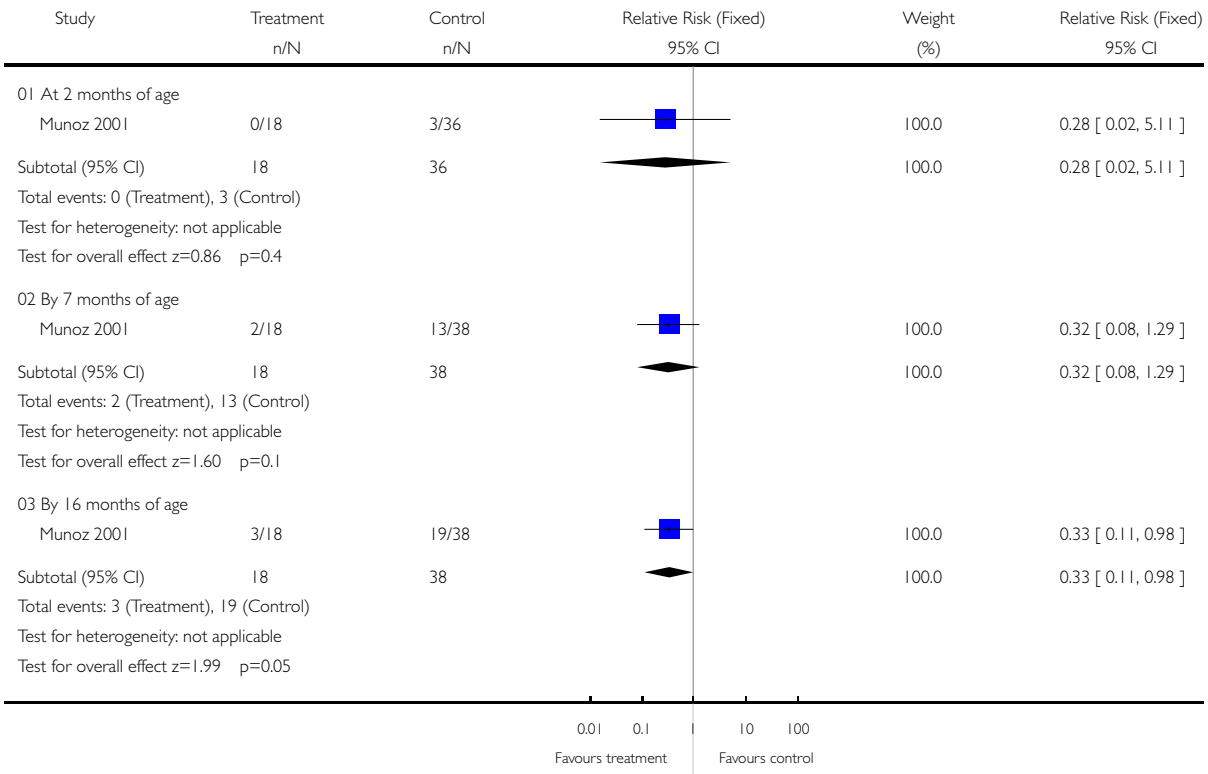
Analysis 01.02. Comparison 01 Pneumococcal vaccine versus control vaccine, Outcome 02 Pneumococcal colonisation

Review: Pneumococcal vaccination during pregnancy for preventing infant infection

Comparison: 01 Pneumococcal vaccine versus control vaccine

Outcome: 02 Pneumococcal colonisation



Analysis 01.03. Comparison 01 Pneumococcal vaccine versus control vaccine, Outcome 03 Neonatal antibody levels at birth

Serotype 6

Study	Treatment N	Treatment IgG GM	Treatment 95% CI	Control N	Control IgG GM	Control 95% CI
Munoz 2001	20	3.7	2.6 - 5.3	40	1.1	0.8 - 1.5
O' Dempsey 1996	43	2.7	1.7 - 4.4	26	5.7	2.9 - 11.3

Serotype 14

Study	Treatment N	Treatment IgG GM	Treatment 95% CI	Control N	Control IgG GM	Control 95% CI
Munoz 2001	19	13.4	7.3 - 25.1	39	3.0	2.2 - 3.9
O' Dempsey 1996	41	13.1	8.6 - 20.0	23	7.1	3.7 - 13.3

Serotype 19

Study	Treatment N	Treatment IgG GM	Treatment 95% CI	Control N	Control IgG GM	Control 95% CI
Munoz 2001	19	3.6	2.3 - 5.6	39	1.5	1.1 - 2.1
O' Dempsey 1996	43	4.1	2.7 - 5.9	24	3.6	1.8 - 7.3

Analysis 01.04. Comparison 01 Pneumococcal vaccine versus control vaccine, Outcome 04 Maternal antibody levels postvaccination

Serotype 6

Study	Treatment N	Treatment IgG GM	Treatment 95% CI	Control N	Control IgG GM	Control 95% CI
Munoz 2001	20	4.4	2.7 - 7.1	40	0.9	0.6 - 1.3
O' Dempsey 1996	49	7.3	4.4 - 12.0	26	14.4	6.4 - 32.7
Shahid 1995	29	13.8	NA	24	5.3	NA

Serotype 14

Study	Treatment N	Treatment IgG GM	Treatment 95% CI	Control N	Control IgG GM	Control 95% CI
Munoz 2001	20	16.8	8.0 - 35.5	40	3.0	2.2 - 4.0
O' Dempsey 1996	49	43.1	39.5 - 70.6	26	18.8	9.2 - 38.8

Serotype 19

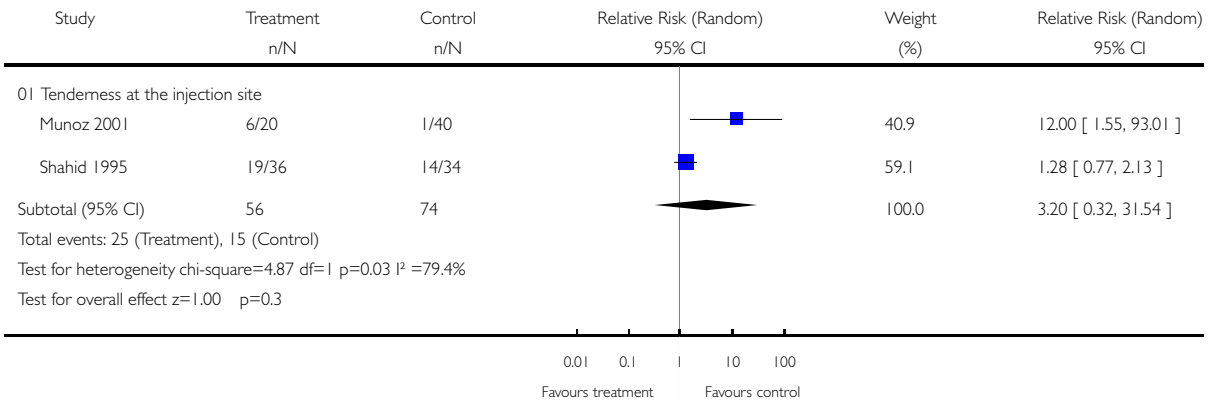
Study	Treatment N	Treatment IgG GM	Treatment 95% CI	Control N	Control IgG GM	Control 95% CI
Munoz 2001	20	3.7	2.3 - 6.0	40	1.4	1.0 - 1.9
O' Dempsey 1996	49	11.8	7.7 - 18.2	26	10.3	4.3 - 25.2
Shahid 1995	29	17.4	NA	24	4.7	NA

Analysis 01.05. Comparison 01 Pneumococcal vaccine versus control vaccine, Outcome 05 Adverse maternal effects

Review: Pneumococcal vaccination during pregnancy for preventing infant infection

Comparison: 01 Pneumococcal vaccine versus control vaccine

Outcome: 05 Adverse maternal effects



Prophylactic antibiotics for manual removal of retained placenta in vaginal birth (Review)

Chongsomchai C, Lumbiganon P, Laopaiboon M

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Prophylactic antibiotics for manual removal of retained placenta in vaginal birth (Review)

Chongsomchai C, Lumbiganon P, Laopaiboon M

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Chongsomchai C, Lumbiganon P, Laopaiboon M. Prophylactic antibiotics for manual removal of retained placenta in vaginal birth. *Cochrane Database of Systematic Reviews* 2006, Issue 2. Art. No.: CD004904. DOI: 10.1002/14651858.CD004904.pub2.

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Date of most recent substantive amendment: 12 December 2005

ABSTRACT

Background
Retained placenta is a potentially life-threatening condition because of its association with postpartum haemorrhage. Manual removal of placenta increases the likelihood of bacterial contamination in the uterine cavity.

Objectives
To compare the effectiveness and side-effects of routine antibiotic use for manual removal of placenta in vaginal birth in women who received antibiotic prophylaxis and those who did not and to identify the appropriate regimen of antibiotic prophylaxis for this procedure.

Search strategy
We searched the Cochrane Pregnancy and Childbirth Group Trials Register (30 November 2005), CENTRAL (*The Cochrane Library*, Issue 4, 2005), MEDLINE (from 1966 to January 2005), EMBASE (from 1980 to January 2005), CINAHL (from 1982 to January 2005) and LILACS (from 1982 to January 2005).

Selection criteria
All randomized controlled trials comparing antibiotic prophylaxis and placebo or non antibiotic use to prevent endometritis after manual removal of placenta in vaginal birth.

Data collection and analysis
If eligible trials were to be identified, trial quality would be assessed and data would be extracted, unblinded by two review authors independently.

Main results
No studies that met the inclusion criteria were identified.

Authors' conclusions
There are no randomized controlled trials to evaluate the effectiveness of antibiotic prophylaxis to prevent endometritis after manual removal of placenta in vaginal birth.

PLAIN LANGUAGE SUMMARY

No trials to say if women with retained placenta after giving birth would benefit from routine antibiotics prior to manual removal of placenta

Following the birth of her baby, a mother normally delivers the placenta with further pushing and support from her caregivers. Sometimes the placenta gets stuck on the wall of the womb (retained placenta) and does not deliver. These women usually require manual removal of the placenta under anaesthesia (either a general or regional). Infection and bleeding are the important complications

of manual removal. The review found no trials to determine whether antibiotics given routinely (prophylactically) to all women with retained placenta reduced the incidence of problems. Future trials need to address the risk of contributing to drug resistant bacterial strains.

BACKGROUND

Retained placenta is a potentially life-threatening condition because of the associated risk of haemorrhage, shock and infection as well as complications related to its removal (Chhabra 2002). This condition continues to be responsible for a high number of maternal fatalities worldwide (WHO 1989). Some studies have reported maternal mortality of 5.6% to nearly 10% in rural areas because of retained placenta (Chhabra 2002; Weeks 2001). Mortality due to retained placenta accounted for 3.33% of all mortality from vaginal deliveries (Chhabra 2002). The main clinical consequence of retained placenta is massive, uncontrolled postpartum haemorrhage, requiring immediate intervention (Stones 1993). This consequence may occur in about 10% of cases (Tandberg 1999).

The reported incidence of retained placenta varied from 1% to 5.5% depending on the definition of prolonged third stage of labour, which ranges from 10 to 60 minutes in various reports (Ely 1995; Selinger 1986; Thomas 1983; Weeks 2001). Retained placenta has been reported with an incidence of 3.3% when 30 minutes was used as the cut-off point (Combs 1991). There is still no definite agreement about the length of time that should elapse in the absence of bleeding before the placenta is removed manually (Cunningham 2001). When the third stage of labour nears 30 minutes or more the risk of haemorrhage increases (Combs 1991). Therefore 30 minutes is generally used as a criterion to diagnose retained placenta. When the placenta is not separated promptly after delivery of the baby, and if at any time there is brisk bleeding, the placenta can be removed by applying pressure to the body of the uterus and lifting the uterus cephalad by the hand over abdomen. This manoeuvre is repeated until the placenta reaches the introitus. Pressure on the uterus is then stopped, allowing the placenta to pass through (Prendiville 1988). If this technique is not possible, manual removal is indicated (Cunningham 2001). There is a Cochrane review indicating that an injection of oxytocin into the umbilical vein may reduce the need for manual removal of retained placenta (Carroli 2001). Even after this effective intervention, about 50% of women with retained placenta require manual removal (Carroli 2001).

Manual removal of the placenta involves inserting one hand through the vagina into the uterus. This procedure increases the likelihood of bacterial contamination in the uterine cavity. There is controversy whether manual removal of the placenta increases the risk of infection in the uterus. Some believe that it does (Ely 1995) but others believe it does not (Gibbs 1980; MacLean 1990). Ely 1995 reported that 6.7% of women with manual removal of placenta while 1.8% of women with normal placental delivery developed endometritis, adjusted odds ratio 2.9, 95% confidence interval 1.7 to 4.9. However, Tandberg 1999 and Thomas 1983 found no increased risk of infection following this procedure. All these studies were from developed countries. A report from low-income country did not give the incidence of endometritis among women undergoing manual removal of placenta. Prophylactic antibiotics after manual removal of placenta are routinely recommended by some (Carroli 1991; Loeffler 1995; Mathai 2000) but not by others (Ely 1995; Tandberg 1999).

Inappropriate use of antibiotics could have potential adverse effects including hypersensitivity, drug resistant strains, etc. Using the best current available data from randomized controlled trials, this review aims to determine whether prophylactic antibiotics reduce the incidence of endometritis.

OBJECTIVES

(1) To compare the effectiveness and side-effects of routine antibiotic use for manual removal of placenta in vaginal birth in women who received antibiotic prophylaxis and those who did not.
(2) To identify the appropriate regimen of antibiotic prophylaxis for this procedure by comparing the incidence of postpartum endometritis after manual removal of placenta in vaginal birth in women who received different antibiotic regimens (if antibiotic prophylaxis is found to be effective).

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomized controlled trials comparing antibiotic prophylaxis and placebo or non antibiotic use to prevent endometritis in manual removal of placenta after vaginal birth.

Types of participants

All pregnant women undergoing manual removal of placenta after vaginal birth with gestational age more than 22 weeks, or birthweight greater than 500 g (delivery regarded as birth not an abortion according to the International Classification of Diseases, 10th revision (ICD-10)) (WHO 1992).

Types of intervention

Antibiotic prophylaxis for manual removal of the placenta in vaginal birth.

Types of outcome measures

Main outcome

Postpartum endometritis (as defined by authors)

Secondary outcomes

Puerperal morbidity (defined as temperature 38.0 °C (100.4 °F) or higher, the temperature to occur on any two of the first 10 days postpartum, exclusive of the first 24 hours, and to be taken orally by a standard technique at least four times daily (Cunningham 2005))
Perineal infection
Duration of hospital stay
Sepsis
Any infection
Blood loss
Haemorrhage greater than 1000 ml
Secondary postpartum haemorrhage
Readmission to hospital
Side effects of drugs: drug resistant, women satisfaction, etc
Neonatal outcomes: jaundice, sepsis, neonatal intensive care unit admission, etc

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We searched the Cochrane Pregnancy and Childbirth Group Trials Register by contacting the Trials Search Co-ordinator (30 November 2005).

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) monthly searches of MEDLINE;
(3) handsearches of 30 journals and the proceedings of major conferences;
(4) weekly current awareness search of a further 37 journals.

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 'Search strategies for identification of studies' 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 searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library,* Issue 4, 2005) using the following search strategy:
#1 PLACENTA, RETAINED (MeSH)
#2 placenta* AND (retained or retention or remov*)
#3 ANTIBIOTICS (MeSH)
#4 antibiotic*
#5 #1 or #2
#6 #3 or #4
#7 #5 and #6

We also searched MEDLINE (from 1966 to January 2005), EMBASE (from 1980 to January 2005), CINAHL (from 1982 to January 2005) and LILACS (from 1982 to January 2005), adapting the search strategy by selecting appropriate subject headings and/or free text terms.

We planned to review abstracts and letters to the editor to identify randomized controlled trials that have not been published. If we had identified a randomized controlled trial, we would have contacted the primary investigator directly to obtain further data. We applied no language restrictions.

METHODS OF THE REVIEW

Three review authors undertook the review, Chompilas Chongsomchai (CC) conducting the literature search. Had there been studies found, we planned for CC and Pisake Lumbiganon to independently screen them, discarding studies that were clearly ineligible but aiming to be overly inclusive rather than risk losing relevant studies. In the process of screening any papers identified, we would not have been blinded to authorship or journal of origin. We would have evaluated trials under consideration for methodological quality using the methods described in the Cochrane Reviewers' Handbook (Higgins 2005). We intended to grade blinding of randomization, intervention and outcome measurement, and completeness of follow up: A: adequate; B: uncertain; C: inadequate. Two authors would have independently assessed whether studies met the inclusion criteria and disagreements would have been resolved by discussion.

Malinee Laopaiboon (a biostatistician) would have analysed the data using Review Manager 4.2 (RevMan 2003). For binary data, we would have calculated event rates, relative risk, and their corresponding 95% confidence intervals. For continuous data, we would have used mean difference. We intended to use forest plot, and the chi-squared test of heterogeneity to examine heterogeneity of results (using a 10% level of statistical significance and measuring the value of the I^2 statistic for degree of inconsistency (Higgins 2003)). If the detected heterogeneity could not be explained by any clinical or methodological variation, we would have used the random-effects model to estimate an overall effect of the prophylactic antibiotic after manual removal

of the placenta. We planned to perform subgroup analysis for preterm and post-term birth because the risk of infection might be different. We planned to perform sensitivity analysis to evaluate the robustness of the conclusion according to methodological quality of the trials.

DESCRIPTION OF STUDIES

No studies that met the inclusion criteria were identified.

METHODOLOGICAL QUALITY

Not relevant.

RESULTS

No results were obtained.

DISCUSSION

It is disappointing that no randomized controlled trials are available to assess the effectiveness of antibiotic prophylaxis in manual removal of placenta after vaginal birth.

AUTHORS' CONCLUSIONS

Implications for practice

There are no randomized controlled trials that have determined whether prophylactic antibiotics reduce the incidence of endometritis. Healthcare providers may consider following the World Health Organization's recent suggestion of a single dose of ampicillin 2 gm intravenously plus metronidazole 500 mg intravenously or cefazolin 1 g intravenously plus metronidazole 500 mg intravenously for manual removal of placenta in vaginal birth. The bases for this recommendation are that the antibiotics recommended cover aerobic and anaerobic flora commonly seen in the genital tract; they are widely available, are inexpensive and safe; and are used only at the time of the procedure to reduce the bacterial load during the procedure - in line with the principles of antibiotic prophylaxis for surgery.

Implications for research

Multicentre randomized controlled trials comparing antibiotic prophylaxis and placebo or no antibiotic use to prevent endometritis after manual removal of placenta in vaginal birth are urgently needed. The sample size for detecting the decreased incidence of endometritis from 6% to 3% with 80% power and two tailed significant level of 0.05 is approximate 780 for a two group comparison.

POTENTIAL CONFLICT OF INTEREST

None known.

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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), 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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GRAPHS AND OTHER TABLES

This review has no analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antibiotic Prophylaxis; Placenta, Retained [*therapy]; Postpartum Hemorrhage [*prevention & control]; Puerperal Infection [etiology; *prevention & control]

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title	Prophylactic antibiotics for manual removal of retained placenta in vaginal birth
Authors	Chongsomchai C, Lumbiganon P, Laopaiboon M
Contribution of author(s)	Chompilas Chongsomchai (CC) and Pisake Lumbiganon (PL) selected the topic. CC drafted the protocol and review. PL reviewed the protocol and review. CC, PL and Malinee Laopaiboon approved the final version of the protocol and review.
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Date of most recent amendment	12 December 2005
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What's New	Information not supplied by author
Date new studies sought but none found	30 November 2005
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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Laparoscopic surgery for presumed benign ovarian tumor during pregnancy (Review)

Bunyavejchevin S, Phupong V

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2007, Issue 4

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Laparoscopic surgery for presumed benign ovarian tumor during pregnancy (Review)

Bunyavejchevin S, Phupong V

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Date of most recent substantive amendment: 14 June 2006

ABSTRACT

Background
The surgical management of ovarian tumors in pregnancy is similar to that of non-pregnant women. The procedures include resection of the tumor (enucleation), removal of an ovary or ovaries (oophorectomy), or surgical excision of the fallopian tube and ovary (salpingo-oophorectomy). The procedure can be done by open surgery (laparotomy) or keyhole surgery (laparoscopy) technique. The benefits of laparoscopic surgery include shorter hospital stay, earlier return to normal activity, and reduced postoperative pain. However, conventional laparoscopic surgery techniques required the infusion of gas carbon dioxide in the peritoneum to distend the abdomen and displace the bowel upward to create the room for surgical manipulation. Serious complications such as abnormally high levels of carbon dioxide in the circulating blood (hypercarbia) and perforation of internal organs have also been reported. These serious complication may be harmful to the fetus.

