were randomised, 25 to PCNL (performed at the Karolinska Hospital) and 30 to ESWL (performed at the Linköping University Hospital). There were six exclusions post-randomisation but pre-intervention (PCNL (4), ESWL (2)). Twenty eight patients (mean age 49 years) were treated with ESWL and 21 (mean age 48.2 years) with PCNL. ESWL treatment used an unmodified Dornier HM-3 lithotripter. PCNL was done under epidural anaesthesia with nephrostomy. The outcomes were success rate, hospital stay, duration of treatment, complications and cost/successful treatment. Stone-free or stone fragments 5 mm or less using radiographic examination were considered successful treatment. Follow-up for stone-free rates were reported by the end of the fourth week and at one year.

Pearle 2005 compared ESWL with RIRS using ureteroscopy for lower pole kidney stones 10 mm or less. This study was supported by Boston Scientific, Natick, Massachusetts. Seventy eight patients were randomised in blocks of 10 based on a random number table to undergo ESWL or RIRS. Eleven dropped out before treatment, leaving 67 (ESWL (32), RIRS (35)). The two treatment groups were comparable in age, sex, body mass index, stone size, operative time, hospital stay and complications (intra-and postoperative). Recognised standards for each ESWL machine were used with power settings and number of shock waves used left to the discretion of the individual physician. Ureteroscopes were used for RIRS, including 7.5 Fr and Flex-X™, ACMI Dur 8™ and Dur 8-Elite™ and URF-P3. The use of a ureteral access sheath, intact stone retrieval versus intracorporeal lithotripsy and stent placement were left to the discretion of the individual physician. Stone-free status was determined by plain X-ray by the end of third month or sooner if stone-free. Noncontrast, thin cut computed tomography (5 mm) was required if there was no evidence of residual stones on plain X-ray. Success rate was being stone-free or fragments less than 4 mm.

Risk of bias in included studies

- **Sequence generation:** Two studies described the method of randomisation (Albala 2001; Pearle 2005) and one did not (Carlsson 1992).
- **Allocation concealment:** Information was not provided by any of the included studies.
- **Blinding:** Patients and investigators could not be blinded to the interventions. Blinding of the outcome and data assessors were not described by any of the included studies.
- **Completeness of follow-up:** The analysis was not done under intention-to-treat basis. Patients discontinued their follow-up after treatments in all studies.
- **Selective reporting:** All studies reported the primary outcomes of interest for this review.

See Figure 2, Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Albala 2001	+	?	?	-	+	-
Carlsson 1992	?	?	?	-	+	?
Pearle 2005	+	?	?	-	+	-

Effects of interventions

Success of treatment

Treatment success was defined as stone-free or clinically insignificant residual fragments (CIRF) (residual fragment < 4 mm).

We were unable to combine the stone-free rates between two studies because they were not measured for the same time period or size of fragment stones. [Albala 2001](#) reported the overall stone-free status (stone fragments ≤ 3 mm in diameter) and according to initial stone size at the end of the third month. [Carlsson 1992](#) measured the stone-free status (free of stones or fragments ≤ 5 mm) at the end of the fourth week and at one year.

[Albala 2001](#) reported success rates of 37% for ESWL and 95% for PCNL. The difference in success between the two interventions was significant ([Analysis 1.1.2](#): RR 0.39, 95% CI 0.27 to 0.56). According to stone size (1-10, 11-20 and 21-30 mm), the success

was 63% (12/19), 23% (6/26) and 14% (1/7) for ESWL and 100% (20/20), 93% (26/28) and 86% (6/7) for PCNL. There was a significant increase in success with PCNL for stone sizes 1-10 mm ([Analysis 1.1.4](#): RR 0.64, 95% CI 0.45 to 0.90) and 11-20 mm ([Analysis 1.1.5](#): RR 0.25, 95% CI 0.12 to 0.51) but not for 21-30 mm stones ([Analysis 1.1.6](#): RR 0.17, 95% CI 0.03 to 1.05), however the numbers in each group were small.

[Carlsson 1992](#) reported success rates of 76% (19/25) for ESWL and 100% (15/15) for PCNL at the end of the fourth week ([Analysis 1.1.1](#): RR 0.77, 95% CI 0.61 to 0.98). At one year these were 77% (20/26) for ESWL and 94% (18/19) for PCNL ([Analysis 1.1.3](#): RR 0.81, 95% CI 0.64 to 1.03).

[Pearle 2005](#) reported stone-free rates of 65% (17/26) for ESWL and 72% (23/32) for RIRS at the end of the third month. The difference was not significant ([Analysis 2.1](#): RR 0.91, 95% CI 0.64 to 1.30).

Re-treatment

Re-treatment was necessary for 10/64 (16%) in the ESWL group and 5/58 (9%) in the PCNL group (Albala 2001). This difference was not significant (Analysis 1.2.1: RR 1.81, 95% CI 0.66 to 4.99). Re-treatment according to stone size (1-10, 11-20 and 21-30 mm) was 9%, 18% and 22% for ESWL and 10%, 3% and 25% for PCNL respectively. The differences were not significant for any of the stone size categories (Analysis 1.2.2 (1-10 mm): RR 0.91, 95% CI 0.14 to 5.86; Analysis 1.2.3 (11-20 mm): RR 5.27, 95% CI 0.67 to 41.26; Analysis 1.2.4 (21-30 mm): RR 1.00, 95% CI 0.18 to 5.63). Carlsson 1992 did not report re-treatment data. Pearle 2005 reported secondary treatments were necessary for five ESWL patients and two RIRS patients (see Characteristics of included studies).

Auxiliary procedures

There were 10/64 (16%) auxiliary procedures in the ESWL group and 1/58 (2%) in the PCNL group (Albala 2001) and this was statistically significant (Analysis 1.3.1: RR 9.06, 95% CI 1.20 to 68.64). Auxiliary procedures according to stone sizes (1-10, 11-20 and 21-30 mm) were 14% (3/22), 21% (7/33) and 0% for ESWL respectively and were only performed in 1/29 (3%) patients in the 11-20 mm PCNL group. The differences were not significant (Analysis 1.3.2 (1-10 mm): RR 6.39, 95% CI 0.35 to 116.57; Analysis 1.3.3 (11-20 mm): RR 6.15 (95% CI 0.80 to 47.07). Carlsson 1992 did not report auxiliary procedures.

Efficiency quotient (EQ)

We calculated overall EQ for Albala 2001 which was 28% for ESWL and 86% for PCNL. However, EQ decreased when stone size increased. It accounted for 51%, 17% and 12% in the ESWL group and 91%, 88% and 71% in the PCNL group for stone sizes 1-10, 11-20 and 21-30 mm respectively. There was no EQ shown in the studies of Carlsson 1992 or Pearle 2005.

Mean procedural and operating times

Procedural time was not reported in Albala 2001. In Carlsson 1992, the duration of treatment was 43 ± 13.8 minutes for ESWL and 79 ± 40.6 minutes for PCNL. The mean duration of treatment was significantly longer for PCNL (Analysis 1.4: MD -36.0 min, 95% CI -54.1 to -17.9).

The mean operating time in Pearle 2005 was 65.5 ± 27.9 minutes for ESWL and 90.4 ± 43.8 minutes for RIRS. The mean operating time was significantly longer for RIRS (Analysis 2.2: MD -24.9 min, 95% CI -42.34 to -7.46).

Mean hospital stay

Albala 2001 reported a mean hospital stay of 0.55 days (range 0-9) for ESWL and 2.66 days (range 1-7) for PCNL. We could not

determine the MD between the two interventions because SDs were not reported.

Carlsson 1992 reported a mean hospital stay of 4.1 days (± 2.6) for ESWL and 7.4 days (± 4.5) for PCNL. The mean hospital stay was significantly shorter for ESWL (Analysis 1.5: MD -3.3 days, 95% CI -5.45 to -1.15).

In the study of Pearle 2005, all patients were discharged home on the day of treatment in the ESWL group, whereas 94% of patients had to stay 0.06 days in hospital after RIRS. We could not determine the MD between the two interventions because the SDs were not reported.

Complications after treatment

Albala 2001 reported the complications for ESWL were; urinary tract infection (1), obstruction (2), colic (2), haematoma (1) and steinstrasse (1). For PCNL the reported complications were; urinary tract infection (1), ileus (3), sepsis (1), haematoma (2), obstruction (1), perforation (3), transfusion (1) and arteriovenous fistula (1).

The complications in Carlsson 1992 were haematuria and fever (over 38°C). Pain was not considered a complication. They measured complications at days 1, 3, 5, 7, and 9. The period of haematuria in ESWL group was longer than in the PCNL group. Haematuria was still present at day 9 in the ESWL group but not in the PCNL group. Fever was reported less in the ESWL group than the PCNL group.

Pearle 2005 reported intra- and postoperative complications. There were 1/32 (3%) Intraoperative complications in the ESWL group and 7/35 (20%) in the RIRS group. There were 7/30 (23%) postoperative complications in the ESWL group and 7/33 (21%) in RIRS group.

DISCUSSION

Summary of main results

This review showed that for treating lower pole kidney stones, PCNL had a significantly higher success rate in terms of being stone-free than ESWL. Treatment success did not differ significantly between RIRS and ESWL. The use of auxiliary procedures were higher in ESWL, however ESWL required less time in hospital and had shorter procedural times.

Overall completeness and applicability of evidence

Two RCTs fulfilled our inclusion criteria and presented the clinical effects between ESWL and PCNL (Albala 2001; Carlsson 1992)

and one study compared ESWL and RIRS for lower pole kidney stones (Pearle 2005). The study by Carlsson 1992 was performed in the early period of ESWL technology and the success criteria for treating kidney stones was measured differently to the later study by Albala 2001. Albala 2001 focused on lower pole kidney stones while Carlsson 1992 did not specify stone location, thus we could not combine the data. The present technology for ESWL reduces the time required to stay in hospital. As a result, the information on hospital stay for ESWL compared to PCNL and RIRS seems less relevant.

Quality of the evidence

None of the included studies provided any information about allocation concealment. Patients and investigators could not be blinded and there were no information about blinding of either the outcome or data assessors in these studies. There were missing patients during the follow-up of all studies but the reasons were not reported. Thus, intention-to-treat was not used to analyse the outcome results. Two studies were supported by the medical device companies (Albala 2001; Pearle 2005). These factors limited the methodological strength of the evidence.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to support the use of ESWL for removing stones from the kidney. This review has shown that for treating lower pole kidney stones, PCNL had a significantly higher success rate in terms of stone-free kidneys than ESWL. The success of RIRS did not differ significantly from ESWL. However, the use of ESWL resulted in less time in hospital and shorter treatment duration when compared to PCNL or RIRS.

Implications for research

Larger RCTs with good methodology comparing ESWL and PCNL or RIRS for kidney stone management are required to evaluate effectiveness and complications, and to determine which modality is more effective for kidney stones. Studies should have standardised outcome measurements including data on quality of life and health economics.

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- * Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Albala 2001

Methods	- Country: USA - Setting: multicentre (18 institutions) - Design: Parallel RCT - Time frame: 3 months (initial results) - Intention-to-treat: Not performed - Follow-up period: 3 months after treatment - Loss to follow-up (at 3 months after treatment): 16.4% (21/128)
Participants	Inclusion criteria: - Patients older than 18 years - Stone burden $\leq$ 30 mm in aggregate diameter - Lower pole stones only - Patients agreeable to randomisation between shock wave lithotripsy and percutaneous stone removal ESWL group - Number: 68 - Age: NS - Sex(M/F): NS - Mean stone size: 13.59 mm PCNL group - Number: 60 - Age: NS - Sex(M/F): NS - Mean stone size: 14.43 mm Exclusion criteria - Ureteropelvic junction obstruction - Caliceal diverticulum - Infundibular stenosis - Shock wave lithotripsy or percutaneous stone removal complicated or not feasible due to body size or habitus, coagulopathy - Stones in renal pelvis, ureter, or mid or upper pole calices - Renal insufficiency with SCr > 3.0 mg/dL - Cystinuria - Kidney transplant - Patients undergoing simultaneous bilateral stone procedures - Pregnancy
Interventions	ESWL - Lithotriptors represented and used according to recognized standards - Modified and unmodified Dornier HM3 (Dornier Medical Systems) - Dornier MFL 5000 (Dornier Medical Systems) - Lithostar (Siemens Medical Systems) - Lithostar Shock Tube C (Siemens Medical Systems) - Medstone STS (Medstone International Inc., Aliso Viejo, California)

	○ Direx Tripter Compact (Direx) ○ Dornier HM4 (Dornier Medical Systems) ○ Storz Modulith (Storz Medical, Kreuzlingen, Switzerland) 2. Treatment goal of ESWL was to achieve fragments ≤ 3 mm in diameter 3. Ureteral stenting for stones between 15 and 25 mm was left to the discretion of the investigator. PCNL ● Most PCNL performed a single stage procedure in the operation ● One centre used 2 stage procedure	
Outcomes	Primary 1. Stone-free rate (for ESWL was stone fragments ≤ 3 mm) ○ Overall ○ According to stone size (1-10, 11-20 and 21-30 mm) 2. Re-treatment rate 3. Auxiliary procedure 4. EQ Secondary 1. Hospital stay 2. Complications 3. Stone burden 4. Stone composition 5. Quality of life	
Notes	Funding: Supported by a grant from Microvasive Exclusion post randomisation but pre-intervention ● Withdrew after randomisation (21) ● Stone moved or passed before surgery (7) ● Violated protocol (4) Completeness of follow-up ● Patients randomised: 160 ● Enrolled: 128 (ESWL (68), PCNL (60)) ● Analysed: 107 (ESWL (52), PCNL (55)) ● Follow-up at 3 months: 88% (107/121)	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomised schedule for each site and stratified by stone size (1-10, 11-20 and 21-30 mm)
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Not feasible to be blinded to participants or investigators. No blinding information of outcomes assessors or data assessors

Albala 2001 (Continued)

Incomplete outcome data addressed? All outcomes	No	There were patients lost to follow-up after interventions
Free of selective reporting?	Yes	The expected outcomes were reported according to the objectives
Free of other bias?	No	Funding: Supported by a grant from Microvasive

Carlsson 1992

Methods	- Country: Sweden - Setting: Karolinska Hospital and Linköping University Hospital - Design: Parallel - Time frame: 1 year - Intention-to-treat: Not performed - Follow-up period: 4 months and 1 year after treatment - Loss to follow-up 9 patients at 4 weeks: ESWL (3), PCNL (6) 4 patients at one year: ESWL (2), PCNL (2)
Participants	Inclusion criteria - Patients with stones of 4-30 mm in diameter - Patients eligible for either ESWL or PCNL ESWL group - Number: 28 - Age: 49.0 years - Sex (M/F): 20/8 - Mean number of stones/patient: 3.4 - Mean size of largest stone: 13 mm (range 5-27 mm) PCNL group - Number: 21 - Age: 48.2 years - Sex(M/F): 12/9 - Mean number of stones/patient: 2.8 - Mean size of largest stone: 12 mm (range 7-25 mm) Exclusions: NS
Interventions	ESWL - Unmodified Dornier HM-3 lithotripter PCNL - Done under epidural anaesthesia in the department of diagnostic radiology with the collaboration of a radiologist and a urologist - Nephrostomy was made with the patient in prone, and the track was dilated to 27 French scale. - Nephroscope was introduced and the stone was usually extracted with forceps under fluoroscopic control. - Ultrasonic disintegration was used for stones > 15 mm.

	Nelaton catheter 20 French scale was used for nephrostomy, often with a coaxial pigtail catheter to keep it in place.	
Outcomes	Primary - Success rate (stone-free or fragments ≤ 5 mm) - Four weeks - One year Secondary - Hospital stay - Duration of treatment - Complications	
Notes	Funding: NS Exclusion post randomisation but pre-intervention - ESWL group: 2 were excluded (pregnancy (1), malignant disease (1)) - PCNL group: 4 did not have operation (passed their stones naturally (2), moved to another area (1), preferred to have ESWL (1)) Completeness of follow-up 55 consecutive patients from one single hospital, the Karolinska Hospital, Stockholm, met the inclusion criteria (25 were randomised to have PCNL at the Karolinska Hospital and 30 have ESWL at Linköping University Hospital) - Patients treated: 49 (ESWL (28), PCNL (21)) - Stone-free status 4 weeks: ESWL (25), PCNL (15) 1 year: ESWL (26), PCNL (19) - Follow-up at 4 weeks and 1 year were 81.6% (40/49) and 91.8% (45/49) respectively	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information of sequence generation
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Not feasible to blind participants or investigators. Blinding of outcomes assessors and data assessors not stated
Incomplete outcome data addressed? All outcomes	No	There were patients lost of follow-up after interventions
Free of selective reporting?	Yes	The expected outcomes were reported according to the objectiveness.
Free of other bias?	Unclear	No information on funding

Methods	- Country: USA - Setting: multi-centre (19 institutions) - Design: Parallel - Time frame: NS - Intention-to-treat: Not performed - Follow-up period - Initial follow-up: 2-6 weeks after treatment documented re-treatments, secondary procedures and complications - Stone-free status: 3 months after treatment - Loss to follow-up: 13.4% (9/67) at 3 months
Participants	Inclusion criteria - Adult patients with isolated, ≤ 1 cm lower pole stones ESWL group - Number: 32 - Mean age $\pm$ SD: 52.5 ± 12.3 years - Sex(M/F): 19/13 - Body mass index $\pm$ SD: 26.9 ± 8.1 - No. rt/lr stones: 11/21 - Mean stone surface area $\pm$ SD: 42.2 ± 21.2 mm² RIRS group - Number: 35 - Mean age $\pm$ SD: 49.3 ± 14.2 years - Sex(M/F): 17/18 - Body mass index $\pm$ SD: 28.1 ± 6.6 - No. rt/lr stones: 14/21 - Mean stone surface area $\pm$ SD: 35.9 ± 18.4 mm² Exclusions criteria - Same size non lower pole stones - Ureteral stricture or ureteropelvic junction obstruction - Infundibular stenosis or caliceal diverticulum associated with target stone - A transplant, pelvic or solitary kidney - Kidney insufficiency (SCr > 3.0 mg/dL) - Pregnancy - Previous failed treatment - Cystinuria - Urinary diversion - Impassable urethral stricture - Planned simultaneous treatment of contralateral stones - Active urinary tract infection or an immunocompromised state
Interventions	ESWL - Lithotriptors used in study with recognized standards for each machine - Doli-S (Dornier Medtech, Kennesaw, Georgia) - HM3 (Dornier) - MFL-5000 (Dornier) - LithoTron - Lithostar - Lithostar Plus - Modulith

	○ Econolith ○ Medstone STS 2. Power settings and number of shock wave administered were left to the discretion of the treating physician with the intent of achieving a fragment size ≤ 3 mm. RIRS 1. A variety of ureteroscopes were used, including ○ 7.5 Fr and Flex-X™ (Karl Storz Endoscopy-America, Culver, California) ○ ACMI Dur 8™ and Dur 8-Elite™ (ACMI, Southborough, Massachusetts) ○ URF-P3 (Olympus, Melville, New York) 2. Dilatation of the intramural ureter was performed as needed. 3. Use of a ureteral access sheath, intact stone retrieval versus intracorporeal lithotripsy and stent placement were left to investigator discretion	
Outcomes	Primary 1. Success rate (stone-free or fragments < 4 mm) Secondary 1. Re-treatment 2. Hospital stay (days) 3. Operating time (min) 4. Complications ○ Intraoperative complications ○ Postoperative complications	
Notes	Exclusion post randomisation but pre-intervention ● Dropped out of the study before treatment: 11 Completeness of follow-up ● Patients randomised: 78 ● Treated on protocol: 67 (ESWL (32), URS (35)) ● Analysed at the end of 3rd month: 58 (ESWL (26), URS (32)) ● Follow-up at the end of 3rd month: 86.6% (58/67) Outcomes ● Re-treatment ○ 5 ESWL patients: ESWL in 2, RIRS in 1 for target stone treatment and RIRS in 2 for obstructing ureteral fragments ○ 2 URS patients: RIRS in 1 for target stone treatment and 1 underwent RIRS for an obstructing fragment	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Using blocks of 10 according to a random number table
Allocation concealment?	Unclear	No stated
Blinding? All outcomes	Unclear	Not feasible to blind participants or investigators. Blinding of outcomes assessors and data assessors not stated

Pearle 2005 (Continued)

Incomplete outcome data addressed? All outcomes	No	There were patients lost of follow-up after interventions.
Free of selective reporting?	Yes	The expected outcomes were reported according to the objectiveness.
Free of other bias?	No	Funding: Supported by Boston Scientific

EQ - efficiency quotient; ESWL - extracorporeal shock wave lithotripsy; NS - not stated; PCNL - percutaneous nephrolithotomy; RIRS - retrograde intrarenal surgery; SCr - serum creatinine

Characteristics of excluded studies [ordered by study ID]

Carr 1996	Not RCT or quasi-RCT for the allocation of the treatments between ESWL and PCNL.
Charig 1986	Time-series treatments among open surgery, PCNL, and ESWL.
Eterovic 2005	Not RCT or quasi-RCT for the allocation of the treatments between ESWL and PCNL.
Liou 2001	Not RCT or quasi-RCT for the allocation of the treatments between ESWL and PCNL.
Mays 1988	Not RCT or quasi-RCT for the allocation of the treatments between ESWL and PCNL.
Menon 1993	Editorial comment.
Turna 2007	Not RCT or quasi-RCT for the allocation of the treatments between ESWL and PCNL.
You 2006	Not RCT or quasi-RCT for the allocation of the treatments between ESWL and PCNL.

DATA AND ANALYSES

Comparison 1. ESWL versus PCNL

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Success of treatment	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Success at 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.2 Success at 3 months	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.3 Success at 1 year	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.4 Success at 3 months according to stone size (1-10 mm)	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.5 Success at 3 months according to stone size 11-20 mm)	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.6 Success at 3 months according to stone size 21-30 mm)	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2 Re-treatment	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Overall re-treatment	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.2 Re-treatment according to stone size (1-10 mm)	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.3 Re-treatment according to stone size (11-20 mm)	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.4 Re-treatment according to stone size (21-30 mm)	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
3 Auxiliary procedures	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Overall auxiliary procedures	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.2 Auxiliary procedures according to stone size (1-10 mm)	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.3 Auxiliary procedures according to stone size (11-20 mm)	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.4 Auxiliary procedures according to stone size (21-30 mm)	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
4 Procedural and operating time (minutes)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Hospital stay (days)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Comparison 2. ESWL versus RIRS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Success of treatment	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Success at 3 months	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2 Procedural and operating time (minutes)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 ESWL versus PCNL, Outcome 1 Success of treatment.

Review: Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones

Comparison: 1 ESWL versus PCNL

Outcome: 1 Success of treatment

Study or subgroup	ESWL n/N	PCNL n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Success at 4 weeks Carlsson 1992	19/25	15/15		0.77 [0.61, 0.98]
2 Success at 3 months Albala 2001	19/52	52/55		0.39 [0.27, 0.56]
3 Success at 1 year Carlsson 1992	20/26	18/19		0.81 [0.64, 1.03]
4 Success at 3 months according to stone size (1-10 mm) Albala 2001	12/19	20/20		0.64 [0.45, 0.90]
5 Success at 3 months according to stone size 11-20 mm) Albala 2001	6/26	26/28		0.25 [0.12, 0.51]
6 Success at 3 months according to stone size 21-30 mm) Albala 2001	1/7	6/7		0.17 [0.03, 1.05]

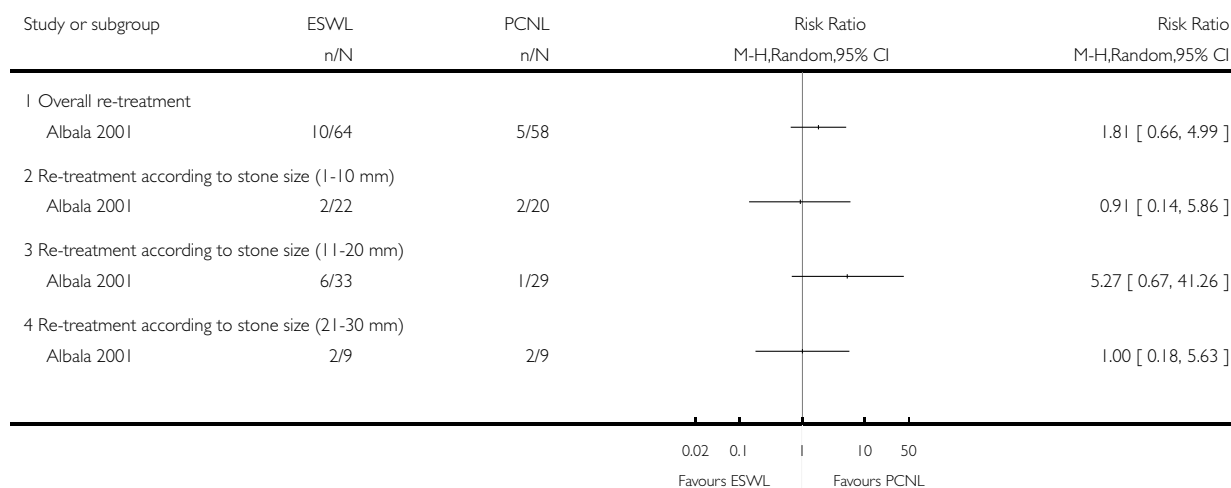
0.02 0.1 1 10 50
Favours PCNL Favours ESWL

Analysis 1.2. Comparison 1 ESWL versus PCNL, Outcome 2 Re-treatment.

Review: Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones

Comparison: 1 ESWL versus PCNL

Outcome: 2 Re-treatment

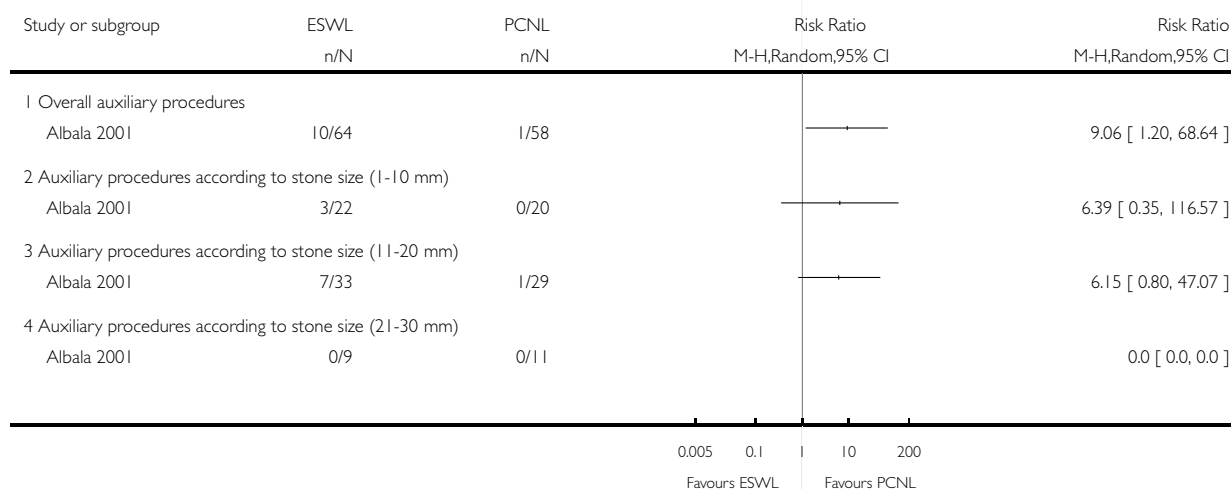


Analysis 1.3. Comparison 1 ESWL versus PCNL, Outcome 3 Auxiliary procedures.

Review: Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones

Comparison: 1 ESWL versus PCNL

Outcome: 3 Auxiliary procedures

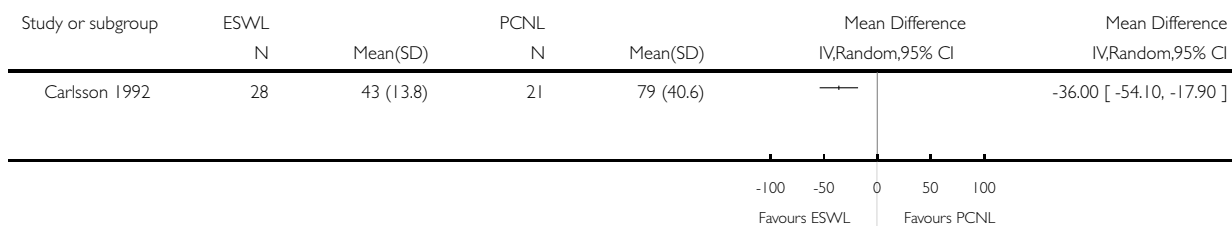


Analysis 1.4. Comparison 1 ESWL versus PCNL, Outcome 4 Procedural and operating time (minutes).

Review: Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones

Comparison: 1 ESWL versus PCNL

Outcome: 4 Procedural and operating time (minutes)

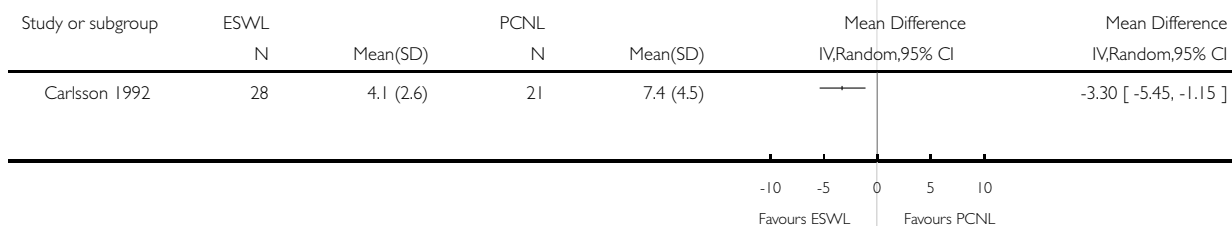


Analysis 1.5. Comparison 1 ESWL versus PCNL, Outcome 5 Hospital stay (days).

Review: Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones

Comparison: 1 ESWL versus PCNL

Outcome: 5 Hospital stay (days)

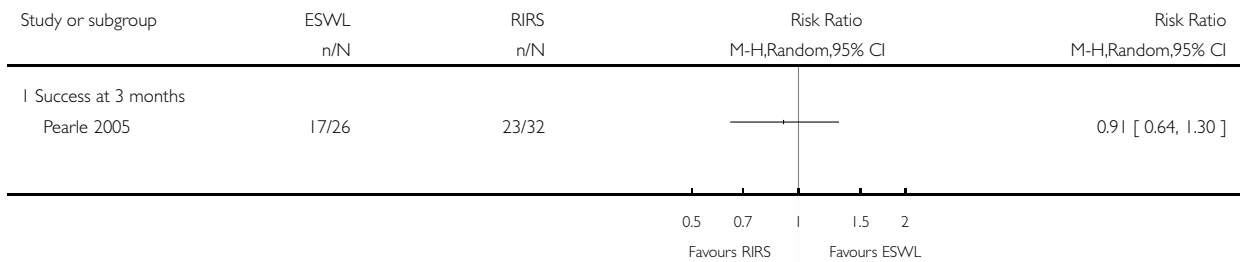


Analysis 2.1. Comparison 2 ESWL versus RIRS, Outcome 1 Success of treatment.

Review: Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones

Comparison: 2 ESWL versus RIRS

Outcome: 1 Success of treatment

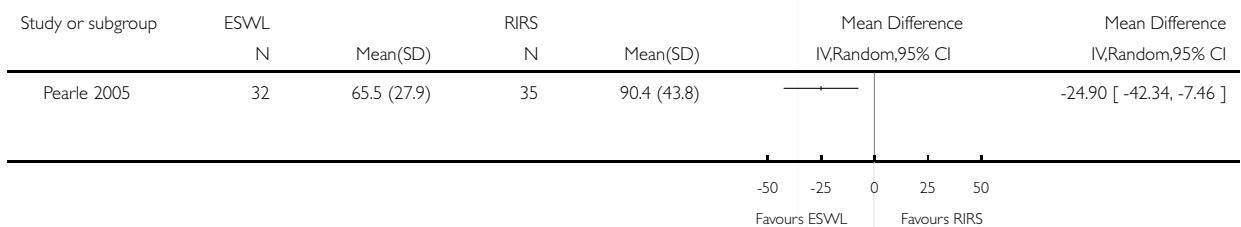


Analysis 2.2. Comparison 2 ESWL versus RIRS, Outcome 2 Procedural and operating time (minutes).

Review: Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones

Comparison: 2 ESWL versus RIRS

Outcome: 2 Procedural and operating time (minutes)



APPENDICES

Appendix I. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor Lithotripsy, this term only 2. (eswl or swl):ti,ab,kw in Clinical Trials 3. shockwave lithotrip*:ti,ab,kw in Clinical Trials 4. extracorporeal shockwave lithotrip*:ti,ab,kw in Clinical Trials 5. electrohydraulic shockwave lithotrip*:ti,ab,kw in Clinical Trials 6. ultrasonic lithotrip*:ti,ab,kw in Clinical Trials 7. (retrograde intrarenal surgery):ti,ab,kw in Clinical Trials 8. rirs:ti,ab,kw in Clinical Trials 9. MeSH descriptor Nephrostomy, Percutaneous, this term only 10. pcnl:ti,ab,kw in Clinical Trials 11. percutaneous nephrolithotom*:ti,ab,kw in Clinical Trials 12. percutaneous nephrolithotrip*:ti,ab,kw in Clinical Trials 13. flexible ureteroscop*:ti,ab,kw in Clinical Trials 14. endorenal surgery:ti,ab,kw in Clinical Trials 15. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14) 16. MeSH descriptor Urolithiasis explode all trees 17. (kidney* AND (stone* OR calcul*)):ti,ab,kw in Clinical Trials 18. (urin* AND (stone* OR calcul*)):ti,ab,kw in Clinical Trials 19. nephrolithiasis:ti,ab,kw in Clinical Trials 20. (#16 OR #17 OR #18 OR #19) 21. (#15 AND #20)
MEDLINE	1. Lithotripsy/ 2. (eswl or swl).tw. 3. shockwave lithotrip\$.tw. 4. extracorporeal shockwave lithotrip\$.tw. 5. electrohydraulic shockwave lithotrip\$.tw. 6. ultrasonic lithotrip\$.tw. 7. Nephrostomy, Percutaneous/ 8. percutaneous nephrolithotom\$.tw. 9. percutaneous nephrolithotrip\$.tw. 10. endorenal surgery.tw. 11. pcnl.tw. 12. retrograde intrarenal surgery.tw. 13. flexible ureteroscop\$.tw. 14. rirs.tw. 15. or/1-14 16. exp Urolithiasis/ 17. urinary lithiasis.tw. 18. (kidney\$ and (stone\$ or calcul\$)).tw. 19. (urin\$ and (stone\$ or calcul\$)).tw. 20. nephrolithiasis.tw. 21. or/16-20

(Continued)

	22. and/16,21
EMBASE	1. LITHOTRIPSY/ 2. extracorporeal lithotripsy/ 3. ultrasonic lithotripsy/ 4. (eswl or swl).tw. 5. extracorporeal shockwave lithotrip\$.tw. 6. electrohydraulic shockwave lithotrip\$.tw. 7. ultrasonic lithotrip\$.tw. 8. Percutaneous Nephrolithotomy/ 9. percutaneous nephrolithotom\$.tw. 10. percutaneous nephrolithotrip\$.tw. 11. pcnl.tw. 12. retrograde intrarenal surgery.tw. 13. rirs.tw. 14. flexible ureteroscopy\$.tw. 15. endorenal surgery.tw. 16. or/1-15 17. exp Urolithiasis/ 18. urolithiasis.tw. 19. urinary lithiasis.tw. 20. ureterolithiasis.tw. 21. (kidney\$ and (stone\$ or calcul\$)).tw. 22. (urin\$ and (stone\$ or calcul\$)).tw. 23. nephrolithiasis.tw. 24. or/17-23 25. and/16,24

Appendix 2. Quality assessment checklist

Sequence generation

- Yes: Randomisation method presented such as random number table, computer random number generator.
- Unclear: Randomisation stated but no information on method used was available.
- No: Method of randomisation used such as date of birth, day of visit, ID or record number, alternate allocation.

Allocation concealment

- Yes: Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study.
- Unclear: Randomisation stated but no information that investigator/participant could not influence intervention group.
- No: Method of randomisation used such as alternate medical record numbers or unsealed envelopes; any information in the study that indicated that investigators or participants could influence intervention group.

Blinding

- Blinding of outcome assessor: Yes/unclear/no.
- Blinding of data analysis: Yes/unclear/no.

Completeness of follow-up

- Per cent of participants excluded or lost to follow-up.

Selective reporting

- Free of selective reporting: Yes/unclear/No

HISTORY

Protocol first published: Issue 2, 2008

Review first published: Issue 4, 2009

CONTRIBUTIONS OF AUTHORS

- Writing of protocol and review: AS, SP, BL, VS, ML
- Screening of titles and abstracts: AS, SP, VS
- Assessment for inclusion: BL, VS
- Risk of bias assessment: AS, SP
- Data extraction: AS, SP
- Data entry into RevMan: ML
- Data analysis: ML

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Department of Medical Services, Ministry of Public Health, Thailand.
- Faculty of Medicine, Chiangmai University, Thailand.
- Department of Surgery, Lerdsin Hospital, Thailand.
- Faculty of Public Health, Khon Kaen University, Thailand.

External sources

- Thailand Research Fund (Senior Research Scholar), Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

With the introduction of RevMan 5 and the new risk of bias assessment criteria, the quality items that we assessed were different from those stated in the protocol. Sequence generation, allocation concealment, blinding, completeness of follow-up and selective reporting were used to assess study quality.

INDEX TERMS

Medical Subject Headings (MeSH)

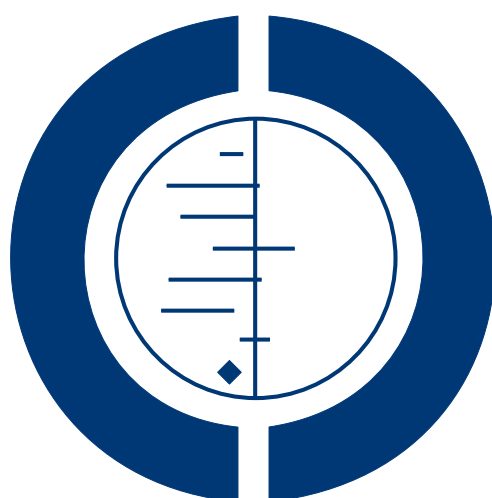
*Lithotripsy; *Nephrostomy, Percutaneous; Kidney Calculi [surgery; *therapy]; Randomized Controlled Trials as Topic; Ureteroscopy

MeSH check words

Humans

Epidural blood patching for preventing and treating post-dural puncture headache (Review)

Boonmak P, Boonmak S



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[Intervention Review]

Epidural blood patching for preventing and treating post-dural puncture headache

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ABSTRACT

Background

This is an update of a Cochrane Review first published in Issue 2, 2002. Dural puncture is a common procedure, but leakage of cerebrospinal fluid (CSF) from the resulting dural defect may cause post-dural puncture headache (PDPH) after the procedure, and this can be disabling. Injecting an epidural blood patch around the site of the defect may stop this leakage.

Objectives

To assess the possible benefits and harms of epidural blood patching in both prevention and treatment of PDPH.

Search strategy

We searched the Cochrane PaPaS Group Trials Register; CENTRAL; MEDLINE and EMBASE in April 2009.

Selection criteria

We sought all randomised controlled trials (RCTs) that compared epidural blood patch versus no epidural blood patch in the prevention or treatment of PDPH among all types of participants undergoing dural puncture for any reason. The primary outcome of effectiveness was postural headache.

Data collection and analysis

One review author extracted details of trial methodology and outcome data from studies considered eligible for inclusion. We invited authors of all such studies to provide any details that were unavailable in the published reports. We performed intention-to-treat (ITT) analyses using the Peto O-E method. We also extracted information about adverse effects (post-dural puncture backache and epidural infection).

Main results

Nine studies (379 participants) were eligible for inclusion. Prophylactic epidural blood patch improved PDPH compared to no treatment (OR 0.11, 95% CI 0.02 to 0.64, one study), conservative treatment (OR 0.06, 95% CI 0.03 to 0.14, two studies) and epidural saline patch (OR 0.16, 95% CI 0.04 to 0.55, one study). However, prophylactic epidural blood patch did not result in less PDPH than a sham procedure (one study). Therapeutic epidural blood patch resulted in less PDPH than conservative treatment (OR 0.18, 95% CI 0.04 to 0.76, one study) and a sham procedure (OR 0.04, 95% CI 0.00 to 0.39, one study). Backache was more common with epidural blood patch. However, these studies had very small numbers of participants and outcome events, as well as uncertainties about trial methodology, which preclude reliable assessments of the potential benefits and harms of the intervention.

Authors' conclusions

The review authors do not recommend prophylactic epidural blood patch over other treatments because there are too few trial participants to allow reliable conclusions to be drawn. However, therapeutic epidural blood patch showed a benefit over conservative treatment, based on the limited available evidence.

PLAIN LANGUAGE SUMMARY

Epidural blood patching for preventing and treating post-dural puncture headache

The role of epidural blood patching in the prevention or treatment of the headache that may follow dural puncture (usually lumbar puncture) is inconclusive. Dural puncture involves passing a needle into the fluid-filled space around the spinal cord and nerve roots. This procedure is used to obtain spinal fluid for laboratory tests or to give a spinal anaesthetic. However, leakage of fluid through the puncture created by the needle can cause headache. One suggestion for preventing or treating this headache is to inject some of the patient's own blood around the puncture to stop the leakage (epidural blood patch). However, this review showed that, according to current evidence, clear conclusions cannot be drawn about the advantage of preventative epidural blood patch over other treatments. The use of epidural blood patch after the onset of the headache, however, showed benefit over conservative treatment. There were too few participants in the included studies, however, to allow a reliable assessment of the potential benefits and harms of this technique.

BACKGROUND

This is an update of a Cochrane Review first published in Issue 2, 2002. Dural puncture (usually lumbar puncture) involves passing a needle through the dura mater into the cerebrospinal fluid (CSF)-filled subarachnoid space around the spinal cord, roots or both. The procedure may be performed:

1. for diagnostic purposes, to measure the CSF pressure or withdraw a CSF sample for laboratory analysis, or both;
2. for therapeutic purposes, to administer intrathecal chemotherapy;
3. in spinal anaesthesia, to introduce an anaesthetic agent (or agents) through the needle into the subarachnoid space;
4. inadvertently during epidural anaesthesia; and
5. in myelography, to instil radio-opaque material into the subarachnoid space prior to radiologic imaging.

Dural puncture is therefore a common procedure. Fortunately, serious, potentially life-threatening complications associated with the treatment, including spinal abscess or meningitis, subdural haematoma and cerebellar tonsillar herniation, are very rare (Evans 1998; van Crevel 2002; Domenicucci 2005; Horlocker 2008; Williams 2008). Headache following dural puncture is, however, much more common. Reported estimates of its frequency vary widely, from less than 1% to over 80%, depending on the types of patients studied, associated procedures such as the introduction of

anaesthetic or radio-opaque material into the CSF, the definition of headache, and the method of follow up used (Turnbull 2003; Kuczkowski 2004; Ahmed 2006; Gaiser 2006; Simmons 2007; Reamy 2009). Post-dural puncture headache (PDPH) is classically postural in nature (i.e. worse on standing and improved by lying flat), and may be accompanied by nausea, vomiting, tinnitus and hearing impairment. The symptoms are thought to be due to leakage of CSF through the dural defect produced by the dural puncture, causing a reduction in CSF pressure and downward traction on the pain-sensitive intracranial veins and meninges, as well as the cranial nerves (Turnbull 2003; Gaiser 2006). Provided the patient stands up, the headache usually occurs within 48 hours of the procedure and resolves spontaneously within a few days. However, symptoms can last for a week or more, and may interfere with activities of daily living, causing disability and necessitating time off work (Tohmo 1998). If severe, the headache may necessitate hospital admission or readmission. Obstetric patients who suffer accidental dural puncture during epidural anaesthesia appear to be particularly at risk, in part because large diameter (usually 16 or 18 gauge) needles tend to be used for the procedure and so leave a larger defect if the dura is accidentally breached. Leakage of CSF may be exaggerated by rises in intra-abdominal pressure during labour (Reynolds1993; Kuczkowski 2004; Kuczkowski 2007; Simmons 2007; Thew 2008).

Both dural puncture and PDPH are common, therefore simple measures to reduce the occurrence of headache, and to reduce or abolish the symptoms should they occur, are well worth identify-

ing. One such measure, the technique of epidural blood patching, is increasingly used in managing patients with persistent PDPH, as well as for its prevention. This involves the epidural injection of around 7.5 to 30 ml of autologous blood into the extradural space around the site where the dural puncture was performed (Turnbull 2003; Gaiser 2006; Thew 2008). Coagulation of the blood is thought to stop the leakage of CSF from the dural defect resulting from dural puncture. High success rates have established the epidural blood patch as the method of choice for the treatment of severe post-dural puncture headache (Turnbull 2003; Thew 2008). However, such 'success' rates cannot necessarily be attributed to the effects of blood patching because PDPH tends to resolve spontaneously in any case. Furthermore, there is a potential risk of epidural infection with epidural blood patching, and the procedure may also be associated with backache and lower limb paraesthesia (Candido 2003; Turnbull 2003; Gaiser 2006; Thew 2008). Randomised evidence is necessary to establish whether the apparent success of this technique is real, and whether the benefits outweigh the risks. As far as we are aware, the technique has never been reviewed systematically. This review therefore addresses the effectiveness of epidural blood patching for the prevention and treatment of PDPH.

OBJECTIVES

We aimed to assess the effectiveness of epidural blood patch in the prevention and treatment of post-dural puncture headache (PDPH) in patients who were undergoing dural puncture for any reason. We also aimed to assess the possibility of harm from this intervention, in particular any excess risk of infection, backache and lower limb paraesthesia.

METHODS

Criteria for considering studies for this review

Types of studies

We aimed to include only properly randomised controlled trials (RCTs), using a method of treatment allocation that precluded foreknowledge of the trial arm to which any participant would be assigned.

Types of participants

We included studies involving participants of any age and either sex.

Types of interventions

We included epidural blood patch versus no blood patch for the prevention (performed immediately after dural puncture) or treatment of post-dural puncture headache (PDPH).

Types of outcome measures

Primary outcomes

Our primary outcome was PDPH (headache after dural puncture that improves on lying flat) of any severity.

Secondary outcomes

Our secondary outcomes were severe PDPH (according to each trialist's definition of severe), all headache, backache and adverse effects of epidural blood patching.

Search methods for identification of studies

Electronic searches

For the original version of this review we searched the Cochrane Controlled Trials Register (*The Cochrane Library* 2000, Issue 4); MEDLINE (1994 to December 1998) and EMBASE (1980 to December 1998). For this updated review, we searched the Cochrane Pain, Palliative and Supportive Care (PaPaS) Group Trials Register (April 2009); the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, Issue 1); MEDLINE (1950 to April 2009) and EMBASE (1980 to April 2009). We developed a specific strategy for each database based on that developed for CENTRAL (Appendix 1). Please also see: Appendix 2 (MEDLINE); Appendix 3 (EMBASE); and Appendix 4 (PaPaS Trials Register).

Searching other resources

We searched the reference lists of all studies and review articles identified by electronic searching, and asked for information about any potentially relevant studies when we contacted trialists from the studies identified.

Data collection and analysis

Selection of studies

Two review authors (PB and SB) independently reviewed titles and abstracts identified from the literature searches for relevant studies

and selected possibly relevant studies. We reviewed these studies using the full text and assessed them using the inclusion criteria detailed above. We (PB and SB) resolved any disagreement by consensus or, if necessary, by consulting a third review author (CW and CS). If we were not able to resolve differences then we intended to add the publication reference to those awaiting assessment and attempt to contact the study authors for clarification.

Data extraction and management

We used a data extraction form to obtain data from individual studies. This was performed by two review authors (PB and SB). We studied the reports of all possibly relevant trials identified and used a specially designed form to extract information on methods of randomisation and blinding, the comparison(s) of interest, the number of participants originally randomised in each arm of the study, any losses to follow up and the occurrence in each arm of the outcomes of interest. For all studies that fulfilled (or that might fulfil) the inclusion criteria (above), we attempted to contact the principal trialist (or, if necessary, one of the other authors) and asked them to check the information and data extracted and to provide any missing information that was available to them but not included in the trial report. We recorded the main reason (or reasons) for the exclusion of any potentially relevant studies, whether based on information extracted from published trial reports or received from trialists. Following data extraction, we performed double data entry and screened the database for inconsistencies as a quality assurance measure.

Assessment of risk of bias in included studies

A study was defined as: A (low risk of bias, all quality criteria met); B (moderate risk of bias, one or more of the quality criteria only partly met); and C (high risk of bias, one or more criteria not met). Any conflicts would be assessed through discussion and, if necessary, through evaluation by a third review author (CW and CS).

Data synthesis

We analysed the two questions (the role of epidural blood patching for the prevention, and for the treatment, of PDPH) separately using Review Manager (RevMan 5.0). We performed analysis on an intention-to-treat (ITT) basis, i.e. all participants randomised remained in their original trial arm, whether or not they had actually received the intervention allocated. In the main analyses we assumed that any patient lost to follow up did not experience the outcome being considered. Individual trial results and summary results for each outcome from a particular comparison were expressed as odds ratios (OR), calculated using the Peto O-E method.

Sensitivity analysis

We performed sensitivity analyses for missing data and study quality. Several sensitivity analyses were formulated *a priori*.

1. Where randomisation was mentioned but the method of treatment allocation remained unclear, even after contact with the trialists, we planned, where possible, to examine the effect on the primary outcome of excluding any such trials, and therefore of including only those studies that had used a method that should definitely ensure truly random treatment allocation.

2. Lack of blinding of patients or observers assessing patient outcomes may seriously bias trial results, particularly when the outcome is a subjective one, such as headache (Schulz 1995). For adequate patient blinding it was necessary for the trial participants to be unaware of their treatment allocation. In trials assessing epidural blood patch for the treatment of PDPH, this meant that patients allocated to the control group had to have undergone a sham procedure without epidural injection of blood. For adequate observer blinding we required someone other than the person performing the blood patch or sham procedure (who must inevitably be aware of the method being used) to have collected the outcome information. We aimed to examine the effect on the primary outcome of excluding trials with inadequate blinding of either trial participants or observers (or both) to the allocated intervention.

3. Bias in the results may also occur when follow up of all patients initially randomised is incomplete. To assess the robustness of our results to losses to follow up, we planned to adopt a 'penalty' system for each comparison. This would assess the effect on the summary result for the primary outcome of assuming that all patients lost to follow up in the arm which appeared superior had experienced the outcome, and all patients lost to follow up in the arm which appeared inferior had remained free of the outcome.

RESULTS

Description of studies

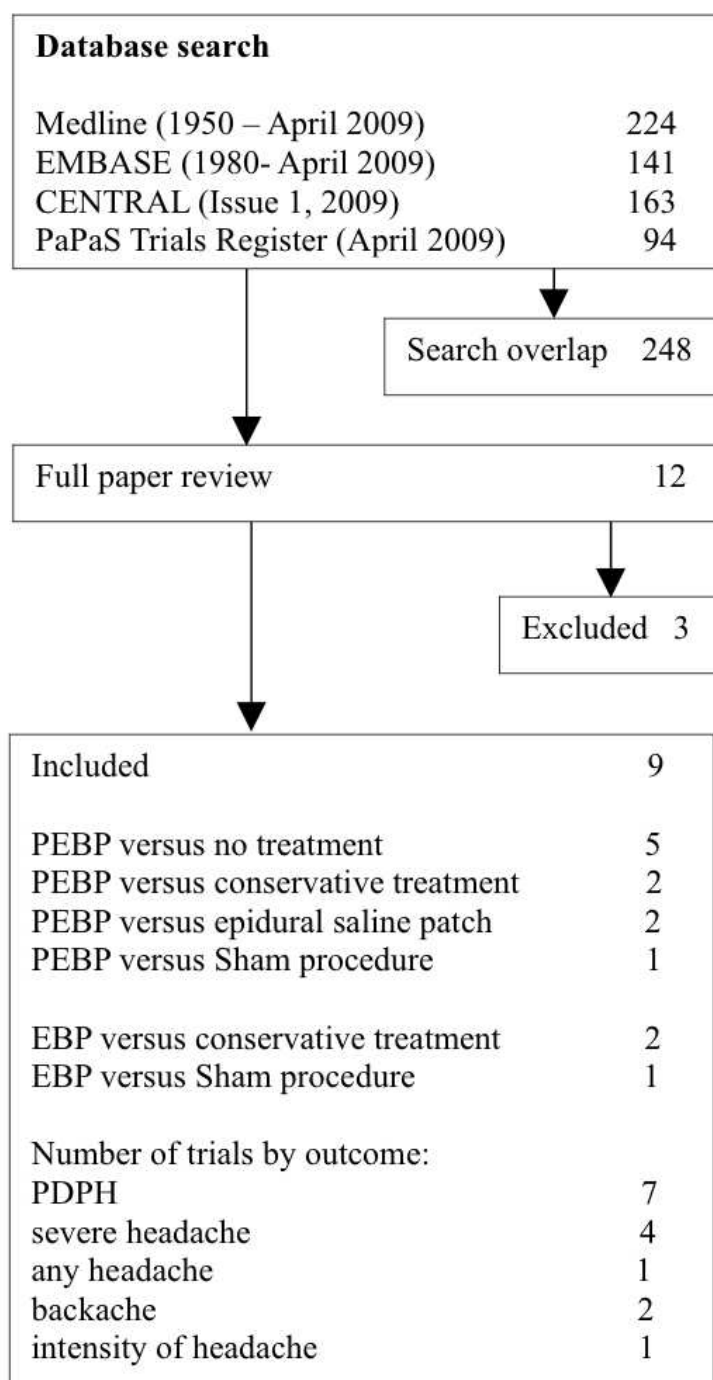
See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

Searching all databases up to April 2009 identified 12 studies including those included for the first version of this review (Ackerman 1989; Seebacher 1989; Trivedi 1993) (see Figure 1). We excluded three of these for the reasons described in the 'Characteristics of excluded studies' table. We identified a total nine studies for possible inclusion in the review (Ackerman 1989;

Colonna 1989; Lowenwirt 1998; Seebacher 1989; Sengupta 1989;
 Trivedi 1993; Scavone 2004; Sandesc 2005; van Kooten 2008).

Figure 1. Search results.



Included studies

Six additional studies were added to this update which added a further 302 participants. Nine studies were included in total for this update involving 379 participants (see 'Characteristics of included studies' table). [Ackerman 1989](#) compared prophylactic epidural blood patch versus no treatment among 21 participants. Three studies compared prophylactic epidural blood patch versus conservative treatment among 132 participants ([Colonna 1989](#); [Trivedi 1993](#); [Lowenwirt 1998](#)). [Sengupta 1989](#) compared prophylactic epidural blood patch versus epidural saline patch among 48 participants. [Scavone 2004](#) compared prophylactic epidural blood patch versus a sham procedure among 64 participants. Two studies compared blood patch versus conservative treatment in 72 participants ([Sandesc 2005](#); [van Kooten 2008](#)). [Seebacher 1989](#) compared epidural blood patch versus a sham procedure in 12 partic-

ipants. We attempted to contact the principal trialist ([Ackerman 1989](#); [Seebacher 1989](#); [Trivedi 1993](#)) of the included studies but were able to obtain additional information from only one study ([Seebacher 1989](#)).

Excluded studies

We excluded three studies (see the 'Characteristics of excluded studies' table). [Heide 1990](#) and [Safa-Tisseront 2001](#) were both non-randomised trials. [Loeser 1978](#) did not include the comparison of interest.

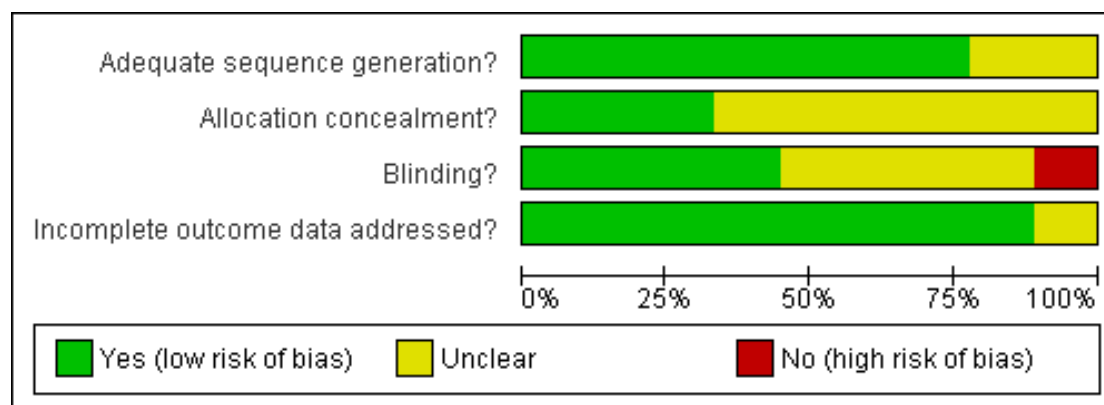
Risk of bias in included studies

Please see [Figure 2](#) and [Figure 3](#) for our assessment of the risk of bias in the included studies.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?
Ackerman 1989	?	?	?	+
Colonna 1989	+	?	?	+
Lowenwirt 1998	+	?	?	+
Sandesc 2005	+	?	?	+
Scavone 2004	+	+	+	+
Seebacher 1989	+	+	+	+
Sengupta 1989	+	?	-	+
Trivedi 1993	?	?	+	?
van Kooten 2008	+	+	+	+

Figure 3. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

Three of the reports of the studies that assessed the effects of prophylactic epidural blood patch had adequate sequence generation and allocation concealment (Seebacher 1989; Scavone 2004; van Kooten 2008). Six of the studies did not describe the allocation concealment (Ackerman 1989; Colonna 1989; Sengupta 1989; Trivedi 1993; Lowenwirt 1998; Sandesc 2005).

Blinding

Four of the studies that assessed the effects of prophylactic epidural blood patch had adequate assessor blinding (Seebacher 1989; Trivedi 1993; Scavone 2004; van Kooten 2008). In two of the studies (Ackerman 1989; Sandesc 2005) outcome assessment was blinded. Participants were not clearly blinded in Colonna 1989, Sengupta 1989 or Lowenwirt 1998.

Incomplete outcome data

Five studies (Ackerman 1989; Colonna 1989; Sengupta 1989; Trivedi 1993; Lowenwirt 1998) assessed the effects of prophylactic epidural blood patch but described no missing data. Since follow up was for one to two days only, it is unlikely that many participants would have been lost to follow up. Scavone 2004 reported the missing data in both groups. Three studies (Seebacher 1989; Sandesc 2005; van Kooten 2008) assessed the effect of epidural blood patch and reported no missing data.

Effects of interventions

Prophylactic epidural blood patch

Please see Analysis 1.1, Analysis 1.2, Analysis 1.3 and Analysis 1.4 for further information.

Post-dural puncture headache (PDPH)

One study (Ackerman 1989) showed a significant difference in post-dural puncture headache (PDPH) between the prophylactic epidural blood patch and no blood patch groups (OR 0.11, 95% CI 0.02 to 0.64, 21 participants, Analysis 1.1: subgroup 1).

Two studies (Colonna 1989; Lowenwirt 1998) showed a significant difference in PDPH between the prophylactic epidural blood patch and conservative treatment groups (OR 0.06, 95% CI 0.03 to 0.14, 88 participants, Analysis 1.1: subgroup 2).

One study (Sengupta 1989) showed a significant difference in PDPH between the prophylactic epidural blood patch and epidural saline patch groups (OR 0.16, 95% CI 0.04 to 0.55, 48 participants, Analysis 1.1: subgroup 3).

One study (Scavone 2004) showed no significant difference in PDPH between the prophylactic epidural blood patch and sham procedure groups (64 participants, Analysis 1.1: subgroup 4).

Severe post-dural puncture headache

One study (Ackerman 1989) showed no significant difference in severe PDPH between the prophylactic epidural blood patch and no blood patch groups (21 participants, Analysis 1.2: subgroup 1).

One study (Sengupta 1989) showed no significant difference in severe PDPH between the prophylactic epidural blood patch and epidural saline patch groups (48 participants, Analysis 1.2: subgroup 2).

One study (Scavone 2004) showed no significant difference in severe PDPH between the prophylactic epidural blood patch and sham procedure groups (64 participants, Analysis 1.2: subgroup 3).

Any headache

One study (Ackerman 1989) showed no significant difference in any headache between the prophylactic epidural blood patch and no blood patch groups (21 participants, Analysis 1.3: subgroup 1).

One study (Trivedi 1993) showed a significant difference in any headache between the prophylactic epidural blood patch and conservative treatment groups (OR 0.04, 95% CI 0.01 to 0.19, 44 participants, Analysis 1.3: subgroup 2).

One study (Trivedi 1993) showed a significant difference in any headache between the prophylactic epidural blood patch and epidural saline patch groups (OR 0.08, 95% CI 0.02 to 0.37, 50 participants, Analysis 1.3: subgroup 3).

One study (Scavone 2004) showed no significant difference in any headache between the prophylactic epidural blood patch and sham procedure groups (64 participants, Analysis 1.3: subgroup 4).

Backache

One study (Scavone 2004) showed no significant difference in headache between the prophylactic epidural blood patch and sham procedure groups (64 participants, Analysis 1.4).

Therapeutic epidural blood patch

Please see Analysis 2.1, Analysis 2.2, Analysis 2.3 and Analysis 2.4 for further information.

Post-dural puncture headache (PDPH)

One study (van Kooten 2008) showed a significant difference in PDPH between the therapeutic epidural blood patch and conservative treatment groups (OR 0.18, 95% CI 0.04 to 0.76, 40 participants, Analysis 2.1: subgroup 1).

One study (Seebacher 1989) showed a significant difference in PDPH between the therapeutic epidural blood patch and sham procedure groups (OR 0.04, 95% CI 0.00 to 0.39, 12 participants, Analysis 2.1: subgroup 2).

Severe post-dural puncture headache

One study (Seebacher 1989) showed a significant difference in severe PDPH between the therapeutic epidural blood patch and sham procedure groups (OR 0.03, 95% CI 0.00 to 0.22, 12 participants, Analysis 2.2).

Backache

One study (Seebacher 1989) showed a significant difference in backache between the therapeutic epidural blood patch and sham procedure groups (OR 23.17, 95% CI 2.57 to 208.60, 12 participants, Analysis 2.3).

Intensity of headache

One study (Sandesc 2005) showed a significant difference in intensity of headache between the therapeutic epidural blood patch and conservative treatment groups (MD -7.10, 95% CI -6.51 to -7.69, 32 participants, Analysis 2.4).

The small numbers of studies, patients and events included in these analyses meant that the planned sensitivity analyses could not be carried out.

DISCUSSION

Summary of main results

Prophylactic epidural blood patch decreased post-dural puncture headache (PDPH) compared to no treatment, conservative treatment and epidural saline patch. Severe PDPH was comparable between prophylactic epidural blood patch, no treatment and epidural saline patch groups. Prophylactic epidural blood patch resulted in less 'any headache' than conservative treatment and epidural saline patch. However, PDPH, severe PDPH, any headache and backache were comparable between prophylactic epidural blood patch and sham procedure groups. There were too few participants to draw reliable conclusions about the benefit of prophylactic epidural blood patch.

Therapeutic epidural blood patch decreased PDPH, severe PDPH and intensity of headache over a sham procedure. Epidural blood patch also decreased PDPH over conservative treatment. However, epidural blood patch resulted in more backache than a sham procedure. We could not draw clear conclusions because of too few studies.

Quality of the evidence

Five studies, with 221 participants, comparing prophylactic epidural blood patch with other treatment (Ackerman 1989; Colonna

1989; Sengupta 1989; Lowenwirt 1998; Scavone 2004) were included in the review. However, lack of blinding, unclear allocation concealment and unclear missing data were found among these studies. Scavone 2004 compared prophylactic epidural blood patch with a sham procedure and had clear allocation concealment and blinding. This trial showed comparable benefits between prophylactic epidural blood patch and a sham procedure. The available studies which looked at the use of prophylactic epidural blood patch therefore had too few randomised participants to allow reliable conclusions to be drawn.

Therapeutic epidural blood patch showed benefit over both conservative treatment and a sham procedure. Three studies, involving 86 participants, had adequate allocation concealment and blinding techniques (Seebacher 1989; Sandesc 2005; van Kooten 2008) (Figure 2). However, again there were too few participants in the three studies to draw reliable conclusions.

Agreements and disagreements with other studies or reviews

Previous studies (Vasdev 2001; Turnbull 2003; Warwick 2007) did not recommend the routine use of prophylactic blood patch after dural puncture. A survey of anaesthesiologists also showed a decrease in the use of prophylactic blood patch, with a fall from 50% (Berger 1998) to 26% (Baraz 2005). Although our data showed an advantage of prophylactic epidural blood patch over no treatment and conservative treatment in reducing PDPH, it did not result in less PDPH than a sham procedure. We therefore cannot draw the same clear conclusions about the benefit of prophylactic epidural blood patch as in previous studies.

Therapeutic epidural blood patch after spinal anaesthesia with PDPH symptoms has shown benefit in many studies (Berger 1998; Turnbull 2003; Thew 2008). However, evidence from large RCTs comparing epidural blood patch with no blood patch is lacking. Epidural blood patch is favoured over conservative treatment (bed rest, oral and intravenous fluid, and caffeine), although most clinicians tend to use conservative treatment before epidural blood patch, which is often carried out when the conservative treatment has failed.

AUTHORS' CONCLUSIONS

Implications for practice

This is an updated review, the conclusions should be re-read as

there is additional, but limited, evidence. Prophylactic epidural blood patch is not recommended as a routine preventative treatment. The studies found unclear benefit over other treatment in the incidence of post-dural puncture headache (PDPH). Prophylactic epidural blood patching should be reserved for exceptional cases only. However, therapeutic epidural blood patch for the treatment of PDPH has been accepted as a standard treatment. This review shows evidence that epidural blood patch could reduce PDPH compared to conservative treatment and sham procedures.