Objectives
To compare the effects of using laparoscopic surgery for benign ovarian tumor during pregnancy on maternal and fetal health and the use of healthcare resources.

Search strategy
We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (1 June 2006).

Selection criteria
Randomized controlled trials with reported data that compared outcomes of laparoscopic surgery for benign ovarian tumor in pregnancy to conventional laparotomy technique.

Data collection and analysis
Two review authors planned to independently assess trial quality and extract data.

Main results
There were no randomized controlled trials identified.

Authors' conclusions
The practice of laparoscopic surgery for benign ovarian tumour during pregnancy is associated with benefits and harms. However, the evidence for the magnitude of these benefits and harms is drawn from case series studies, associated with potential bias. The results and conclusions of these studies must therefore be interpreted with caution.

The available case series studies of laparoscopic surgery for benign ovarian tumour during pregnancy provide limited insight into the potential benefits and harms associated with this new surgical technique in pregnancy. Randomized controlled trials are required to provide the most reliable evidence regarding the benefits and harms of laparoscopic surgery for benign ovarian tumour during pregnancy.

PLAIN LANGUAGE SUMMARY

No randomized controlled trials to compare 'open surgery' with 'keyhole surgery' in pregnant women for non-malignant tumors of the ovary

A small number of women have tumors of the ovaries diagnosed during pregnancy. Most of these tumors are not malignant, and if they are small then treatment can be left until after the birth. However, if the tumour is larger that 6 cm in diameter, it is suggested that it is better to operate and remove them during pregnancy, as they may interfere with the birth of the baby. Surgical procedures for these non-malignant tumors of the ovary in pregnancy can be performed by open surgery (laparotomy) or keyhole surgery (laparoscopy) techniques. Historically, open surgery has been used, but new keyhole surgery seems attractive in that it appears to require a shorter hospital stay and there is a quicker return to normal activities for women. However, the infusion of gas into the abdomen during the key-hole procedure may have adverse effects on the baby, and an additional gasless technique is also under study. This review aimed to address the question of which surgical technique might be better as all have benefits and risks to the mother and the baby. There were no randomized controlled trials identified that compared the effects of using keyhole surgery for benign tumors of the ovary during pregnancy on maternal and fetal health. There was some evidence available from case series studies, but more research is needed on the potential benefits and harms associated with this new surgical technique in pregnancy.

BACKGROUND

Ultrasound scanning during early pregnancy has increased the number of ovarian tumors identified. The ovarian tumor can be classified as benign or malignant. During pregnancy, ovarian tumors are mostly benign. Most women present with the problem of discrepancy between the uterine size and gestational age, palpable mass, and abdominal pain. The serous cystadenoma and dermoid cyst are the two most common pathologies found (Hess 1988; Jacob 1990). Ovarian tumor in pregnancy requiring surgical intervention has an incidence ranging from 0.0004% to 0.36% (Graber 1974; Sherard 2003; Wang 1999). The surgical procedure is similar to that of non-pregnant women. Elective surgical removal is recommended for any mass larger than 6 cm in diameter that continues to exist into the second trimester, unless the mass is suspected to be a uterine fibroid (leiomyoma) (Hess 1988). There are the risks of torsion, rupture or leakage of the cysts as pregnancy advances.

The surgical treatment performed is resection of the tumor (enucleation), removal of an ovary or ovaries (oophorectomy), or surgical excision of the fallopian tube and ovary (salpingo-oophorectomy). The surgery can be done by open surgery (laparotomy) or keyhole surgery (laparoscopy) technique (Pittaway 1994). Laparoscopic surgery involves using an endoscope inserted into or through the abdominal wall to view abdominal, or pelvic organs, or both, while operating with instruments introduced through separate small incisions.

Laparoscopic surgery has been extensively used as a treatment for many diseases. It has been performed successfully in pregnancy for many conditions, for example removal of the gallbladder (cholecystectomy) (Pucci 1991; Soper 1992), removal of the appendix (appendectomy) (Schreiber 1990), and ovarian torsion (Lang 1992; Shalev 1990). In case of suspected malignant ovarian tumor, the laparoscopic surgery should be avoided due to the risk of port site metastasis and inadequate surgical staging (Agostini 2002; Morice 2000; Morice 2004).

The benefits of laparoscopic surgery include shorter hospital stay, earlier return to normal activity, and reduced postoperative pain (Mais 1995). However, conventional laparoscopic surgery techniques required the infusion of gas carbon dioxide in the peritoneum to distend the abdomen and displace the bowel upward to create the room for surgical manipulation. Serious complications such as hypercarbia and perforation of internal organs have also been reported. Many reports recommend clinicians avoid using the gas carbon dioxide to inflate the abdomen, as animal studies suggest that it increases intra-abdominal pressure which leads to the decrease of the uterine blood flow which can be hazardous to the fetus (Jansen 1979). A further animal study confirmed this finding and reported decreased uterine blood flow from using the gas carbon dioxide pneumoperitoneum (Curet 1996). Thus, the new method of the gasless laparoscopic technique has been suggested (Akira 1999).

Since the 1990s, there have been many reports exploring the relative merits and potential risks of laparoscopic surgery for benign ovarian tumors in pregnancy (Lin 2003; Nezhat 1991; Yamada 2004). Evidence for the safety of the laparoscopic technique during pregnancy has not been fully evaluated.

OBJECTIVES

To compare the effects of using laparoscopic surgery for benign ovarian tumor during pregnancy on maternal and fetal health and the use of healthcare resources.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomized controlled trials examining laparoscopic surgery for benign ovarian tumor in pregnancy compared to conventional laparotomy technique.

Types of participants

Women with benign ovarian tumor during pregnancy.

Types of intervention

Randomized allocation of women with benign ovarian tumor in pregnancy to laparoscopic surgery or conventional laparotomy technique.

Types of outcome measures

Primary outcome

Maternal complications: wound infection, thromboembolism, surgical injury to bladder, ureter, bowel.

Secondary outcomes

Maternal

Operating time (minutes)
Intraoperative blood loss
Recurrent rate: the incidence of second operation due to the reoccurrence of the tumor in the same ovary
Complications during labor; uterine rupture
Miscarriage
Caesarean section
Postpartum hemorrhage
Anemia (hematocrit is less than 33%)
Need for conversion (defined as a procedure initiated as laparoscopic but converted to open, or a procedure initiated as open but converted to laparoscopic)
Time to return to usual activities (days)
Rate of adhesion detections
Pain intensity (during the first three postoperative days)
Maternal death
Quality of life assessment
Participant's acceptability

Neonatal

Gestational age less than 37 weeks at birth
Gestational age at birth
Apgar score (less than seven at five minutes)
Low cord pH
Intubation required
Use of mechanical ventilation
Seizures
Infection
Jaundice
Intracranial pathology
Perinatal death

Use of health service resources

For the woman: length of postoperative hospital stay, re-admission to hospital
For the infant: admission to special care

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (1 June 2006).

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) monthly searches of MEDLINE;
(3) handsearches of 30 journals and the proceedings of major conferences;
(4) weekly current awareness search of a further 37 journals.

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 'Search strategies for identification of studies' 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.

We did not apply any language restrictions.

METHODS OF THE REVIEW

Selection of studies

We planned to assess for inclusion all potential studies identified as a result of the search strategy and resolve any disagreement through discussion. All assessments of the quality of trials and data extraction would have been performed independently by both review authors (S Bunyavejchevin (SB) and V Phupong (VP)) using forms designed according to Cochrane guidelines. Both authors (SB and VP) are experts on clinical issues and one author has statistical expertise (SB). If necessary, additional information on trial methodology or actual original trial data would had been

sought from the principal author of any trials which appeared to meet the eligibility criteria.

Assessment of study validity

We planned to assess the validity of each study using the criteria outlined in the Cochrane Reviewers' Handbook (Alderson 2004). Each study was to be assessed for quality of allocation of concealment, completeness to follow up and blinding in the assessment of outcome.

(1) Allocation concealment

We planned to 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;
(C) inadequate concealment of allocation, such as open list of random number tables, sealed envelopes;
(D) not used.

(2) Completeness to follow up

We planned to assess completeness to follow up using the following criteria:
(1) A - less than 5% participants excluded;
(2) B - 5% to 10% of participants excluded;
(3) C - more than 10% and less than 20% of participants excluded;
(4) D - more than 20% of participants excluded.

We would have excluded studies if:
(1) more than 20% of participants excluded;
(2) more than 20% of analysis not in randomization groups and not possible to restore participants to correct group;
(3) large differences (more than 10%) in withdrawal of participants between randomized groups.

(3) Blinding

We planned to 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).

(4) Data extraction

We planned to design a form to extract data. Both authors would have extracted the data using the agreed form. Both authors planned to separately extract and double-enter the data. Discrepancies would have been resolved through discussion. We planned to use the Review Manager software (RevMan 2003) to enter the data and double check them. There was to be no blinding of authorship.

(5) Statistical analyses

We planned to carry out statistical analysis using the Review Manager software (RevMan 2003). We planned to use fixed-effect meta-analysis for combining data if trials are sufficiently similar.

For dichotomous data, we were to present results as summary relative risk with 95% confidence intervals.

For continuous outcomes the weighted mean difference was to be used if outcomes were measured in the same way between trials. We planned to use the standardized mean difference to combine trials that measure the same outcome, but use different methods. If there was evidence of skewness this would be reported.

We planned to analyze data on an intention-to-treat basis. Therefore all participants would be included in the analysis in the group to which they were allocated, regardless of whether or not they received the allocated intervention. If in the original reports participants were not analyzed in the group to which they were randomized, and there was sufficient information in the trial report, we planned to attempt to restore them to the correct group.

Tests of heterogeneity between trials was to be applied if appropriate using the I^2statistic and reported as a fixed-effect summary. If we identified high levels of heterogeneity among the trials, levels exceeding 50%, we planned to explore it by prespecified subgroup analysis and perform sensitivity analysis. A random-effects meta-analysis would be used as an overall summary.

Planned subgroup analysis

We planned to carry out subgroup analyses on gas laparoscopic surgery versus gasless laparoscopic surgery.

DESCRIPTION OF STUDIES

There were no randomized controlled trials identified from the search strategy.

METHODOLOGICAL QUALITY

There were no randomized controlled trials identified from the search strategy.

RESULTS

There were no randomized controlled trials identified from the search strategy.

DISCUSSION

There were no randomized controlled trials identified that compared the effects of using laparoscopic surgery for benign ovarian tumor during pregnancy on maternal and fetal health and the use of healthcare resources.

There are risks and benefits for both laparoscopic surgery and laparotomy in pregnancy, current sources of information are limited

to only case series reports (Loh 1998; Oguri 2005; Patacchiola 2005).

To confirm the safety of laparoscopic treatment for benign ovarian tumour during pregnancy, there is a need for methodologically rigorous studies to provide direct evidence about the relative benefits and harms of and for laparoscopic surgery for benign ovarian tumor compared to laparotomy in pregnancy. This information is best obtained from randomized controlled trials, as this methodology limits the potential for bias and provides the most reliable evidence regarding the benefits and harms of both forms of surgery.

AUTHORS' CONCLUSIONS

Implications for practice

The practice of laparoscopic surgery for benign ovarian tumour during pregnancy are associated with benefits and risks. However, the evidence for the magnitude of these benefits and harms is drawn from case series studies, associated with potential bias. The results and conclusions of these studies must therefore be interpreted with caution.

Implications for research

The available case series studies of laparoscopic surgery for the benign ovarian tumour during pregnancy provide limited insight into the potential benefits and harms associated with this new surgical technique in pregnancy. Randomized controlled trials are required to provide the most reliable evidence regarding the benefits and harms of laparoscopy surgery for the benign ovarian tumour during pregnancy. Outcomes of interest could be those listed in this review.

POTENTIAL CONFLICT OF INTEREST

None known.

ACKNOWLEDGEMENTS

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), one or more members of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

SOURCES OF SUPPORT

External sources of support

- Thai Cochrane Network THAILAND

Internal sources of support

- Faculty of Medicine, Chulalongkorn University THAILAND

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GRAPHS AND OTHER TABLES

This review has no analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

*Laparoscopy [adverse effects]; Ovarian Neoplasms [*surgery]; Pregnancy Complications, Neoplastic [*surgery]

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title Laparoscopic surgery for presumed benign ovarian tumor during pregnancy

Authors	Bunyavejchevin S, Phupong V
Contribution of author(s)	S Bunyavejchevin: developed the basis of the protocol, performed the background literature search, drafted the protocol and the review, and revised the drafts in response to editorial comments. V Phupong: performed the background literature search, and helped draft the protocol and review.
Issue protocol first published	2005/3
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What's New	Information not supplied by author
Date new studies sought but none found	01 June 2006
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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Prophylactic use of ergot alkaloids in the third stage of labour (Review)

Liabsuetrakul T, Choobun T, Peeyananjarassri K, Islam QM

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2007, Issue 4

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Prophylactic use of ergot alkaloids in the third stage of labour (Review)

Liabsuetrakul T, Choobun T, Peeyananjarassri K, Islam QM

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ABSTRACT

Background
Previous research has shown that the prophylactic use of uterotonic agents in the third stage of labour reduces postpartum blood loss and moderate to severe postpartum haemorrhage. This is one of a series of systematic reviews assessing the effects of prophylactic use of uterotonic drugs - here, prophylactic ergot alkaloids compared with no uterotonic agents, and different regimens of administration of ergot alkaloids.

Objectives
To determine the effectiveness and safety of prophylactic use of ergot alkaloids in the third stage of labour compared with no uterotonic agents, as well as with different routes or timing of administration for prevention of postpartum haemorrhage.

Search strategy
We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 December 2006), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2006, Issue 4) and MEDLINE (1966 to December 2006).

Selection criteria
All randomised or quasi-randomised controlled trials comparing prophylactic ergot alkaloids with no uterotonic agents or comparing different routes or timings of administration of ergot alkaloids in the third stage of labour among women giving birth vaginally.

Data collection and analysis
We systematically reviewed the potential studies, considered eligible studies, assessed the validity of each included study and extracted data independently.

Main results
We included six studies comparing ergot alkaloids with no uterotonic agents, with a total of 1996 women in ergot alkaloids group and 1945 women in placebo or no treatment group. The use of injected ergot alkaloids in the third stage of labour significantly decreased mean blood loss (weighted mean difference -83.03 ml, 95% confidence interval (CI) -99.39 to -66.66 ml) and postpartum haemorrhage of at least 500 ml (relative risk (RR) 0.38, 95% CI 0.21 to 0.69). The risk of retained placenta or manual removal of the placenta, or both, were inconsistent. Ergot alkaloids increased the risk of vomiting (RR 11.81, 95% CI 1.78 to 78.28), elevation of blood pressure (RR 2.60, 95% CI 1.03 to 6.57) and pain after birth requiring analgesia (RR 2.53, 95% CI 1.34 to 4.78). One study compared oral ergometrine with placebo and showed no significant benefit of ergometrine over placebo. No maternal adverse effects were reported. There were no included trials that compared different administration regimens of ergot alkaloids.

Authors' conclusions
Prophylactic intramuscular or intravenous injections of ergot alkaloids are effective in reducing blood loss and postpartum haemorrhage, but adverse effects include vomiting, elevation of blood pressure and pain after birth requiring analgesia, particularly with the intravenous route of administration.

PLAIN LANGUAGE SUMMARY

Active management of third stage of labour with ergot alkaloid drugs (e.g. ergometrine)

The third stage of labour is the period from birth of the baby to the expulsion of the placenta and membranes. As the placenta separates, there is inevitably some blood loss from the placental site until the muscles of the uterus clamp the blood vessels. Fit, healthy women cope with this normal blood loss without problems, but where poor nutrition, poor sanitation and limited or no access to clinical care are complications of pregnancy, severe morbidity and mortality can result from excessive blood loss at birth. This is very common in low- and middle-income countries. Active intervention, called 'active management of third stage', is recommended for the third stage of labour to reduce excess blood loss. Active intervention incorporates 1) the administration of a uterotonic drug, given either just before or just after the baby is born to help the muscles of the uterus contract; 2) early cord clamping and 3) the use of controlled cord traction to deliver the placenta. This review of studies looked at the use of one group of uterotonic drugs called ergot alkaloids, e.g. ergometrine, as part of this active management. The review found six trials involving 3941 women receiving ergometrine by mouth (orally), into the muscle (intramuscularly, IM) or into the vein (intravenously, IV). Evidence indicates that the oral route was not very effective. The IV route, although it reduced blood loss, was associated with the adverse effects of retained placenta, raised blood pressure, nausea, vomiting and pain, and so is unlikely to be used. The IM route showed benefit in terms of reducing blood loss, and although there were adverse effects similar to those associated with the IV route, these were less common. So, while the ergot alkaloid group of drugs given IM is an option, there are other drugs, namely oxytocin and prostaglandins (which are assessed in other Cochrane reviews), that can be used and may be preferable.

BACKGROUND

The third stage of labour is defined as the period of labour from birth of the baby to the expulsion or extraction of the placenta and membranes. Placental separation involves capillary haemorrhage and shearing of decidua spongiosa because of the mechanical action of uterine contraction. Blood loss during the third stage of labour depends on the time between placental separation and contraction of the placental bed by uterine activity. Most women experience mild to moderate blood loss. However, the third stage of labour can be a potentially hazardous period of childbirth resulting in postpartum haemorrhage (PPH). The World Health Organization (WHO) defines PPH as blood loss after delivery of 500 ml or more (WHO 2000).

According to WHO estimates of maternal mortality in 2000, approximately 529,000 maternal deaths occur globally every year (WHO 2004). Almost all maternal deaths occur in low- and middle-income countries. The most common preventable causes of maternal death are haemorrhage, pregnancy-induced hypertension and sepsis (Sloan 2001). Unfortunately, due to socio-economic conditions, dwindling investment in health, and non- or poorly-functioning health systems, many women are unable to access essential care during pregnancy, childbirth and the postpartum period. One of the most common causes of maternal death worldwide is PPH (McCormick 2002; WHO 2001).

Active management of the third stage of labour

Active management of the third stage of labour before the occurrence of PPH is better than treatment when blood loss is of 500 ml or more. The third stage of labour is an important and critical period for interventions to reduce the incidence of PPH (De Groot 1995). PPH can be reduced by the active management of the third stage of labour. Active management involves prophylactic use of oxytocic drugs; early clamping and division of the umbilical cord; and controlled cord traction for delivery of the placenta (WHO 2003). The advantages of active management over expectant management - which is waiting for signs of placental separation and allowing the placenta to deliver spontaneously or aided by gravity or nipple stimulation, is the reduction in blood loss, PPH and other serious complications of the third stage of labour (Prendiville 2000). The most common cause of PPH is uterine atony. Active management of the third stage of labour helps to increase uterine contractions and prevent PPH. Although active management of the third stage of labour is associated with reductions of PPH, prolonged third stage of labour, and the use of therapeutic oxytocic drugs, it results in an increase in nausea, vomiting, headache and hypertension when ergometrine is used (Prendiville 2000). Three recommendations for active management in the third stage of labour are administration of an uterotonic drug within one minute of the birth of the baby, clamping and cutting the umbilical cord soon after birth, and delivering the placenta by applying controlled cord traction during a strong uterine contraction (Den Hertog 2001; McCormick 2002). Combined controlled cord traction in active management of the third stage reduces the time of the third stage, the incidence of PPH and retained placenta and the need for additional oxytocic agents when compared to using only uterotonic drugs (Brucker 2001).

Uterotonic agents

The uterotonic agents are divided into three groups: ergot alkaloids, oxytocin and prostaglandins (De Groot 1998; Den Hertog 2001). Their mechanisms of preventing PPH are different. Methylergometrine is the most common type of ergot alkaloid; it

increases the muscle tone of the uterus, with superimposed fast rhythmic contractions of the myometrium and tetanic contraction for several hours resulting in compressed myometrial blood vessels. Oxytocin acts through oxytocin receptors in myometrium and decidua leading to fast and long-lasting contractions upon basal tone of the myometrium. Syntometrine, consisting of five units of oxytocin and 0.5 mg of ergometrine, has been designed to take advantage of the rapid onset of action of oxytocin with longer action of ergometrine. Carbetocin is similar to oxytocin, but it has a rapid onset and prolonged duration of action relative to oxytocin. Its effectiveness compared to oxytocin is still awaiting final evaluation. Finally, prostaglandins induce strong myometrial contraction by increasing uterine tone (De Groot 1995). There are several Cochrane systematic reviews already published about the use of various uterotonic drugs in the third stage of labour for preventing PPH (Cotter 2001; Gulmezoglu 2004; McDonald 2004; Prendiville 2000).

Recent studies have highlighted oxytocin as the first line drug used for prophylaxis based on the evidence of its benefit in terms of reducing PPH compared to using no uterotonic drugs, and its favourable side effect profile (Cotter 2001). However, the use of the combination preparation of ergot alkaloid plus oxytocin, syntometrine, is associated with a statistically significant reduction of PPH when compared with oxytocin alone, attributable to the ergometrine effect (McDonald 2004). Because of the effect of strong and lasting uterine contraction, ergometrine has been used as one of the uterotonic drugs of choice for preventing PPH.

Ergometrine is ergot in origin and was recovered first as a product of a fungus, *Claviceps Purpurea*, and used in obstetrics for the first time in 1582. This use ended in 1822 due to uterine rupture, stillbirth and maternal death from inaccurate doses and ergotism (gangrene and convulsive forms) (De Groot 1998; Van Dongen 1995). However, ergot alkaloids were found to be more useful and less harmful for obstetric practice in the form of ergometrine in 1932 by Moir and Dale (Dunn 2002). They have specific uterotonic action through adrenergic receptors with less vasoconstrictive ability and they prevent excessive bleeding after childbirth. Two chemical ergot alkaloids are ergonovine/ergometrine maleate (ergotrate) and methylergonovine/methylergometrine maleate (methergine). They produce persistent uterine contractions in the inner zone of myometrium through calcium channel mechanisms and actinmyosin interaction leading to the shearing effect on placental separation and less blood loss or PPH, but they may increase the risk of maternal side-effects such as hypertension and other complications of vasoconstriction (Brucker 2001; De Groot 1998; Dua 1994; Gowri 2003; Sultatos 1997; Taylor 1985). In addition, the risks of partial retention or trapping of the placenta or both, manual removal of placenta, uterine inversion or cord avulsion are still concerns with ergometrine administration (Sorbe 1978).

Different types of ergot alkaloid, and different routes and timing of administration have been used for both prophylactic and therapeutic purposes (Andersen 1998; Borri 1986; De Groot 1996b; Moir 1979; Van Selm 1995). The most common ergot alkaloids for obstetric treatment are ergometrine and methylergometrine. Both injectable ergometrine and methylergometrine are very unstable when stored unrefrigerated, and deteriorate with higher storage temperatures and exposure to light; therefore, they need to be stored in a dark place at a temperature of 4º to 8º Celsius. Their oral forms also deteriorate within weeks or immediately after being taken from a sealed package or container or when stored in increased temperatures and high humidity. Intravenous methylergometrine administration induces both increased frequency of uterine contractions and basal tone with a decrease of amplitude lasting at least 30 minutes and maintained for 60 to 90 minutes. On the other hand, the uterine effect following oral administration is detected in 20 to 30 minutes, peaks at 60 to 70 minutes and is maintained for 120 minutes but its effect is unpredictable (De Groot 1996a; De Groot 1996b). Injectable oxytocin is much more stable than ergometrine and methylergometrine (De Groot 1996a; De Groot 1998; Hogerzeil 1996). Although the chemical instability and the side effects of ergot alkaloids are of concern, clinical trials on the use of ergot alkaloids in the third stage of labour for prevention of PPH have been conducted (Andersen 1998; De Groot 1996b; Sorbe 1978). Oral or vaginal forms of ergot alkaloids might be useful for women in some areas where intravenous administration is not possible. A systematic review on the effectiveness and safety of ergot alkaloids in the third stage of labour is needed.

Previous systematic reviews on the prevention of PPH

Systematic reviews on the comparison of ergot alkaloid versus prostaglandins, oxytocin and syntometrine are published in *The Cochrane Library* (Cotter 2001; Gulmezoglu 2004; McDonald 2004; Prendiville 2000). Nevertheless, there still is a gap in knowledge on the effectiveness and safety of prophylactic use of ergot alkaloids in the third stage of labour compared to no uterotonic drugs, as well as of different routes or timings of administration for prevention of PPH.

OBJECTIVES

To determine the effectiveness and safety of the prophylactic use of ergot alkaloids in the third stage of labour, compared with no uterotonic agents, and to assess different routes or timing of administration for prevention of postpartum haemorrhage.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomised or quasi-randomised controlled trials comparing prophylactic ergot alkaloids (using any route and timing of admin-

istration) with no uterotonic agents or trials comparing different routes or timing of administration of ergot alkaloids in the third stage of labour.

Types of participants

Pregnant women anticipating a vaginal delivery.

Types of intervention

Any ergot alkaloid given prophylactically, by whatever route or timing of administration, compared with no uterotonic agents. Due to pharmacokinetic differences between different routes and timings of administration, we planned to evaluate separately oral versus intravenous or intramuscular ergot alkaloids and administration before versus after placental delivery.

The following three comparisons were reviewed:
(1) ergot alkaloids versus no uterotonic agents;
(2) different routes of ergot alkaloids: oral versus intravenous;
(3) different timing of administration: before versus after placental delivery.

As comparisons of ergot alkaloids with other uterotonic agents have been reviewed in other reviews in *The Cochrane Library*, such studies were not eligible for inclusion in this review.

Types of outcome measures

We selected the outcome measures based on factors relating to the effectiveness and safety of ergot alkaloids in terms of clinical relevance in both maternal and neonatal outcomes.

Maternal outcomes
(1) Mean blood loss
(2) Postpartum haemorrhage (PPH) (clinically estimated or measured blood loss of 500 mls or more)
(3) 'Severe' PPH (clinically estimated or measured blood loss of 1000 mls or more)
(4) Maternal haemoglobin concentration at 24 to 48 hours postpartum
(5) Retained placenta or manual removal of the placenta, or both
(6) Blood transfusion
(7) Use of therapeutic uterotonics
(8) Third stage of labour lasting more than 30 minutes
(9) Vomiting
(10) Nausea
(11) Elevation of blood pressure
(12) Headache (not prespecified)
(13) Pain after birth requiring analgesia (not prespecified)
(14) Eclamptic fit (not prespecified)
(15) Postnatal haemoglobin less than 10 gm (not prespecified)
(16) Uterine subinvolution at routine follow up (not prespecified)
(17) Postpartum febrile morbidity (not prespecified)

Neonatal outcomes
(1) Apgar score equal to or less than six at five minutes
(2) Jaundice
(3) Not breastfed at discharge
(4) Admission to neonatal intensive care unit

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (December 2006).

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) monthly searches of MEDLINE;
(3) handsearches of 30 journals and the proceedings of major conferences;
(4) weekly current awareness search of a further 37 journals.

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 'Search strategies for identification of studies' 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 searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2006, Issue 4) and MEDLINE (1966 to 30 December 2006) using the following search strategy (adapted for each database):

#1 ERGOT ALKALOIDS explode tree 1 (MeSH)
#2 (ergot next alkaloid*)
#3 ergoline*
#4 ergotamine*
#5 ergonovine
#6 metergoline
#7 methysergide
#8 nicergoline
#9 dihydroergotamine
#10 dihydroergotoxine
#11 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10)
#12 POSTPARTUM HEMORRHAGE single term (MeSH)
#13 (postpartum next hemorrhage)
#14 (postpartum next haemorrhage)
#15 (post next partum next haemorrhage)
#16 (post next partum next hemorrhage)

#17 (uterine next atony)
#18 (uterine next bleed*)
#19 pph
#20 LABOR STAGE THIRD single term (MeSH)
#21 (third next stage)
#22 (#12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21)
#23 (#11 and #22)

We did not apply any language restrictions.

METHODS OF THE REVIEW

We used the methods as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005).

Selection of studies

The contact author (Tippawan Liabsuetrakul (TL)) assessed all potential studies identified as a result of the search strategy, using title and abstract, and searched for the full texts. Two authors (TL and Krantarat Peeyananjarassri) reviewed the full texts regarding types of studies, participants, interventions and outcomes, based on the prespecified inclusion criteria and using a trial eligibility form. We resolved any disagreement through discussion.

Assessment of study validity

Two authors (TL and Thanapan Choobun (TC)) assessed the validity of each included study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005). We assessed each study for quality of allocation of concealment, completeness to follow up and blinding. We considered the analysis of participants in the groups to which they were initially assigned (intention to treat). There was no attempt to mask the authors' names, institutions, source of the publication or results when applying the inclusion criteria. TL and TC independently assessed the study validity using prepared data extraction forms. The quality of included studies was assessed qualitatively using the CONSORT statement on reporting the results of randomised controlled trials (Moher 2001). We resolved any discrepancies by discussion and reached consensus through discussion.

(1) Allocation concealment

We assigned a quality score for each trial, using the following criteria:
(A) adequate concealment of allocation: centralized randomisation schemes; randomisation schemes controlled by a pharmacy; numbered or coded containers in which capsules from identical-looking, numbered bottles are administered sequentially; on-site computer systems, where allocations are in a locked unreadable file; and sequentially numbered opaque, sealed envelopes;
(B) unclear concealment of allocation such as list or table used, sealed envelopes or study does not report any concealment approach;
(C) inadequate concealment of allocation: alternation, the use of case record numbers, dates of birth or day of the week or open list of random numbers;
(D) not used.

(2) Completeness of follow up

We assessed completeness of follow up using the following criteria:
(A) less than 5% of participants excluded;
(B) 5% to 10% of participants excluded;
(C) more than 10% to 20% of participants excluded;
(D) more than 20% of participants excluded.

(3) Blinding

We assessed blinding using the following criteria:
(A) blinding of participants (yes/no/unclear);
(B) blinding of caregiver (yes/no/unclear);
(C) blinding of outcome assessment (yes/no/unclear).

Data extraction

We designed a form to extract the data. TL and TC extracted the data using the agreed form. We resolved discrepancies through discussion. We used the Review Manager software (RevMan 2003) to enter the data and double check them.

Statistical analyses

We carried out statistical analysis using the Review Manager software (RevMan 2003). We used fixed-effect meta-analysis for combining data if studies are sufficiently similar. The data on specific comparison groups between ergot alkaloids versus placebo or no treatment were extracted for analysis.

For dichotomous data, we presented the results as summary relative risks with 95% confidence intervals.

For continuous outcomes, the weighted mean difference was used if outcomes were measured in the same way between studies. We used the standardised mean difference to combine studies that measured the same outcome but used different methods.

We analysed data on an intention-to-treat basis. Therefore all included participants were analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. If, in the original reports, participants were not analysed in the group to which they were randomised, and there was sufficient information in the study report, we attempted to restore them to the correct group.

Assessment of heterogeneity

Tests of heterogeneity between studies were applied if appropriate using the I-squared statistic. If there was no evidence of heterogeneity, the results were reported as a fixed-effect summary. If we identified levels of heterogeneity among the studies exceeding 50%, we explored them by subgroup analysis and performed sensitivity analysis based on trial quality. A random-effects meta-analysis was used as an overall summary when this was considered appropriate.

Sensitivity analysis

We prespecified that we would perform the following sensitivity analysis by the quality of included studies: excluding trials where allocation concealment is inadequate (C).

Subgroup analyses

We planned to carry out the following subgroup analyses:

- Risk of having a postpartum haemorrhage: high risk versus low risk.
- Route of administration of ergot alkaloids: intramuscular or intravenous compared with oral route.

DESCRIPTION OF STUDIES

We identified 55 references from the literature search. We excluded 29 studies by screening using title, abstract or repetitive references of previous Cochrane Reviews; these include nine studies where the comparison was with prostaglandin (Amant 1999; Baumgarten 1983; Caliskan 2002; Chatterjee 2000; Diab 1999; Lam 2004; Penaranda 2002; Rajwani 2000; Vimala 2004), 11 studies where oxytocin was the comparator (Barbaro 1961; Bonham 1963; Docherty 1981; Francis 1965a; Francis 1965b; Fugo 1958; Huh 2004; Kikutani 2003; Soiva 1964; Stearn 1963; Symes 1984), syntometrine in seven studies (Khan 1995; Lamont 2001; Mitchell 1993; Nieminen 1963; Vaughan 1974; Yardim 1967; Yuen 1995), nipple stimulation in one study (Badhwar 1991), and syntometrine (OCM 505) in one study (Carpén 1968). We then evaluated the full texts of the remaining 26 studies, and excluded 20 of these: 12 because the studied intervention was not that of this review (Chukudebelu 1963; Forster 1957; Groeber 1960; Moir 1979; Moore 1956; Paull 1977; Pei 1996; Ramesh 1983; Reddy 2001; Rooney 1985; Thilaganathan 1993; Thornton 1988); three because the studies were not randomised controlled trials (Friedman 1957; Hacker 1979; Sorbe 1978); four because there were no outcomes of interest (Ilancheran 1990; Jolivet 1978; Terry 1970; Weiss 1975), and the remaining study because it did not include women having a vaginal delivery (Dweck 2000). Therefore, this review includes six randomised controlled trials. The details of all excluded studies are in the table 'Characteristics of excluded studies'.

Included studies

A total of 3941 women participated in the six included studies comparing any ergot alkaloids with placebo or no treatment (Begley 1990; Daley 1951; De Groot 1996b; Howard 1964; Kerekes 1979; McGinty 1956). There were no included trials that compared different administration regimens of ergot alkaloids.

(1) Study location and settings

All studies were conducted in developed countries with low maternal mortality ratios, namely England, Hungary, Ireland, the Netherlands, and the United States.

(2) Participants

All participants included in these studies were delivered vaginally. The criteria for inclusion and exclusion were clearly defined in three studies (Begley 1990; Daley 1951; De Groot 1996b). One study identified participants as women who had a spontaneous vaginal delivery without complications; definition of complications were not given (Kerekes 1979). The remaining two studies included women who delivered vaginally; the exclusion criteria were not provided in the report (Howard 1964; McGinty 1956). Women with hypertension or cardiovascular diseases were excluded from participating in two studies (Begley 1990; De Groot 1996b).

(3) Interventions

The studies compared ergot alkaloids with no treatment (Begley 1990; Daley 1951; Kerekes 1979) or a placebo (De Groot 1996b; Howard 1964; McGinty 1956). Three studies randomised participants into three comparison groups (De Groot 1996b; Howard 1964; Kerekes 1979) and one study randomised into four comparison groups (McGinty 1956). Ergot alkaloids used were either ergometrine/ergonovine or methylergometrine/methylergonovine. There were various routes of administration: intravenous in four studies (Begley 1990; Howard 1964; Kerekes 1979; McGinty 1956), intramuscular in one study (Daley 1951) and oral in one study (De Groot 1996b). Doses of intravenous or intramuscular ergometrine or methylergometrine varied from 0.2 milligrams (Howard 1964; Kerekes 1979; McGinty 1956) to 0.5 milligrams (Begley 1990; Daley 1951) and the dose of oral ergometrine was 0.4 milligrams (De Groot 1996b). All studies administered ergot alkaloids in the third stage of labour (Begley 1990; Daley 1951; De Groot 1996b; Howard 1964; Kerekes 1979; McGinty 1956), except one study where administration occurred after placental delivery (Howard 1964). There were three studies which described the method of placental delivery: one by active management of third stage of labour (Begley 1990) and two by physiological placental separation (Daley 1951; De Groot 1996b). The remaining studies gave no details of the method of placental delivery (Howard 1964; Kerekes 1979; McGinty 1956). There were four studies with three or more arms comparing ergot alkaloids with placebo or other uterotonic drugs (De Groot 1996b; Howard 1964; Kerekes 1979; McGinty 1956).

(4) Outcomes

The largest study (Begley 1990) reported all prespecified outcome measures. The following maternal outcomes not prespecified in the review are reported: postnatal haemoglobin less than 10 gm (Begley 1990); headache (Begley 1990; McGinty 1956); pain after birth requiring analgesia (Begley 1990); eclamptic fit (Begley 1990; McGinty 1956); uterine subinvolution at routine follow up (Kerekes 1979) and postpartum febrile morbidity (Kerekes 1979). Blood loss was observed in five studies; clinically estimated in three (Begley 1990; Daley 1951; Howard 1964), and measured by gravimetric method (De Groot 1996b) and collection of blood in a container (Kerekes 1979). Maternal haemoglobin concentration was checked at 48-72 hours postpartum in two trials (Beg-

ley 1990; Kerekes 1979). However, mean blood loss and maternal haemoglobin concentration data could not be extracted in one study because the authors did not report the number in the result and noted only a significant difference between the comparison groups (Kerekes 1979). Two studies reported manual removal of the placenta (Begley 1990; De Groot 1996b) and one study reported retained placenta for 60 minutes or more (Daley 1951). The incidence of blood transfusion was noted in three studies (Begley 1990; De Groot 1996b; McGinty 1956). The use of therapeutic uterotonics was described in three studies (Begley 1990; De Groot 1996b; Howard 1964). The duration of the third stage of labour was described as the mean length of the third stage (Begley 1990; Daley 1951; De Groot 1996b; Kerekes 1979), and not as third stage of labour lasting more than 30 minutes, which was a prespecified outcome of this review; one of the studies did not present the standard deviations (De Groot 1996b), so only three studies were analysed for this outcome. The elevation of blood pressure was measured in three studies (Begley 1990; Howard 1964; McGinty 1956) but the definitions varied; diastolic blood pressure greater than 90 mmHg (Begley 1990), the increase of systolic or diastolic blood pressure greater than 10 mmHg (Howard 1964) or the increase of systolic blood pressure 20 mmHg or more or systolic blood pressure greater than 170 mmHg (McGinty 1956). Vomiting and nausea were reported in two studies (Begley 1990; McGinty 1956). None of the neonatal outcomes were reported in the included studies.

Please see the table 'Characteristics of included studies' for further details.

METHODOLOGICAL QUALITY

Three studies reported adequate concealment of allocation (Begley 1990; De Groot 1996b; Howard 1964). Inadequate concealment of allocation occurred in one study due to using alternation by weekends when teams of obstetricians and midwives changed (Daley 1951). No allocation concealment was noted in two studies (Kerekes 1979; McGinty 1956). We did not request additional information regarding allocation concealment from the trial authors of these studies because they were published before 1980. All trials had less than 5% loss of participants at follow up. Method of blinding (participants and caregiver) was reported in three studies (De Groot 1996b; Howard 1964; McGinty 1956) that compared ergometrine/methylergometrine with placebo. Due to the comparison being no treatment in the remaining studies (De Groot 1996b; Howard 1964; McGinty 1956), it was not possible to blind. No information on blinding of outcome assessment was presented for any of the studies. Intention-to-treat analysis was used in five of the included studies for outcome data extracted (Begley 1990; Daley 1951; De Groot 1996b; Kerekes 1979; McGinty 1956). in the remaining study (Howard 1964), not all participants who entered the study were accounted for in outcome measures and analyses.

We assessed the quality of included studies qualitatively using the CONSORT statement (Moher 2001). According to the number of criteria met from the item checklist, one study had a low risk of bias (De Groot 1996b), three studies showed a moderate risk of bias (Begley 1990; Howard 1964; McGinty 1956) and two studies showed a high risk of bias (Daley 1951; Kerekes 1979). Risk of bias resulted mostly from trials not reporting adequately who generated the allocation sequence (Begley 1990; Daley 1951; Howard 1964; Kerekes 1979; McGinty 1956); who enrolled participants or assigned participants to their groups (Begley 1990; Daley 1951; De Groot 1996b; Howard 1964; Kerekes 1979; McGinty 1956); blinding (Begley 1990; Daley 1951; Kerekes 1979); the method used to generate the random allocation sequence (Daley 1951; Howard 1964; Kerekes 1979; McGinty 1956); how sample size was determined (Daley 1951; Howard 1964; Kerekes 1979; McGinty 1956); and how allocation was concealed (Kerekes 1979; McGinty 1956).

RESULTS

This review includes data from six studies comparing ergot alkaloids with no uterotonic agents with a total of 1996 women in ergot alkaloids group and 1945 women in placebo or no treatment group. To explore causes of heterogeneity, oral administration was analysed separately from intravenous or intramuscular administration as a subgroup analysis. Sensitivity analysis by excluding trials where allocation concealment was inadequate (C) was performed.