Implications for research

Although prophylactic epidural blood patch showed benefit over no treatment, conservative treatment and epidural saline patch, the data did not show a benefit over a sham procedure. The evidence from studies included in this review is therefore uncertain. Large trials of prophylactic epidural blood patch versus other treatments are required to allow reliable conclusions to be drawn. More trials of therapeutic epidural blood patch are also required to clarify the conclusions of benefit over conservative treatment and sham procedures.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ackerman 1989

Methods	Randomisation and treatment allocation method: not stated Blinding of outcome assessment: yes Blinding of patients: unclear	
Participants	21 obstetric patients, ASA Physical Status I - II, who sustained inadvertent dural tear during epidural anaesthesia for labour analgesia	
Interventions	18 to 20 ml epidural autologous blood patch through epidural catheter on admission to recovery room after delivery versus no blood patch	
Outcomes	Postural headache and severe postural headache up to 24 hours post-partum (requiring blood patch or further blood patch)	
Notes	-	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Blinding of outcome assessment: yes Blinding of patients: unclear
Incomplete outcome data addressed? All outcomes	Yes	No missing data

Colonna 1989

Methods	Randomisation and treatment allocation method: yes Blinding of outcome assessment: not stated Blinding of patients: not stated	
Participants	39 obstetric patients who receive epidural catheter placement with dural puncture	
Interventions	Prophylactic epidural blood patch (injected 15 ml autologous blood) via epidural catheter within 2 to 14 hours versus conservative treatment (drinking fluids, avoiding ambulation)	
Outcomes	PDPH, any headache	
Notes	-	

Colonna 1989 (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "Each patient was then randomly assigned to control group (CG) or to the study group (SG)."
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Not stated
Incomplete outcome data addressed? All outcomes	Yes	No missing data

Lowenwirt 1998

Methods	Randomisation and treatment allocation method: unclear Blinding of outcome assessment: not stated Blinding of patients: not stated	
Participants	49 obstetric patients who had accidental dural puncture from 16 to 17-gauge needle	
Interventions	Prophylactic epidural blood patch (injected 15 to 20 ml autologous blood) via epidural catheter versus conservative treatment (IV hydration, bed rest, theophylline or caffeine)	
Outcomes	PDPH, any headache	
Notes	Abstract only	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "... were randomized and allocated to two treatment group."
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Not stated
Incomplete outcome data addressed? All outcomes	Yes	No missing data

Sandesc 2005

Methods	Randomisation and treatment allocation method: yes Blinding of outcome assessment: yes Blinding of patients: not stated
Participants	32 patients who had PDPH symptoms for less than 24 hours
Interventions	Epidural blood patch versus conservative treatment (oral and IV replacement, non steroidal anti-inflammatory drug, caffeine)
Outcomes	Intensity of headache (a visual analogue scale (VAS) from 0 to 10), intensity of PDPH
Notes	-

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "randomized, double-blinded manner"
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Not stated
Incomplete outcome data addressed? All outcomes	Yes	No missing data

Scavone 2004

Methods	Randomisation and treatment allocation method: yes Blinding of outcome assessment: yes Blinding of patients: yes
Participants	64 obstetric patients who incurred an inadvertent dural puncture with a 17-gauge epidural needle during initiation of neuraxial analgesia/anaesthesia, and subsequently had an epidural catheter placed successfully at the same or a different interspace, were eligible to participate
Interventions	Epidural blood patch (injected 20 ml autologous blood until have lower back pain/sacral pain) after resolution of analgesia/anaesthesia through the epidural catheter versus sham procedure
Outcomes	PDPH, headache severity (verbal rating pain score), severe headache (required epidural blood patch), backache
Notes	-

Scavone 2004 (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "...subjects were randomized (via a computer-generated random number table) to a treatment (PEBP) group or a control/sham (SHAM) group."
Allocation concealment?	Yes	Quote: "...subjects were randomized (via a computer-generated random number table) to a treatment (PEBP) group or a control/sham (SHAM) group."; "Group assignment was determined by opening an opaque envelope labelled with the study subject number."
Blinding? All outcomes	Yes	Quote: "Her family members, physicians, and nurses were blinded as to treatment group." and "An anesthesiologist investigator unaware of treatment group evaluated the subjects postpartum to ascertain the presence of PDPH."
Incomplete outcome data addressed? All outcomes	Yes	No missing data

Seebacher 1989

Methods	Randomisation and treatment allocation method: yes Blinding of outcome assessment: yes Blinding of patients: yes	
Participants	12 patients with persistent (i.e. > 4 days) postural headache following dural puncture	
Interventions	10 to 20 ml autologous blood patch versus placebo (sham procedure)	
Outcomes	Persistent postural headache, persistent severe postural headache, backache, potential adverse effects up to 24 hours post blood patch	
Notes	-	
<i>Risk of bias</i>		
Item	Authors' judgement	Description

Seebacher 1989 (Continued)

Adequate sequence generation?	Yes	Quote: "Randomisation and treatment allocation method: sealed envelopes (sequentially numbered and opaque)."
Allocation concealment?	Yes	Quote: "Randomisation and treatment allocation method: sealed envelopes (sequentially numbered and opaque)."
Blinding? All outcomes	Yes	Quote: "Blinding of outcome assessment and patients"
Incomplete outcome data addressed? All outcomes	Yes	No missing data

Sengupta 1989

Methods	Randomisation and treatment allocation method: yes Blinding of outcome assessment: no Blinding of patients: no
Participants	48 patients undergoing extracorporeal shock wave lithotripsy, ASA I-II, 18 to 60 years old, spinal anaesthesia
Interventions	10 ml of autologous blood into the epidural space versus 10 ml of normal saline into the epidural space after spinal anaesthesia
Outcomes	Headache, backache, loin pain
Notes	-

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "... were assigned randomly to receive either 10 ml of autologous blood or 10 ml of normal saline..."
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	No	Quote: "As the questions were put by one or other of the investigators, who were not blinded to the patients' grouping, some bias would be a possibility"
Incomplete outcome data addressed? All outcomes	Yes	No missing data

Trivedi 1993

Methods	Randomisation and treatment allocation method: not stated Blinding of outcome assessment: yes Blinding of patients: no
Participants	74 obstetric patients who sustained inadvertent dural puncture during epidural anaesthesia for labour analgesia
Interventions	15 ml autologous epidural blood patch immediately after dural puncture versus 40 to 60 ml epidural saline versus no prophylactic treatment (epidural saline arm not included in analyses)
Outcomes	Any headache up to 2 days post-dural puncture
Notes	-

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Yes	Blinding of outcome assessment: yes Blinding of patients: no
Incomplete outcome data addressed? All outcomes	Unclear	Not stated

van Kooten 2008

Methods	Randomisation and treatment allocation method: yes Blinding of outcome assessment: yes Blinding of patients: no
Participants	42 patients who presented with PDPH (lasting 24 hours to 1 week)
Interventions	15 to 20 ml autologous epidural blood patch versus conservative treatment (24-hour bed rest, drink more than 2 litres of fluid/day)
Outcomes	Headache at 24 hours and at day 7, associated symptoms
Notes	-

Risk of bias

Item	Authors' judgement	Description

Adequate sequence generation?	Yes	Quote: "Patients with PDPH were randomised using a computer database which allocated the patient to active (EDBP) or control (conservative) treatment through a random number generator."
Allocation concealment?	Yes	Quote: "Patients with PDPH were randomised using a computer database which allocated the patient to active (EDBP) or control (conservative) treatment through a random number generator."
Blinding? All outcomes	Yes	Quote: "The research nurse was blinded to treatment allocation."
Incomplete outcome data addressed? All outcomes	Yes	No missing data

EDBP = epidural blood patch; IV = intravenous; PDPH = post-dural puncture headache; VAS = visual analogue scale

Characteristics of excluded studies [ordered by study ID]

Heide 1990	Non-randomised (comparison of prophylactic epidural blood patch versus no blood patch)
Loeser 1978	Comparison not included within the scope of this review: epidural blood patch for treatment of post-dural puncture headache performed less than 24 hours versus more than 24 hours after dural puncture
Safa-Tisseront 2001	Prospective observational study

DATA AND ANALYSES

Comparison 1. Prophylactic epidural blood patch (PEBP)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Post-dural puncture headache (PDPH)	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 PEBP versus no treatment	1	21	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.11 [0.02, 0.64]
1.2 PEBP versus conservative treatment	2	88	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.06 [0.03, 0.14]
1.3 PEBP versus epidural saline patch	1	48	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.16 [0.04, 0.55]
1.4 PEBP versus sham procedure	1	64	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.0 [0.38, 2.66]
2 Severe PDPH	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 PEBP versus no treatment	1	21	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.19 [0.03, 1.22]
2.2 PEBP versus epidural saline patch	1	48	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.34 [0.05, 2.61]
2.3 PEBP versus sham procedure	1	64	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.60 [0.22, 1.62]
3 Any headache	3		Peto Odds Ratio (Peto, Fixed, 99% CI)	Subtotals only
3.1 PEBP versus no treatment	1	21	Peto Odds Ratio (Peto, Fixed, 99% CI)	0.11 [0.01, 1.10]
3.2 PEBP versus conservative treatment	1	44	Peto Odds Ratio (Peto, Fixed, 99% CI)	0.04 [0.01, 0.19]
3.3 PEBP versus epidural saline patch	1	50	Peto Odds Ratio (Peto, Fixed, 99% CI)	0.08 [0.02, 0.37]
3.4 PEBP versus sham procedure	1	64	Peto Odds Ratio (Peto, Fixed, 99% CI)	0.87 [0.23, 3.31]
4 Backache	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 PEBP versus sham procedure	1	64	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.39, 3.52]

Comparison 2. Epidural blood patch (EBP)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PDPH	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 EBP versus conservative treatment	1	40	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.18 [0.04, 0.76]
1.2 EBP versus sham procedure	1	12	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.04 [0.00, 0.39]
2 Severe PDPH	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 EBP versus sham procedure	1	12	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.03 [0.00, 0.22]

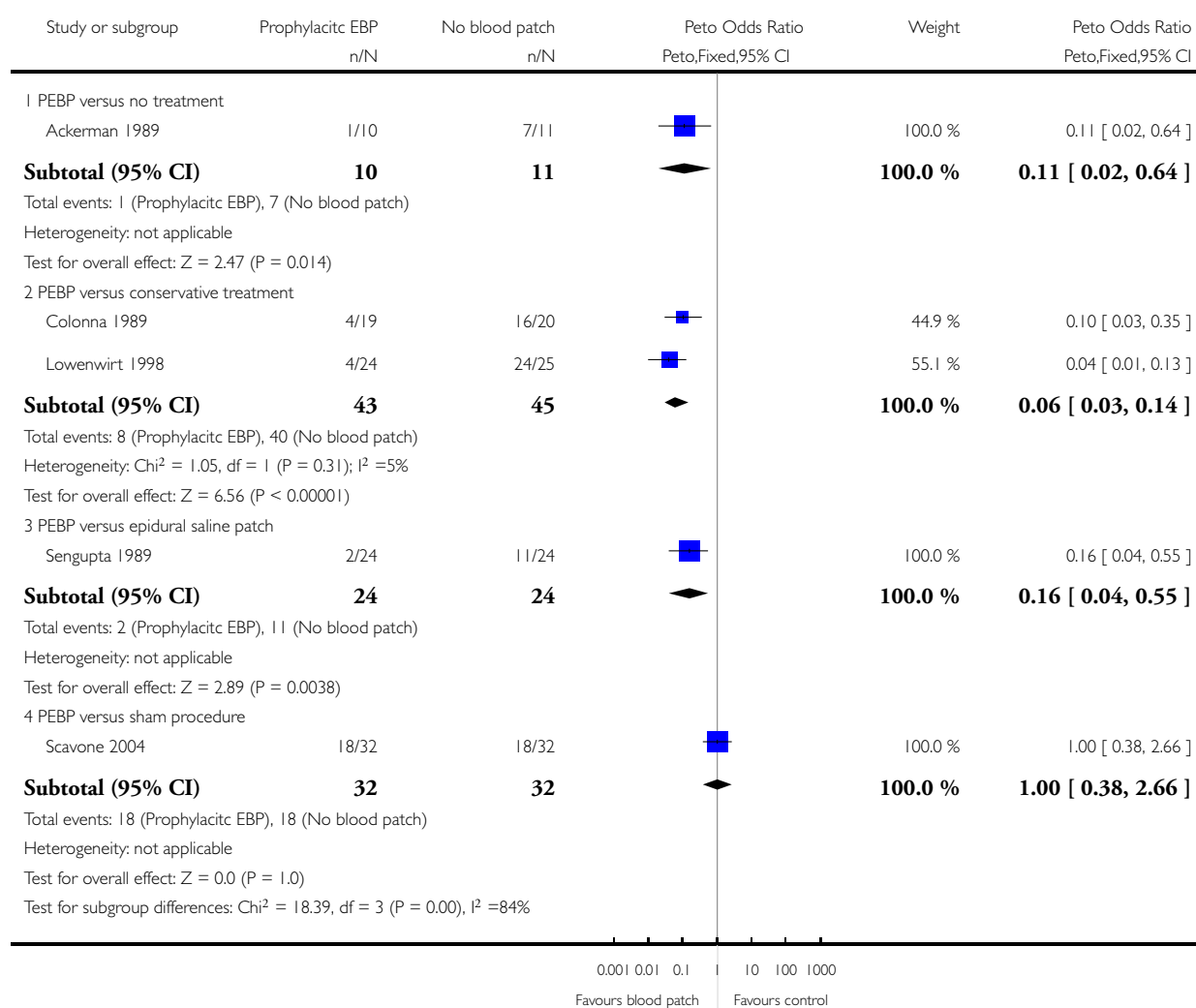
3 Backache	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 EBP versus sham procedure	1	12	Peto Odds Ratio (Peto, Fixed, 95% CI)	23.17 [2.57, 208.60]
4 Intensity of headache	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 EBP versus conservative treatment	1	32	Mean Difference (IV, Fixed, 95% CI)	-7.1 [-7.69, -6.51]

Analysis 1.1. Comparison 1 Prophylactic epidural blood patch (PEBP), Outcome 1 Post-dural puncture headache (PDPH).

Review: Epidural blood patching for preventing and treating post-dural puncture headache

Comparison: 1 Prophylactic epidural blood patch (PEBP)

Outcome: 1 Post-dural puncture headache (PDPH)

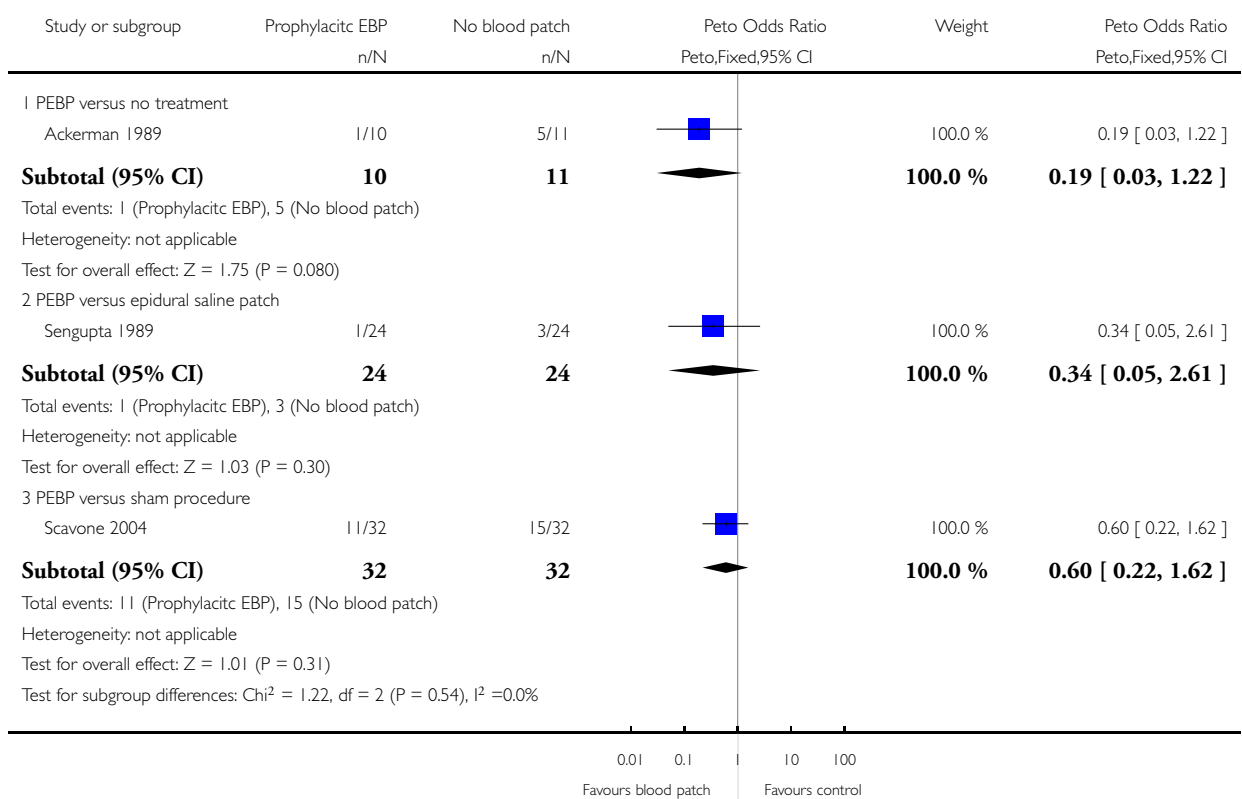


Analysis 1.2. Comparison 1 Prophylactic epidural blood patch (PEBP), Outcome 2 Severe PDPH.

Review: Epidural blood patching for preventing and treating post-dural puncture headache

Comparison: 1 Prophylactic epidural blood patch (PEBP)

Outcome: 2 Severe PDPH

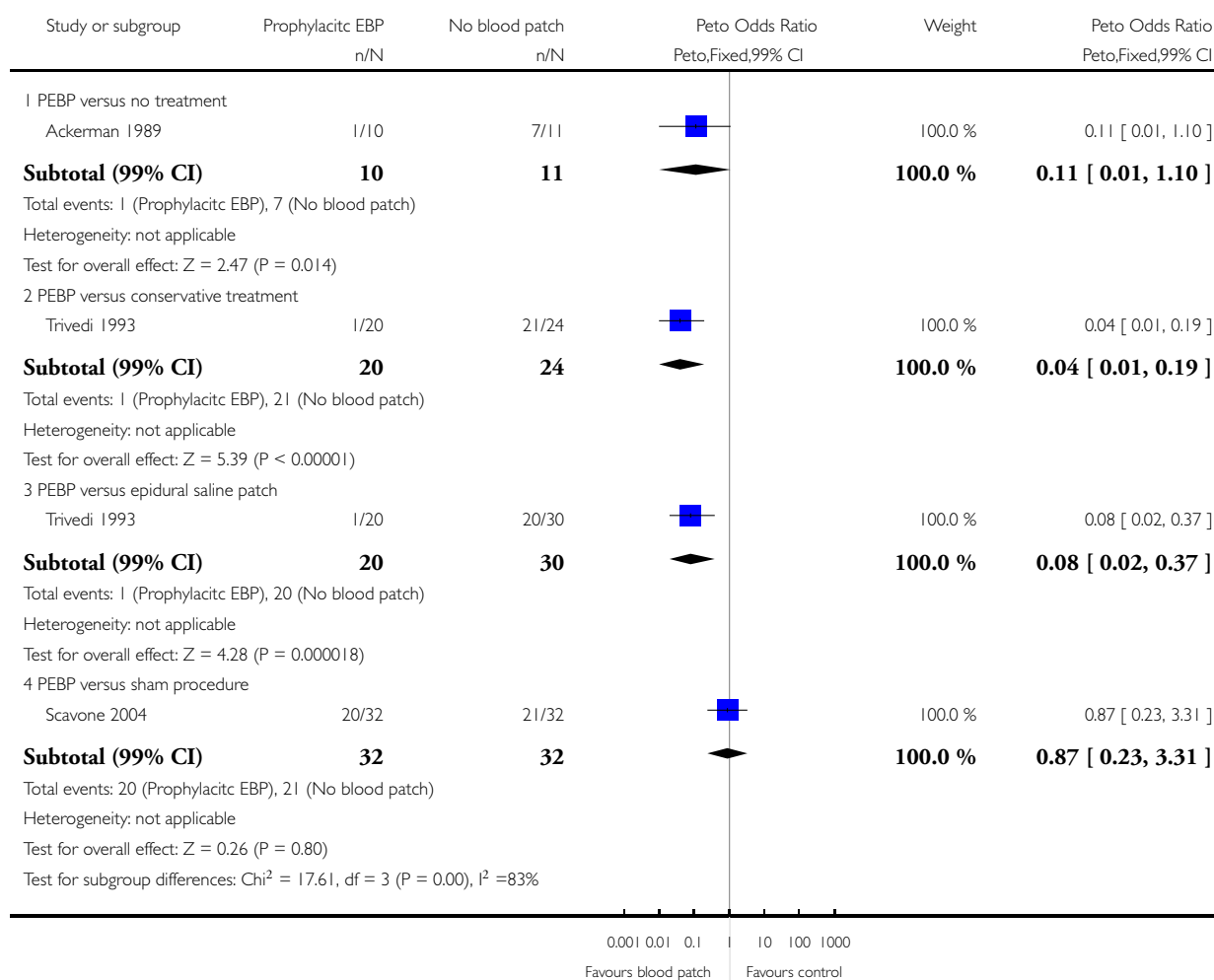


Analysis 1.3. Comparison 1 Prophylactic epidural blood patch (PEBP), Outcome 3 Any headache.

Review: Epidural blood patching for preventing and treating post-dural puncture headache

Comparison: 1 Prophylactic epidural blood patch (PEBP)

Outcome: 3 Any headache

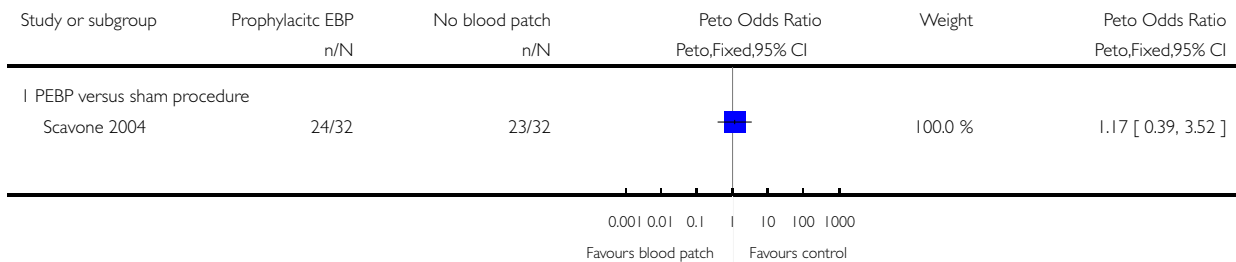


Analysis 1.4. Comparison 1 Prophylactic epidural blood patch (PEBP), Outcome 4 Backache.

Review: Epidural blood patching for preventing and treating post-dural puncture headache

Comparison: 1 Prophylactic epidural blood patch (PEBP)

Outcome: 4 Backache

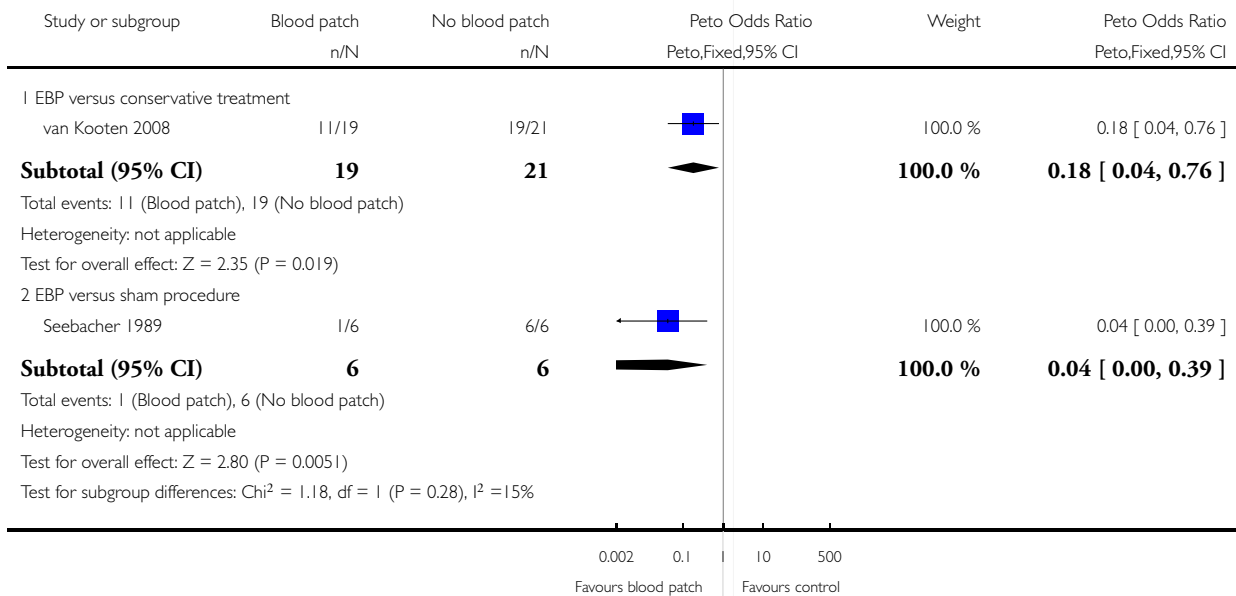


Analysis 2.1. Comparison 2 Epidural blood patch (EBP), Outcome 1 PDPH.

Review: Epidural blood patching for preventing and treating post-dural puncture headache

Comparison: 2 Epidural blood patch (EBP)

Outcome: 1 PDPH

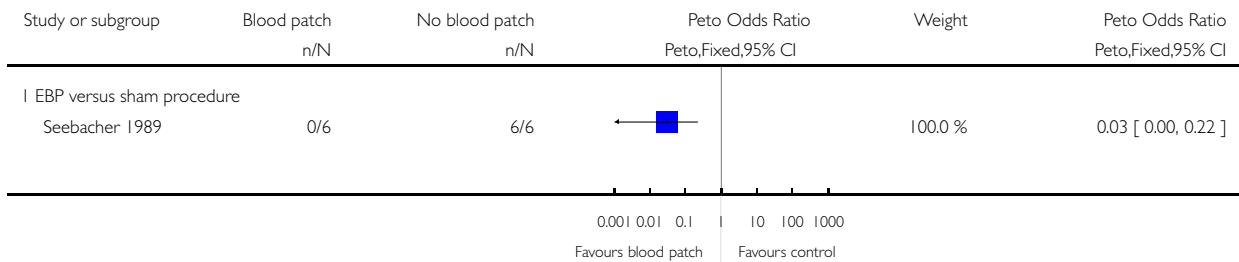


Analysis 2.2. Comparison 2 Epidural blood patch (EBP), Outcome 2 Severe PDPH.

Review: Epidural blood patching for preventing and treating post-dural puncture headache

Comparison: 2 Epidural blood patch (EBP)

Outcome: 2 Severe PDPH

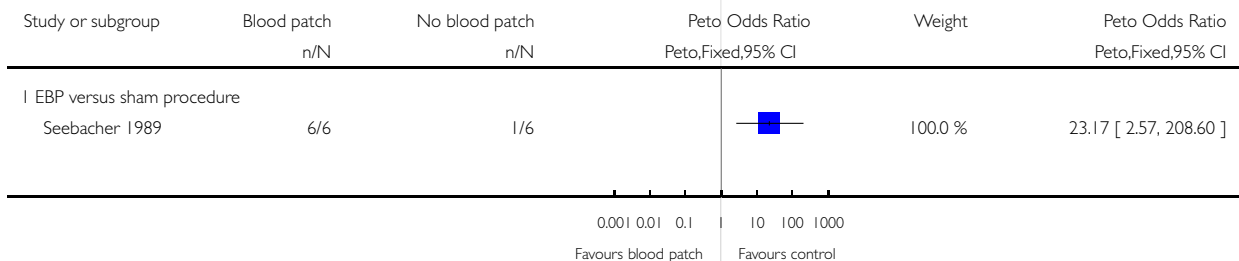


Analysis 2.3. Comparison 2 Epidural blood patch (EBP), Outcome 3 Backache.

Review: Epidural blood patching for preventing and treating post-dural puncture headache

Comparison: 2 Epidural blood patch (EBP)

Outcome: 3 Backache



Analysis 2.4. Comparison 2 Epidural blood patch (EBP), Outcome 4 Intensity of headache.

Review: Epidural blood patching for preventing and treating post-dural puncture headache

Comparison: 2 Epidural blood patch (EBP)

Outcome: 4 Intensity of headache



APPENDICES

Appendix I. CENTRAL

Search strategy for CENTRAL, The Cochrane Library 2009, Issue I

Search number	Search terms
1	POST-DURAL PUNCTURE HEADACHE
2	("post dural puncture headache*" or "postdural puncture headache*" or "post-dural puncture headache*")
3	((dura* NEAR/3 puncture*) and headache*)
4	#1 or #2 or #3
5	randomized controlled trial.pt.
6	controlled clinical trial.pt.
7	randomized controlled trials.sh.
8	random allocation.sh.
9	double blind method.sh.

(Continued)

10	single blind method.sh.
11	or/5-10
12	(ANIMALS not HUMAN).sh.
13	11 not 12
14	clinical trial.pt.
15	exp clinical trials/
16	(clin\$ adj25 trial\$).ti,ab.
17	((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
18	placebos.sh.
19	placebo\$.ti,ab.
20	random\$.ti,ab.
21	research design.sh.
22	or/14-21
23	22 not 12
24	23 not 13
25	13 or 23
26	25 and 4

Appendix 2. MEDLINE

Search strategy for MEDLINE (OVID) (1950 to April 2009)

Search number	Search terms
1	Post-Dural Puncture Headache/
2	("post dural puncture headache\$" or "postdural puncture headache\$" or "post-dural puncture headache\$").mp. [mp=title, original title, abstract, name of substance word, subject heading word]

(Continued)

3	((dura\$ adj2 puncture\$) and headache\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4	or/1-3

Appendix 3. EMBASE

Search strategy for EMBASE (OVID) (1980 to April 2009)

Search number	Search terms
1	Post-Dural Puncture Headache/
2	("post dural puncture headache\$" or "postdural puncture headache\$" or "post-dural puncture headache\$").mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3	((dura\$ adj2 puncture\$) and headache\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4	or/1-3
5	random\$.ti,ab.
6	factorial\$.ti,ab.
7	(crossover\$ or cross over\$ or cross-over\$).ti,ab.
8	placebo\$.ti,ab.
9	(doubl\$ adj blind\$).ti,ab.
10	(singl\$ adj blind\$).ti,ab.
11	assign\$.ti,ab.
12	allocat\$.ti,ab.
13	volunteer\$.ti,ab.
14	CROSSOVER PROCEDURE.sh.
15	DOUBLE-BLIND PROCEDURE.sh.
16	RANDOMIZED CONTROLLED TRIAL.sh.

(Continued)

17	SINGLE BLIND PROCEDURE.sh.
18	or/5-17
19	ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/
20	HUMAN/
21	19 and 20
22	19 not 21
23	18 not 22
24	23 and 4

Appendix 4. PaPaS register

Search strategy for PaPaS Trials Register (April 2009)

Search number	Search terms
1	("post dural puncture headache*" or "postdural puncture headache*" or "post-dural puncture headache*" or (("dura* puncture*") and headache*))

WHAT'S NEW

Last assessed as up-to-date: 31 March 2009.

6 November 2009	New citation required and conclusions have changed	This review has been updated by two new review authors. The conclusions should be re-read as this update adds limited evidence to the previous review that therapeutic epidural blood patch showed a benefit over conservative treatment. However, the review authors still do not recommend prophylactic epidural blood patch over other treatments because there are too few trial participants to allow reliable conclusions to be drawn.
3 September 2009	New search has been performed	This review has been updated. Six additional studies (Colonna 1989 ; Lowenwirt 1998 ; Sandesc 2005 ; Scavone 2004 ; Sengupta 1989 ; van Kooten 2008) have

(Continued)

	been included adding a further 302 participants.

HISTORY

Protocol first published: Issue 1, 2000

Review first published: Issue 2, 2002

3 November 2008	New search has been performed	Converted to new review format.
22 August 2002	Feedback has been incorporated	Feedback submitted and addressed by the authors.

CONTRIBUTIONS OF AUTHORS

Both review authors conceived the idea and methods for this review. In discussion with Charles Warlow, Cathie Sudlow, Polpun Boonmak and Suhattaya Boonmak developed and ran the search strategy for the update, identified studies for inclusion and exclusion, extracted and entered data, and ran the analyses. Cathie Sudlow wrote the original version of this review. Polpun Boonmak and Suhattaya Boonmak wrote the updated review. All review authors contributed to the published version.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Thai Cochrane Network, Thailand.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Blood Patch, Epidural; Post-Dural Puncture Headache [prevention & control; *therapy]; Randomized Controlled Trials as Topic; Spinal Puncture [*adverse effects]

MeSH check words

Humans

Haemostatic drugs for traumatic brain injury (Review)

Perel P, Roberts I, Shakur H, Thinkhamrop B, Phuenpathom N, Yutthakasemsunt S



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Haemostatic drugs for traumatic brain injury (Review)

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[Intervention Review]

Haemostatic drugs for traumatic brain injury

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ABSTRACT

Background

Traumatic brain injury (TBI) is a leading cause of death and disability. Intracranial bleeding is a common complication of TBI, and intracranial bleeding can develop or worsen after hospital admission. Haemostatic drugs may reduce the occurrence or size of intracranial bleeds and consequently lower the morbidity and mortality associated with TBI.

Objectives

To assess the effects of haemostatic drugs on mortality, disability and thrombotic complications in patients with traumatic brain injury.

Search strategy

We searched the electronic databases: Cochrane Injuries Group Specialised Register (3 February 2009), CENTRAL (*The Cochrane Library* 2009, Issue 1), MEDLINE (1950 to Week 3 2009), PubMed (searched 3 February 2009 (last 180 days)), EMBASE (1980 to Week 4 2009), CINAHL (1982 to January 2009), ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to January 2009), ISI Web of Science: Conference Proceedings Citation Index - Science (CPCI-S) (1990 to January 2009).

Selection criteria

We included published and unpublished randomised controlled trials comparing haemostatic drugs (antifibrinolytics: aprotinin, tranexamic acid (TXA), aminocaproic acid or recombinant activated factor VIIa (rFVIIa)) with placebo, no treatment, or other treatment in patients with acute traumatic brain injury.

Data collection and analysis

Two review authors independently examined all electronic records, and extracted the data. We judged that there was clinical heterogeneity between trials so we did not attempt to pool the results of the included trials. The results are reported separately.

Main results

We included two trials. One was a post-hoc analysis of 30 TBI patients from a randomised controlled trial of rFVIIa in blunt trauma patients. The risk ratio for mortality at 30 days was 0.64 (95% CI 0.25 to 1.63) for rFVIIa compared to placebo. This result should be considered with caution as the subgroup analysis was not pre-specified for the trial. The other trial evaluated the effect of rFVIIa in 97 TBI patients with evidence of intracerebral bleeding in a computed tomography (CT) scan. The corresponding risk ratio for mortality

Haemostatic drugs for traumatic brain injury (Review)

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at the last follow up was 1.08 (95% CI 0.44 to 2.68). The quality of the reporting of both trials was poor so it was difficult to assess the risk of bias.

Authors' conclusions

There is no reliable evidence from randomised controlled trials to support the effectiveness of haemostatic drugs in reducing mortality or disability in patients with TBI. New randomised controlled trials assessing the effects of haemostatic drugs in TBI patients should be conducted. These trials should be large enough to detect clinically plausible treatment effects.

PLAIN LANGUAGE SUMMARY

Haemostatic drugs for traumatic brain injury

Injury (also called trauma) is a leading cause of death for children and young adults. Traumatic brain injury, such as from a blow to the head, is a frequent cause of death for patients with trauma who survive to reach hospital. Approximately half of patients with traumatic brain injury develop bleeding into the brain within the first 48 hours of hospital admission. If bleeding occurs, accumulating blood within the skull can put pressure on the brain and this may be fatal or result in serious long-term disability for the patient. Therefore, drugs that promote the production of clots or reduce the destruction of existing clots (known as haemostatic drugs) might reduce the bleeding into the brain after an injury and thereby reduce the risk of death or disability.

We searched for randomised clinical trials looking at the effectiveness of haemostatic drugs for reducing mortality and disability in patients with traumatic brain injury. We found two studies that evaluated the effects of a type of haemostatic drug called recombinant activated factor VII. We reviewed the data presented in the reports of these trials. Both trials were too small to confirm or refute any plausible clinical effect, so we were unable to reach any conclusions regarding the effectiveness of haemostatic drugs for traumatic brain injury patients. More trials are needed to answer this question. Future trials should be large enough to detect plausible and important clinical effects.

BACKGROUND

Description of the condition

Traumatic brain injury is one of the main causes of death in patients with injuries, and is a leading cause of death and disability in young people (Ghajar 2000). Every year approximately 1.5 million people die and at least 10 million people are killed or hospitalised because of a traumatic brain injury (Langlois 2006). The incidence, fatality and disability rates are higher in low- and middle- income countries than in high income countries (Hyder 2007).

Although much of the damage to the brain occurs at the time of the injury, secondary brain damage due to ongoing intracranial bleeding and brain swelling is an important and potentially avoidable cause of morbidity and mortality. Intracranial bleeding is a common complication of traumatic brain injury. In the CRASH trial, which included patients with mild, moderate and severe traumatic brain injury, 56% of trial participants had at least one intracranial

bleed that could have been epidural, subdural, subarachnoid or intra-parenchymal (CRASH Trial).

There is evidence that intracranial bleeding can develop or worsen after hospital admission. Prospective observational studies have shown that traumatic intracranial haemorrhage expansion occurs in up to 51% of patients with traumatic brain injury during the first 24 to 48 hours after hospital admission (Narayan 2008). Prognostic studies have shown that intracranial haemorrhage is associated with increased mortality and disability six months after injury (Maas 2007; Perel 2008). Intracranial bleeding exerts significant pressure on brain tissue (Bullock 2006), and prompt neurosurgical intervention is an important part of the therapeutic approach. However, not all intracranial haemorrhages can be controlled by surgical intervention and there is interest in pharmacological approaches that use haemostatic drugs to reduce the occurrence or size of intracranial bleeds (Ceylan 1992; Mander 1999; Holcomb 2004).

Description of the intervention

Haemostatic drugs have the potential to reduce bleeding by influencing the coagulation cascade. In the haemostatic process, coagulation occurs rapidly to build a tight net of fibrin at the site of the damaged vessel. At the same time, the fibrinolytic system removes fibrin deposits that could cause permanent occlusion of blood vessels once vascular repair has taken place (Prentice 1980). Thus, the coagulation and fibrinolytic systems are in a state of dynamic balance that maintains an intact vascular system.

The treatments that have been most extensively evaluated as haemostatic drugs include antifibrinolytics and pro-coagulant drugs such as recombinant activated factor VII (rFVIIa) (Mannucci 2007). Antifibrinolytic drugs maintain the stability of blood clots, whereas pro-coagulant drugs act directly on the coagulation cascade (Holcomb 2004).

The pro-coagulant rFVIIa acts locally at the site of tissue injury. It is believed that it binds to exposed tissue factor and generates thrombin, which activates the platelets. The activated platelet surface forms a template on which recombinant factor VIIa can directly or indirectly mediate further activation of coagulation, resulting in the generation of more thrombin and, ultimately, in the conversion of fibrinogen to fibrin.

Antifibrinolytic agents suppress fibrinolysis, thereby reducing excessive or recurrent bleeding. Antifibrinolytics can be divided into lysine analogues (tranexamic acid (TXA) and aminocaproic acid) and plasmin inhibitors (aprotinin). The former impairs endogenous fibrinolysis by blocking lysine binding sites on plasminogen molecules. In contrast, aprotinin directly inhibits the fibrinolytic enzyme plasmin, plasma and tissue kallikrein, trypsin and activated coagulation factor XII.

How the intervention might work

Haemostatic drugs have been used to prevent or reduce blood loss and the need for blood transfusion.

For example, antifibrinolytic drugs are widely used in general surgery to reduce bleeding and the need for transfusions (Slaughter 1997). A systematic review of the use of antifibrinolytic agents in surgical patients identified 211 randomised controlled trials that included 20,781 participants (Henry 2007). The results showed that TXA reduced the risk of blood transfusion by 39% (risk ratio (RR) 0.61, 95% confidence interval (CI) 0.54 to 0.69), while aprotinin lowered the risk by 34% (RR 0.66, 95% CI 0.61 to 0.71). Antifibrinolytic agents also reduced the need for blood transfusion and reoperation due to bleeding. There was a trend toward a decreased risk of death in patients treated with aprotinin (RR 0.90, 95% CI 0.67 to 1.20) and TXA (RR 0.60, 95% CI 0.32 to 1.12) but this was not statistically significant. There was no evidence of an increased risk of thrombotic events with either treatment.

The effects of haemostatic drugs in non-traumatic intracranial bleeding have also been evaluated. A systematic review of ran-

domised controlled trials of antifibrinolytic drugs in patients with aneurysmal subarachnoid haemorrhage showed that antifibrinolytic drugs reduced the rate of re-bleeding by approximately 40% but, because of the associated increase in cerebral ischaemia, there was no overall benefit (Roos 2003). However, the length of treatment in these trials was six weeks. It is possible that a shorter treatment period might prevent re-bleeding without increasing the risk of ischaemia. The systematic review was conducted in 2003. Since then, a randomised controlled trial of early administration of a short course (three days) of TXA in patients with aneurysmal subarachnoid haemorrhage has found that TXA reduced the occurrence of re-bleeding from 10.8% to 2.4%, with no evidence of increased side effects (Astrup 2006).

A systematic review of haemostatic drugs in primary intracerebral haemorrhage (non-traumatic) found four phase II trials and reported that haemostatic drugs reduced the risk of death and dependence measured on the modified Rankin Scale (RR 0.79, 95% CI 0.67 to 0.93) and the Glasgow Outcome Scale (RR 0.90, 95% CI 0.81 to 1.01) (You 2006). A recent clinical trial, which was not included in that systematic review, showed that activated factor VIIa reduced intracerebral haemorrhage expansion but did not improve the survival or functional outcomes of patients (Mayer 2008).

Why it is important to do this review

If haemostatic agents reduce intracranial bleeding in patients with traumatic brain injury, they could substantially reduce the extent of secondary brain damage and subsequently lower the mortality and morbidity rates associated with brain injury. Given the number of cases of traumatic brain injury that occur each year, even a modest reduction in the risk of unfavourable outcomes could have major public health implications.

OBJECTIVES

To assess the effects of haemostatic drugs on mortality, disability and thrombotic complications in patients with traumatic brain injury.

METHODS

Criteria for considering studies for this review

Types of studies

We included published and unpublished randomised controlled trials comparing haemostatic drugs with placebo, no treatment, or other treatment in patients with acute traumatic brain injury. Comparisons between different types of haemostatic drugs were also to be included.

Types of participants

Any patient with traumatic brain injury.

Types of interventions

Any of the systemic haemostatic drugs listed below compared with placebo, no treatment, or another haemostatic drug. For studies in which different doses of the intervention were compared with placebo, the intervention groups were combined and compared with the control group. For the purpose of this review, we considered the following haemostatic drugs.

- Antifibrinolytics: aprotinin, tranexamic acid (TXA), aminocaproic acid.
- Activated factor VIIa.

Types of outcome measures

Primary outcomes

1. Mortality
2. Disability (Glasgow Outcome Scale (GOS), Disability Rating Scale (DRS), or other measure of neurological function)
3. Thrombotic complications: deep venous thrombosis (DVT), pulmonary embolism (PE), stroke, and myocardial infarction (MI)

Secondary outcomes

1. Volume of intracranial bleeding
2. Brain ischaemic lesions
3. Need for neurosurgical operation or reoperation
4. Renal failure

Search methods for identification of studies

The searches were not restricted by date, language, or publication status.

Electronic searches

We searched the following electronic databases:

- Cochrane Injuries Group Specialised Register (searched 3 February 2009),
- CENTRAL (*The Cochrane Library* 2009, Issue 1),

- MEDLINE (1950 to Week 3 2009),
- PubMed (searched 3 February 2009 (last 180 days)),
- EMBASE (1980 to Week 4 2009),
- CINAHL (1982 to January 2009),
- ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to January 2009),
- ISI Web of Science: Conference Proceedings Citation Index - Science (CPCI-S) (1990 to January 2009).

The full search strategies can be found in [Appendix 1](#).

Searching other resources

We searched the Internet for relevant information and conference abstracts. We also sought other potentially relevant published, unpublished, or ongoing studies by:

1. checking the reference lists of relevant papers and literature reviews,
2. communicating with relevant trial authors,
3. contacting the manufacturers of relevant drugs.

Data collection and analysis

Selection of studies

Two review authors (PP and IR) independently examined all electronic records and their abstracts to establish eligibility. They decided on whether or not to acquire the full report and, in cases of uncertainty, obtained the full report. We planned to resolve any disagreements through discussion and consultation with a third review author. Any duplicate trials were planned to be examined individually to verify that they presented unique sets of data. If we were unsure about whether a study should be included, because additional information was necessary, we allocated the study to the list of those awaiting assessment and contacted the study authors for clarification. The reasons for excluding studies are described in the '[Characteristics of excluded studies](#)' table.

Data extraction and management

Two review authors (PP and IR) extracted the data from the included studies. We extracted data on the study methods, participants, interventions, and outcomes. We extracted data so that an intention-to-treat analysis could be performed. For binary outcomes, we determined the number of participants experiencing the outcome of interest in each group. For continuous outcomes, we used the mean change from baseline at final assessment, together with the number of participants and standard deviation for each group.

Assessment of risk of bias in included studies

Two review authors (PP and IR) evaluated the risk of bias of the included studies with respect to six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. The risk of bias in each domain was rated as high risk, low risk, and unclear. Any disagreement between raters was resolved by consensus.

Measures of treatment effect

For dichotomous data, we calculated the risk ratio (RR) and 95% CI. We calculated the mean difference (MD) and 95% CI for continuous outcomes that were measured on the same scale, otherwise we planned to calculate the standardised mean difference.

Dealing with missing data

We attempted to contact study authors to obtain any missing information.

Assessment of heterogeneity

We planned to examine the participants, interventions, and outcomes of the trials for evidence of clinical heterogeneity. Statistical heterogeneity was planned to be examined with the I^2 statistic and Chi^2 test. The I^2 statistic describes the percentage of total variation across studies that is due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity; larger values show increasing heterogeneity. Substantial heterogeneity is considered to exist when I^2 is more than 50%. For the Chi^2 test, a P value of less than 0.10 was considered as indicating the presence of statistically significant heterogeneity. We planned that if there was any evidence of clinical or statistical heterogeneity, we would not conduct a meta-analysis and would report findings in a narrative form.

Assessment of reporting biases

We planned to assess reporting bias using a funnel plot.

Data synthesis

We planned to conduct a meta-analysis if the included trials were clinically homogeneous and there was no evidence of statistical heterogeneity. For dichotomous outcomes, we planned to use the Mantel-Haenszel method.

Subgroup analysis and investigation of heterogeneity

If significant heterogeneity was present, and the number of studies was sufficient, we planned to investigate heterogeneity using the following subgroups.

1. Severity of acute traumatic brain injury (mild, moderate, or severe).
2. Type of traumatic brain injury lesion (focal or diffuse).
3. Type of intervention (i.e. kind of haemostatic drug used).

Sensitivity analysis

We planned to perform a sensitivity analysis to investigate the effect of the methodological quality of the included studies on the results.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#); [Characteristics of ongoing studies](#).

Results of the search

The search of the databases identified a total of 659 records. These were screened by two authors (PP and IR) and the full text of 12 potentially eligible reports were obtained for closer examination. Of these, only two studies met the inclusion criteria. A further study was identified by searching the reference lists of selected seminal papers.

Included studies

Two trials were included in this systematic review. Both evaluated the effects of recombinant factor VIIa (rFVIIa). The earlier of these trials ([Kluger 2007](#)) was a post-hoc analysis of traumatic brain injury (TBI) patients from a randomised controlled trial of rFVIIa in blunt trauma patients ([Boffard 2005](#)). The later paper evaluated the effects of rFVIIa in TBI patients with evidence of intracerebral bleeding of at least 2 ml on a baseline computed tomography (CT) scan obtained within six hours of the injury ([Narayan 2008](#)). More details about the studies are reported in the '[Characteristics of included studies](#)' table.

Excluded studies

We identified a trial that evaluated the effects of aprotinin in patients with severe TBI ([Auer 1979](#)). It was reported as a randomised controlled trial; however after randomly allocating the first 20 patients, five patients were added to the aprotinin group. It was not possible to separate the outcome data for the 20 randomised and the five non-randomised patients. Therefore, this study provided no useable outcome data and was excluded.

Pending study results

Another trial that could contribute useful data to this systematic review was a phase 3 randomised controlled trial that evaluated the effect of rFVIIa in trauma patients. This trial planned to recruit 1502 patients but it was stopped by its sponsor after 550 patients because of futility ([Novoseven Study](#)). Although we contacted the sponsor of this trial, as of July 2009 we were not able to obtain any data.

Ongoing studies

There are three ongoing trials that could contribute to this systematic review. The CRASH-2 trial ([CRASH-2 Trial](#)) is an international study evaluating the effects of TXA in patients with trauma and significant bleeding; a subgroup analysis of TBI patients is planned. CRASH-2 aims to recruit 20,000 patients and will be

finished by December 2009. An explanatory study, CRASH-2 IBS (Intracranial Bleeding Study) is also being conducted among a sample of 300 CRASH-2 participants. In patients recruited to CRASH-2 IBS, a second CT scan is obtained within 24-48 hours after randomisation to evaluate changes in the volume of intracranial bleeding. Another trial is being conducted in Thailand to evaluate the effectiveness and safety of TXA for adult patients with moderate to severe TBI. It was to recruit 240 patients and should have been finished by May 2009 ([Tranexamic acid in TBI](#)).

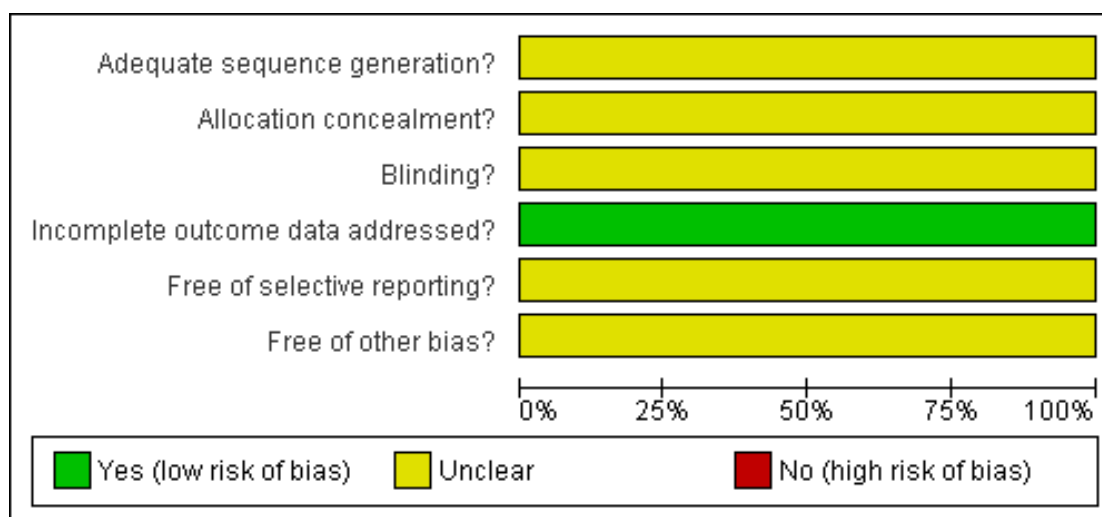
Risk of bias in included studies

The review authors' assessment of the risk of bias for each included study can be found in [Figure 1](#) and [Figure 2](#).

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Kluger 2007	?	?	?	+	?	?
Narayan 2008	?	?	?	+	?	?

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies. Two studies are included in this review.



Allocation

Method of allocation concealment was not reported in either of the included studies.

Blinding

Although both studies were reported to be 'double blind' they did not describe the method of blinding.

Incomplete outcome data

Both studies reported the pre-specified outcomes for all included patients. However, in the trial by Narayan and collaborators only mortality at 15 days was reported. They also reported in-hospital mortality after 15 days but it was not clear if this information was collected for all the patients.

Selective reporting

A protocol was not available for either of the included studies, so it was not possible to assess the presence of reporting bias.

Effects of interventions

We did not attempt to combine the results of the two included trials as we judged that they included two different populations. One study evaluated the effect of rFVIIa in trauma patients with extracranial bleeding who also had a TBI (Kluger 2007), and the other study only included patients with mild and moderate TBI

and evidence of traumatic intracranial bleeding in the CT scan (Narayan 2008).

Primary outcomes

Mortality

Both studies reported on mortality.

Kluger 2007 reported a RR for mortality at 30 days of 0.64 (95% CI 0.25 to 1.63) for patients receiving rFVIIa in comparison to those receiving placebo.

Narayan 2008 reported a RR for mortality at the last follow-up time of 1.08 (95% CI 0.44 to 2.68) for patients receiving rFVIIa in comparison to those receiving placebo.

Disability

Kluger 2007 did not report the effect of rFVIIa on disability.

Narayan 2008 evaluated the effect on disability using the GOS and the Barthex Index (BI).

The BI was evaluated in only 71 (76%) patients. The authors reported that the median scores were 46.3 and 43.9 for the placebo and rFVIIa arms, respectively. However, their report did not provide enough data (SD and denominators) to estimate the mean difference between the two groups. Similarly, insufficient data were reported to evaluate the effect on GOS. It was reported that at 15 days, 17% of the patients in the placebo and 18% in the rFVIIa group had moderate to good recovery according to the GOS.

Thrombotic complications

Both studies reported the effect of rFVIIa on thrombotic complications.

Kluger 2007 followed the 'local diagnostic procedures' in the case of clinical symptoms of thromboembolic events. They reported two serious adverse thromboembolic events in the placebo arm

and none in the rFVIIa arm (RR 0.16, 95% CI 0.01 to 2.99 for rFVIIa in comparison to placebo).

Narayan 2008 conducted a more intense follow up of patients to detect thromboembolic complications. An ultrasound screening of the lower extremities (USLE) was mandated by protocol at 72 ± 8 hours to detect the presence of DVT. A 12-lead electrocardiogram (ECG) and a centralised laboratory measurement of troponin I were mandated at baseline and 24 hours after trial drug administration. The authors reported that eight patients (13%) from the rFVIIa arm presented with a thromboembolic complication, while only two patients (6%) presented with such a complication in the placebo arm. The estimated RR for thrombotic complications in this study was 2.36 (95% CI 0.53 to 10.51).

Secondary outcomes

The secondary outcomes were only reported by Narayan 2008.

Intracranial bleeding volume

Narayan 2008 analysed the effect of rFVIIa on intracranial bleeding volume in different ways. For each arm, the investigators reported the: 1) mean volume at baseline, 24, and 72 hours; 2) mean volume change (defined as volume increase, no change, or decrease) at 24 and 72 hours; and 3) volume increase at 24 and 72 hours, only considering patients in whom an increase was reported. We reported the mean volume change at 72 hours as we considered this to be both the most relevant outcome and the most powerful analysis. The mean difference in volume change at 72 hours was -3.10 (95% CI -10.47 to 4.27) for patients receiving rFVIIa in comparison to patients receiving placebo.

For the other secondary outcomes there were too few events to obtain effect estimate measures.

Brain ischaemic lesions

Narayan 2008 reported one cerebral infarction in the placebo arm and no events in the rFVIIa arm.

Need for neurosurgical operation or reoperation

Narayan 2008 reported the need for emergency intracranial bleeding evacuation for three patients in the placebo group and for one in the rFVIIa group. Two of the three placebo-treated patients who underwent the emergency evacuation needed a reoperation, while a reoperation was not conducted for the rFVIIa-treated patients who underwent the emergency evacuation.

Renal failure

Neither of the studies reported on renal failure.

DISCUSSION

Summary of main results

There is no reliable evidence that haemostatic drugs are effective in reducing mortality or disability in patients with TBI. Only two studies evaluating the effects of rFVIIa were found. One of them was a post-hoc analysis of a trial including 30 bleeding trauma

patients with a concomitant moderate or mild TBI. This result should be considered with caution as it was a post-hoc analysis of a subgroup of patients (with TBI) within a larger trial of trauma patients. Posteriori subgroup analyses are likely to be misleading as they can be the result of data dredging and chance. The other study included 97 TBI patients with evidence of intracerebral bleeding in the initial CT scan.

Both studies were too small to confirm or refute a clinically plausible effect in the TBI population. We did not find a single randomised controlled trial of an antifibrinolytic drug for TBI patients. The pending results of the Novoseven study and the results of the ongoing studies with tranexamic acid (TXA) will provide useful information about the effects of haemostatic drugs in TBI patients.

Quality of the evidence

Neither of the trial reports provided enough data to assess the risk of bias for sequence generation, allocation concealment, blinding, or selective reporting.

Potential biases in the review process

Although our search was comprehensive and we used validated search strategies, the possibility of publication bias cannot be ruled out. Because few studies were included in this review we were not able to conduct formal analysis of publication bias (a funnel plot). Full protocols of the included studies were not available so we could not assess the presence of selective reporting bias, however for our primary outcome (mortality) this type of bias is very unlikely. Finally, one of the included trials was a post-hoc subgroup analysis and its result should be considered with caution.

Agreements and disagreements with other studies or reviews

This is the first review to evaluate the effects of haemostatic drugs in TBI patients. However, other reviews related to this question have been published.

Stanworth and collaborators conducted a systematic review on rFVIIa for the prevention and treatment of bleeding in patients without haemophilia (Stanworth 2007). This review included the randomised controlled trial in trauma patients from which the post-hoc analysis reported in our systematic review was conducted (Boffard 2005). However, that review did not analyse the effect of rFVIIa in TBI patients.

Another Cochrane review evaluated the effects of antifibrinolytic agents in trauma patients (Coats 2004). That review included two studies, one of them (Auer 1979) is among the excluded studies for our review. The trial involved TBI patients and the intervention under study was aprotinin, but the report provided no useable

outcome data. The other study reported in the review by Coats and collaborators did not include TBI patients.

A recent review of the clinical use of rFVIIa evaluated the effects of rFVIIa in different conditions usually treated in the emergency department (Fishman 2008). Among the outcomes, the effect on trauma patients was reported although TBI patients were not specifically included. The only included randomised controlled trial involving trauma patients was by Boffard 2005, which is included in this systematic review.

AUTHORS' CONCLUSIONS

Implications for practice

There is no reliable evidence to recommend the use of haemostatic drugs for TBI patients.

Implications for research

New randomised clinical trials assessing the effects of haemostatic drugs in TBI patients should be conducted. These trials should be large enough to detect clinically plausible effects.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Kluger 2007

Methods	Randomised clinical trial.
Participants	30 adult patients (between 16 and 65 years old) with severe blunt trauma and moderate or mild traumatic brain injury (based on CT scan results). Exclusion criteria were: cardiac arrest pre-hospital or in the emergency or operating room, prior to trial drug administration; gunshot wound to the head; base deficit of greater than 15 mEq/l or severe acidosis with pH of less than 7.00; transfusion of 8 or more units of RBCs prior to arrival at the trauma center; injury sustained greater than or equal to 12 hours before randomisation; and severe TBI, defined as a Glasgow Coma Scale (GCS) score of less than or equal to 8, unless in the presence of a normal head CT scan.
Interventions	Eligible patients were randomly assigned to treatment groups within a 4-hour period. Treatment arms were either three intravenous injections of rFVIIa (200, 100, and 100 µg/kg) or three placebo injections. The first dose of study drug was administered immediately after transfusion of the eighth unit of RBCs. The second and third doses followed 1 and 3 hours after the first dose, respectively.
Outcomes	Mortality was categorised as: early (<48 hours) or late (between 48 hours and 30 days).
Notes	This study was a post hoc analysis of patients with traumatic brain injury enrolled into a randomised, placebo-controlled study of patients with severe blunt trauma.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not described.
Allocation concealment?	Unclear	Not described.
Blinding? All outcomes	Unclear	Reported as "double blind" but method of blinding was not reported.
Incomplete outcome data addressed? All outcomes	Yes	Outcome reported for all included patients.
Free of selective reporting?	Unclear	The protocol is not available.
Free of other bias?	Unclear	-

Narayan 2008

Methods	Randomised clinical trial.	
Participants	97 adult patients (>18 years old) with traumatic brain injury, a Glasgow Coma Scale (GCS) score between 4 and 14, and evidence of traumatic intracerebral bleeding with a total volume of at least 2 ml on the baseline CT scan obtained within 6 hours of the injury. Exclusion criteria were: the presence of penetrating head or spinal cord injury; life expectancy of less than 24 hours after hospital admission; any planned surgical evacuation of intracerebral haematoma within 24 hours after dosing; isolated subarachnoid haemorrhage, intraventricular haemorrhage, epidural or subdural haematomas or sICH; significant cardiovascular disease or dysfunction; haemodynamic instability; known history of hypercoagulability or thromboembolism; current vitamin K antagonist use; and pregnancy.	
Interventions	Five doses of rFVIIa (40, 80, 120, 160, and 200 µg/kg) were compared with placebo in escalating dose tiers. The first dose tier (40 µg/kg) was assigned in a 1:1 ratio to the treatment or placebo group. Subsequent dose tiers were assigned in a 2:1 ratio.	
Outcomes	The primary objective of this study was to evaluate safety of the intervention. All adverse events, defined as deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, cerebral infarction, disseminated intravascular coagulation or coagulopathy were reported until day 15. Early mortality was defined as within 15 days of recruitment, and late mortality as any death after 15 days of recruitment. The effectiveness assessment focused on changes in haematoma volumes on CT scans between baseline, 24 hours, and 72 hours after the intervention.	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not described.
Allocation concealment?	Unclear	Not described.
Blinding? All outcomes	Unclear	Reported as “double blind” but method of blinding was not reported.
Incomplete outcome data addressed? All outcomes	Yes	Outcome reported for all the patients included. The only exception was late mortality (more than 15 days) for which the authors stated that they did not record it systematically for all the patients but recorded only those in-hospital deaths reported by collaborators.
Free of selective reporting?	Unclear	Protocol not available.
Free of other bias?	Unclear	-

Characteristics of excluded studies *[ordered by study ID]*

Auer 1979	This study is described as a randomised controlled trial of aprotinin versus placebo in patients with severe traumatic brain injury but, after randomly allocating the first 20 patients, five patients were added to the aprotinin group. Because it was not possible to separate the outcome data for the 20 randomised and the five non-randomised patients, this study provided no useable outcome data.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Novoseven Study

Methods	Randomised controlled trial.
Participants	550 severely injured trauma patients with bleeding refractory to standard treatment.
Interventions	Three single doses of rFVIIa (200 µg/kg + 100 µg/kg + 100 µg/kg) or placebo.
Outcomes	Mortality at 30 days.
Notes	This study planned to recruit 1502 patients but after recruiting 550 patients, in June 2008 the sponsor (Novo Nordisk) made the announcement that they were stopping this trial as it was futile. Some of the patients recruited in this trial had traumatic brain injury and could provide useful data for this systematic review. We contacted Novo Nordisk but we were unable to obtain any data.

Characteristics of ongoing studies *[ordered by study ID]*

CRASH-2 Trial

Trial name or title	CRASH-2.
Methods	Randomised clinical trial.
Participants	Adults with trauma who are within 8 hours of injury and have either significant haemorrhage or are considered to be at risk of significant haemorrhage. The trial will recruit 20,000 patients and is planned to finish in December 2009.
Interventions	2 g of tranexamic acid or placebo.
Outcomes	Primary outcome: death in hospital within four weeks of injury. Secondary outcome: receipt of a blood product transfusion, the number of units of blood products transfused, surgical intervention, and the occurrence of thromboembolic episodes.
Starting date	May 2005
Contact information	CRASH@lshtm.ac.uk

CRASH-2 Trial (Continued)

Notes	

Tranexamic acid in TBI	
Trial name or title	Tranexamic Acid for Preventing Progressive Intracranial Haemorrhage in Traumatic Brain Injury.
Methods	Randomised clinical trial.
Participants	Adult patients with moderate or severe TBI.
Interventions	2 g of tranexamic acid or placebo.
Outcomes	Primary outcome: progressive intracranial haemorrhage at 24 ± 8 hours confirmed by repeated CT of the brain. Secondary outcome: functional scale (GOS, DRS), mortality, operative treatment (later surgery for bleeding) , adverse effect and transfusion needed.
Starting date	October 2008
Contact information	surakrant@gmail.com
Notes	

DATA AND ANALYSES

Comparison 1. Outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Thrombotic complication	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Change in volume of intracranial bleeding	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Outcomes, Outcome 1 Mortality.

Review: Haemostatic drugs for traumatic brain injury

Comparison: 1 Outcomes

Outcome: 1 Mortality

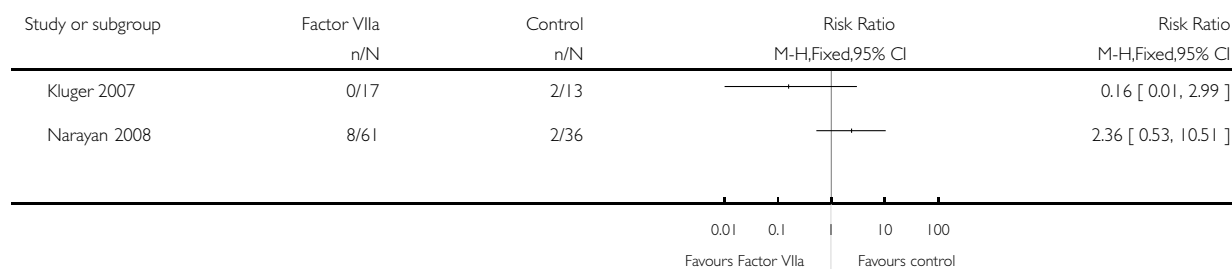
Study or subgroup	Factor VIIa n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Kluger 2007	5/17	6/13		0.64 [0.25, 1.63]
Narayan 2008	11/61	6/36		1.08 [0.44, 2.68]
				

Analysis 1.2. Comparison 1 Outcomes, Outcome 2 Thrombotic complication.

Review: Haemostatic drugs for traumatic brain injury

Comparison: 1 Outcomes

Outcome: 2 Thrombotic complication

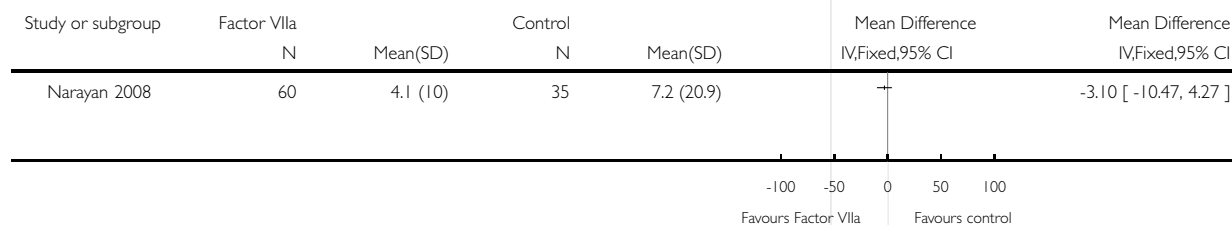


Analysis 1.3. Comparison 1 Outcomes, Outcome 3 Change in volume of intracranial bleeding.

Review: Haemostatic drugs for traumatic brain injury

Comparison: 1 Outcomes

Outcome: 3 Change in volume of intracranial bleeding



APPENDICES

Appendix I. Search strategy

Cochrane Injuries Group Specialised Register (searched 3 February 2009)

1. ((haemosta* or hemosta* or antihemorrhag* or antihemorrhag*) and (drug* or agent* or treat* or therap*)) or ((coagulat* or clotting) and (factor*)) or ("Tranexamic Acid" or Antithrombins* or anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin* or "plasmin inhibitors" or "thrombin inhibitors" or "factor 7a" or "factor VIIa" or factor IXa)
2. ((head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) and (injur* or trauma* or damag* or wound* or fracture* or contusion*)) or ((head or crani* or cerebr* or brain* or intra-cran* or inter-cran*) and (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or pressure)) or ((brain or cerebral or intracranial) and (oedema or edema or swell*)) or ((unconscious* or coma* or concuss* or 'persistent vegetative state') and (injur* or trauma* or damag* or wound* or fracture*)) or ("Glasgow coma score") or ("Glasgow outcome score") or ("Glasgow coma scale") or ("Glasgow outcome scale") or ("diffuse axonal injury" or "diffuse axonal injuries")
3. 1 and 2

CENTRAL (*The Cochrane Library 2009, Issue 1*)

- #1 MeSH descriptor Craniocerebral Trauma explode all trees
- #2 MeSH descriptor Cerebrovascular Trauma explode all trees
- #3 MeSH descriptor Brain Edema explode all trees
- #4 (brain or cerebral or intracranial) next (oedema or edema or swell*)
- #5 MeSH descriptor Glasgow Coma Scale explode all trees
- #6 MeSH descriptor Glasgow Outcome Scale explode all trees
- #7 MeSH descriptor Unconsciousness explode all trees
- #8 glasgow next (coma or outcome) next (score or scale)
- #9 (Unconscious* or coma* or concuss* or 'persistent vegetative state') near5 (injur* or trauma* or damag* or wound* or fracture*)
- #10 "Rancho Los Amigos Scale"
- #11 (head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) near3 (injur* or trauma* or damag* or wound* or fracture* or contusion*)
- #12 Diffuse next axonal next injur*
- #13 (head or crani* or cerebr* or brain* or intra-cran* or inter-cran*) near3 (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or pressure)
- #14 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)
- #15 MeSH descriptor Hemostatics explode all trees
- #16 MeSH descriptor Blood Coagulation Factors explode all trees
- #17 MeSH descriptor Hemostasis explode all trees with qualifier: DE
- #18 MeSH descriptor Blood Coagulation explode all trees with qualifier: DE
- #19 MeSH descriptor Fibrinolysis explode all trees with qualifier: DE
- #20 MeSH descriptor Platelet Activation explode all trees with qualifier: DE
- #21 MeSH descriptor Antithrombins explode all trees with qualifier: DE
- #22 MeSH descriptor Thrombin explode all trees with qualifier: DE
- #23 (haemosta* or hemosta* or antihemorrhag* or antihemorrhag*) near5 (drug* or agent* or treat* or therap*):ab,ti
- #24 (coagulat* or clotting) next (factor*):ab,ti
- #25 MeSH descriptor Factor VIIa explode all trees
- #26 (factor) next (7a or VIIa or VII):ab,ti
- #27 MeSH descriptor Factor IXa explode all trees
- #28 MeSH descriptor Estrogens, Conjugated (USP) explode all trees
- #29 (conjugated next estrogen*) or (carentil or congest or dagynil or oestrofeminal or estro-feminal or oestro-feminal or prelestrin or premarin or climarest or climopax or presomen or progens or transannon or femavit):ab,ti
- #30 MeSH descriptor Erythropoietin explode all trees
- #31 MeSH descriptor Erythropoietin, Recombinant explode all trees
- #32 erythropoietin or recormon or epoetin alfa or epogen or eprex:ti,ab
- #33 MeSH descriptor Deamino Arginine Vasopressin explode all trees

#34 (deamino next arginine) or (desmopressin or adiuretin or apo-desmopressin or ddavp or desmopressine or desmospray or desmotabs or octim or octostim or minirin or minurin or desmogalen or nocutil or stimate or Arginine or Vasopressins or DDVAP):ti
 #35 MeSH descriptor Antifibrinolytic Agents explode all trees
 #36 MeSH descriptor Aprotinin explode all trees
 #37 MeSH descriptor Aminocaproic Acids explode all trees
 #38 MeSH descriptor Tranexamic Acid explode all trees
 #39 (aminocaproic or 6-aminohexanoic or epsilon-aminocaproic) next (acid*):ti
 #40 (tranexamic acid or TXA or amcha or amca or cyklokapron or kabi-2161 or transamin or ugurol or t-amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid or EACA):ab,ti
 #41 (amicar or caprocid or epsamon or epsikapron or aprotinin* or BPTI or antilysin or contrical or contrykal or dilmintal or iniprol or kontrikal or kontrykal or pulmin or trasylol or zymofren or argatroban):ab,ti
 #42 (Basic or bovine or kunitz or kallikrein) next (trypsin inhibitor* or trypsin inactivator*):ab,ti
 #43 (kallikrein-trypsin or bovine pancreatic trypsin or tranexamic or cyklokapron or pharmacia or t-amcha or amcha or ugurol or transamin or kabi or epsilon-aminocaproic acid or aminocaproic or lederle):ab,ti
 #44 (anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin*) or (plasmin next inhibitor*) or (thrombin next inhibitor*):ab,ti
 #45 (#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44)
 #46 (#14 AND #45)

MEDLINE (Ovid SP) 1950 to week 3 January 2009

1. exp Craniocerebral Trauma/
2. exp Brain Edema/
3. exp Glasgow Coma Scale/
4. exp Glasgow Outcome Scale/
5. exp Unconsciousness/
6. exp Cerebrovascular Trauma/
7. ((head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) adj3 (injur* or trauma* or damag* or wound* or fracture* or contusion*)):ab,ti.
8. ((head or crani* or cerebr* or brain* or intra-cran* or inter-cran*) adj3 (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or pressure)):ti,ab.
9. (Glasgow adj (coma or outcome) adj (scale* or score*)):ab,ti.
10. "rancho los amigos scale".ti,ab.
11. ("diffuse axonal injury" or "diffuse axonal injuries").ti,ab.
12. ((brain or cerebral or intracranial) adj (oedema or edema or swell*)):ab,ti.
13. ((unconscious* or coma* or concuss* or 'persistent vegetative state') adj5 (injur* or trauma* or damag* or wound* or fracture*)):ti,ab.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. exp hemostatics/
16. exp blood coagulation factors/
17. hemostasis/de or blood coagulation/de or fibrinolysis/de or exp platelet activation/de or exp antithrombins/ or thrombin/ai
18. ((h?emosta* or antih?emorrhag*) adj5 (drug* or agent* or treat* or therap*)):ab,ti.
19. ((coagulat* or clotting) adj factor*):ab,ti.
20. exp Factor VIIa/
21. (factor adj (7a or VIIa or VII)):ab,ti.
22. exp factor ixa/
23. exp "Estrogens, Conjugated (USP)"/
24. ((conjugated adj3 estrogen*) or carentil or congest or dagynil or oestrofeminal or estro-feminal or oestro-feminal or prelestrin or premarin or climarest or climopax or presomen or progens or transannon or femavit):ab,ti.
25. exp Erythropoietin/ or exp Erythropoietin, Recombinant/ or exp Receptors, Erythropoietin/
26. (erythropoietin or recormon or epoetin alfa or epogen or eprex):ti,ab.
27. exp Deamino Arginine Vasopressin/
28. ((deamino adj arginine) or desmopressin or adiuretin or apo-desmopressin or ddavp or desmopressine or desmospray or desmotabs or octim or octostim or minirin or minurin or desmogalen or nocutil or stimate or Arginine or Vasopressins or DDVAP):ti.
29. exp Antifibrinolytic Agents/

30. exp Aprotinin/
31. exp Aminocaproic Acids/
32. exp Tranexamic Acid/
33. ((aminocaproic or 6-aminohexanoic or epsilon-aminocaproic) adj acid*).ti,ab.
34. (tranexamic acid or TXA or amcha or amca or cyklokapron or kabi-2161 or transamin or ugurol or t-amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid or EACA).ab,ti.
35. (amicar or caprocid or epsamon or epsikapron or aprotinin* or BPTI or antilysin or contrical or contrykal or dilmintal or iniprol or kontrikal or kontrykal or pulmin or trasyolol or zymofren or argatroban).ab,ti.
36. ((Basic or bovine or kunitz or kallikrein) adj (trypsin inhibitor* or trypsin inactivator*)).ab,ti.
37. (kallikrein-trypsin or bovine pancreatic trypsin or tranexamic or cyklokapron or pharmacia or t-amcha or amcha or ugurol or transamin or kabi or epsilon-aminocaproic acid or aminocaproic or lederle).ab,ti.
38. (anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin* or (plasmin adj inhibitor*) or (thrombin adj inhibitor*)).ab,ti.
39. 15 or 16 or 17 or 18 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40. 14 and 39
41. randomi?ed.ab,ti.
42. randomized controlled trial.pt.
43. controlled clinical trial.pt.
44. placebo.ab.
45. clinical trials as topic.sh.
46. randomly.ab.
47. trial.ti.
48. 41 or 42 or 43 or 44 or 45 or 46 or 47
49. (animals not (humans and animals)).sh.
50. 48 not 49
51. 40 and 50

PubMed (www.ncbi.nlm.nih.gov/sites/entrez/) (searched 3 Feb 2009; added to PubMed in the last 180 days)

#1((haemosta* or hemosta* or antihemorrhag* or antihemorrhag*) and (drug or drugs or agent* or treatment* or therapy or therapies or therapeutic*)) or ((coagulat* or clotting) and (factor or factors)) or ("Tranexamic Acid" or Antithrombins* or anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin* or "plasmin inhibitors" or "thrombin inhibitors" or "factor 7a" or "factor VIIa" or factor IXa)

#2((head or craniu* or crania* or cerebra* or cerebru* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) and (injury or injuries or trauma or traumas or traumatic or damag* or wound* or fracture* or contusion*)) or ((head or craniu* or crania* or cerebra* or cerebru* or brain* or intra-cran* or inter-cran*) and (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or pressure)) or ((brain or cerebral or intracranial) and (oedema or edema or swell*)) or ((unconscious* or coma* or concuss* or 'persistent vegetative state') and (injury or injuries or trauma or traumas or traumatic or damag* or wound* or fracture*)) or ("Glasgow coma score") or ("Glasgow outcome score") or ("Glasgow coma scale") or ("Glasgow outcome scale") or ("diffuse axonal injury" or "diffuse axonal injuries"))

#3((randomized controlled trial[pt] OR controlled clinical trial[pt]) OR (randomized OR randomised OR randomly OR placebo[tiab]) OR (trial[ti] OR ("Clinical Trials as Topic"[MeSH Major Topic])) NOT (("Animals"[Mesh]) NOT ("Humans"[Mesh] AND "Animals"[Mesh]))

#4#1 and #2 and #3

EMBASE (Ovid SP) 1980 to week 4 January 2009

- 1.exp Brain Injury/
- 2.exp Brain Edema/
- 3.exp Glasgow Coma Scale/
- 4.exp Glasgow Outcome Scale/
- 5.exp Rancho Los Amigos Scale/
- 6.exp Unconsciousness/
- 7.((brain or cerebral or intracranial) adj5 (oedema or edema or swell\$)).ab,ti.

Haemostatic drugs for traumatic brain injury (Review)

8.((head or crani\$ or cerebr\$ or capitis or brain\$ or forebrain\$ or skull\$ or hemispher\$ or intra-cran\$ or inter-cran\$) adj5 (injur\$ or trauma\$ or damag\$ or wound\$ or fracture\$ or contusion\$)).ab,ti.
9.(Glasgow adj (coma or outcome) adj (scale\$ or score\$)).ab,ti.
10.Rancho Los Amigos Scale.ab,ti.
11.((unconscious\$ or coma\$ or concuss\$ or 'persistent vegetative state') adj3 (injur\$ or trauma\$ or damag\$ or wound\$ or fracture\$)).ti,ab.
12.Diffuse axonal injur\$.ab,ti.
13.((head or crani\$ or cerebr\$ or brain\$ or intra-cran\$ or inter-cran\$) adj3 (haematoma\$ or hematoma\$ or haemorrhag\$ or hemorrhag\$ or bleed\$ or pressure)).ab,ti.
14.or/1-13
15.exp Randomized Controlled Trial/
16.exp controlled clinical trial/
17.randomi?ed.ab,ti.
18.placebo.ab.
19.*Clinical Trial/
20.randomly.ab.
21.trial.ti.
22.15 or 16 or 17 or 18 or 19 or 20 or 21
23.exp animal/ not (exp human/ and exp animal/)
24.22 not 23
25.14 and 24
26.exp Hemostatic Agent/
27.exp Blood Clotting Factor/
28.hemostasis/de or blood coagulation/de or fibrinolysis/de or exp platelet activation/de or exp antithrombins/ or thrombin/ai
29.((h?emosta* or antih?emorrhag*) adj5 (drug* or agent* or treat* or therap*)).ab,ti.
30.((coagulat* or clotting) adj factor*).ab,ti.
31.exp Blood Clotting Factor 7a/
32.(factor adj (7a or VIIa or VII)).ab,ti.
33.exp Blood Clotting Factor 9a/
34.exp "Estrogens, Conjugated (USP)"/
35.((conjugated adj3 estrogen*) or carenil or congest or dagynil or oestrofeminal or estro-feminal or oestro-feminal or prelestrin or premarin or climarest or climopax or presomen or progens or transannon or femavit).ab,ti.
36.exp Erythropoietin/ or exp Recombinant Erythropoietin/ or exp Erythropoietin Receptor/
37.(erythropoietin or recormon or epoetin alfa or epogen or epex).ti,ab.
38.exp "Argipressin[1 Deamino]"/
39.((deamino adj arginine) or desmopressin or adiuretin or apo-desmopressin or ddavp or desmopressine or desmospray or desmotabs or octim or octostim or minirin or minurin or desmogalen or nocutil or stimite or Arginine or Vasopressins or DDVAP).ti.
40.exp Antifibrinolytic Agent/
41.exp Aprotinin/
42.exp Aminocaproic Acid/ or exp Aminocaproic Acid Derivative/
43.exp Tranexamic Acid/
44.((aminocaproic or 6-aminohexanoic or epsilon-aminocaproic) adj acid*).ti,ab.
45.(tranexamic acid or TXA or amcha or amca or cyklokapron or kabi-2161 or transamin or ugurol or t-amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid or EACA).ab,ti.
46.(amicar or caprocid or epsamon or epsikapron or aprotinin* or BPTI or antilysin or contrical or contrykal or dilmintal or iniprol or kontrikal or kontrykal or pulmin or trasylol or zymofren or argatroban).ab,ti.
47.((Basic or bovine or kunitz or kallikrein) adj (trypsin inhibitor* or trypsin inactivator*)).ab,ti.
48.(kallikrein-trypsin or bovine pancreatic trypsin or tranexamic or cyklokapron or pharmacia or t-amcha or amcha or ugurol or transamin or kabi or epsilon-aminocaproic acid or aminocaproic or lederle).ab,ti.
49.(anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin* or (plasmin adj inhibitor*) or (thrombin adj inhibitor*)).ab,ti.
50.or/26-49
51.25 and 50

CINAHL (EBSCO) 1982 to January 2009

- 1.S35 (S24 and S34)
- 2.S34 (S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33)
- 3.S33 TI (anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or
- 4.anti-fibrinolysin* or antiplasmin* or anti-plasmin*) or TI plasmin
- 5.inhibitor* or TI thrombin inhibitor*
- 6.S32 AB (anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or
- 7.anti-fibrinolysin* or antiplasmin* or anti-plasmin*) or AB plasmin
- 8.inhibitor* or AB thrombin inhibitor*
- 9.S31 AB (coagulat* or clotting) and AB factor*
- 10.S30 TI (coagulat* or clotting) and TI factor*
- 11.S29 TI (haemosta* or hemosta* or antihemorrhag* or antihemorrhag*) and
- 12.TI (drug* or agent* or treat* or therap*)
- 13.S28 AB (haemosta* or hemosta* or antihemorrhag* or antihemorrhag*) and
- 14.AB (drug* or agent* or treat* or therap*)
- 15.S27 (MH "Blood Coagulation+")
- 16.S26 (MH "Blood Coagulation Factors+")
- 17.S25 (MH "Hemostatics+") or (MH "Hemostatic Techniques+")
- 18.S24 (S11 and S23)
- 19.S23 (S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or
- 20.S22)
- 21.S22 AB singl* W3 blind* or AB doubl* W3 blind* or AB trebl* W3 blind* or
- 22.AB tripl* W3 blind*
- 23.S21 TI singl* W3 blind* or TI doubl* W3 blind* or TI trebl* W3 blind* or
- 24.TI tripl* W3 blind*
- 25.S20 MH quantitative studies
- 26.S19 TX random* N3 allocat*
- 27.S18 MH random assignment
- 28.S17 TX placebo*
- 29.S16 MH placebos
- 30.S15 TX randomi?ed N3 control* N3 trial*
- 31.S14 TX clinical N3 trial*
- 32.S13 PT clinical trial*
- 33.S12 MH clinical trials
- 34.S11 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10
- 35.S10 TI (head or crani* or cerebr* or brain* or intra-cran* or inter-cran*
- 36.) and AB (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed*
- 37.or pressure)
- 38.S9 AB (head or crani* or cerebr* or capitis or brain* or forebrain* or
- 39.skull* or hemispher* or intra-cran* or inter-cran*) and TI (injur* or
- 40.trauma* or damag* or wound* or fracture* or contusion*)
- 41.S8 TX Diffuse W1 axonal N3 injur*
- 42.S7 TX Rancho Los Amigos Scale
- 43.S6 AB (Unconscious* or coma* or concuss* or "persistent vegetative state"
- 44.) and TI (injur* or trauma* or damag* or wound* or fracture*)
- 45.S5 TX glasgow and TX (coma or outcome) and TX (score or scale)
- 46.S4 (MH "Unconsciousness+") or (MH "Brain Concussion+")
- 47.S3 (MH "Glasgow Coma Scale")
- 48.S2 (MH "Brain Injuries+")
- 49.S1 (MH "Head Injuries+")

ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to January 2009) and Conference Proceedings Citation Index- Science (CPCI-S) (1990 to January 2009)

1. Topic=((haemosta* or hemosta* or antihæmorrhag* or antihæmorrhag*) SAME (drug* or agent* or treat* or therap*)) OR Topic=((coagulat* or clotting) SAME (factor*)) OR Topic=((factor) SAME (7a or VIIa or VII OR IX)) OR Topic=((conjugated) SAME (estrogen* OR oestrogen*))
2. Topic=(carenil or congest or dagynil or oestrofeminal or estro-feminal or oestro-feminal or prelestrin or premarin or climarest or climopax or presomen or progens or transannon or femavit) OR Topic=(erythropoietin or recormon or epoetin alfa or epogen or eprex) AND Topic=(desmopressin or adiuretin or apo-desmopressin or ddavp or desmopressine or desmospray or desmotabs or octim or octostim or minirin or minurin or desmogalen or nocutil or stimate or Arginine or Vasopressins or DDVAP) AND Topic=(deamino SAME arginine)
3. Topic=(amicar or caprocid or epsamon or epsikapron or aprotinin* or BPTI or antilysin or contrical or contrykal or dilmintal or iniprol or kontrikal or kontrykal or pulmin or trasylol or zymofren or argatroban OR Aminocaproic Acid* OR Tranexamic Acid*) OR Topic=(anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin*) OR Topic=(plasmin SAME inhibitor*) OR Topic=(thrombin SAME inhibitor*)
4. Topic=(kallikrein-trypsin or bovine pancreatic trypsin or tranexamic or cyklokapron or pharmacia or t-amcha or amcha or ugurol or transamin or kabi or epsilon-aminocaproic acid or aminocaproic or lederle) OR Topic=((Basic or bovine or kunitz or kallikrein) SAME (trypsin inhibitor* or trypsin inactivator*))
5. 1 or 2 or 3 or 4
6. Topic=(glasgow SAME (coma or outcome) SAME (score or scale)) OR Topic=((Unconscious* or coma* or concuss* or 'persistent vegetative state') SAME (injur* or trauma* or damag* or wound* or fracture*)) OR Topic=(“Rancho Los Amigos Scale” OR diffuse axonal injur*) OR Topic=((head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) same (injur* or trauma* or damag* or wound* or fracture* or contusion*)) OR Topic=((head or crani* or cerebr* or brain* or intra-cran* or inter-cran*) SAME (haematoma* or hematoma* or hæmorrhag* or hemorrhag* or bleed* or pressure))
7. TS=((injur* or trauma* or lesion* or damage* or wound* or oedema* or edema* or fracture* or contusion* or concus* or commotion* or pressur*) SAME (head or crani* or capitis or brain* or forebrain* or skull* or hemisphere or intracran* or orbit*)) OR TS=(Craniocerebral Trauma OR Cerebrovascular Trauma OR Brain Edema) OR TS=((brain or cerebral or intracranial) SAME (oedema or edema or swell*))
8. 6 or 7
9. Topic=((singl* OR doubl* OR trebl* OR tripl*) SAME (blind* OR mask*))
10. Topic=(randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial) OR Topic=(controlled clinical trial OR controlled trial OR clinical trial OR placebo)
11. 9 or 10
12. 5 and 8 and 11

HISTORY

Protocol first published: Issue 3, 2009

Review first published: Issue 1, 2010

CONTRIBUTIONS OF AUTHORS

PP and IR developed the search strategy, scanned the search results, extracted the data and drafted the first version of the review. SY drafted the first version of the protocol, which provides the foundation of the review.

All the authors edited and approved the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Thai Cochrane Network, Thailand.
- Faculty of Medicine, Khon Kaen University, Thailand.
- Khon Kaen Hospital, Ministry of Public Health, Thailand.
- Cochrane Injuries Group, UK.
- London School of Hygiene & Tropical Medicine, UK.

External sources

- The Thailand Research Fund, Senior Research Scholar, Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We removed desmopressin, oestrogens, and activated factor IX from the interventions, and we focused on the most commonly used haemostatic drugs (antifibrinolytics, and rFVIIa).

INDEX TERMS

Medical Subject Headings (MeSH)

Cerebral Hemorrhage, Traumatic [*drug therapy]; Factor VIIa [*therapeutic use]; Head Injuries, Closed [*complications]; Hemostatics [*therapeutic use]; Randomized Controlled Trials as Topic; Recombinant Proteins [therapeutic use]

MeSH check words

Humans

Roselle for hypertension in adults (Review)

Ngamjarus C, Pattanittum P, Somboonporn C



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<http://www.thecochranelibrary.com>



Roselle for hypertension in adults (Review)

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[Intervention Review]

Roselle for hypertension in adults

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Editorial group: Cochrane Hypertension Group.

Publication status and date: New, published in Issue 1, 2010.

Review content assessed as up-to-date: 30 September 2009.

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ABSTRACT

Background

Hypertension is considered a serious health problem worldwide. Controlling and lowering blood pressure have a significant benefit to the hypertensive patients because hypertension is a risk factor for stroke, heart disease and cardiovascular disease. A tropical plant called Roselle, or Red Sorrel in English-speaking countries, has been used both as a thirst-quenching drink and for medical purposes.

Objectives

To explore the effect of Roselle on blood pressure in hypertensive adult patients.

Search strategy

Roselle for hypertension in adults (Review)

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The following databases were searched (Date of most recent search was September 2009):

- Cochrane Database of Systematic Reviews (2nd Quarter 2009)
- DARE (2nd Quarter 2009)
- Ovid MEDLINE (1950 to Present with Daily Update)
- EMBASE (1980 to 2009 Week 22)
- AMED (1985 to May 2009)
- EBSCO CINAHL
- BIOSIS (1969 to 2008)
- AGRICOLA (1970 to May 2009)
- Food Science and Technology Abstract (1969 to 2009 June Week 1)
- International Pharmaceutical Abstracts
- International Bibliographic Information on Dietary Supplements
- Clinical Trials.gov and Current Controlled Trials
- OpenSIGLE
- Hand searching of journals
- ISI Web of Knowledge

Selection criteria

We sought randomised control trials (RCTs) evaluating use of any forms of Roselle with placebo or no treatment in hypertensive patients. Change in trough and/or peak systolic and diastolic blood pressure were primary outcomes. Secondary outcomes were withdrawals due to adverse effects, change of pulse pressure and change of heart rate.

Data collection and analysis

Two review authors (C Ngamjarus, CN and P Pattanittum, PP) independently scanned titles and abstracts, as well as independently screened the full reports of the potentially relevant studies. At each stage, the results were compared and disagreements were solved by discussion.

Main results

No studies were identified that met the inclusion criteria. However, one abstract of an ongoing study is likely to meet the inclusion criteria, when completed.

Authors' conclusions

There is insufficient evidence to support the benefit of Roselle for either controlling or lowering blood pressure in patients with hypertension. Based on the information of this review, there is a clear need to develop well-designed studies to assess the efficacy of Roselle on hypertensive patients.

PLAIN LANGUAGE SUMMARY

No evidence that red tea (Roselle) lowers blood pressure in adults

Hypertension is a serious health problems worldwide. Controlling and lowering blood pressure have a significant benefit to the hypertensive patients because hypertension is a risk factor for stroke, heart disease and cardiovascular disease. A tropical plant called Roselle or red tea has been used as a thirst-quenching drink and for medical purposes. We searched for evidence from clinical studies to evaluate the effectiveness of red tea compared with placebo or no treatment in hypertensive patients. There is a lack of evidence from

randomised control trials to demonstrate a benefit of Roselle tea in reducing blood pressure. Rigorous studies need to be done in order to answer this question.

BACKGROUND

Description of the condition

The classification of hypertension in adults according to blood pressure values was recently described in the Australian 'Guide to management of hypertension 2008'. This guideline considers a patient as hypertensive when either systolic blood pressure ≥ 140 millimetres of mercury (mmHg) or diastolic blood pressure ≥ 90 mmHg. (National 2008)

Hypertension is considered a serious health problem worldwide. It is ranked among the top 20 global risk factors for mortality (Majid 2002). Between a fifth and a quarter of most adults would meet the classification of hypertension (MacMahon 2005).

Description of the intervention

Hibiscus Sabdariffa Linne, a member of the family Malvaceae, known as Roselle or Red Sorrel in English-speaking countries, is a tropical plant, widely grown in Central and West Africa, South-East Asia, and elsewhere. Common names, besides Roselle, are Red Sorrel, Karkade, sour tea and red tea (Mozaffari-Khosravi 2009, Ali 2005). Various parts of Roselle (flower, leaves, calyx and corolla) are used in beverages in China, Taiwan and Thailand both as a thirst-quenching drink and for medical purposes (Wright 2007) and recently, for its alleged antihypertensive properties (Herrera-Arellano 2004). The chemical components contained in Roselle include anthocyanins, flavonoids and polyphenols (Lin 2007). The extracts of Roselle are also used in folk medicine against many complaints that include high blood pressure, liver disease and fever. The red anthocyanin pigments in the calyces are used as food colouring agents (Ali 2005).

How the intervention might work

Many studies investigated the capabilities of Roselle on blood pressure. In animal studies, it was found by Mojiminiyi 2007 that an aqueous extract of the calyx of Roselle possesses anti-hypertensive, hypotensive and negative chronotropic effects (Roselle was administered as dissolved in normal saline). Odigie 2003 conducted their study in renovascular hypertensive rats. They suggested that the aqueous extract of Roselle petal exhibited antihypertensive and cardioprotective properties, which supported the public belief that

Roselle may be a useful antihypertensive agent. Onyenekwe 1999 reported that Roselle calyx infusion was found to lower significantly both systolic and diastolic pressure in spontaneously hypertensive and normotensive Wistar-Kyoto rats.

In humans, Herrera-Arellano 2007 assessed the effects of dried extract of Roselle calyces on patients with stage I or II hypertension, aged 25-61 years. The results showed that the dried extract of Roselle calyces decreased blood pressure from 146/98 to 130/86 mmHg. They concluded that Roselle exerted important antihypertensive effectiveness with a wide margin of tolerability and safety. McKay 2007 reported in their research project that consuming Roselle tea lowered blood pressure in mildly hypertensive adults (Roselle tea compared with artificial flavouring and colour). The information from a non-Cochrane systematic review (Thavorn 2006) and a mini-review (Ernst 2005) confirmed the modest antihypertensive effects observed in the study of Herrera-Arellano 2004 (dry calyx from Roselle significantly decreased both systolic and diastolic blood pressure of hypertensive patients, aged 30-80 years) and found a marked effect (11% reduction) on both systolic and diastolic blood pressure in patients with moderate essential hypertension (Haji 1999).

Why it is important to do this review

As mentioned above, hypertension is a global risk factor for mortality and there are many people who suffer from hypertension. Lowering blood pressure level will likely decrease the risk of stroke and cardiovascular disease. Therefore, it is important to explore the effectiveness of Hibiscus Sabdariffa Linne for lowering blood pressure in hypertensive patients.

OBJECTIVES

To determine the effect of Roselle (Hibiscus Sabdariffa Linne) on blood pressure in patients with primary hypertension.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCT) comparing the use of any forms of Roselle with placebo (or no intervention) in patients with hypertension. Minimum duration of study was 3 weeks and maximum duration was 12 weeks.

Types of participants

Adults (18 years or older) who had at least 140 mmHg systolic blood pressure or at least 90 mmHg diastolic blood pressure. At least two BP measurements were needed at baseline to qualify patients as being hypertensive. Pregnant women were excluded.

Types of interventions

Any forms of Roselle compared to placebo or no treatment.

Types of outcome measures

Primary outcomes

Change in trough (13 to 26 hours after the dose) and/or peak (1 to 12 hours after the dose) systolic (SBP) and diastolic blood pressure (DBP) compared to placebo or no treatment. If blood pressure measurements were available at more than one time within the acceptable window, the weighted means of blood pressures taken in the 3-12 week range were used.

Secondary outcomes

1. withdrawals due to adverse effects
2. change of pulse pressure (mm Hg)
3. change of heart rate (beats/min)

Search methods for identification of studies

Electronic searches

The Database of Abstracts of Reviews of Effectiveness (DARE) and the Cochrane Database of Systematic Reviews were searched for related reviews (see [Appendix 1](#)).

The following electronic databases were searched for primary studies in June 2009:

1. The Cochrane Central Register of Controlled Trials (CENTRAL) (see [Appendix 2](#))
2. English language databases, including MEDLINE (2005-9) (see [Appendix 3](#)), EMBASE (2007-9) (see [Appendix 4](#)), AMED - Allied and Complementary Medicine Database (1985- May 2009) (see [Appendix 5](#)), CINAHL (1982-2009) (see [Appendix 6](#)), BIOSIS (1969-2008) (see [Appendix 7](#)), AGRICOLA (1970-

May 2009) (see [Appendix 8](#)), Food Science and Technology Abstracts (1969 - June 2009 Week 1) (see [Appendix 9](#)), International Pharmaceutical Abstracts (1970 - May 2009) (see [Appendix 10](#)) and International Bibliographic Information on Dietary Supplements (IBID) (see [Appendix 11](#)).

Electronic databases were searched using a modified version of the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity-maximizing version (2008 revision) with selected MeSH terms and free text terms relating to Roselle and hypertension. No language restrictions were used. The MEDLINE search strategy ([Appendix 3](#)) was translated into the other databases using the appropriate controlled vocabulary as applicable.

Full strategies for English language databases have been included in the Appendices of the review.

Searching other resources

1. Clinical Trials.gov and Current Controlled Trials (see [Appendix 12](#)).
2. OpenSIGLE (System for Information on Grey Literature in Europe) (see [Appendix 13](#)).
3. Hand searching of those high-yield journals and conference proceedings which have not already been hand searched on behalf of the Cochrane Collaboration (see [Appendix 14](#)).
4. Reference lists of all papers and relevant reviews identified.
5. Authors of relevant papers were contacted regarding any further published or unpublished work.
6. Authors of trials reporting incomplete information were contacted to provide the missing information.
7. ISI Web of Science (see [Appendix 15](#)).

Data collection and analysis

We created and pilot test a data collection form. This form was used to collect the data from the potential studies that were selected by the review authors. We collected any data of the potential studies, including details of methods, participants, interventions, outcomes and results.

For selecting the studies, two review authors (CN and PP) independently screened the titles and abstracts that were obtained by the search strategies mentioned above. Any disagreement in screening resolved by discussion and consultation with the third review author (C Somboonporn, CS). We identified potential studies by applying the inclusion criteria before data extraction.

We found that there were no studies which met our criteria. Therefore, CN wrote reasons for exclusion of the excluded studies in tables of characteristics of excluded studies in the RevMan software ([RevMan 2008](#)). To addition, we contacted authors of the original studies to provide additional information when information from the potential studies was unclear. CN did not conduct the meta-

analysis due to no studies were identified for inclusion in this review.

Although no studies were included in this reviews, the methods of data extraction, data management, assessment of risk of bias and data analysis will be applied in subsequent updates of this review when future studies meet our criteria (see [Appendix 16](#)).

RESULTS

Description of studies

See: [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#).

No studies found met the inclusion criteria for this review. For the reasons of exclusion see [Characteristics of excluded studies](#).

Results of the search

The search of 14 electronic databases and 3 hand searching of journals (see '[Appendix 1](#)'; to [Appendix 15](#)' for database name and search terms) resulted in 159 records. A total of 137 records were excluded after screening the titles and the abstracts by two review authors (CN and PP). Twenty-six records were considered relevant and were retrieved for further assessment. After 17 duplicates were removed, 9 articles were retrieved for the full text. There were 6 full texts available and for the other three only the abstracts could be obtained.

We excluded 2 articles after reviewing the full text because they were not done in hypertensive patients and one abstract was excluded because it was not an RCT.

Four of the full texts and two abstracts were comprehensively considered. For the two abstracts, we contacted the authors and were informed that [McKay 2007](#) was an initial report of [McKay 2008](#); therefore [McKay 2007](#) was excluded, whereas [McKay 2008](#) is in the process of publishing the full article (see '[Characteristics of studies awaiting classification](#)' for further details). None of the remaining four full texts met our inclusion criteria (see '[Characteristics of excluded studies](#)' for further details).

Included studies

No studies met the inclusion criteria for this review.

Excluded studies

Studies found through our literature search were excluded because they did not meet the inclusion criteria. The reasons for exclusion are reported in the [Characteristics of excluded studies](#).

Risk of bias in included studies

No studies were included.

Effects of interventions

No data available for analysis because no studies were included.

DISCUSSION

No reliable conclusions can be drawn about the benefit of Roselle for either controlling or lowering blood pressure in patients with hypertension compared to placebo or no treatment.

Although the evidence does not exist to demonstrate the efficacy of Roselle for hypertension compared to placebo or no treatment, studies were conducted comparing Roselle with antihypertensive agents. [Herrera-Arellano 2004](#) compared Roselle tea to captopril, an angiotensin converting enzyme (ACE) inhibitor that is used for the treatment of hypertension. In this study Roselle tea administered for 4 weeks decreased SBP and DBP of 53 mild and moderate hypertensive patients from 139 to 124 mmHg and 91 to 80 mmHg, respectively, and no side-effects or intolerability were detected. [Herrera-Arellano 2007](#) studied the effect of Roselle compared to lisinopril (another ACE inhibitor) and reported that after one hundred hypertensive patients consumed Roselle for 4 weeks, the SBP and DBP dropped from 146 to 130 mmHg and 98 to 86 mmHg, respectively.

In addition, two studies showed an advantage of Roselle compared to ordinary tea and black tea. [Haji 1999](#) evaluated the effect of Roselle tea and ordinary tea in essential hypertensive patients. The information from 31 patients in the Roselle group revealed that at 12 days SBP and DBP were reduced by 11.2% and 10.8% as compared to the first day. [Mozaffari-Khosravi 2009](#) compared Roselle tea to black tea in hypertensive patients with type II diabetes. It was found that SBP of 27 patients before and after drinking Roselle tea for 15 and 30 days were 134, 123 and 113 mmHg, respectively. The DBP of those patients at days 0, 15 and 30 were 82, 83 and 81 mmHg, respectively.

At this time, there is a need for well-designed studies evaluating the advantages and adverse effects of Roselle compared with placebo or no treatment in both short- and long-term administration in hypertensive patients.

AUTHORS' CONCLUSIONS

Implications for practice

There is no RCT evidence to indicate whether Roselle can control or lower blood pressure in hypertensive patients compared with placebo or no treatment.

Implications for research

A high quality study is needed to investigate the effects of Roselle compared with placebo or no treatment in hypertensive patients on controlling or lowering blood pressure in both short- and long-

term administration of treatment.

ACKNOWLEDGEMENTS

We would like to thank the Thai Cochrane Network for training on developing a protocol and training on using RevMan 5, Doug Salzwedel for helping in literature searching and Cochrane Hypertension Group for their comments on the protocol and the review.

REFERENCES

References to studies excluded from this review

Haji 1999 *{published data only}*

Haji Faraji M, Haji Tarkhani AH. The effect of sour tea (Hibiscus Sabdariffa) on essential hypertension. *Journal of Ethnopharmacology* 1999; Vol. 65, issue 3:231–6.

Herrera-Arellano 2004 *{published data only}*

Herrera-Arellano A F-RSC-SMATJ. Effectiveness and tolerability of a standardized extract from Hibiscus sabdariffa in patients with mild to moderate hypertension: a controlled and randomized clinical trial. *Phytomedicine* 2004;**11**(5):375–82.

Herrera-Arellano 2007 *{published data only}*

Herrera-Arellano A, Miranda-Sanchez J, Avila-Castro P, Herrera-Alvarez S, Jimenez-Ferrer JE, Zamilpa A, et al. Clinical effects produced by a standardized herbal medicinal product of Hibiscus Sabdariffa on patients with hypertension. A randomized, double-blind, lisinopril-controlled clinical trial. *Planta Medica* 2007; Vol. 73, issue 1:6–12. [: 0032–0943]

McKay 2007 *{published data only}*

McKay DL, Blumberg JB. Hibiscus tea (Hibiscus sabdariffa L.) lowers blood pressure in pre- and mildly hypertensive adults. *Faseb Journal* 2007; Vol. 21, issue 6:A1086. [: 0892–6638]

Mozaffari-Khosravi 2009 *{published data only}*

Mozaffari-Khosravi H, Jalali-Khanabadi BA, Afkhami-Ardekani M, Fatehi F, Noori-Shadkam M. The effects of sour tea (Hibiscus Sabdariffa) on hypertension in patients with type II diabetes. *Journal of Human Hypertension* 2009; Vol. 23, issue 1:48–54. [: 0950–9240]

References to studies awaiting assessment

McKay 2008 *{published data only}*

McKay DL, Saltzman E, Chen CY, Blumberg J. Hibiscus sabdariffa L. Tea (Tisane) Lowers Blood Pressure In Prehypertensive and Mildly Hypertensive Adults. *Circulation* 2008; Vol. 118, issue 18: S1123. [: 0009–7322]

Additional references

Ali 2005

Ali BH, Al Wabel N, Blunden G. Phytochemical, pharmacological and toxicological aspects of Hibiscus Sabdariffa L.: A review.

Phytotherapy Research 2005; Vol. 19, issue 5:369–75. [: 0951–418X]

Ernst 2005

Ernst E. Complementary/alternative medicine for hypertension: A mini-review. *Wiener Medizinische Wochenschrift* 2005; Vol. 155, issue 17–18:386–91. [: 0043–5341]

Herrera-Arellano 2004

Herrera-Arellano A, Flores-Romero S, Chavez-Soto MA, Tortoriello J. Effectiveness and tolerability of a standardized extract from Hibiscus Sabdariffa in patients with mild to moderate hypertension: A controlled and randomized clinical trial. *Phytomedicine* 2004; Vol. 11, issue 5:375–82. [: 0944–7113]

Higgins 2008

Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 [updated February 2008]*. The Cochrane Collaboration, 2008.

Lin 2007

Lin H-H, Chen J-H, Kuo W-H, Wang C-J. Chemopreventive properties of Hibiscus sabdariffa L. on human gastric carcinoma cells through apoptosis induction and JNK/p38 MAPK signaling activation. *Chemico-Biological Interactions* 2007;**165**:59–75.

MacMahon 2005

MacMahon S, Neal B, Rodgers A. Hypertension—time to move on. *The Lancet* 19 March 2005–25 March 2005;**365**(9464):1108–9.

Majid 2002

Majid Ezzati, Alan D Lopez, Anthony Rodgers, Stephen Vander Hoorn, Christopher J L Murray, The Comparative Risk Assessment Collaborating Group. Selected major risk factors and global and regional burden of disease. *The Lancet* 2002;**360**(9343):1347–60.

Mckay 2007

Diane Mckay, Jeffrey Blumberg. The Effect of Hibiscus Sabdariffa L. Tisane on Blood Pressure in Prehypertensive and Mildly Hypertensive Men and Women. *Experimental Biology* April 28, 2007.

Mojiminiyi 2007

Mojiminiyi FBO, Dikko M, Muhammad BY, Ojobor PD, Ajagbonna OP, Okolo RU, et al. Antihypertensive effect of an aqueous extract of the calyx of Hibiscus Sabdariffa. *Fitoterapia* 2007; Vol. 78, issue 4:292–7. [: 0367–326X]

National 2008

National Heart Foundation of Australia (National Blood Pressure and Vascular Disease Advisory Committee). Guide to management of hypertension 2008. Assessing and managing raised blood pressure in adults. Australia, 2008.

Odigie 2003

Odigie IP, Ettarh RR, Adigun SA. Chronic administration of aqueous extract of Hibiscus Sabdariffa attenuates hypertension and reverses cardiac hypertrophy in 2K-1C hypertensive rats. *Journal of Ethnopharmacology* 2003; Vol. 86, issue 2-3:181-5. [: 0378-8741]

Onyenekwe 1999

Onyenekwe PC, Ajani EO, Ameh DA, Gamaniel KS. Antihypertensive effect of Roselle (Hibiscus Sabdariffa) calyx infusion in spontaneously hypertensive rats and a comparison of its toxicity with that in Wistar rats. *Cell Biochemistry and Function* 1999; Vol. 17, issue 3:199-206. [: 0263-6484]

RevMan 2008

The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen, The Nordic Cochrane Centre: The Cochrane Collaboration, 2008.

StataCorp 2007

StataCorp. Stata Statistical Software: Release 10. College Station, TX: StataCorp LP, 2007.

Thavorn 2006

Kednapa Thavorn, Nathorn Chaiyakunapruk, Visanu Thamalikitkul. A Systematic Review of Clinical Efficacy of Hibiscus Sabdariffa. *Thai Pharmaceutical and Health Science Journal* Sep. - Dec. 2006;1:219-225.

Wright 2007

Wright CI, Van-Buren L, Kroner CI, Koning MMG. Herbal medicines as diuretics: A review of the scientific evidence. *Journal of Ethnopharmacology* 2007; Vol. 114, issue 1:1-31. [: 0378-8741]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Haji 1999	Systolic and diastolic blood pressures were measured before and 15 days after the intervention, which does not meet our criteria in types of studies.
Herrera-Arellano 2004	This study compared the effectiveness and tolerability of a standardized extract from Roselle with captopril, which does not meet our criteria in types of interventions.
Herrera-Arellano 2007	This study compared therapeutic effectiveness, tolerability, and safety, as well as the effect on serum electrolytes and the angiotensin-converting enzyme inhibitory effect of a herbal medicinal product prepared from the dried extract of <i>H. sabdariffa</i> calyces with those of lisinopril, which does not meet our criteria in types of interventions.
McKay 2007	This abstract presented the results from first 20 subjects, which were the preliminary data. It was only available as an abstract and was subsequently established that it is a sub-study of McKay 2008 .
Mozaffari-Khosravi 2009	This study compared the antihypertensive effectiveness of sour tea (Roselle) with black tea, which does not meet our criteria in types of interventions.

Characteristics of studies awaiting assessment *[ordered by study ID]*

McKay 2008

Methods	A double-blind, placebo-controlled clinical trial of 6 weeks duration
Participants	65 men and women, aged 30 - 70 years, with SBP 120 - 150 and DBP $\leq$ 95 mm Hg, Subjects were not on BP lowering medications.
Interventions	Hibiscus sabdariffa tisane (3 c/d hibiscus tea) compared with placebo
Outcomes	Lowering of SBP and DBP
Notes	It claims that a standardized method was used to measure BP at 2 baseline visits, 1 week apart, and at weekly intervals thereafter. Treatment lowered SBP (mean $\pm$ SEM) compared with placebo (-7.2 $\pm$ 1.9 vs. -1.3 $\pm$ 1.8 mmHg, p-value=0.030). The change in DBP was not significantly different from placebo (-3.1 $\pm$ 1.2 vs. -0.5 $\pm$ 1.4 mmHg, p-value=0.160). However only the abstract could be found. We contacted the first author via e-mail and the author replied that "the manuscript of our full study is still under review. We are not sure how long this review process will take."

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Cochrane Database of Systematic Reviews search strategy (2nd Quarter 2009)

Searched on 05 June 2009

-
1. (hibiscus or rosella or roselle or ambary or anthocyanin\$ or burao or chemparathampoo or erragogu or esculetin or gogu or karkad\$ or kenaf or sorrel or red tea or sabdarifa or sabdariffa or sour tea or tellagogu or zobo).mp.
 2. hypertens\$.tw.
 3. ((diastolic or systolic or arterial or blood) adj pressure).tw.
 4. 1 and (2 or 3)

Appendix 2. DARE (2nd Quarter 2009) search strategy

Searched on 05 June 2009

-
1. (hibiscus or rosella or roselle or ambary or anthocyanin\$ or burao or chemparathampoo or erragogu or esculetin or gogu or karkad\$ or kenaf or sorrel or red tea or sabdarifa or sabdariffa or sour tea or tellagogu or zobo).mp.
 2. hypertens\$.tw.
 3. ((diastolic or systolic or arterial or blood) adj pressure).tw.
 4. 1 and (2 or 3)

Appendix 3. Ovid MEDLINE (1950 to Present with Daily Update) search strategy

Searched on 05 June 2009

-
1. Hibiscus/
 2. (hibiscus or rosella or roselle or kenaf or red sorrel or karkade or sour tea or red tea).tw.
 3. 1 or 2
 4. Hypertension/
 5. hypertens\$.tw.
 6. (blood adj pressure).tw.
 7. or/4-6
 8. 3 and 7
 9. randomized controlled trial.pt.
 10. controlled clinical trial.pt.
 11. randomized.ab.
 12. placebo.ab.
 13. drug therapy.fs.
 14. randomly.ab.
 15. trial.ab.
 16. groups.ab.
 17. or/9-16
 18. animals/ not (humans/ and animals/)

19. 17 not 18
20. 8 and 19
21. limit 20 to yr="2005 - 2009"

Appendix 4. EMBASE (1980 to 2009 Week 22) search strategy

Searched on 05 June 2009

-
1. hibiscus/
 2. hibiscus sabdariffa extract/
 3. (hibiscus or rosella or roselle or ambary or anthocyanin\$ or burao or chemparathampoo or erragogu or esculetin or gogu or karkad\$ or kenaf or sorrel or red tea or sabdarifa or sabdariffa or sour tea or tellagogu or zobo).mp.
 4. or/1-3
 5. exp hypertension/
 6. hypertens\$.tw.
 7. exp blood pressure/
 8. blood pressure.mp.
 9. bloodpressure.tw
 10. ((diastolic or systolic or arterial) adj pressure).tw.
 11. or/5-10
 12. controlled clinical trial\$.mp.
 13. random\$.mp.
 14. placebo\$.mp.
 15. dt.fs.
 16. trial.ab.
 17. groups.ab.
 18. (doubl\$ adj3 blind\$).mp.
 19. or/12-18
 20. animals/ not (humans/ and animals/)
 21. 19 not 20
 22. 4 and 11 and 21
 23. limit 22 to yr="2007 - 2009"

Appendix 5. AMED (1985 to May 2009) search strategy

Searched on 05 June 2009

-
1. Hibiscus/
 2. (hibiscus or rosella or roselle or ambary or anthocyanin\$ or burao or chemparathampoo or erragogu or esculetin or gogu or karkad\$ or kenaf or sorrel or red tea or sabdarifa or sabdariffa or sour tea or tellagogu or zobo).mp.
 3. or/1-2
 4. hypertension/
 5. hypertens\$.mp
 6. blood pressure/
 7. bloodpressure.tw.
 8. ((diastolic or systolic or arterial or blood) adj pressure).mp.
 9. or/4-8
 10. controlled clinical trial.mp.
 11. randomized controlled trials/
 12. random\$.mp.
 13. placebo\$.mp.
 14. trial.ab.

15. groups.ab.
16. (doubl\$ adj3 blind\$).mp.
17. or/10-16
18. 3 and 9 and 17

Appendix 6. EBSCO CINAHL search strategy

Searched on 05 June 2009

-
- S1 TX hypertens*
 - S2 (MH "Blood Pressure+")
 - S3 TX diastolic n1 pressure or TX systolic n1 pressure or TX arterial n1 pressure or TX blood n1 pressure
 - S4 TX bloodpressure
 - S5 (MH "Clinical Trials")
 - S6 random*
 - S7 placebo*
 - S8 doubl* n3 blind*
 - S9 TX trial
 - S10 AB groups
 - S11 (MH "Hibiscus")
 - S12 TX hibiscus
 - S13 TX (hibiscus or rosella or roselle or ambary or anthocyanin\$ or burao or chemparathampoo or erragogu or esculetin or gogu or karkad\$ or kenaf or sorrel or red tea or sabdarifa or sabdariffa or sour tea or tellagogu or zobo)
 - S14 S1 or S2 or S3 or S4
 - S15 S5 or S6 or S7 or S8 or S9 or S10
 - S16 S11 or S12 or S13
 - S17 S14 and S15 and S16

Appendix 7. BIOSIS (1969 to 2008) search strategy

Searched on 05 June 2009

-
1. (hibiscus or rosella or roselle or ambary or anthocyanin\$ or burao or chemparathampoo or erragogu or esculetin or gogu or karkad\$ or kenaf or sorrel or red tea or sabdarifa or sabdariffa or sour tea or tellagogu or zobo).tw.
 2. hypertens\$.tw.
 3. bloodpressure.tw.
 4. ((diastolic or systolic or arterial or blood) adj pressure).tw.
 5. or/2-4
 6. controlled clinical trial\$.tw.
 7. random\$.tw.
 8. placebo\$.tw.
 9. trial.ab.
 10. groups.ab.
 11. (doubl\$ adj3 blind\$).tw.
 12. or/6-11
 13. animals/ not (humans/ and animals/)
 14. 12 not 13
 15. 1 and 5 and 14

Appendix 8. AGRICOLA (1970 to May 2009) search strategy

Searched on 05 June 2009

-
1. exp hibiscus/
 2. (hibiscus or rosella or roselle or ambary or anthocyanin\$ or burao or chemparathampoo or erragogu or esculetin or gogu or karkad\$ or kenaf or sorrel or red tea or sabdarifa or sabdariffa or sour tea or tellagogu or zobo).mp.
 3. or/1-2
 4. exp hypertension/
 5. hypertens\$.tw.
 6. exp blood pressure/
 7. blood pressure.mp.
 8. bloodpressure.tw.
 9. ((diastolic or systolic or arterial) adj pressure).tw.
 10. or/4-9
 11. controlled clinical trial\$.mp.
 12. random\$.mp.
 13. placebo\$.mp.
 14. trial.ab.
 15. groups.ab.
 16. (doubl\$ adj3 blind\$).mp.
 17. or/11-16
 18. animals/ not (humans/ and animals/)
 19. 17 not 18
 20. 3 and 10 and 19
 21. from 20 keep 1

Appendix 9. Food Science and Technology Abstract (1969 to 2009 June Week 1) search strategy

Searched on 05 June 2009

-
1. (hibiscus or rosella or roselle or ambary or anthocyanin\$ or burao or chemparathampoo or erragogu or esculetin or gogu or karkad\$ or kenaf or sorrel or red tea or sabdarifa or sabdariffa or sour tea or tellagogu or zobo).mp.
 2. hypertens\$.tw.
 3. blood pressure.mp.
 4. bloodpressure.tw.
 5. ((diastolic or systolic or arterial) adj pressure).tw.
 6. or/2-5
 7. controlled clinical trial\$.mp.
 8. random\$.mp.
 9. placebo\$.mp.
 10. trial.ab.
 11. groups.ab.
 12. (doubl\$ adj3 blind\$).mp.
 13. or/7-12
 14. 1 and 6 and 13

Appendix 10. International Pharmaceutical Abstracts search strategy (1970 to May 2009)

Searched on 05 June 2009

-
1. (hibiscus or rosella or roselle or ambary or anthocyanin\$ or burao or chemparathampoo or erragogu or esculetin or gogu or karkad\$ or kenaf or sorrel or red tea or sabdarifa or sabdariffa or sour tea or tellagogu or zobo).mp.
 2. hypertens\$.mp.
 3. blood pressure.mp.
 4. bloodpressure.tw.
 5. ((diastolic or systolic or arterial) adj pressure).mp.
 6. or/2-5
 7. controlled clinical trial\$.mp.
 8. random\$.mp.
 9. placebo\$.mp.
 10. trial.ab.
 11. groups.ab.
 12. (doubl\$ adj3 blind\$).mp.
 13. or/7-12
 14. animals/ not (humans/ and animals/)
 15. 13 not 14
 16. 1 and 6 and 15

Appendix 11. International Bibliographic Information on Dietary Supplements search strategy

Searched on 17 September 2009

+(hibiscus rosella roselle karkade kardada karkadi kenaf sorrel sabdarifa sabdariffa "sour tea" "red tea") +(hypertens* blood pressure arterial pressure systolic pressure diastolic pressure) +(random* control* trial placebo double blind*)

Appendix 12. Clinical Trials.gov and Current Controlled Trials

Searched on 17 September 2009 (via <http://www.controlled-trials.com/mrct/search.html>)

hypertension AND (hibiscus OR roselle OR sour tea)

Appendix 13. OpenSIGLE

Searched on 17 September 2009 (via <http://opensigle.inist.fr/>)

((title:hibiscus) OR (title:roselle) OR (title:sabdarifa)) AND (hypertension)

Appendix I4. Hand searching of journals

1. American Journal of Nursing - using search strategy: (hibiscus OR roselle OR sabdarifa) AND (hypertens*)
2. BMC -(hibiscus OR roselle OR sabdariffa) AND hypertension AND human AND randomized controlled trial
3. Journal of Urban Health- ti:(roselle) or ti:(hibiscus and sabdariffa)

Appendix I5. ISI Web of Knowledge search strategy

Searched on 16 September 2009

-
1. TI=(hibiscus)
 2. TI=((hibiscus or rosella or roselle or kenaf or red sorrel or karkade or sour tea or red tea))
 3. #2 OR #1
 4. TI=(Hypertension)
 5. TI=(hypertens*)
 6. TI=((blood adj pressure))
 7. #6 OR #5 OR #4
 8. #7 AND #3
 9. TS=(randomized controlled trial)
 10. TS=(controlled clinical trial)
 11. TS=(randomized)
 12. TS=(placebo)
 13. TS=(drug therapy)
 14. TS=(randomly)
 15. TS=(trial)
 16. TS=(groups)
 17. #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9
 18. TS=(animals)
 19. #17 NOT #18
 20. #8 AND #19

Appendix I6. Methods of data extraction, data management, assessment of risk of bias and data analysis for subsequent updates of this review

Data extraction and management

Two review authors (CN and PP) will independently extract the data from all potential studies. Any disagreement in data extraction will be resolved by discussion and consultation with the third review author (CS).

We will try to contact authors of the original studies to provide additional information when information from the potential studies is unclear. All relevant data will be entered into Review Manager Software ([RevMan 2008](#)).

Assessment of risk of bias in included studies

Two review authors (CN and PP) will independently assess the risk of bias in the included studies according to the Cochrane Collaboration's tool for assessing risk of bias ([Higgins 2008](#)).

The result of assessing the risk of bias will be recorded in the data collection form. Any disagreements in the assessment of the risk of bias will be resolved by discussion and consultation with the third review author (CS). The assessment of the risk of bias in the included studies will be presented in the risk of bias tables, risk of bias graph and risk of bias summary.

Measures of treatment effect

We will use mean difference (MD) with 95% confidence intervals (CI) for changes in blood pressure, heart rate and pulse pressure. We will use relative risk (RR) and risk difference (RD) with their 95% CI for withdrawals due to adverse effects.

Unit of analysis issues

Studies with multiple treatment groups

In the case of studies with multiple treatment groups, we will combine all relevant intervention groups into a single group, and all relevant control groups into a single control group ([Higgins 2008](#)).

Repeated observations on participants

We will select a single time point and analyse only data at this time for studies in which it is presented ([Higgins 2008](#)).

Dealing with missing data

We will try to contact the original investigators (using e-mail, letter and/or fax) to request missing data.

In the case of missing standard deviation of the change in blood pressure, the standard deviation will be imputed based on the information in the same study or from other studies using the same drug. The following hierarchy (listed from high to low preference) will be used to impute standard deviation values:

1. standard deviation of change in blood pressure taken in a different position than that of the blood pressure data used
2. standard deviation of blood pressure at the end of treatment
3. standard deviation of blood pressure at the end of treatment measured in a different position than that of the blood pressure data used
4. standard deviation of blood pressure at baseline (except if this measure is used for entry criteria)
5. mean standard deviation of change in blood pressure from other studies using the same drug

Assessment of heterogeneity

We will use the chi-squared test and I^2 to assess the heterogeneity of treatment effect among the studies.

Assessment of reporting biases

If the number of studies is enough (at least 10 studies included in the meta-analysis), we will use the funnel plot, the Egger's test and the Egger's plot to investigate publication bias. The Egger's test and the Egger's plot will be conducted in the STATA program ([StataCorp 2007](#)).

Data synthesis

Data synthesis and analyses will be done using the Cochrane Review Manager software, RevMan 5. We will use the fixed-effect model to pool the treatment effect from the studies if there is no significant heterogeneity. On the other hand, we will use the random-effects model to pool the treatment effect from the studies if there is significant heterogeneity.

Subgroup analysis and investigation of heterogeneity

If we find statistical heterogeneity between studies, we will investigate the source of heterogeneity by subgroup analysis using the following categories:

1. Type of Roselle's form
2. Underlining disease of the patients

Sensitivity analysis

We will conduct a sensitivity analysis to explore the effect of study quality.

HISTORY

Protocol first published: Issue 3, 2009

Review first published: Issue 1, 2010

CONTRIBUTIONS OF AUTHORS

C Ngamjarus (CN) developed the protocol, did the literature searching, screened the studies from literature searching, and wrote the review.

P Pattanittum (PP) edited and commented on the protocol, screened the studies from literature searching, and commented on the review.

C Somboonporn (CS) commented on the protocol and the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Department of Biostatistics and Demography, Faculty of Public Health, Khon Kaen University, Thailand.
- Department of Radiology (Division of Nuclear Medicine), Faculty of Medicine, Khon Kaen University, Thailand.

External sources

- Thailand Research Fund (Senior Research Scholar), Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. CAMPAIN (Complementary and Alternative Medicine and Pain Database) could not be accessed for searching the studies.
2. Chinese language databases were not searched because we could not access them.
3. The detail of measures of treatment effect and data synthesis were changed for a minor degree from the protocol (see [Appendix 16](#)).

INDEX TERMS

Medical Subject Headings (MeSH)

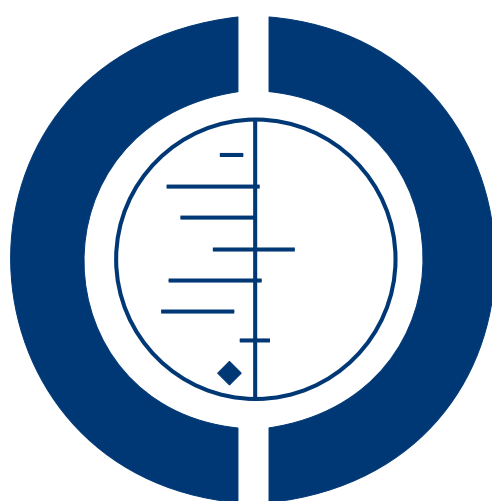
*Rumex; Antihypertensive Agents [*pharmacology]; Blood Pressure [*drug effects]; Hypertension [*drug therapy]; Phytotherapy [*methods]

MeSH check words

Adult; Humans

Interval debulking surgery for advanced epithelial ovarian cancer (Review)

Tangjitgamol S, Manusirivithaya S, Laopaiboon M, Lumbiganon P, Bryant A



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[Intervention Review]

Interval debulking surgery for advanced epithelial ovarian cancer

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ABSTRACT

Background

Interval debulking surgery (IDS), following induction or neoadjuvant chemotherapy, may have a possible role in treating advanced epithelial ovarian cancer (stage III to IV) where primary debulking surgery is not an option.

Objectives

To assess the effectiveness and complications of IDS for patients with advanced stage epithelial ovarian cancer.

Search strategy

We searched the Cochrane Gynaecological Cancer Group's Specialised Register to July 2009, the Cochrane Central Register of Controlled Trials (CENTRAL) Issue 2, 2009, MEDLINE from January 1966 to June week 4 2009, and EMBASE from January 1966 to week 27 2009.

Selection criteria

Randomised controlled trials (RCTs) comparing survival of women with advanced epithelial ovarian cancer, who had IDS performed between cycles of chemotherapy after primary surgery with survival of women who had conventional treatment (primary debulking surgery and adjuvant chemotherapy).

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. Searches for additional information from study authors were attempted. Meta-analysis of overall and progression-free survival (PFS) were performed using random-effects models.

Interval debulking surgery for advanced epithelial ovarian cancer (Review)

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Main results

Three RCTs randomising 853 women, of whom 781 were evaluated, met the inclusion criteria. Meta-analysis of three trials for overall survival (OS) found no statistically significant difference between IDS and chemotherapy alone (hazard ratio (HR) = 0.80, 95% confidence interval (CI) 0.61 to 1.06, $I^2 = 58\%$). Subgroup analysis for OS in two trials, where the primary surgery was not performed by gynaecologic oncologists or was less extensive, showed a benefit of IDS: HR = 0.68, 95% CI 0.53 to 0.87, $I^2 = 0\%$). Meta-analysis of two trials for progression-free survival (PFS) found no statistically significant difference between IDS and chemotherapy alone (HR = 0.88, 95% CI 0.57 to 1.33, $I^2 = 83\%$). Rates of toxic reactions to chemotherapy were similar in both arms (risk ratio = 1.19, 95% CI 0.53 to 2.66, $I^2 = 0\%$), but little information was available for other adverse events or quality of life.

Authors' conclusions

No conclusive evidence was found to determine whether IDS between cycles of chemotherapy would improve or decrease the survival rates of women with advanced ovarian cancer, compared with conventional treatment of primary surgery followed by adjuvant chemotherapy. IDS appeared to yield benefit only in patients whose primary surgery was not performed by gynaecologic oncologists or was less extensive. Data on QoL and adverse events were inconclusive.

PLAIN LANGUAGE SUMMARY

Interval debulking surgery for advanced epithelial ovarian cancer

Ovarian cancer frequently presents at an advanced stage so it may not be possible to remove all tumours during surgery. Several cycles of chemotherapy are generally given after primary surgery. Secondary surgery, performed after a few cycles of chemotherapy before further cycles of chemotherapy, is called interval debulking surgery (IDS). This review compares the survival of patients with advanced epithelial ovarian cancer, who had IDS performed between cycles of chemotherapy after primary surgery with survival of patients who had conventional treatment (primary debulking surgery and adjuvant chemotherapy). It found similar survival rates in patients who did and did not receive IDS. No adequate information regarding adverse effects was available. Data on quality of life (QoL) of the patients were also inconclusive.

BACKGROUND

Ovarian cancer is the sixth most common cancer among women and the leading cause of death in women with gynaecological malignancies (GLOBOCAN 2002). A woman's risk of developing cancer of the ovaries by age 75 years varies between countries, ranging from 0.5% to 1.6% (IARC 2002). Primary surgery is the mainstay of treatment for ovarian cancer, followed by adjuvant chemotherapy to destroy any gross or microscopic residual tumour cells.

Primary ovarian cancer surgery is performed to achieve optimal cytoreduction as the amount of residual tumour is one of the most important prognostic factors for survival of women with epithelial ovarian cancer (Bristow 2002; Griffiths 1975; Hoskin 1994). An optimal surgical procedure, defined as a reduction of tumours to < 1 to 2 cm in size, required for advanced stage disease (III to IV) is not always possible especially in patients whose diseases are extensive. Such surgery can be complicated requiring extensive bowel resection and major blood loss, with a high risk of morbid-

ity. Another obstacle to extensive primary surgery lies in the patients' medical condition, e.g. poor projected performance status or medical contraindications.

Induction chemotherapy can play an alternative role in these circumstances. The term induction chemotherapy generally describes the administration of chemotherapy to reduce tumour size, allowing further surgery. The term neoadjuvant chemotherapy (NAC) is more specific in that it describes the administration of chemotherapy when primary debulking surgery is not feasible, and only biopsy is done for histologic diagnosis. However, the two terms are sometimes used interchangeably. In this review, if chemotherapy administration does not fit the definition of NAC, we will use the term induction chemotherapy.

When a few cycles of chemotherapy are administered with some tumour response, secondary surgery may be possible before further chemotherapy is considered. This secondary surgery between the courses of chemotherapy is called interval debulking surgery

(IDS). Although the optimal timing of IDS has not been agreed, it is usually performed after 2 to 4 cycles of chemotherapy. A longer interval between primary surgery and IDS (with more cycles of chemotherapy) could result in the chemotherapy selectively destroying chemosensitive tumour cells leaving chemoresistant clones. Many retrospective or prospective non-randomised trials report the beneficial effects of NAC or induction chemotherapy after inoperable advanced ovarian cancer or those with gross residual diseases, respectively. Chemotherapy may increase the number of patients suitable for secondary surgery (IDS); many authors reported the rates of optimal resection in IDS after induction chemotherapy ranging from 77% to 94% (Ansquer 2001; Chan 2003; Giannopoulos 2006; Jacob 1991; Kuhn 2001; Lawton 1989; Lee 2006; Morice 2003; Surwit 1996).

Another potential benefit of IDS after NAC or induction chemotherapy compared to aggressive primary debulking surgery, as reported in retrospective (Lawton 1989; Morice 2003) and prospective (Giannopoulos 2006) cohort studies, may be lower associated morbidity, e.g. less blood loss, requirement of intensive care unit admission, and duration of hospital stay due to the tumours being smaller. However, this was not found in another study (Kuhn 2001). The QoL of patients treated with IDS after NAC was also reported in one study to be better than those who had conventional treatment (primary debulking surgery followed by a complete and continual cycle of adjuvant chemotherapy) (Chan 2003). By removing the smaller size tumour masses induced by chemotherapy, IDS would facilitate the response of the residual tumours (if any) or the microscopic lesions to subsequent chemotherapy.

Unlike the advantage on the resectability and response rates which were demonstrated in most studies, there is still conflicting evidence from various studies regarding the survival benefit of IDS after chemotherapy compared to conventional treatment. Most studies of IDS after NAC or induction chemotherapy are non-randomised and retrospective in nature. Many of them show that the survival rates of patients who underwent IDS, after sub-optimal primary surgery followed by chemotherapy, were similar to those patients who had primary debulking surgery (Jacob 1991; Kayikcioglu 2001; Loizzi 2005; Morice 2003; Schwartz 1999; Shibata 2003; Surwit 1996). Only a few studies reported significantly longer median survival of patients who had IDS after chemotherapy than of those who had conventional treatment of primary surgery and adjuvant chemotherapy (Kuhn 2001; Vergote 1998), and even fewer studies showed an inferior result of IDS than optimal primary cytoreduction (Fanfani 2003). This conflicting result on the survival benefit of IDS may depend on various characteristics of the patients and their disease, e.g. extent of residual tumour after primary surgery or IDS, tumour response after induction chemotherapy and prior to IDS etc. (Fanfani 2003; Jacob 1991; Kuhn 2001; Mazzeo 2003; Vergote 1998).

We are aware of three major RCTs (Redman 1994; Rose 2004; Van der Burg 1995) which have been conducted to evaluate the

survival benefit of IDS in ovarian cancer. These trials did not agree on the benefit of survival outcomes of patients with IDS. Redman 1994 and Rose 2004 showed similar survival rates between patients who had IDS and those who had conventional treatment, while Van der Burg 1995 showed significantly longer survival in the IDS group which was still present after a 10-year follow-up.

One previous meta-analytical study (Bristow 2006) and two systematic reviews (Bristow 2007; Morrison 2007) addressed the question of whether the advanced ovarian cancer patients should have primary surgery before or after chemotherapy. The first meta-analytical study reviewed the role of platinum-based NAC and IDS for advanced ovarian cancer, involving 835 patients from 51 studies (Bristow 2006). The result showed that survival of patients who had NAC after an attempt of primary surgery was inferior to those who had primary surgery. However, the review included only phase I to II and retrospective studies. The other systematic review of NAC or induction chemotherapy and IDS in advanced ovarian cancer was recently published in 2007 (Bristow 2007). The review included the three major RCTs, six non-randomised studies, and the other 26 retrospective and phase I/II studies. The authors categorized the studies into three groups according mainly to the survival outcomes of the patients in the NAC or induction chemotherapy/IDS arm compared to the conventional arm: inferior survival outcome by NAC; no significant difference; and those with limited validation of inclusion criteria for NAC. The results from these studies were simply described and tabulated without a meta-analysis for survival. The Cochrane systematic review (Morrison 2007) identified only one RCT (Liu 2004) of NAC given by intra-arterial route before IDS comparing conventional primary surgery and adjuvant chemotherapy. This study by Liu et al (Liu 2004) found no significant difference in overall survival between the two treatment arms. The objective of these systematic reviews and meta-analysis was to evaluate if NAC could be used in lieu of primary surgery, which was different from the aim of our review which focuses on the role of repeated surgery (IDS) after primary surgery which had been attempted but resulted in sub-optimal surgery.

We found only one previous meta-analytical study which reviewed the role of IDS after neoadjuvant chemotherapy in advanced ovarian cancer (Elit 1995). The two authors from that review identified 33 publications and included three RCTs and three historical cohort trials in their review (Elit 1995). Homogeneity testing was not statistically significant by the Breslow-Day method. Significant survival benefit from the IDS was identified by the Mantel-Haenszel method with odds ratio of 0.5 ($P = 0.02$) (Elit 1995).

Since there are potential intrinsic biases of patient selection and variations of several factors, such as chemotherapeutic agents or cycles of administration in many retrospective or phase I/II studies, together with conflicting data from the RCTs, a definite conclusion about the advantage of IDS after attempted primary surgery could not be made. Hence, a thorough systematic review in this subject

focusing only on the high quality data or trials is warranted to give a better view of the use of IDS in advanced epithelial ovarian cancers.