(1) Ergot alkaloids versus no uterotonic agents

Intravenous or intramuscular ergot alkaloids compared with no uterotonic agents

Two studies comparing intravenous/intramuscular ergot alkaloids with no treatment found that the use of ergot alkaloids significantly decreased mean blood loss (weighted mean difference (WMD) -83.03 ml, 95% confidence interval (CI) -99.39 to -66.66 ml) (Begley 1990; Daley 1951). When blood loss of at least 500 ml (moderate postpartum haemorrhage (PPH)) was considered, there was significant heterogeneity observed (I square = 73.6%); thus, this outcome was analysed with a random-effects model and ergot alkaloids were associated with a significantly lower moderate PPH rate (relative risk (RR) 0.38, 95% CI 0.21 to 0.69) (Begley 1990; Daley 1951; Howard 1964). Sensitivity analysis based on excluding one trial (Daley 1951) with a high risk of bias did not significantly alter the results (RR 0.27, 95% CI 0.17 to 0.43). One study (Begley 1990) comparing ergot alkaloids with no treatment reported a significant reduction in blood loss of at least 1000 ml (RR 0.09, 95% CI 0.01 to 0.72) and postnatal haemoglobin less than 10 gm (RR 0.30, 95% CI 0.14 to 0.67) and increased mean postnatal haemoglobin concentration at 48 to 72 hours (weighted mean difference 0.50 gm/dl (95% CI 0.38 to 0.62 gm/dl) compared with no treatment.

The risk of retained placenta or manual removal of the placenta, or both (RR 3.75, 95% CI 0.14 to 99.71) was not demonstrated (Begley 1990; Daley 1951) but with a significant heterogeneity (I square = 89.7%), thus this outcome was analysed with a random-effects model. The outcomes of these two studies were different. In one study (Begley 1990), the risk of manual removal of placenta was increased in the ergot alkaloid group (RR 19.51, 95% CI 2.62 to 145.36), but in the other study (Daley 1951), the risk of retained placenta 60 minutes or more was not increased.

No difference was demonstrated in the incidence of blood transfusion when ergot alkaloid was compared to no uterotonic agents (RR 0.34, 95% CI 0.05 to 2.16) (Begley 1990; McGinty 1956). The summary RR for the use of therapeutic uterotonics was analysed by a random-effects model due to significant heterogeneity (I square = 86.2%) (Begley 1990; Howard 1964). When intravenous ergot alkaloids were compared, there was a significant reduction of uterotonics use (RR 0.25, 95% CI 0.10 to 0.66). Mean length of third stage of labour was significantly less in ergot alkaloid group (WMD -1.70 minutes, 95% CI -3.33 to -0.06 minutes) using random-effects analysis (Begley 1990; Daley 1951; Kerekes 1979). This finding changed to nonsignificance after excluding one study based on trial quality (Daley 1951) and this result was a lot of uncertainty due to skewness in one study (Begley 1990). One study reported no significant difference of uterine subinvolution at routine follow up and postpartum febrile morbidity (Kerekes 1979).

Maternal adverse effects were significantly increased with intravenous or intramuscular ergot alkaloids compared to no treatment: vomiting (RR 11.81, 95% CI 1.78 to 78.28) (Begley 1990; McGinty 1956); elevation of blood pressure (RR 2.60, 95% CI 1.03 to 6.57) (Begley 1990; Howard 1964; McGinty 1956); and pain after birth requiring analgesia (RR 2.53, 95% CI 1.34 to 4.78) (Begley 1990). However, the elevation of blood pressure showed a significant heterogeneity (I square = 84.1%), which might be because different definitions of elevation of blood pressure were used. There was no evidence of difference in the incidence of nausea, headache and eclamptic fits (Begley 1990; McGinty 1956).

Oral ergot alkaloids compared with placebo

One study (De Groot 1996b) compared oral ergometrine with placebo and showed no significant benefit of ergometrine over placebo in terms of mean blood loss, blood loss of at least 500 ml and 1000 ml, manual removal of the placenta, requiring blood transfusion, or use of further oxytocics. Data presented for length of third stage in this study could not be extracted. No maternal adverse effects were reported.

There was a difference in treatment effect between subgroups for the routes of administration (intravenous or intramuscular versus oral) for two outcomes: postpartum blood loss of 500 mls or more and the use of therapeutic uterotonic agents.

(2) Different routes of ergot alkaloids: oral versus intravenous route

No study compared these interventions.

(3) Different timing of administration: before versus after placental delivery

No study compared these interventions.

DISCUSSION

Intravenous/intramuscular ergot alkaloids significantly decreased mean blood loss and reduced the incidence of postpartum blood loss of at least 500 ml. Postpartum blood loss of 1000 mls or more and postnatal haemoglobin concentration less than 10 gm were decreased, and there was an increase in mean postnatal haemoglobin in the intravenous ergot alkaloids group, but data were from one study only (Begley 1990). These effects can result from strong uterine contractions after giving ergot alkaloids (De Groot 1995; De Groot 1996a; De Groot 1998), leading to a reduction in the need for therapeutic uterotonics, but no change in the incidence of blood transfusion. Mean length of the third stage of labour in the ergot alkaloid group in this review was minimally decreased (two minutes); however, previous Cochrane reviews on prophylactic use of other uterotonics in the third stage of labour compared to no uterotonic agents had not shown this benefit (Cotter 2001; Gulmezoglu 2004; McDonald 2004; Prendiville 2000). Two-minute reduction in the third stage of labour seems unlikely to be clinically significant; however, it is a very critical period in case of bleeding.

No difference was demonstrated from three trials (Begley 1990; Daley 1951; De Groot 1996b) for the risk of retained placenta or manual removal of the placenta, or both; heterogeneity was high (80.9%) and confidence intervals wide. One of the studies (Daley 1951) could not demonstrate any difference in the risk of retained placenta of 60 minutes or more. In contrast, Begley 1990 showed an increased risk of requiring manual removal of placenta in the intravenous ergot alkaloid group in accordance with the result of a Cochrane Review assessing the effectiveness of active versus expectant management in the third stage of labour (Prendiville 2000). The review showed the risk of removal of placenta was increased when ergot alkaloids alone, or a combination of ergot alkaloid and oxytocin, were used with active management of the third stage of labour.

Significant adverse events for vomiting, elevation of blood pressure and pain after birth requiring analgesia result from the effects of ergot alkaloids caused by persistent uterine contraction and vasoconstriction (De Groot 1998; Den Hertog 2001; Van Dongen 1995). Data from case reports reported severe adverse effects (cerebral ischemia, vasospasm and hypertensive encephalopathy) (Dua 1994; Taylor 1985), indicating that the drug should be used with caution. There was only one study (De Groot 1996b) comparing oral ergometrine versus placebo, showing no significant risk or benefit of ergometrine. This may be explained by the small

number of women in the study and therefore insufficient power to detect any difference. Easy deterioration of oral ergot alkaloids immediately after being taken from a sealed package or container, and increased temperature and high humidity (De Groot 1998), or longer latency time and less effect on uterine motility when compared to intravenous route, can lead to unpredictable bioavailability (De Groot 1996a).

The use of intravenous/intramuscular ergot alkaloids reduced mean blood loss, moderate and severe postpartum haemorrhage (PPH), postnatal haemoglobin less than 10 gm and the use of therapeutic uterotonics, but increased vomiting, elevation of blood pressure and pain after birth requiring analgesia when compared with not using ergot alkaloids in the third stage of labour in this review. According to the magnitude of ergot alkaloid effect, 19 pregnant women are needed to be given ergot alkaloids to prevent one additional pregnant woman from moderate PPH (number needed to treat 19; 95% confidence interval (CI) 14 to 29) with simultaneous harm of vomiting (number needed to harm (NNH) 67; 95% CI 42 to 167), pain after birth (NNH 37; 95% CI 22 to 111) and elevation of blood pressure (NNH 10; 95% CI 8 to 15), thus ergot alkaloids should be used with caution in the case of women with high blood pressure.

When we identified high levels of heterogeneity among the trials, we explored it by prespecified subgroup analysis (intravenous or intramuscular versus oral route). A random-effects analysis was used as an overall summary when this was considered appropriate. However, high levels still existed, possibly due to other related procedures such as active or physiologic management of the third stage or other unknown details of placental delivery that were not presented in trial reports.

AUTHORS' CONCLUSIONS

Implications for practice

Ergot alkaloid injection (intravenous or intramuscular) is one of the prophylactic agents used during the third stage of labour to prevent postpartum haemorrhage (PPH). Side effects include vomiting, elevation of blood pressure and pain requiring analgesia after birth. The risk and benefit of uterotonic agents chosen for preventing PPH therefore should be considered carefully under appropriate resource settings.

Implications for research

When ergot alkaloids were compared with no uterotonic agents, the beneficial effects on less postpartum blood loss and additional use of therapeutic uterotonics but higher risk of vomiting and elevation of blood pressure were explicit. However, the participants in these trials were not at increased risk of PPH and so the possible benefits to this group of women have not really been assessed. In the Cochrane Review (Cotter 2001), the advantages of ergot alkaloids alone compared with oxytocin, there was little evidence of differential effects. In addition, the optimal dosing of and route of administration for ergot alkaloids is inconclusive. Therefore, future large, well-designed studies are required: these should compare the different types of uterotonic agents with different dosage and route, as well as assess serious morbidity from PPH to fill the knowledge gap of the appropriate uterotonic agents for preventing PPH, especially in developing countries where haemorrhage is the leading cause of maternal deaths. None of the studies included in this review addressed neonatal outcomes or serious morbidity from PPH, thus there is the need to measure neonatal outcomes, serious morbidity in the mother and possible adverse effects of ergometrine on lactation in future trials.

POTENTIAL CONFLICT OF INTEREST

None known.

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Begley 1990
Methods	Randomisation in batches of 100 and allocation by sealed envelopes. No blinding.
Participants	Eligibility: women attending the antenatal clinic at Coombe hospital who were public and semi-private clients, singleton cephalic presentation, gestational age of 35-36 weeks, no medical complications which would contraindicate the use of ergometrine or increase risk of bleeding (such as cardiovascular disease, use of heparin and hypertension), low risk to haemorrhage such as age 35 years or less, parity 5 or less, no previous history of primary PPH, Hb 11 gm or more (IV sample) or 10.6 or more (capillary sample). Exclusions: women who had hypertension (140/95 or greater), epidural anaesthesia, antenatal haemorrhage, first stage of labour in excess of 15 hours and operative delivery were excluded.

Characteristics of included studies (*Continued*)

Interventions	Intravenous ergometrine 0.5 mg following the birth of the baby (n = 705) versus no ergometrine (n = 724).
Outcomes	Mean blood loss; blood loss of at least 500 ml and 1000 ml; mean postnatal haemoglobin (48-72 hours); haemoglobin less than 10 gm; manual removal of placenta; blood transfusion; elevation of diastolic blood pressure (> 95 mmHg); eclamptic fit; vomiting; nausea; headache; atonic haemorrhage requiring IV or IM ergot; length of third stage of labour; after-birth pain needing IM or oral analgesia.
Notes	If eligible pregnant women were excluded, the envelope was returned unopened and reallocated to next batch.
Allocation concealment	A – Adequate

Study	**Daley 1951**
Methods	Randomisation by alternative weekends changing with each team of obstetricians and midwives. No blinding.
Participants	Eligibility: women having delivered spontaneously of a single fetus after less than 48 hours of labour, parity less than 5 and no antepartum haemorrhage or hydramnios at St Helier Hospital.
Interventions	Intramuscular ergometrine 0.5 mg as soon as the head was crowned (n = 490) versus no ergometrine (n = 510).
Outcomes	Mean blood loss; blood loss of at least 500 ml; retained placenta for 60 min or more; mean length of third stage of labour.
Notes	Two women excluded because of traumatic haemorrhage as clinicians felt convinced of the value of ergometrine. All outcomes were stratified by gravida.
Allocation concealment	C – Inadequate

Study	**De Groot 1996b**
Methods	A double-blind multicentre trial with randomisation by computer-generated randomisation list. Ergometrine and placebo were identical. The boxes of ergometrine and placebo were numbered by hospital pharmacy.
Participants	Eligibility: all delivered women in two university hospitals (Leiden, Nijmegen), a midwifery school (Kerkrade) and by independent midwives in the area of the university hospital of Nijmegen in the study period. Exclusions: refusal to participate, cardiovascular diseases, multiple pregnancies, non-cephalic presentation, polyhydramnios, tocolysis given 2 hours prior to delivery, anticoagulant therapy, stillbirth, antepartum haemorrhage, induction or augmentation, operative vaginal deliveries, anaemia less than 6.8 gm, former complications in the third stage of labour or women who wish natural births.
Interventions	Total 367 women were assigned to 2:2:1 of oral ergometrine 0.4 mg (n = 146), oral placebo tablets (n = 143) and standard intramuscular oxytocin (n = 78) after birth immediately.
Outcomes	Mean blood loss measured by gravimetric method; blood loss of at least 500 ml and 1000 ml; removal of placenta; requiring blood transfusion; use of further oxytocics; length of third stage.
Notes	Data for length of third stage were presented as mean only, no standard deviation given.
Allocation concealment	A – Adequate

Study	**Howard 1964**
Methods	A double-blind trial with simple randomisation. The vials were coded and identical in appearance.
Participants	Eligibility: all vaginally delivered women at the University of Iowa Hospital. Exclusion: women delivered by caesarean section.
Interventions	Three groups of comparisons: intravenous methylergonovine maleate 0.2 mg (n = 505), intravenous 0.9% sodium chloride (n = 475) and oxytocin (n = 479) following placental delivery.
Outcomes	Blood loss of at least 500 ml; elevation of systolic or diastolic blood pressure greater than 10 mmHg; need further treatment (vigorous uterine massage, IV or IM methylergonovine and/or oxytocin).
Notes	Elevation of blood pressure was stratified by normotensive or hypertensive and pre-eclamptic women.

Allocation concealment	A – Adequate

Study	**Kerekes 1979**
Methods	Simple randomisation into three comparison groups without concealment or blinding.
Participants	Eligibility: women with spontaneous uncomplicated vaginal deliveries at Korvin Hospital. Exclusions: no details given.
Interventions	Three groups of comparisons were intravenous ergometrine 0.2 mg (n = 50), no treatment (n = 43) and intramyometrial prostaglandins (PGF2alpha) 1 mg (n = 47) after clamping of umbilical cord.
Outcomes	Mean blood loss measured by cylinder after the collection of blood from container; maternal haemoglobin concentration at 48 hours postpartum; duration of third stage of labour; uterine subinvolution at routine follow up; postpartum febrile morbidity.
Notes	No data shown for mean blood loss or maternal haemoglobin.
Allocation concealment	B – Unclear

Study	**McGinty 1956**
Methods	Simple randomisation into four comparison groups.
Participants	Eligibility: women delivering vaginally at the Creighton Memorial St Joseph's Hospital and Bramwell Booth Memorial Hospital. Exclusions: no details provided.
Interventions	Four groups of comparisons were intravenous methergine 0.2 mg (n = 50), ergonovine 0.2 mg (n = 50), pitocin 5 units (n = 50) and normal saline 1 ml (n = 50) after birth of anterior shoulder.
Outcomes	Blood transfusion, elevation of blood pressure (increase of systolic blood pressure 20 or more) and severe elevation (systolic blood pressure more than 170); vomiting; nausea; headache; eclamptic fit.
Notes	Elevation of blood pressure were stratified by normotensive or hypertensive women. Five severe PPH (no criteria shown) were found in the placebo group.
Allocation concealment	B – Unclear

IM: intramuscular
IV: intravenous
min: minute(s)
PPH: postpartum haemorrhage

Characteristics of excluded studies

Study	**Reason for exclusion**
Amant 1999	Comparisons of oral misoprostol and intravenous methylergometrine included in previous Cochrane review.
Badhwar 1991	Management with nipple stimulation.
Barbaro 1961	Comparisons of intramuscular syntometrine and ergometrine included in previous Cochrane review.
Baumgarten 1983	Comparisons of ergometrine, oxytocin and sulprostone on uterine contractility by intra-catheter pressure excluded in previous Cochrane review due to no possible outcomes.
Bonham 1963	Comparisons of syntometrine, ergometrine and ergometrine plus hyaluronidase included in previous Cochrane review.
Caliskan 2002	Comparisons of misoprostol plus oxytocin, misoprostol, oxytocin and oxytocin plus ergometrine included in previous Cochrane review.
Carpén 1968	Comparisons of intramuscular OCM 505 and intravenous methergine.
Chatterjee 2000	No data can be extracted, excluded in previous Cochrane review.

Chukudebelu 1963	Not randomised controlled trial comparing 0.5 U of syntocinon plus 0.5 mg of ergometrine, 0.5 mg of ergometrine and 1 mg of ergometrine.
Diab 1999	Comparisons of misoprostol and ergometrine excluded in previous Cochrane review.
Docherty 1981	Data were not suitable for extraction and failed contact with author excluded in previous two Cochrane reviews.
Dweck 2000	Participants were women who underwent caesarean section and received 0.2 mg of methergine orally every 6 hours until hospital discharge with the first dose being within the first 6 hours after caesarean section. The outcome was diagnosed endometritis.
Forster 1957	Not randomised controlled trial comparing 0.2 mg of methergine versus ergometrine given intravenously immediately after the delivery of the baby for 24 weeks and for next 8 weeks, 0.2 mg of methergine or ergometrine given additionally by intramuscular injection after the expression of the placenta.
Francis 1965a	Comparisons of syntometrine before placental delivery and ergometrine after placental delivery excluded in previous Cochrane review.
Francis 1965b	Comparisons of intramuscular syntometrine and ergometrine included in previous Cochrane review.
Friedman 1957	Not randomised controlled trial comparing no medication as a control, 10 units of oxytocin intramuscularly, 0.2 mg of ergonovine maleate intramuscularly or intravenously, 0.2 mg of methylergonovine tartrate intramuscularly or intravenously and 1 mg of dihydroergotamine methanessulfonate intramuscularly after delivery of placenta.
Fugo 1958	Comparisons of intravenous oxytocin, syntometrine, U3772 and ergometrine included in previous Cochrane review.
Groeber 1960	Comparisons of 0.2 mg of methergine and 0.2 mg of ergonovine intravenously after delivery of placenta.
Hacker 1979	Not randomised controlled trial comparing no drug as a control, syntometrine (combining 5 U of oxytocin and 0.5 mg of ergometrine maleate) intramuscularly and 0.5 mg of ergometrine maleate intravenously.
Huh 2004	Comparisons of oxytocin administered before and after placental delivery excluded in previous Cochrane review due to comparison of oxytocin with time difference.
Ilancheran 1990	No outcome of interest, only prostaglandin level. Comparisons of no oxytocic drug, oxytocin, syntometrine and ergometrine after delivery of anterior shoulder given intravenously and in standard doses included in previous Cochrane review.
Jolivet 1978	No outcome of interest, only milk secretion and infant weight gain in 6 days. Comparisons of 0.2 mg of methylergobasine intramuscularly immediately after delivery and then 3 tablets of 1 mg of ergotamine tartrate per month daily for 6 days postpartum and no treatment after delivery.
Khan 1995	Comparisons of intramuscular syntometrine and oxytocin included in previous Cochrane review.
Kikutani 2003	Comparisons of oxytocin and ergometrine on epidural pressure.
Lam 2004	Comparisons of sublingual misoprostol and intravenous syntometrine.
Lamont 2001	Comparisons of syntometrine and prostaglandin.
Mitchell 1993	Comparisons of syntometrine and oxytocin included in previous Cochrane review.
Moir 1979	Comparisons of 0.5 mg of ergometrine and 10 IU of oxytocin given at the time of delivery of anterior shoulder .
Moore 1956	Not randomised controlled trial comparing 0.2 mg of ergonovine maleate and 0.2 mg of methylergonovine tartrate intravenously after expulsion of placenta.
Nieminen 1963	Comparisons of ergometrine, syntometrine and oxytocin included in previous Cochrane Review.
Paull 1977	Comparisons of 0.25 mg and 0.5 mg of ergometrine maleate intravenously after completion of second stage of labour.
Pei 1996	Not randomised controlled trial and no outcomes of interest comparing oxytocin and ergotocin on postpartum lactation.
Penaranda 2002	Comparisons of sublingual misoprostol, oxytocin and methylergometrine included in previous Cochrane review.
Rajwani 2000	No data can be extracted, excluded in previous Cochrane review.

Characteristics of excluded studies (*Continued*)

Ramesh 1983	Not randomised controlled trial comparing 0.5 mg of PGE2 intramyometrial at the fundus of the uterus at the time of crowning of fetal head and 0.25 mg of methylergotamine maleate.
Reddy 2001	Comparisons of 0.2 mg of methylergometrine intravenously at the time of anterior shoulder delivery, 10 IU of oxytocin diluted with 10 ml of normal saline via umbilical cord immediately after clamping the cord and 250 mg of carboprost intramuscularly with the delivery of anterior shoulder of the baby.
Rooney 1985	Quasi-randomised controlled trial using odd-even cases comparing syntometrine with the delivery of anterior shoulder intramuscularly and no syntometrine.
Soiva 1964	Comparisons of intravenous methylergometrine and intramuscular oxytocin included in previous Cochrane review.
Sorbe 1978	Not randomised controlled trial comparing 0.2 mg of ergometrine, 10 IU of oxytocin intravenously after delivery of anterior shoulder and control group which was not described how to select.
Stearn 1963	Comparisons of syntometrine and ergometrine excluded in previous Cochrane review due to allocation.
Symes 1984	Comparisons of oxytocin and oxytocin plus ergometrine excluded in previous Cochrane review due to no clinical outcomes.
Terry 1970	Quasi-randomised controlled trial comparing syntometrine (0.5 mg of ergometrine and 5 IU of oxytocin) intramuscularly at the delivery of anterior shoulder and syntometrine with free bleeding. Outcome of interest was fetal cells in maternal blood.
Thilaganathan 1993	Comparing of 1 ml of syntometrine after the delivery of baby and no drug.
Thornton 1988	Quasi-randomised controlled trial comparing intramuscular oxytocin on the delivery of anterior shoulder.
Vaughan 1974	Comparisons of syntometrine and oxytocin excluded in previous Cochrane review due to one outcome on central venous pressure.
Vimala 2004	Comparisons of sublingual misoprostol and intramuscular methylergometrine.
Weiss 1975	Quasi-randomised controlled trial comparing 0.2 mg of methylergonovine maleate after delivery of placenta and 1 ml of normal saline intramuscularly. Only serum prolactin was measured.
Yardim 1967	Comparisons of oxytocin plus ergometrine and no drug.
Yuen 1995	Comparisons of syntometrine and oxytocin included in previous Cochrane review.

IU: international unit(s)
U: unit(s)

ANALYSES

Comparison 01. Ergot alkaloids and no uterotonic agents

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mean blood loss (ml)	3	2718	Weighted Mean Difference (Fixed) 95% CI	-81.72 [-97.81, -65.63]
02 Estimated or measured blood loss of at least 500 ml	4	3698	Relative Risk (Random) 95% CI	0.49 [0.26, 0.90]
03 Estimated or measured blood loss of at least 1000 ml	2	1718	Relative Risk (Random) 95% CI	0.32 [0.04, 2.59]
04 Mean postnatal haemoglobin (48-72 hours)	1	1429	Weighted Mean Difference (Fixed) 95% CI	0.50 [0.38, 0.62]
05 Retained placenta or manual removal of placenta, or both	3	2718	Relative Risk (Random) 95% CI	3.86 [0.36, 41.78]
06 Blood transfusion	3	1868	Relative Risk (Fixed) 95% CI	0.33 [0.08, 1.40]
07 Use of therapeutic uterotonics	3	2698	Relative Risk (Random) 95% CI	0.37 [0.15, 0.90]
08 Elevation of blood pressure	3	2559	Relative Risk (Random) 95% CI	2.60 [1.03, 6.57]
09 Length of third stage of labour	3	2522	Weighted Mean Difference (Random) 95% CI	-1.70 [-3.33, -0.06]

10 Vomiting	2	1579	Relative Risk (Fixed) 95% CI	11.81 [1.78, 78.28]
11 Nausea	2	1579	Relative Risk (Random) 95% CI	8.63 [0.26, 284.55]
12 Headache (not prespecified)	2	1579	Relative Risk (Fixed) 95% CI	3.93 [0.51, 30.50]
13 Pain after birth requiring analgesia (not prespecified)	1	1429	Relative Risk (Fixed) 95% CI	2.53 [1.34, 4.78]
14 Eclamptic fit (not prespecified)	2	1579	Relative Risk (Fixed) 95% CI	3.34 [0.38, 29.43]
15 Postnatal haemoglobin < 10 gm (not prespecified)	1	1429	Relative Risk (Fixed) 95% CI	0.30 [0.14, 0.67]
16 Uterine subinvolution at routine follow up (not prespecified)	1	93	Relative Risk (Fixed) 95% CI	0.86 [0.56, 1.32]
17 Postpartum febrile morbidity (not prespecified)	1	93	Relative Risk (Fixed) 95% CI	1.03 [0.34, 3.15]

Comparison 04. Sensitivity analysis based on trial quality

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Estimated or measured blood loss of at least 500 ml	2	2409	Relative Risk (Random) 95% CI	0.27 [0.17, 0.43]
02 Length of third stage of labour	2	1522	Weighted Mean Difference (Random) 95% CI	-1.07 [-2.32, 0.19]

INDEX TERMS

Medical Subject Headings (MeSH)

Ergot Alkaloids [administration & dosage; *therapeutic use]; Injections, Intramuscular; Injections, Intravenous; *Labor Stage, Third; Postpartum Hemorrhage [*prevention & control]; Randomized Controlled Trials

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title	Prophylactic use of ergot alkaloids in the third stage of labour
Authors	Liabsuetrakul T, Choobun T, Peeyananjarassri K, Islam QM
Contribution of author(s)	Tippawan Liabsuetrakul Involved in all parts of preparing the review. Wrote the first and final draft of the review. Krantarat Peeyananjarassri Involved in assessing the included or excluded studies. Commented on the first draft of review. Thanapan Choobun Involved in assessing the quality of included studies and extracting the data. Commented on the first draft of review. Monir Islam Commented on the draft of review.
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Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	30 December 2006
Date authors' conclusions section amended	Information not supplied by author
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GRAPHS AND OTHER TABLES

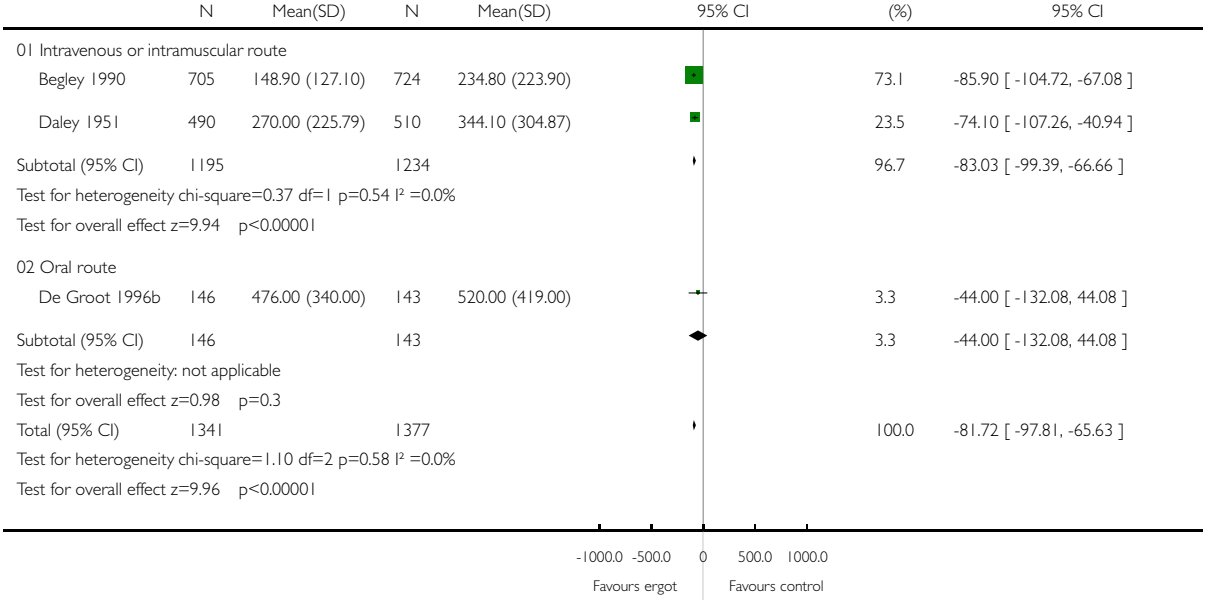
Analysis 01.01. Comparison 01 Ergot alkaloids and no uterotonic agents, Outcome 01 Mean blood loss (ml)

Review: Prophylactic use of ergot alkaloids in the third stage of labour

Comparison: 01 Ergot alkaloids and no uterotonic agents

Outcome: 01 Mean blood loss (ml)

Study	Ergot alkaloids		Placebo or no agents		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
01 Intravenous or intramuscular route							
Begley 1990	705	148.90 (127.10)	724	234.80 (223.90)		73.1	-85.90 [-104.72, -67.08]
Daley 1951	490	270.00 (225.79)	510	344.10 (304.87)		23.5	-74.10 [-107.26, -40.94]
Subtotal (95% CI)	1195		1234			96.7	-83.03 [-99.39, -66.66]
Test for heterogeneity chi-square=0.37 df=1 p=0.54 I^2 =0.0%							
Test for overall effect z=9.94 p<0.00001							
02 Oral route							
De Groot 1996b	146	476.00 (340.00)	143	520.00 (419.00)		3.3	-44.00 [-132.08, 44.08]
Subtotal (95% CI)	146		143			3.3	-44.00 [-132.08, 44.08]
Test for heterogeneity: not applicable							
Test for overall effect z=0.98 p=0.3							
Total (95% CI)	1341		1377			100.0	-81.72 [-97.81, -65.63]
Test for heterogeneity chi-square=1.10 df=2 p=0.58 I^2 =0.0%							
Test for overall effect z=9.96 p<0.00001							



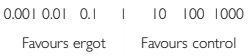
Analysis 01.02. Comparison 01 Ergot alkaloids and no uterotonic agents, Outcome 02 Estimated or measured blood loss of at least 500 ml

Review: Prophylactic use of ergot alkaloids in the third stage of labour

Comparison: 01 Ergot alkaloids and no uterotonic agents

Outcome: 02 Estimated or measured blood loss of at least 500 ml

Study	Ergot alkaloids n/N	Placebo or no agents n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Intravenous or intramuscular route					
Begley 1990	14/705	60/724		23.8	0.24 [0.14, 0.42]
Daley 1951	45/490	80/510		27.4	0.59 [0.42, 0.83]
Howard 1964	9/505	25/475		20.7	0.34 [0.16, 0.72]
Subtotal (95% CI)	1700	1709		71.9	0.38 [0.21, 0.69]
Total events: 68 (Ergot alkaloids), 165 (Placebo or no agents)					
Test for heterogeneity chi-square=7.58 df=2 p=0.02 I^2 =73.6%					
Test for overall effect z=3.15 p=0.002					
03 Oral route					
De Groot 1996b	54/146	55/143		28.1	0.96 [0.72, 1.29]
Subtotal (95% CI)	146	143		28.1	0.96 [0.72, 1.29]
Total events: 54 (Ergot alkaloids), 55 (Placebo or no agents)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.26 p=0.8					
Total (95% CI)	1846	1852		100.0	0.49 [0.26, 0.90]
Total events: 122 (Ergot alkaloids), 220 (Placebo or no agents)					
Test for heterogeneity chi-square=23.09 df=3 p=<0.0001 I^2 =87.0%					
Test for overall effect z=2.31 p=0.02					

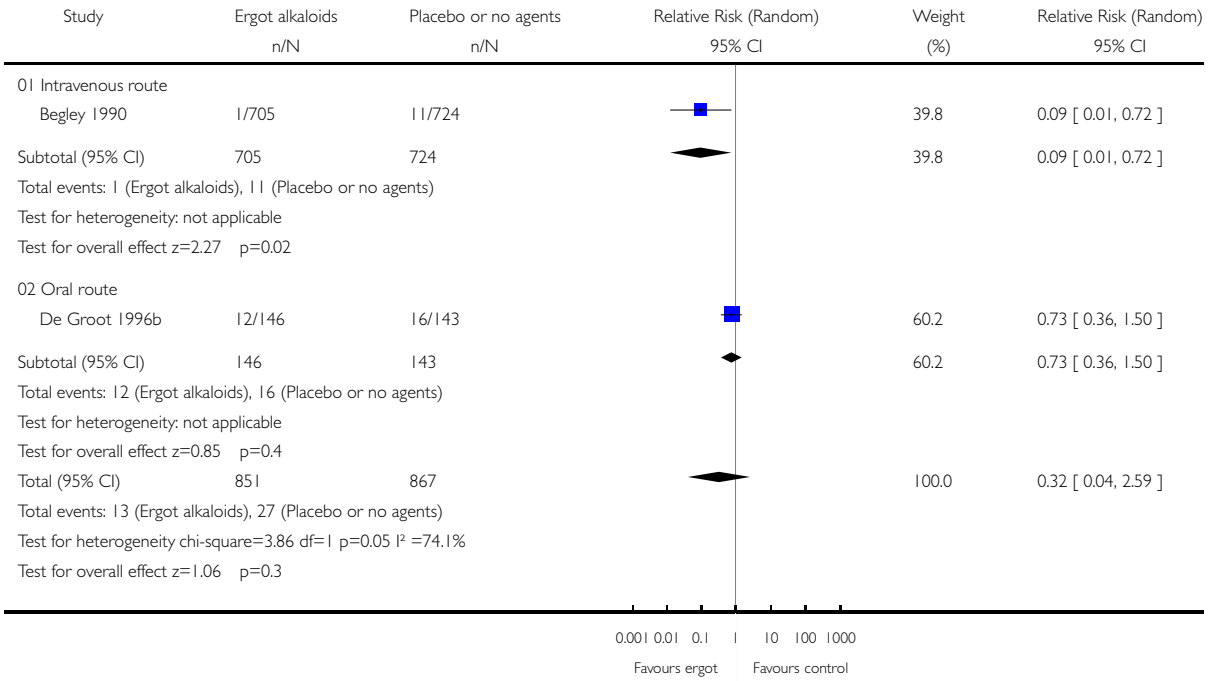


Analysis 01.03. Comparison 01 Ergot alkaloids and no uterotonic agents, Outcome 03 Estimated or measured blood loss of at least 1000 ml

Review: Prophylactic use of ergot alkaloids in the third stage of labour

Comparison: 01 Ergot alkaloids and no uterotonic agents

Outcome: 03 Estimated or measured blood loss of at least 1000 ml

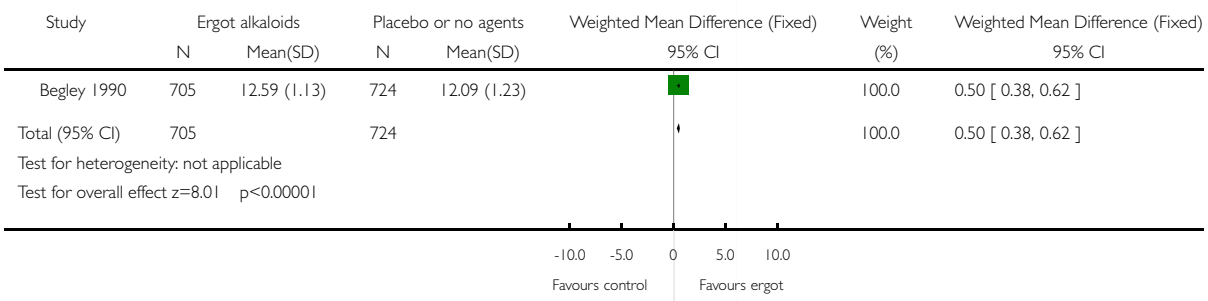


Analysis 01.04. Comparison 01 Ergot alkaloids and no uterotonic agents, Outcome 04 Mean postnatal haemoglobin (48-72 hours)

Review: Prophylactic use of ergot alkaloids in the third stage of labour

Comparison: 01 Ergot alkaloids and no uterotonic agents

Outcome: 04 Mean postnatal haemoglobin (48-72 hours)



Analysis 01.05. Comparison 01 Ergot alkaloids and no uterotonic agents, Outcome 05 Retained placenta or manual removal of placenta, or both

Review: Prophylactic use of ergot alkaloids in the third stage of labour

Comparison: 01 Ergot alkaloids and no uterotonic agents

Outcome: 05 Retained placenta or manual removal of placenta, or both

Study	Ergot alkaloids n/N	Placebo or no agents n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Intravenous or intramuscular route					
Begley 1990	19/705	1/724		32.9	19.51 [2.62, 145.36]
Daley 1951	17/490	19/510		41.7	0.93 [0.49, 1.77]
Subtotal (95% CI)	1195	1234		74.6	3.75 [0.14, 99.71]
Total events: 36 (Ergot alkaloids), 20 (Placebo or no agents)					
Test for heterogeneity chi-square=9.74 df=1 p=0.002 I^2 =89.7%					
Test for overall effect z=0.79 p=0.4					
02 Oral route					
De Groot 1996b	2/146	0/143		25.4	4.90 [0.24, 101.14]
Subtotal (95% CI)	146	143		25.4	4.90 [0.24, 101.14]
Total events: 2 (Ergot alkaloids), 0 (Placebo or no agents)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.03 p=0.3					
Total (95% CI)	1341	1377		100.0	3.86 [0.36, 41.78]
Total events: 38 (Ergot alkaloids), 20 (Placebo or no agents)					
Test for heterogeneity chi-square=10.46 df=2 p=0.005 I^2 =80.9%					
Test for overall effect z=1.11 p=0.3					

Analysis 01.06. Comparison 01 Ergot alkaloids and no uterotonic agents, Outcome 06 Blood transfusion

Review: Prophylactic use of ergot alkaloids in the third stage of labour

Comparison: 01 Ergot alkaloids and no uterotonic agents

Outcome: 06 Blood transfusion

Study	Ergot alkaloids n/N	Placebo or no agents n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Intravenous route					
Begley 1990	1/705	2/724		28.2	0.51 [0.05, 5.65]
McGinty 1956	0/100	1/50		28.5	0.17 [0.01, 4.06]
Subtotal (95% CI)	805	774		56.7	0.34 [0.05, 2.16]
Total events: 1 (Ergot alkaloids), 3 (Placebo or no agents)					
Test for heterogeneity chi-square=0.30 df=1 p=0.58 I^2 =0.0%					
Test for overall effect z=1.14 p=0.3					
02 Oral route					
De Groot 1996b	1/146	3/143		43.3	0.33 [0.03, 3.10]
Subtotal (95% CI)	146	143		43.3	0.33 [0.03, 3.10]
Total events: 1 (Ergot alkaloids), 3 (Placebo or no agents)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.97 p=0.3					
Total (95% CI)	951	917		100.0	0.33 [0.08, 1.40]
Total events: 2 (Ergot alkaloids), 6 (Placebo or no agents)					
Test for heterogeneity chi-square=0.30 df=2 p=0.86 I^2 =0.0%					
Test for overall effect z=1.50 p=0.1					

Analysis 01.07. Comparison 01 Ergot alkaloids and no uterotonic agents, Outcome 07 Use of therapeutic uterotonics

Review: Prophylactic use of ergot alkaloids in the third stage of labour

Comparison: 01 Ergot alkaloids and no uterotonic agents

Outcome: 07 Use of therapeutic uterotonics

Study	Ergot alkaloids n/N	Placebo or no agents n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Intravenous route					
Begley 1990	14/705	93/724		32.7	0.15 [0.09, 0.27]
Howard 1964	25/505	58/475		34.1	0.41 [0.26, 0.64]
Subtotal (95% CI)	1210	1199		66.9	0.25 [0.10, 0.66]
Total events: 39 (Ergot alkaloids), 151 (Placebo or no agents)					
Test for heterogeneity chi-square=7.23 df=1 p=0.007 I^2 =86.2%					
Test for overall effect z=2.80 p=0.005					
02 Oral route					
De Groot 1996b	21/146	26/143		33.1	0.79 [0.47, 1.34]
Subtotal (95% CI)	146	143		33.1	0.79 [0.47, 1.34]
Total events: 21 (Ergot alkaloids), 26 (Placebo or no agents)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.87 p=0.4					
Total (95% CI)	1356	1342		100.0	0.37 [0.15, 0.90]
Total events: 60 (Ergot alkaloids), 177 (Placebo or no agents)					
Test for heterogeneity chi-square=18.51 df=2 p=<0.0001 I^2 =89.2%					
Test for overall effect z=2.19 p=0.03					

Analysis 01.08. Comparison 01 Ergot alkaloids and no uterotonic agents, Outcome 08 Elevation of blood pressure