OBJECTIVES

To assess the effectiveness and complications of IDS for patients with advanced stage epithelial ovarian cancer.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Patients with advanced stage epithelial ovarian cancer who have a confirmed pathological diagnosis from primary surgery which was sub-optimal, with residual tumours of more than 1 to 2 cm. Primary surgical procedures range from tumour biopsy, tumour removal, or standard surgical staging for epithelial ovarian cancer.

Types of interventions

Treatment: Interval debulking surgery (IDS), defined as secondary surgery which is performed after 2 to 4 cycles of neoadjuvant chemotherapy (NAC) or induction chemotherapy, to remove the bulk of the tumour, and followed by adjuvant chemotherapy of the same type.

Control: Adjuvant chemotherapy only.

Types of outcome measures

Primary outcomes

- Overall survival (OS): Survival until death from all causes. Survival was assessed from the time when women were enrolled in the study.

Secondary outcomes

- Progression-free survival (PFS).
- Adverse events.
- Quality of life (QoL), measured using a scale that had been validated through reporting of norms in a peer-reviewed publication.

Search methods for identification of studies

Papers in all languages were sought and translations carried out if necessary.

Electronic searches

See: [Cochrane Gynaecological Cancer Group](#) methods used in reviews.

Searches were run on the following databases: Cochrane Gynaecological Cancer Group's Specialised Register (CGCSR) to June 2008, the Cochrane Central Register of Controlled Trials (CENTRAL) Issue 2, 2008, MEDLINE from January 1966 to June 2008, and EMBASE from January 1966 to June 2008. For this update the searches were extended to: CGCSR to July 2009, CENTRAL Issue 2, 2009, MEDLINE Ovid to June week 4 2009, EMBASE to 2009 week 27 (see [Appendix 1](#); [Appendix 2](#); [Appendix 3](#); [Appendix 4](#)).

All relevant articles found were identified on PubMed and using the 'related articles' feature, a further search was carried out for newly published articles.

Searching other resources

Unpublished and grey literature

We searched Metaregister, Physicians Data Query, www.controlled-trials.com/rct, www.clinicaltrials.gov and www.cancer.gov/clinicaltrials and Gynaecologic Oncologists of Canada (<http://www.g-o-c.org>) for ongoing trials. The main investigators of any relevant ongoing trials were contacted for further information, as were major co-operative trials groups active in this area.

Reference lists and correspondence

We checked the citation lists of included trials to identify further reports of trials. We also contacted authors of all trials and/or reviews relevant to the reviewed topic to request information on any similar trials. Colleagues, collaborators and other experts in the field were requested to identify missing or unreported trials.

Data collection and analysis

Selection of studies

All titles and abstracts retrieved by electronic searching were downloaded to a reference management database (Endnote), duplicates were removed and the remaining references were examined by two review authors (ST and SM) independently. Those studies which clearly did not meet the inclusion criteria were excluded and copies

of the full text of potentially relevant references were obtained. The English abstracts of non-English studies were evaluated, and if eligible, the full text studies were obtained and translated. The eligibility of retrieved papers was assessed independently by ST and SM. Disagreements were resolved by discussion.

Data extraction and management

For included studies, we abstracted data as recommended in chapter 7 of the Cochrane Handbook (Higgins 2008).

We collected data on author, year of publication, journal citation, country, setting, inclusion and exclusion criteria, study design and methodology, study population (total number enrolled, patient characteristics, age, size and number of residual tumours after primary surgery, performance status, stage, histology, size and number of residual tumours before and after IDS), interventions (expertise of surgeons, type and schedule of chemotherapy, duration of the treatment), risk of bias, duration of follow-up and outcomes (OS, PFS, QoL and adverse events). We also recorded the following information for each outcome of interest:

- outcome definition;
- unit of measurement (if relevant);
- for scales: upper and lower limits, and whether high or low score is good;
- results: number of participants allocated to each intervention group;
- sample size; missing participants.

Data on outcomes were extracted as below:

- for time to event (OS) data, we extracted the log of the hazard ratio [log(HR)] and its standard error from trial reports; if these were not reported, we attempted to estimate them from other reported statistics using the methods of Parmar 1998;
- for dichotomous outcomes (e.g. adverse events), we extracted the number of patients in each group who experienced the outcome of interest and the number of patients assessed at endpoint, in order to estimate a risk ratio (RR).

Both unadjusted and adjusted statistics were extracted, if reported. Where possible, all data extracted were those relevant to an intention-to-treat (ITT) analysis, in which participants were analysed in groups to which they were assigned.

The time points at which outcomes were collected and reported were noted.

Data were abstracted independently by two review authors (ST, SM) onto a data abstraction form specially designed for the review. Disagreement between authors was resolved by discussion. If this failed a third author (PL) was consulted.

Assessment of risk of bias in included studies

The risk of bias in included RCTs was assessed using the Cochrane Collaboration's tool and the criteria specified in chapter 8 of the

Cochrane Handbook (Higgins 2008). This included assessment of:

- sequence generation;
- allocation concealment;
- blinding (of outcome assessors since it was not possible to blind either patients or physicians to the patient's assigned treatment);
- incomplete outcome data: we coded the satisfactory level of loss to follow-up for each outcome as
 - Yes, if fewer than 20% of patients were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms;
 - No, if more than 20% of patients were lost to follow-up or reasons for loss to follow-up differed between treatment arms;
 - Unclear if loss to follow-up was not reported;
- selective reporting of outcomes;
- other possible sources of bias.

The risk of bias tool was applied independently by two review authors (ST, SM) and differences resolved by discussion or by appeal to a third reviewer (PL). Results are summarised in both a risk of bias graph and a risk of bias summary. Results of meta-analyses were interpreted in light of the findings with respect to risk of bias.

Measures of treatment effect

We used the following measures of the effect of treatment:

- for time to event data, we used the HR, where possible;
- for dichotomous outcomes, we used the RR.

Dealing with missing data

We attempted to extract data on the outcomes only among participants who were assessed at endpoint. We did not impute missing outcome data; if only imputed outcome data were reported, we contacted trial authors to request data on the outcomes only among participants who were assessed.

Assessment of heterogeneity

Heterogeneity between studies was assessed by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials which cannot be ascribed to sampling variation (Higgins 2003), by a formal statistical test of the significance of the heterogeneity (Deeks 2001), and, if possible, by subgroup analyses (see below). If there was evidence of substantial heterogeneity, the possible reasons for this were investigated and reported.

Assessment of reporting biases

We were unable to assess reporting bias as only three trials met our inclusion criteria.

Data synthesis

If sufficient clinically similar trials were available, their results were pooled in meta-analyses. Adjusted summary statistics were used where available; otherwise unadjusted results were used.

- For time-to-event data, HRs were pooled using the generic inverse variance facility of RevMan 5.
- For any dichotomous outcomes, the RR was calculated for each study and these were then pooled.

Random-effects models with inverse variance weighting were used for all meta-analyses (DerSimonian 1986).

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were performed, where possible, grouping trials by:

- expertise of surgeons (gynaecological oncologist, gynaecologist, general surgeon).

Factors such as age, stage, type of intervention, length of follow-up, adjusted/unadjusted analysis were considered in interpretation of any heterogeneity.

Sensitivity analysis

Sensitivity analysis was not performed as there were insufficient trials in the review.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#).

Results of the search

The original search identified 134 references whose titles and abstracts were examined. Eighteen studies were potentially relevant to this review. Two studies were readily excluded from the abstracts' data (Evdokimova 1982; Kumar 2007). Full text articles of 16 studies were obtained and were assessed for eligibility by two authors (ST, SM) independently. Thirteen studies were additionally excluded. The reasons for exclusion are presented in the [Characteristics of excluded studies](#) table. Three RCTs met all inclusion criteria and were included (Redman 1994; Rose 2004; Van

der Burg 1995). The updated search identified 336 references, of which there were 17 possible relevant articles. Only two RCTs were identified; one was of a Japanese study that referred to a study that was excluded in the primary review. The other was an abstract of the EORTC 55971 trial, which was presented at the IGCS 2008 meeting in Bangkok and was also excluded.

We identified one study that is still awaiting classification (JCOG 0206).

Included studies

All three RCTs were multicentre studies: one from United Kingdom involved four institutions which were the referral centres for cancer care (Redman 1994); one by the European Organisation for Research and Treatment of Cancer (EORTC) involved 14 participating institutions in Europe (Van der Burg 1995) and one by the Gynecologic Oncology Group (GOG) from the United States involved more than 42 cancer centres (Rose 2004).

All of the trials (Redman 1994; Rose 2004; Van der Burg 1995) compared IDS and chemotherapy with chemotherapy only.

Median length of follow-up was reported in all three trials: 48 months (Redman 1994), 47 months (Rose 2004) and 42 months (Van der Burg 1995). Although Van der Burg et al. from the EORTC presented their long term follow-up (10 years) as an oral presentation in the European Society of Gynaecological Oncology annual meeting in 2005 (Van der Burg 2005), sufficient data were not available for meta-analysis.

The trial of Redman 1994 supplied data relating to non-assignment of treatment as: death, disease progression, pulmonary embolus, and patient refusal. The other two trials reported only the numbers or percentages of those not undergoing surgery but the reasons were not stated (Rose 2004; Van der Burg 1995).

All three trials reported HRs for OS (Redman 1994; Rose 2004; Van der Burg 1995). Two trials (Rose 2004; Van der Burg 1995) used Cox regression to assess the prognostic significance of numerous covariates (such as age, performance status, stage, tumour grade, response to induction chemotherapy, number of lesions, ascites, and residual diseases or size of tumours at three time points: after primary surgery, before IDS and after IDS). The definitions of optimal debulking or size of residual tumours after primary surgery varied between these trials. Optimal surgery was either defined as < 2 cm (Redman 1994) or < 1 cm (Rose 2004; Van der Burg 1995). OS was variously calculated from the day of induction chemotherapy initiation at enrolment (Van der Burg 1995), or date of randomisation, which was either after primary surgery but before chemotherapy in the Redman study (Redman 1994) or after three cycles of chemotherapy in the GOG trial (Rose 2004). Both the GOG and the EORTC trials reported HRs adjusted for prognostic factors; Redman 1994 also reported unadjusted HRs. One included trial reported HR, adjusted for prognostic factors, for PFS data (Rose 2004) and one presented Kaplan-Meier disease-free survival curves (Van der Burg 1995), from which we used

Parmar's method (Parmar 1998) to estimate the HR. The definitions of response and recurrence varied amongst these trials: Redman 1994 applied The International Union Against Cancer (UICC) criteria for response evaluation using physical examination, imaging studies, but not CA125; the EORTC trial used the World Health Organization (WHO) criteria allowing physical examination, imaging studies, and CA125; the GOG trial also used physical examination, imaging studies, and two CA125 levels two weeks apart - they defined progressive disease as an increase of at least 100 U/ml or doubling of the nadir in those whose level did not return to baseline.

Adverse events were reported in all three trials (Redman 1994; Rose 2004; Van der Burg 1995). However, Redman 1994 and Van der Burg 1995 described postoperative complications only in the IDS group while Rose 2004 compared general adverse effects between the IDS group and chemotherapy only group.

QoL was assessed only in the GOG trial and the results were reported subsequently by Wenzel et al. (Wenzel 2005). The assessment tool used was the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) questionnaire and treatment-specific supplemental questions at the third and sixth chemotherapy cycles and at 6 and 12 months after starting treatment.

Redman 1994

The trial of Redman 1994 from the UK is the first known RCT of IDS for the management of epithelial ovarian cancer. From April 1986 to February 1990, the authors randomised 86 patients with stage II to IV disease, who underwent primary surgery in 25 hospitals by 40 different surgeons and had residual disease > 2 cm. It was not clear how experienced the 40 surgeons were but the primary surgery had to be performed with an attempt to remove as much tumour as possible. Stage IV included only malignant pleural effusion without other evidence of distant spread or unresectable diseases. The patients received chemotherapy consisting of either a regimen of cisplatin and cyclophosphamide for eight cycles or a regimen of cisplatin, doxorubicin and bleomycin for three cycles followed by an escalated dose of cyclophosphamide for up to five cycles. Either regimen was given without detailed criteria for regimen selection. The control group had only chemotherapy after primary surgery. The intervention group had chemotherapy for one to four cycles and underwent IDS, which was performed by the primary surgeon, and then received further chemotherapy. Although our inclusion criteria for this review is IDS to be performed after chemotherapy for a minimum of two cycles, this study is included because only one out of 37 patients in the IDS group had only one cycle of chemotherapy before IDS. Interval debulking surgery was not performed if there was progressive disease, stable disease, or insufficient response after three cycles. Seven of the 86 randomised patients were excluded after randomisation because primary surgery was not sub-optimal. Of the remaining 79 patients, 37 were in the IDS arm and 42 in the conven-

tional arm. There were no significant differences between arms in patient or disease characteristics. Overall, 25 patients (68%) in the IDS arm actually underwent IDS. The reasons for not performing IDS in 12 patients (32%) were: death or progressive disease, pulmonary embolism, and patient refusal. In the conventional arm, one patient (2%) had IDS upon request.

Adverse effects of IDS were reported as perioperative death and significant postoperative complications including deep vein thrombosis, intestinal fistulae, chest or wound infections, or postoperative ileus. Adverse effects in the chemotherapy only group were not exhaustively reported. Toxicity was reported in both treatment groups.

Van der Burg 1995

The trial of Van der Burg 1995 enrolled 425 stage IIB to IV epithelial ovarian cancer patients between March 1987 to May 1993 who had undergone primary surgery and had residual disease > 1 cm. Neither the extent nor the aim of primary surgery nor the expertise of the surgeon were described in their primary report. However, the authors provided additional data from their reply to letter to the Editor (Kehoe 1995) and their subsequent review article (Van der Burg 2003) that the maximum effort to perform primary surgery was not attempted in all patients with different extents of debulking surgery, resulting in a high proportion of large residual tumours (> 5 cm) after primary surgery (Van der Burg 2003).

All patients received three cycles of chemotherapy consisting of intra-venous cisplatin and cyclophosphamide. Those who had response or stable diseases were randomised to undergo IDS or no IDS. Both groups would receive three more cycles of the same chemotherapy (continuation after six cycles based on institution policy).

Overall, 106 patients were not randomised; this number consisted of 39 patients with progressive disease who were removed from the study and also patients who had contraindications to surgery, died, declined to participate in the study, were ineligible, lost to follow-up, and those who were still receiving induction chemotherapy. Of 319 patients who were randomised, 278 were evaluated (140 patients who underwent surgery and 138 patients who did not). The two groups were well balanced with respect to stage, histologic type and grade, number and size of lesions, peritoneal carcinomatosis, ascites, and response to induction chemotherapy. Rate of optimal debulking surgery (residual tumour < 1 cm) was 64%. The following adverse events were reported in the trial: bowel injury, urinary bladder injury, blood loss and postoperative fever, ileus, urinary tract infection, wound infection, deep vein thrombosis, lung embolism for peri- and postoperative adverse events, respectively.

Rose 2004

Rose 2004 enrolled 550 patients from June 1994 to January 2001,

with stage III to IV (malignant pleural effusion or a resected anterior abdominal wall tumour) who underwent primary surgery to remove as much tumour as possible, but who still had residual disease > 1 cm. However, after March 1996 when the EORTC trial reported a greater benefit from secondary surgery after the exclusion of patients with stage IV diseases, only patients with stage III disease were included. The primary surgeons were either fellowship-trained or certified gynaecologic oncologists in 95% of patients. Patients whose disease had not progressed and who had residual extraperitoneal tumour of < 1 cm after three cycles of chemotherapy with paclitaxel and cisplatin were randomly assigned to secondary surgical cytoreduction (IDS) and further chemotherapy or chemotherapy alone. Overall, 102 patients were not randomised; the most common reasons were: progressive disease or death in 40 patients, the others were either medically contraindicated, declined, had extraperitoneal disease > 1 cm, experienced excessive delay before randomisation, or other reasons not specified.

A total of 448 patients were randomised: 226 patients to IDS and 222 to chemotherapy only. Patient characteristics were well balanced in the two groups. A considerable number of patients in both groups had protocol violations including: 7% in the IDS group did not have secondary surgery versus 3% in chemotherapy only arm had this surgery; 7% and 2% in the IDS and chemotherapy only arms, respectively, had fewer than three cycles of additional chemotherapy; and 10% and 13% in the IDS and chemotherapy only arms, respectively, had non-protocol consolidation therapy before progressive disease. All randomised patients were included in the analysis of OS and PFS and were counted in the group comparisons.

Cox regression for OS and PFS was performed to evaluate the prognostic importance of: the maximal diameter of residual tumour (2.0 cm or less, 2.1 to 5.0 cm, or 5.0 cm or more) after initial surgery, the patient's age, performance status, the presence or absence of measurable disease before chemotherapy, and the size of residual tumour after IDS (< 1 cm versus > 1 cm).

QoL of patients who did and did not undergo IDS in the GOG study were evaluated and subsequently reported by Wenzel et al (Wenzel 2005). The self-reported QoL was assessed in four settings, according to the Functional Assessment of Cancer Therapy-Ovarian (FACT-O), version 2-questionnaire which consists of 33 general questions for cancer patients and 12 questions specific to ovarian cancer patients. The first evaluation was at baseline after

primary surgery and the third cycle of chemotherapy but before allocation to IDS or chemotherapy only. The three subsequent evaluations were at the sixth cycle of chemotherapy, at 6 and 12 months after starting treatment. Completion rates for these questionnaires declined from 90% for the first questionnaire to 83%, 83%, and 80% for the second, third, and fourth questionnaires, respectively. Nevertheless, lower completion rates were noted in the IDS group compared to chemotherapy only group especially at the second assessment, 77% and 89%, respectively ($P < 0.001$). The included trials are described in detail below and in the table of [Characteristics of included studies](#).

Excluded studies

Fifteen references were excluded, after obtaining the full text, for the following reasons:

- eight references reported data on non-comparable controlled trials or non-randomised studies (Angioli 2006; Chan 2003; Fuso 2006; Giannopoulos 2006; Ikeba 2004; Kuhn 2001; Lee 2006; Recchia 2001);
- IDS was allowed in both arms of the trial in two trials (EORTC 55971; Park-Simon 2006);
- in one trial survival outcomes were not analysed (Dutta 2005);
- IDS was selectively performed in subset of patients in one trial (Solomon 1988);
- in one trial (Evdokimova 1982), women with ascites were not randomly assigned to interventions;
- either histology or cytology was allowed for a pathologic diagnosis of ovarian cancer in one trial (Kumar 2007);
- one RCT (Liu 2004) was considered ineligible because NAC was given for only 1 cycle via intra-arterial route before the IDS.

For further details of all the excluded studies see the table [Characteristics of excluded studies](#).

Risk of bias in included studies

Two trials (Redman 1994; Van der Burg 1995) were at moderate risk of bias: they satisfied three of the criteria that we used to assess risk of bias. The trial of Rose 2004 was at high risk of bias as it satisfied only one of the criteria (see [Figure 1](#); [Figure 2](#)).

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

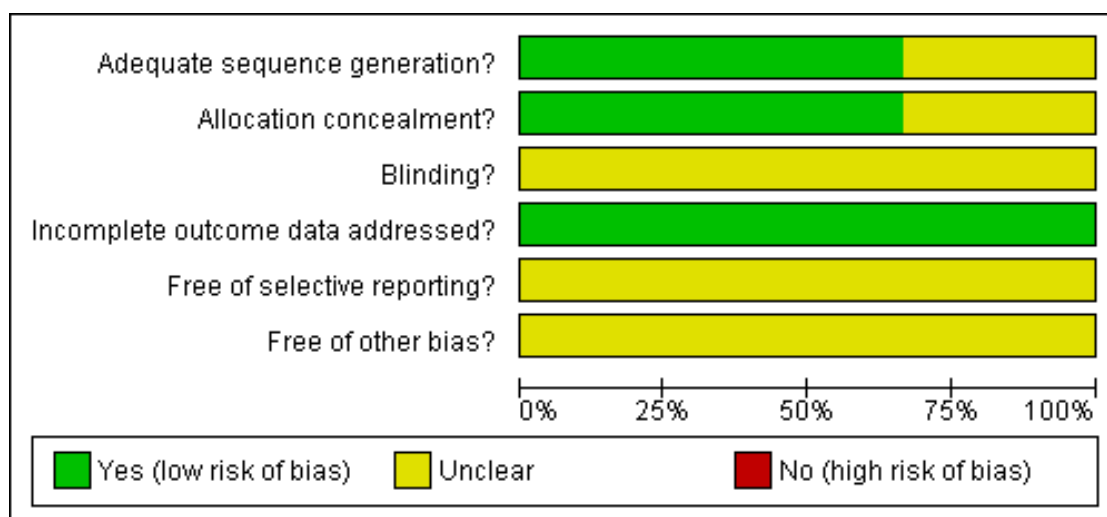


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Redman 1994	+	+	?	+	?	?
Rose 2004	?	?	?	+	?	?
Van der Burg 1995	+	+	?	+	?	?

Two trials (Redman 1994; Van der Burg 1995) reported the method of generation of the sequence of random numbers used to allocate women to treatment arms. These trials also reported concealment of this allocation sequence from patients and health-care professionals involved in the trial. The other trial (Rose 2004) did not report on either the method of sequence generation or concealment of allocation. None of the trials reported whether the outcome assessors were blinded. It was not certain whether all trials reported all the outcomes that they assessed and it was unclear whether any other bias may have been present. At least 87% of women who were enrolled were assessed at endpoint in the three trials (Redman 1994; Rose 2004; Van der Burg 1995).

Effects of interventions

Since only a small number of trials were included in meta-analyses, funnel plots were not examined.

IDS versus chemotherapy only

Survival

Overall survival (Analysis 1.1)

Meta-analysis of three trials (Redman 1994; Rose 2004; Van der Burg 1995), assessing 781 participants, found no statistically significant difference in the risk of death between IDS with chemotherapy and chemotherapy alone (HR = 0.80, 95% CI 0.61 to 1.06). The percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) may represent substantial heterogeneity ($I^2 = 58\%$). Hence, we explored the sources of heterogeneity from the clinical factor of expertise of surgeon in the primary surgery and subsequently performed subgroup meta-analysis for OS based on this factor.

The conclusions above were not robust to subgroup analyses examining patients who received surgery from general surgeons (or had less extensive primary surgery) or gynaecologic oncologists separately. Meta-analysis of two trials (Redman 1994; Van der Burg

1995) assessing 357 women who received surgery by a general surgeon found that IDS with chemotherapy was associated with a statistically significant decrease in the risk of death compared with chemotherapy alone (HR = 0.68, 95% CI 0.53 to 0.87, $I^2 = 0\%$). The trial of Rose 2004, assessing 424 participants, found no statistically significant difference in the risk of death between IDS with chemotherapy and chemotherapy alone (HR = 0.99, 95% CI 0.79 to 1.24). Analysis 1.1

Progression-free survival (Analysis 1.2)

Meta-analysis of two trials (Rose 2004; Van der Burg 1995), assessing 781 participants, found no statistically significant difference in the risk of disease progression between IDS with chemotherapy and chemotherapy alone (HR = 0.88, 95% CI 0.57 to 1.33). The percentage of the variability in effect estimates that is due to heterogeneity rather than chance may represent considerable heterogeneity ($I^2 = 83\%$). Analysis 1.2

Adverse events

Toxic reactions were the only adverse events which could be meta-analysed. They were reported in both treatment groups in Redman 1994 and Van der Burg 1995. It was not possible to meta-analyse other adverse events as they were not reported in sufficient detail for both treatment arms.

Toxic reactions to chemotherapy (Analysis 1.3)

Meta-analysis of two trials (Redman 1994; Van der Burg 1995), assessing 357 participants, found no statistically significant difference in the risk of disease progression between IDS with chemotherapy and chemotherapy alone (HR = 1.19, 95% CI 0.53 to 2.66). The percentage of the variability in effect estimates that is due to heterogeneity rather than by chance is not important ($I^2 = 0\%$).

The following adverse events were reported in the trial of Rose 2004: Analysis 1.3

Peripheral neuropathy of grade 2 or higher (Analysis 1.4)

Women who received IDS with chemotherapy for treatment of advanced epithelial ovarian cancer had a significantly higher risk of high grade peripheral neuropathy than women who received chemotherapy alone (RR = 0.62, 95% CI 0.43 to 0.91). Analysis 1.4

Grade 3 or 4 gastrointestinal adverse events (Analysis 1.5)

There was no statistically significant difference in the risk of a high grade gastrointestinal adverse event between IDS with chemotherapy and chemotherapy alone (RR = 1.81, 95% CI 0.78 to 4.17). Analysis 1.5

Grade 4 pulmonary adverse events (Analysis 1.6)

There was no statistically significant difference in the risk of a grade 4 pulmonary adverse event between IDS with chemotherapy and chemotherapy alone. There were only two observed events in the IDS group and no events in the chemotherapy only group. Analysis 1.6

Grade 4 cardiovascular adverse events (Analysis 1.7)

There was no statistically significant difference in the risk of a grade 4 cardiovascular adverse event between IDS with chemotherapy and chemotherapy alone (RR = 2.89, 95% CI 0.30 to 27.55). Analysis 1.7

Quality of life (QoL)

Only Rose 2004 evaluated QoL, which was subsequently reported by Wenzel (Wenzel 2005). At six months after starting treatment, significantly more patients who had only chemotherapy experienced persistent numbness or tingling than those who had IDS, 54% versus 38% ($P = 0.01$). Otherwise, QoL was not significantly different in the two treatment groups at any time point.

DISCUSSION

Our systematic review included three RCTs, which evaluated 781 patients out of 853 randomised and a further RCT in abstract form which randomised 718 women, but it was unclear how many of these were evaluated. These four RCTs provided inconclusive evidence as to whether IDS improves or worsens the overall survival rate of patients. The random-effects model showed substantial heterogeneity between the results of the three trials. Likewise, meta-analysis of two RCTs, which evaluated 702 patients out of 767 randomised, provided inconclusive evidence about whether IDS improves or worsens progression-free survival; again, there was substantial heterogeneity between the trials.

Potential reasons for the inconclusive evidence are explained. Firstly, the small number of included studies, evaluating 781 patients, may not have had adequate statistical power to detect a small effect. Furthermore, the studies had different characteristics which may explain the heterogeneity in their results.

A major difference between these trials was the expertise and/or the level of effort given by the surgeons performing the primary debulking surgical procedures in the participating institutions in each study, which may partly explain the heterogeneity between trials. The majority of operations in the GOG trial were performed by the gynaecologic oncologists or fellowship-trained surgeons in various cancer centres (Rose 2004) while the surgical procedures in the Redman trial were performed mostly by general

surgeons or gynaecologists in various hospitals (Redman 1994). In the EORTC trial where the expertise of the surgeon was not specified (Van der Burg 1995) but was subsequently revealed in other publications (Kehoe 1995; Van der Burg 2003), the maximum effort to perform primary surgery was not attempted in all patients with different extents of debulking surgery. Since there is substantial evidence from many retrospective studies that the extent of optimal surgery affects the survival of patients with epithelial ovarian cancer (Bristow 2002; Griffiths 1975; Hoskin 1994), the maximum primary surgical efforts in the optimal surgical setting in the GOG trial might indicate that their primary surgery was sufficient and subsequent surgical attempts would not affect the survival further. Compared to Redman 1994 and Van der Burg 1995, in which primary surgery was performed in sub-optimal settings, when most of the operations were not performed by gynaecologic oncologists (Redman 1994), without maximum effort (with less extensive primary debulking surgery) resulting in a high proportion of large residual tumours (Kehoe 1995; Van der Burg 1995; Van der Burg 2003), so the secondary surgery (IDS) after the tumours were down-sized by chemotherapy appeared worthwhile, although significant only in the EORTC trial. Our subgroup meta-analysis confirmed that IDS had benefits in this particular subgroup of patients. Nevertheless, this should be interpreted with caution because our subgroup analysis was based on only two trials (Redman 1994; Van der Burg 1995).

The second minor difference between these trials is the timing of randomisation. Redman was the only trial which randomised patients into two groups (to have or not to have IDS) at the start of the trial (Redman 1994) and only 67% of patients in the IDS group actually underwent surgery because the other assigned patients had disease progression or died precluding IDS. The other two larger trials of GOG and EORTC randomised only the patients who showed some response to induction chemotherapy (Rose 2004; Van der Burg 1995): this resulted in a high percentage of the patients (approximately 93% in both trials) who were randomised to undergo IDS. This difference may affect the result from each trial, based on the intention-to-treat analysis in all of these trials.

We explored the patients or their disease characteristics as the other potential reason for different effects of IDS on survival outcomes from the three trials: Redman 1994 and Rose 2004 did not show any advantage of IDS while Van der Burg 1995 showed significant survival improvement with IDS. Redman 1994 evaluated only 79 of the total of 86 patients included in the meta-analysis of OS and, therefore, did not have much influence on the results of the meta-analysis. The difference in outcomes from Rose 2004 and Van der Burg 1995 may be due to the different proportion of patients who had poor response to induction chemotherapy (who generally had poorer prognosis than those who showed some response): approximately 52% of patients in the GOG trial had residual diseases of > 1 cm after induction chemotherapy (Rose 2004) compared to 44% in the EORTC trial (van der Burg 1995). This might be

interpreted that the GOG trial had a higher proportion of patients who had more aggressive tumours and so would not have a survival benefit from any treatment, even the optimal IDS. However, this mechanism of tumour aggressiveness and prognosis may not solely explain the ultimate outcome of the patients because the patients in the EORTC trial (Van der Burg 1995) who had tumour > 1 cm after induction chemotherapy but were removed to < 1 cm had better survival benefit than any other group of women in the trial. This might suggest that the IDS may play some role in survival improvement.

To emphasize the importance of the sensitivity of response to chemotherapy before IDS, we would like to point out the findings from the GOG and EORTC trials which showed that the patients whose tumour masses were reduced by chemotherapy to < 1 cm before the IDS (Rose 2004; Van der Burg 1995) had superior survival than the other groups. This response to chemotherapy might be used as a selective criterion for the patients who are likely to gain survival benefit from an IDS.

As we have mentioned in the results, meta-analysis of adverse events was not possible due to different formats of presentation of data in each RCT. The only obvious advantage appears to be fewer neurologic complications in the IDS group than in the chemotherapy only group in the GOG trial (Rose 2004). However, this adverse effect may be related to a particular drug and might not be experienced in the other settings using other chemotherapeutic regimens.

For the QoL comparison, which was only assessed in the GOG trial (Wenzel 2005), patients in the chemotherapy only arm had a higher rate of neurotoxicity than those in the IDS arm at one of the four time points when they were assessed, despite a similar total dose of chemotherapy exposures. The authors ascribed this finding to intermission from chemotherapy exposure allowing a certain degree of recovery, but it may be a chance finding as 48 tests of possible differences in QoL were made. Although other aspects of QoL were similar in the two groups of patients at every time point of assessment, definitive conclusions cannot be made because a significantly lower proportion of patients in the IDS group completed the QoL questionnaires in the second assessment compared to those in the chemotherapy only group, and it is possible that this lower questionnaire completion rate may be associated with QoL.

AUTHORS' CONCLUSIONS

Implications for practice

The heterogeneity of the results in our review precludes any definitive guidance or recommendations for clinical practice. Without strong evidence to support the superior advantages of IDS in combination with chemotherapy over the conventional primary

surgery and chemotherapy, a clinician may remain unconvinced of the benefit of IDS instead of aggressive primary surgery for a patient with advanced ovarian cancer. The choice of extensive primary surgery or upfront chemotherapy followed by IDS in a patient must be individualized. Since we found the benefit of IDS in the subgroup of patients whose primary surgery had not been performed under the optimum condition by the oncologic surgeons or without maximum surgical effort, we would like to make a comment that IDS may improve patient survival in this setting. However, if the primary surgery has already been performed by the oncologic surgeons or with maximal surgical effort, IDS may not yield any further benefit to survival. Nevertheless, in a situation when there is evidence that primary surgery would be impossible or the morbidity from surgery would outweigh the benefit, induction chemotherapy followed by IDS may have a certain role.

Implications for research

This theoretical advantage of IDS needs further well designed RCTs to generate evidence to resolve the equivocal findings of this review.

These studies should focus on a comparison of current conventional primary surgery with adjuvant chemotherapy versus neoadjuvant chemotherapy (without any attempt to remove the bulk of tumours except a biopsy for histologic diagnosis) followed by IDS and then by further chemotherapy.

The level and expertise of the surgeon or the effort in performing the primary surgery should be standardized as far as possible, in order to obtain the best surgical outcome. The particular subgroup of patients with their specific disease characteristics should be a set criteria for IDS, e.g. patients with only small tumours after induction or neoadjuvant chemotherapy.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Redman 1994

Methods	Study duration: April 1986 to February 1990 Type of trial: Multicentre RCT, intention-to-treat analysis
Participants	Stage II-IV (except unresectable stage IV diseases) Performance status ECOG: at least 2 Histology proven, with exclusion of borderline tumour Primary surgery must be performed through an appropriate incision/ a maximal attempt to remove tumours Residual disease status > 2 cm No evidences of progressive disease, extraperitoneal tumour > 1 cm, or had excessive delay after induction chemotherapy and before randomisation Baseline characteristics: 24 women were under the age of 50, 25 between 50-60 and 30 were over 60 years 50 women had performance status 0 or 1, 20 status 2 and 9 women had status 3 or 4 6 women were diagnosed with FIGO stage IIB, 62 stage III and 11 had stage IV disease 39 women had residual disease between 2-5 cm, 29 between 5-10 cm and 11 more than 10 cm Histology type was as follows: Serous 32, mucinous 6, endometrioid 13, clear cell 4, undifferentiated 6 and unspecified 20 Histology differentiation was as follows: Poor 37, moderate 27, well 6 and unspecified 9
Interventions	Intervention: IDS: after 1-4 cycles of induction chemotherapy composing of IV cisplatin 75 mg/m ² + cyclophosphamide 750 mg/m ² or cisplatin 75 mg/m ² + doxorubicin 50 mg/m ² + bleomycin 50 mg/m ² followed by escalated dose of cyclophosphamide (0.5 g/m ² -2.5 g/m ²) up to 5 cycles. Chemotherapy cycles were repeated every 3 weeks. Control: No IDS: the same regimen of chemotherapy were given in a row every 3 weeks.
Outcomes	Overall survival Perioperative complications: primary haemorrhage, blood transfusion, deep vein thrombosis, intestinal fistula, postoperative febrile morbidity, postoperative ileus
Notes	Randomised at entry (within 4 weeks after primary surgery) Number ineligible: 7 (primary surgery was not sub-optimal) Only 9% of primary surgeons were gynaecologic oncologists IDS performed by the primary surgeon Response evaluation by physical examination, imaging studies (CA125 not used) OS was measured from the date of entry Rate of complications were described only in the IDS group
<i>Risk of bias</i>	

Redman 1994 (Continued)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"Randomisation sheets were produced by the random permuted blocks methods utilising the NAG Fortran Library subroutine to generate random numbers"
Allocation concealment?	Yes	"These preprinted sheets were kept at the trial's office and medical personnel were given no access to them"
Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed? All outcomes	Yes	% analysed: 79/86 (92%)
Free of selective reporting?	Unclear	Insufficient information to permit judgement
Free of other bias?	Unclear	Insufficient information to assess whether an important risk of bias exists

Rose 2004

Methods	Study duration: June 1994 to January 2001 Type of trial: Multicentre RCT, intention-to-treat basis
Participants	Stage III-IV (malignant pleural effusion or a resected anterior abdominal wall tumour) (exclusion of stage IV after March 1996 after EORTC reported a greater benefit from secondary surgery after the exclusion of such patients from the analyses) Age < 75 years Performance status ACOG: 0-2 with life expectancy of at least 8 weeks Primary surgery performed within 6 weeks before chemotherapy Primary surgery were aimed to remove as much as possible Histology proven, with central pathologic review Residual disease status > 1 cm Had no delay of chemotherapy treatment > 2 weeks The median age was 58.1 (Range: 25.4-81.6 years) in the IDS group and 57 (Range: 27-81.6 years) in the no IDS group 166 women had GOG performance status 0, 227 had status 1 and 31 women had status 2 400 women were diagnosed with FIGO stage III and 24 had stage IV disease 297 women had measurable disease 53 women had residual disease between 1-2 cm, 183 between 2.1-5 cm, 150 between 5.1-10 cm and 38 more than 10 cm Histology type was as follows: Serous 324, mucinous 3, endometrioid 28, clear cell 7, mixed epithelial 37, adenocarcinoma (unspecified) 12 and undifferentiated or other 13

Rose 2004 (Continued)

	Histology grade was as follows: 1: 40, 2: 167, 3 or clear cell: 217	
Interventions	Intervention: IDS: after 3 cycles of chemotherapy composing of IV paclitaxel 135 mg/m ² + cisplatin 75 mg/m ² every 3 weeks. Three more cycles of the same chemotherapy regimen were given after IDS No IDS: the same regimen of chemotherapy was given in a row every 3 weeks for 6 cycles	
Outcomes	Overall survival Progression-free survival Adverse effects: peripheral neuropathy, haematologic effects, gastrointestinal events, pulmonary events, cardiovascular events, and cause of death Quality of life	
Notes	Randomised after 3 cycles of chemotherapy Number ineligible: 24 Majority of surgeons for primary and secondary surgery (IDS) were gynaecologic oncologists Response evaluation by physical examination, imaging studies, and CA125 Consolidation chemotherapy were allowed OS and progression-free survival were measured from the date of randomisation and also from the date of enrolment	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed? All outcomes	Yes	% analysed: 424/448 (95%)
Free of selective reporting?	Unclear	Insufficient information to permit judgement
Free of other bias?	Unclear	Insufficient information to assess whether an important risk of bias exists

Van der Burg 1995

Methods	Study duration: March 1987 to May 1993 Type of trial: Multicentre RCT, intention-to-treat analysis	
Participants	Stage IIB-IV Age of patients < 75 years Performance status WHO: 0-2 Primary surgery performed within 6 weeks before induction chemotherapy Histology proven, with central pathologic review Residual disease status > 1 cm Have some response or stable disease after induction chemotherapy without evidences of progressive diseases or had contraindication to surgery The median age in the trial was 59 years in both groups (Range: 32-74) 68 women had performance status 0, 99 status 2 and 33 women had status 2 10 women were diagnosed with FIGO stage IIB, 146 stage III and 44 had stage IV disease 10 women had residual disease between 1-2 cm, 45 between 2-5 cm, 44 between 5-10cm, 60 more than 10 cm and unknown but > 2 cm: 41 Histology type was as follows: Serous 115, mucinous 12, endometrioid 17, clear cell 5, and unclassified 51 Histology grade was as follows: 1: 17, 2: 59, 3: 105 and unknown: 9	
Interventions	Intervention: IDS: after 3 cycles of induction chemotherapy composing of IV cyclophosphamide 750 mg/m ² + IV cisplatin 75 mg/m ² every 3 weeks. Three more cycles of the same chemotherapy regimen were given after IDS No IDS: the same regimen of chemotherapy was given in a row every 3 weeks for 6 cycles	
Outcomes	Overall survival Progression-free survival Perioperative complications: bowel injury, urinary bladder injury, blood loss, postoperative fever, ileus, urinary tract infection, wound infection, deep vein thrombosis, lung embolism Clinical response rate after 6 cycles of chemotherapy	
Notes	Randomized after 3 cycles of induction chemotherapy at Central EORTC data centre, after stratification with a minimization technique to account for institution, performance status, and clinical response Number ineligible: 4 Response evaluation by WHO response criteria Consolidation chemotherapy after 6 cycles was allowed based on institutions policy Survivals were measured from the first date of chemotherapy (after enrolment) Rate of complications were detailed only in the IDS group	
Risk of bias		
Item	Authors' judgement	Description

Van der Burg 1995 (Continued)

Adequate sequence generation?	Yes	“Randomization was done ... after stratification with a minimization technique to account for institution, performance status, and clinical response”
Allocation concealment?	Yes	“Randomization was done centrally at the EORTC Data Center”
Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed? All outcomes	Yes	% analysed: 278/319 (87%)
Free of selective reporting?	Unclear	Insufficient information to permit judgement
Free of other bias?	Unclear	Insufficient information to assess whether an important risk of bias exists

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Angioli 2006	This study was evaluated as non-comparable controlled clinical trial. Neoadjuvant chemotherapy followed by IDS was selectively given to the patients based on initial laparoscopic findings of inoperability.
Chan 2003	This study was evaluated as uncontrolled clinical trial. Neoadjuvant chemotherapy was given to the studied patients without control group. The patients were selected by their inoperability based on CT scan without primary operation being attempted. Either histology or only cytology was allowed for a pathologic diagnosis of ovarian cancer.
Dutta 2005	This was an RCT of ovarian cancer patients to have either 3 cycles of NAC followed by IDS and further chemotherapy versus 6 cycles of NAC before surgery. Main objective was to study proapoptotic and antiapoptotic proteins in ovarian cancer tissue without survival outcome evaluation.
EORTC 55971	This study did not focus on IDS, but on NAC versus primary surgery. IDS was primarily allowed in the primary surgery arm too (upon the discretion of the physician).
Evdokimova 1982	This was an RCT comparing survival of patients with ovarian carcinoma patients who had NAC/IDS versus conventional treatment of surgery then chemotherapy. However, patients without ascites were selected to have primary surgery followed by chemotherapy while those with ascites had either NAC/IDS or conventional treatment.

(Continued)

Fuso 2006	This uncontrolled prospective study was to assess the feasibility of triple chemotherapy composing of gemcitabine, carboplatin, and paclitaxel as first line drug in advanced ovarian cancer. The patients were selectively assigned to have 2 different types of treatment. After laparoscopic biopsy in all patients, those who were judged to be operable underwent primary surgery followed by chemotherapy while the inoperable patients were given NAC followed by IDS. However, few patients who had primary surgery also had IDS.
Giannopoulos 2006	This study was evaluated as a non-comparable controlled clinical trial. Neoadjuvant chemotherapy and IDS was selectively given to the patients who were determined to be inoperable based on CT scan and initial laparoscopic findings. Either histology or cytology was allowed for a pathologic diagnosis of ovarian cancer.
Ikeba 2004	This study was evaluated as an uncontrolled clinical trial. Neoadjuvant chemotherapy were given to the studied patients without control group.
Kuhn 2001	This study was evaluated as a non-comparable controlled clinical trial. Neoadjuvant chemotherapy was selectively given to the patients who had poor general health for primary surgery. Patients in the control group were those who did not agree to the study protocol or were incompatible with the trial because of psychological reasons.
Kumar 2007	This was an RCT presented as a conference abstract. The patients were randomised to have upfront debulking surgery followed by chemotherapy versus having NAC followed by IDS and further chemotherapy. No randomisation details were provided. Either histology or cytology was allowed for a pathologic diagnosis of ovarian cancer.
Lee 2006	This study was evaluated as a non-comparable controlled clinical trial. Neoadjuvant chemotherapy was selectively given to the patients who agreed to undergo the NAC treatment protocol. NAC cycles ranged from 3 cycles to 6 cycles. Some patients had secondary surgery which was not in an interval setting.
Liu 2004	This RCT was considered as ineligible because NAC was given only for 1 cycle via intra-arterial route before the IDS.
Park-Simon 2006	This RCT compared survivals of ovarian cancer patients who had ascites > 500 cc who were given NAC for either 2 versus 3 cycles, however, followed by IDS in both arms.
Recchia 2001	This study was evaluated as an uncontrolled clinical trial. Neoadjuvant chemotherapy was given to the studied patients without control group. Either histology or only cytology was allowed for a pathologic diagnosis of ovarian cancer.
Solomon 1988	This study was presented in conjunction with the prior RCT comparing combination versus sequential chlorambucil and cisplatin. IDS in this study was selectively performed only in the subset of patients who had not been debulked at primary surgery. Second-look surgery or surgical re-exploration were also performed in those with clinical complete remission or in those with complications requiring surgery, respectively.

Characteristics of studies awaiting assessment *[ordered by study ID]*

JCOG 0206

Methods	
Participants	56 patients with stage III/IV mullerian carcinomas such as ovarian, tubal and peritoneal carcinomas Diagnosed by pre-laparoscopic clinical findings including imaging studies (CT, MRI or ultrasonography) and cytology of ascites, pleural effusions or fluids obtained by tumour centesis Malignancies of other origins, such as breast and digestive tract, should be excluded by endoscopy, opaque enema or ultrasonography (if suspected from symptoms, physical examination or imagings) To rule out malignancy of digestive tract , CA125 must be > 200 U/ml and CEA must be < 20 ng/ml
Interventions	- Diagnostic laparoscopy to confirm diagnosis, histology and stage - Biopsy from the main tumour or metastatic tumours - Resection of any organs or tumours attempting to reduce tumour volume not allowed. - Neoadjuvant chemotherapy (NAC) as paclitaxel (175 mg/m², day 1) and carboplatin (AUC = 6, day 1) for 4 cycles. - Interval cytoreductive surgery performed after the 4th cycle of NAC (unless PD) - An additional 4 cycles of the same chemotherapy regimen after surgery
Outcomes	Primary endpoint: clinical complete remission after protocol completion Secondary endpoints regarding NAC: response rate to NAC among patients whose clinical diagnosis is confirmed by laparoscopy proportion of patients who received ICS among patients whose clinical diagnosis is confirmed by laparoscopy Overall survival Progression-free survival Operative morbidity Adverse events
Notes	Plan for subsequent phase III study, comparing NAC therapy with current standard procedure

DATA AND ANALYSES

Comparison 1. IDS vs chemotherapy only

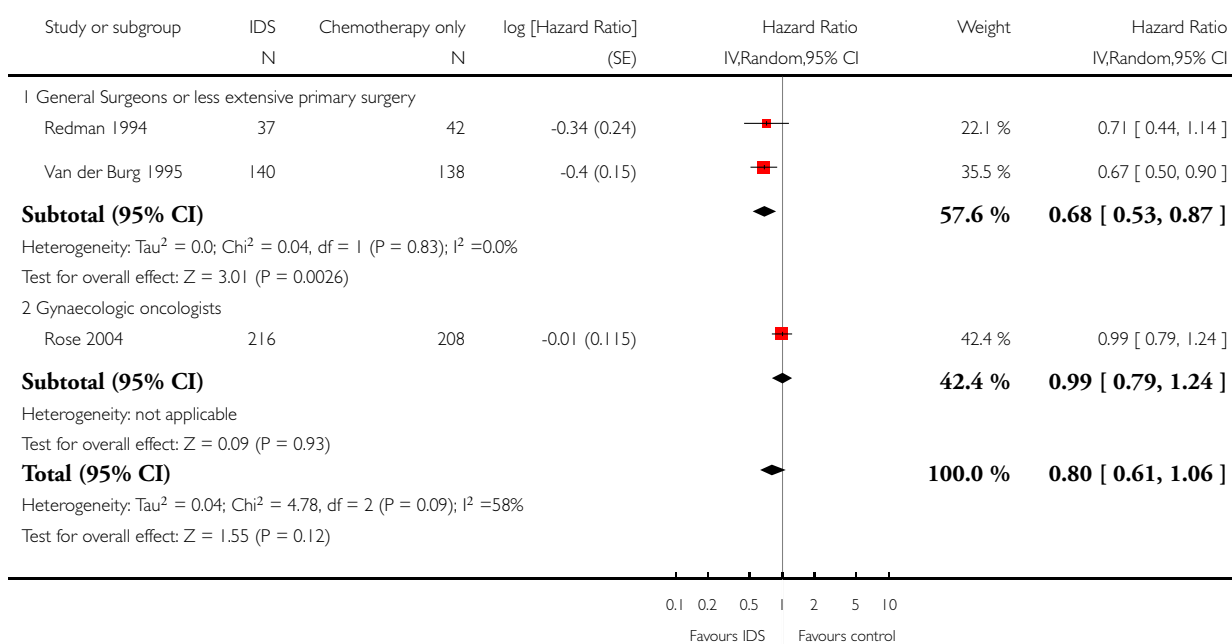
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	3	781	Hazard Ratio (Random, 95% CI)	0.80 [0.61, 1.06]
1.1 General Surgeons or less extensive primary surgery	2	357	Hazard Ratio (Random, 95% CI)	0.68 [0.53, 0.87]
1.2 Gynaecologic oncologists	1	424	Hazard Ratio (Random, 95% CI)	0.99 [0.79, 1.24]
2 Progression-free survival	2	702	Hazard Ratio (Random, 95% CI)	0.88 [0.57, 1.33]
3 Toxic reactions to chemotherapy	2	357	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.53, 2.66]
4 Peripheral neuropathy of grade 2 or higher	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5 Grade 3 or 4 gastrointestinal adverse events	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
6 Grade 4 pulmonary adverse events	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
7 Grade 4 cardiovascular adverse events	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 IDS vs chemotherapy only, Outcome 1 Overall survival.

Review: Interval debulking surgery for advanced epithelial ovarian cancer

Comparison: 1 IDS vs chemotherapy only

Outcome: 1 Overall survival

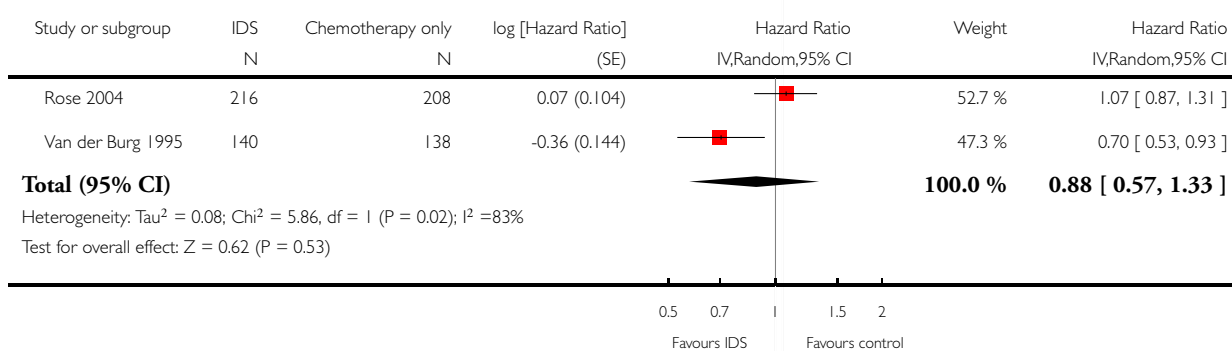


Analysis 1.2. Comparison 1 IDS vs chemotherapy only, Outcome 2 Progression-free survival.

Review: Interval debulking surgery for advanced epithelial ovarian cancer

Comparison: 1 IDS vs chemotherapy only

Outcome: 2 Progression-free survival

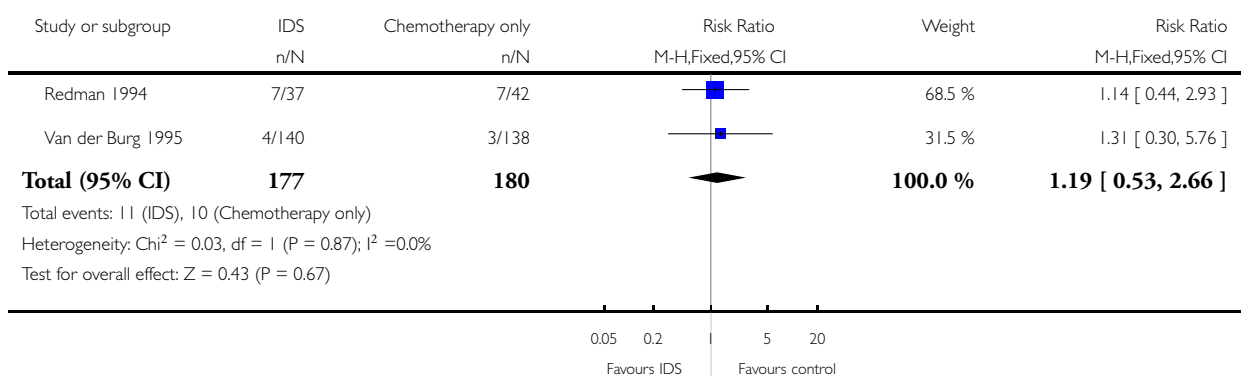


Analysis 1.3. Comparison 1 IDS vs chemotherapy only, Outcome 3 Toxic reactions to chemotherapy.

Review: Interval debulking surgery for advanced epithelial ovarian cancer

Comparison: 1 IDS vs chemotherapy only

Outcome: 3 Toxic reactions to chemotherapy

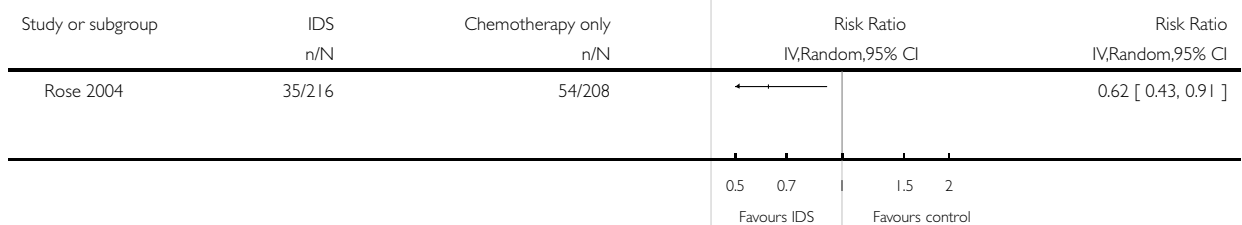


Analysis 1.4. Comparison 1 IDS vs chemotherapy only, Outcome 4 Peripheral neuropathy of grade 2 or higher.

Review: Interval debulking surgery for advanced epithelial ovarian cancer

Comparison: 1 IDS vs chemotherapy only

Outcome: 4 Peripheral neuropathy of grade 2 or higher

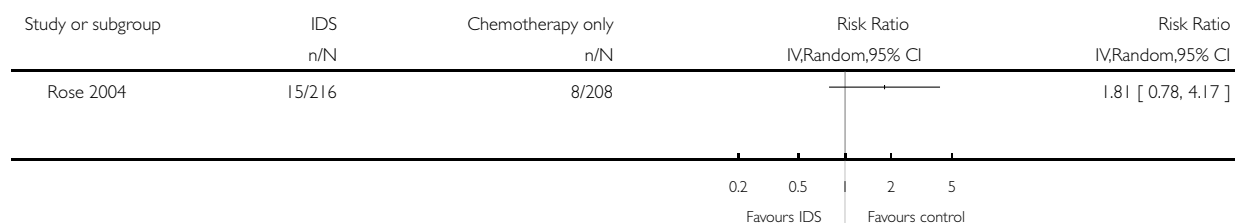


Analysis 1.5. Comparison 1 IDS vs chemotherapy only, Outcome 5 Grade 3 or 4 gastrointestinal adverse events.

Review: Interval debulking surgery for advanced epithelial ovarian cancer

Comparison: 1 IDS vs chemotherapy only

Outcome: 5 Grade 3 or 4 gastrointestinal adverse events

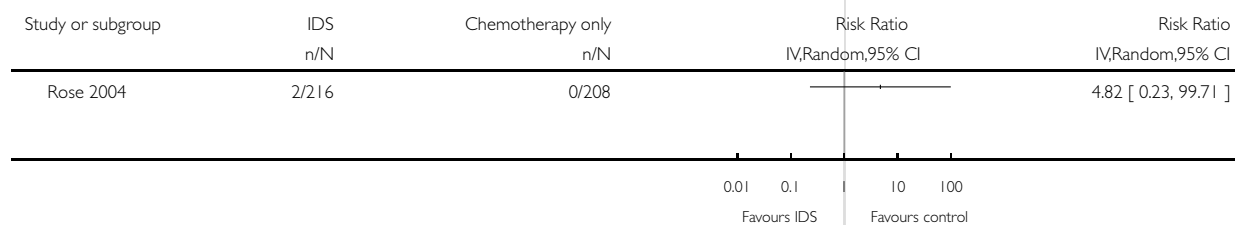


Analysis 1.6. Comparison 1 IDS vs chemotherapy only, Outcome 6 Grade 4 pulmonary adverse events.

Review: Interval debulking surgery for advanced epithelial ovarian cancer

Comparison: 1 IDS vs chemotherapy only

Outcome: 6 Grade 4 pulmonary adverse events

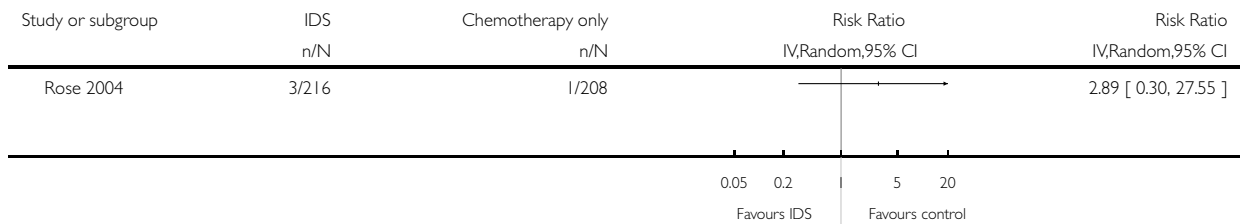


Analysis 1.7. Comparison 1 IDS vs chemotherapy only, Outcome 7 Grade 4 cardiovascular adverse events.

Review: Interval debulking surgery for advanced epithelial ovarian cancer

Comparison: 1 IDS vs chemotherapy only

Outcome: 7 Grade 4 cardiovascular adverse events



APPENDICES

Appendix 1. MEDLINE Ovid

- 1 exp Ovarian Neoplasms/
- 2 (ovar* adj5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).mp.
- 3 1 or 2
- 4 exp Surgical Procedures, Operative/
- 5 surg*.mp.
- 6 surgery.fs.
- 7 4 or 5 or 6
- 8 (interval or debulk* or cytoreduc* or secondary).mp.
- 9 3 and 7 and 8
- 10 randomized controlled trial.pt.
- 11 controlled clinical trial.pt.
- 12 randomized.ab.
- 13 randomly.ab.
- 14 trial.ab.
- 15 groups.ab.
- 16 10 or 11 or 12 or 13 or 14 or 15
- 17 9 and 16
- 18 limit 17 to yr="2008 - 2009"
- 19 (animals not (humans and animals)).sh.
- 20 18 not 19

key:

mp = title, original title, abstract, name of substance word, subject heading word

fs = floating subheading

pt = publication type

ab = abstract

sh = subject heading

Appendix 2. EMBASE

- 1 exp ovary tumor/
- 2 (ovar* adj5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).mp.
- 3 1 or 2
- 4 exp surgery/
- 5 surg*.mp.
- 6 su.fs.
- 7 4 or 5 or 6
- 8 (interval or debulk* or cytoreduc* or secondary).mp.
- 9 7 and 8
- 10 exp cytoreductive surgery/
- 11 9 or 10
- 12 3 and 11
- 13 exp controlled clinical trial/
- 14 randomized.ab.
- 15 randomly.ab.
- 16 trial.ab.
- 17 groups.ab.
- 18 13 or 14 or 15 or 16 or 17
- 19 12 and 18
- 20 limit 19 to yr="2008 - 2009"
- 21 exp animal/
- 22 human/
- 23 21 not (21 and 22)
- 24 20 not 23

key:

mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name

fs = floating subheading

ab = abstract

Appendix 3. CENTRAL

- #1 MeSH descriptor Ovarian Neoplasms explode all trees
- #2 ovar* near/5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)
- #3 (#1 OR #2)
- #4 MeSH descriptor Surgical Procedures, Operative explode all trees
- #5 surg*
- #6 Any MeSH descriptor with qualifier: SU
- #7 (#4 OR #5 OR #6)
- #8 interval or debulk* or cytoreduc* or secondary
- #9 (#3 AND #7 AND #8)
- #10 (#9), from 2008 to 2009

Appendix 4. Cochrane Gynaecological Cancer Review Group's Specialised Register

#8=OVY AND #11=SU AND #11= CT AND (#4=ADVANCED OR #4=RECURRENT OR #4=REFRACTORY OR #43=ADVANCED OR #43=RECURRENT OR #43=REFRACTORY)

WHAT'S NEW

Last assessed as up-to-date: 18 August 2010.

Date	Event	Description
19 August 2010	New citation required but conclusions have not changed	Searches re-run in July 2009. Seventeen possible relevant articles were identified. Only two RCTs were found; one RCT of a Japanese study and the EORTC 55971 trial. However, the Japanese study referred to a study that was excluded in our primary review and EORTC 55971 trial allowed IDS in both arms at discretion of physician.

HISTORY

Protocol first published: Issue 2, 2006

Review first published: Issue 4, 2008

Date	Event	Description
10 February 2009	Feedback has been incorporated	Feedback regarding new trial incorporated.
10 November 2008	New citation required but conclusions have not changed	Errors in reporting HR and RR corrected. Explanation regarding surgical expertise included.
20 March 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

ST and SM: protocol development, search for and determine the relevance of trials for the review, assess their methodological quality, extract data, and review development. ML: protocol development, data analysis, and review development. PL: protocol development, provide methodological advice throughout the review, arbitrate over any disagreements, advise over the content and presentation of the review. AB: methodological and statistical support.

DECLARATIONS OF INTEREST

There is no conflict of interest amongst the authors of this review.

SOURCES OF SUPPORT

Internal sources

- Bangkok Metropolitan Administration Medical College and Vajira Hospital, Thailand.
- Faculty of Medicine, Khon Kaen University, Thailand.
- Faculty of Public Health, Khon Kaen University, Thailand.

External sources

- Thailand Research Fund (Senior Research Scholar), Thailand.
- Thai Cochrane Network, Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None of the trials reported continuous outcomes such as quality of life or had multiple treatment groups. We had originally specified the following in various sections of the protocol.

- For continuous outcomes (e.g. QoL measures), we will extract the final value and standard deviation of the outcome of interest and the number of patients assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference (if trials measured outcomes on the same scale) or standardised mean differences (if trials measured outcomes on different scales) between treatment arms and its standard error.
- For continuous outcomes, we will use the mean difference between treatment arms.
- For continuous outcomes, the mean differences between the treatment arms at the end of follow-up will be pooled if all trials measured the outcome on the same scale, otherwise standardised mean differences were pooled.
- If any trials had multiple treatment groups, the 'shared' comparison group will be divided into the number of treatment groups and comparisons between each treatment group and the split comparison group will be treated as independent comparisons.
- Where possible, indirect comparisons, using the methods of [Bucher 1997](#) will be used to compare competing interventions that have not been compared directly with each other.

We had planned to compute funnel plots but this was not possible due to an insufficient number of included trials in the review. The protocol stated the following:

Funnel plots corresponding to meta-analysis of the primary outcome will be examined for evidence of small study effects. If such evidence exists, publication bias and other possible explanations will be considered. If funnel plots suggest that treatment effects may not be sampled from a symmetric distribution, as assumed by the random-effects model, sensitivity analyses will be performed using fixed-effect models.

We planned to perform sensitivity analyses to evaluate whether the pooled effect sizes were robust across components of methodological quality. However, only one trial reported adequate concealment of allocation ([Redman 1994](#)) and other components of quality were similar across studies, so these sensitivity analyses were not performed.

INDEX TERMS

Medical Subject Headings (MeSH)

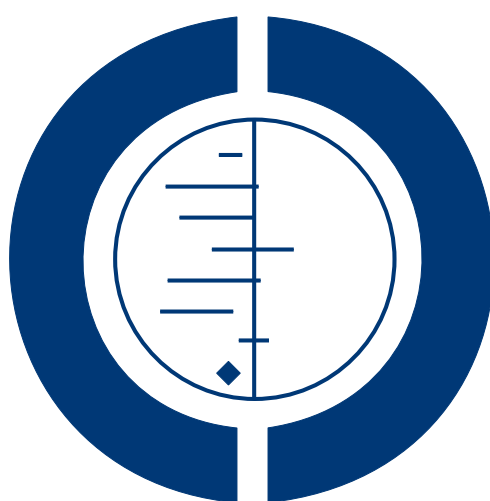
Antineoplastic Agents [therapeutic use]; Chemotherapy, Adjuvant; Ovarian Neoplasms [drug therapy; mortality; pathology; *surgery]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans

Meditation therapies for attention-deficit/hyperactivity disorder (ADHD) (Review)

Krisanaprakornkit T, Ngamjarus C, Witoonchart C, Piyavhatkul N



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[Intervention Review]

Meditation therapies for attention-deficit/hyperactivity disorder (ADHD)

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Review content assessed as up-to-date: 20 April 2010.

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ABSTRACT

Background

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common developmental disorders experienced in childhood and can persist into adulthood. The disorder has early onset and is characterized by a combination of overactive, poorly modulated behavior with marked inattention. In the long term it can impair academic performance, vocational success and social-emotional development. Meditation is increasingly used for psychological conditions and could be used as a tool for attentional training in the ADHD population.

Objectives

To assess the effectiveness of meditation therapies as a treatment for ADHD.

Search strategy

Our extensive search included: CENTRAL, MEDLINE, EMBASE, CINAHL, ERIC, PsycINFO, C2-SPECTR, dissertation abstracts, LILACS, Virtual Health Library (VHL) in BIREME, Complementary and Alternative Medicine specific databases, HSTAT, Informit, JST, Thai Psychiatric databases and ISI Proceedings, plus grey literature and trial registries from inception to January 2010.

Selection criteria

Randomized controlled trials that investigated the efficacy of meditation therapy in children or adults diagnosed with ADHD.

Data collection and analysis

Two authors extracted data independently using a pre-designed data extraction form. We contacted study authors for additional information required. We analyzed data using mean difference (MD) to calculate the treatment effect. The results are presented in tables, figures and narrative form.

Main results

Four studies, including 83 participants, are included in this review. Two studies used mantra meditation while the other two used yoga compared with drugs, relaxation training, non-specific exercises and standard treatment control. Design limitations caused high risk of bias across the studies. Only one out of four studies provided data appropriate for analysis. For this study there was no statistically significant difference between the meditation therapy group and the drug therapy group on the teacher rating ADHD scale (MD -2.72, 95% CI -8.49 to 3.05, 15 patients). Likewise, there was no statistically significant difference between the meditation therapy group and the standard therapy group on the teacher rating ADHD scale (MD -0.52, 95% CI -5.88 to 4.84, 17 patients). There was also no statistically significant difference between the meditation therapy group and the standard therapy group in the distraction test (MD -8.34, 95% CI -107.05 to 90.37, 17 patients).

Authors' conclusions

As a result of the limited number of included studies, the small sample sizes and the high risk of bias, we are unable to draw any conclusions regarding the effectiveness of meditation therapy for ADHD. The adverse effects of meditation have not been reported. More trials are needed.

PLAIN LANGUAGE SUMMARY

Meditation therapies for attention-deficit/hyperactivity disorder (ADHD)

Attention-deficit/hyperactivity disorder (ADHD) is a disorder that affects a significant number of children and adults in a variety of ways. It is characterized by chronic levels of inattention, impulsiveness and hyperactivity. Meditation therapy could be a beneficial treatment for those diagnosed with ADHD. The objective of this review was to assess the efficacy of this treatment. As a result of the small number of studies that we were able to include in this review and the limitations of those studies, we were unable to draw any conclusions regarding the effectiveness of meditation therapy for ADHD. No adverse effects of meditation in children have been reported. More trials are needed on meditation therapies for ADHD so that conclusions can be drawn regarding its effectiveness.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [\[Explanation\]](#)

Meditation therapy versus drug therapy for attention deficit /hyperactivity disorder						
Patient or population: patients with attention deficit /hyperactivity disorder Settings: Intervention: meditation therapy versus drug therapy						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	meditation therapy versus drug therapy				
Teacher rating ADHD overall scale The Abbreviated Parent-Teacher Questionnaire (Conners, 1973) Follow-up: mean 4 weeks	The mean teacher rating adhd overall scale in the control groups was 14.83	The mean Teacher rating ADHD overall scale in the intervention groups was 2.72 lower (8.49 lower to 3.05 higher)		15 (1 study ⁴)	⊕○○○ very low ^{1,2,3}	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval;						
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.						

¹ Unclear randomization method, unclear allocation concealment, no blinding, unclear attrition rate, other biases presented

² Wide confidence interval, small sample size

³ Only one study(since 1987) presented for this outcome

⁴ Study Moretti-Altuna, 1987

BACKGROUND

Description of the condition

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common developmental problems experienced in childhood and can persist into adulthood. The major symptoms are inconsistent development and chronic levels of inattention, impulsiveness and hyperactivity (Scahill 2000).