Review: Prophylactic use of ergot alkaloids in the third stage of labour

Comparison: 01 Ergot alkaloids and no uterotonic agents

Outcome: 08 Elevation of blood pressure

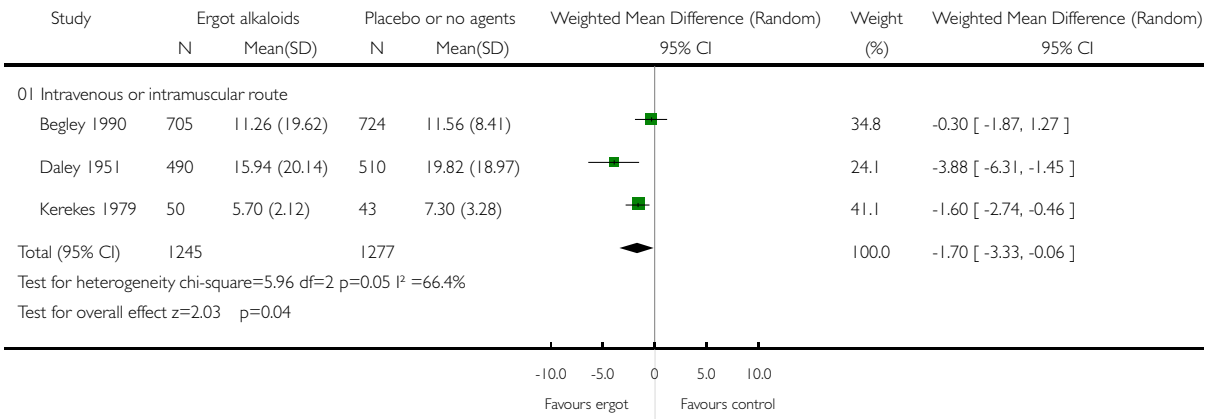
Study	Ergot alkaloids n/N	Placebo or no agents n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Begley 1990	35/705	5/724		28.9	7.19 [2.83, 18.24]
Howard 1964	238/505	155/475		40.3	1.44 [1.23, 1.69]
McGinty 1956	26/100	6/50		30.9	2.17 [0.95, 4.92]
Total (95% CI)	1310	1249		100.0	2.60 [1.03, 6.57]
Total events: 299 (Ergot alkaloids), 166 (Placebo or no agents)					
Test for heterogeneity chi-square=12.60 df=2 p=0.002 I^2 =84.1%					
Test for overall effect z=2.02 p=0.04					

Analysis 01.09. Comparison 01 Ergot alkaloids and no uterotonic agents, Outcome 09 Length of third stage of labour

Review: Prophylactic use of ergot alkaloids in the third stage of labour

Comparison: 01 Ergot alkaloids and no uterotonic agents

Outcome: 09 Length of third stage of labour

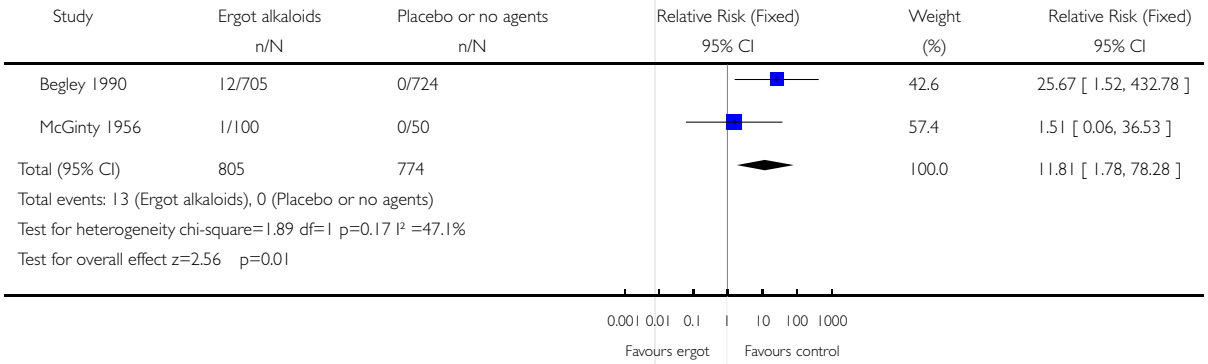


Analysis 01.10. Comparison 01 Ergot alkaloids and no uterotonic agents, Outcome 10 Vomiting

Review: Prophylactic use of ergot alkaloids in the third stage of labour

Comparison: 01 Ergot alkaloids and no uterotonic agents

Outcome: 10 Vomiting



Analysis 01.11. Comparison 01 Ergot alkaloids and no uterotonic agents, Outcome 11 Nausea

Review: Prophylactic use of ergot alkaloids in the third stage of labour

Comparison: 01 Ergot alkaloids and no uterotonic agents

Outcome: 11 Nausea

Study	Ergot alkaloids n/N	Placebo or no agents n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Begley 1990	20/705	0/724		52.3	42.10 [2.55, 694.80]
McGinty 1956	1/100	0/50		47.7	1.51 [0.06, 36.53]
Total (95% CI)	805	774		100.0	8.63 [0.26, 284.55]
Total events: 21 (Ergot alkaloids), 0 (Placebo or no agents)					
Test for heterogeneity chi-square=2.72 df=1 p=0.10 I^2 =63.3%					
Test for overall effect z=1.21 p=0.2					

Analysis 01.12. Comparison 01 Ergot alkaloids and no uterotonic agents, Outcome 12 Headache (not prespecified)

Review: Prophylactic use of ergot alkaloids in the third stage of labour

Comparison: 01 Ergot alkaloids and no uterotonic agents

Outcome: 12 Headache (not prespecified)

Study	Ergot Ikaloids n/N	Placebo or no agents n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Begley 1990	3/705	0/724		42.6	7.19 [0.37, 138.91]
McGinty 1956	1/100	0/50		57.4	1.51 [0.06, 36.53]
Total (95% CI)	805	774		100.0	3.93 [0.51, 30.50]
Total events: 4 (Ergot Ikaloids), 0 (Placebo or no agents)					
Test for heterogeneity chi-square=0.50 df=1 p=0.48 I^2 =0.0%					
Test for overall effect z=1.31 p=0.2					

Analysis 01.13. Comparison 01 Ergot alkaloids and no uterotonic agents, Outcome 13 Pain after birth requiring analgesia (not prespecified)

Review: Prophylactic use of ergot alkaloids in the third stage of labour

Comparison: 01 Ergot alkaloids and no uterotonic agents

Outcome: 13 Pain after birth requiring analgesia (not prespecified)

Study	Ergot alkaloids n/N	Placebo or no agents n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Begley 1990	32/705	13/724		100.0	2.53 [1.34, 4.78]
Total (95% CI)	705	724		100.0	2.53 [1.34, 4.78]
Total events: 32 (Ergot alkaloids), 13 (Placebo or no agents)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.86 p=0.004					

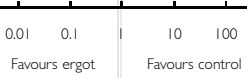
Analysis 01.14. Comparison 01 Ergot alkaloids and no uterotonic agents, Outcome 14 Eclamptic fit (not prespecified)

Review: Prophylactic use of ergot alkaloids in the third stage of labour

Comparison: 01 Ergot alkaloids and no uterotonic agents

Outcome: 14 Eclamptic fit (not prespecified)

Study	Ergot alkaloids n/N	Placebo or no agents n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Begley 1990	1/705	0/724		42.6	3.08 [0.13, 75.50]
McGinty 1956	3/100	0/50		57.4	3.53 [0.19, 67.13]
Total (95% CI)	805	774		100.0	3.34 [0.38, 29.43]
Total events: 4 (Ergot alkaloids), 0 (Placebo or no agents)					
Test for heterogeneity chi-square=0.00 df=1 p=0.95 I^2 =0.0%					
Test for overall effect z=1.09 p=0.3					



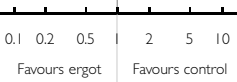
Analysis 01.15. Comparison 01 Ergot alkaloids and no uterotonic agents, Outcome 15 Postnatal haemoglobin < 10 gm (not prespecified)

Review: Prophylactic use of ergot alkaloids in the third stage of labour

Comparison: 01 Ergot alkaloids and no uterotonic agents

Outcome: 15 Postnatal haemoglobin < 10 gm (not prespecified)

Study	Ergot alkaloids n/N	Placebo or no agents n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Begley 1990	8/705	27/724		100.0	0.30 [0.14, 0.67]
Total (95% CI)	705	724		100.0	0.30 [0.14, 0.67]
Total events: 8 (Ergot alkaloids), 27 (Placebo or no agents)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.98 p=0.003					



Analysis 01.16. Comparison 01 Ergot alkaloids and no uterotonic agents, Outcome 16 Uterine subinvolution at routine follow up (not prespecified)

Review: Prophylactic use of ergot alkaloids in the third stage of labour

Comparison: 01 Ergot alkaloids and no uterotonic agents

Outcome: 16 Uterine subinvolution at routine follow up (not prespecified)

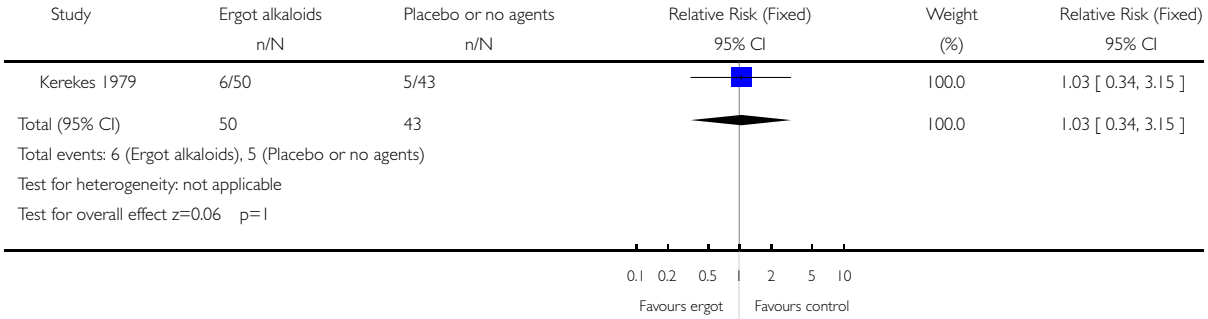
Study	Ergot alkaloids n/N	Placebo or no agents n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kerekes 1979	22/50	22/43		100.0	0.86 [0.56, 1.32]
Total (95% CI)	50	43		100.0	0.86 [0.56, 1.32]
Total events: 22 (Ergot alkaloids), 22 (Placebo or no agents)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.69 p=0.5					

Analysis 01.17. Comparison 01 Ergot alkaloids and no uterotonic agents, Outcome 17 Postpartum febrile morbidity (not prespecified)

Review: Prophylactic use of ergot alkaloids in the third stage of labour

Comparison: 01 Ergot alkaloids and no uterotonic agents

Outcome: 17 Postpartum febrile morbidity (not prespecified)

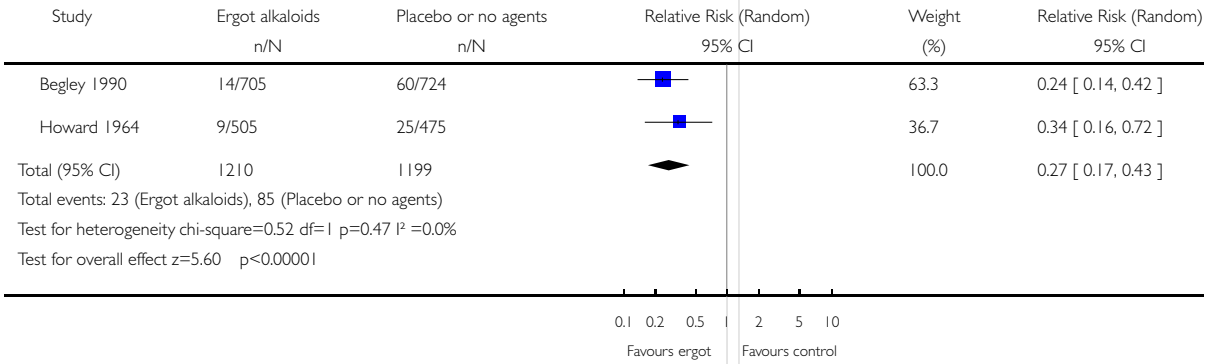


Analysis 04.01. Comparison 04 Sensitivity analysis based on trial quality, Outcome 01 Estimated or measured blood loss of at least 500 ml

Review: Prophylactic use of ergot alkaloids in the third stage of labour

Comparison: 04 Sensitivity analysis based on trial quality

Outcome: 01 Estimated or measured blood loss of at least 500 ml

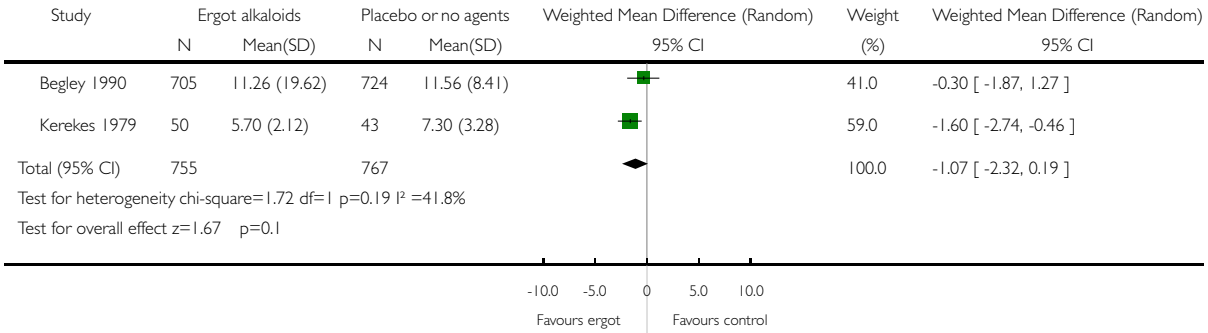


Analysis 04.02. Comparison 04 Sensitivity analysis based on trial quality, Outcome 02 Length of third stage of labour

Review: Prophylactic use of ergot alkaloids in the third stage of labour

Comparison: 04 Sensitivity analysis based on trial quality

Outcome: 02 Length of third stage of labour



Prophylactic antibiotics for transcervical intrauterine procedures (Review)

Thinkhamrop J, Laopaiboon M, Lumbiganon P

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2007, Issue 4

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Prophylactic antibiotics for transcervical intrauterine procedures (Review)

Thinkhamrop J, Laopaiboon M, Lumbiganon P

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ABSTRACT

Background
The transcervical intrauterine route is commonly used for operative gynecological procedures in women. The vagina is an area of the body that is abundant with normal bacterial flora. An operative procedure through the vagina may, therefore, be considered to have added potential for resulting in post-procedure infection. Prophylactic antibiotics may play a role in the prevention of post-procedure transcervical intrauterine infections.

Objectives
To assess the effectiveness and safety of antibiotic prophylaxis compared to placebo or no treatment in women undergoing transcervical intrauterine procedures.

Search strategy
The search strategy was based on the Menstrual Disorders and Subfertility Group's search strategy. The following databases were searched:
Menstrual Disorders and Subfertility Group Specialized Register;
Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library 2006, Issue 4;
MEDLINE (1966 to November 2006);
EMBASE (1966 to November 2006);
Biological Abstracts (1966 to October 2006);
AMED (1966 to November 2006).

Key words were prepared, in consultation with the Trials Search Coordinator, according to the terms related to our objective: antibiotic, antibiotics, prophylaxis, transvaginal, transcervical intrauterine, endometrial sample, endometrium sampling, endometrial biopsy, hysterosalpingography, hysteroscope, hysteroscopy, hysteroscopic surgery, endometrial ablation, and endometrial resection.

Selection criteria
The review authors planned to include only truly randomized controlled trials that compared antibiotic prophylaxis with placebo or no treatment in order to prevent infectious complications after transcervical intrauterine procedures. Controlled clinical trials without randomization and pseudo-randomized trial were excluded.

Data collection and analysis
No data collection or analysis was done because no trials were eligible for inclusion in the review.

Main results
The search did not identify any randomized controlled trials investigating the effect of antibiotic prophylaxis compared to placebo or no treatment in women undergoing transcervical intrauterine procedures.

Authors' conclusions
At this time, there are no published randomized controlled trials that assess prophylactic antibiotics effects on infectious complications following transcervical intrauterine procedures. It is, therefore, not possible to draw any conclusions regarding the use of prophylactic antibiotics for the prevention of post-procedure transcervical intrauterine infections.

PLAIN LANGUAGE SUMMARY

Giving antibiotics before or following transcervical intrauterine procedures to prevent infection

The lower genital tract is an area which is abundant with normal flora (resident bacteria) so that operative procedures which pass through it may be at increased risk for infection. The operative procedure may cause contamination of the uterine cavity with vaginal or cervical flora, or both. In addition, the associated trauma may compromise the ability of the uterus to combat infection. The prophylactic administration of antibiotics (giving antibiotics before the development of any infection) in women undergoing transcervical intrauterine procedures may prevent infection post procedure. There have been no randomized controlled trials evaluating the usefulness of antibiotics for the prevention of infection after these procedure

BACKGROUND

Antibiotic prophylaxis is the use of antibiotics for the prevention of infection. There are special considerations regarding the use of antibiotic prophylaxis in obstetric and gynecological procedures. Because the lower genital tract is abundant with normal vaginal flora, operation through or adjacent to this area leads to a moderate to high incidence of infection. There are established recommendations for using antibiotic prophylaxis in many major procedures, for example, vaginal hysterectomy (ACOG 2001), abdominal hysterectomy (ACOG 2001; Mittendorf 1993), and caesarean section (ACOG 2003; Chelmow 2001; Smail 2002). There are no clear recommendations for minor operative procedures such as dilatation and curettage for evacuation of conceptive products, fractional curettage for abnormal uterine bleeding, hysterosalpingography for infertility evaluation, and hysteroscopy for intrauterine cavity diagnosis and treatment. It is likely that there are no recommendations for these minor operative procedures because they cause relatively small areas of raw surface and tissue trauma. It is questionable as to whether or not antibiotic prophylaxis for these minor procedures is associated with more benefit than harm. However, these procedures have a high possibility of ascending infection from the lower genital tract to the upper genital tract, especially for those procedures that pass through the endocervical canal into the uterine cavity. Therefore, antibiotic prophylaxis might have a role in the prevention of infection with these procedures.

The incidence of infectious morbidity from transcervical intrauterine procedures varies widely according to the background prevalence for the study population and the procedure involved. A study of pelvic inflammatory disease (PID) after dilatation and curettage in women with metrorrhagia found that 4 of 33 women who received doxycycline for one week and 3 of 34 women who did not receive any antibiotic regimen after the procedure had PID (Makris 2000). The incidence of infectious morbidity after hysterosalpingography has been reported as 3.1% in 448 women (Stumpf 1980) and 44% in 150 women (Lema 1993). A randomized controlled trial to assess the effect of prophylactic antibiotics on the incidence of bacteremia following hysteroscopic surgery found the incidence to be 16% of 61 women in the non-antibiotic group and 2% of 55 women in the antibiotic group (Bhattacharya 1995). A study of metronidazole in prostaglandin-induced abortion reported pyrexia in 24% of 142 women without prophylactic antibiotics and 4.1% of 145 women with prophylactic antibiotics. A study of PID after hysterosalpingography in 116 women that was associated with Chlamydia trachomatis and Mycoplasma hominis reported that two of the four cases who developed PID were positive for C. trachomatis before the procedure. The authors concluded that C. trachomatis should be identified in patients before hysterosalpingography and, if detected, appropriate antibiotic cover given before the procedure (Moller 1984). Another study of tubo-ovarian abscess after operative hysteroscopy found that the women who did not receive antibiotic prophylaxis had a higher incidence of infection following the procedure than the group who had antibiotic prophylaxis. These findings were found in a high risk group with a history of PID (McCausland 1993).
It is not clear from the literature if antibiotic prophylaxis protects against infection following transcervical intrauterine procedures and so this systematic review was undertaken. There are already reviews of antibiotic prophylaxis for intrauterine contraceptive device insertion, medical or surgical first trimester induced abortion, and antibiotics for incomplete abortion (Grimes 1999; May 1999; Snieders 2005). We have adjusted the published protocol, which initially included women undergoing intrauterine insemination or instillation and embryo transfer, to exclude these women since this is now the topic of other Cochrane systematic reviews.

OBJECTIVES

To assess the effectiveness and safety of antibiotic prophylaxis compared to placebo or no treatment in women undergoing transcervical intrauterine procedures.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

The review authors included only truly randomized controlled trials that compared antibiotic prophylaxis with placebo or no treatment in the prevention of infectious complications after transcervical intrauterine procedures. Controlled clinical trials without randomization and pseudo-randomized trial were excluded.

Types of participants

Inclusion criteria

Non-pregnant women undergoing diagnostic or therapeutic intrauterine manipulation, or both, where the instrument was passed through the uterine cervical canal. Procedures included:
a. fractional curettage for evacuation of the whole endometrial lining tissue;
b. endometrial sampling for removal of some part of the endometrial lining tissue;
c. hysterosalpingography;
d. hysteroscopy;
e. hysteroscopic surgery, including endometrial ablation and endometrial resection.

Exclusion criteria

a. Women using antibiotics for any indication
b. Women undergoing embryo transfer
c. Women undergoing intrauterine insemination (IUI)
d. Women undergoing intrauterine device insertion

Types of intervention

Antibiotics given by oral or parenteral administration versus placebo or no treatment to prevent infection in women undergoing transcervical intrauterine procedures.