Prevalence estimates vary according to the diagnostic criteria used and the population sampled. These estimates can be further affected by influences on the diagnosis, such as the cultural environment and the differing attitudes of parents, clinicians and society towards acceptable children's behavior (Dwivedi 2005). According to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) (APA 2000), prevalence estimates among school children in the US are between 3% and 7% (APA 2000), but other estimates range from 1.7% to 16.0% (Pritchard 2005). Boys are diagnosed with ADHD three times more often than girls. Evidence attests to the strong influence of genetic factors on the expression of symptoms, however psychosocial, environmental and cultural factors also play a role (Swanson 2001).

An independent diagnostic test for ADHD does not exist, thus the diagnosis of ADHD is clinically based. The essential criteria for a diagnosis of ADHD are a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequently displayed and more severe than is typically observed in individuals at a comparable level of development, and is not better explained by the presence of another mental disorder. Symptoms evolve over time. In adolescence, signs of excessive gross motor activity (e.g. excessive running and climbing, not remaining seated) are less common, and hyperactivity symptoms may be confined to fidgeting or an inner feeling of jitteriness or restlessness. In adulthood, restlessness may lead to difficulty in participating in sedentary activities and to avoiding pastimes or occupations that provide limited opportunity for spontaneous movement (e.g. desk jobs) (APA 2000). Other adults may retain only some of the symptoms, in which case the diagnosis should be ADHD in partial remission.

In order to qualify for a diagnosis of ADHD, hyperactive-impulsive or inattentive symptoms must have presented before the age of seven, with some impairment from the symptoms present in at least two settings (e.g. at home and at school). There must be clear evidence of interference with developmentally appropriate social, academic or occupational functioning. Care must be taken to ensure that the disturbance does not occur exclusively during the course of a pervasive developmental disorder, schizophrenia or other psychotic disorder and is not better accounted for by another mental disorder (APA 2000).

The DSM-IV-TR provides subtypes for specifying the predominant symptom presentation: predominantly inattentive type, predominantly hyperactive/impulsive type and combined type. In the International Classification of Diseases (ICD-10) (WHO 1992)

the disorders are defined under the category of 'Hyperkinetic Disorders' and are characterized by early onset, a combination of over-active, poorly modulated behavior with marked inattention and lack of persistent task involvement, pervasiveness across situations and persistence over time (WHO 1992).

Children with ADHD have pronounced impairments and can experience enduring adverse effects in their academic performance, vocational success and social-emotional development. These impairments, in turn, can have a profound impact on individuals, families, schools and society (NIH 1998). Moreover, studies indicate that children diagnosed as having ADHD and a comorbid anxiety or depressive disorder have higher levels of coexisting life stresses and parental symptoms than children who have the single diagnosis of ADHD (Jensen 1993).

Description of the intervention

Non-pharmacological treatment of ADHD in childhood can be divided into three categories: parent- or family-focused strategies, child-directed interventions and school-based interventions (ICSI 2005). Psychostimulant medications are considered first-line therapy as they are effective in 70% to 80% of children with ADHD, although their use may be limited both by tolerability and acceptability (AAP 2001). Augmentation of psychostimulant treatment with psychosocial interventions provides no advantage over medication alone for the core symptoms of ADHD, but appears to have an advantage for associated problems such as anxiety disorders, social skills difficulties, consumer satisfaction and possibly academic achievement (MTA 1999).

Due to an increase in scientific evidence, clinical experience and community attitudes are encouraging a shift towards more natural and holistic forms of therapy as alternatives or adjuncts to pharmacological approaches in a variety of conditions (Arias 2006; Krisanaprakornkit 2006; Mansky 2006).

Meditation is becoming increasingly popular as a treatment for psychological conditions and has a wide range of applications. A psychologically-oriented definition states that "meditation is a set of attentional practices leading to an altered state or trait of consciousness characterized by expanded awareness, greater presence, and a more integrated sense of self" (Davis 1998), which suggests that meditation might be a useful tool for attentional training in the ADHD population. In addition to increased attention, meditation may produce a state of calmness and contentment which is generally lacking in the ADHD population (Jensen 2004). Adequately trained practitioners who have first-hand experience can easily adapt meditation to the general medical setting (Hassed 1996).

Meditation originated in India more than three thousand years ago and has played a prominent role in the ritual practice of major religions and secular organizations alike. Meditation can be divided into two general types: concentrative meditation and mindfulness meditation (Barrows 2002).

Concentrative meditation is best represented in modern medicine by two programs: Transcendental Meditation® (TM®) which was introduced to the West during 1960s and the 'Relaxation Response' developed subsequently by Benson (Benson 1975). Concentrative meditation involves focusing attention on an object and sustaining attention until the mind achieves stillness. A diverse range of items could be chosen as the focal object, for example words, light, colors, geometric forms, ideas etc. Continuous practice should result in relaxation, clarity of mind and calmness.

Mindfulness meditation emphasizes an open awareness to any contents of the mind that are emerging. After a period of practice the patient should develop a sustainable attentive observational capability, without reacting to their own thoughts and emotions. Achieving this state of mindfulness and equanimity helps to re-train or decondition previous patterns of reaction which are usually poorly adapted to external reality. This form of meditation is commonly represented by mindfulness-based stress reduction programs (Kabat-Zinn 1992). The techniques of mindfulness meditation, with their emphasis on developing detached observation and awareness of the contents of consciousness, may represent a powerful cognitive behavioral coping strategy for transforming the ways in which we respond to life events (Astin 1997).

Meditation, either concentrative or mindfulness, is able to enhance the attentional ability of the practitioners. Whilst concentrative meditation emphasizes sustained attention, mindfulness meditation aims to improve self-control and inhibitions to various internal and external stimuli, thereby helping to relieve the core symptoms of ADHD. However, any single meditation program will usually use both concentrative and mindfulness together.

Recently, five broad categories of meditation practices were identified by a group of experts using modified Delphi methodology (Ospina 2007).

- Mantra meditation (comprising the Transcendental Meditation® technique (TM®), Relaxation Response (RR) and Clinically Standardized Meditation (CSM)).
- Mindfulness meditation (comprising Vipassana, Zen Buddhist meditation, Mindfulness-based Stress Reduction (MBSR) and Mindfulness-based Cognitive Therapy (MBCT)).
- Yoga (various yogic meditative techniques).
- Tai Chi (encompassing Chinese traditional exercises that promote posture, flexibility, relaxation, well-being and mental concentration).
- Qi Gong (a category of 'energy healing', including Reiki, therapeutic touch and the Korean practice of Chundosunbup).

However, in this review we adhere to the old classification since it is generally well accepted and commonly used in the literature, although both classifications substantially overlap.

Thus, the operational definitions of meditation are the specific techniques of mind training which have two fundamental attentional strategies (Barrows 2002).

1. Concentrative meditation entails sustained attention directed towards a single object or point of focus. The aim is one-pointed attention to a single perception without distraction in order to produce concentration or a one-minded state.

2. Mindfulness meditation (opening-up, insight meditation) involves the continual maintenance of a specific perceptual-cognitive mind set towards objects as they spontaneously arise in ones awareness with a non-reactive attitude. The salient features are full awareness or mindfulness of any contents of consciousness with equanimity.

There are many methods which represent meditation in the above definitions, i.e. insight meditation, mindfulness-based meditation, Vipassana, Qiqong therapy, yoga (Asana, Pranayama, Raja yoga, Asthanga yoga, Laya yoga, Sahaj Marg etc), Tai Chi, Transcendental Meditation, Kundalini yoga, Anapanasathi (Buddhist breathing meditation), Zen and ChunDoSupBup. It is noted that Asana yoga (yoga of posture) and Tai Chi are also considered to be dynamic aspects of concentrative meditation.

Although historically meditation is associated with religious or spiritual movements, this is no longer always the case. It is now necessary to confirm the effectiveness of these meditation techniques by using non-cult, faith-free and specifically designed methods to treat patients. Nowadays there are increasing numbers of organizations which use scientific-based, less mystical terms to identify their techniques (Krisanaprakornkit 2006).

How the intervention might work

Some reports exist which detail the usefulness of meditation for children with ADHD. Grosswald (reported in Micucci 2005) conducted a study in April 2004 at Chelsea School in Silver Spring, Maryland, a private school for children with learning disabilities. The study compared ten students with ADHD before and after they learned and practiced Transcendental Meditation for ten minutes twice daily for three months. Participants reported being calmer, less distracted, less stressed and better able to control their anger and frustration. However, there was no control/comparison group in this study.

Preliminary bibliographic searching has not identified many studies using meditation therapy for ADHD. Jensen et al conducted a randomized controlled trial of the effect of yoga on boys with ADHD (n = 11) (Jensen 2004). This program consisted of respiratory training, postural training, relaxation training and concentration training and involved a technique called Trataka where participants focused on a word or shape, followed by seeing the image with their eyes closed and continuing to see the image on a blank piece of paper. The results only slightly supported the use of yoga for ADHD and there were some limitations of this study, such as low statistical power and inconsistency of home practices. Hassasiri et al (Hassasiri 2002) developed a meditation program for children with ADHD in Thailand based on neo-humanist concepts which comprised meditation and imagery. The program was

tested in a before-after design and found a statistically significant difference in change scores ($P < 0.05$).

In terms of adverse effects, reports exist suggesting that meditation can cause temporary depersonalization and derealization ([Castillo 1990](#)), and there are several reports of a possible association between meditation and psychotic state ([Chan-Ob 1999](#); [French 1975](#); [Lazarus 1976](#); [Walsh 1979](#)). Studies of meditation in pediatric populations are still limited. It is not considered advisable for children to sit for extended lengths of time with closed eyes, which might in any case 'go against the grain' of the active nature of children. Different meditation techniques have different recommended practices for children, e.g. Sahaj Marg Meditation, a system of Raja yoga, recommends a minimum age of 18 before beginning the practice of meditation, implying that this technique is not suitable for younger people. In Transcendental Meditation, it is recommended that children of five years old meditate twice a day for five minutes at a time and thereafter add one minute for each year of their age until reaching 20-minute sessions when aged 20 and above. Reports of adverse effects of meditation in children are lacking.

Why it is important to do this review

To our knowledge no systematic review has been carried out specifically considering the effectiveness of meditation for ADHD, although several clinical trials have been conducted. This review aims to address that evidence gap.

OBJECTIVES

To assess the effects of concentrative and mindfulness meditation therapies for treating attention-deficit/hyperactivity disorders (ADHD) in children, adolescents and adults.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials comparing meditation therapy alone or in combination with conventional treatment (consisting of drugs or any other psychological interventions) to i) conventional treatment or ii) no intervention/waiting list control.

We excluded studies where meditation therapy was not a well-organized program (i.e. no structure, no schedule of practice, no formal setting).

Types of participants

Participants of any age diagnosed with attention-deficit/hyperactivity disorder (ADHD) or hyperkinetic disorders (HKD) according to established diagnostic criteria.

Types of interventions

Meditation therapy, consisting of concentrative meditation, mindfulness meditation or a combination of both, provided as the main intervention in the case of multi-component therapy.

Comparison conditions could be one or a combination of the following:

1. pharmacological therapy;
2. no intervention or waiting list;
3. other psychological treatment: cognitive behavioral therapy, parent training program, counseling etc.

Types of outcome measures

Primary outcomes

A. Symptoms of ADHD

Incidence/severity of the core symptoms (inattention, impulsivity, hyperactivity) measured by a validated symptoms rating scale ;

- The revised Conners' Parent Rating Scale (CPRS-R) ([Conners 1997](#); [Conners 1998](#)).
- Conners' Teacher Rating Scale (CTRS-R) ([Conners 1998/2](#)).
- ADHD Rating Scale IV ([Zhang 2005](#)).
- Attention-Deficit Disorder Evaluation Scale (ADDES) ([Adesman 1991](#)).
- Conners' Continuous Performance Test ([Conners 1995](#)).
- Yale Children's Inventory ([Shaywitz 1988](#)).
- The ADD/H Adolescent Self-Report Scale ([Robin 1996](#)).
- The Internal Restlessness Scale ([Weyandt 2003](#)).

B. Quantitative laboratory assessment measures of ADHD symptoms

1. Psychological test

- Continuous Performance Test (CPT).
- The Gordon Diagnostic System (GDS).
- The Children's Checking Task (CCT).
- Test of Variable of Attention (TOVA) ([Greenberg 1999](#)).
- Delay of Gratification Tasks.
- The Choice-Delay Task (C-DT).
- The Stop Signal Task (SST) ([Nichols 2004](#)).
- The Auditory Continuous Performance Test ([Riccio 1996](#)).

2. Psychophysiological measures

- Electroencephalography (EEG).

- Actograph pedometer which uses devices to monitor a child's movements and displays these as an actograph which provides an objective indicator of general motor activity.

C. Overall incidence/severity of the problem behaviors

- Child Behavior Checklist (CBCL) (Achenbach 2000).
- The Adolescent Behavior Checklist (Adams 1997).
- Children's Aggression Scale - Parent Version (Halperin 2002).
- Children's Aggression Scale - Teacher Version (Halperin 2003).
- Swanson Kotkin Atkins M-Flynn Pelham Scale (SKAMP) (Wigal 1998).
- Behavior Assessment System for Children (BASC) (Reynolds 1992).

Secondary outcomes

A. Intelligence

Standardized measures, including these intelligence scales.

- Wechsler Intelligence Scale for Children-III (Wechsler 1991).
- Stanford-Binet Intelligence Scales (Becker 2003).
- Tower of London Test (Shallice 1988).

B. School/academic performance

Measured by scale, grades or teacher reports, including:

- Wechsler Individual Achievement Test (WIAT) (Wechsler 1992);
- The Peabody Individual Achievement Test (Klinge 1974).

C. Psychopathology outcomes

Depression/anxiety-related outcome including:

- The Diagnostic Inventory for Depression (Zimmerman 2004);
- Multidimensional Anxiety Scale for Children (MASC) (March 1997).

Conduct/oppositional disorder outcomes, including:

- The Oppositional Defiant Behavior Inventory (Harada 2004).

D. Family and social outcomes

- Parenting Stress Index (Loyd 1985).
- Parenting Scale for Parents of Children with ADHD (Harvey 2001).
- Social Adjustment Inventory for Children and Adolescents (SAICA) (Biederman 1993).

E. Quality of life scales

- The ADHD Impact Module (Landgraf 2002).
- Adult Attention-Deficit/Hyperactivity Disorder Quality-of-Life Scale (AAQoL) (Brod 2006).
- Clinical Global Impression score changes (NIMH 1985).
- Children's Global Assessment Scale (CGAS) (Shaffer 1983).

F. Any adverse effects of meditation reported in the trials

Search methods for identification of studies

To determine whether meditation is the main intervention in multi-component therapy, the authors of the studies must specify meditation or related words in the title or keywords of the articles. Operational definitions of meditation are mentioned in the background section.

The following searches were conducted without language restriction.

Electronic searches

We searched the following electronic databases with the help of the Trials Search Co-ordinator of the Cochrane Developmental, Psychosocial and Learning Problems Group (CDPLPG).

- Cochrane Central Register of Controlled Trials (CENTRAL) (2010, Issue 1);
 - MEDLINE (from 1966 to Jan 2010);
 - OLDMEDLINE (pre 1966);
 - EMBASE from 1980 to 2010 week 5;
 - CINAHL from 1982 to Jan 2010;
 - the Campbell Collaboration SPECTR (C2-SPECTR) database to Jan 2010;
 - Educational Resources Information Center (ERIC) to Jan 2010;
 - Virtual Health Library (VHL) in BIREME: Pan American Health Organization (PAHO) Specialized Center;
 - LILACS (Latin American Health Sciences Literature) to Jan 2010;
 - PsycINFO (psychological literature) to Feb 2010 week 2;
- and
- UMI Dissertation Express.

We searched the following complementary and alternative medicine specific databases to January 2010:

- CAM on PubMed;
- Cochrane Complementary and Alternative Medicine field;
- Complementary Medicine Resources for Health Professionals and Researchers;
- Complementary and Alternative Medicine Specialist Library in the National Library for Health (supported by the NHS); and

- Complementary and Alternative Therapies databases of Bandolier.

We also searched the following sources to January 2010:

- OpenSIGLE - System for Information on Grey Literature in Europe;
- Health Services/Technology Assessment Text (HSTAT) database;
- Informit Databases: Humanities and Social Sciences Collection, Australia;
- English Databases of the Japan Science and Technology Agency (JST); and
- Research database of Thailand psychiatry and mental health and Thai Thesis Online.

The search strategies for these databases are shown in the appendices two to seven (see [Appendices](#)).

Searching other resources

We carried out a search of conference proceedings at ISI Proceedings from 1990 to January 2010 and searched for relevant studies cited in book chapters on the treatment of ADHD.

Personal communication

We consulted the authors of the included studies and experts in the fields to find out whether they knew of any published or unpublished RCTs/ CCTs of meditation therapy and ADHD, which have not yet been identified. We contacted persons and organizations whose work relates to meditation (i.e. Asociacion de Medicinas Complementarias (AMC), the National Center for Complementary and Alternative Medicine (NCCAM), Sat Bir Sinah Khalas). We contacted religious/spiritual organizations around the world (internet web sites were extensively searched) to find out whether they had conducted or knew of the application of meditation in ADHD.

We also contacted worldwide organizations with resources for ADHD: Attention-Deficit Disorder Association, Attention-Deficit Disorder Resources; ADHD Support, Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD), the National Resource Center on AD/HD (NRC), Children and Adults with Attention-Deficit Disorders, Learning Disabilities Association of America, the Attention-Deficit Resource Network (ADRN) and the National Center for Girls and Women with AD/HD.

Ongoing trials

We sought ongoing trials by searching the *metaRegister* of Controlled Trials (*mRCT*) ; Health Services Research Projects in Progress (HSRProj); the National Centre for Complementary and Alternative Medicine sponsored trials; www.ClinicalTrials.gov; UKCRN Clinical Research Portfolio and the Trials Register of

Promoting Health Interventions (TRoPHI). All trial registry were search to January 2010.

We checked the reference lists of all relevant studies for further references.

Data collection and analysis

Selection of studies

KT and WC independently screened the titles and abstracts obtained by the search strategies against the eligibility criteria stated above. KT and WC verified study eligibility before data extraction with no disagreement on inclusion/exclusion decisions. For articles that appeared to be eligible RCTs, we obtained the full articles and inspected these to assess their relevance, based on the pre-defined inclusion criteria.

Data extraction and management

Two authors independently extracted data using a pre-designed data collection form, which was saved electronically. Any unpublished information, if used, was recorded and coded with a specific remark. We contacted authors either by e-mail or telephone call to obtain any missing data. KT entered all relevant data into RevMan 5 ([RevMan 2008](#)) and NC checked data for correctness. The reliability of data extraction and data entry were examined throughout the process.

For cross-over designs, we extracted all data but, because of the strong carry-over effect of meditation, we used only data from the first phase of study in our analyses. The data from the second phase after crossing over were described in the '[Characteristics of included studies](#)' table and recorded in an additional table.

Assessment of risk of bias in included studies

We assessed risk of bias in the included studies using The Cochrane Collaboration's tool, which is based on multiple domain evaluation ([Higgins 2008](#)). There are six domains as follows:

1. Sequence generation
Was the allocation sequence adequately generated?
2. Allocation concealment
Was allocation adequately concealed?
3. Blinding of participants, personnel, outcome assessors
Was knowledge of the allocated intervention adequately prevented during the study?
4. Incomplete outcome data
Were incomplete outcome data adequately addressed?
5. Selective outcome reporting
Are reports of the study free of suggestion of selective outcome reporting?
6. Others sources of bias

Was the study apparently free of other problems that could put it at a high risk of bias?

The review authors' judgments involved answering these questions for each entry, i.e. 'Yes' indicates low risk of bias; 'No' indicates high risk of bias; 'Unclear' indicates insufficient detail is reported or the risk of bias is unknown.

The risk of bias is presented in the 'Risk of bias' table with two additional figures: a 'Risk of bias graph' (Figure 1) and a 'Risk of bias summary' (Figure 2).

Figure 1. Methodological quality graph: review authors' judgments about each methodological quality item presented as percentages across all included studies.

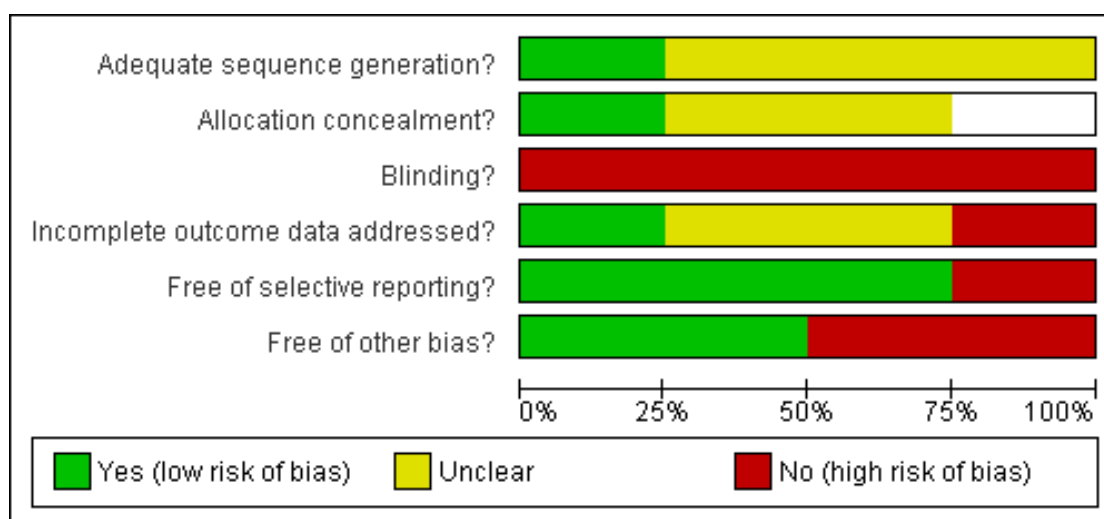


Figure 2. Methodological quality summary: review authors' judgments about each methodological quality item for each included study.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Haffner 2006	+	+	-	+	+	-
Jensen 2004	?	?	-	-	-	-
Kratter 1983	?	?	-	?	+	+
Moretti-Altuna 1987	?		-	?	+	+

To determine selective outcome reporting we planned to compare the study with its protocol, which might be registered in trial registries, however no included studies were registered in any trial registries. Two out of four included studies, however, came from PhD dissertations which had an extensive published report which could be used to determine the completeness of reporting indirectly (Kratter 1983; Moretti-Altuna 1987).

The summary assessment of risk of bias used the authors' judgment for primary outcomes (symptoms of ADHD, quantitative laboratory assessment measures of ADHD symptoms, overall incidence/severity of the problem behaviors) both within and across studies.

Disagreements were discussed with a third author (WC) and resolved through consensus.

Measures of treatment effect

Dichotomous outcomes

Dichotomous outcomes were not presented in any of the included studies.

Continuous outcomes

We analyzed the endpoint score (because the change score data were not reported in the included studies) in RevMan 5 using mean differences (MD) and their 95% confidence intervals (CI). When considering the skewed data, we compared the mean to the standard deviation. If the mean was smaller than twice the

standard deviation the data were probably skewed (Altman 1996). We present the skewed data in Additional table.

Unit of analysis issues

In trials of cross-over design (two included studies), because of the strong carry-over effect of meditation, we only used the data from phase one before crossing over in meta-analysis. The additional data were described in the 'Characteristics of included studies' table.

In a study with multiple treatment groups (meditation versus drug versus standard treatment control), we carried out the analysis for each pair between meditation and other treatments.

No cluster-randomized trials were identified.

Dealing with missing data

All of the included studies for this review used per protocol analysis. The reasons for missing data were clarified by the study authors and were described in the Notes sections of the 'Characteristics of included studies' table.

Assessment of heterogeneity

This review included one trial for each comparison. We therefore did not conduct assessment of heterogeneity. We have provided full methods for assessment of heterogeneity for future updates of this review in Appendix 1.

Assessment of reporting biases

If possible, we will use a funnel plot (Egger 1997; Light 1984) to determine potential publication bias.

The authors dealt with selective outcome reporting by searching for the original protocols for each included study in trial registries and comparing these (where available) with the list of outcomes in the methods section of the final report. In cases where there is a suspicion of selective outcome reporting, we contacted the study authors. The assessment of risk of bias due to selective reporting of outcome was made for each study as a whole.

This review included one trial for each comparison. We therefore did not create funnel plots to assess publication bias. For future updates of this review, we have provided full methods for assessment of reporting biases in Appendix 1.

Any other types of bias encountered in each study are reported in the Results and Discussion.

Data synthesis

Each comparison had only one included trial and had continuous outcomes. We therefore calculated MDs with their 95% CIs.

Subgroup analysis and investigation of heterogeneity

We did not conduct subgroup analysis because there was only one included trial for each comparison.

Sensitivity analysis

We did not conduct sensitivity analysis due to the limited number of included studies in the review.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

We carried out extensive searches, as described in 'Search methods for identification of studies'. We searched the electronic databases from their inception without language restrictions. We checked the titles from the preliminary search results and there were 17 potentially relevant studies at this stage. After checking the abstracts, we excluded 7 studies that were obviously irrelevant to the review. We obtained the full text of the 11 potentially relevant studies which required further clarification. Four studies met the eligibility criteria while 7 studies were put into the excluded studies category. All included studies were carried out by different research teams between 1983 and 2006. We contacted the first authors of three of the included studies to ask for additional data and details of their studies. One author (Kratter 1983) could not be contacted. One author (Haffner 2006) sent an original article in German and an English translated version.

Included studies

Settings

Two of the four studies included in this review were carried out in the USA. Both studies were dissertations submitted to the faculty of the Department of Psychology at St. John's University, New York (Kratter 1983; Moretti-Altuna 1987). Haffner 2006 was carried out in Germany and Jensen 2004 was carried out in Australia. Only one study (Kratter 1983) mentioned the meditation room, which was a quiet room with low lighting and comfortable chairs. Both studies of mind-based meditation (Kratter 1983; Moretti-Altuna 1987) used a padded, straight-back chair. Haffner 2006 and Jensen 2004 did not give details about their settings. None of the studies reported the time of year of the study, therefore it is

unclear whether participants were in school or on holiday/vacation during the trials.

Participants

All participants were children with ADHD, with an age range between six and 13 years old. Three of the studies indicated that participants must be boys in the inclusion criteria; only (Haffner 2006) included girls. Three studies reported that they used the DSM diagnostic system (DSM-III, DSM-IV). One study, which was carried out in Germany (Haffner 2006), used the Diagnostic System for Psychic Disorders in Childhood and Adolescence, which corresponded to ICD-10 diagnosis. Jensen 2004 used Conners' Parent Rating Scales: Long (CPRS: R (L)) that demonstrated scores (over 70 t-score) to confirm the diagnosis of ADHD in all participants. Moretti-Altuna 1987 used a multidisciplinary intake committee to confirm the diagnosis. In the other two studies (Haffner 2006; Kratter 1983) no diagnostic re-confirmation procedures were used.

Interventions

Two studies used mantra meditation, which is mind-based. Kratter 1983 used the word "Ahnām", a Sanskrit word which means "nameless". Moretti-Altuna 1987 used "One", with the aim that by repeating the word the participants would learn to focus and re-focus their attention. These techniques were adapted from the well-known concentrative meditation developed by Benson 1975 and Carrington 1975, which has some roots in the Hindu religion. Apart from the different mantra used in their studies, other aspects of the intervention (duration, frequency, sitting position, passive attitude) were almost the same.

Haffner 2006 and Jensen 2004 used Hatha yoga, which is more physical-based. However, Jensen 2004 also used a visualization technique to accompany Hatha yoga and Haffner 2006 used breathing meditation combined with postures. They claimed that their yoga program was a standardized program and developed by a yoga instructor. The yoga program consisted of multiple components (respiratory, postural, relaxation concentration training). The details of each program are described below.

Concerning the qualification and skills of the meditation instructors, only Haffner 2006 used a well-trained yoga teacher while in the other three included studies the subjects were taught by the investigators themselves.

The intervention program ranged from four weeks (Kratter 1983; Moretti-Altuna 1987), to eight weeks (Haffner 2006) to 20 weeks (Jensen 2004). The frequency of visits varied from one session per week (Jensen 2004) to three sessions per week (Haffner 2006; Kratter 1983; Moretti-Altuna 1987). Some studies used the parents to assist and supervise their children while practicing meditation at home (Jensen 2004; Kratter 1983; Moretti-Altuna 1987), while Haffner 2006 just let the children practice yoga freely on their own at home or at school during the intervention period.

The intensity of meditation is determined from the duration of practice. Haffner 2006 and Jensen 2004 used a one-hour training session but do not mention the exact time spent in meditation. Kratter 1983 and Moretti-Altuna 1987 state that the actual meditation duration was gradually increased from one minute to eight minutes by the end of the four-week training period.

Comparator/control group

Haffner 2006 and Jensen 2004 compared yoga versus co-operative games/activities. Medicated participants were unevenly distributed between intervention groups. In Haffner 2006 five out of nine of the yoga group were medicated while three out of 11 of the control group were medicated.

Kratter 1983 compared three intervention groups: meditation training versus relaxation training versus waiting list control. The medicated participants were distributed evenly between treatment groups using a modified randomization method.

Moretti-Altuna 1987 compared meditation training versus drug therapy versus standard therapy control. Only participants in the drug therapy group received medication.

Outcome measures

The reported outcomes were:

1. Validated outcome scales rated by parents/teacher, which reflected the core symptoms of ADHD.
 - Fremdbeurteilungsbogen für hyperkinetische Störungen (FBB-HKS), used in Haffner 2006.
 - Conners' Parent (CPRS-R:L) Teacher (CTRS-R:L) Rating Scales - Revised: Long (Conners 1997), used in Jensen 2004.
 - Abbreviated Parent-Teacher Questionnaire (PTQ) (Conners 1973), used in Kratter 1983 and Moretti-Altuna 1987.
 - Werry-Weiss-Peters Activity Scale (WWPAS) (Werry 1968), used in Kratter 1983 and Moretti-Altuna 1987.
 - Nowicki-Strickland Locus of Control Scale (LCS), used in Kratter 1983.
2. Psychological testing to measure the symptoms profile of ADHD.
 - Dortmund Attention Test (DAT), used in Haffner 2006.
 - Test of Variables of Attention (TOVA) (Greenburg 1991), used in Jensen 2004.
 - Matching Familiar Figure Test (MFFT) (Kagan 1996), used in Kratter 1983 and Moretti-Altuna 1987.
 - Fruit Distraction Test (FDT) (Santostefano 1978), used in Kratter 1983 and Moretti-Altuna 1987.
 - The Children's Embedded Figures Test (CEFT) (Karp 1963), used in Moretti-Altuna 1987.
3. Psychophysiological measurements.
 - Motion logger - Actigraph, used in Jensen 2004.

Study design

Haffner 2006 used a cross-over design in which the participants in the yoga group and the control (motor exercise) group crossed over to the other treatment after eight weeks, with a six-week break (wash-out period). As stated earlier, to prevent carry-over effects, we have only included the data from the first phase of each study in the analysis. Data from the second phase after cross-over are recorded in Tables. Jensen 2004 also stated that the study had a “randomized cross-over design”, but only the participants in the control group were allowed to move to the yoga group; the yoga group did not cross over to the control group. This design cannot therefore be described as cross-over. The study is downgraded from RCT to only a before-after design when the study authors pooled all data together.

Excluded studies

There were 7 excluded studies. Four were carried out in the USA (Evans 2007; Kratter 1982; Peck 2005; Zylowska 2008), one was from Australia (Harrison 2004) one from Thailand (Hassasiri 2002) and one was carried out in Iran but get published in India (Abadi 2008) . One of the excluded studies involved development of an audio program for the treatment of adult ADHD and used a group of experts to give opinions about the program (Evans 2007). Three used a before-after design which did not have a control group (Harrison 2004; Hassasiri 2002; Zylowska 2008). One study (Peck 2005) was excluded due to the participants not having been diagnosed with ADHD. We also excluded one duplicate report (Kratter 1982). One study(Abadi 2008) have a control group but did not mention about the randomization.

Risk of bias in included studies

Systematic biases directly affected the validity of the included studies. See also the 'Risk of bias' graph (Figure 1) and 'Risk of bias' summary (Figure 2).

Allocation

Only one of the four included studies reported the method of randomization which was the use of drawing lots (Haffner 2006).

The other three studies just mentioned randomization without giving any details in their methods. The method of allocation concealment was not reported in any trial but because Haffner 2006 used the drawing of lots we have assumed that allocation concealment automatically occurred because the sequence cannot be known in advance. In one trial (Jensen 2004) the process of randomization was terminated when five participants from the control group were allowed to move to the treatment group after 20 weeks. Allocation concealment was therefore not carried out in this trial. In Kratter 1983 the randomization method was modified to equalize the medicated children evenly between each group. This modification made the study potentially more susceptible to bias, as randomization could not guarantee the distribution of confounding factors and allocation concealment was not adequate. Moretti-Altuna 1987 did not give details of randomization methods and we therefore judged the adequacy of randomization and allocation concealment to be 'Unclear'.

Blinding

Only the blinding of of raters/assessors is possible in such trials. However, no trials reported blinding of the raters/assessors.

Incomplete outcome data

No studies in the included studies carried out an intention-to-treat analysis. Only patients who completed the entire trial were analyzed by per-protocol analysis. In Haffner 2006 one nine-year old boy left the study because of a change of residence during the 21st week. The reason why the child left the study was adequately described and it would not have had a clinically relevant impact on the observed effect size. Jensen 2004 reported the number of boys who began the trial (n = 16) but only data for 14 boys were used in analysis. No reasons for drop-outs were described. Kratter 1983 reported that 24 boys participated the study but did not mention the attrition of participants at the end of the study. Moreover, the analysis table did not give the number of participants left in each group, therefore the data were not used in meta-analysis but are shown in Table 1.

Table 1. Data from Kratter 1983

Outcome	Meditation			Relaxation			Waiting list Control		
	Mean	SD	n	Mean	SD	n	Mean	SD	n
MFFT latency scores	12.412	6.675	-	10.462	3.986	-	10.962	5.125	-

Table 1. Data from Kratter 1983 (Continued)

FDT card 1 Latency	40.312	9.051	-	41.687	8.062	-	42.375	10.905	-
FDT card 2 Latency	44.812	10.261	-	49.500	14.310	-	49.687	13.905	-
FDT card 3 Latency	45.687	8.856	-	46.625	8.895	-	53.375	16.153	-
FDT card 4 Latency	70.750	8.912	-	83.250	24.036	-	83.437	20.576	-
LCS scores	14.000	3.295	-	18.875	4.824	-	16.000	5.555	-
TRS scores	15.625	8.141	-	16.625	8.158	-	13.500	6.024	-
PTQ scores	14.250	6.840	-	15.375	2.774	-	18.625	1.061	-
WWPAS	25.000	7.709	-	26.375	10.169	-	28.125	7.827	-

No N in each group provided.

FDT = Fruit Distraction Test

LCS = Nowicki-Strickland Locus of Control Scale

MFFT = Matching Familiar Figure Test

PTQ = Parent-Teacher Questionnaire

TRS = Teacher Rating Scale

WWPAS = Werry-Weiss-Peters Activity Scale

In [Moretti-Altuna 1987](#) there was no mention of the number of enrolled participants at the beginning of the trial. The authors reported that 23 boys participated in the trial and used this number in the final analysis. Completeness of outcome data is therefore doubtful.

Selective reporting

None of the four included studies appeared in trial registries and therefore we were not able to obtain protocols for these studies. Pre-specified outcomes were therefore not known and it is difficult to determine whether outcomes were omitted from reporting. [Haffner 2006](#), [Kratter 1983](#) and [Moretti-Altuna 1987](#) reported all the outcomes specified in their Methods section. Moreover,

[Kratter 1983](#) and [Moretti-Altuna 1987](#) were dissertations which should guarantee the completeness of reporting.

[Jensen 2004](#) used an Actigraph motion logger (a portable electronic activity monitor designed to be worn on the wrist, waist or ankle) and reported that “there were many technical problems encountered mainly due to their use in a naturalistic setting. On occasions they were damaged, stopped recording data, or failed to be activated at set times. As a consequence an incomplete set of data was collected. Due to these problems, data were deemed unreliable and were discarded.” Even though the study authors had addressed the reason for non-reported outcomes, we still judged that this outcome was selectively reported.

Other potential sources of bias

In [Haffner 2006](#) more boys in the yoga group received medication (five of nine) than in the exercise group (three of 11). This unequal co-intervention could have substantial effects. Using a cross-over design in a trial of an intervention which needs practicing by the participants means it is difficult to discard the carry-over effect during phase two of the trial. Even during phase one (before crossing over) participants in both intervention arms might have some expectations of the treatment effects of the next intervention.

In [Jensen 2004](#) there were significant differences between the control and yoga groups' pretest sub-scale scores on almost all Conners' Rating Scales for both parents and teachers.

Effects of interventions

See: [Summary of findings for the main comparison Meditation therapy versus drug therapy for attention deficit /hyperactivity disorder](#); [Summary of findings 2 meditation therapy versus standard treatment without drug for attention deficit /hyperactivity disorder](#)

We collected data for three comparisons from the included studies

which were non-skewed outcome data to put into the analyses and present in the 'Summary of Findings' table: this was the teacher rating ADHD overall scale. The distraction test was considered to be the intermediate outcomes which reflected psychological state but might not directly related to behavior of the child.

The effects of interventions are compared in a pair-wise manner as follows.

Meditation therapy versus drug therapy for ADHD

One study ([Moretti-Altuna 1987](#)) compared mantra meditation and drug therapy for ADHD. There were six outcomes which are considered to be the primary outcomes in this review. The study provided both endpoint scores with standard deviations (SD) and change scores with SD for each outcome after four weeks of treatment. The endpoint scores were selected for use in analysis. There was no statistically significant difference between the meditation therapy group and the drug therapy group in the teacher rating ADHD overall scale (MD -2.72, 95% CI -8.49 to 3.05, 15 patients, see Figure 3). In addition, we found that five outcomes had skewed data (see [Table 2](#)).

Table 2. Meditation therapy versus drug therapy (skewed data) (Moretti-Altuna 1987)

Outcome	Study	Meditation			Drug		
		Mean	SD	Total	Mean	SD	Total
1. Parent rating ADHD overall scale	Moretti-Altuna 1987	15.78	8.74	9	18.17	7.39	6
2. Parent rating activity level scale	Moretti-Altuna 1987	28.0	16.87	9	30.83	22.31	6
3. Impulsivity test (error scores)	Moretti-Altuna 1987	12.22	8.03	9	17.00	4.98	6
4. Distraction test	Moretti-Altuna 1987	247.72	117.77	9	238.25	123.07	6
5. Attention test	Moretti-Altuna 1987	14.11	6.09	9	11.0	5.76	6

Meditation therapy versus standard treatment without drugs for ADHD

[Moretti-Altuna 1987](#) also compared mantra meditation and stan-

dard treatment without drugs for ADHD using the same outcome measures as the above comparison. The analysis was done by calculating the endpoint scores after four weeks of treatment. There was no statistically significant difference between the meditation

therapy group and the standard therapy group in the teacher rating ADHD scale (MD -0.52, 95% CI -5.88 to 4.84, 17 patients, see Figure 4). In the same way there was no statistically significant difference between the meditation therapy group and the standard therapy group in the distraction test (MD -8.34, 95% CI -107.05 to 90.37, 17 patients, see Figure 5). Skewed data for this comparison are shown in Table 3.

Table 3. Meditation therapy versus standard treatment without drug (Moretti-Altuna 1987)

Outcome	Study	Meditation			Standard therapy control		
		Mean	SD	Total	Mean	SD	Total
1. Parent rating ADHD scale	Moretti-Altuna 1987	15.78	8.74	9	19.0	7.29	8
2. Parent rating activity level scale	Moretti-Altuna 1987	28.0	16.87	9	30.75	14.25	8
3. Attention test	Moretti-Altuna 1987	14.11	6.09	9	12.13	7.36	8
4. Impulsivity test (error scores)	Moretti-Altuna 1987	12.22	8.03	9	17.50	9.78	8

Meditation therapy versus relaxation training versus waiting list controls with drugs for ADHD

In Kratter 1983 there were three intervention groups. Mantra meditation was compared to relaxation training and to waiting list controls with drugs. The three groups had an equal number of medicated participants. There were five outcomes which are considered to be the primary outcomes in this review. The study provided both endpoint scores with SD and change scores with SD for each outcome. The data are shown in Table 1. From the published report, the authors used ANOVA to analyze the treatment effects. The findings were that mantra meditation as well as relaxation training significantly decreased impulsivity and improved behavior at home when rated by the parents. Only the meditation group improved in the selective deployment of attention, which was claimed as an essential aspect of meditation training. The sense

of internal control and classroom behavior were not improved in any treatment group.

Hatha yoga versus non-specific physical exercise for ADHD

There were two studies which compared Hatha yoga and non-specific physical exercise for ADHD (Haffner 2006; Jensen 2004). However, only Haffner 2006 provided data for this comparison. In the study by Jensen 2004, the authors did not provide the data from truly randomized participants. In the published report analysis the authors combine the data from true randomized participants with data from the control group who moved to the treatment group. Mixing the participants from the two groups together ruined the randomization effects. We decided to discard these data from analysis, but the data are shown in Table 4.

Table 4. Yoga versus control for ADHD (Jensen 2004)

Conners' Parent Rating Scales - Revised: Long (Conners 1997) (Figure 6)
Conners' Teacher Rating Scale - Revised: Long (Conners 1997) (Figure 7)
Test of Variables of Attention (TOV) (Greenburg 1991) (Figure 8)

To eliminate the carry-over effect in Haffner 2006 only the data from the first phase of trial were extracted and put into the comparison for meta-analysis. There were five outcomes for this comparison but their data were skewed (see Table 5). The data from phase two of the trial (after crossing over) are shown in Table 6.

Table 5. Hatha yoga versus non-specific physical exercise (skewed data)

Outcome	Study	Hatha yoga			Non-specific exercises		
		Mean	SD	Total	Mean	SD	Total
1. Parent rating ADHD overall scale	Haffner 2006	0.93	0.53	8	1.47	0.7	11
2. Parent rating attention-deficit	Haffner 2006	0.92	0.5	8	1.65	0.65	11
3. Parent rating hyperactivity	Haffner 2006	0.75	0.57	8	1.29	0.84	11
4. Parent rating impulsivity	Haffner 2006	1.26	0.67	8	1.39	0.88	11
5. Attention test	Haffner 2006	8.37	1.8	8	4.36	3.1	11

Table 6. Hatha yoga versus non-specific exercise for ADHD (phase 2: after crossing over) (Haffner 2006)

Measurements	Hatha Yoga N = 11 Mean (SD)	Exercise N = 8 Mean (SD)
DAT	9.81(1.5)	7.0(2.7)
FBB-HKS	-	-

Table 6. Hatha yoga versus non-specific exercise for ADHD (phase 2: after crossing over) (Haffner 2006) (Continued)

Total scale	1.18(0.76)	1.03(0.65)
Attention-deficit	1.34(0.73)	0.9(0.6)
Hyperactivity	1.07(0.82)	0.86(0.72)
Impulsiveness	1.02(0.88)	1.61(0.79)

DAT = Dortmund Attention Test

FBB-HKS = Fremdbeurteilungsbogen für hyperkinetische Störungen (FBB-HKS): a rating scale for parents, teachers and educators

ADDITIONAL SUMMARY OF FINDINGS [\[Explanation\]](#)

meditation therapy versus standard treatment without drug for attention deficit /hyperactivity disorder					
Patient or population: patients with attention deficit /hyperactivity disorder Settings: Intervention: meditation therapy versus standard treatment without drug					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	meditation therapy versus standard treatment without drug			
Teacher rating ADHD overall scale Abbreviated Parent-Teacher Questionnaire (Conner, 1973) Follow-up: mean 4 weeks	The mean teacher rating adhd overall scale in the control groups was 12.63	The mean Teacher rating ADHD overall scale in the intervention groups was 0.52 lower (5.88 lower to 4.84 higher)		17 (1 study ⁴)	⊕○○○ very low ^{1,2,3}
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval;					
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.					

¹ Unclear randomization, unclear allocation concealment, no blinding, unclear attrition rate, other biases presented

² Wide confidence interval, small sample size

³ Only one study(since 1987) present for this outcome

⁴ Study Moretti-Altuna, 1987

DISCUSSION

Summary of main results

Four studies were included in this review. Two studies were dissertations submitted to the faculty of the Department of Psychology at St. John's University, New York in 1983 and 1987 (Kratter 1983; Moretti-Altuna 1987). One study was carried out in Sydney, Australia (Jensen 2004) and the other in Heidelberg, Germany (Haffner 2006). The first randomized controlled trial using meditation for ADHD was the study of Kratter 1983, which took place 25 years ago. Further studies have followed Kratter's trial but many of these have used a before-after design which has several methodological limitations. These studies were excluded from the review (Harrison 2004; Hassasiri 2002; Zylowska 2008). Haffner 2006, Jensen 2004 and Moretti-Altuna 1987 were randomized controlled trials with different comparators: 1) meditation therapy versus drug therapy, 2) meditation therapy versus standard treatment without drugs, 3) meditation therapy versus relaxation training versus waiting list controls with drugs and 4) Hatha yoga versus non-specific physical exercise.

The type of meditation used in these trials can be differentiated into two groups according to the different characteristics of meditation. Mind-based meditation (mantra meditation) was used in the Kratter 1983 and Moretti-Altuna 1987 studies. Physical-based meditation was used in Jensen 2004 and Haffner 2006. Mind-based meditation emphasizes the cognitive process which focuses on the use of selective deployment of attention: the participants learned to focus and re-focus their attention (Kratter 1983). Physical-based meditation (Hatha yoga, moving meditation) focuses on behavioral control. However, due to the complexity of body-mind interaction, and the concept of holistic approach, it is hard to differentiate body and mind and each meditation technique usually incorporates both components together. Due to the variety of theories and practices of meditation the inclusion of different techniques under the same umbrella of meditation is inappropriate. Five broad categories of meditation practice were identified by a group of experts using modified Delphi methodology: mantra meditation (comprising the Transcendental Meditation® technique (TM®), Relaxation Response (RR) and Clinically Standardized Meditation (CSM)), mindfulness meditation (comprising Vipassana, Zen Buddhist meditation, Mindfulness-based Stress Reduction (MBSR) and Mindfulness-based Cognitive Therapy (MBCT)), yoga, Tai Chi and Qi Gong (Ospina 2007)). The classifications in this system are more suited to defining the broad range and variety of meditation than the previously used classification (concentrative meditation and mindfulness meditation). The four included studies in this review fell into the categories of mantra meditation and yoga by this classification.

Only Haffner 2006 used a well-trained yoga teacher while participants in Jensen 2004, Kratter 1983 and Moretti-Altuna 1987 were taught by the investigators themselves. Qualification and experience in teaching meditation are important to guarantee proper teaching. When applying meditation therapy in clinical settings,

the knowledge, attitude and skill of the therapist should be considered (Krisanaprakornkit 2006).

There were only two studies from which the data were appropriate for meta-analysis. Due to the limited number of studies, small sample size in each trial, apparent risk of bias and skew-ness of data we found no consistent evidence that meditation (either mind-based or physical-based) had a significant effect on core ADHD symptoms or psychological tests of attention, impulsivity and distraction. Mind-based meditation did not yield any significantly different effects compared to drugs and standard therapy controls. While physical-based meditation (Hatha yoga) showed some positive effects (parent rating attention-deficit, attention test), it did not show consistent results.

All of the included studies had differences in the number of meditation sessions and the amount and quality of home practice, which could affect the treatment effects. Some studies used the parents to assist and supervise their children while practicing meditation at home (Jensen 2004; Kratter 1983; Moretti-Altuna 1987). Haffner 2006 just let the children practice yoga freely on their own at home, at school and during lessons. Therefore the intensity of practice differed widely among participants and studies. There were no descriptions of monitoring of practice at home in any studies, therefore the quality and quantity of self-practice could not be guaranteed. This might be affected the results of each studies.

Data for the side effects of meditation and quality of life were not reported in any trials. Randomized trials usually focus on intended effects and focus less on possible adverse effects. Data on adverse effects are often sparse but the absence of information does not mean that the intervention is safe (Higgins 2008). The issue of side effects should therefore be addressed in any future meditation trials.

There is insufficient evidence to support the effectiveness of any types of meditation for ADHD at present given that only four randomized controlled trials have been carried out, and all were relatively small in size and limited in design, with inconsistent results across the outcomes.

Overall completeness and applicability of evidence

We considered the parent rating, teacher rating and self-rating ADHD symptoms scales to be the most important outcomes for patients. Quantitative laboratory assessment measures of ADHD symptoms, psychological testing etc. are surrogate outcomes which are less important. In the included studies all the participants were children with ADHD, therefore a self-rating scale is not necessary to measure outcomes because it is difficult for school-age children to rate their symptoms accurately.

No studies gave details of adverse effects, but this is an important outcome to be considered in every study, especially in trials in children. Despite this, a well-structured meditation program is

considered safe and is promoted for children in many settings, including schools (Helen 2004).

In our protocol for this review we defined 'Overall severity of problem behaviors' and 'Quality of life' as outcome measures because these outcomes provide a broader perspective on the patient's life rather than merely focusing on symptoms. Meditation can not only improve attention but also the quality of mind (calmness, equanimity, contentment), all of which can affect the life of a patient as a whole (Ospina 2007). Outcomes which are measured at the end of a program cannot detect intermediate-term and long-term changes in personality profile. Data will be more complete if trials can follow up outcomes for six months to 12 months afterwards.

Due to the lack of consistent evidence to support the use of meditation for ADHD in the present review, we cannot comment on applicability and generalizability at this time. In some countries, for example Thailand, meditation is accepted as a means to improve attention, temperament, discipline, school performance, character, morals and for religious purposes (Krisanaprakornkit 2006). The included studies were carried out in the USA, Germany and Australia. As the effects of globalization and the holistic view of health expand, meditation may become more accepted and widely used in the clinical setting. Therefore, if the effectiveness of meditation can be established, it may be used more widely as a therapy in the future.

Quality of the evidence

In a Cochrane Review the quality of evidence reflects the extent to which we are confident that an estimate of the effect is correct. We therefore rate the quality of evidence for each outcome separately. Two included studies were dissertations submitted to the faculty of the Department of Psychology at St. John's University, New York in 1983 and 1987 (Kratter 1983; Moretti-Altuna 1987). We have assumed that the dissertations were generally supervised and verified by the committee. The inclusion of dissertations may mean more balanced results as they are less likely to overestimate treatment effects, as can occur in published trials (McLeod 2004). Trial quality is discussed in the 'Assessment of risk of bias in included studies' section, with graphical presentations in Figure 1 and Figure 2. We then assessed the risk of bias for an outcome across studies using the GRADE system. We judged the quality of the evidence by assessing limitations in design, inconsistency, indirectness, imprecision and publication bias.

As such a limited number of trials was found, we suspect the possibility of publication bias. Concentrative meditation (mantra meditation) was introduced to the West during the 1960s and many pioneers in the field have developed modified forms of meditation suitable for use in the clinical setting, for example the 'relaxation response' of Herbert Benson (Bensonian meditation) (Benson 1975). Mindfulness meditation has emerged as a new approach to stress reduction and is an important innovation in

the treatment of psychiatric disorders (Baer 2003). The Mindfulness-based Stress Reduction Program (Kabat-Zinn 1992) has subsequently been researched in ADHD adults and adolescents (Zylowska 2008). A Google search results in more than 1,170,000 hits for "meditation AND ADHD". This issue has also appeared in the news (e.g. 'Meditation helps kids with ADHD' (Helen 2004)) and meditation has gained acceptability in many primary and junior school in England (Eliaz 2008). Another reason for the small number of studies might be that meditation trials are less supported than medication trials, which may be funded by drug companies.

The graphical risk of bias presentations (Figure 1; Figure 2) show the serious limitations in design (high risk of bias) in the included studies overall. Randomization methods are not mentioned, therefore we cannot assess the adequacy of allocation concealment. Only the study of Kratter 1983 described the use of the drawing of lots, which automatically concealed the allocation. There was no mention of blinding. In Haffner 2006, the yoga instructors themselves carried out the assessment of the participants in both the yoga and control group; detection bias was therefore inevitable. Only Haffner 2006 described the reason for drop-out of one participant (moved home). The attrition rate of the other three studies was unclear or not described. The drop-out rate might be related to adverse effects or to some discomfort with meditation.

The consistency of results across studies could not be determined because there was only one study to provide data for each comparison. However, when checking the direction of the result in any one study the inconsistency of outcomes in each study was obvious. Each study measured many outcomes. Some outcomes were considered to be important, while others were surrogate outcomes (e.g. attention test, distractibility test). When many outcomes are used in one study this will increase the possibility of a significant difference which occurred by chance. The authors may also selectively accentuate the significance of positive outcomes while omitting to clarify the negative outcomes (reporting bias).

Most of the means differences had wide confidence intervals reflecting the small sample size, differences in baseline characteristics of study samples and different treatment effects in individuals.

No studies had problems of indirectness of evidence.

We therefore summarized quality for each comparison as follows.
Meditation therapy compared to drug therapy for attention-deficit/hyperactivity disorder

The quality of evidence was "very low" according to the GRADE classification for 'Teacher rating ADHD overall scale' (see Summary of findings table 1).

Meditation therapy compared to standard treatment without drug for attention-deficit/hyperactivity disorder

The quality of evidence was "very low" according to the GRADE classification for 'Teacher rating ADHD overall scale' (see Summary of findings table 2).

Potential biases in the review process

Due to limited access our literature searching could not cover some sources, such as literature in Chinese.

Agreements and disagreements with other studies or reviews

Meditation for ADHD has been reviewed as a psychological treatment along with other psychosocial interventions. At this time there is no specific systematic review of meditation for ADHD only. Arnold 2001 was a narrative review on alternative treatment for adults with ADHD. This review included the two studies of Kratter 1983 and Moretti-Altuna 1987, which were carried out in children with ADHD. The authors concluded that meditation showed some benefit and warrants further study for both children and adults. The recent narrative review by Greydanus 2007 emphasized medication and meditation was only mentioned under the heading of psychological management, which included many types of psychological interventions (psychotherapy, cognitive behavioral therapy, support groups, parent training, educator/teacher training, biofeedback, meditation and social skills training). The authors stated that empirical evidence regarding these interventions was inconsistent (Greydanus 2007). These narrative reviews commonly failed to assess the methodological quality of the primary studies, therefore the results tend to overestimate the effects.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to draw conclusions about the effectiveness of any types of meditation for attention-deficit/hyperactivity disorder (ADHD). The adverse effects of meditation in children with ADHD are unknown.

Implications for research

There is a lack of evidence to support the effectiveness of meditation for ADHD. This review has highlighted the need for further research. Meditation therapy research protocols need to be rigorous in design and delivery, and use standardized meditation therapy programs which can be replicated by other researchers. The operational definition of meditation techniques used should be specified and relate to ADHD core symptoms. The trainers should be skilled or be experts in the meditation methods used. The monitoring of meditation practice at home in addition to the therapy sessions is a crucial element of adherence. The involvement of parents in practice should be considered and controlled. The concomitant use of medication should be distributed evenly between comparison groups. All the outcomes should be validated and described, including adverse effects. We plan to update this review within 24 months to incorporate any new studies and respond to any comments or criticisms.

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- * Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Haffner 2006

Methods	Randomized controlled trial 2 x 2 cross-over design using the drawing of lots Analyzed by means of an analysis of variance for repeated measurements
Participants	20 grade school age children (13 boys and 7 girls) diagnosed with ADHD (Diagnostic System for Psychic Disorders in childhood and adolescence according to ICD-10 and DSM-IV (DISYPS-KJ)) Trial was conducted in the University Hospital in Heidelberg, Germany between May 2000 and March 2001 Yoga group (n = 9 ; 8 boys + 1 girl) Exercise group (n = 11; 5 boys + 6 girls) One 9-year old boy in the yoga group left the study because of a change of residence during the 21st week Exclusion criteria: severe developmental disturbances, low intelligence level (IQ < 70) , and extreme behavioral disturbances which would be incompatible with participation in a group
Interventions	Intervention 1: body-oriented yoga exercise program A standardized program consisting of elements of Hatha yoga (postures, breathing exercises, meditative exercises) especially developed for children with ADHD, consisting of 16 exercise units for children and documented in a therapy manual Individual practice of yoga at home or school was carried out by each participant independently, without schedule Intervention 2: conventional motor training exercises A program of various well-known active games was put together. These contained all the elements that occur in normal grade school and leisure-sport activities (running games, throwing and catching games, agility games, ball games, concentration games, social games) and are thus fundamentally different from the yoga exercises. Using a cross-over study design, both groups received 2 consecutive 8-week intervention/ training sessions (each with 2 training sessions of 1 hour per week), separated by a training break of 6 weeks
Outcomes	1. Fremdbeurteilungsbogen für hyperkinetische Störungen (FBB-HKS) Döpfner 2000, Brühl 2000: 20 items each with 4 levels (0 = not at all, 1 = a little, 2 = to a large extent, 3 = especially), summarized in 3 symptom groups: attention-deficit, hyperactivity and impulsiveness. Categorized severity scores: 0 to -0.5 = not at all, 0.5 to 1.5 = a little, 1.5 to 2.5 = quite/to a large extent, 2.5 to 3.0 = very much/especially 2. Dortmund Attention Test (DAT) Lauth 1993 : comparison of differed pictures to determine the response latency and rate of error, which reflects attention-deficit Measurements: first baseline (baseline 1 / period of 6 weeks with parents ratings of ADHD symptoms, 1 measurement per week, using a standardized rating scale for parents, teachers and educators: FBB-HKS). A second baseline was taken after the 8-week intervention (baseline 2 / period of 6 weeks with standardized parent ratings of ADHD symptoms) by means of weekly measurements. Following the program, a third baseline was measured (baseline 3 / period of 6 weeks), with one assessment done per week.

Haffner 2006 (Continued)

	During both training phases weekly assessments were made. The Dortmund Attention Test was carried out in all 3 baseline time periods.	
Notes	Data were abstracted from the translated original German paper (translation was done by the investigator) 8 received medication (in 7 cases methylphenidate, in 1 case pipamperone) 7 received complementary therapy (in 3 cases ergotherapy, in 2 cases dyslexia therapy and in 2 cases behavioral therapy) Only the data from the first phase of the study (before cross over) were included in the analysis	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "the children were randomly (by drawing lots) assigned" Comment: probably done
Allocation concealment?	Yes	Comment: automatically done by drawing lots for each participant at the time of sequence generation
Blinding? All outcomes	No	Comment: the intervention cannot be blinded
Incomplete outcome data addressed? All outcomes	Yes	Quote: "one 9-year-old boy left the study because of a change of residence during the 21st week" Comment: the drop-out case would not have had a clinically relevant impact on the observed effect size
Free of selective reporting?	Yes	Comment: the outcomes were reported as mentioned in the methods section. The study author was contacted and completeness of outcome reporting was confirmed.
Free of other bias?	No	Comment: co-intervention - more boys in the yoga group received medication (5 of 9) than the exercise group (3 of 11)

Methods	Randomized controlled trial Initially a 20-week program. After 20 weeks, 5 of the control group moved to the treatment group
Participants	16 boys aged 8 to 13 years. Mean age for boys in the yoga group 10.63 years (SD = 1.78 years) and for boys in the control group 9.35 years (SD = 1.70 years). Participants diagnosed with ADHD according to DSM-IV criteria by experienced pediatricians and diagnosis confirmed by the results of pre-test Conners' Parent Rating Scales: Long (CPRS: R (L)). All medicated participants were stabilized after appropriate periods of titration on dexamphetamine and/or methylphenidate. All participants were Caucasian except one (Chinese) and were assessed as having average or high intelligence Participants were also required to be fluent in English and free from serious family pathology (e.g. parental clinical depression or substance abuse, criminality in one or both parents, or domestic violence). Families with these characteristics were excluded because they were unlikely to be compliant with the extensive time commitment required. Participants were excluded if they were receiving other forms of treatment (except medication for ADHD). Participants had to be able to attend weekly classes for the 20-week duration of the yoga program. Yoga group: 11 boys (6 originally randomized to yoga group, 5 crossed over from control group) Control group: 8 boys
Interventions	1. Yoga program Nagendra 1988 , Saraswati 1990 which incorporated standard yogic practices and comprised: - Respiratory training: selective use of oral and nasal passages for respiratory flow intended to increase the child's breath awareness as well as train him to breathe naturally through both nares. All exercises were repeated several times during each session and in a regulated rhythmical manner. - Postural training: involved stretching, load bearing, backward, forward, lateral flexion, and extensions and inversions performed in sitting, standing, supine and prone positions. These were performed in combination with respiratory exercises in static and dynamic positions. - Relaxation training: involved becoming progressively aware of and relaxing body parts and tensing and relaxing muscles - Concentration training: involved a technique called Trataka where participants focused on a word or shape, followed by seeing the image with eyes closed and continuing to see the image on a blank piece of paper 20 1-hour weekly instructional group sessions took place at Westmead Hospital, New South Wales, Australia. Parents were encouraged to assist with daily practice sessions at home. 2. Control group: engaged in co-operative games and activities. These groups were conducted for 1 hour, once a month and at the same location as the yoga groups
Outcomes	1. Conners' Parent (CPRS-R:L) Teacher (CTRS-R:L) Rating Scales - Revised: Long (Conners 1997) 2. Test of Variables of Attention (TOVA) Greenberg 1991 : a continuous performance test designed to avoid confounding attention with language processing skills or short-term memory problems

	3. Motion Logger - Actigraph. The Actigraph is a portable electronic activity monitor designed to be worn on the wrist, waist or ankle.	
Notes	Of the 14 boys who completed the trials, 6 participated in the yoga group only, 5 who were originally in the control group moved from the control group to the yoga group, and 3 were in the control group only. This gave a total of 11 boys who completed the yoga training and 8 boys who acted as controls.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "boys who were randomly allocated to the control group in the first allocation"
Allocation concealment?	Unclear	Comment: not mentioned in the report
Blinding? All outcomes	No	Comment: the intervention cannot be blinded. Probably not done.
Incomplete outcome data addressed? All outcomes	No	Quote "Letters were sent to 80 parents with eligible sons. Of the 25 who responded, 16 began the trials and completed them." Comment: the attrition rate and reason for drop-out were not reported in each intervention group
Free of selective reporting?	No	Quote: "On the Actigraph motion logger, many technical problems were encountered ... Due to these problems, data were deemed unreliable and were discarded." Comment: not all of the pre-specified outcomes were reported
Free of other bias?	No	Quote: "there were significant differences between the control and yoga groups on pretest sub-scale scores on almost all Conners' Rating Scales for both parents and teachers." Comment: significant baseline differences.

Kratter 1983

Methods	Randomized controlled trial, but used a modified randomization method to ensure the medicated subjects were equally distributed between the 3 groups Dissertation submitted to the faculty of the Department of Psychology at St. John's University, New York in 1983
Participants	24 boys from the Five Towns area of Lang Island, New York, USA diagnosed with ADHD (DSM-III) based on parent and child interviews Age range 93 to 142 months (mean = 120.63 months) Participants had a minimum score of 15 on the Abbreviated Parent-Teacher Questionnaire and were free from neurological disease or psychosis. The participants who received stimulants were equally assigned into each group
Interventions	Three intervention groups: 1. Meditation training (MT): individual sessions twice weekly for 4 weeks. Meditation technique was modified from Benson 1975 and Carrington 1975 : repeating the word "Ahnem" out loud and progressively more softly until the word was repeated silently. The actual meditation duration was gradually increased from 2 minutes to 8 minutes by the end of the 4-week training period. Practice was at least 3 times per week at home. 2. Relaxation training (RT): individual sessions twice weekly for 4 weeks, using modified progressive muscle relaxation by reduction in the number of muscle groups when compare to the standard progressive muscle relaxation, deep and slowing breathing phase before and after the tension-relaxation cycles and 5-second tension periods. The actual relaxation training duration was gradually increased from 2 minutes to 8 minutes by the end of 4 weeks. Practice was at least 3 times per week at home. 3. Waiting list controls (WLC): received no experimental manipulation
Outcomes	1. Matching Familiar Figure Test (MFFT) Kagan 1966 which measures the dimension of reflection-impulsivity by participants choosing identical pictures from an array of 6 variants. Errors reflect impulsivity. 2. Fruit Distraction Test (FDT) Santostefano 1978 which tests the selective deployment of attention between relevant and irrelevant stimuli by naming the color with and without distraction and contradictions 3. Nowicki-Strickland Locus of Control Scale (LCS) which is used in the identification of hyperactive children and to evaluate treatment effectiveness (consists of 39-items; 4-point scale) 4. Abbreviated Parent -Teacher Questionnaire (PTQ) Conners 1973 consisted of 10 overlapping items from the Conners' Teacher Rating Scale and the Parent Symptoms Questionnaire 5. Werry-Weiss-Peters Activity Scale (WWPAS) Werry 1968 : a rating scale which assesses activity level in specific situations
Notes	Parents were to be included in the training sessions Results table did not show number in each group. Data cannot be used in meta-analysis.

Risk of bias

Item	Authors' judgement	Description

Kratter 1983 (Continued)

Adequate sequence generation?	Unclear	Quote: “were randomly assigned to one of three conditions” Quote: “subjects who received stimulant medication... were assigned in a modified random fashion such that they were represented in approximately equal numbers” Comment: the randomization was not adequately done
Allocation concealment?	Unclear	Comment: No mention about allocation concealment.
Blinding? All outcomes	No	Comment: the intervention cannot be blinded. No description of blinding of the assessors.
Incomplete outcome data addressed? All outcomes	Unclear	Comment: no mention of attrition
Free of selective reporting?	Yes	Comment: all outcomes were reported as mentioned in the method section
Free of other bias?	Yes	

Moretti-Altuna 1987

Methods	Randomized controlled trial Conducted in New York, USA Dissertation submitted to the faculty of the Department of Psychology at St. John’s University, New York in 1987. This study has many similar characteristics to Kratter 1983 , which was also a dissertation from the same university.
Participants	23 boys, age range 6 to 10 years, 5 black, 5 white, 13 Hispanic Participants diagnosed with ADHD (DSM-III), confirmed by an intake committee (administrative team leader, a psychiatrist, multidisciplinary staff member). The participants had to be free from psychosis, neurological disease and not currently on psychoactive medication.
Interventions	1) Drug therapy (DT): medication + conventional treatment 2) Meditation-relaxation training (MT): individual sessions, 30 minutes twice weekly for 4 weeks. Meditation technique was modified from Benson 1975 : participants repeated the word “One” out loud and progressively more softly until the word was repeated silently. The actual meditation duration was gradually increased from 1 minute to 8 minutes by the end of the 4-week training period. Practice was at least 3 times per week at home. 3) Standard therapy control (STC): conventional treatment without medication, i.e. milieu, individual, group and/or family therapy

Moretti-Altuna 1987 (Continued)

Outcomes	1. Matching Familiar Figure Test (MFFT) Kagan 1966 , which measures the dimension of reflection-impulsivity by participants choosing identical pictures from array of 6 variants. Errors reflected impulsivity. 2. Fruit Distraction Test(FDT) Santostefano 1978 , which tests the selective deployment of attention between relevant and irrelevant stimuli by naming the color with and without distraction and contradictions 3. The Children’s Embedded Figures Test (CEFT) Karp 1963 , which measures the extent to which perception of part of a stimulus field is influenced by the entire field and requires the subject to find a simple form in a complex one 4. Abbreviated Parent-Teacher Questionnaire (PTQ) Conners 1973 , which consists of 10 overlapping items from the Conners’ Teacher Rating Scale and the Parent Symptoms Questionnaire 5. Werry-Weiss-Peters Activity Scale (WWPAS) Werry 1968 : a rating scale which assesses activity level in specific situations	
Notes	Parents were to be included in the training sessions	
<i>Risk of bias</i>		
Item	Authors’ judgement	Description
Adequate sequence generation?	Unclear	Quote: “Subjects were randomly assigned to one of three conditions”
Blinding? All outcomes	No	Comment: the intervention cannot be blinded. No description of blinding of the assessors.
Incomplete outcome data addressed? All outcomes	Unclear	Comment: no mention of attrition rate
Free of selective reporting?	Yes	Comment: all outcome were reported as mentioned in the methods section
Free of other bias?	Yes	

ADHD = attention-deficit/hyperactivity disorder

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abadi 2008	No randomization
Evans 2007	Not a clinical trial
Harrison 2004	Before-after design in 2 sequential groups, no true control group
Hassasiri 2002	Before-after design, no control group
Kratter 1982	Duplicate publication, less detailed than Kratter 1983
Peck 2005	Not diagnosed with ADHD
Zylowska 2008	Before-after design, no control group

Characteristics of ongoing studies *[ordered by study ID]*

Krisanaprakornkit 2008

Trial name or title	Breathing meditation with methylphenidate for the treatment of attention-deficit/hyperactivity disorder children: a randomized controlled trial
Methods	Randomized controlled trial
Participants	Inclusion criteria: - Children diagnosed with ADHD by a child psychiatrist using DSM-IV-TR criteria - Any religious background - Aged between 7 and 12 years Exclusion criteria: - Autistic spectrum disorders - Mental retardation
Interventions	Breathing meditation versus standard treatment control
Outcomes	1. Conners' Abbreviated Parent Questionnaire (continuous outcome) assessed by the parents at baseline, at the end of 4 weeks, at 8 weeks and at 12 weeks 2. Child Attention Problems (CAP) Rating Scale assessed at the same time
Starting date	April 2006
Contact information	Associate Professor Thawatchai Krisanaprakornkit Department of Psychiatry, Faculty of Medicine, Khon Kaen University, Thailand
Notes	Registered at www.ClinicalTrials.gov

DATA AND ANALYSES

Comparison 1. Meditation therapy versus drug therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Teacher rating ADHD overall scale	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 2. Meditation therapy versus standard treatment without drug

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Teacher rating ADHD scale	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Distraction test	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Meditation therapy versus drug therapy, Outcome 1 Teacher rating ADHD overall scale.