Types of outcome measures

Primary outcomes

1. Potential beneficial outcomes
1.1 Postoperative febrile morbidity (defined as a post-operative body temperature greater than 38 ?Celsius after the operation, within 10 days but not the first 24 hours)
1.2 Postoperative infectious complications (defined as any documented sites of infection identified by cultivation or clinical symptoms and signs, or both) including:
1.2.1 endometritis;
1.2.2 pelvic inflammatory disease;
1.2.3 pelvic abscess.
1.3 Postoperative treatment needed for infection including:
1.3.1 antibiotic treatment;
1.3.2 hospitalization needed for longer duration than usual;
1.3.3 surgical treatment, for example exploratory laparotomy for abscess evacuation or drainage.

Secondary outcomes

2. Potential adverse outcomes
2.1 Antibiotic side-effects including:
2.1.1 nausea;
2.1.2 vomiting;
2.1.3 diarrhea;
2.1.4 allergic reaction;
2.1.5 anaphylactic reaction.
2.2 Antibiotic resistance
2.3 Alteration of bacterial flora resulting in:
2.3.1 pseudomembranous enterocolitis.

We planned to assess these outcomes separately using subgroup analysis of participants with different risks of infection, such as where the procedure was done with or without vaginal cleaning, in an operating theatre versus outpatient clinic, in women with high versus low risk of sexually transmitted infection, and with or without regular steroid use.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

The original protocol for this review included IUI and embryo transfer (ET) but this is now the topic of other Cochrane systematic reviews.
The review authors (JT and PL) searched for relevant trials which described studies that compared antibiotic prophylaxis with placebo or no treatment to prevent infectious complications after transcervical intrauterine procedures in the following databases.
a) Menstrual Disorders and Subfertility Group Specialized Register.

b) Cochrane Central Register of Controlled Trials (CENTRAL in The Cochrane Library 2006, Issue 4).

The following search strategy was used.
1. reproductive techniques/
2. reproductive techniques.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3. fallopian tube patency tests.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4. insemination, artificial.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
5. reproductive techniques, assisted.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

6. embryo transfer.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
7. zygote intrafallopian transfer.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
8. (embry$ adj5 transf$).tw.
9. hysteroscop$.tw.
10. endometrial sampl$.tw.
11. endometrial biopsy.tw.
12. hysterosalpingograph$.tw.
13. (chorionic villi sampl$ or chorionic villi biopsy).tw.
14. (IUI or intrauterine insemination).tw.
15. Anti-Bacterial Agent$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
16. antibiotic$.tw.
17. or/1-14
18. or/15-16
19. 17 and 18
20. from 19 keep 1-9

c) MEDLINE (1966 to November 2006) using the following MeSH terms
1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. Randomized controlled trials/
4. random allocation/
5. double-blind method/
6. single-blind method/
7. or/1-6
8. clinical trial.pt.
9. exp clinical trials/
10. (clin$ adj25 trial$).ti,ab,sh.
11. ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).ti,ab,sh.
12. placebos/
13. placebo$.ti,ab,sh.
14. random$.ti,ab,sh.
15. Research design/
16. or/8-15
17. animal/ not (human/ and animal/)
18. 7 or 16
19. 18 not 17
20. reproductive techniques/ or contraception/ or fallopian tube patency tests/ or insemination, artificial/ or reproductive techniques, assisted/
21. embryo transfer/ or zygote intrafallopian transfer/
22. Intrauterine Devices, Medicated/ or Intrauterine Devices, Copper/ or Intrauterine Devices/
23. (embry$ adj5 transf$).tw.
24. Hysteroscopy/
25. hysteroscop$.tw.
26. "DILATATION AND CURETTAGE"/ or VACUUM CURETTAGE/ or CURETTAGE/
27. endometrial sampl$.tw.
28. endometrial biopsy.tw.
29. hysterosalpingograph$.tw.
30. Hysterosalpingography/
31. (chorionic villi sampl$ or chorionic villi biopsy).tw.
32. (IUI or intrauterine insemination).tw.
33. (IUD insert$ or intrauterine device insert$).tw.
34. curettag$.tw.
35. or/20-34
36. Anti-Bacterial Agents/
37. Antibiotic Prophylaxis/
38. antibiotic$.tw.
39. or/36-38
40. 35 and 39
41. 19 and 40
42. from 41 keep 1-75

d) EMBASE (1980 to 2007, week 07) using the following MeSH terms
1. reproductive techniques/ or contraception/ or fallopian tube patency tests/ or insemination, artificial/ or reproductive techniques, assisted/
2. embryo transfer/ or zygote intrafallopian transfer/
3. Intrauterine Devices, Medicated/ or Intrauterine Devices, Copper/ or Intrauterine Devices/
4. (embry$ adj5 transf$).tw.
5. Hysteroscopy/
6. hysteroscop$.tw.
7. "DILATATION AND CURETTAGE"/ or VACUUM CURETTAGE/ or CURETTAGE/
8. endometrial sampl$.tw.
9. endometrial biopsy.tw.
10. hysterosalpingograph$.tw.
11. Hysterosalpingography/
12. (chorionic villi sampl$ or chorionic villi biopsy).tw.
13. (IUI or intrauterine insemination).tw.
14. (IUD insert$ or intrauterine device insert$).tw.
15. curettag$.tw.
16. intrauterine insemination/
17. Anti-Bacterial Agents/
18. Antibiotic Prophylaxis/
19. antibiotic$.tw.
20. antibacter$.tw.
21. anti-bacter$.tw.
22. or/1-16
23. or/17-21
24. 22 and 23
25. Controlled study/ or randomized controlled trial/
26. double blind procedure/
27. single blind procedure/
28. crossover procedure/
29. drug comparison/
30. placebo/
31. random$.ti,ab,hw,tn,mf.

32. latin square.ti,ab,hw,tn,mf.
33. crossover.ti,ab,hw,tn,mf.
34. cross-over.ti,ab,hw,tn,mf.
35. placebo$.ti,ab,hw,tn,mf.
36. ((doubl$ or singl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).ti,ab,hw,tn,mf.
37. (comparative adj5 trial$).ti,ab,hw,tn,mf.
38. (clinical adj5 trial$).ti,ab,hw,tn,mf.
39. or/25-38
40. nonhuman/
41. animal/ not (human/ and animal/)
42. or/40-41
43. 39 not 42
44. 24 and 43
45. from 44 keep 1-149

e) Biological Abstracts (1966 to October 2006) using the following MeSH terms
1. (embry$ adj5 transf$).tw.
2. hysteroscop$.tw.
3. endometrial sampl$.tw.
4. endometrial biopsy.tw.
5. hysterosalpingograph$.tw.
6. (chorionic villi sampl$ or chorionic villi biopsy).tw.
7. (IUI or intrauterine insemination).tw.
8. (IUD insert$ or intrauterine device insert$).tw.
9. curettag$.tw.
10. antibiotic$.tw.
11. antibacter$.tw.
12. anti-bacter$.tw.
13. random$.ti,ab,hw,tn,mf.
14. latin square.ti,ab,hw,tn,mf.
15. crossover.ti,ab,hw,tn,mf.
16. cross-over.ti,ab,hw,tn,mf.
17. placebo$.ti,ab,hw,tn,mf.
18. ((doubl$ or singl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).ti,ab,hw,tn,mf.
19. (comparative adj5 trial$).ti,ab,hw,tn,mf.
20. (clinical adj5 trial$).ti,ab,hw,tn,mf.
21. or/1-9
22. or/10-12
23. or/13-20
24. 21 and 22
25. 23 and 24
26. from 25 keep 1-31

f) AMED (1985 to 2006,November week 3) using the following MeSH terms
1. reproductive techniq$.tw.
2. fallopian tube patency test$.tw. 3. reproduct$.tw.
4. embryo/
5. hysteroscop$.tw.
6. endometrial sampl$.tw.
7. endometrial biopsy.tw.
8. hysterosalpingograph$.tw.
9. (chorionic villi sampl$ or chorionic villi biopsy).tw.
10. (IUI or intrauterine insemination).tw.
11. antibiotic$.tw.
12. Anti-Bacter$.tw.
13. antibacter$.tw.
14. or/1-10
15. or/11-13
16. 14 and 15
17. from 16 keep 1-3

g) CINAHL (1982 to 2006, November Week 3) using the following MeSH terms
1. reproductive techniques/ or contraception/ or fallopian tube patency tests/ or insemination, artificial/ or reproductive techniques, assisted/
2. embryo transfer/ or zygote intrafallopian transfer/
3. Intrauterine Devices, Medicated/ or Intrauterine Devices, Copper/ or Intrauterine Devices/
4. (embry$ adj5 transf$).tw.
5. Hysteroscopy/
6. hysteroscop$.tw.
7. "DILATATION AND CURETTAGE"/ or VACUUM CURETTAGE/ or CURETTAGE/
8. endometrial sampl$.tw.
9. endometrial biopsy.tw.
10. hysterosalpingograph$.tw.
11. Hysterosalpingography/
12. (chorionic villi sampl$ or chorionic villi biopsy).tw.
13. (IUI or intrauterine insemination).tw.
14. (IUD insert$ or intrauterine device insert$).tw.
15. curettag$.tw.
16. Controlled study/ or randomized controlled trial/
17. placebo/
18. random$.ti,ab,hw,tn,mf.
19. latin square.ti,ab,hw,tn,mf.
20. crossover.ti,ab,hw,tn,mf.
21. cross-over.ti,ab,hw,tn,mf.
22. placebo$.ti,ab,hw,tn,mf.
23. ((doubl$ or singl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).ti,ab,hw,tn,mf.
24. (comparative adj5 trial$).ti,ab,hw,tn,mf.
25. (clinical adj5 trial$).ti,ab,hw,tn,mf.
26. exp Antibiotics/
27. Antibiotic Prophylaxis/
28. antibiotic$.tw.
29. antibacter$.tw.
30. anti-bacter$.tw.
31. or/1-15
32. or/26-30
33. or/16-25
34. 31 and 32
35. 33 and 34

36. from 35 keep 1-5

h) Handsearching of
1. conference proceedings;
2. bibliographies.

i) The reference lists of identified articles.

METHODS OF THE REVIEW

The following methods for conducting the review were planned at the protocol stage. As no randomized controlled trials were relevant to the review, despite extensive searching, these methods were not followed but are included here for the purpose of the planned update of the review. These are the criteria for considering whether studies are relevant.

Study selection

We will select trials in which the administration of antibiotics was done before or immediately after the procedure and without any documentation of an existing infection at that time. The study selection will be undertaken by two review authors (JT and PL). The titles and abstracts of articles found in the search will be screened by JT, who will discard studies that are clearly ineligible but will aim to be overly inclusive rather than risk losing relevant studies. JT will obtain copies of the full text articles and will make copies for PL; details of the authors and institutions will have been struck out and the results section removed. Both review authors will independently assess whether the studies meets the inclusion criteria, with disagreements to be resolved by discussion. Further information will be sought from the authors where papers contain insufficient information to make a decision about eligibility.

Quality assessment

The quality of included studies will be assessed using the following quality criteria.

Allocation concealment, which will be graded as adequate (A), unclear (B), or inadequate (C).
The use of blinding for outcome assessment.
Intention-to-treat analysis.

This information will be presented in the text of the review and we will provide details summarising the quality in additional tables called 'Quality of included studies.' This will help to provide a context for discussing the reliability of results. Sensitivity analysis will also be done, if there are enough studies in order to compare results from trials with various grades of allocation concealment, blinding of outcome assessment and intention-to-treat analysis.

The following information will be extracted from the included studies and presented in a table entitled 'Characteristics of included studies'.

Trial characteristics

(a) Type of transcervical intrauterine procedure
(b) Allocation concealment
(c) Number of patients randomized, excluded, and analysed
(d) Follow-up rate
(e) Duration, timing, and location of the trial
(f) Existing underlying diseases in the participants, e.g. HIV infection, history of sexually transmitted infection

Intervention

(a) Detailed description of the antibiotic regimen used (including type of drug, dose, frequency and timing)
(b) Type of control (placebo or no treatment)

Outcomes

(a) Outcomes reported as specified above
(b) How are outcomes defined?
(c) How are outcomes measured? (Blinding of assessors)
(d) Timing of outcome measurement
(e) Summary measures of the outcomes and their variation

JT will then provide PL with the results sections of the included studies and both review authors will independently extract information. Discrepancies will be resolved by discussion. Where possible, missing data will be sought from the authors.

All trials that meet, or appear to meet, the inclusion criteria but are then excluded from the review will be described with the reason why the trials have been excluded listed in the table 'Characteristics of excluded studies'.

Analysis

As no studies were found all planned forms of analysis were not conducted.

Meta-analysis would have been performed in accordance with the guidelines for statistical analysis developed by The Cochrane Collaboration. For binary data, we would have calculated relative risk and the corresponding 95% confidence interval. We would have used forest plots and the chi-squared test of heterogeneity to examine the heterogeneity of results (using a 10% level of statistical significance) and measuring the value of the I2 statistic for degree of inconsistency (Higgins 2003). Subgroup analysis would have been performed for each type of control group and according to degree of risk of infection to assess which had a substantial effect on antibiotic prophylaxis, such as if the procedure was done with or without vaginal cleaning, in an operating theatre versus outpatient clinic, in women with high versus low risk of sexually transmitted infection, and with or without regular steroid use.
If the detected heterogeneity could not be explained by any clinical or methodological variation, we would have used the random-effects model to estimate an overall effect of the prophylactic antibiotic on preventing infection complications after transcervical intrauterine procedures.

We would have performed sensitivity analysis to evaluate the robustness of the conclusion according to methodological quality and publication bias (published and unpublished articles).

DESCRIPTION OF STUDIES

No studies were identified which met the inclusion criteria for this review.

METHODOLOGICAL QUALITY

No studies were included.

RESULTS

No randomized controlled trials investigating the effects of prophylactic antibiotics for transcervical intrauterine procedures were found.

DISCUSSION

Antibiotic prophylaxis is recommended for major operative obstetric and gynecologic procedures, such as hysterectomy and caesarean section (ACOG 2001; Chelmow 2001; Mittendorf 1993; Smail 2002). For minor operative procedures there is conflicting evidence regarding the use of routine prophylactic antibiotics (Bhattacharya 1995; Lema 1993; Makris 2000; McCausland 1993; Moller 1984; Stumpf 1980). In this review we planned to assess antibiotic effects in randomized controlled trials on prevention of infection as well as the occurrence of adverse events after minor procedures such as fractional curettage for evacuation of the whole endometrial lining tissue, endometrial sampling for some part of the endometrial lining tissue, hysterosalpingography, hysteroscopy, hysteroscopic surgery, endometrial ablation, and endometrial resection. While prophylactic antibiotics for transcervical intrauterine procedures may be of value, we have not been able to determine whether there are any benefits or harms of this intervention.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence to either support or discourage the use of antibiotics to prevent infection for transcervical intrauterine procedures. Prophylactic antibiotics may be considered in populations and areas where the incidence of infection after transcervical intrauterine procedures is high.

Implications for research

Transcervical intrauterine procedures may increase the risk of infection after the procedure. However, there is conflicting evidence as to the benefit of routine prophylactic antibiotics. Some observational studies have found prophylaxis useful. Double-blinded randomized trials comparing prophylactic antibiotics to placebo are needed before any conclusions can be made about the role of prophylactic antibiotics for intracervical intrauterine procedures.

POTENTIAL CONFLICT OF INTEREST

None known.

ACKNOWLEDGEMENTS

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SOURCES OF SUPPORT

External sources of support

- Thailand Research Fund, Senior Research Scholar THAILAND

Internal sources of support

- Khon Kaen University THAILAND
- Thai Cochrane Network THAILAND

REFERENCES

References to studies excluded from this review

Bhattacharya 1995

Bhattacharya S, Parkin DE, Reid TMS, Abramovich DR, Mollison J, Kitchener HC. A prospective randomised study of the effects of prophylactic antibiotics on the incidence of bacteremia following hysteroscopic surgery. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 1995;**63**:37–40.

Brook 2006

Brook N, Khalaf Y, Coomarasamy, Edgeworth J, Braude. A randomized controlled trial of prophylactic antibiotics (co-amoxiclav) prior to embryo transfer. *Human Reproduction* 2006;**21**:2911–5.

Makris 2000

Makris N, Iatrakis G, Sakellaropoulos G, Rodolakis A, Michalas S. The role of antibiotics after dilatation and curettage in women with metrorrhagia in the prevention of pelvic inflammatory disease. *Clinical and Experimental Obstetrics & Gynecology* 2000;**27**(1):27–8.

Marchino 1994

Marchino GL, Mazza O, Baccarini G, Zaccheo F, Grio R. Antibiotic prophylaxis with cefotaxime in gynecological surgery. *Minerva Ginecologia* 1994;**46**(6):337–41.

McCausland 1993

McCausland VM, Fields GA, McCausland AM, Townsend DE. Tuboovarian abscesses after operative hysteroscopy. *The Journal of Reproductive Medicine* 1993;**38**(3):198–200.

N'Gbesso 2003

N'Gbesson RD, Tan B, Beddi MO, Quenum C. Systemic preventive antibiotic therapy during hysterosalpingography in an African tropical environment: is this practice justified?. *Sante* 2003;**13**(1):23–7.

Peikrishvili 2004

Peikrishvili R, Evrard B, Pouly JL, Janny L. Prophylactic antibiotic therapy (amoxicillin + clavulanic acid) before embryo transfer for IVF is useless, results of a randomized study. *Journal de Gynecologie, Obstetrique et Biologie de la Reproduction(Paris)* 2004;**33**(8):713–9.

Pittaway 1983

Pittaway DE, Winfield AC, Maxson W, Daniell J, Herbert C, Wentz AC. Prevention of acute pelvic inflammatory disease after hysterosalpingography: efficacy of doxycycline prophylaxis. *American Journal of Obstetrics and Gynecology* 1983;**147**(6):623–6.

Primi 2004

Primi MP, Senn A, Montag M, Van der Ven H, Mandelbaum J, et al. A European multicentre prospective randomized study to assess the use of assisted hatching with a diode laser and the benefit of an immunosuppressive/antibiotic treatment in different patient populations. *Human Reproduction* 2004;**19**:2325–33.

Additional references

ACOG 2001

American College of Obstetricians and Gynecologists Committee. Antibiotic prophylaxis for gynecologic procedures. ACOG Practice Bulletin, clinical management guidelines for obstetrician-gynecologists. 2001; Vol. 23.

ACOG 2003

American College of Obstetricians and Gynecologists Committee. Prophylactic antibiotics in labour and delivery. ACOG Practice Bulletin, clinical management guidelines for obstetrician-gynecologists. 2003; Vol. 47.

Chelmow 2001

Chelmow D, Ruehli MS, Huang E. Prophylactic use of antibiotics for nonlabouring patients undergoing cesarean delivery with intact membranes: a meta-analysis. *American Journal of Obstetrics and Gynecology* 2001;**184**:656–61.

Grimes 1999

Grimes DA, Schulz FK. Antibiotic prophylaxis for intrauterine contraceptive device insertion. *Cochrane Database of Systematic Reviews* 1999, Issue 3. Art. No.: CD001327. DOI: 10.1002/14651858.CD001327.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. *BMJ* 2003;**327(7414)**:557–60.

Lema 1993

Lema VM, Majinge CR. Acute pelvic infection following hysterosalpingography at the Kenyatta National Hospital, Nairobi. *East African Medical Journal* 1993;**70(9)**:551–5.

May 1999

May W, G?lmezoglu AM, Ba-Thike K. Antibiotics for incomplete abortion. *Cochrane Database of Systematic Reviews* 1999, Issue 4. Art. No.: CD001779. DOI:10.1002/14651858.CD001779.pub2.

Mittendorf 1993

Mittendorf R, Aronson MP, Berry RE, Williams MA, Kupelnick B, Klickstein A, et al. Avoiding serious infections associated with abdominal hysterectomy: a meta-analysis of antibiotic prophylaxis. *American Journal of Obstetrics and Gynecology* 1993;**169**:1119–24.

Moller 1984

Moller BR, Allen J, Toft B, Hansen B, Taylor-Ribinson D. Pelvic inflammatory disease after hysterosalpingography associated with Chlamydia trachomatis and Mycoplasma hominis. *British Journal of Obstetrics and Gynaecology* 1984;**91**:1181–7.

Smail 2002

Smail F, Hofmeyr GJ. Antibiotic prophylaxis for cesarean section. *Cochrane Database of Systematic Reviews* 2002, Issue 3. Art. No.: CD000933. DOI:10.1002/14651858.CD000933.

Snieders 2005

Snieders MNE, Van Vliet HAAM, Helmerhorst FM, Low N. Antibiotic prophylaxis for medical and surgical first-trimester induced abortion. *Cochrane Database of Systematic Reviews* 2005, Issue 2. Art. No.: CD005217. DOI:10.1002/14651858.CD005217.