Review: Meditation therapies for attention-deficit/hyperactivity disorder (ADHD)

Comparison: 1 Meditation therapy versus drug therapy

Outcome: 1 Teacher rating ADHD overall scale

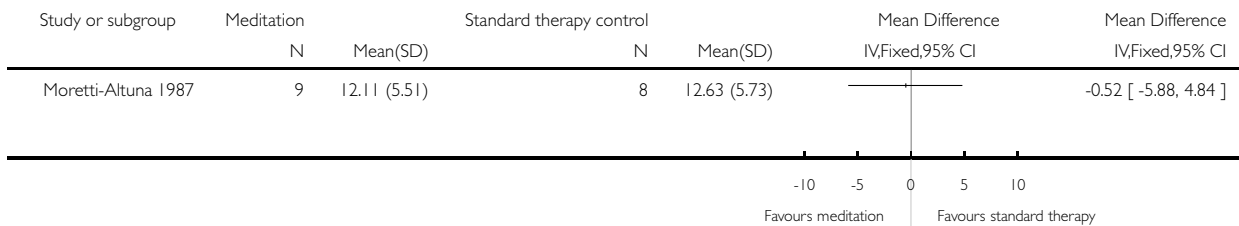
Study or subgroup	Meditation		Drug		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Moretti-Altuna 1987	9	12.11 (5.51)	6	14.83 (5.64)		-2.72 [-8.49, 3.05]

Analysis 2.1. Comparison 2 Meditation therapy versus standard treatment without drug, Outcome 1 Teacher rating ADHD scale.

Review: Meditation therapies for attention-deficit/hyperactivity disorder (ADHD)

Comparison: 2 Meditation therapy versus standard treatment without drug

Outcome: 1 Teacher rating ADHD scale

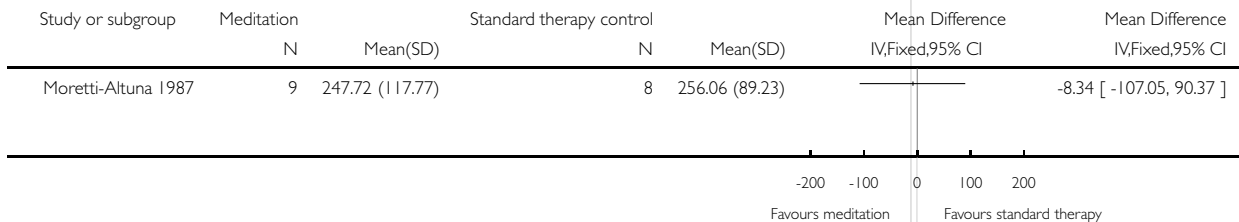


Analysis 2.2. Comparison 2 Meditation therapy versus standard treatment without drug, Outcome 2 Distraction test.

Review: Meditation therapies for attention-deficit/hyperactivity disorder (ADHD)

Comparison: 2 Meditation therapy versus standard treatment without drug

Outcome: 2 Distraction test



APPENDICES

Appendix I. Methods for data analysis in future updates of this review

Data analysis

Measures of treatment effect

Dichotomous outcomes

We will pool dichotomous outcomes using the risk ratio (RR) as the summary statistic. In cases where the numbers of participants and numbers of events are not available, but results calculated from them are (risk ratio, odds ratio, adjusted odds ratio), we will include the data in meta-analyses only if they are accompanied by measures of uncertainty such as 95% confidence intervals or exact P values. We will then pool the study-specific effect sizes using the generic inverse variance method in RevMan 5.0 ([RevMan 2008](#)).

Continuous outcomes

We will analyze data for continuous outcomes in RevMan 5.0 using either mean differences (MD) or standardized mean differences (SMD) if continuous outcomes are measured with similar, but not identical, instruments across studies. If the studies provide another statistic other than means and standard deviations (e.g. standard error, t-value, P value) we will perform the proper mathematical transformation to obtain standard deviations.

To ensure the appropriateness of meta-analysis, the following standards will be applied to all data before inclusion. To check for skewed data we will compare the mean to the standard deviation. If the mean is smaller than twice the standard deviation the data is probably skewed ([Altman 1996](#)). For data with finite limits, such as endpoint data, the observed mean minus the lowest possible value (or the highest possible value minus the observed mean), and dividing by the standard deviation. If the ratio is less than 1 there is strong evidence of a skewed distribution ([Altman 1996](#)). We will reveal the skewed data in additional tables. The endpoint score with standard deviation will be considered first in analysis if both endpoint score and change score are available. In cases where only change score is reported, we will contact authors of studies for endpoint figures. If only the change score is available, standard deviation of change score is needed for analysis and, if available, we will combine the data with endpoint scores (unless the standardized mean difference is used). If the available data cannot be managed by the above methods, we will present the data in 'other data' tables and use a narrative approach to synthesis.

If adjusted estimates of mean differences are presented from multiple regression analyses and analyses of covariance, the process of data extraction and analysis using the generic inverse variance method will be performed.

Unit of analysis issues

For cross-over studies, to exclude the potential additive effect in the second or further stages of these trials, we will only use data from the first stage in analysis. In studies with multiple treatment groups, we will carry out the analysis for each pair between meditation and other treatments. In studies with cluster-randomization (e.g. randomization by clinician or treatment settings), unless the cluster effect was accounted for, analysis and pooling of clustered data will result in unit of analysis error and overestimate statistical significance. In these cases, we will contact the authors of studies will be contacted to obtain intra-class correlation coefficients (ICC) of their clustered data and adjust by using accepted methods after consulting the Cochrane Developmental, Psychosocial and Learning Problems Group. Where clustering has been incorporated into the analysis of primary studies, we will also present these data as if from a non-clustered randomized study. If the cluster effect was not accounted for in primary studies and the ICC was not available, we will present the data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. The imputation of appropriate effect will be done by using the 'design effect' to calculate effective sample size. The design effect is $1 + (m - 1)r$, where m is the average cluster size and r is the intra-cluster correlation coefficient. If the ICC was not reported it will be assumed to be 0.05 ([Higgins 2008](#)).

In studies with repeated measures, we will carry out the analysis by separating the outcomes into short-term (up to three months), intermediate-term (three to 12 months) and long-term (more than 12 months).

Dealing with missing data

For included studies which used an intention-to-treat analysis by filling in or imputation of data for missing cases (such as last observation carried forward method or assumed no changes), we will contact authors for available data.

Assessment of heterogeneity

We will carry out a test for homogeneity and calculate the I^2 statistic, which provides an estimate of the percentage of variability due to heterogeneity, using Review Manager 5.0 (RevMan 2008).

Heterogeneity can occur from many sources. An important aspect of every meta-analysis is to consider and emphasize the existence of heterogeneity and to take account of this in the interpretation of results. Sources of heterogeneity (clinical heterogeneity) can be divided into two groups: clinical data and type of meditation.

Clinical data:

- Subtypes of attention deficit/hyperactivity disorders, etc.
- Disorder severity and chronicity: mild, moderate, severe.
- Comorbidity of emotional/psychiatric problems, speech /language problems, learning problems, psychosocial problems, conduct disorder.

Type of meditation:

(a) Techniques:

- Concentrative, mindfulness meditation or combination.
- Combination of different techniques of meditation (physical and mental practice, such as yoga).
- Other ingredients of treatment: group activities, prayer, recreational activities, etc.

(b) Intensity and frequency of practice: duration of meditation per treatment session, frequency of practice, duration of practice.

- Different follow-up periods: at the end of trial, any specified period after trial, repeated follow-up measures.
- Multi-component intervention: drugs, counseling, biofeedback, parent training, psychotherapy, family therapy, etc.

Data synthesis

Meta-analysis should only be considered when a group of trials is sufficiently homogeneous in terms of participants, interventions and outcomes to provide a meaningful summary. We will use a fixed-effect model for all analyses if there is no statistical heterogeneity. We may use a random-effects meta-analysis to incorporate heterogeneity among trials only after exploring the causes of heterogeneity or when heterogeneity cannot readily be explained.

The data analysis will seek to answer the following questions.

1. What is the direction of effect of meditation?
2. What is the size of the effect of meditation?
3. Is the effect of meditation consistent across studies?
4. What is the strength of evidence for the effect of meditation?

Any meta-analysis will consider the following.

1. Different types of outcome (dichotomous, continuous, survival data).
2. Study design.
3. Follow up length (short-term, intermediate, long-term).

Subgroup analysis and investigation of heterogeneity

Due to clear differences in characteristics, rather than undertaking an overall pooled analysis, we will analyze the data in subgroups according to the following categories.

- Childhood (under 13 years).
- Adolescence (13 to 18 years).
- Adult ADHD (age more than 18 years).

We will only undertake subgroup analyses if a sufficient number of studies is identified.

Sensitivity analysis

We will use a sensitivity analysis to test the robustness of effects of assumptions by examining the influence of the following on the results of the statistical analyses:

- the effect of the quality criteria (determine the effect of studies with high risk of bias on the overall effect); and
- blinding (masking) of raters.

Appendix 2. PubMed search strategy

("meditation"[mh] OR meditation[tw] OR "mindfulness-based"[tw] OR vipassana[tw] OR Zen[tw] OR yoga[tw] OR yogic[tw] OR pranayama[tw] OR Sudarshan[tw] OR Qi-gong[tw] OR Qigong[tw] OR "Chi kung"[tw] OR Kundalini[tw] OR ChunDoSunBup[tw] OR Reiki[tw] OR Tai Chi[tw]) AND ("Attention Deficit Disorder with Hyperactivity"[mh] OR "attention deficit/hyperactivity"[tw] OR attention def*[tw] OR ADHD[tw] OR ADD[tw] OR ADDH[tw] OR ADHS[tw] OR hyperactiv*[tw] OR hyperkin*[tw] OR "brain dysfunction"[tw]) AND (randomised controlled trial[pt] OR controlled clinical trial[pt] OR randomised controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR "clinical trial"[tw] OR singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw] OR mask*[tw] OR blind*[tw] OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[mh] OR evaluation studies[mh] OR follow-up studies[mh] OR prospective studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT human[mh]).

Appendix 3. EMBASE search strategy

```
1  meditation/
2  meditation.tw.
3  mindfulness-based.tw.
4  vipassana.tw.
5  zen.tw.
6  yoga/
7  yoga.tw.
8  yogic.tw.
9  pranayama.tw.
10 sudarshan.tw.
11 qi-gong.tw.
12 qigong.tw.
13 chi kung.tw.
14 kundalini.tw.
15 ChunDoSunBup.tw.
16 reiki.tw.
17 tai chi.tw.
18 or/1-17
19 Attention Deficit Disorder/
20 (attention adj3 deficit$.tw.
21 adhd.tw.
22 addh.tw.
23 adhs.tw.
24 hyperactiv$.tw.
25 hyperkin$.tw.
26 minimal brain dysfunction$.tw.
27 or/19-26
28 18 and 27
29 clin$.tw.
30 trial$.tw.
31 (clin$ adj3 trial$.tw.
```

32 singl\$.tw.
 33 doubl\$.tw.
 34 trebl\$.tw.
 35 tripl\$.tw.
 36 blind\$.tw.
 37 mask\$.tw.
 38 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw.
 39 randomi\$.tw.
 40 random\$.tw.
 41 allocat\$.tw.
 42 assign\$.tw.
 43 (random\$ adj3 (allocat\$ or assign\$)).tw.
 44 crossover.tw.
 45 44 or 43 or 39 or 38 or 31[M1]
 46 exp Randomized Controlled Trial/
 47 exp Double Blind Procedure/
 48 exp Crossover Procedure/
 49 exp Single Blind Procedure/
 50 exp RANDOMIZATION/
 51 46 or 47 or 48 or 49 or 50 or 45
 52 51 and 28

Appendix 4. PSYCInfo Search Strategy

1. meditation/
 2 meditation.tw.
 3 mindfulness-based.tw.
 4 vipassana.tw.
 5 zen.tw.
 6 yoga/
 7 yoga.tw.
 8 yogic.tw.
 9 pranayama.tw.
 10 sudarshan.tw.
 11 qi-gong.tw.
 12 qigong.tw.
 13 chi kung.tw.
 14 kundalini.tw.
 15 ChunDoSunBup.tw.
 16 reiki.tw.
 17 tai chi.tw.
 18 or/1-17
 19 Attention Deficit Disorder/
 20 (attention adj3 deficit\$).tw.
 21 adhd.tw.
 22 addh.tw.
 23 adhs.tw.
 24 hyperactiv\$.tw.
 25 hyperkin\$.tw.
 26 minimal brain dysfunction\$.tw.
 27 or/19-26
 28 18 and 27

29 Treatment Effectiveness Evaluation/
 30 exp Treatment Outcomes/
 31 Psychotherapeutic Outcomes/
 32 PLACEBO/
 33 exp Followup Studies/
 34 placebo\$.tw.
 35 random\$.tw.
 36 comparative stud\$.tw.
 37 randomi#ed controlled trial\$.tw.
 38 (clinical adj3 trial\$).tw.
 39 (research adj3 design).tw.
 40 (evaluat\$ adj3 stud\$).tw.
 41 (prospectiv\$ adj3 stud\$).tw.
 42 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw.
 43 control\$.tw.
 44 43 or 35 or 33 or 41 or 40 or 36 or 29 or 34 or 30 or 42 or 38 or 32 or 31 or 39 or 37
 45 28 and 44

Appendix 5. CINAHL Search Strategy

1 meditation/
 2 meditation.tw.
 3 mindfulness-based.tw.
 4 vipassana.tw.
 5 zen.tw.
 6 yoga/
 7 yoga.tw.
 8 yogic.tw.
 9 pranayama.tw.
 10 sudarshan.tw.
 11 qi-gong.tw.
 12 qigong.tw.
 13 chi kung.tw.
 14 kundalini.tw.
 15 ChunDoSunBup.tw.
 16 reiki.tw.
 17 tai chi.tw.
 18 or/1-17
 19 Attention Deficit Disorder/
 20 (attention adj3 deficit\$).tw.
 21 adhd.tw.
 22 addh.tw.
 23 adhs.tw.
 24 hyperactiv\$.tw.
 25 hyperkin\$.tw.
 26 minimal brain dysfunction\$.tw.
 27 or/19-26
 28 18 and 27
 29 randomi\$.mp.
 30 clin\$.mp.
 31 trial\$.mp.
 32 (clin\$ adj3 trial\$).mp.

33 singl\$.mp.
 34 doubl\$.mp.
 35 tripl\$.mp.
 36 trebl\$.mp.
 37 mask\$.mp.
 38 blind\$.mp.
 39 (33 or 34 or 35 or 36) and (37 or 38)
 40 crossover.mp.
 41 random\$.mp.
 42 allocate\$.mp.
 43 assign\$.mp.
 44 (random\$ adj3 (allocate\$ or assign\$)).mp.
 45 Random Assignment/
 46 exp Clinical Trials/
 47 exp Meta Analysis/
 48 44 or 40 or 39 or 32 or 29 or 45 or 46 or 47
 49 28 and 48

Appendix 6. LILACS search strategy

mediation or yoga or tai chi or reiki or mindfulness-based [Palavras] and attention deficit or adhd or addh or adhs

Appendix 7. OPENSIGLE search strategy

((meditation or yoga or reiki or tai chi or zen or mindfulness or vipassana or yogic or qigong or chi kung or kundalini or ChunDoSunBup))
 AND
 ((attention deficit or adhd or addh or adhs or hyperactiv* or hyperkin* or minimal brain))

HISTORY

Protocol first published: Issue 2, 2007

Review first published: Issue 6, 2010

CONTRIBUTIONS OF AUTHORS

TK: protocol development, searching, data extraction, quality assessment and analysis.

CN: data extraction, quality assessment and statistical analysis.

CW: screening the potential included studies.

NP: quality assessment.

DECLARATIONS OF INTEREST

TK runs the Meditation Therapy Clinic for various types of patients at the Department of Psychiatry, Faculty of Medicine, Khon Kaen University, Thailand.

TK is conducting a randomized controlled trial 'Breathing meditation with methylphenidate for the treatment of attention-deficit/hyperactivity disorder children', which is registered at www.ClinicalTrials.gov ([Krisanaprakornkit 2008](#)).

There are no potential conflict of interest for the other authors.

SOURCES OF SUPPORT

Internal sources

- Thai Cochrane Network, Thailand.
- Faculty of Medicine, Khon Kaen University, Thailand.
- Cochrane Developmental, Psychosocial and Learning Problems Group (CDPLPG), UK.

External sources

- Thailand Research Fund, Senior Research Scholar, Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed some sources of databases to be searched. We searched LILACS through the Virtual Health Library (VHL) in BIREME: Pan American Health Organization (PAHO), which incorporates many bibliographic databases in general health science (LILACS, MEDLINE, *The Cochrane Library*, SciELO), specialized areas (ADOLEC, BBO, BDENF, DESASTRES, HISA, HOMEINDEX, LEYES, MEDCARIB, REPIDISCA) and international agencies (PAHO, WHOLIS).

The CISCOM database of The Research Council for Complementary Medicine was closed, therefore we searched other complementary and alternative medicine databases, i.e. CAM on PubMed, the web-site of the Cochrane Complementary and Alternative Health field, the Complementary Medicine Resources for Health Professionals and Researchers, and the Complementary and Alternative Therapies databases of Bandolier.

INDEX TERMS

Medical Subject Headings (MeSH)

*Yoga; Adolescent; Attention Deficit Disorder with Hyperactivity [drug therapy; * therapy]; Meditation [*methods]; Relaxation Therapy [methods]

MeSH check words

Child; Female; Humans; Male

Antibiotic prophylaxis for third- and fourth-degree perineal tear during vaginal birth (Review)

Buppasiri P, Lumbiganon P, Thinkhamrop J, Thinkhamrop B



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[Intervention Review]

Antibiotic prophylaxis for third- and fourth-degree perineal tear during vaginal birth

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ABSTRACT

Background

One to eight per cent of women suffer third-degree perineal tear (anal sphincter injury) and fourth-degree perineal tear (rectal mucosa injury) during vaginal birth, and these tears are more common after forceps delivery (28%) and midline episiotomies. Third- and fourth-degree tears can become contaminated with bacteria from the rectum and this significantly increases in the chance of perineal wound infection. Prophylactic antibiotics might have a role in preventing this infection.

Objectives

To assess the effectiveness of antibiotic prophylaxis for reducing maternal morbidity and side effects in third- and fourth-degree perineal tear during vaginal birth.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 August 2010) and the reference lists of retrieved articles.

Selection criteria

Randomised controlled trials comparing outcomes of prophylactic antibiotics versus placebo or no antibiotics in third- and fourth-degree perineal tear during vaginal birth.

Data collection and analysis

Two review authors independently assessed the reports and extracted data.

Main results

We identified and included one trial (147 participants) that compared the effect of prophylactic antibiotic (single-dose, second generation cephalosporin, intravenously) on postpartum perineal wound complications in third- or fourth-degree perineal tears. Perineal wound complications (wound disruption and purulent discharge) at the two-week postpartum check up were 8.20% and 24.10% in the treatment and the control groups respectively (risk ratio 0.34, 95% confidence interval 0.12 to 0.96).

Authors' conclusions

Although the data suggest that prophylactic antibiotics help to prevent perineal wound complications following third- or fourth-degree perineal tear, loss to follow-up was very high. The results should be interpreted with caution as they are based on one small trial.

PLAIN LANGUAGE SUMMARY

Antibiotic prophylaxis for third- and fourth-degree perineal tear during vaginal birth

Most women are able to give birth without serious damage to their perineum. However, severe perineal trauma, which affects the muscle or tissue in the back passage, occurs in 1% to 8% of women giving birth and is common when forceps are used. There is an increased chance of infection when this happens, and antibiotics are often prescribed. The review of routine antibiotics for women with severe perineal tears identified one trial, involving 147 participants. This trial was conducted to explore the benefit of routine prophylactic antibiotics for women with severe perineal tears. The result showed fewer perineal wound complications when prescribing prophylactic antibiotic. However, the results are based on one small trial and there was a high loss to follow-up. More research is needed.

BACKGROUND

Episiotomy is the incision in the perineal area to enlarge the vaginal orifice for easier vaginal birth. It consists of two types: midline or median and mediolateral style. Many studies have shown that routine episiotomy can cause such problems as persistent perineal pain, unsatisfied postpartum sexual function, and increasing anal sphincter injury leading to faecal or flatus incontinence (Christianson 2003; Jones 2000; Labrecque 1997; Nager 2001; Signorello 2001). Pain in this area can impact not only on a woman's daily activity but also on her relationship with her baby and her partner. A restrictive episiotomy policy (strict criteria to perform episiotomy only in proper cases such as short stature mother with short perineum, large size baby, or imminent severe laceration of perineum) has been in place for many years and is strongly supported by a Cochrane systematic review (Carroll 1999). In addition, prenatal perineal massage has also been introduced into practice to prevent perineal tears (Davidson 2000; Eason 2000; Johanson 2000; Labrecque 1999). One randomised controlled trial failed to show the effectiveness of perineal massage but concluded that it did no harm (Stamp 2001).

Most women are able to give birth without serious damage to the perineum, but 1% to 8% of women suffer severe perineal tears (anal sphincter injury with or without rectal mucosa injury) during vaginal birth (De Leeuw 2001; Riskin-Mashiah 2002; Samuelsson 2000; Samuelsson 2002; Sultan 1994). These tears are more common after operative vaginal birth, especially when forceps are used. The incidence of severe perineal lacerations after the use of forceps has been reported as 21% for third-degree and 7% for fourth-degree tears (Bofill 1996). Other risk factors include race (Asian women have the highest risk, perhaps due to small size

mother and short perineum), midline episiotomy (short distance to anal sphincter), nulliparity (lesser elasticity than a multiparous mother), and high birthweight baby (De Leeuw 2001; Goldberg 2003; Homs 1994; Jones 2000; Labrecque 1997; Nager 2001; Sultan 1994).

When a woman has a severe perineal tear during vaginal birth, there is thought to be an increased risk of infection. Laceration of the vagina and perineum during vaginal birth are classified as first, second, third and fourth degree. First-degree tears involve the vaginal mucosa and connective tissue. Second-degree tears involve the vaginal mucosa, connective tissue and underlying muscles. Third-degree tears involve a complete transection of anal sphincter and fourth-degree tears involve the rectal mucosa (Cunningham 2001; WHO 2003). When the rectal mucosa is ruptured, the wound is classified as contaminated (Waddell 1994) or clean-contaminated (Mangram 1999). Antibiotic prophylaxis is generally used where wounds have become, or are likely to become, contaminated, such as in colorectal surgery (Oates 1986; Song 1998). A Cochrane review has also shown antibiotic prophylaxis to be effective in reducing puerperal morbidity after cesarean section (Smaill 2002). On the other hand, a Cochrane review on antibiotic prophylaxis after operative vaginal birth could not conclude its effectiveness (Liabsuetrakul 2004).

A woman contracting infection after a severe perineal tear may also be at risk of other morbidities as a result of the tear, such as haematoma, dyspareunia, incontinence and recto-vaginal fistula (Crawford 1993; Homs 1994; Labrecque 1997; Nager 2001; Signorello 2001; Sorensen 1988; Sultan 2002; WHO 2003).

While some authorities recommend that prophylactic antibiotics

be used for severe perineal tears (WHO 2003), others have recommended against this course of action (Whitfield 1995). As widespread use of antibiotics may contribute to antibiotic-resistant bacteria (Towers 1998; Weinstein 1996), the over-use of antibiotics is being discouraged by many groups. However, antibiotic prophylaxis is a low-cost, accessible intervention which may prevent considerable maternal morbidity. It is therefore, important to establish the benefits of prophylactic antibiotics for infection after severe perineal tears, and also to assess whether there are any adverse effects on mother or infant, by systematically reviewing the evidence.

OBJECTIVES

To assess the effectiveness of antibiotic prophylaxis for reducing maternal morbidity and side effects in third- and fourth-degree perineal tear during vaginal birth.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials. We did not plan to include quasi-randomised controlled, crossover trials or include studies that were presented only as abstracts.

Types of participants

Mothers with third- and fourth-degree perineal tears as a result of vaginal birth.

Types of interventions

Antibiotic regimens used to prevent perineal wound infection compared either to placebo, or to no treatment, antibiotic treatment in women who get infection only, and comparisons between different antibiotic regimens.

Types of outcome measures

Primary outcomes

1. Fever or puerperal febrile morbidity (body temperature of 38°C or higher occurring on any two occasions in the first 10 days postpartum, exclusive of the first 24 hours).

2. Perineal wound complications, including infection (edematous, erythematous, wound edge with pain, serosanguinous or frankly purulent material), or wound dehiscence (wound separation).

Secondary outcomes

1. Serious infectious complications (such as bacteraemia, septic shock, septic thrombophlebitis, necrotising fasciitis, or death attributed to infection).
2. Pain (wound pain score or variously measured by authors).
3. Woman's comfort (unable to sit down or breast feed) while in hospital and six weeks postpartum.
4. Length of hospital stay for mother.
5. Adverse reaction (such as allergic reaction, anaphylaxis, diarrhoea).
6. Maternal-infant interactions including breastfeeding.
7. Sexual function including dyspareunia (pain on sexual intercourse), sexual satisfaction, sexual sensation, time to resuming sexual intercourse.
8. Woman's satisfaction.
9. Recto-vaginal fistula (hole between the vagina and rectum).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group Trials Register by contacting the Trials Search Co-ordinator (31 August 2010).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

For details of additional searching carried out by authors for the initial version of the review, see: [Appendix 1](#).

Searching other resources

We checked the references of retrieved articles to locate other relevant trials.

We did not apply any language restrictions.

Data collection and analysis

For this update we used the following methods when assessing the one trial identified by the updated search ([Duggal 2008](#)).

Selection of studies

Two review authors independently assessed for inclusion the report we identified as a result of the updated search. There were no disagreements.

Data extraction and management

We designed a form to extract data. For the eligible study, two review authors extracted the data using the agreed form. We would have resolved discrepancies through discussion or consulted a third person. We entered data into Review Manager software ([RevMan 2008](#)) and checked them for accuracy.

We contacted the contact author of the original report who provided additional data.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for the study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2009](#)). We would have resolved any disagreement by discussion or by involving a third assessor.

(1) Sequence generation (checking for possible selection bias)

We described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- adequate (any truly random process, e.g. random number table; computer random number generator);
- inadequate (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear.

(2) Allocation concealment (checking for possible selection bias)

We described the method used to conceal the allocation sequence and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear.

(3) Blinding (checking for possible performance bias)

We described the methods used, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding could not have affected the results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We described for the included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we re-included missing data in the analyses which we undertook. We assessed methods as:

- adequate; lost follow-up rate was 20% or less;
- inadequate; lost follow-up rate more than 20%;
- unclear; no information.

(5) Selective reporting bias

We described how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were

not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);

- unclear.

(6) Other sources of bias

We described any important concerns we have about other possible sources of bias, such as the trial stopped early due to some data-dependent process, extreme baseline imbalance, the study been claimed to be fraudulent:

- yes;
- no;
- unclear.

(7) Overall risk of bias

We made explicit judgements about whether the study was at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2009). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - see [Sensitivity analysis](#).

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we used the mean difference if outcomes are measured in the same way between trials. We used the standardised mean difference to combine trials that measure the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials

We planned to include cluster-randomised trials in the analyses along with individually randomised trials. We planned to adjust their sample size using the methods described in the *Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we planned to report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-

randomised trials and individually-randomised trials, we planned to synthesise the relevant information. We planned to consider it reasonable to combine the results from both if there was little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit was considered to be unlikely.

We planned to acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Dealing with missing data

For included studies, we noted levels of attrition. We explored the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and to analyse all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial would be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the T^2 , I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if T^2 was greater than zero and either I^2 was greater than 30% or there was a low P-value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there were 10 or more studies in the meta-analysis, we planned to investigate reporting biases (such as publication bias) using funnel plots. We planned to assess funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry. For continuous outcomes, we planned to use the test proposed by Egger 1997, and for dichotomous outcomes we planned to use the test proposed by Harbord 2006. If asymmetry was detected in any of these tests or was suggested by a visual assessment, we planned to perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2008). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. If there was clinical

heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary if an average treatment effect across trials was considered clinically meaningful. We would treat the random-effects summary as the average range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we would not combine trials.

If we used random-effects analyses, we planned to present the results as the average treatment effect with its 95% confidence interval, and the estimates of T^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

If we had identified substantial heterogeneity, we planned to investigate it using subgroup analyses and sensitivity analyses. We planned to consider whether an overall summary was meaningful, and if it was, use random-effects analysis to produce it.

We planned to carry out the following subgroup analyses.

1. Immunocompromised versus not immunocompromised pregnant women, such as HIV infection, chronic steroid use.
2. Women with prolonged prelabour rupture membranes versus women not.
3. Women with preterm prelabour rupture membranes versus not.
4. Third degree tears compared with fourth degree tears.

We would restrict subgroup analysis to the following outcomes:

1. Fever or puerperal febrile morbidity.
2. Perineal wound infection.

For fixed-effect inverse variance meta-analyses we would assess differences between subgroups by interaction tests. For random-effects and fixed-effect meta-analyses using methods other than inverse variance, we would assess differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis

We would perform sensitivity analyses for aspects of the review that might affect primary outcomes (fever or puerperal febrile morbidity and perineal wound infection), such as where there was risk of bias associated with the quality of some of the included trials. We planned to carry out sensitivity analysis to explore the effects of fixed-effect or random-effects analyses for primary outcomes with statistical heterogeneity and the effects of any assumptions made, such as the value of the ICC used for cluster-randomised trials.

RESULTS

Description of studies

See: [Characteristics of included studies](#).

Results of the search

The updated search in December 2009 identified two reports of one study ([Duggal 2008](#)) - see [Characteristics of included studies](#) for details.

Risk of bias in included studies

The one included study was terminated before it reached the preplanned sample size and had a high rate of loss to follow-up ([Duggal 2008](#)).

Effects of interventions

Single dose, second generation cephalosporin intravenously (cefotetan or cefoxitin, 1 g, intravenously, or clindamycin, 900 mg intravenously if allergic to penicillin, in 100 ml of saline) was used as the intervention to prevent perineal wound infection or disruption in the third- or fourth-degree perineal tear compared with placebo (100 ml of normal saline intravenously).

The primary outcome of the included study was gross disruption or purulent discharge at the site of perineal repair by two weeks postpartum.

Perineal wound complications at two weeks postpartum in treatment and control groups were four of 49 (8.20%) and 14 of 58 (24.10%) respectively ($P = 0.037$, risk ratio (RR) 0.34, 95% confidence interval (CI) 0.12 to 0.96).

Perineal wound infection before discharge and at six weeks postpartum was also reported. There were no perineal wound complications before hospital discharge in both groups. One hundred and twenty-eight participants were checked at six weeks postpartum (19 of 147 (12.9%) did not come for follow-up at six-weeks). There were perineal wound complications in four out of 55 (7.3%) and 14 out of 73 (19.2%) women in the treatment and control groups respectively, ($P = 0.07$, RR 0.38, 95% CI 0.13 to 1.09).

DISCUSSION

Summary of main results

There were marginally significantly fewer perineal wound complications at two weeks postpartum in the intervention group. There was no statistically significant difference in perineal wound complications before discharge and at six weeks postpartum. However,

loss to follow-up was 27.2% and 12.9 % at two and six weeks postpartum respectively.

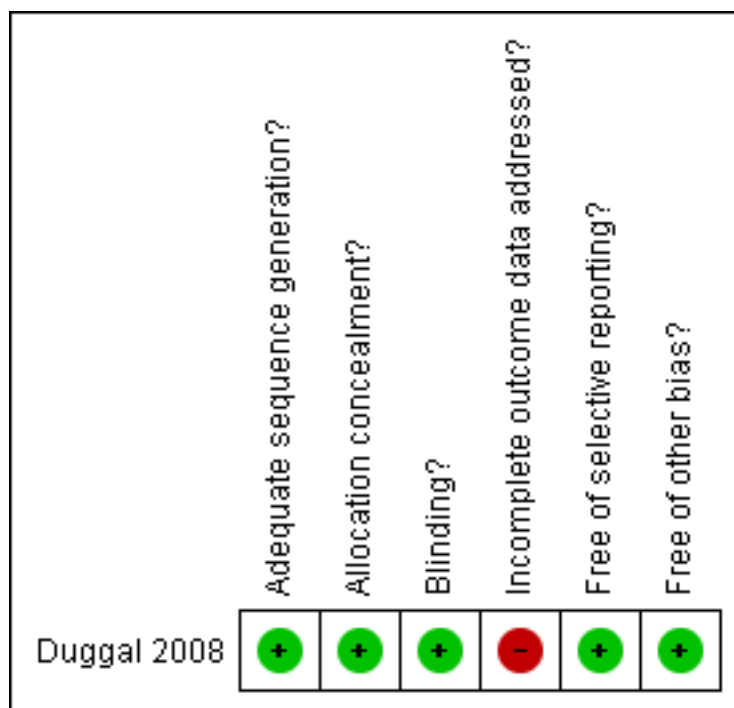
Overall completeness and applicability of evidence

The one included study, conducted in a developed country, with a relatively high loss of follow-up, provides insufficient data to address the objectives of this review.

Quality of the evidence

The risk of bias for the one included study in this review is high - see Figure 1. Inadequate sample size and high loss to follow-up rate do not allow us to draw a firm conclusion about the benefit of antibiotic prophylaxis in third- or fourth-degree perineal tear after vaginal birth.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Potential biases in the review process

We adhered to the Cochrane Pregnancy and Childbirth Group search strategies and review process. We are not aware of any potential bias in the review process.

Agreements and disagreements with other studies or reviews

There are no other studies or reviews addressing this clinical question.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence from the one included study is not strong enough to recommend prophylactic antibiotics for third- or fourth-degree perineal tear after delivery.

Implications for research

Well-designed, multicentre, randomised controlled trials are

needed before prophylactic antibiotics for third- and fourth-degree perineal tear after vaginal birth can be recommended.

ACKNOWLEDGEMENTS

The review authors would like to thank the authors of [Duggal 2008](#) for providing additional data which will be incorporated into the next update of this review. The review authors would also like to thank the editorial board for their comments, members of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Duggal 2008

Methods	Type of study: prospective, randomised, placebo-controlled trial. Method: randomisation was done by using a random-numbers table. Women were randomly assigned to a single dose of antibiotic (cefotetan or cefoxitin, 1 g, intravenously, or clindamycin, 900 mg intravenously if allergic to penicillin, in 100 ml of saline) or placebo (100 ml of normal saline intravenously). The nurse was instructed to open the envelope and administer the medication or placebo. The log book was kept in a secure location in medication room. Placebo: yes, normal saline was used. Sample size: to demonstrate a 75% reduction in perineal infection rate with an alpha of 0.05 and a power of 80%, 310 participants (155 on each arm) were needed. Only 147 participants (83 in placebo group, 64 in treatment group) were enrolled in a 3-year period. Intention-to-treat basis: yes. Loss to follow-up: 27.2% (40 of 147) participants lost at 2-week postpartum check up. 107 participants visited at 2-week postpartum check up. 23.4% (15 of 64) were missed in treatment group, and 30.1% (25 of 83) in control group. 19 of 147 (12.9%) participants were lost to follow-up at the 6-week postpartum check up.
Participants	Location: Santa Clara Valley Medical Center and Stanford University Medical Center's Lucile Parkard Children's Hospital. California, San Francisco, USA. Time frame: September 2003-June 2006. Eligible criteria: women who sustained third- or fourth-degree perineal laceration after vaginal deliveries. Exclusion: age < 18 years, group B streptococcus positive, human immunodeficiency virus positive, had chorioamnionitis or history of inflammation bowel disease, or were already on antibiotics for any reason. Total recruited: 147 participants. Treatment group: 64 participants, control group = 83 participants.
Interventions	Treatment group: 64 participants. Control group: 83 participants.
Outcomes	Perineal wound infection rate (gross disruption or purulent discharge at site of perineal repair) by 2 weeks postpartum.
Notes	There were 310 preplanned participants (155 in each arm). The authors decided to terminated the study after 3 years of enrolment because they could not achieve the pre-planned number of participants within a reasonable time period. Many women refused to participate and many missed enrolment due to busy labour and delivery wards. Only 147 participants were recruited: 64 cases in intervention group and 83 in the control group.
<i>Risk of bias</i>	

Duggal 2008 (Continued)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation was done by using a random numbers table.
Allocation concealment?	Yes	The nurse from another ward was instructed to open the randomisation envelope and administer the medication or placebo. The logbook was kept in a secure location in the medication room.
Blinding? All outcomes	Yes	No physician was involved in preparing the study medication, and obstetricians did not in practice prepare or retrieve medication from the medication room. The registered nurse providing postpartum care was on another floor and did not have access to the log book. The clinician evaluating the women postpartum did not have access to the log book and did not have a way of determining which arm a woman had been randomised to.
Incomplete outcome data addressed? All outcomes	No	107 of 147 participants visited for the 2-week postpartum check up, then 27.2 % were lost to follow-up; 15 of 64 (23.4%) in intervention group and 25 of 83 (30.1%) in the control group.
Free of selective reporting?	Yes	The authors reported perineal wound complication rates before discharge, and at the 2- and 6-week postpartum check ups.
Free of other bias?	Yes	It is unlikely to have other bias.

DATA AND ANALYSES

Comparison 1. Antibiotic prophylaxis versus no treatment for perineal tear

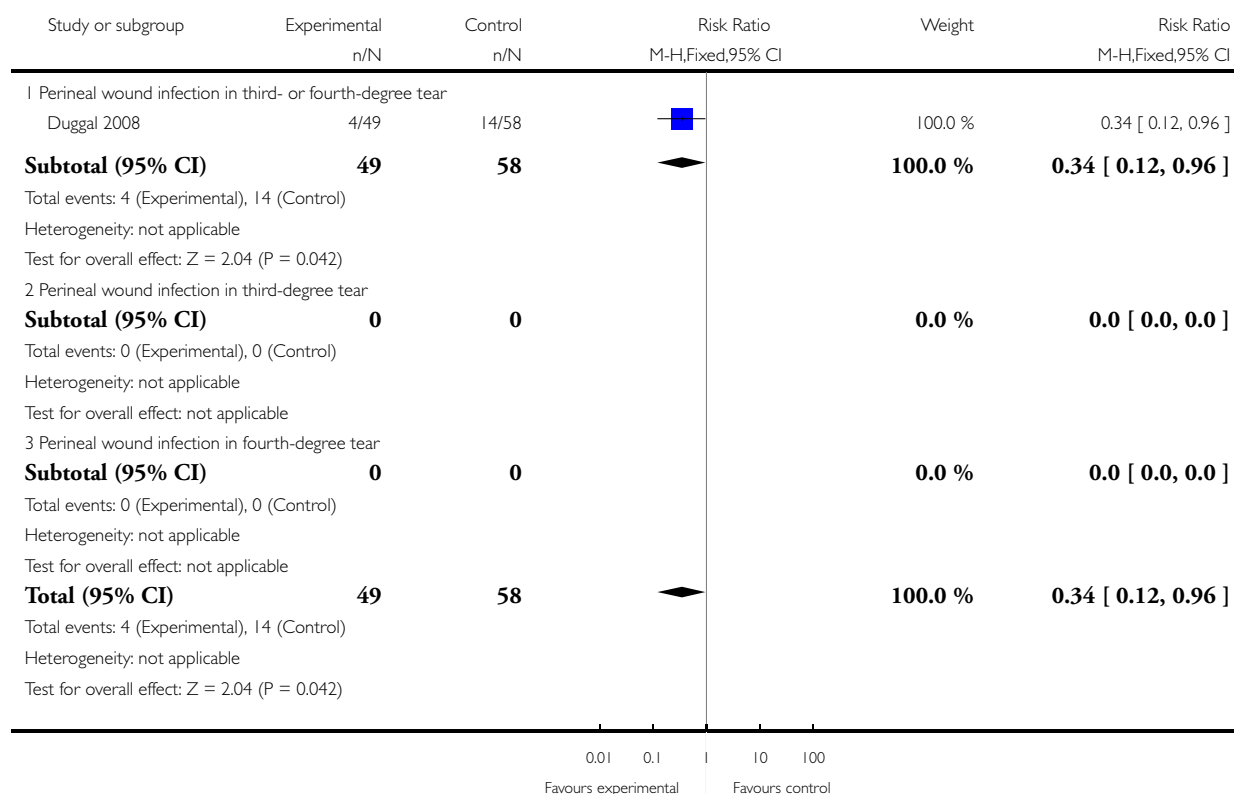
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Infection rate at 2 weeks postpartum	1	107	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.12, 0.96]
1.1 Perineal wound infection in third- or fourth-degree tear	1	107	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.12, 0.96]
1.2 Perineal wound infection in third-degree tear	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3 Perineal wound infection in fourth-degree tear	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Infection rate at 6 weeks postpartum	1	128	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.13, 1.09]
2.1 Perineal wound infection in third- or fourth-degree tear	1	128	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.13, 1.09]
2.2 Perineal wound infection in third-degree tear	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.3 Perineal wound infection in fourth-degree tear	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 1.1. Comparison 1 Antibiotic prophylaxis versus no treatment for perineal tear, Outcome 1 Infection rate at 2 weeks postpartum.

Review: Antibiotic prophylaxis for third- and fourth-degree perineal tear during vaginal birth

Comparison: 1 Antibiotic prophylaxis versus no treatment for perineal tear

Outcome: 1 Infection rate at 2 weeks postpartum

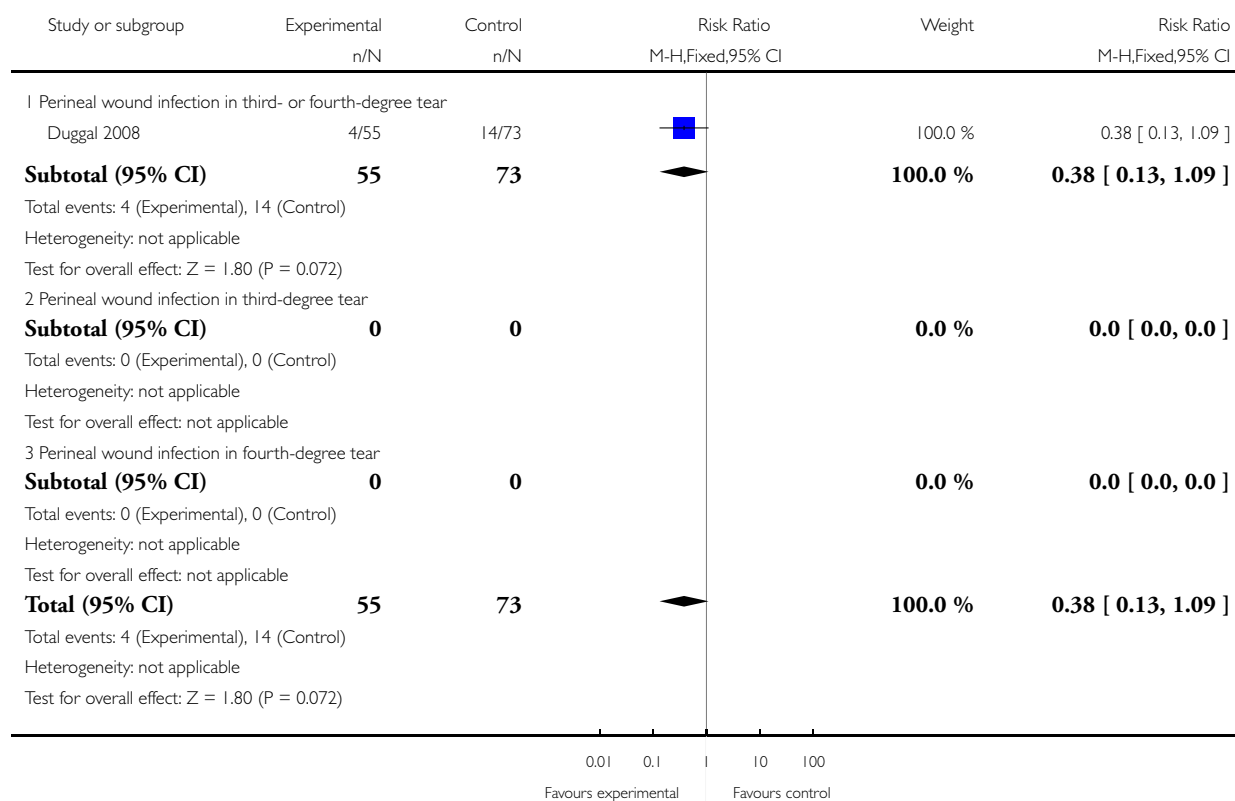


Analysis 1.2. Comparison 1 Antibiotic prophylaxis versus no treatment for perineal tear, Outcome 2 Infection rate at 6 weeks postpartum.

Review: Antibiotic prophylaxis for third- and fourth-degree perineal tear during vaginal birth

Comparison: 1 Antibiotic prophylaxis versus no treatment for perineal tear

Outcome: 2 Infection rate at 6 weeks postpartum



APPENDICES

Appendix I. Search strategy

For the initial version of the review, authors searched CENTRAL (*The Cochrane Library* 2005, Issue 2), MEDLINE (1966 to 15 July 2005) using the strategy below:

#1 PERINEUM single term (MeSH)

#2 perine*

#3 (tear* or injur* or lacerat* or trauma or damage*)

#4 (#2 and #3)

#5 (anal near sphincter) or (rectal mucosa) or rectum or (anal epithelium) or anus or (recto-vaginal fistulae) or (anorectal mucosa) or (anal skin)

#6 (tear* or injur* or damage* or lacerat* or rupture* or trauma)

#7 (#5 and #6)

#8 (obstetric* near tear*) or (obstetric near lacerat*)

#9 EPISIOTOMY single term (MeSH)

#10 episiotom* or postepisiotom*

#11 EXTRACTION OBSTETRICAL explode tree 1 (MeSH)

#12 vacuum or ventouse or forcep*

#13 deliver*

#14 (birth or childbirth or child-birth or (child next birth))

#15 antibio*

#16 ANTIBIOTICS explode all trees (MeSH)

#17 (#1 or #4 or #7 or #8)

#18 (#9 or #10 or #11 or #12 or #13 or #14)

#19 (#15 or #16)

#20 (#17 and #18 and #19)

WHAT'S NEW

Last assessed as up-to-date: 3 October 2010.

Date	Event	Description
31 August 2010	New search has been performed	Search updated, no new studies identified. One trial identified in the previous updated search has now been included (Duggal 2008). The methods have been updated to reflect the latest Cochrane Handbook. A note about the next update of this review has been added to Published notes .
31 August 2010	New citation required and conclusions have changed	The scope of the review has changed to include both 3rd and 4th degree perineal tears.

HISTORY

Protocol first published: Issue 1, 2005

Review first published: Issue 4, 2005

Date	Event	Description
1 December 2009	Amended	Search updated. Two new reports identified.
13 February 2009	Amended	Contact details updated.
1 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Pranom Buppasiri (PB) and Pisake Lumbiganon (PL) formulated the review question. PB drafted the protocol. PB, PL, Jadsada Thinkhamrop (JT) and Bandit Thinkhamrop (BT) revised and approved the final version of the protocol. PB drafted the review. PL, JT and BT revised and approved the final version of the review. All authors approved the final version of the update review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Faculty of Medicine, Khon Kaen University, Thailand.

External sources

- Thai Cochrane Network, Thailand.
- Thailand Research Fund (Senior Research Scholar), Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have broadened the inclusion criteria to include women with third-degree tears and divided the outcomes into primary and secondary.

NOTES

The review authors have contacted the trialists of the one included trial ([Duggal 2008](#)) in order to obtain the data separated by degree of perineal tear (3rd or 4th degree). These data will be added to the next update of this review, and we plan to carry out subgroup analysis by degree of perineal tear.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antibiotic Prophylaxis; Anal Canal [injuries]; Delivery, Obstetric [*adverse effects]; Rectum [*injuries]; Rupture [etiology]; Wound Infection [*prevention & control]

MeSH check words

Female; Humans; Pregnancy

Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections (Review)

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Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections (Review)
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[Intervention Review]

Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections

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ABSTRACT

Background

Chorioamnionitis is more likely to occur when meconium-stained amniotic fluid (MSAF) is present. Meconium may enhance the growth of bacteria in amniotic fluid by serving as a growth factor, inhibiting bacteriostatic properties of amniotic fluid. Many adverse neonatal outcomes related to MSAF result from Meconium Aspiration Syndrome (MAS). MSAF is associated with both maternal and newborn infections. Antibiotics may be an effective option to reduce such morbidity.

Objectives

The objective of this review is to assess the efficacy and side effects of prophylactic antibiotics for MSAF during labour in preventing maternal and neonatal infections.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 September 2010).

Selection criteria

Randomized controlled trials (RCTs) comparing prophylactic antibiotics with placebo or no treatment during labour for women with MSAF.

Data collection and analysis

Two review authors independently assessed the results of the only available trial and extracted data on maternal and neonatal outcomes.

Main results

We included one study with 120 pregnant women. It compared ampicillin-salvactam (N = 60) versus normal saline (N = 60) in pregnant women with MSAF. Prophylactic antibiotics appeared to have no statistically significant reduction in the incidence of neonatal sepsis (risk ratio (RR) 1.00, 95% CI 0.21 to 4.76), neonatal intensive care unit (NICU) admission (RR 0.83, 95% CI 0.39 to 1.78) and postpartum endometritis (RR 0.50, 95% CI 0.18 to 1.38). However, significant decrease in the risk of chorioamnionitis (RR 0.29, 95% CI 0.10 to 0.82). No serious adverse effects were reported.

Authors' conclusions

Current evidence indicates that compared to placebo, antibiotics for MSAF in labour may reduce chorioamnionitis. There was no evidence that antibiotics could reduce postpartum endometritis, neonatal sepsis and NICU admission. This systematic review identifies the need for more well-designed, adequately powered RCTs to assess the effect of prophylactic antibiotics in the incidence of maternal and neonatal complications.

PLAIN LANGUAGE SUMMARY

Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections

Meconium-stained amniotic fluid (MSAF) is the result of waste maternal from the fetal colon passing into the mother's amniotic cavity. Its incidence increases in post-term pregnancies. Pregnant women with MSAF are more likely to develop maternal complications including inflammation of the fetal membranes caused by a bacterial infection (chorioamnionitis), postpartum inflammation of the lining of the uterus (endometritis) and neonatal complications such as neonatal sepsis and need for admission to a neonatal intensive care unit (NICU). Fetal stress or hypoxia may trigger gasping fetal respirations, which results in the aspiration of meconium.

Our review was based on one identified randomized controlled study (involving 120 women) and found that prophylactic antibiotics may reduce the risk of intra-amniotic infection in women with MSAF. Antibiotics use did not clearly reduce neonatal sepsis, NICU admission or postpartum endometritis. Studies with much larger numbers of pregnant women with MSAF would be needed to examine these issues.

BACKGROUND

Description of the condition

Meconium-stained amniotic fluid (MSAF), as a result of the passage of fetal colonic contents into the amniotic cavity, occurs in approximately 12% of all deliveries (Cleary 1998). The incidence of intrapartum MSAF ranges from 7% to 22% for a term pregnancy but this figure increases to up to 40% in a post-term pregnancy (Katz 1992). The composition of meconium from a term fetus is primarily water (70% to 80%). Other constituents include mucopolysaccharides, cholesterol and its precursors, proteins, lipids, bile acids and salts (giving the characteristic green colour), pancreatic enzymes, interleukin-8, phospholipase A2, squamous cells, and vernix caseosa (Cleary 1998; Usta 2000).

MSAF may act directly and indirectly on exposed tissue. Its effects depend on the concentration of meconium, duration of exposure, and the presence of associated stress factors (hypoxia, infection). MSAF has long been associated with potentially adverse fetal outcomes including meconium aspiration syndrome (MAS), admission to neonatal intensive care unit (NICU), neonatal sepsis, cerebral palsy, seizure and pulmonary diseases (Berkus 1994; Katz 1992; Nathan 1994). Many adverse neonatal outcomes related to MSAF result from MAS. MAS occurs in 5% of the cases of MSAF and more than 4% of infants with MAS die, accounting for 2%

of all perinatal deaths (Cleary 1998; Wiswell 1990). Hypoxia is the key factor that triggers gasping fetal respirations, which results in the aspiration of meconium. Most cases of MAS probably result from in utero aspiration rather than aspiration at the time of delivery. In addition to possibly contributing to respiratory distress in the neonate, MSAF has been associated with a higher risk of neonatal infection (Romero 1991). Chorioamnionitis is a risk factor for neonatal sepsis, which results in NICU admissions and potential fetal morbidity and death (Alexander 1999). Fetal microbial invasion has been proposed to cause inflammatory brain damage through the effects of elevated cytokines (e.g. TNF alpha, IL-1 beta, and IL-6) (Hoskins 1987).

Chorioamnionitis is also more likely to occur when MSAF is present (Mazor 1995; Romero 1991; Usta 2000). The risk of clinical chorioamnionitis and histological chorioamnionitis in patients with intrapartum MSAF is significantly higher than those with clear fluid. The risk for clinically diagnosed endometritis is two-fold (Markovitch 1993; Mazor 1995). Intrapartum chorioamnionitis is associated with dystocia and increased risk for operative delivery (Casey 1997; Mark 2000). Unrecognized or undertreated chorioamnionitis can lead to postpartum endomyometritis which can result in further maternal morbidity, and increased length of stay in hospital and hospital costs. MSAF is the risk factor for microbial invasion of the amniotic cavity in patients

with intact membranes and preterm labour (Romero 1991). Maternal infection is also more likely in the presence of MSAF. Patients with MSAF were almost two and a half times as likely to develop postoperative endometritis (Josephson 1984). There are statistically significant associations between MSAF and puerperal infection in term deliveries (Piper 1998). Puerperal infection rates are associated with the degree of meconium staining, with rates rising as meconium thickness increases (Tran 2003). There is a three-fold increase in positive amniotic fluid cultures in patients with MSAF compared to those with clear amniotic fluid (Mazor 1995; Romero 1991). The most common amniotic fluid isolates in MSAF are anaerobes, *Ureaplasma urealyticum*, *Streptococci*, *Escherichia coli*, *Candida albicans* and *Listeria monocytogenes* (Mazor 1995; Romero 1991).

Meconium may enhance the growth of bacteria in amniotic fluid by serving as a growth factor, inhibiting bacteriostatic properties of amniotic fluid, or antagonizing host defence systems, thus increasing the risk of chorioamnionitis. Generally, amniotic fluid is a poor culture medium for *Escherichia coli*, *Listeria monocytogenes* and *Staphylococcus aureus*; however, with enough meconium, amniotic fluid becomes an excellent culture medium (Florman 1969). Meconium may alter the zinc-to-phosphorous ratio in amniotic fluid and facilitate bacterial growth and decrease host defences (Hoskins 1987). Light and very light MSAF significantly impair mechanisms for intracellular microbial killing. Phagocytic ability of neutrophils was also significantly diminished in the presence of moderate MSAF (Clark 1995). Mechanisms of meconium associated puerperal infections include altering the antibacterial properties of amniotic fluid and enhancing bacterial growth, impairing the host immune response through the inhibition of phagocytosis and neutrophil oxidative burst (Clark 1995; Katz 1992).

Description of the intervention

One study has shown a significant reduction in the rate of clinical chorioamnionitis when the intervention ampicillin-sulbactam was administered prophylactically for the indication of MSAF (Edwards 1999).

How the intervention might work

Antibiotics can be bacteriostatic (they stop bacteria from multiplying) or bactericidal (they kill the bacteria). To perform either of these functions, antibiotics must be brought into contact with the bacteria. Antibiotics are thought to interfere with the surfactant of bacteria cells, causing a change in their ability to reproduce (Heizmann 2007). Gentamicin is an aminoglycoside antibiotic with bactericidal activity that acts at the 30S bacterial ribosomal subunit, inhibiting the synthesis of bacterial proteins (Ward 2008).

Why it is important to do this review

Cochrane reviews have addressed a number of issues about MAS including steroid therapy, endotracheal intubation, surfactant and antibiotics for neonates (Halliday 2001; Shivananda 2006; Ward 2003). Other interventions include amnioinfusion for MSAF in labour (Hofmeyr 2002). Prophylactic intravenous intrapartum ampicillin-sulbactam therapy or cefazolin infusion into the amniotic cavity during amnioinfusion in mothers with MSAF did not show any benefit in reducing chorioamnionitis, endometritis and neonatal sepsis (Adair 1996; Edwards 1999). However, the role of antibiotics for MSAF during labour has not been systematically evaluated.

OBJECTIVES

The objective of this review is to assess the efficacy and side effects of prophylactic antibiotics for meconium-stained amniotic fluid during labour in preventing maternal and neonatal infections.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomized controlled trials (RCTs) of prophylactic antibiotic administration during labour for women with MSAF. We excluded quasi-RCTs.

Types of participants

Pregnant women with a gestational age of more than 22 weeks who were in labour and had MSAF.

Types of interventions

Systemic prophylactic antibiotics started during labour in women with MSAF compared with no treatment or placebo.

Types of outcome measures

The primary outcomes were the most clinically important for the neonate, whereas the secondary outcomes also included maternal and neonatal complications.

Primary outcomes

1. Early onset neonatal sepsis (symptomatic before 72 hours of age).
 2. Late onset neonatal sepsis (symptomatic after 72 hours of age).
- (Definition of sepsis as defined by authors)

Secondary outcomes

Maternal

1. Intrapartum chorioamnionitis.
2. Postpartum endometritis.
3. Side effects of treatment, e.g. drug allergy, anaphylactic shock.
4. Drug resistance.

Neonatal

1. Mortality and morbidity prior to discharge, e.g. birth asphyxia, intracranial haemorrhage, intraventricular haemorrhage, necrotizing enterocolitis and admission to neonatal intensive care unit.
2. Duration of mechanical ventilation (days).
3. Duration of admission to neonatal intensive care unit/hospital.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (30 September 2010).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Thitiporn Siriwachirachai (TS) and Ussanee Sangkomkamhang (US) independently assessed trials for inclusion and methodological quality. There were no disagreements.

Data extraction and management

We designed a form to extract data. For eligible studies, TS and US independently extracted the data using the agreed form. There were no discrepancies. We entered the data into Review Manager software ([RevMan 2008](#)) and checked for accuracy. We did not contact the original study authors because the reported information was sufficient in the report.

Assessment of risk of bias in included studies

TS and US independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2009](#)).

(1) Sequence generation (checking for possible selection bias)

We described for included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- adequate (any truly random process, e.g. random number table; computer random number generator);
- inadequate (any non random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear.

(2) Allocation concealment (checking for possible selection bias)

We described for included study the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- adequate (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear.

(3) Blinding (checking for possible performance bias)

We described for included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We judged studies at low risk of bias if they were blinded, or if we judged that the lack of blinding could not have affected the results. We assessed blinding separately for different outcomes or classes of outcomes. We assessed the methods as:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors;

where 'adequate' is when there was blinding or where we assess that the outcome or the outcome measurement is not likely to have been influenced by lack of blinding.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We described for included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, we assessed methods as:

- adequate;
- inadequate;
- unclear.

We discussed whether missing data greater than 20% might (a) be reasonably expected (acknowledging that complete data are difficult to attain), and (b) impact on outcomes.

(5) Selective reporting bias

We described for the included trial how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- adequate (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely

and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);

- unclear.

(6) Other sources of bias

We described for the included study any important concerns we have about other possible sources of bias. We assessed whether study was free of other problems that could put it at risk of bias:

- yes;
- no;
- unclear.

(7) Overall risk of bias

We made explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We did not explore the impact of the level of bias through undertaking sensitivity analyses because we included only one study.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratios (RR) with 95% confidence intervals (CIs) .

Continuous data

For continuous data, we used the mean difference if outcomes were measured in the same way between trials. We used the standardized mean difference to combine trials that measure the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomized trials

We included only one RCTs. In future updates, if we identify cluster-randomized trials, we will include these in the analyses along with individually randomized trials. We will adjust their sample sizes using the methods described in the *Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population (Higgins 2009). If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both

cluster-randomized trials and individually-randomized trials, we plan to synthesize the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and we consider the interaction between the effect of intervention and the choice of randomization unit to be unlikely.

We will also acknowledge heterogeneity in the randomization unit and perform a subgroup analysis to investigate the effects of the randomization unit.

Dealing with missing data

For the included study, we noted levels of attrition. We explored the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we have carried out analyses, as far as possible, on an intention-to-treat basis; i.e. we attempted to include all participants randomized to each group in the analyses, and analyze all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial is the number randomized minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

This review did not include meta-analysis. In future updates, as more data become available, we will assess statistical heterogeneity in each meta-analysis using the T^2 , I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if T^2 is greater than zero and either I^2 is greater than 30% or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

In subsequent updates of this review, if there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry. For continuous outcomes we will use the test proposed by Egger 1997, and for dichotomous outcomes we will use the test proposed by Harbord 2006. If asymmetry is detected in any of these tests or is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2008). This review only included one RCT so we did not pool any data. In future updates, if more data become available, we will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the

same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials is considered clinically meaningful. We will treat the random-effects summary as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful we will not combine trials.

If we use random-effects analyses, we will present the results as the average treatment effect with its 95% confidence interval, and the estimates of T^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

In future updates of this review, when sufficient data become available, we plan to carry out the following subgroup analyses:

1. intact versus rupture membrane;
2. single versus combine antibiotic regimens;
3. duration of antibiotics less than 24 hours versus more than 24 hours.

We will use the following outcomes in subgroup analysis:

- early onset neonatal sepsis (symptomatic before 72 hours of age);
- late onset neonatal sepsis (symptomatic after 72 hours of age).

For fixed-effect inverse variance meta-analyses we will assess differences between subgroups by interaction tests. For random-effects and fixed-effect meta-analyses using methods other than inverse variance, we will assess differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis

In subsequent updates we also plan to conduct a sensitivity analysis comparing the results using all studies and using only those of high methodological quality.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

We identified four publications as potentially eligible for inclusion in this review.

Excluded studies

We assessed and excluded two retrospective cohort studies (Adair 1998; Edwards 1999) and one conference abstract (Adair 1999); see Characteristics of excluded studies.

Included studies

This review includes one RCT (Adair 1996) in which 120 pregnancies were randomized and analyzed; see Characteristics of included studies.

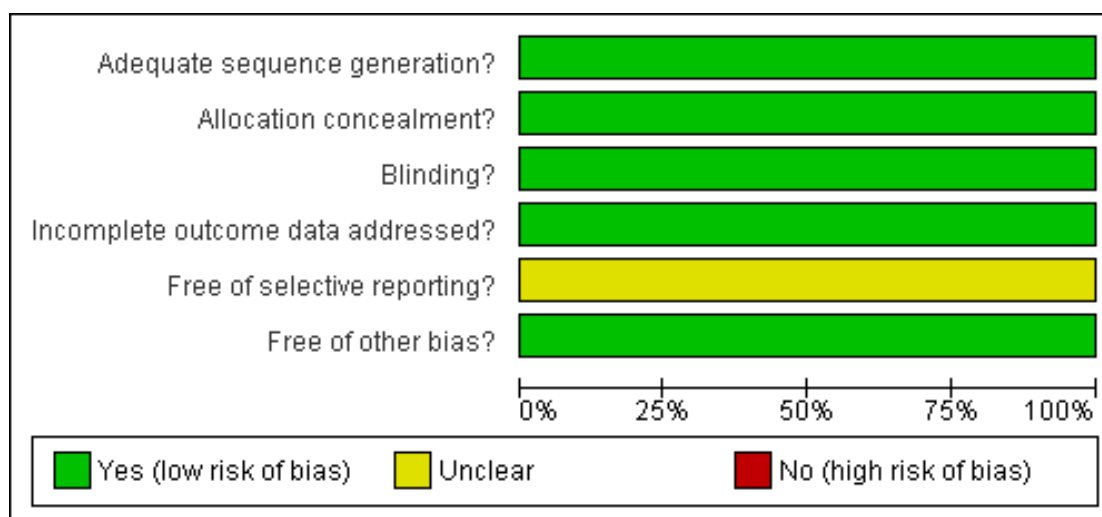
Risk of bias in included studies

We have summarized the risk of bias of the included study (Adair 1996) in Figure 1 and Figure 2. We classified it as a trial with low risk of bias because it had 'clear' allocation concealment, blinding and no withdrawal.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

The trial reported clear information of allocation concealment. The randomization schedule was generated and kept in an area away from the clinical area and was unavailable to caregivers (Adair 1996).

Blinding

Participants and all caregivers were thoroughly blinded until the study was completed. Interventions were identically prepared in 100 ml fluid bags and issued by one of two research nurses, independent to the trial investigators. The outcome assessors were also blinded to the randomization status.

Incomplete outcome data

No withdrawals occurred and analysis could be done based on intention-to-treat basis.

Selective reporting

We do not have access to this study protocol; therefore we could not evaluate this risk of bias..

Other potential sources of bias

None.

Effects of interventions

Results are based on one RCT (120 pregnancies/120 newborns).

Antibiotic versus placebo

Primary outcomes

There was no significant reduction in the incidence of neonatal sepsis (RR 1.00, 95% CI 0.21 to 4.76), see Analysis 1.1. The authors (Adair 1996) did not report their results in terms of early and late onset neonatal sepsis.

Secondary outcomes

There was a significant reduction in the incidence of chorioamnionitis in the ampicillin-sulbactam group compared with placebo (RR 0.29, 95% CI 0.10 to 0.82), see Analysis 1.2. There was no significant reduction in the incidence of endometritis (RR 0.50, 95% CI 0.18 to 1.38), see Analysis 1.3 or neonatal intensive care unit admission (RR 0.83, 95% CI 0.39 to 1.78), see Analysis 1.4. No serious adverse effects were reported.

DISCUSSION

Summary of main results

There was a significant reduction in the incidence of chorioamnionitis in mothers who received ampicillin-sulbactam compared to placebo. Neonatal sepsis was not differentiated into 'early' or 'late' onset but there was no difference in the incidence of neonatal sepsis between the two groups. Endometritis was not statistically reduced. There was no information about adverse effects.

Overall completeness and applicability of evidence

Only one RCT from a developed country was found by this review and it did not report the primary outcome 'neonatal sepsis' in terms of early or late onset. The evidence may be insufficient to evaluate the efficacy and side effects of prophylactic antibiotics for meconium-stained amniotic fluid in labour for preventing neonatal sepsis.

Quality of the evidence

The included trial is of high methodological quality based on adequate random allocation concealment. However, the sample size was not adequate to make any firm conclusion.

Potential biases in the review process

We followed the process of review as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* Higgins 2009. We also did an exhaustive search which included many clinical trial registries.

Agreements and disagreements with other studies or reviews

There are no other reviews and studies related to the efficacy and side effects of prophylactic antibiotics for MSAF during labour in preventing maternal and neonatal infections.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to support the use of prophylactic antibiotics in women with MSAF during labour because the rates of neonatal sepsis were not different in the two groups.

Implications for research

This systematic review has identified the need for more well-designed, adequately powered RCTs to assess the benefits and harms of antibiotic prophylactic in MSAF during labour for preventing neonatal sepsis. The trials should include clinical outcomes of neonatal sepsis.

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As part of the pre-publication editorial process, this review has been commented on by two peers (an editor and referee who is external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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Ward K, Theiler RN. Once-daily dosing of gentamicin in obstetrics and gynecology. *Clinical Obstetrics and Gynecology* 2008;**51**(3): 498–506.
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Wiswell TE, Tuggle JM, Tumer BS. Meconium aspiration syndrome: have we made a difference?. *Pediatrics* 1990;**85**:715–21.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Adair 1996

Methods	Randomized trial with allocation concealment using computer-generated randomization list. All participants, caregivers and outcome assessors were blinded to the treatment regimen.	
Participants	Intervention group: 60 pregnant women (mean age 24.5, SD 6.3) with gestational age more than 24 weeks (mean 39.8, SD 1.0). Control group: 60 pregnant women (mean age 25.9, SD 6.3), (mean gestational age 39.9, SD 1.2). Inclusion criteria: gestational age more than 24 weeks with MSAF complicating the intrapartum. Exclusion criteria: patients with penicillin and/or cephalosporin allergy, evidence of active infection, presence of intrauterine death, GA < 24 weeks, or history of antibiotics use in 7 days. Location: North Carolina, United States.	
Interventions	Intervention: ampicillin-sulbactam 3.0 g intravenous prepared in 100 ml fluid bags, and was repeated every 6 hours until delivery. Control: normal saline infused as an IV bolus.	
Outcomes	Mother Chorioamnionitis. Postpartum endometritis. Neonatal Number of NICU admissions. Incidence of sepsis (not defined), and adverse outcomes including enterocolitis and respiratory distress.	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomization was performed by a computer-generated list.
Allocation concealment?	Yes	Adequate: there was randomization by computer-generated list and both IV preparations were prepared by 1 of 2 research nurses who were not involved in this study.

Adair 1996 (Continued)

Blinding? All outcomes	Yes	Adequate: there was blinding of participants, caregivers and outcome assessor.
Incomplete outcome data addressed? All outcomes	Yes	Adequate: there was no withdrawal.
Free of selective reporting?	Unclear	Unclear, because we don't have access to this trial's outcomes.
Free of other bias?	Yes	Study appeared to be free of other sources.

GA: gestational age

IV: intravenous

MSAF: meconium-stained amniotic fluid

NICU: neonatal intensive care unit

RCT: randomized controlled trial

SD: standard deviation

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Adair 1998	Not a RCT, this was a retrospective cohort study.
Adair 1999	This is a conference abstract.
Edwards 1999	Intervention not of interest to systematic review, it is not systematic prophylactic antibiotics.

RCT: randomized controlled trial

DATA AND ANALYSES

Comparison 1. Antibiotic versus placebo

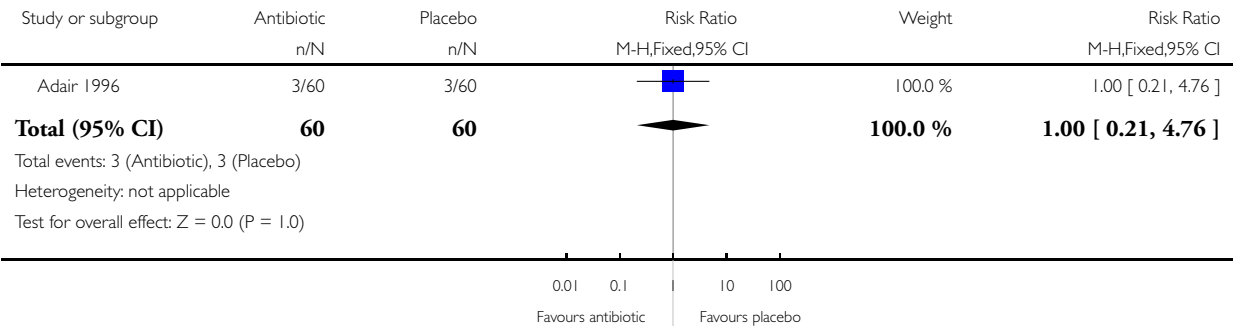
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal sepsis	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.21, 4.76]
2 Chorioamnionitis	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.10, 0.82]
3 Postpartum endometritis	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.18, 1.38]
4 Neonatal intensive care admissions	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.39, 1.78]

Analysis 1.1. Comparison 1 Antibiotic versus placebo, Outcome 1 Neonatal sepsis.

Review: Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections

Comparison: 1 Antibiotic versus placebo

Outcome: 1 Neonatal sepsis

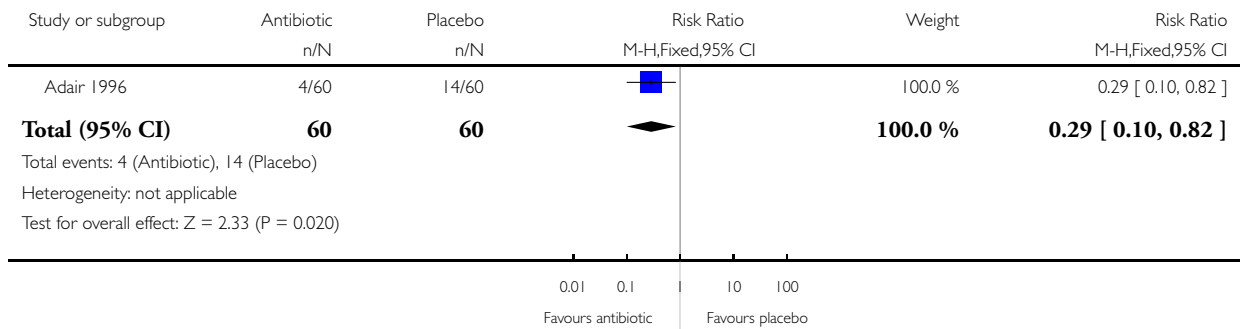


Analysis 1.2. Comparison 1 Antibiotic versus placebo, Outcome 2 Chorioamnionitis.

Review: Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections

Comparison: 1 Antibiotic versus placebo

Outcome: 2 Chorioamnionitis

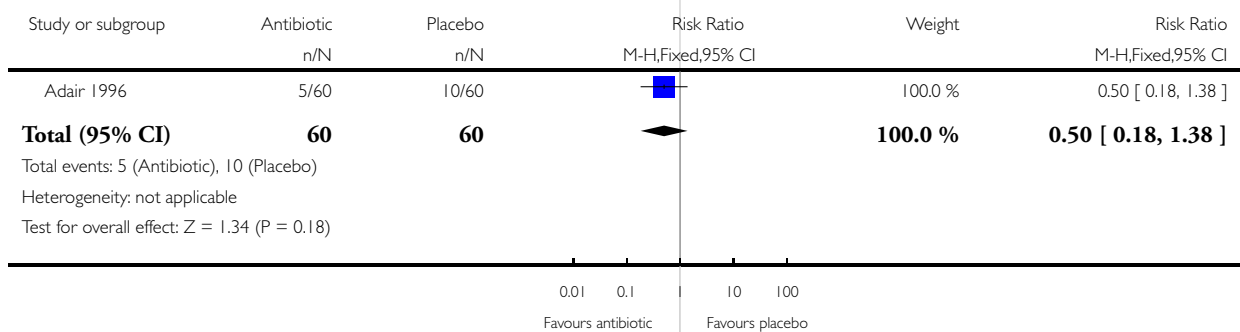


Analysis 1.3. Comparison 1 Antibiotic versus placebo, Outcome 3 Postpartum endometritis.

Review: Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections

Comparison: 1 Antibiotic versus placebo

Outcome: 3 Postpartum endometritis

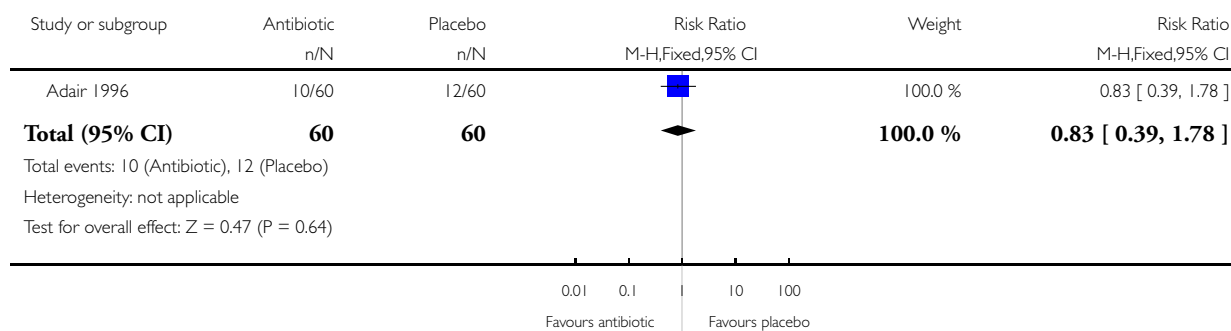


Analysis 1.4. Comparison 1 Antibiotic versus placebo, Outcome 4 Neonatal intensive care admissions.

Review: Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections

Comparison: 1 Antibiotic versus placebo

Outcome: 4 Neonatal intensive care admissions



HISTORY

Protocol first published: Issue 2, 2009

Review first published: Issue 12, 2010

CONTRIBUTIONS OF AUTHORS

Thitiporn Siriwachirachai and Ussanee Sangkomkamhang drafted the review, Pisake Lumbiganon and Malinee Laopaiboon revised and approved the final version of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Khon Kaen Hospital, Ministry of Public Health, Thailand.
- Faculty of Medicine, Khon Kaen University, Thailand.
- Faculty of Public Health, Khon Kaen University, Thailand.

External sources

- Thailand Research Fund, Senior Research Scholar, Thailand.
- Thai Cochrane Network, Thailand.

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ภาคผนวกที่ 3

มีนักวิจัยเข้าร่วมในโครงการจำนวน 43 คน จาก 11 สถาบัน

23. อ.เพชรา งามจิรัส	อาจารย์	ภาควิชาชีวิตวิถี คณะสาธารณสุขศาสตร์ มข.	ผู้ร่วมวิจัย	อาจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
24. อ.พอใจ ภักธนิตย์ธรรม	อาจารย์	ภาควิชาชีวิตวิถี คณะสาธารณสุขศาสตร์ มข.	ผู้ร่วมวิจัย	อาจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
25. รศ.เบญจา มุกตพันธ์	รองศาสตราจารย์	ภาควิชาโภชนาการ คณะสาธารณสุขศาสตร์ มข.	ผู้ร่วมวิจัย	รองศาสตราจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
26. พญ.ศิริวรรณ ตั้งจิตมด	แพทย์หญิง	วิทยาลัยแพทยศาสตร์ศรีนครินทร์	ผู้ร่วมวิจัย	แพทย์หญิง	วิทยาลัยแพทยศาสตร์ศรีนครินทร์	ยังอยู่ในโครงการ
27. รศ.พญ.ศฤงคาร วัลลภกมล	รองศาสตราจารย์	ภาควิชาสูติศาสตร์ โรงพยาบาลรามาธิบดี	ผู้ร่วมวิจัย	รองศาสตราจารย์	มหาวิทยาลัยมหิดล	ยังอยู่ในโครงการ
28. พญ.สุนิสา ถัดรมงคลชาติ	แพทย์หญิง	ภาควิชาสูติศาสตร์ คณะแพทยศาสตร์ มอ.	ผู้ร่วมวิจัย	แพทย์หญิง	มหาวิทยาลัยสงขลานครินทร์	ยังอยู่ในโครงการ
29. ศศ.สุหทัยา บุญมาก	ผู้ช่วยศาสตราจารย์	ภาควิชาชีวิตวิถี คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	ผู้ช่วยศาสตราจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
30. ศศ. พิชรี คำวิสัยศักดิ์	ผู้ช่วยศาสตราจารย์	ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	ผู้ช่วยศาสตราจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
31. นพ.บรรพจน์ สุวรรณชาติ	นายแพทย์	กลุ่มงานสูติศาสตร์และนรีเวชกรรม โรงพยาบาลกาฬสินธุ์	ผู้ร่วมวิจัย	นายแพทย์	โรงพยาบาลกาฬสินธุ์	ยังอยู่ในโครงการ
32. พญ.บุษรินทร์ เทียนมน	พยาบาล	กลุ่มงานสูติศาสตร์และนรีเวชกรรม โรงพยาบาลกาฬสินธุ์	ผู้ร่วมวิจัย	พยาบาล	โรงพยาบาลกาฬสินธุ์	ยังอยู่ในโครงการ
33. นพ.ธีรวิทย์ ชื่นประกอบ	นายแพทย์	กลุ่มงานสูติศาสตร์และนรีเวชกรรม โรงพยาบาลขอนแก่น	ผู้ร่วมวิจัย	นายแพทย์	โรงพยาบาลขอนแก่น	ยังอยู่ในโครงการ
34. นพ.อรรถสิทธิ์ ศรีสุบัติ	นายแพทย์	สำนักพัฒนาวิชาการแพทย์ กรมการแพทย์ กระทรวงสาธารณสุข	ผู้ร่วมวิจัย	นายแพทย์	กระทรวงสาธารณสุข	ยังอยู่ในโครงการ
35. พญ. เกศนี บุญวัฒนาขกุล	พยาบาลชำนาญการ	โรงพยาบาลศรีนครินทร์ คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	พยาบาลชำนาญการ	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
36. พญ.จิตติพร สิริวิรัชย์	พยาบาลชำนาญการ	กลุ่มงานสูติศาสตร์และนรีเวชกรรม โรงพยาบาลขอนแก่น	ผู้ร่วมวิจัย	พยาบาลชำนาญการ	โรงพยาบาลขอนแก่น	ยังอยู่ในโครงการ
37. พญ.รัตนา คำวิสัยศักดิ์	พยาบาล	ภาควิชาสูติศาสตร์ คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	พยาบาล	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
38. ทพญ. มุขดา ศิริเทพทวี	รองศาสตราจารย์	ภาควิชาวินิจฉัยโรคช่องปาก คณะทันตแพทยศาสตร์	ผู้ร่วมวิจัย	รองศาสตราจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
39. นพ.ธนินิตย์ สังคมคำแหง	นายแพทย์	ภาควิชาอโศกวิทยา โรงพยาบาลขอนแก่น	ผู้ร่วมวิจัย	นายแพทย์	โรงพยาบาลขอนแก่น	ยังอยู่ในโครงการ

หมายเหตุ

ให้ใส่รายละเอียดที่อยู่ต้นสังกัด เช่น ภาควิชา / คณะ / มหาวิทยาลัย

สำนักงานปัจจุบัน

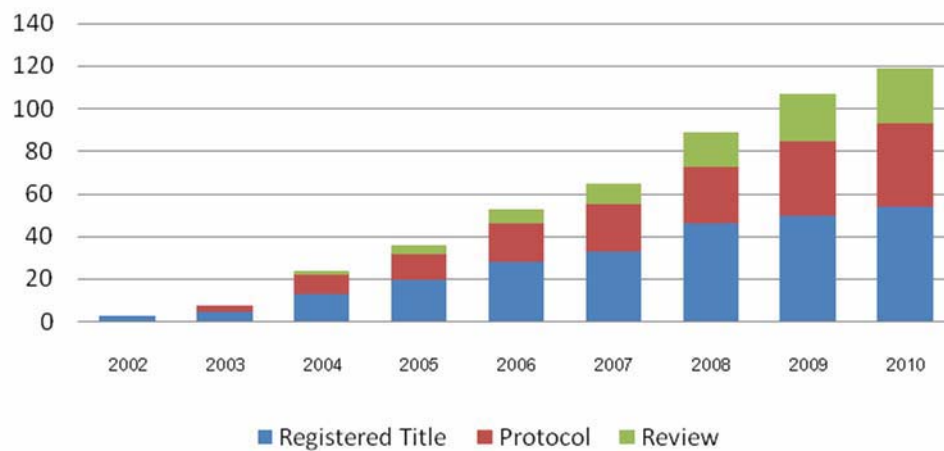
- ยังอยู่ในโครงการหรือไม่ หากไม่อยู่ในโครงการแล้ว ให้ระบุหน่วยงานใหม่ด้วย

- หากเริ่มเข้าโครงการเป็นนักศึกษาริทยุทธศาสตร์ ให้ระบุปีปัจจุบันสำเร็จการศึกษาหรือไม่สำเร็จการศึกษา

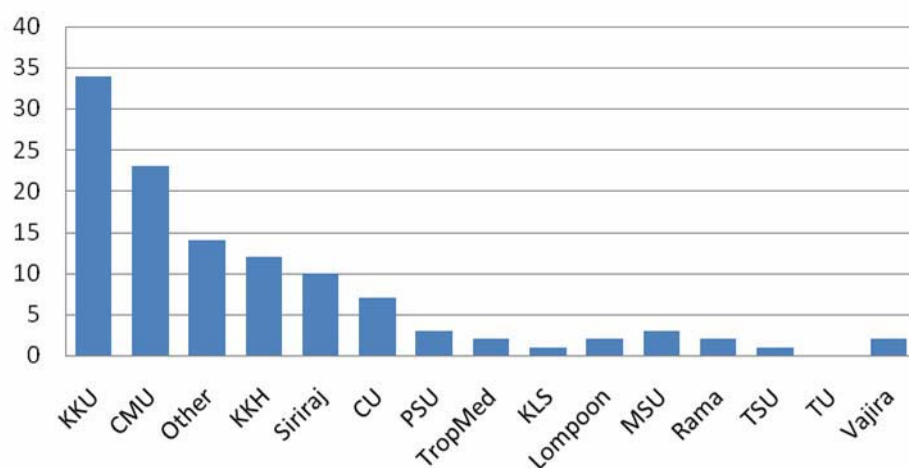
ภาคผนวกที่ 4

ประเทศไทยมีโครงการวิจัยเชิงสังเคราะห์ที่ทำร่วมกับ
Cochrane Collaboration มากขึ้นอย่างรวดเร็วและปัจจุบันเป็นอันดับ
ที่ 3 ใน Asia รองจากจีน และอินเดีย

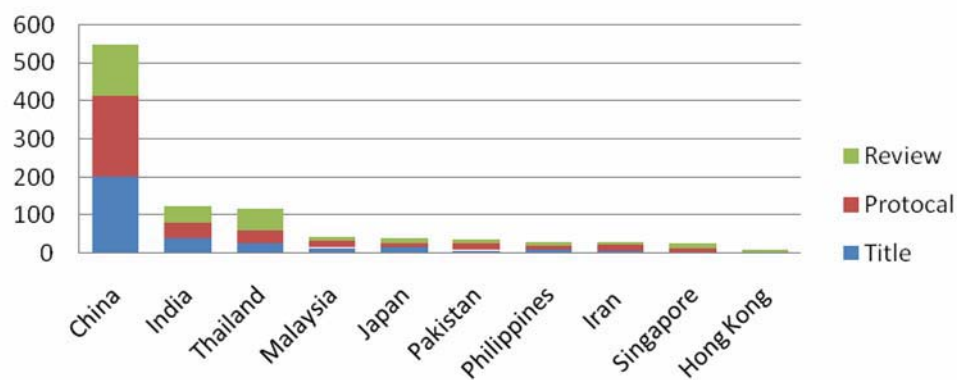
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Cochrane systematic reviews by the first 10 Asian countries



ภาคผนวกที่ 5

ตีพิมพ์ Protocols for Cochrane reviews ใน Cochrane
Library จำนวน 9 เรื่อง

Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes (Protocol)

Buppasiri P, Lumbiganon P, Thinkhamrop J, Ngamjarus C



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[Intervention Protocol]

Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

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Editorial group: Cochrane Pregnancy and Childbirth Group.

Publication status and date: New, published in Issue 2, 2008.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To determine the effect of calcium supplementation on maternal, fetal and neonatal outcome as well as on possible side effects (other than for preventing or treating hypertension).

BACKGROUND

Calcium metabolism

Calcium is an essential mineral for many of the body's processes (Trichopoulos 1990). Calcium is a key and important intracellular component for maintaining cell membranes in nerve, muscle contraction, enzyme and hormone actions. Bone formation is also dependent on calcium levels. Maternal nutrition during pregnancy is known to have a significant effect on fetal growth and development (Luke 1994; Susser 1991). Pregnancy and lactation are the periods when the mother needs to consume a great amount of calcium (Cross 1995; Prentice 1995; Ritchie 1998). Calcium is transported to the fetus by an active transport process across the placenta. The mother has to maintain her calcium levels to keep normal balance and reduce the risk of osteoporosis in later life (Bonner 1994). The fetus needs calcium for skeletal development as well (Thomas 2006). During pregnancy and lactation, maternal bone mineral density (BMD) decreases in multiple sites of body such as the lumbar spine, femoral neck, total hip, and radius wrist. After weaning this is relatively quickly reversed (Cross 1995; Kalkwarf 1997; Laskey 1999; Prentice 1995; Sowers 1993; Sowers 1995). Inadequate intake of calcium may harm both mother and her fetus. Risks include osteopenia, osteoporosis, tremor, paresthesia, muscle cramp, tetany, delayed fetal growth, low birth weight, and poor fetal mineralization (Inzucchi 1999; Koo 1999). Recommendation for calcium intake during pregnancy and lactation differ around the world from 600 to 1425 mg per day, 400 to 600 mg per day higher than nonpregnant or nonlactating women (Prentice 1994; Prentice 1995). A breastfeeding mother secretes 200 mg calcium into breast milk every day (Prentice 1995).

Calcium supplementation

Calcium supplementation to the daily diet has been recommended to meet the body's demands during pregnancy and lactation to benefit the mother and fetus. The recommended dosages in the literature vary from 300 to 2000 mg/d of elemental calcium (Jarjou 2006; Kalkwarf 1997; Prentice 1995; Villar 1990). Providing extra calcium tablets is attractive because it is cheap, readily available with few side effects, such as difficult swallowing, increase in urinary stones, increase in urinary tract infection, and reduced absorption of other minerals such as iron, zinc and magnesium that could harm the pregnant women (Hallberg 1992).

Current approach to calcium supplementation

Currently, there is no consensus on the role of routine calcium supplementation for pregnant women. Extra calcium tablets are not routinely prescribed for pregnant women because the real benefit is still questionable. In a recent Cochrane meta-analysis of calcium

supplementation for hypertension, a significant beneficial effect in reducing the risk of pregnancy-induced hypertension was found (Hofmeyr 2006). For maternal bone mineral density and fetal mineralization, there is still conflicting data. Many studies show that fetal femur length, fetal weight and fetal mineralization are significantly better in calcium-supplemented mothers (Chang 2003; Chan 2006; Janakiraman 2003; Merialdi 2003; Raman 1978). This is in contrast with other studies that suggest that calcium supplementation has no additional effects (Jarjou 2006; Prentice 1995). The effectiveness of calcium supplementation in reducing preterm birth is also uncertain; some studies show a protective effect (Carroli 1994; Villar 1990) while others do not (Belizan 1991; Lopez-Jaramillo 1989; Villar 1998). Leg cramps are the most common symptom of calcium deficiency, particularly in pregnant women (Hammar 1981). The role of calcium supplementation in reducing leg cramps remains unclear (Hammar 1981; Hammar 1987; Young 2002). Possible explanations for differences in the results of these studies include differences in baseline calcium intake, socioeconomic status, dosage and duration of calcium supplementation, etc.

There is need for a systematic review to evaluate the effectiveness of calcium supplementation during pregnancy for improving maternal, fetal and neonatal outcomes other than preventing or treating hypertension because of the varying results reported in the literature.

OBJECTIVES

To determine the effect of calcium supplementation on maternal, fetal and neonatal outcome as well as on possible side effects (other than for preventing or treating hypertension).

METHODS

Criteria for considering studies for this review

Types of studies

All published, unpublished and ongoing simple and cluster-randomized controlled trials comparing maternal, fetal, and neonatal outcomes in calcium supplementation versus placebo or no treatment in pregnant women. We will include studies reported only in abstract form in the "Studies awaiting classification" category and will include them in the analysis when they are published as full reports. We will exclude quasi- and pseudo-randomized controlled trials.

Types of participants

Pregnant women who received any calcium supplementation compared with placebo or no treatment.

Types of interventions

Calcium supplementation during pregnancy and placebo or no treatment.

Types of outcome measures

Primary outcomes

Maternal outcomes

1. Preterm delivery
- (a) Birth prior to 37 weeks
- (b) Birth prior to 34 weeks

Infant outcomes

1. Low birth weight (< 2,500 gm)

Secondary outcomes

Maternal outcomes

1. Maternal weight gain
2. Maternal bone mineral density (BMD)
3. Leg cramps
4. Backache
5. Tetany (muscle spasm and twitching)
6. Osteopenia
7. Osteoporosis
8. Incidence of fracture
9. Duration of breastfeeding
10. Tremor
11. Paresthesia
12. Mother need to admit intensive care unit
13. Maternal death

Fetal and neonatal outcomes

1. Stillbirth
2. Fetal death
3. Neonatal death
4. Perinatal mortality
5. Admission to neonatal intensive care unit
6. Birth weight
7. Birth length
8. Head circumference
9. Intrauterine growth restriction

10. Neonatal BMD
11. Osteopenia
12. Limb pain
13. Ricket
14. Fracture

Adverse outcomes

1. Side effects of calcium supplementation
2. Compliance
3. Satisfaction
4. Urinary stones
5. Urinary tract infection
6. Nephrocalcinosis
7. Impair renal function
8. Maternal anemia

Search methods for identification of studies

Electronic searches

We will contact the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register. The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We will not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors (P Buppasiri (PB) and J Thinkhamrop (JT)) will independently assess for inclusion all potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or by involving the third review author (P Lumbiganon (PL)). The fourth review author (C Ngamjarus (CN)) will be responsible for the planning of the data analysis.

Assessment of methodological quality of included studies

Two review authors (PB and JT) will assess the validity of each study independently using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2006). We will use only the criteria of selection bias and detection bias that are feasible for our review. Methods used for generation of the randomisation sequence will be described for each trial.

(1) Selection bias (randomisation and allocation concealment)

We will assign a quality score for each trial, using the following criteria:

- (A) adequate concealment of allocation: such as telephone randomisation, consecutively numbered, sealed opaque envelopes;
- (B) unclear whether adequate concealment of allocation: such as list or table used, sealed envelopes, or study does not report any concealment approach;
- (C) inadequate concealment of allocation: such as open list of random-number tables, use of case record numbers, dates of birth or days of the week.

(2) Attribution bias (loss of participants, eg, withdrawal, dropouts, protocol deviation)

We will assess completeness to follow up using the following criteria:

- (A) less than 5% loss of participants;
- (B) 5% to 9.9 % loss of participants;
- (C) 10% to 19.9 loss of participants;
- (D) more than 20% loss of participants.

(3) Performance bias (blinding of participants, researchers and outcome assessment)

We will assess blinding using the following criteria:

1. blinding of participants (yes /no /unclear);
2. blinding of caregiver (yes /no /unclear);
3. blinding of outcome assessment (yes/no /unclear).

Data extraction and management

We will adapt the Cochrane Pregnancy and Childbirth Group's data extraction form template to extract data. At least two review authors will extract the data using the agreed form. We will resolve

discrepancies through discussion. We will use the Review Manager software (RevMan 2007) to double enter all the data or a subsample.

When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually randomised trials. Their sample sizes will be adjusted using the methods described in Gates 2005 using an estimate of the intraclass correlation co-efficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources are used, this will be reported and sensitivity analyses conducted to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a separate meta-analysis. Therefore, the meta-analysis will be performed in two parts as well.

Data analysis

Measures of treatment effect

We will compare categorical data using relative risks and their 95% confidence intervals. For continuous data, we will calculate mean difference with 95% confidence intervals (CI) if the outcomes are measured in the same way among trials. We will use the standardized mean difference to combine trials that measure the same outcome, but use different methods. We will test for statistical heterogeneity between trials using the I-squared statistic, with values greater than 50% indicating significant heterogeneity. In the absence of significant heterogeneity, we will pool data using a fixed-effect model. If there is significant heterogeneity, a random-effects model will be used and an attempt made to identify potential sources of heterogeneity based on subgroup analyses by baseline dietary calcium intake.

Dealing with missing data

We will analyse data on all participants with available data in the group to which they are allocated, regardless of whether or not they received the allocated intervention. If in the original reports participants are not analysed in the group to which they were

randomised, and there is sufficient information in the trial report, we will attempt to restore them to the correct group.

Assessment of publication bias

Where sufficient trials are included, we will consider publication bias using funnel plots of between-treatment effect and its precision on individual trials. If we find asymmetry funnel plots with statistical publication bias, we will further examine the effect of the bias on the meta-analysis conclusion using sensitivity analyses.

Sensitivity analyses

We will carry out sensitivity analyses to explore the effect of trial quality. The trial quality will involve an analysis based on concealment of allocation. Trials with clearly inadequate allocation of concealment will be excluded in order to assess for any substantive difference to the overall result.

Subgroup analyses

We will conduct the following subgroup analysis:

1. Total dose per day of calcium supplementation: high/low ($< 1,000$ and $\geq 1,000$ mg).
2. Time of supplementation taken from: first half of pregnancy (< 20 weeks); and second half of pregnancy (≥ 20 weeks).
3. Type of calcium supplementation preparation: calcium carbonate, lactate, gluconate.

ACKNOWLEDGEMENTS

The authors would like to thank Professor Caroline Crowther, Phillippa Middleton, Ruth Martis and the SEA-ORCHID project for supporting a fellowship for PB enabling her to complete this systematic review.

As part of the pre-publication editorial process, this protocol has been commented on by three peers (an editor and two referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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- * Indicates the major publication for the study

HISTORY

Protocol first published: Issue 2, 2008

CONTRIBUTIONS OF AUTHORS

P Buppasiri developed the protocol.

P Lumbiganon and J Thinkhamrop edited and commented on the protocol.

C Ngamjarus commented on the protocol.

DECLARATIONS OF INTEREST

None known.

Interventions for preventing excessive weight gain during pregnancy (Protocol)

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[Intervention Protocol]

Interventions for preventing excessive weight gain during pregnancy

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the effectiveness of interventions for preventing excessive weight gain during pregnancy.

BACKGROUND

Appropriate gestational weight gain may be important for achieving healthy pregnancies and deliveries, and birth outcomes, as well as long-term health for childbearing women.

In 1990, the Institute of Medicine (IOM) in the United States advised underweight women (body mass index (BMI) less than 19.8 kg/m²) to gain 12.5 to 18 kg and normal weight women (BMI 19.8 to 25.9 kg/m²) to gain 11.5 to 16.0 kg; whereas overweight women (BMI 26 to 29 kg/m²) were advised to gain between 7 to 11.5 kg and obese women (BMI at least 30 kg/m²) to gain approximately 7 kg with no upper limit proposed (Medicine 1990). These guidelines were widely adopted but not universally accepted. However, a substantial review examined fetal and maternal outcomes according to the IOM's weight-gain recommendations in women with a normal prepregnancy weight (Abrams 2000). These studies showed that pregnancy weight gain within the IOM's recommended ranges is associated with the best outcome for both mothers and infants. Abrams 2000 also stated that there was no published scientific evidence to support the concept that weight gain within the IOM's recommended ranges is harmful for either mothers or their infants.

Different countries have differing recommendations on weight gain. There are currently no official recommendations for weight gain during pregnancy in the UK. The UK also does not have clinical guidelines for gestational weight gain. It is the responsibility of health professionals such as general practitioners, midwives and obstetricians to monitor normal pregnancies by preventing abnormal weight gain, yet typically in the UK, women are weighed only once, i.e. at the antenatal booking appointment, which is primarily undertaken for the interpretation of screening tests (Ford 2001). Recently, gestational weight gain limits for BMI categories based on significant risk estimates of adverse maternal and fetal outcome determined by a large population-based cohort study was published from Swedish Medical Registers. The optimal gestational weight gain in Swedish women was 4 to 10 kg for BMI less than 20; 5 and 2 to 10 kg for BMI 20 to 24.9. For women with a BMI of 25 to 29.9, a weight gain of less than 9 kg was recommended and pregnant women with a BMI of 30 or more were recommended to gain less than 6 kg in weight (Cedergren 2007). Pregnant Asian women in general had lower weight gains (Abrams 1995; Siega-Riz 1993). Hence, maternal weight gain recommendations based on data compiled from white women may be not applicable to Asian females. A study to produce ethnic-specific maternal weight gain recommendations was performed in China. A maternal weight gain chart and recommendations for the total weight gain of Chinese women were derived from the distribution of weight gained in women with a good pregnancy outcome. The recommended total weight gain was 13 to 16.7 kg, 11 to 16.4 kg, and 7.1 to 14.4 kg respectively for women of low (BMI less than 19), moderate (BMI 19 to 23.5), and high (BMI greater than 23.5) BMI. Women who did not achieve the lower quartile range had more than twice the risk of having a low-birth-

weight infant. Those with excessive weight gain were at risk of needing an assisted delivery (Wong 2000).

Although the IOM guidelines have been promoted for over a decade, only 30% to 40% of pregnant women in the United States gain gestational weight within the IOM recommended ranges (Abrams 2000; Cogswell 1999; Medicine 1990; Olson 2003). Furthermore, gestational weight gain above the guidelines is more common than gestational weight gain below (Stotland 2006). Several studies on gestational weight gain in the USA and Europe indicate that about 20% to 40% of women are gaining weight above the recommendations (Cedergren 2006; Medicine 1990; Olson 2003) and the prevalence of excessive gestational weight gain is increasing (Abrams 2000; Rhodes 2003; Schieve 1998). In an investigation of over 120,000 women enrolled in women, infants, and children (WIC) clinics over a six-year period (from 1990 to 1996), Schieve 1998 found that the percentage of women reporting a pregnancy weight gain greater than the IOM recommendation significantly increased from 41.5% to 43.7%. Two studies examined trends in excess gestational weight gain which was classified by using upper limits of the IOM recommendations (more than 18 kg) due to lack of prepregnancy BMI data. A study by Rhodes 2003, examining trends in excess gestational weight gain (more than 18 kg) by analysing US Natality Files of birth certificate data, found that between 1990 and 2000, excess weight gain (more than 18 kg) rose steadily from 18.6% to 24.2%. A retrospective cohort study was undertaken to examine the trend in weight gain during pregnancy of 1,463,936 women over 16 years in North Carolina and found that the proportion of women gaining excessive gestational weight (more than 18 kg) increased from 15.5% in 1988 to 19.5% in 2003; an additional 40 women per 1000 gained excessive weight by 2003 (Helms 2006).

Several studies indicated that the incidence of weight gain during pregnancy varied by prepregnancy weight category. Obese women tend to gain the least weight and normal weight women tend to gain the most weight (Abrams 1989; Bianco 1998; Edwards 1996; Walling 2006). Two large population-based studies in the United States and in Sweden reported similar findings. They found that approximately 30% of average and overweight women had high gestational weight gain, whereas approximately 20% of obese women had high gestational weight gain (Cedergren 2006; Cogswell 1995). A descriptive study of over 4000 pregnant women from the University of California, San Francisco Perinatal Database, found that total gestational weight gain exceeded the guidelines for 23% of the underweight women, 49% of the normal-weight women, 70% of the overweight women, and 57% of the obese women (Carmichael 1997). Similarly, in a prospective cohort study of 622 women in prenatal care in a 10-county area of upstate New York, 11% of underweight women, 37% of normal-weight women, 70% of overweight women, and 41% of obese women exceeded the weight gain recommendations (Olson

2003).

It is well known that excessive weight gain during pregnancy is associated with multiple maternal and neonatal complications. A retrospective cohort study of 20,465 non-diabetic, term, singleton births was undertaken to examine the relationship between gestational weight gain and adverse neonatal outcomes among infants born at term (37 weeks or more). Through a multivariate analyses it was established that gestational weight gain above the upper limit of the IOM guideline (more than 18 kg) was associated with multiple adverse neonatal outcomes such as a low five-minute Apgar score (adjusted odds ratio (AOR) 1.33, 95% confidence interval (CI) 1.01 to 1.76), seizure (AOR 6.50, 95% CI 1.43 to 29.65), hypoglycemia (AOR 1.52, 95% CI 1.06 to 2.16), polycythemia (AOR 1.44, 95% CI 1.06 to 1.94), meconium aspiration syndrome (AOR 1.79, 95% CI 1.12 to 2.86), and large-for-gestational age (AOR 1.98, 95% CI 1.74 to 2.25) compared with women within weight gain guidelines (Stotland 2006). Similar results were found in a cohort of 45,245 women who delivered singletons at Kaiser Permanente Medical Care Program Northern California in 1996 to 1998. It was found that women who gained more weight than was recommended by the IOM were three times more likely to have an infant with macrosomia (odds ratio (OR) 3.05, 95% confidence interval (CI) 2.19 to 4.26), and nearly 1.5 times as likely to have an infant with hypoglycemia (OR 1.38, 95% CI 1.01 to 1.89), or hyperbilirubinemia (OR 1.43, 95% CI 1.06 to 1.93) than women whose weight gain was in the recommended range. Women who gained less than the IOM recommendations were less likely than women in the recommended range to have an infant with macrosomia (OR 0.38, 95% CI 0.20 to 0.70), but equally likely to have an infant with hypoglycemia or hyperbilirubinemia (Hedderson 2006). A prospective population-based cohort study of 245,526 singleton term pregnancies was studied in Sweden to estimate the effects of gestational weight gain on obstetric outcome. Women were grouped in five categories of BMI and in three gestational weight gain categories; less than 8 kg (low weight gain), 8 to 16 kg and greater than 16 kg (high weight gain). Obese women with low gestational weight gain had a decreased risk for the following outcomes: pre-eclampsia (AOR 0.52, 95% CI 0.42 to 0.62), cesarean section (AOR 0.81, 95% CI 0.73 to 0.90), instrumental delivery (AOR 0.75, 95% CI 0.63 to 0.88), and large-for-gestational age births (AOR 0.66, 95% CI 0.59 to 0.75). There was a two-fold increased risk for pre-eclampsia and large-for-gestational age infants among average and overweight women with excessive weight gain. High gestational weight gain increased the risk for cesarean delivery in all maternal BMI classes (Cedergren 2006). The relationship between the incidence of high birthweight and weight gain during pregnancy varied by pregnancy weight categories. Average-weight women who gained more than 18 kg were more than three times likely to deliver a large infant as were women in the reference group. Overweight women who gained more than 18 kg were more than four times as likely to deliver a large infant as were women in the reference group. Very

overweight women who gain more than 18 kg were more than twice as likely to deliver a large infant as were women in the reference group (Cogswell 1995). Kabali and Werler studied the combined effects of prepregnant women's BMI and weight gain in relation to macrosomia in offspring of 815 non-diabetic women, using data collected from a retrospective study. Compared to mothers with a normal prepregnancy BMI and pregnancy weight gain, risk of macrosomia in offspring was significantly elevated only in overweight women with excess weight gain (AOR 2.6, 95% CI 1.2 to 5.4) but not among normal weight mothers with excess gain (AOR 1.1, 95% CI 0.5 to 2.4) or overweight mothers with normal or low gain (AOR 1.1, 95% CI 0.4 to 3.1). It was concluded that given the complications that are associated with delivering large babies, overweight women may benefit from not gaining excess weight in pregnancy (Kabali 2007). There have been a number of studies which conclude that excessive gestational weight gain increases postpartum weight retention (Gunderson 2000; Keppel 1993; Polley 2002; Rooney 2002; Rossner 1997; Scholl 1995) and is related to a two- to three-fold increase in the risk of becoming overweight after delivery (Gunderson 2000). Moreover, mothers who gained more weight during pregnancy had children at higher risk of being overweight in early childhood (Oken 2007).

However, too strict a weight gain restriction might result in adverse birth outcomes. A systematic review was undertaken to assess the effects of advice to increase or reduce energy or protein intake during pregnancy on gestational weight gain, and the outcome of pregnancy. It was established that in three trials involving 384 women, energy or protein restriction of pregnant women who were overweight or exhibited high weight gain significantly reduced weekly maternal weight gain and reduced mean birthweight but had no effect on pregnancy-induced hypertension or pre-eclampsia. It concluded that protein or energy restriction of pregnant women is unlikely to be beneficial and may be harmful to the infant (Kramer 2003). There is some evidence that too low a weight gain is associated with preterm deliveries (Medicine 1990). A study of low-income women in Alabama used the lower limit of the IOM's recommended range to define low weight gain during the third trimester in non-obese women (Hickey 2005). After a variety of other risk factors were controlled for, women with a low rate of weight gain during the third trimester had a statistically significant higher risk of spontaneous preterm delivery than did women without a low weight gain in the third trimester (odds ratio 2.46, 95% CI 1.53 to 3.92). A similar relation between low weight gain and preterm birth was reported in a primarily Hispanic cohort in Los Angeles (Siega-Riz 1994). Weight gain in pregnancy is also related to fetal growth. Too low a weight gain is associated with reduced fetal growth, ie, low birthweight (less than 2500 g) or small-for-gestational-age infants (less than the 10th percentile of weight for a given gestation). A retrospective cohort study found that mothers who gained lower than the IOM's guideline had increased rates of small-for-gestational-age infants, seizure, meconium aspiration syndrome, and prolonged hospital

stay (Stotland 2006). Thus, either low or excessive weight gain during pregnancy should be avoided to optimize birth outcome.

Given the increasing prevalence and negative consequences of excessive gestational weight gain, preventing excessive weight gain during pregnancy is potentially important. The best intervention is to help pregnant women to achieve the recommended weight gain, with the objective of ensuring the best possible outcome for their infants and themselves. Dietary control, exercise and eating behavior modification are the main elements for controlling weight. Pregnancy may be an optimal time to inform and challenge women to change their eating habits and physical activities, and thereby prevent excessive weight gain. There are systematic reviews which aimed to assess the effect of dietary advice, exercise intervention and psychosocial intervention for achieving weight loss in overweight and obese adults. The results of the review on exercise for overweight or obesity support the use of exercise as a weight loss intervention, particularly when combined with dietary change (Shaw 2006). People who are overweight or obese benefit from psychological interventions, particularly behavioral and cognitive-behavioural strategies, to enhance weight reduction. These measures are predominantly useful when combined with dietary and exercise strategies (Shaw 2005). In addition, overall, weight loss strategies using dietary, physical activity, or behavioral interventions produced significant improvement in weight among people with pre diabetes (Norris 2005).

The aim of this review is to identify and systematically review all randomized controlled trials of interventions for limiting weight gain during pregnancy to provide the best available evidence for clinical decision-making and to stimulate further research about preventing excessive weight gain during pregnancy.

OBJECTIVES

To evaluate the effectiveness of interventions for preventing excessive weight gain during pregnancy.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomized controlled trials and quasi-randomized controlled trials of interventions aimed at preventing excessive weight gain during pregnancy, irrespective of their country of origin or language.

Types of participants

Pregnant women.

Types of interventions

Any intervention (e.g., nutrition intervention, exercise intervention, health education or counseling) for preventing excessive weight gain compared with routine care.

Types of outcome measures

Primary outcomes

Excessive weight gain as defined by triallists.

Secondary outcomes

For the mothers

1. Behaviour change: physical activity, diet
2. Weight gain
3. Low-weight gain as defined by triallists
4. Preterm birth
5. Preterm premature rupture of membranes
6. Pre-eclampsia or eclampsia
7. Need for and indication for induction of labour
8. Postpartum complication including postpartum haemorrhage, wound infection, endometritis, need for antibiotics, perineal trauma, thromboembolic disease, maternal death
9. Cesarean delivery rate

For the newborns

1. Birthweight greater than 4000 grams and greater than the 90th centile for gestational age and infant sex
2. Birthweight less than 2500 grams and less than the 10th centile for gestational age and infant sex
3. Complication related to macrosomia including hypoglycaemia, hyperbilirunaemia, infant birth trauma (palsy, fracture, shoulder dystocia)

Long-term health outcomes

1. Maternal weight retention postpartum
2. Childhood weight

Search methods for identification of studies

Electronic searches

We will contact the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register. The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords. In addition, we will search MEDLINE (1966 to current) using the search strategy given in [Appendix 1](#). We will not apply any language restrictions.

Data collection and analysis

Selection of studies

We will assess for inclusion all potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, consult an outside person.

Assessment of methodological quality of included studies

We will assess the validity of each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions ([Higgins 2005](#)). We will describe the methods used for generation of the randomization sequence for each trial.

(1) Selection bias (randomization and allocation concealment)

We will assign a quality score for each trial, using the following criteria:

(A) adequate concealment of allocation: such as telephone randomization, consecutively numbered, sealed opaque envelopes;

(B) unclear whether adequate concealment of allocation: such as list or table used, sealed envelopes, or study does not report any concealment approach;

(C) inadequate concealment of allocation: such as open list of random-number tables, use of case record numbers, dates of birth or days of the week.

if we identify and include quasi-randomized controlled trials, we will perform a sensitivity analysis by trial quality.

(2) Attrition bias (loss of participants, for example, withdrawals, dropouts, protocol deviations)

We will assess completeness to follow up using the following criteria:

- (A) less than 5% loss of participants;
- (B) 5% to 9.9% loss of participants;
- (C) 10% to 19.9% loss of participants;
- (D) more than 20% loss of participants.

(3) Detection bias (blinding of outcome assessment)

We will assess detection bias using the following criteria:

- (A) adequate blinding explanation: such as outcome assessors measured weight of the pregnant women without awareness of the intervention they received;
- (B) unclear blinding explanation: such as study does not report if outcome assessors blinded;
- (C) inadequate blinding explanation: such as outcome assessors measured weight of the pregnant women with knowledge of their randomized group.

High-quality trials will be defined as those receiving an A rating for selection bias, attrition bias and detection bias.

Data extraction and management

We will adapt for our use the Cochrane Pregnancy and Childbirth data extraction form template to extract data. At least two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion. We will use the Review Manager software ([RevMan 2007](#)) to double enter all the data or a subsample.

When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Data analysis

Measures of treatment effect

We will carry out statistical analysis using the Review Manager software ([RevMan 2007](#)). We will use fixed-effect meta-analysis

for combining data in the absence of significant heterogeneity if trials are sufficiently similar. If heterogeneity is found, this will be explored by sensitivity analysis followed by random-effects if required. For dichotomous data, we will present results as summary relative risk with 95% confidence intervals. For continuous data, we will use the weighted mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods. If there is evidence of skewness, this will be reported.

Assessment of heterogeneity

We will apply tests of heterogeneity between trials, if appropriate, using the I-squared statistic. If we identify high levels of heterogeneity among the trials (exceeding 50%), we will explore it by prespecified subgroup analysis and perform sensitivity analysis. A random-effects meta-analysis will be used as an overall summary if this is considered appropriate.

Subgroup analyses

We will conduct planned subgroup analyses classifying whole trials by interaction tests as described by [Deeks 2001](#).

If sufficient data are available, we plan to carry out the subgroup analyses according to:

1. criteria of excessive weight gain as defined by trialists. Different trials may use different criteria to categorize weight gain of pregnant women. There are classified in two ways. The first is classified according to the Institute of Medicine of USA guidelines, excess weight gain is any amount over 'normal' gain, adequate weight gain is any amount within 'normal' gain and low weight gain is any amount under 'normal' gain of each body mass index (BMI) categories. The second classification split weight gain into less than the lower or greater than upper limits of recommended.
2. prepregnancy BMI: (1) underweight (2) normal weight (3) overweight (4) obese. These BMI categories as defined by trialists. Each trial may use difference classification of BMI. Some trials may categorize BMI using cut-off point of industrial criteria and some using Asian criteria.
3. types of intervention.
4. gestational age at first visit prenatal clinic: (1) 20 weeks or lower (2) more than 20 weeks. Gestational age at 20 weeks is the middle age of gestation.
5. gestational age at first visit prenatal clinic: (1) 28 weeks or lower (2) more than 28 weeks. Gestational age at 28 weeks is early of the 3rd trimester which weight gain is rapidly increasing.

Cluster-randomized trials

We will include cluster-randomized trials in the analyses along with individually randomized trials. Their sample sizes will be ad-

justed using the methods described in [Gates 2005](#) using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources are used, this will be reported and sensitivity analyses conducted to investigate the effect of variation in the ICC. If we identify both cluster-randomized trials and individually-randomized trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomization unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomization unit and perform a separate meta-analysis; therefore the meta-analysis will be performed in two parts as well.

Dealing with missing data

We will analyse data on all participants with available data in the group to which they are allocated, regardless of whether or not they received the allocated intervention. If in the original reports participants are not analysed in the group to which they were randomized, and there is sufficient information in the trial report, we will attempt to restore them to the correct group.

Assessment of publication bias

Where sufficient trials are included, we will consider publication bias using funnel plots of between-treatment effect and its precision on individual trials, and Egger's test ([Egger 1997](#)). If we find asymmetry funnel plots with statistical publication bias, we will further examine the effect of the bias on the meta-analysis conclusion using sensitivity analyses.

Sensitivity analyses

We will carry out sensitivity analysis to explore the effect of trial quality. This will involve analysis based on an A, B, C, or D rating of selection bias and attrition bias. Studies of poor quality will be excluded in the analysis (those rating B, C, or D) in order to assess for any substantive difference to the overall result. For clustering effect, we will perform a sensitivity analysis to see what the effect of different values of the ICC on the results of the analysis would be.

ACKNOWLEDGEMENTS

As part of the pre-publication editorial process, this protocol has been commented on by three peers (an editor and two referees who are external to the editorial team), one or more members of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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* Indicates the major publication for the study

APPENDICES

Appendix I. MEDLINE search strategy

1 exp Pregnancy/
2 Pregnant Women/
3 1 or 2
4 Weight Gain/
5 exp Obesity/pc [Prevention & Control]
6 exp Clinical Trial/
7 randomized.ti,ab.
8 placebo.ti,ab.
9 dt.fs.
10 randomly.ti,ab.
11 trial.ti,ab.
12 groups.ti,ab.
13 or/6-12
14 Animals/
15 Humans/
16 14 not (14 and 15)
17 13 not 16
18 4 or 5
19 17 and 18 and 3

HISTORY

Protocol first published: Issue 2, 2008

CONTRIBUTIONS OF AUTHORS

B Muktabhant conceived and designed the draft protocol. P Lumpiganon and C Ngamjarus reviewed and commented on the revisions of the protocol.

DECLARATIONS OF INTEREST

None known.

Cyclo-oxygenase (COX) inhibitors for preventing preterm labour (Protocol)

Khanprakob T, Laopaiboon M, Lumbiganon P, Sangkomkarnhang US



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[Intervention Protocol]

Cyclo-oxygenase (COX) inhibitors for preventing preterm labour

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effectiveness and safety of COX inhibitors for preventing preterm labour in high-risk women.

BACKGROUND

Description of the condition

Preterm birth is defined as delivery before 37 completed weeks (Cunningham 2005). Incidence of preterm birth among Swedish during 1973 - 2001 was around 5.6% (Morken 2005).

Preterm labour is documented by three criteria (Cunningham 2005): uterine contractions of four in 20 minutes or eight in 60 minutes plus progressive change in the cervix; cervical dilatation greater than 1 cm; and cervical effacement of 80% or greater.

If preterm labour is not managed properly, active labour can occur and result in preterm birth. Preterm birth is one of the major complications in obstetrics. The mortality rate of preterm infants has continued to decline over the past 60 years, but infant mortality associated with preterm birth or low birthweight has not declined (Arias 2003). Preterm birth is also the leading cause of perinatal morbidities such as low birthweight, respiratory distress syndrome, intraventricular haemorrhage, anaemia, etc. Moreover, these complications may cause both major and minor consequences for these newborn infants (Kliegman 2007).

Factors associated with preterm birth include: medical and obstetric complications (Meis 1995); multiple pregnancy (Blondel 2006; Kurdi 2004; Murphy 2007); threatened abortion (Weiss 2004); cigarette smoking (Tsai 2008); short stature; low pre-pregnancy body mass index (BMI); inadequate weight gain (Kramer 1995; Schieve 2000); young or advanced maternal age (Morken 2005); prolonged walking or standing; strenuous working conditions; long weekly work hours (Luke 1995); stress (Hobel 2003); genetic factors (Hoffman 1999); chorioamnionitis (Ustun 2001); lower genital tract infections (Kiss 2004); history of previous abortion; socioeconomic status and nulliparity (Meis 1995).

Description of the intervention

Prevention of preterm labour is the most important step for preventing preterm birth. Prostaglandins have been proposed as playing an important role in parturition (Gibb 2002; Olson 1995). Prostaglandins have a diverse effect on the uterus (Narumiya 1999). They are commonly considered as uterotonics (which increase myometrial tone) (Olson 2007) but can sometimes act as smooth muscle relaxants (Toppozada 1975).

Cyclo-oxygenase (COX) is a type of enzyme in the pathway of prostaglandins synthesis. This pathway can be obstructed by COX inhibitors resulting in the hindrance of prostaglandin production.

How the intervention might work

Prostaglandins are produced from plasma arachidonic acid, which is usually released by the action of enzymes called phospholipases A2 or C. Arachidonic acid can act as substrate for cyclo-oxygenase-

1 and -2 (COX-1 and -2) (Smith 1996). These enzymes are the target of many nonsteroidal anti-inflammatory drugs (NSAIDs) (Vane 1998).

The effect of prostaglandins on tissue targets is complicated by prostaglandin receptors. The prostaglandin family of receptors is classified according to the specificity of binding of a given receptor to a particular prostaglandin. These receptors are thromboxane A2 (TP), PGD2 (DP), prostacyclin or PGI2 (IP), PGF2alpha (FP), and EP1 to EP4 (PGE2) (Narumiya 1999). PGE2 and PGI2 have been shown to cause relaxation of vascular smooth muscle and vasodilatation in many circumstances (Henry 2005; Williams 1994). Thus, either the generation of specific prostaglandins or the relative expression of the various prostaglandin receptors may determine the responses of human myometrium to prostaglandins (Myatt 2004). In addition to changes with gestation, several studies show that there may be regional changes in the upper and lower uterine segments (Brodt-Eppley 1999; Grigsby 2006). Thus, it is entirely possible that prostanoids contribute to myometrial relaxation at one stage of pregnancy and to regional myometrial contraction of the fundus after the initiation of parturition. In the process of labour, many investigators have accepted and fostered the view that prostaglandins, particularly PGF2alpha and PGE2, are involved. The following evidence may support the role of COX inhibitors in preventing preterm labour.

1. The levels of prostaglandins in amniotic fluid, maternal plasma, and the uterus increase during labour (Gibb 1998).
2. Prostaglandins cause abortion or labour (Novy 1980).
3. An observational study by Loudon found that COX-2 inhibitors was effective in treating preterm labour (Loudon 2003).

4. Prostaglandin treatment of myometrial smooth muscle tissues in vitro sometimes causes contraction, dependent on the prostanoid tested and the physiological status of the tissue treated (Myatt 2004).

However, like oxytocin, prostaglandins produced directly in or adjacent to myometrial tissue are likely to play a major role in the effectiveness of myometrial contractions of active labour once labour is initiated. Based on the evidence that during the parturition process prostaglandins play an important role in labour, COX inhibitors may help to relieve myometrial tone (tocolytic effect) and result in cessation of labour (Dawood 1993; Olson 2003). COX-2 progressively increases expression while gestational age increases, so there is a potential role for COX-2 in normal parturition (Vermillion 2005). Thus, selective COX-2 inhibitors may be more effective in preventing uterine contraction than non-selective COX inhibitors.

Why it is important to do this review

There is no Cochrane review addressing the effectiveness and safety of COX inhibitors in preventing preterm labour. A previous Cochrane review on COX inhibitors found insufficient data

to draw conclusions about its role in treating preterm labour and there was limited information on serious maternal outcomes such as death, cardiac arrest, respiratory arrest and admission to intensive care unit (King 2005). There is no Cochrane review on the effectiveness and safety of antenatal COX inhibitors for preventing preterm labour in high risk women.

OBJECTIVES

To assess the effectiveness and safety of COX inhibitors for preventing preterm labour in high-risk women.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all published and unpublished randomised trials evaluating administration of any COX inhibitors for preventing preterm labour. We will exclude quasi-randomised trials and studies with crossover designs. We will include cluster-randomised trials.

Types of participants

Pregnant women at 22 to 36 weeks' gestation, at risk for but not experiencing preterm labour.

Types of interventions

Administration of COX inhibitors compared with placebo or any other interventions (including conservative management) for preventing preterm labour.

Types of outcome measures

Primary outcomes

1. Preterm labour (less than 37 completed weeks)
2. Preterm birth (less than 37 completed weeks)

Secondary outcomes

Maternal outcomes

1. Preterm labour at gestational age of 34 - < 37 completed weeks
2. Preterm labour at gestational age of 28 - < 34 completed weeks
3. Preterm labour at gestational age of 22 - < 28 completed weeks
4. Labour-free interval
5. Preterm birth < 34 weeks
6. Adverse effects
7. Length of hospital stay
8. Pregnant women's satisfaction

Neonatal outcome

1. Birthweight
 - 1.1 Low birthweight (LBW): birthweight less than 2500 grams
 - 1.2 Very low birthweight (VLBW): birthweight less than 1500 grams
 - 1.3 Extremely low birthweight (ELBW): birthweight less than 1000 grams
2. Neonatal morbidity index (the presence of one or more of the following conditions: premature closure of ductus arteriosus; patent ductus arteriosus; sepsis; necrotising enterocolitis; intraventricular haemorrhage; respiratory distress syndrome)
3. Admission to NICU
4. Perinatal mortality
5. Long-term outcomes e.g. developmental delay, cerebral palsy, educational attainment etc.

Search methods for identification of studies

Electronic searches

We will contact the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register. The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and

the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We will not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors will independently assess for inclusion all potential studies identified as a result of the search strategy. We will resolve any disagreement through discussion, or if required, consult the third reviewer.

Data extraction and management

We will design a form for data extraction. At least two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion. We will use the Review Manager software ([RevMan 2008](#)) to double enter all the data.

When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2008](#)). We will resolve any disagreement by discussion or by involving a third assessor.

(1) Sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We will assess the method as:

- adequate (any truly random process e.g. random number table; computer random number generator);
- inadequate (any non random process e.g. odd or even date of birth; hospital or clinic record number); or
- unclear.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We will assess the methods as:

- adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear.

(3) Blinding (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will judge studies at low risk of bias if they were blinded, or if we judge that the lack of blinding could not have affected the results. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess the methods as:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors; or
- partial for some situations e.g. data from unblinded participant been recorded by blinded personnel.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported; the numbers included in the analysis at each stage (compared with the total randomised participants); reasons for attrition or exclusion where reported; and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake. We will assess methods as:

- adequate;
- inadequate;
- unclear.

We will discuss whether missing data greater than 20% might (a) be reasonably expected (acknowledging that with long-term follow up, complete data are difficult to attain), and (b) impact on outcomes.

(5) Selective reporting bias

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:

- adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear.

(6) Other sources of bias

We will describe for each included study any important concerns we have about other possible sources of bias.

We will assess whether each study was free of other problems that could put it at risk of bias:

- yes;
- no;
- unclear.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the Handbook (Higgins 2008). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - see 'Sensitivity analysis'.

Measures of treatment effect

We will carry out statistical analysis using the Review Manager software (RevMan 2008). We will use fixed-effect meta-analysis for combining data in the absence of significant heterogeneity if trials are sufficiently similar. If heterogeneity is found, we will explore this by sensitivity analysis followed by random-effects if required.

Dichotomous data

For dichotomous data, we will present results as summary risk ratio (RR) with 95% confidence intervals (CI).

Continuous data

For continuous data, we will use the mean difference (MD) if outcomes are measured in the same way between trials. We will use the standardised mean difference (SMD) to combine trials that

measure the same outcome, but use different methods. If there is evidence of skewness, we will report this.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually randomised trials. We will adjust their sample sizes using the methods described in the *Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources are used, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a separate meta-analysis.

Dealing with missing data

We will analyse data on all participants with available data in the group to which they are allocated, regardless of whether or not they received the allocated intervention. If in the original reports participants are not analysed in the group to which they were randomised, and there is sufficient information in the trial report, we will attempt to restore them to the correct group.

Assessment of heterogeneity

We will apply tests of heterogeneity between trials, if appropriate, using the I^2 statistic. If we identify high levels of heterogeneity among the trials (exceeding 50%), we will explore it by prespecified subgroup analysis and perform sensitivity analysis. A random-effects meta-analysis will be used as an overall summary if this is considered appropriate.

Assessment of reporting biases

Where we suspect reporting bias (see 'Selective reporting bias', above), we will attempt to contact study authors asking them to provide missing outcome data. Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2008). We will use fixed-effect inverse variance meta-analysis for combining data where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. Where we suspect clinical or methodological heterogeneity between studies sufficient to suggest that treatment effects may differ between trials, we will use random-effects meta-analysis.

If we identify substantial heterogeneity in a fixed effect meta-analysis, we will note this and repeat the analysis, using a random-effects method.

Subgroup analysis and investigation of heterogeneity

We will conduct planned subgroup analyses classifying whole trials by interaction tests as described by Deeks 2001.

We plan to carry out the following subgroup analyses:

1. Nonselective COX inhibitors versus selective COX-2 inhibitors
2. Singleton versus multiple pregnancies

Sensitivity analysis

We will carry out sensitivity analysis to explore the effect of trial quality, only including studies which have been assessed as having adequate control of the potential for bias.

ACKNOWLEDGEMENTS

As part of the pre-publication editorial process, this protocol has been commented on by three peers (an editor and two referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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* Indicates the major publication for the study

HISTORY

Protocol first published: Issue 2, 2009

CONTRIBUTIONS OF AUTHORS

Thirawut Khanprakob (TK) registered the review title and drafted the protocol. Ussanee Swadpanich (US), Pisake Lumbiganon (PL) and Malinee Laopaiboon (ML) revised and approved the final version of the protocol. TK will draft the review. US, PL and ML will revise and approve the final version of the review.

DECLARATIONS OF INTEREST

None known.

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Internal sources

- Khon Kaen Hospital, Ministry of Public Health, Thailand.
- Faculty of Medicine, Khon Kaen University, Thailand.
- Faculty of Public Health, Khon Kaen University, Thailand.

External sources

- Thailand Research Fund, Senior Research Scholar, Thailand.
- Thailand Cochrane Network, Thailand.

Hepatitis B vaccination during pregnancy for preventing infant infection (Protocol)

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[Intervention Protocol]

Hepatitis B vaccination during pregnancy for preventing infant infection

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effectiveness and adverse effects of hepatitis B vaccine administered to pregnant women for preventing HBV infection in infants.

BACKGROUND

Description of the condition

Hepatitis B virus (HBV) is an enveloped, double-stranded DNA virus. Hepatitis B is an infection caused by the HBV and occurs worldwide. The highest rates of HBV carriers are found in developing countries with limited medical facilities. In highly endemic areas of Asia, Africa, and the Pacific, approximately 75% of hepatitis B carriers usually acquire the virus perinatally or in childhood (Safary 2000). Whereas in western and northern European countries and North America, HBV infection is relatively rare and acquired primarily in adulthood. HBV infections result in 500,000 to 1.2 million deaths per year caused by chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) (Lavanchy 2004). Globally, HBV causes 60% to 80% of the world's primary liver cancers (Parkin 2001).

Diagnosis of hepatitis is made by biochemical assessment of liver function and coagulation studies (Hollinger 2001). Diagnosis is confirmed by demonstration of specific antigens and/or antibodies. Three clinically useful antigen antibody systems have been identified for hepatitis B: (1) hepatitis B surface antigen (HBsAg) and antibody to HBsAg (anti-HBs IgG); (2) antibody (anti-HBc IgM) and anti-HBc IgG to hepatitis B core antigen (HBcAg); and (3) hepatitis B e antigen (HBeAg) and antibody to HBeAg (anti-HBe) to determine infectivity.

For infants and children, the two primary sources of HBV infection are perinatal transmission from infected mothers and horizontal transmission from infected household contacts. Perinatal transmission is common in hyperendemic areas, especially when HBsAg carrier mothers are also HBeAg positive (Hollinger 2001; Mahoney 1999). For a newborn infant whose mother is positive for both HBsAg and HBeAg, the risk for chronic HBV infection is 70% to 90% by age six months in the absence of postexposure immunoprophylaxis (Wong 1984). By comparison, the infant risk for chronic infection is less than 10% in the mother with HBeAg negative (Stevens 1985). Of persons who are infected with HBV as infants or young children, 25% to 90% become chronic carriers, and approximately 25% of those with chronic infection die prematurely from cirrhosis or liver cancer (hepatocellular carcinoma) (Gitlin 1997; McMahon 1990). Development of chronic HBV infection at an early age increases the risk of HCC more than infection at older age (Hsieh 1992). Nearly 100% of HCC children were hepatitis B surface antigen seropositive (Chang 1998). Breastfeeding by an HBsAg positive mother does not increase the risk for acquisition of HBV infection in the infant (Beasley 1975).

Description of the intervention

Hepatitis B vaccines are composed of the surface antigen of HBV (HBsAg), and are produced by two different methods: plasma derived or recombinant DNA (Assad 1999). Plasma-derived vac-

cines, derived from the plasma of HBsAg-positive donors, consist of highly purified, formalin-inactivated and/or heat-inactivated, alum-adsorbed, hepatitis B subviral particles (22 nm) of HBsAg that are free of detectable nucleic acid, and, therefore, non-infectious. Recombinant DNA yeast-derived or mammalian cell-derived vaccines, the S gene (pre-S1, pre-S2, S), is cloned and isolated, inserted into an expression plasmid and introduced into yeast or mammalian cells. The desired protein is expressed and assembled into 22 nm antigenic particles. As on natural HBsAg particles, the epitope that elicits the most important immune response is exposed on the surface of artificial particles. Vaccines used for primary prevention have effectively reduced risk of infection in most populations (Mahoney 1993). Completion of hepatitis B vaccine programmes induces protection in about 95% of recipients (Jackson 2007). Vaccination during pregnancy is safe and provides passive transfer of antibodies to the newborn (Anonymous 1991; Gupta 2003; Levy 1991). There are no known side effects from vaccination, in either pregnant women or their offspring (Grosheide 1993). The most common side effects from hepatitis B vaccination are pain at the injection site and mild to moderate fever (Andre 1989; Greenberg 1993).

Hepatitis B vaccine is given into the deltoid intramuscularly in a series of three doses (de Lalla 1988; Krugman 1981). The first shot is given at the elected date; the second dose a month later; and the third dose six months after the first dose. Vaccine batches should be stored at 2° to 8°C. Freezing destroys the potency of the vaccine. Factors that may reduce the immunogenicity of hepatitis vaccines include age (greater than 40 years), weight, genetics, haemodialysis, HIV infection, immunosuppression, tobacco smoking, subcutaneous injection, injection into the buttocks, and accelerated schedule (Ingardia 1999).

How the intervention might work

The mechanism of hepatitis B vaccination during pregnancy for preventing neonatal infection is the production of maternal antibodies that can be transferred across the placenta and provide the neonate with high antibody titers. This could protect the neonate from horizontal infection until active immunization after birth is protective (Reddy 1994).

Why it is important to do this review

Complex HBV epidemiology makes it difficult to evaluate and compare the effectiveness of different immunization policies. HBV infection rates vary in different parts of the world according to the pattern of hepatitis B transmission. In high endemic populations, perinatal transmission has been documented to result in a high rate of hepatitis B infection (Beasley 1983). Many countries have implemented universal hepatitis B immunization at birth, which provides long-term protection against infection in more than 90%

of healthy people ([Shepard 2006](#)). Despite this, some infants who are born to HBV sero-positive mothers have become infected by HBV despite having received passive-active immunoprophylaxis ([Nguï 1998](#)). Maternal hepatitis B vaccine immunization may be a way of preventing hepatitis B infection in infants before hepatitis B vaccine can be administered and provide protection. However, the ideal plan for hepatitis B vaccine administration during pregnancy, taking into consideration risk factors (high risk of HBV infection or the general population); endemic populations (high or low); and cost effectiveness, is not known.

OBJECTIVES

To assess the effectiveness and adverse effects of hepatitis B vaccine administered to pregnant women for preventing HBV infection in infants.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomized controlled trials (RCTs) of hepatitis B vaccination during pregnancy for preventing infant infection. The randomized units could be individual or clustered (e.g. hospitals). We will exclude cross-over trials and quasi-randomized trials.

Types of participants

All pregnant women unaware of marker results of hepatitis B virus serology.

Types of interventions

Hepatitis B vaccine compared with placebo or no treatment.

Types of outcome measures

Primary outcomes

Incidence of hepatitis B virus infection in infants.

Secondary outcomes

1. Hepatitis B antibody for hepatitis B virus (HBs Ab) in newborns up to six months after birth.
2. Maternal antibody for hepatitis B virus (HBs Ab).
3. Adverse maternal effects such as local reactions at injection site (soreness, swelling, erythema); fatigue; fever; headache.

Search methods for identification of studies

Electronic searches

We will contact the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register. The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We will not apply any language restrictions.

Data collection and analysis

The methodology for data collection and analysis is based on the *Cochrane Handbook of Systematic Reviews of Interventions* ([Higgins 2008](#)).

Selection of studies

Two review authors, Ussanee S Sangkomkamhang (US) and Pisake Lumbiganon (PL) will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult an additional review author.

Data extraction and management

We will design a form to extract data. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult an additional review author. We will enter data into Review Manager software (RevMan 2008) and check for accuracy. When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). We will resolve any disagreement by discussion or by involving an additional assessor.

(1) Sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We will assess the method as:

- adequate (any truly random process, e.g. random number table; computer random number generator);
- inadequate (any non random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We will assess the methods as:

- adequate (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear.

(3) Blinding (checking for possible performance bias)

We will describe for each included study all the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will also provide information on whether the intended blinding was effective.

We will assess the methods as:

- adequate, inadequate, or unclear for participants;
- adequate, inadequate, or unclear for personnel;
- adequate, inadequate, or unclear for outcome assessors;

where 'adequate' is when there was blinding or where we assess that the outcome or the outcome measurement is not likely to have been influenced by lack of blinding.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We will describe for each included trial, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake. We will assess methods as:

- adequate;
- inadequate;
- unclear.

We will discuss whether missing data greater than 20% might (a) be reasonably expected (acknowledging that with long-term follow up, complete data are difficult to attain); and (b) impact on outcomes.

(5) Selective reporting bias

We will describe for each included trial how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:

- adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear.

(6) Other sources of bias

We will describe for each included study any important concerns we have about other possible sources of bias.

We will assess whether each study was free of other problems that could put it at risk of bias:

- yes;

- no;
- unclear.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - see 'Sensitivity analysis'.

When information regarding any of the above (1) to (6) is unclear, we will attempt to contact authors of the original reports to provide further details.

Measures of treatment effect

Dichotomous data

For dichotomous data, such as the incidence of hepatitis B virus infection in infants, we will present results as summary risk ratio with 95% confidence interval.

Continuous data

For continuous data, such as maternal antibody levels, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomized trials in the analyses, along with individually randomized trials. We will adjust their sample sizes using the methods described in the *Handbook*, using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources are used, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomized trials and individually-randomized trials, we plan to synthesize the relevant information. We will consider it reasonable to combine the results from both, if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomization unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomization unit and perform a separate meta-analysis.

Dealing with missing data

For included trials, we will note levels of attrition. We will explore the impact of including trials with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. For all outcomes we will carry out analyses, as far as possible, on an intention-to-treat basis: i.e. we will attempt to include all participants randomized to each group in the analyses. The denominator for each outcome in each trial will be the number randomized minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity (I^2 greater than 50%), we will explore it by prespecified subgroup analysis.

Assessment of reporting biases

Where we suspect reporting bias (see selective reporting bias above), we will attempt to contact study authors, asking them to provide missing outcome data. Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such trials in the overall assessment of results by a sensitivity analysis.

Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2008). We will use fixed-effect inverse variance meta-analysis for combining data where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. Where we cannot explain heterogeneity between trials' treatment effects, we will use random-effects meta-analysis.

Subgroup analysis and investigation of heterogeneity

If we can include a number of trials, we plan to carry out subgroup analyses for the primary outcome of incidence of hepatitis B virus infection in infant as following:

1. low risk of hepatitis B virus (HBV) infection versus high risk (as defined by authors e.g. injection drug users, healthcare workers) of HBV infection;
2. low endemic setting versus high endemic setting of HBV infection;
3. vaccination schedule (e.g. three doses versus two doses regimen);
4. maternal negative versus positive for marker of hepatitis B virus serology.

For fixed-effect meta-analyses we will conduct planned subgroup analyses classifying whole trials by interaction tests as described by

(Deeks 2001). For random-effects meta-analyses we will assess differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis

We will perform sensitivity analysis based on trial quality, separating high-quality trials from trials of lower quality. For the purposes of this sensitivity analysis, we will define 'high quality' as a trial having adequate allocation concealment, and classify an 'unreasonably expected loss to follow up' as less than 20%, given the stated importance of attrition as a quality measure (Tierney 2005). If we include any cluster-randomized trials, other sensitivity analysis may also be desirable. If cluster trials have been incorporated with an estimate of the ICC borrowed from a different trial, we will perform a sensitivity analysis to see what the effect of different values of the ICC on the results of the analysis would be.

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As part of the pre-publication editorial process, this protocol has been commented on by three peers (an editor and two referees who are external to the editorial team) and the Group's Statistical Adviser.

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* Indicates the major publication for the study

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CONTRIBUTIONS OF AUTHORS

Ussanee S Sangkomkamhang selected the topic from vacant list and drafted the protocol. Pisake Lumbiganon and Malinee Laopaiboon revised and approved the protocol.

DECLARATIONS OF INTEREST

None known.

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Internal sources

- Khon Kaen Hospital, Khon Kaen, Ministry of Public Health, Thailand.
- Khon Kaen University, Faculty of Medicine, Khon Kaen, Thailand.
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External sources

- Thai Cochrane Network, Thailand.
- Thailand Research Fund (Senior Research Scholar), Thailand.

Antibiotics for chronic rhinosinusitis in adults (Protocol)

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[Intervention Protocol]

Antibiotics for chronic rhinosinusitis in adults

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

1. To determine the effectiveness of systemic antibiotic therapy for chronic rhinosinusitis in adults.
2. To determine the adverse reactions associated with systemic antibiotic therapy for chronic rhinosinusitis in adults.

BACKGROUND

Description of the condition

Rhinosinusitis is the inflammation of the paranasal sinus mucosa. It is defined as chronic when it has lasted longer than three months without complete resolution of symptoms (EPOS 2007; Rosenfeld 2007). Symptoms may consist of purulent nasal discharge, nasal obstruction, facial pain/pressure/fullness or decreased sense of smell, in addition to evidence of inflammation, including purulent discharge or oedema of the middle meatus or ethmoid region, polyps in the nasal cavity or the middle meatus and/or radiographic imaging showing inflammation of the paranasal sinuses. Rhinosinusitis is categorised as with or without nasal polyps. Although various infective and non-infective inflammatory processes are involved in the pathogenesis of chronic rhinosinusitis, bacterial infection is believed to play an important role. A study by Merino et al demonstrated bacterial growth in 98% of aspirates from 510 patients with chronic rhinosinusitis; most were mixed aerobic and anaerobic bacteria (Merino 2003). The bacteriology of chronic rhinosinusitis study by Brook also demonstrated 41% mixed organisms, 34% anaerobes and 25% aerobes (Brook 2006). Chronic rhinosinusitis is a common health problem which significantly affects quality of life (Gliklich 1995; van Agthoven 2001; Wang 2003). According to a national health interview survey of the prevalence of chronic conditions, chronic rhinosinusitis has been estimated to affect 12.5% to 15.5% of the total population, making it the second most common chronic condition in the United States (Adams 1999; Collins 1997). However, the prevalence of doctor diagnosed chronic rhinosinusitis is much lower; a prevalence of 2% was found using ICD-9 codes as an identifier (Shashy 2004). The prevalence rate is substantially higher in females with a female/male ratio of 6/4 (Collins 1997) and increases with age, with a mean of 2.7% and 6.6% in the age groups of 20 to 29 and 50 to 59 years, respectively, and levelling off at 4.7% after 60 years (Bonfils 2005).

Description of the intervention

A wide range of medical and surgical therapies have been used to treat chronic rhinosinusitis. Medical therapy includes antibiotics, corticosteroids, decongestants, antihistamines, mast cell stabilisers, anti-leukotrienes, nasal douching, immunotherapy and reduction of environmental factors (EPOS 2007). A recent Cochrane Review found nasal saline irrigation, both as a sole modality and as an adjunct to medical treatment for chronic rhinosinusitis, to be beneficial (Harvey 2007). Surgical treatment by functional endoscopic sinus surgery (FESS) has also become a well-established strategy for the treatment of chronic rhinosinusitis refractory to medical treatment. However, a Cochrane Review has suggested that FESS has not been demonstrated to confer additional benefit to that obtained by medical treatment (Khalil 2006).

How the intervention might work

Systemic and topical antibiotics are used in chronic rhinosinusitis with the aim of eliminating infection and inflammation (Inamura 2000; Miyanojara 2000; Wallwork 2006), altering bacterial biofilm formation (Wozniak 2004), reversing ostial occlusion and improving symptoms. However, unnecessary antibiotic prescriptions should be avoided. Some adverse effects have been reported, including allergy (MacLaughlin 2000), diarrhoea and abdominal pain (Bucher 2004). Overuse is associated with increasing resistance to antibiotics among community acquired pathogens. There is evidence of conflict in the definition of chronic rhinosinusitis and this makes evaluation of the effectiveness of antibiotic treatment difficult. In recent clinical practice guidelines (EPOS 2007; Rosenfeld 2007), it was proposed that chronic rhinosinusitis diagnosis requires appropriate signs/symptoms for more than 12 weeks and documented inflammation. The definition of chronic rhinosinusitis in this systematic review is based primarily on these guidelines.

Why it is important to do this review

Various groups of systemic antibiotics have been studied in the treatment of chronic rhinosinusitis, including penicillins (Huck 1993; Legent 1994; Namyslowski 2002), cephalosporins (Huck 1993; Namyslowski 2002), quinolones (Legent 1994) and macrolides (Ragab 2004; Wallwork 2006). The duration of antibiotic course in these studies has ranged from nine days (Legent 1994) to 12 weeks (Ragab 2004; Wallwork 2006), and types of study design varied from descriptive studies to randomised controlled trials. Clinical cure rates reported in the studies are inconsistent and range from as low as 50% (Legent 1994) to 95% (Namyslowski 2002).

Topical antibiotics have also been used to treat chronic rhinosinusitis with the theoretical advantage of acting directly on the site of infection and producing a higher concentration of antibiotic at the target site (Desrosiers 2007). However, a systematic review of topical treatment of rhinosinusitis in children found no evidence of effectiveness (Fiocchi 2007). A systematic review of topical antibiotics for chronic rhinosinusitis (Lim 2008) and antibiotic nasal washes in chronic rhinosinusitis (Elliott 2006) also demonstrated low-level corroborative evidence.

There are systematic reviews which support the use of systemic antibiotics in acute rhinosinusitis (Ahovuo-Saloranta 2008; González 2006). However, the evidence for systemic antibiotics in chronic rhinosinusitis is still in question.

The recent European practice guideline states that while there are randomised controlled studies on the efficacy/effectiveness of short-term oral antibiotics for chronic rhinosinusitis, the results show a negative outcome, while long-term oral antibiotic use has been shown to be beneficial (EPOS 2007). Although at present the US Food and Drug Administration has not approved any medica-

tions for the treatment of chronic rhinosinusitis, oral antibiotics and nasal corticosteroids are the two most commonly used medications in most cases (Dubin 2007; Kaszuba 2006).

To our knowledge, no meta-analysis of randomised controlled trials of systemic antibiotics for chronic rhinosinusitis is currently available. A Cochrane Review assessing the effects of antibiotics in the treatment of chronic rhinosinusitis is therefore warranted.

OBJECTIVES

1. To determine the effectiveness of systemic antibiotic therapy for chronic rhinosinusitis in adults.
2. To determine the adverse reactions associated with systemic antibiotic therapy for chronic rhinosinusitis in adults.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

Chronic rhinosinusitis defined by at least 12 weeks of two or more of the following signs and symptoms:

- mucopurulent drainage (anterior/posterior nasal drip);
- nasal blockage/obstruction/congestion;
- facial pain/pressure/fullness; or
- decrease or loss of smell.

Inflammation is also documented by one or more of the following findings:

- purulent (not clear) mucus or oedema in the middle meatus or ethmoid region;
- polyps in nasal cavity or the middle meatus; and/or
- radiographic imaging showing inflammation of the paranasal sinuses.

Inclusion criteria:

Patients aged at least 18 years with chronic rhinosinusitis without nasal polyps.

We will exclude patients with the following conditions:

1. cystic fibrosis, based on positive sweat test or DNA alleles;
2. gross immunodeficiency (congenital or acquired);
3. congenital mucociliary problems, e.g. primary ciliary dyskinesia (PCD);

4. fungal rhinosinusitis;
5. systemic vasculitis and granulomatous diseases;
6. cocaine abuse;
7. neoplasia;
8. acute exacerbation on chronic rhinosinusitis at the time of study entry;
9. using topical or systemic corticosteroids within four weeks before entering the study;
10. aspirin hypersensitivity;
11. receiving antibiotics within two weeks before entering the study.

Types of interventions

Systemic antibiotics versus placebo.

Types of outcome measures

Primary outcomes

- Clinical cure rate post-treatment; cure defined as no clinical symptoms or signs, or substantially improved.

Secondary outcomes

- Bacteriological cure rate.
- Radiographic response rate.
- Relapse rate: new episodes of sinusitis after 60 days from the start of the initial treatment.
- Adverse effects.

Search methods for identification of studies

We will conduct systematic searches for randomised controlled trials. There will be no language, publication year or publication status restrictions. We may contact original authors for clarification and further data if trial reports are unclear and we will arrange translations of papers where necessary.

Electronic searches

Published, unpublished and ongoing studies will be identified by searching the following databases from their inception: the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, current issue); PubMed; EMBASE; CINAHL; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts; Web of Science; BIOSIS Previews; CNKI; *mRCT* (Current Controlled Trials); ClinicalTrials.gov; ICTRP (International Clinical Trials Registry Platform) and Google.

Subject strategies for databases will be modelled on the search strategy designed for CENTRAL shown in [Appendix 1](#). Where appropriate, we will combine subject strategies with adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in *The Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.1, Box 6.4.b. ([Handbook 2008](#))).

Searching other resources

We will scan reference lists of identified publications for additional trials and contact authors if necessary. PubMed; TRIPdatabase; NHS Evidence ENT & Audiology; and Google will be searched to retrieve existing systematic reviews possibly relevant to this systematic review, so that we can scan their reference lists for additional trials.

Data collection and analysis

Selection of studies

Papers that appear loosely to meet the inclusion criteria (based on title and abstract) will be selected by one author. If the information relevant to the inclusion criteria is not available in the abstract, or if the title is relevant but the abstract is not available, we will obtain the full text of the report. Papers that pass this initial review will be assessed by two authors. We will resolve disagreements between authors by discussion until a consensus is reached.

Data extraction and management

Two authors will extract data independently, using a paper data extraction form. We will compare results and resolve disagreements by discussion until a consensus is reached. Data will be entered into RevMan ([RevMan 2008](#)) and pooled where appropriate.

We will extract the following information relating to the study methodology or quality: randomisation concealment as described in the study, blinding, timing of follow up, percentage of drop-outs during follow up and baseline comparability of the groups.

We will extract the following characteristics relating to methods: criteria for accepting participants into the study (diagnosis on clinical/radiography/culture basis), definition of cure/failure and treatment compliance.

We will extract the following characteristics relating to participants: number of participants in treatment and control groups at start, mean age of participants (plus age range), gender, year study published and study setting.

We will extract the following characteristics of the intervention: intervention comparisons, courses of antibiotics and information about co-interventions.

We will extract information on clinical, bacteriological and radiographic outcomes and adverse event rates. We will mainly extract outcome information as numbers of participants with cure rate by study group. We will classify relapse within 60 days from the onset of the treatment will be classified as a clinical failure. In some studies, the results may be reported at more than one period of follow up. We will extract the data for all periods. We will carry out meta-analyses based on the available data.

Assessment of risk of bias in included studies

Two review authors will independently carry out the assessment of risk of bias in the included studies. We will resolve any disagreements between the authors by consensus. We will assess the risk of bias of included studies using the suggested six domains of sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias ([Higgins 2008](#)).

We will base the overall 'Risk of bias' table on the *Cochrane Handbook for Systematic Reviews of Interventions* 5.0.1 (section 8.5 ([Higgins 2008](#))) and the domains outlined in the previous paragraph. Overall risk of bias will be classified as low, unclear or high.

Measures of treatment effect

We will assess treatment effect by calculating the risk ratio (RR) (and 95% confidence intervals (CI)) of cure at a specific time point (dichotomous variable) for each trial. We will use mean difference (MD) and 95% CI for continuous variables (severity scores, duration of symptoms, etc.).

When trials are sufficiently homogeneous, we will pool intervention effects.

Unit of analysis issues

For cross-over studies, we will calculate the mean treatment differences between the periods where possible and enter these using the fixed-effect generic inverse variance (GIV) analysis in RevMan ([RevMan 2008](#)), to provide summary mean differences and 95% CIs. In cross-over studies, if we believe there is a carry-over effect which will outlast any washout period included in the study, we will include only data from the first period in the meta-analysis. In studies with multiple treatment groups we will combine similar groups if possible to create a single pair-wise comparison.

Dealing with missing data

In assessing the influence of missing data on the overall results of the placebo controlled studies (primary outcome measures only), we will use three ways of imputing data: assuming the outcomes of participants for whom no outcome was recorded a) as failures, b) as non-failures or c) according to the event rate observed in the control group.

Assessment of heterogeneity

We will assess the significance of any discrepancies in the estimates of the treatment effects from the different trials by means of Cochran's Q test for heterogeneity and by a measure of the I^2 statistic. The I^2 statistic describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. A value greater than 50% may be considered to represent substantial heterogeneity. We will also use the forest plot to assess heterogeneity visually.

Assessment of reporting biases

We will assess publication bias by means of a funnel plot if there are a sufficient number of trials.

Data synthesis

We will conduct meta-analyses for trials with similar characteristics using RevMan (RevMan 2008). We will use fixed-effect inverse variance meta-analysis for combining data where trials are judged sufficiently similar. Where there is clinical or methodological heterogeneity between studies sufficient to suggest that treatment effects may differ between trials, we will use random-effects meta-analysis. Where the heterogeneity between studies cannot be explained by any potential factor, we will use random-effects meta-analysis to pool the treatment effects.

Subgroup analysis and investigation of heterogeneity

The following conditions will be considered for subgroup analysis if heterogeneity of treatment effect is found:

1. short-term versus long-term treatment;
2. asthma/bronchial hyper-reactivity/chronic obstructive pulmonary disease (COPD)/bronchiectases based on symptoms, respiratory function tests;
3. allergy based on specific serum IgE or skin prick tests (SPTs).

Sensitivity analysis

To test the robustness of results, we plan to use sensitivity analyses to examine the effect of chronic rhinosinusitis diagnostic criteria (signs/symptoms, presence of inflammation and/or radiograph), and the classification of the risk of bias, on the overall estimates of effect for important outcomes.

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Wozniak 2004

Wozniak DJ, Keyser R. Effects of subinhibitory concentrations of macrolide antibiotics on *Pseudomonas aeruginosa*. *Chest* 2004;**125**: 62S–69S.

* Indicates the major publication for the study

APPENDICES

Appendix I. Search strategy

CENTRAL search strategy

- #1 MeSH descriptor Sinusitis explode all trees
- #2 rhinosinusitis OR nasosinusitis OR sinusitis OR pansinusitis OR ethmoiditis OR antritis OR sphenoiditis
- #3 (kartagener* near syndrome)
- #4 (inflamm* near sinus*)
- #5 (#1 OR #2 OR #3 OR #4)
- #6 MeSH descriptor Chronic Disease explode all trees
- #7 MeSH descriptor Recurrence explode all trees
- #8 (chronic* OR persist* OR recur*)
- #9 (#6 OR #7 OR #8)
- #10 (#5 AND #9)
- #11 MeSH descriptor Anti-Bacterial Agents explode all trees
- #12 MeSH descriptor Antibiotic Prophylaxis explode all trees
- #13 MeSH descriptor Lactams explode all trees
- #14 MeSH descriptor Quinolones explode all trees
- #15 MeSH descriptor Macrolides explode all trees
- #16 ANTIBIOT* OR ANTI NEXT BIOT* OR ANTIMICROBIAL* OR ANTI NEXT MICROBIAL* OR BACTERIOCID* OR ANTIBACTERIAL* OR ANTI NEXT BACTERIAL*
- #17 PENICILLIN* OR AMOXICILLIN OR AMPICILLIN OR CLAVULANIC NEXT ACID OR AMOXICLAV OR AUGMENTIN OR TICARCILLIN OR TIMENTIN OR FLUCLOXACILLIN OR FLUAMPICIL OR MAGNAPEN OR PIPERACILLIN OR TAZOCIN OR CEPHALOSPORIN* OR CEFACLOX OR DISTACLOX OR CEFADROXIL OR BAXAN OR CEFALEXIN OR CEPOREX OR KEFLEX OR CEFAMANDOLE OR KEFADOL OR CEFAZOLIN* OR KEFZOL OR CEFIXIME OR SUPRAX OR CEFOTAXIME OR CLAFORAN OR CEFOXITIN OR MEFOXIN OR CEFPIROME OR CEFROM OR CEFPODOXIME OR ORELOX OR CEFPROZIL OR CEFZIL OR CEFRADINE OR VELOSEL OR CEFTAZIDIM OR FORTUM OR KEFADIM OR CEFTRIAZONE OR ROCEPHIN OR CEFUROXIME OR ZINACEF OR ZINNAT OR CEFONICID OR AZTREONAM OR AZACTAM OR IMIPENEM OR CILASTATIN OR PRIMAXIN OR MEROPENEM OR TETRACYCLINE* OR DETECLOX OR DEMECLEOCYCLIN OR LEDERMYCIN OR DOXYCYCLINE OR VIBRAMYCIN OR MINOCYCLINE OR MINOCINE OR OXYTETRACYCLINE OR TERRAMYCIN OR MACROLIDE* OR ERYTHROMYCIN OR ERYMAX OR ERYTHROCIN OR ERYTHROPEX OR AZITHROMYCIN OR ZITHROMAX OR CLARITHROMYCIN OR KLARICID OR TELITHROMYCIN OR KETEK OR TRIMOXAZOLE OR SEPTRIN OR TRIMETHOPRIM OR MONOTRIM OR TRIMOPAN OR METRONIDAZOLE OR FLAGYL OR METROLYL OR PHENOXYMETHYLPENICILLIN OR SULFAMETHOXAZOLE OR OXACILLIN OR CEPHALOTHIN OR SULBACTAM OR OFLOXACIN OR CLINDAMYCIN OR GENTAMYCIN OR VANCOMYCIN

#18 (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)
#19 (#10 AND #18)

HISTORY

Protocol first published: Issue 1, 2010

CONTRIBUTIONS OF AUTHORS

Patorn Piromchai wrote the first draft of protocol and will be responsible for study selection, data extraction and analysis, and writing the review.

Sanguansak Thanaviratananich commented on the draft and will be responsible for study selection, data extraction and analysis, and writing the review.

Malinee Laopaiboon drafted the analysis plan in the protocol, reviewed the protocol, and will carry out data analysis and presentation.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

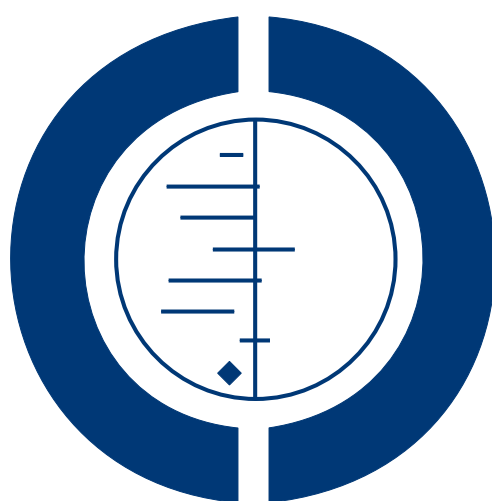
- Thai Cochrane Network, Thailand.

External sources

- No sources of support supplied

Vitamin K for the prevention and treatment of osteoporosis in post-menopausal women (Protocol)

Sangkomkamhang T, Sangkomkamhang US, Ngamjarus C



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[Intervention Protocol]

Vitamin K for the prevention and treatment of osteoporosis in post-menopausal women

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Editorial group: Cochrane Musculoskeletal Group.

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Citation: Sangkomkamhang T, Sangkomkamhang US, Ngamjarus C. Vitamin K for the prevention and treatment of osteoporosis in post-menopausal women. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No.: CD008329. DOI: 10.1002/14651858.CD008329.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess efficacy and safety of vitamin K1 or vitamin K2 for prevention and treatment of postmenopausal osteoporosis.

BACKGROUND

Description of the condition

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength primarily reflects the integration of bone density and bone quality. Bone density is expressed as grams of mineral per area or volume, and in any given individual is determined by peak bone mass and amount of bone loss. Bone quality refers to architecture, turnover, damage accumulation (e.g., microfractures), and mineralization (NIH 2001). The most common clinical manifestations of osteoporosis are fractures of the hip, vertebrae or wrist.

Approximately 30% of postmenopausal females have osteoporosis according to the World Health Organization (WHO) definition of osteoporosis (WHO 1994). In the USA, approximately 1.5 million fractures annually are attributable to osteoporosis. These include 700,000 vertebral fractures, 250,000 distal forearm (Colles') fractures, 250,000 hip fractures, and 300,000 fractures of other limb sites (Riggs 1995). Hip fracture is a significant cause of morbidity and mortality worldwide, the risk of death is increased in patients with osteoporotic fractures and that the highest risk is found immediately after the fracture event (Johnell 2004a; Johnell 2004b). Following a hip fracture, there is a 10% to 20% mortality over the subsequent 6 months, 50% of sufferers will be unable to walk without assistance, and 25% will require long term domiciliary care (Riggs 1995). For 2005, total costs in the United States including prevalent fractures are more than \$19 billion (Burge 2007).

Treatments for osteoporosis includes both non pharmacological and pharmacological methods. Five classes of osteoporosis drugs were studied in osteoporotic fractures: hormone replacement therapy (HRT), bisphosphonates (BSP), calcitonin, selective estrogen receptor modulators (SERMs) and vitamin D derivative (Rocaltrol). Comparing between the treated and untreated patients, mortality is significantly lower in the treated group, the lower mortality in the treated group, combined with the knowledge that antiresorptive drugs reduce fractures and increase bone density (Cree 2003). However, bisphosphonate groups have higher cost and gastrointestinal side effect than other drugs. Hormonal therapy also has uncommon side effects after long-time use such as increased risks of mammary cancer (CGHF 1997). Other Cochrane reviews have addressed a number of issues regarding prevention and treatment of postmenopausal osteoporosis. Exercise therapy appears to be effective in increasing bone density at the lumbar spine and hip in postmenopausal women but no prevention fractures (Bonaiuti 2002). Alendronate (Wells 2008a), Risedronate (Wells 2008c) and Strontium ranelate (O'Donnell 2006) demonstrate benefit in the secondary prevention of vertebral and non-vertebral fractures. Etidronate (Wells 2008b) demonstrate benefit in the secondary prevention of vertebral fractures but no reductions in non-vertebral fractures. Fluoride (Haguenauer 2000) has

an ability to increase BMD at lumbar spine but no reduction of vertebral fractures. None of these reviews are studied with vitamin K for the prevention and treatment of osteoporosis in postmenopausal women.

Description of the intervention

Vitamin K denotes a group of lipophilic, hydrophobic vitamins that are needed for the posttranslation modification of certain proteins, mostly required for blood coagulation. There are two types of natural vitamin K (K1; Phylloquinone and K2; Menatetrenone, Menaquinone). The major dietary sources of vitamin K are green leafy vegetables (such as kale, spinach, salad greens, cabbage, broccoli and Brussels sprouts) and plant oils (such as soybean and canola oils). Vitamin K2 synthesized by bacteria (Schurgers 1999). Several decades ago, study demonstrated that vitamin K promotes fracture healing and vitamin K has an important role in regulating bone turnover, including bone formation (Hara 1995; Koshihara 1997).

How the intervention might work

Vitamin K is a coenzyme for glutamate carboxylase which mediates the gamma-carboxylation of glutamyl residues on several bone proteins, notably osteocalcin. High serum concentrations of undercarboxylated osteocalcin and low serum concentrations of vitamin K are associated with lower bone mineral density and increased risk of hip fracture (Minisola 1996; Szulc 1993; Vergnaud 1997; Sugiyama 2001). Besides, there is increasing evidence that vitamin K can effect the synthesis and excretion of nephrocalcin and interleukin-1,6 which can regulate calcium balance and bone metabolism (Luo 2003).

Why it is important to do this review

Today there are a number of effective treatment options available that have been shown to act quickly (within one year), to maintain bone density and to reduce the risk of having fractures. Some medications are high cost and some have more complications or side effects. It is important that the choice of treatment be tailored to patient's specific medical needs and lifestyle. However, there is lack of evidence on the potential benefits of using menatetrenone (vitamin K2) therapy in postmenopausal women for preventing and treatment of osteoporosis.

OBJECTIVES

To assess efficacy and safety of vitamin K1 or vitamin K2 for prevention and treatment of postmenopausal osteoporosis.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomized controlled trials (RCTs) of vitamin K in postmenopausal women for preventing and treating postmenopausal osteoporosis. We will exclude quasi-randomized trials.

Types of participants

Postmenopausal women, including those with natural or surgical menopause will be included. Osteoporosis should be diagnosed on a bone mineral density (BMD) test, which can be detected by one of the examinations but not limited to: single photon absorptiometry, dual photon absorptiometry, quantitative computed tomography (QCT), dual energy X-ray absorptiometry (DXA), peripheral dual energy X-ray absorptiometry (pDXA). A T score of < -2.0 SD is a reference criteria for osteoporosis. Women with secondary osteoporosis including corticosteroid-induced due to diseases affecting metabolism of bone, disability of the heart and cerebral vessels, liver, kidney, and hematopoietic system, will be excluded.

Types of interventions

- (1) Vitamin K (in all forms) alone or in combination with calcium and/or vitamin D versus placebo, alone or in combination with calcium and/or vitamin D;
- (2) Vitamin K (in all forms) alone or in combination with calcium and/or vitamin D versus other osteoporosis treatment, alone or in combination with calcium and/or vitamin D;
- (3) Vitamin K (in all forms) administered in different doses, comparing dose effects.

Types of outcome measures

Primary outcomes

- (1) incidence of fractures (vertebral, non-vertebral, hip and wrist)
- (2) Vertebral deformities
- (3) Adverse effects, including:
 - a) change of prothrombin time
 - b) thromboembolism
 - c) abdominal discomfort
 - d) skin rash
 - e) abnormal liver enzymes
- (4) Serious adverse event (SAE, which means any adverse experience that results in any of the following outcomes: death, a life-

threatening experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or requiring intervention to prevent permanent impairment or damage).

Secondary outcomes

- (1) Bone mineral density (BMD) (as defined by authors e.g. DXA, QUS, CT)
- (2) Bone biochemical markers (e.g. Collagen Type-1 C-Telopeptide (CTX), N-telopeptide of type I collagen (NTX), total osteocalcin, bone specific alkaline phosphatase and undercarboxylated osteocalcin level).
- (3) Quality of life, patient satisfaction.

Search methods for identification of studies

See: Cochrane Musculoskeletal Group methods used in reviews. We will search the following electronic bibliographic databases: Cochrane Musculoskeletal trials register, Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 3, 2009), MEDLINE (1950 to present), Embase (1980 to present), CINAHL (1982 to present).

Hand searching will be searched. The list of handsearched journals can be found in the Cochrane Musculoskeletal Group.

We will develop the search strategies set out in [Appendix 1](#) for MEDLINE. We will adapt similar search strategies to search the other databases.

We will not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors, Thananit Sangkomkamhang (TS) and Ussanee S Sangkomkamhang (US) will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through consultation a third person.

Data extraction and management

We will design a form to extract data. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third person. Data will be entered into Review Manager software ([RevMan 2008](#)) and checked for accuracy.

When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). Any disagreement will be resolved by discussion or by involving a third assessor.

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias.

We will use the Cochrane 'Risk of bias' tool in RevMan 5, which involves describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry. This involves answering a pre-specified question whereby a judgement of 'Yes' indicates low risk of bias, 'No' indicates high risk of bias, and 'Unclear' indicates unclear or unknown risk of bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we will use the weighted mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We will not include cluster randomized trials as they are not suitable for our intervention.

Crossover trials

If we identify any crossover trials on this topic, and such trials are deemed eligible for inclusion, they will be included in the analyses with parallel group trials, using methods described by (Elbourne 2002).

Dealing with missing data

For included studies, levels of attrition will be noted. The impact of including studies with high levels of missing data in the overall assessment of treatment effect will be explored by using sensitivity analysis.

For all outcomes analyses will be carried out, as far as possible, on an intention-to-treat basis i.e. we will attempt to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity (I^2 greater than 50%), we will explore it by pre-specified subgroup analysis.

Assessment of reporting biases

Where we suspect reporting bias (*see* selective reporting bias above), we will attempt to contact study authors asking them to provide missing outcome data. Where this is not possible, and the missing data are thought to introduce serious bias, the impact of including such studies in the overall assessment of results will be explored by a sensitivity analysis.

Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2008). We will use fixed-effect inverse variance meta-analysis for combining data where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. Where we suspect clinical or methodological heterogeneity between studies sufficient to suggest that treatment effects may differ between trials we will use random-effects meta-analysis.

If substantial heterogeneity is identified in a fixed effect model of meta-analysis this will be noted and the analysis repeated using a random-effects method.

Subgroup analysis and investigation of heterogeneity

If we can include a number of trials, we plan to carry out subgroup analyses for the primary outcome of incidence of fractures in postmenopausal women as following:

1. primary versus secondary fracture prevention;
2. age group 45 to 60 years versus older than 60 years;
3. severity of osteoporosis (osteoporosis versus severe osteoporosis);
4. duration of drugs used (less than one year versus more than one year);

The following outcomes will be used in subgroup analysis:

5. vertebral fracture versus non-vertebral fracture (fracture around hip and wrist)

For fixed effect model of meta-analyses we will conduct planned subgroup analyses classifying whole trials by interaction tests as described by (Deeks 2001). For random effects model of meta-analyses we will assess differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis

We will perform sensitivity analysis based on trial quality, separating high-quality trials from trials of lower quality. 'High quality' will, for the purposes of this sensitivity analysis, be defined as a trial having adequate allocation concealment and an 'unreasonably expected loss to follow-up' classified as less than 20%, given the stated importance of attrition as a quality measure (Tierney 2005).

Levels of quality of a body of evidence in the GRADE approach

We will use the GRADE approach for grading the quality of evidence, according to the criteria given in the Handbook (Higgins 2008).

Underlying methodology Quality rating

Randomized trials; or double-upgraded observational studies.

High

Downgraded randomized trials; or upgraded observational studies.

Moderate

Double-downgraded randomized trials; or observational studies.

Low

Triple-downgraded randomized trials; or downgraded observational studies or case series/case reports. Very low

ACKNOWLEDGEMENTS

Many thanks to Maria Benkhalti, Research Assistant.

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* Indicates the major publication for the study

APPENDICES

Appendix I. MEDLINE search strategy

1. exp bone diseases, metabolic/
2. osteoporosis#.tw.
3. bone density/
4. bone densit\$.tw.
5. bone mineral densit\$.tw.
6. exp bone/ and bones.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7. bone loss\$.tw.
8. osteomalacia.tw.
9. osteodystrophy.tw.
10. exp bone demineralization, pathologic/
11. (bone adj demineralization).tw.
12. osteopenia.tw.
13. bone mass.tw.
14. exp densitometry/
15. densitometry.tw.
16. dexam\$.tw.
17. exp fractures/
18. fracture\$.tw.
19. or/1-18
20. exp Vitamin K/
21. vitamin k1.sh,rn,tw.
22. vitamin k2.sh,rn,tw.
23. vitamin k3.sh,rn,tw.
24. aquamephyton.tw.
25. konakion.tw.
26. menadione.tw.
27. menaquinone\$.tw.
28. phyllohydroquinone.tw.
29. phylloquinone.tw.
30. phytomenadione.tw.
31. phytonadione.tw.
32. vi?asol.tw.
33. or/21-32
34. 19 and 33

WHAT'S NEW

5 November 2008	Amended	CMSG ID: C161-P

HISTORY

Protocol first published: Issue 1, 2010

CONTRIBUTIONS OF AUTHORS

Thananit Sangkomkamhang (TS) and Ussanee S Sangkomkamhang (US) selected the review topic.

TS drafted the protocol. US and Chetta Ngamjarus (CN) revised and approved the protocol.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Khon Kaen Hospital, Khon Kaen, Ministry of Public Health, Thailand.
- Khon Kaen University, Faculty of Public Health, Thailand.

External sources

- Thai Cochrane Network, Thailand.
- Thailand Research Fund (Senior Research Scholar), Thailand.

Admission tests other than cardiotocography for fetal assessment during labour (Protocol)

Khunpradit S, Lumbiganon P, Laopaiboon M



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[Intervention Protocol]

Admission tests other than cardiotocography for fetal assessment during labour

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Editorial group: Cochrane Pregnancy and Childbirth Group.

Publication status and date: New, published in Issue 3, 2010.

Citation: Khunpradit S, Lumbiganon P, Laopaiboon M. Admission tests other than cardiotocography for fetal assessment during labour. *Cochrane Database of Systematic Reviews* 2010, Issue 3. Art. No.: CD008410. DOI: 10.1002/14651858.CD008410.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effectiveness of admission tests other than cardiotocography in preventing adverse perinatal outcomes.

BACKGROUND

Description of the condition

According to WHO estimates, around 3% of approximately 120 million infants born every year in developing countries develop birth asphyxia requiring resuscitation. It is estimated that some 900,000 of these newborns die each year (Costello 1994; WHO 1997).

The goal of intrapartum fetal surveillance is to detect potential fetal decompensation and to allow timely and effective intervention to prevent perinatal morbidity or mortality such as perinatal asphyxia, neonatal hypoxic ischaemic encephalopathy, stillbirth and neonatal death (Liston 2007). The fetal brain is the primary organ of interest, but at present it is not clinically feasible to assess its function during labour. However, fetal heart (FH) rate characteristics can be assessed, and changes in FH rate that precede brain injury constitutes the rationale for FH monitoring; that is, timely response to abnormal FH patterns might be effective in preventing brain injury (Liston 2007).

Description of the intervention

The fetal admission test is a means to identify women who may require caesarean delivery for a non-reassuring FH rate tracing during labour, and be delivered of a depressed newborn infant (Ingemarsson 1986). Cardiotocography for 20 minutes (Ingemarsson 1986), response to vibroacoustic stimulation (Sarno 1990), biophysical profile (Kim 2003), modified biophysical profile (MBPP) (Lalor 2008), rapid biophysical profile (rBPP; the combination of amniotic fluid index and sound-provoked fetal movement detected by ultrasound in predicting intrapartum fetal distress) (Tongprasert 2006; Tongsong 1999), Doppler scans of the umbilical artery (Malcus 1991; Mires 2001), and sonographic assessment of amniotic fluid (Moses 2004; Sarno 1989) are diagnostic modalities that have been used for the assessment of fetal well-being on admission.

Vibroacoustic stimulation

Fetal vibroacoustic stimulation is a simple, non-invasive technique where a device is placed on the maternal abdomen over the region of the fetal head and sound is emitted at a predetermined level for several seconds (East 2005).

Biophysical profile

The BPP combines the assessment of electronic FH rate monitoring (CTG) with four biophysical features, namely (i) fetal movements, (ii) fetal tone, (iii) fetal breathing and (iv) estimation of amniotic fluid volume. These latter four variables are observed using real-time ultrasonography. The FH rate is recorded, usually over a 20-minute period, and is achieved by using a Doppler

ultrasound transducer to monitor the FH through the mother's abdomen. Uterine contractions are monitored simultaneously by a pressure transducer on the mother's abdomen. Both transducers are linked to a monitor and this results in a paper trace known as a CTG.

The BPP is performed in an effort to identify babies that may be at risk of poor pregnancy outcome, so that additional assessments of well-being may be performed, or labour may be induced or a caesarean section performed to expedite birth (Lalor 2008; Manning 1980).

The MBPP

A shortened version of the BPP, known as the MBPP, consists of: (i) recording an antenatal CTG (with or without vibroacoustic stimulation) combined with (ii) ultrasound measurement of the amniotic fluid. The MBPP is employed as a first-line screening test (Archibong 1999) and should be followed by the complete BPP as a back-up test when indicated (Lalor 2008).

The rBPP

The rBPP, the combination of amniotic fluid index and sound-provoked fetal movement detected by ultrasound. The rBPP is an effective predictor of intrapartum fetal distress in high-risk pregnancies (Tongprasert 2006).

Doppler scans of the umbilical artery

Doppler ultrasound study of umbilical artery waveforms helps identify the compromised fetus in 'high-risk' pregnancies. Doppler ultrasound detects changes in the pattern of blood flow through the baby's circulation. It may be that problems for the baby could be identified through these changes. Interventions, like early delivery, might then be able to reduce the mortality and morbidity (Alfirevic 2009).

Sonographic assessment of amniotic fluid

Amniotic fluid volume is an important parameter in the assessment of fetal well-being. Oligohydramnios occurs in many high-risk conditions and is associated with poor perinatal outcomes (Nabhan 2008).

A systematic review was conducted to assess the effectiveness of admission FH tracings in preventing adverse outcomes, compared with auscultation only, and to assess the test's prognostic value in predicting adverse outcomes. Three randomised controlled trials including 11,259 women and 11 observational studies including 5831 women were reviewed. Meta-analyses of the controlled trials found that women randomised to the labour admission test were more likely to have minor obstetric interventions like epidural analgesia (risk ratio (RR) 1.2; 95% confidence interval (CI) 1.1 to 1.4), continuous electronic fetal monitoring (RR 1.3; 95% CI 1.2 to 1.5) and fetal blood sampling (RR 1.3; 95% CI 1.1 to 1.5)

compared with women randomised to auscultation on admission. There were no significant differences in any of the other outcomes. From the observational studies, prognostic value for various outcomes was found to be generally poor. There is no evidence to support the hypothesis that the labour admission test is beneficial in women with no risk factors for adverse perinatal outcome (Blix 2005).

Continuous cardiotocography during labour was associated with a reduction in neonatal seizures, but no significant differences in cerebral palsy, infant mortality or other standard measures of neonatal well-being. However, continuous cardiotocography was associated with an increase in caesarean sections and instrumental vaginal births (Alfirevic 2006).

There is a separate Cochrane protocol on the effectiveness of cardiotocography versus intermittent auscultation of FH on admission to labour ward for assessment of fetal well-being (Devane 2005)

These interventions might have different effects in high-risk versus low-risk pregnancy, preterm versus term versus post term.

We plan to conduct subgroup analyses based on these two variables.

How the intervention might work

Ideally, these tests would identify the fetus at risk for decompensation during labour. This could allow timely and effective interventions to prevent perinatal morbidity or mortality.

At present, there is no evidence about the effectiveness of labour admission tests other than cardiotocography.

Why it is important to do this review

Hence, it is important to systematically review the evidence on the effectiveness of labour admission tests other than cardiotocography, such as BPP, Doppler, MBPP, rBPP, sonographic assessment of amniotic fluid, in preventing adverse perinatal outcomes.

OBJECTIVES

To assess the effectiveness of admission tests other than cardiotocography in preventing adverse perinatal outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

Any randomised (individual and cluster) controlled trials, trials comparing other labour admission tests in preventing adverse perinatal outcomes. We will exclude quasi-random study designs and trials using crossover design.

Types of participants

All women at admission to labour room, both primigravidae and multigravidae. We will seek trials of both low and high obstetric risk groups.

Types of interventions

Labour admission tests including vibroacoustic stimulation, biophysical profile (BPP), modified BPP, rapid BPP, Doppler scans of the umbilical artery, and sonographic assessment of amniotic fluid.

Types of outcome measures

Primary outcomes

Mother

1. Incidence of caesarean section
2. Incidence of operative vaginal delivery
3. Incidence of serious maternal complications (e.g. admission to intensive care unit, septicemia (a form of blood infection, organ failure))

Infant

1. Birth asphyxia
2. Stillbirths
3. Early neonatal death

Secondary outcomes

1. Incidence of continuous electronic fetal monitoring during labour
2. Incidence of artificial rupture of membranes during labour
3. Incidence of artificial oxytocin for augmentation of labour
4. Mobility during labour
5. Perceived control and/or self-confidence during labour
6. Incidence of use of pharmacological analgesia during labour and birth (including epidural)
6. Incidence of use of non-pharmacological methods of coping with labour, e.g. transcutaneous electrical nerve stimulation, hydrotherapy
7. Satisfaction with labour experience
8. Incidence of fetal blood sampling

9. Length of hospital stay (maternal and neonatal)
10. Neonatal neurodevelopment
11. Breastfeeding
12. Maternal and neonatal infection

Search methods for identification of studies

Electronic searches

We will contact the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register. The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We will not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors (Suthit Khunpradit and Pisake Lumbiganon) will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult a third person.

Data extraction and management

We will design a form to extract data. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third person. We will enter data into Review Manager software ([RevMan 2008](#)) and check for accuracy.

When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2009](#)). We will resolve any disagreement by discussion or by involving a third assessor.

(1) Sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

- We will assess the method as:
 - adequate (any truly random process, e.g. random number table; computer random number generator),
 - inadequate (any non-random process, e.g. odd or even date of birth; hospital or clinic record number) or,
 - unclear.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal the allocation sequence and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We will assess the methods as:

- adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear.

(3) Blinding (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding could not have affected the results. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess the methods as:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake. We will assess methods as:

- adequate;
- inadequate;
- unclear.

(5) Selective reporting bias

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:

- adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear.

(6) Other sources of bias

We will describe for each included study any important concerns we have about other possible sources of bias.

We will assess whether each study was free of other problems that could put it at risk of bias:

- yes;
- no;
- unclear.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the Handbook (Higgins 2009). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - see 'Sensitivity analysis'.

Measures of treatment effect

Dichotomous data

For dichotomous data, such as caesarean section, birth asphyxia, etc, we will present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, such as length of hospital stay, etc., we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Ordinal data

For ordinal data, we will use median and interquartile range.

We will compare:

1. one intervention versus no intervention;
2. one intervention versus another intervention.

Unit of analysis issues

For multiple pregnancies, we will account for dependency of data for the outcomes of the infants who have the same mother in the analysis..

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually randomised trials. We will adjust their sample sizes using the methods described in the Handbook using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the T^2 , I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if T^2 is greater than zero and either I^2 is greater than 30% or there is a low P-value (< 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry. For continuous outcomes we will use the test proposed by [Egger 1997](#), and for dichotomous outcomes we will use the test proposed by [Harbord 2006](#). If asymmetry is detected in any of these tests or is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We will carry out statistical analysis using the Review Manager software ([RevMan 2008](#)). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with its 95% confidence interval, and the estimates of T^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We plan to carry out the following subgroup analyses:

1. high-risk versus low-risk pregnancy;
2. preterm versus term versus post term

Subgroup analyses will be restricted to the primary outcomes.

For fixed-effect inverse variance meta-analyses we will assess differences between subgroups by interaction tests. For random-effects and fixed-effects meta-analyses using methods other than inverse variance, we will assess differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis

We will carry out sensitivity analysis to explore the effect of study quality. This will involve analyses based on the trial quality ratings for sequence generation, allocation concealment and incomplete outcome data. We will exclude studies of poor quality in the analysis (those categorised as 'no' or 'unclear') in order to assess for any substantive difference to the overall result.

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As part of the pre-publication editorial process, this protocol has been commented on by three peers (an editor and two referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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* Indicates the major publication for the study

HISTORY

Protocol first published: Issue 3, 2010

CONTRIBUTIONS OF AUTHORS

Suthit Khunpradit devised the idea, applied for the protocol, wrote the draft of the protocol, and approved the final edition. Pisake Lumbiganon and Malinee Laopaiboon edited and approved the final protocol.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

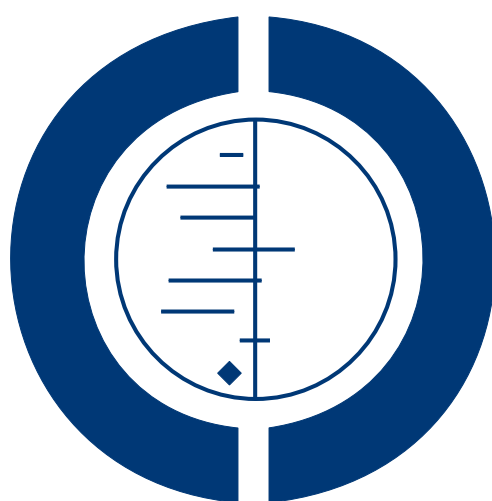
- Lamphun Hospital, Thailand.
- Khon Kaen University, Thailand.

External sources

- Thai Cochrane Network, Thailand.
- Thailand Research Fund(Senior Research Scholar Program), Thailand.

Double-bundle versus single-bundle reconstruction for anterior cruciate ligament rupture in adults (Protocol)

Tiamklang T, Sumanont S, Foocharoen T, Laopaiboon M



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[Intervention Protocol]

Double-bundle versus single-bundle reconstruction for anterior cruciate ligament rupture in adults

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of anatomic double-bundle versus standard single-bundle for anterior cruciate ligament reconstruction in adults with ACL deficiency.

BACKGROUND

The anterior cruciate ligament (ACL), which is located within the knee joint, performs a key role in stabilising the knee. It acts to prevent forward movement (anterior translation) of the tibia (shin bone) relative to the femur (thigh bone) as well as to control rotational movements within the knee joint. It is made up of dense connective tissue covered with a synovial membrane (Arnoczky 1983; Dienst 2002). The ACL mainly consists of two distinct portions or 'bundles': an anteromedial (AM) bundle and a posterolateral (PL) bundle, named according to their insertion sites to the tibia (Girgis 1975). Both bundles are critical to knee stability but act differently. The anteromedial band is tight in flexion (knee is bent) whereas the posterolateral band is tight in extension (knee is straightened out). A biomechanical study found that the anteromedial bundle is the primary restraint against anterior tibia translation, while the posterolateral bundle secures the knee when near full extension, particularly against rotational loads (Petersen 2007).

Description of the condition

The exact incidence of anterior cruciate ligament injuries is unknown; however, approximately 200,000 people per year sustain an ACL injury (usually a rupture) in the USA (AAOS 2007). These injuries are most often a result of deceleration, non contact injuries, jumping, or cutting action (Griffin 2000). The person often hears or feels a pop as the knee popped out of joint and then reduced (moved back in). Resumption of activity is usually not possible, and walking with full weight bearing is often difficult. Within two hours, the knee often swells and there is bleeding within the joint. The Lachman test, the most sensitive test for anterior cruciate ligament tears, is usually positive (Benjaminse 2006). Other injuries often occur at the time of the anterior cruciate ligament injury. Approximately 50% to 70% of patients with anterior cruciate ligament injuries also have meniscal injuries. In acute anterior cruciate ligament injuries, the lateral meniscus is more commonly torn (Bellabarba 1997); while in chronic anterior cruciate ligament tears, the medial meniscus is more commonly torn (Naranje 2008). Osteochondral injuries also occur with anterior cruciate ligament tears and are associated with a worse prognosis. In general, people with anterior cruciate ligament-deficient knees who continue sport activities with repeat incidents of instability risk further meniscus tears and osteochondral injuries that ultimately lead to osteoarthritis of the knee (Lohmander 2007).

Description of the intervention

Surgical treatment for ACL rupture usually involves reconstruction of the anterior cruciate ligament by use of a graft (a piece of tendon) that is passed through tunnels drilled into the tibia and femur at the insertion points of the ligament and then fixed.

ACL reconstruction is an increasingly common orthopaedic procedure (Lyman 2009). Lyman 2009 estimated there had been over 105,000 reconstructions in the USA in 2006. Reconstruction of the ACL produces better knee stability during daily activities and strenuous activities than non-surgical treatment especially in active individuals (Linko 2005). Over the years, an increased understanding of technical issues of graft selection, placement, tension, and fixation as well as of postoperative rehabilitation has led to improved outcomes from ACL reconstruction. The standard technique for anterior cruciate ligament reconstruction is currently arthroscopic single-bundle (SB) reconstruction with autografts (graft is taken from the patient) such as bone-patellar tendon-bone (BPTB), medial hamstring tendons (semitendinosus and gracilis), or the quadriceps tendon. The single-bundle reconstruction technique has mainly focused on the restoration of the anteromedial bundle while giving limited attention to the posterolateral bundle. Thus single-bundle ACL reconstructions are successful at restoring anterior stability to the knee, but not rotational stability (Woo 2002). Recent advances in arthroscopic knee surgery have allowed separate reconstruction of the two bundles to restore more closely the natural anatomy of the anterior cruciate ligament. The double-bundle anterior cruciate ligament reconstruction technique was first described by Mott 1983. Numerous technical modifications to the procedure have occurred since its introduction. However, double-bundle reconstruction will always be more technically demanding and invasive (four bone tunnels are required instead of two) than single-bundle reconstruction.

How the intervention might work

Theoretically, double-bundle reconstruction is more likely restore normal knee kinematics compared with a single-bundle technique. Anatomical and biomechanical studies have shown that double-bundle ACL reconstruction restores anterior knee stability and rotational stability in an ACL-deficient knee better than single-bundle ACL reconstruction because of better 'footprint' recreation (restoration of ACL attachments) and restoration of biomechanical functions (Buoncristiani 2006). With the additional restoration of the posterolateral bundle as in double-bundle reconstruction, rotational stability in particular is increased significantly (Yagi 2002). There is also a theoretical advantage to improved graft-bone healing of the double-bundle ACL reconstruction resulting from greater graft-bone contact area than that in single-bundle reconstruction.

Why it is important to do this review

Single-bundle techniques remain the standard approach and are generally but not fully successful. However, the potential for improved knee stability and the proven technical feasibility of double-bundle ACL reconstruction have led to an increased interest

and application of this relatively 'young' and technically more demanding arthroscopic procedure. But there is concern that double-bundle ACL reconstruction may result in a worse outcome for patients, including in those cases where revision surgery is required. A systematic review of the evidence from randomised clinical trials comparing double-bundle versus single-bundle reconstruction should help to inform decisions in this controversial area of current practice.

OBJECTIVES

To assess the effects of anatomic double-bundle versus standard single-bundle for anterior cruciate ligament reconstruction in adults with ACL deficiency.

METHODS

Criteria for considering studies for this review

Types of studies

Any randomised or quasi-randomised (method of allocating participants to a treatment which is not strictly random: e.g. by date of birth, hospital record number, alternation) controlled clinical trials comparing double-bundle versus single bundle reconstruction for anterior cruciate ligament (ACL) rupture in adults will be considered.

Types of participants

Skeletally mature patients with documented ACL rupture, either isolated or combined with other soft-tissue knee injuries, requiring primary ACL reconstruction.

Types of interventions

Randomised comparisons of double-bundle versus single-bundle reconstruction for treating ACL rupture in adults. Types of tendon graft, which can be either autograft or allograft, include semitendinosus tendon alone, gracilis and semitendinosus tendon, quadriceps tendon, and bone-patellar tendon-bone. Methods of surgical fixation include screw fixation and Endobutton fixation. We will exclude trials that only compare different methods of double-bundle reconstruction or different methods of single-bundle reconstruction.

Types of outcome measures

Primary outcomes

1. Patient or clinician-rated functional knee scores (e.g. IKDC score, Tegner activity score, Lysholm score ([Lysholm 1982](#))) and patient-derived health related quality of life measures (e.g. physical domain of the SF-36)
2. Long-term knee pain (visual analogue scale)
3. Adverse effects and complications (e.g. graft failure; infection; arthrofibrosis)

Secondary outcomes

1. Return to pre-injury level of activity / sport participation
2. Objective measures of knee stability (e.g. KT-1000 arthrometer, KT-2000 arthrometer results; rotational stability (Pivot shift test); anterior stability (e.g. Lachman test, anterior drawer test))
3. Range of motion (flexion-extension deficit)
4. Recurrent injury with and without re-operation

Timing of outcome assessment

We will consider grouping outcomes as follows:

1. Short term (within six months of ACL reconstruction)
2. Intermediate term (within six months up to two years of ACL reconstruction)
3. Long term (greater than two years following ACL reconstruction)

Search methods for identification of studies

Electronic searches

We will search the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (to present), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, current issue), MEDLINE (1966 to present) and EMBASE (1980 to present). We will also search [Current Controlled Trials](#), the [WHO International Clinical Trials Registry Platform](#) and the [National Research Register \(NRR\) Archive](#) (to September 2007) for ongoing and recently completed trials. No language restrictions will be applied.

In MEDLINE (OVID WEB), the subject specific strategy will be combined with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version ([Lefebvre 2009](#)). In EMBASE (OVID WEB), the subject specific strategy will be combined with the RCT search filter developed by the [Scottish Intercollegiate Network](#). Details of search strategies, including *The Cochrane Library* (Wiley InterScience), are shown in [Appendix 1](#).

Searching other resources

The bibliographies of all relevant papers identified by the search strategies will be handsearched. Specific proceedings of knee surgery, arthroscopic surgery and sports medicine meetings and conferences will be searched from the following organizations: European Society of Sports Traumatology Knee Surgery and Arthroscopy (ESSKA), American Orthopaedic Society for Sports Medicine (AOSSM), International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine (ISAKOS), American Academy of Orthopaedic Surgeons (AAOS), World Congress on Orthopaedic Sports Trauma, and Arthroscopy Association of North America (AANA). To avoid publication bias, the investigators of the trials identified from the proceedings will be contacted to obtain results and data of any unpublished studies. Where appropriate and possible, the corresponding authors of studies identified by the search strategies will be contacted to obtain other relevant studies not previously included for review.

Data collection and analysis

The methodology for data collection and analysis is based on the Cochrane Handbook of Systematic Reviews of Interventions (Lefebvre 2009).

Selection of studies

Two authors, Thavatchai Tiamklang (TT) and Sermsak Sumanont (SS), will independently select references identified by the searches for retrieval of full articles. Where there is disagreement or doubt, the full article will be retrieved. Two authors (TT and SS) will

independently assess the full study report to see if it meets the review inclusion criteria. Another review author, Thanit Foocharoen (TF), will be consulted in cases of unresolved disagreement. If necessary, the trial authors will be contacted for more information.

Data extraction and management

Two authors (TT and SS) will independently extract trial details and data for the included trials using a data collection form. The third author (TF) will be consulted in cases of unresolved disagreement. When necessary, trial authors will be contacted directly to complete data forms or clarify methodology. Data will be entered into Review Manager software (RevMan 2008) and checked for accuracy.

Assessment of risk of bias in included studies

Two authors (TT and SS) will independently assess the risk of bias for each study using The Cochrane Collaboration's tool (see Table 1). Each study will be graded for risk of bias (low, high, unclear) in each of the following domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and two other sources of bias (selection bias from major differences in baseline characteristics; and performance bias from important differences in the provision of care other than the trial interventions). We will assess separately the risk of bias associated with patient-rated outcomes and clinician-rated outcomes for blinding and incomplete outcome data. Any unresolved disagreement will be resolved by discussion with the third author (TF). Titles of journals, names of authors or supporting institutions will not be masked at any stage.

Table 1. Risk of bias tool

Domain	Description	Review authors' judgement
Sequence generation		Was the allocation sequence adequately generated? YES / NO / UNCLEAR
Allocation concealment		Was allocation adequately concealed? YES / NO / UNCLEAR
Blinding of participants, personnel and outcome assessors <i>Outcome:</i> Patient-rated outcomes (e.g. functional knee scores, joint position sense, pain, recurrent injury)		Was knowledge of the allocated intervention adequately prevented during the study? YES / NO / UNCLEAR
Blinding of participants, personnel and outcome assessors <i>Outcome:</i> Clinician-rated outcomes (e.g. knee stability tests, range of motion, complications)		Was knowledge of the allocated intervention adequately prevented during the study? YES / NO / UNCLEAR

Table 1. Risk of bias tool (Continued)

Incomplete outcome data <i>Outcome:</i> Patient-rated outcomes (e.g. functional knee scores, joint position sense, pain, recurrent injury)		Were incomplete outcome data adequately addressed? YES / NO / UNCLEAR
Incomplete outcome data <i>Outcome:</i> Clinician-rated outcomes (e.g. knee stability test, range of motion, complications)		Were incomplete outcome data adequately addressed? YES / NO / UNCLEAR
Selective outcome reporting		Are reports of the study free of suggestion of selective outcome reporting? YES / NO / UNCLEAR
Other sources of bias Selection bias: imbalance in confounders at entry. Major differences in baseline characteristics: age, sex, acute versus chronic injuries, isolated ACL rupture versus ACL rupture combined with other soft-tissue knee injuries.		Was the study apparently free of other problems that could put it at a high risk of bias? YES / NO / UNCLEAR
Other sources of bias Performance bias: for instance, provision of other interventions that should be comparable in both groups (e.g. various forms of fixation methods, number of strands of tendon graft, operative techniques, rehabilitation protocols, timing of intervention; or major differences in experience or personal characteristics of treatment providers, especially experience)		Was the study apparently free of other problems that could put it at a high risk of bias? YES / NO / UNCLEAR

Measures of treatment effect

Where appropriate, quantitative data reported in individual trial reports for outcomes listed in the inclusion criteria will be presented in the text and in the analyses. Risk ratios with 95% confidence intervals will be calculated for dichotomous outcomes, and mean differences with 95% confidence intervals for continuous outcomes.

Unit of analysis issues

The unit of randomisation in these trials is usually the individual patient. Exceptionally, as in the case of trials including people with bilateral ACL ruptures, data for trials may be presented

for ACL ruptures rather than individual participants. Where such unit of analysis issues arise and appropriate corrections have not been made, we will consider presenting the data for such trials only where the disparity between the units of analysis and randomisation is small. Where data are pooled, we will perform a sensitivity analysis to examine the effects of pooling these incorrectly analysed trials with the other correctly analysed trials.

Dealing with missing data

Where appropriate, we will perform intention-to-treat analyses to include all people randomised to the intervention groups. We will investigate the effect of drop outs and exclusions by conducting

worst and best scenario analyses. We will be alert to the potential mislabelling or non-identification of standard errors and standard deviations. Unless missing standard deviations can be derived from confidence interval data, we will not assume values in order to present these in the analyses.

Assessment of heterogeneity

Heterogeneity will be assessed by visual inspection of the forest plot (analysis) along with consideration of the test for heterogeneity and the I^2 statistic (Higgins 2003).

Assessment of reporting biases

Where sufficient data are available, we will attempt to assess publication bias by preparing a funnel plot. Our pursuit of trials listed in clinical trial registers should help to avoid publication bias.

Data synthesis

If considered appropriate, results of comparable groups of trials will be pooled. Initially we will use the fixed-effect model and 95% confidence intervals. We will also consider using the random-effects model, especially where there is unexplained heterogeneity.

Subgroup analysis and investigation of heterogeneity

Heterogeneity will be explored by subgroup analyses. Our primary subgroup analyses will be by gender, acute versus chronic injuries, isolated ACL rupture versus ACL rupture combined with other soft-tissue knee injuries and autograft versus allograft. Other subgroup analyses of various types of grafts, forms of fixation methods, numbers of strands of tendon graft, operative techniques and rehabilitation protocols may be considered also. To test whether the subgroups are statistically significantly different from one another, we will test the interaction using the technique outlined in Altman 2003.

Sensitivity analysis

Where possible, we plan sensitivity analyses examining various aspects of trial and review methodology, including the effects of missing data, and inclusion of trials at high risk of bias (such as from lack of allocation concealment) and trials only reported in abstracts.

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* Indicates the major publication for the study

APPENDICES

Appendix I. Search strategies

The Cochrane Library (Wiley InterScience)

- #1 MeSH descriptor Anterior Cruciate Ligament explode all trees
- #2 (anterior NEAR/2 cruciate* NEAR/2 ligament*):ti,ab,kw
- #3 (#1 OR #2)
- #4 MeSH descriptor Joint Instability, this term only
- #5 MeSH descriptor Orthopedic Procedures, this term only
- #6 MeSH descriptor Tendon Transfer, this term only
- #7 MeSH descriptor Arthroscopy, this term only
- #8 MeSH descriptor Reconstructive Surgical Procedures, this term only
- #9 MeSH descriptor Transplants explode all trees
- #10 MeSH descriptor Transplantation, Autologous explode all trees
- #11 MeSH descriptor Tendons, this term only with qualifier: TR
- #12 (graft* or reconstruct* or autograft*):ti,ab,kw
- #13 (#4 OR #5 OR #6 OR #7 OR #8 or #9 or #10 or #11 or #12)
- #14 (double-bundle* or double bundle* or anatomic*):ti,ab,kw

#15 (single-bundle* or single bundle* or standard*):ti,ab,kw
 #16 (#14 AND #15)
 #17 (#3 AND #13 AND #16)

MEDLINE (OVID WEB)

1. Anterior Cruciate Ligament/
2. (anterior adj2 cruciate\$ adj2 ligament\$).tw.
3. or/1-2
4. Joint Instability/
5. Orthopedic Procedures/
6. Tendon Transfer/
7. Arthroscopy/
8. Reconstructive Surgical Procedures/
9. Transplants/
10. Transplantation, Autologous/
11. Tendons/tr or Tendons, Para-Articular/tr
12. (graft\$ or reconstruct\$ or autograft\$).tw.
13. or/4-12
14. (double-bundle\$ or double bundle\$ or anatomic\$).tw.
15. (single-bundle\$ or single bundle\$ or standard\$).tw.
16. and/14-15
17. and/3,13,16
18. randomized controlled trial.pt.
19. controlled clinical trial.pt.
20. randomized.ab.
21. placebo.ab.
22. drug therapy.fs.
23. randomly.ab.
24. trial.ab.
25. groups.ab.
26. or/18-25
27. exp animals/ not humans/
28. 26 not 27
29. and/17,28

EMBASE (OVID WEB)

1. Anterior Cruciate Ligament Rupture/
2. Anterior Cruciate Ligament/
3. (anterior adj2 cruciate\$ adj2 ligament\$).tw.
4. or/1-3
5. Tendon Graft/ or Tissue Graft/ or Muscle Graft/
6. Autograft/
7. exp Transplantation/
8. (graft\$ or reconstruct\$ or autograft\$).tw.
9. or/5-8
10. (double-bundle\$ or double bundle\$ or anatomic\$).tw.
11. (single-bundle\$ or single bundle\$ or standard\$).tw.
12. and/10,11
13. and/4,9,12
14. Clinical trial/
15. Randomized controlled trial/

16. Randomization/
17. Single blind procedure/
18. Double blind procedure/
19. Crossover procedure/
20. Placebo/
21. Randomized controlled trial\$.tw.
22. Rct.tw.
23. Random allocation.tw.
24. Randomly allocated.tw.
25. Allocated randomly.tw.
26. (allocated adj2 random).tw.
27. Single blind\$.tw.
28. Double blind\$.tw.
29. ((treble or triple) adj (blind\$)).tw.
30. Placebo\$.tw.
31. Prospective study/
32. Or/14-31
33. Case study/
34. Case report.tw.
35. Abstract report/ or letter/
36. Or/33-35
37. 32 not 36
38. and/13,37

HISTORY

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CONTRIBUTIONS OF AUTHORS

Thavatchai Tiamklang drafted the protocol. Sermsak Sumanont, Thanit Foocharoen and Malinee Laopaiboon revised and approved the protocol..

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Khon Kaen Hospital, Ministry of Public Health, Thailand.
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External sources

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ภาคผนวกที่ 6

รายชื่อผลงานวิจัยที่ได้รับการอ้างอิงในวารสารต่างประเทศ

มี Citation จำนวน 57 ครั้ง

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