Stumpf 1980

Stumpf PG, March CM. Febrile morbidity following hysterosalpingography: identification of risk factors and recommendations for prophylaxis. *Fertility and Sterility* 1980;**33(5)**:487–92.

TABLES

Characteristics of excluded studies

Study	Reason for exclusion
Bhattacharya 1995	The study reported on the outcome bacteraemia following hysteroscopic surgery which is not relevant to this review's objective to assess the effect of antibiotic prophylaxis on infectious morbidity.
Brook 2006	This is a randomized controlled trial to assess the rate of bacterial contamination on the transfer catheter tip during embryo transfer and the success rate for a clinical pregnancy. The study's outcomes of interest are not relevant to this review's objective to assess effect of antibiotic prophylaxis on infectious morbidity.
Makris 2000	There were two groups in the study. The authors did not mention how they separated participants into the two groups. We cannot confirm from the publication that this was a randomized trial. We sent a letter to the first author to clarify this issue. However, we did not receive any information at the time of completing the review. The authors mentioned in the article that this is a follow-up study in women given antibiotics or not after endometrial curettage for menorrhagia. It seems to us that this is not a randomized controlled trial.
Marchino 1994	This was a one-arm clinical trial. There was no controlled group in the study
McCausland 1993	There were two groups in the study. The authors did not mention how they separated participants into the two groups. We cannot confirm from the publication that this was a randomized trial. We have sent a letter to contact the first author to clarify this issue. However, we did not receive any information at the time of completing the review. There were 200 women who did not receive prophylactic antibiotics, 500 women who received prophylactic antibiotics. There was a large difference between the numbers of participants in the two groups. It seems to us that this could not be a randomized controlled trial.
N'Gbesso 2003	This was a clinical controlled trial where even and odd numbers of enrolment were used to assign the participants to receive intervention or not.
Peikrishvili 2004	The study reported on the outcome of interest which was pregnancy loss rate during IVF cycles according to the prescription of antibiotics or not, which is not relevant to this review's objective to assess effect of antibiotic prophylaxis on infectious morbidity.
Pittaway 1983	The study reported on acute pelvic inflammatory disease after hysterosalpingogram in the first group without antibiotic prophylaxis who were recruited between October 1, 1980 and September 1, 1981 and the second group recruited between October 1, 1981, and October 1, 1982 who received antibiotic prophylaxis. So this study is a non-concurrent control trial.
Primi 2004	This was a randomized controlled trial to assess the success rate of implantation on assisted hatching and immunosuppressive/antibiotic treatment. The study's outcome of interest was not relevant to this review's objective to assess effect of antibiotic prophylaxis on infectious morbidity.

GRAPHS AND OTHER TABLES

This review has no analyses.

COVER SHEET

Title	Prophylactic antibiotics for transcervical intrauterine procedures
Authors	Thinkhamrop J, Laopaiboon M, Lumbiganon P
Contribution of author(s)	JT: selected the topic, searched and selected for papers, drafting the review. PL: co-drafting and final approval of the review. ML: final approval of the review.

Issue protocol first published	2006/1
Review first published	2007/3
Date of most recent amendment	20 April 2007
Date of most recent SUBSTANTIVE amendment	22 April 2007
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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DOI	10.1002/14651858.CD005637.pub2
Cochrane Library number	CD005637
Editorial group	Cochrane Menstrual Disorders and Subfertility Group
Editorial group code	HM-MENSTR

Antibiotics for brain abscesses in people with cyanotic congenital heart disease (Review)

Lumbiganon P, Chaikitpinyo A

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2007, Issue 4

http://www.thecochranelibrary.com

TABLE OF CONTENTS

Antibiotics for brain abscesses in people with cyanotic congenital heart disease (Review)

Lumbiganon P, Chaikitpinyo A

This record should be cited as:
Lumbiganon P, Chaikitpinyo A. Antibiotics for brain abscesses in people with cyanotic congenital heart disease. *Cochrane Database of Systematic Reviews* 2007, Issue 3. Art. No.: CD004469. DOI: 10.1002/14651858.CD004469.pub2.

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Date of most recent substantive amendment: 14 May 2007

ABSTRACT

Background
Brain abscess is a focal, intracerebral infection that begins as a localized area of brain infection and develops into a collection of pus surrounded by a well-vascularized capsule. People with cyanotic congenital heart disease are at risk of developing brain abscess.

Objectives
To evaluate the effectiveness of antibiotic regimens for treating brain abscess in people with cyanotic congenital heart disease.

Search strategy
We searched the Cochrane Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library* 2006, Issue 2, MEDLINE (January 1966 to June 2006), EMBASE (January 1998 to June 2006), and LILACS (accessed in June 2006). No language or publication restrictions were used.

Selection criteria
Randomized controlled trials that reported clinically meaningful outcomes and presented results on an intention to treat basis, irrespective of blinding, publication status, or language.

Data collection and analysis
Data were to be extracted, unblinded, by the two reviewers independently. The search identified 489 articles of which 152 were articles on brain abscess. Most of the articles were case series and case reports.

Main results
No studies that met the inclusion criteria were identified.

Authors' conclusions
There are no randomized controlled trials about the effectiveness of antibiotic regimens for treating people with cyanotic congenital heart disease who developed a brain abscess. Currently, the antibiotic regimens used are based on previous retrospective studies and clinical experience. There is a need for a well designed multicentre randomized controlled trial to evaluate the effects of different antibiotic regimens.

PLAIN LANGUAGE SUMMARY

Serious congenital heart disease leads to abnormal blood flow through the heart and lungs. This results in an inability to carry enough oxygen around the body which makes patients blue (cyanotic) and severely limits their physical activity. People with cyanotic congenital heart disease are at risk of developing brain abscess. This condition is serious and can lead to death because the abscess causes abnormal brain function. Treatment includes antibiotic therapy to kill the bacteria that cause the infection. In people with a large abscess, an operation to drain the abscess may be carried out. Antibiotic therapy for brain abscess should include drugs that penetrate into the

abscess cavity. The drugs chosen should also be matched to the sensitivity of the bacteria obtained from the abscess in laboratory culture. There is no evidence from randomized controlled trials to show the best antibiotic regimen for treating people with cyanotic congenital heart disease who develop brain abscess.

BACKGROUND

Brain abscess

Brain abscess is a focal, intracerebral infection that begins as a localized area of infection and develops into a collection of pus surrounded by a well-vascularized capsule (Mathisen 1997). It can originate from infection of contiguous structure (e.g. otitis media, dental infection, mastoiditis, sinusitis), as the result of hematogenous spread from a remote site (particularly in people with cyanotic congenital heart disease), after skull trauma or surgery and, rarely, following meningitis. In at least 15% of cases no source can be identified.

Cyanotic congenital heart disease

Cyanotic congenital heart disease is a congenital defect of the heart that leads to hemodynamic abnormality. Systemic venous return to the right-side of the heart is shunted across the defect into the systemic circulation, resulting in persistent arterial desaturation and cyanosis. People with cyanotic congenital heart disease are at risk of developing brain abscess. Intracardiac right-to-left shunt bypass, by which blood is not filtered through pulmonary circulation where bacteria are intercepted by phagocytosis, may allow direct entry to cerebral circulation. In addition, decreased arterial oxygenation can result in compensatory polycythemia. Increased blood viscosity can cause a focal area of ischemia that serves as a nidus for infection. Shunted blood containing micro-organisms may be seeded in such lesions, forming a cerebral abscess (Matson 1961; Fischbein 1974).

Size of the problem

Brain abscess is not common and is a rare complication of cyanotic congenital heart disease. In one study the frequency of brain abscess in people with cyanotic congenital heart disease was 2% among 1,270 patients during a 13-year period (Fischbein 1974). The peak incidence occurs when the patient is between 4 years and 7 years of age, although cases of brain abscess may occur in adults with cyanotic congenital heart disease (Kagawa 1983). Among the 149 patients with brain abscess in one report, 103 (69.1%) had cyanotic congenital heart disease. In this study, the most common form of cyanotic congenital heart disease was tetralogy of Fallot (51 patients), followed by complete transposition of the great arteries (12 patients) and double outlet of right ventricle (10 patients) (Takeshita 1997). The reported case fatality rates for cyanotic brain abscess in the pre-computerized tomography (CT) era were 38% (Fischbein 1974), 40% (Brewer 1975) and 37% (Kagawa 1983). In the CT era, the in-hospital case fatality in one report was 13.3% (Prusty 1993).

Interventions used

Treatments include intravenous antibiotics alone, or concomitantly combined with surgical interventions such as aspiration of the abscess (Takeshita 1997) and /or abscess excision (Mathisen 1997). The most common organisms isolated in cyanotic brain abscess include *Streptococcus viridans*, microaerophilic streptococci, anaerobic streptococci, and occasionally, *Haemophilus* species (De Louvois 1978; Saez-Llorens 1989). On theoretical grounds, antibiotic therapy for bacterial brain abscess should include agents that penetrate into the abscess cavity and have in vitro activity against the pathogens isolated. Drugs should be given intravenously in order to yield high serum levels and therefore high levels in the abscess cavity. Other adjunctive therapy includes the use of corticosteroid to control cerebral edema in patients with potentially life-threatening complications such as impending cerebral herniation. Severe brain edema may also necessitate the administration of intravenous mannitol and intubation with forced hyperventilation. Rarely, placement of a ventriculostomy catheter for cerebrospinal fluid drainage, to relieve intracranial pressure, may prove lifesaving. Seizures are a frequent complication of brain abscess and anticonvulsants may be needed (Mathisen 1997).

Specific antibiotic treatment

For the past 20 years high dose intravenous penicillin G and chloramphenicol have been used to treat brain abscess in this setting with satisfactory outcomes (Jadavji 1985). The most important drawback of chloramphenicol is its toxic hematologic effect including a common and predictable, but reversible, erythroid suppression of the bone marrow. However, serious irreversible aplastic anemia, leading in many cases to fatal pancytopenia, has been described in patients who received chloramphenicol (Jimenez 1987). Third generation cephalosporins, either cefotaxime or ceftriaxone have good central nervous system penetration (Sjolin 1991; Yamamoto 1993), and excellent in vitro activity against many pathogens isolated from bacterial brain abscess. Metronidazole is highly active against anaerobic bacteria, including *Bacteroides fragilis*, the most resistant anaerobe. Therefore, metronidazole is usually combined with third generation cephalosporins or penicillin G for the treatment of cyanotic brain abscess (Sjolin 1993). As third generation cephalosporins are much more expensive than penicillin G there is a need to evaluate the effects of different antibiotic regimens for the treatment of brain abscess in children with cyanotic congenital heart disease.

OBJECTIVES

To determine, from the best available evidence, the effects (both harms and benefits) of antibiotic regimens for treating people with cyanotic congenital heart disease who develop a brain abscess.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomized controlled trials, irrespective of blinding, publication status, or language were to have been included because it was expected that only a small number of trials would be found. This included unpublished trials if the methodology and the data of the trial could be accessed in written form. Only data from the first period of crossover trials would have been included. Trials in which patients were allocated by a quasi-random method, e.g. day of birth or date of admission, were excluded.

Types of participants

People who have cyanotic congenital heart disease and have developed brain abscess. No restrictions on age were made in the search.

Types of intervention

Trials were considered if they compared at least two different antibiotic regimens. In addition to the comparison of different antimicrobial agents, studies were also included if there was a comparison between the route of administration, the timing of administration and the number of doses of drugs given.

Types of outcome measures

All outcomes were considered at the end of treatment and at maximum follow-up according to the individual trial.

Primary outcomes

Complete recovery rate.
Mortality rate.

Secondary outcomes

Adverse events, defined as any untoward medical occurrence in a patient which did not necessarily have a causal relationship with the treatment, but resulted in a dose reduction or discontinuation of treatment.
Severe adverse events, defined according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines (ICH-GCP 1997) as any event that would increase mortality; was life-threatening; required in-patient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability; or any important medical event, which might have jeopardized the patient or required further intervention.
Length of hospital stay.
Cost-effectiveness analysis.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

A search was made of the Cochrane Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library* issue 2, 2006. We also searched MEDLINE (January 1966 to June 2006) on Ovid, EMBASE (January 1998 to June 2006) on Ovid, and Latin American and Caribean Health Science (LILACS; accessed June 2006). The search strategy below was used to search CENTRAL and strategies for MEDLINE and EMBASE can be found in additional Table 01 and Table 02. The search included the addition of a standard randomized controlled trial filter for MEDLINE (Dickersin 1994) and EMBASE (Lefebvre 1996). The reference lists of relevant articles were checked for any unidentified trials and the authors of included studies, and pharmaceutical companies, contacted where necessary. No language restriction was applied.

#1(HEART-DEFECT-CONGENITAL)
#2 (BRAIN* near ABSCESS*)
#3 (CEREBRAL near ABSCESS*)
#4 (CEREBELLA* near ABSCESS*)
#5 (TETRALOGY* near FALLOT*)
#6 (CYANOTIC near HEART)
#7 (CONGENITAL near HEART)
#8 (#1 or #2) or #3) or #4) or #5) or #6) or #7)
#9 ANTIBIOTICS*:ME
#10 ANTIBIOTIC*
#11 CHLORAMPHENICOL*
#12 PENICILLIN*
#13 METRONIDAZOLE*
#14 CEPHALOSPORINS*
#15 CEFOTAXIME*
#16 CEFTRIAXONE*
#17 AMPICILLIN*
#18 CLINDAMYCIN*
#19 CEFTAZIDIME*
#20 ANTI-INFECTIVE*
#21 (#9 or #10) or #11) or #12) or #13) or #14) or #15) or #16) or #17) or #18) or #19) or #20)
#22 (#8 and #21)

METHODS OF THE REVIEW

Selection of trials for inclusion

Decisions on which trials to be included were taken independently by both reviewers who were unblinded with regard to the names of the authors, investigators, institution, source, and results.

Disagreements were resolved by discussion. Excluded trials are listed with the reason for exclusion in the characteristics of excluded studies table.

Methodological quality

Methodological quality was defined as the level of confidence that the design and report restricted bias in the intervention comparison (Moher 1998). According to empirical evidence (Jadad 1996; Juni 2001; Kjaergard 2001; Moher 1998; Schulz 1995), we planned to assess methodological quality in relation to the allocation sequence, allocation concealment, and double blinding. Further, we planned to extract the number of dropouts and withdrawals (Jadad 1996) and how these were included in the analyses (if and how intention-to-treat analyses had been performed) (Hollis 1999).

Data extraction

We planned to extract the following data (by the two reviewers, independently, using standardised extraction sheets). The authors of the trials would be approached to specify the following data, if they had not been reported sufficiently in the article.

Trial characteristics

Methodological quality.
Parallel or crossover design.
Number of intervention arms.
Length of follow-up.
Estimation of sample size.
Use of intention-to-treat analyses.

Patient characteristics

Number of patients randomised to each intervention arm.
Mean (or median) age.
Number of male and female.
Type of cyanotic congenital heart disease.
Method for detection of brain abscess.
Site and size of brain abscess.
Inclusion and exclusion criteria.

Intervention characteristics

Type of antibiotics.
Dose of antibiotics.
Duration of antibiotics.
Route of administration.
Type and dose of additional intervention(s) and type of surgical interventions, e.g. aspiration or excision of the abscess.

Outcome measures

All outcome measures will be extracted from each randomized controlled trial.

Statistical methods

We planned to perform all analyses according to the intention-to-treat method using the last reported observed response (carry forward) and including all patients irrespective of compliance or follow-up. Binary outcomes would be expressed as relative risks and 95% confidence intervals. Continuous data would be analysed using weighted mean difference. Depending on the presence or absence of trial variability (significant heterogeneity defined as $P < 0.1$) a random-effects model (DerSimonian 1986) or a fixed-effect model (Demets 1987) would be used. Rare events would be estimated by Peto odds ratio (Deeks 1998). In case of significant heterogeneity, the potential causes for the heterogeneity would be explored by performing sensitivity analyses. All studies would be combined. Subgroup analyses would be performed analysing all-cause mortality, type of cyanotic congenital heart disease, according to methodological quality, class of antibiotics and duration of treatment. If sufficient trials were found the presence of publication bias would be assessed by funnel plots (Egger 1997).

DESCRIPTION OF STUDIES

We found 498 articles (including 8 non-English articles), of which 152 were articles on brain abscess. Most of these 152 articles were case series and case reports. We found eight potentially eligible reports. There were case series of patients, some with cyanotic congenital heart disease, with brain abscess and most articles mentioned the type of antibiotic used for treatment (Abdullah 2001; Gonzalez-Garcia 1999; Hirsch 1983; Jansson 2004; Lu 2002; Mampalum 1988; Seneviratne Rde 2003; Yang 1981). A review on the rational use of antibiotics in the treatment of brain abscess was published in the *British Journal of Neurosurgery* (British Society 2000). These reports are described below.

We found no studies that met the criteria for inclusion in this review. There are no ongoing studies on antibiotic regimens for brain abscess in cyanotic congenital heart disease.

METHODOLOGICAL QUALITY

No studies were identified that met the inclusion criteria.

RESULTS

No studies were identified that met the inclusion criteria. We did not find any quasi-randomized studies.

DISCUSSION

The treatment of brain abscess requires a multidisciplinary approach. Imaging studies allow early diagnosis and permit rapid and precise localization of brain lesions that may require surgical intervention. Stereotactic needle aspiration permits therapeutic drainage and provides diagnostic specimens for identification

of the causative organisms. Empirical antibiotic therapy should be started on the basis of the likely associated pathogens which depend on the presumptive precipitating source of infection and the Gram stain results. The antibiotic regimen can be modified, if necessary, once culture results on aspirated pus are available. Serial imaging studies are done to monitor the therapeutic response and identify recurrent or secondary lesions that may require repeated drainage.

Not surprising, as brain abscess is a rare condition, randomized controlled trials of different therapies do not appear to have been conducted. All of the published studies were retrospective, and most of the reports focused on neurosurgical and radioimaging, and as a result did not contain comprehensive information on microbiological data or details of the antibiotic regimens used.

Yang 1981 reviewed 400 cases of brain abscess treated in China over 20 years (April 1952 to December 1972). Sixteen cases had congenital heart disease as a predisoposing factor. The antibiotic regimens were penicillin and streptomycin in the earlier cases, when they routinely used penicillin and chloramphenicol. Mampalum 1988 described 102 cases over 17 years. They grouped their patients according to the treatment received: excision, aspiration and nonsurgical therapy. Hirsch 1983 reported 34 children treated for brain abscess during 15 years. Thirteen cases had cyanotic heart disease. Their treatment included puncture of the abscess, antibiotic administration and redraining if indicated. Gonzalez-Garcia 1999 retrospectively analysed 100 cases of brain abscess diagnosed between 1979 and 1998. Abdullah 2001 reported 60 cases of brain abscesss during the 7-year period from 1990 to 1996. Twenty patients had cyanotic heart disease. The combination of a beta-lactam agent with chloramphenicol and/or metronidazole was used as standard treatment. Lu 2002 reported 123 cases of brain abscess over a period of 15 years (January 1986 to December 2000). Of these 123 patients, 103 had community-acquired infections, while the other 20 were diagnosed with nosocomial infection. The portal of entry in 94 culture-positive cases included hematogenous spread (n = 32), postneurosurgical states (n = 17), contiguous infection from parameningeal foci (n = 22) and unknown (n = 24). No information regarding congenital heart disease as a predisposing factor was described. Seneviratne Rde 2003 reported 41 patients with cerebral abscess, 30% of cases had congenital heart disease as the predisposing factor. The antibiotic regime used in this neurosurgical unit consisted of cefotaxime and metronidazole and the result of treatment was satisfactory. Jansson 2004 described 66 cases of brain abscess treated initially with cefotaxime over a period of 10 years (January 1990 to December 1999). The predisposing factor was cardiopathy (type not specified) in nine cases. Sixty-two of these patients were treated additionally with metronidazole and surgery was also performed in 53 patients. Side effects which included nonpruritic rash, leukopenia, drug fever etc., were reported in 42 patients, of whom cefotaxime was terminated prematurely in 38 patients. The overall mortality was 12%.The Infection in Neurosurgery Working Party of the British Society for Antimicrobial Chemotherapy reviewed the rational use of antibiotics in the treatment of brain abscess by reviewing all English language publications between 1975 and 1999. They found no randomized controlled trials (British Society 2000). Their recommendations are inevitably based on pathological and surgical principles of choosing the most appropriate antibiotic combination based on likely pathogens and in vitro antibiotic sensitivity, abscess drainage and supportive treatment.

AUTHORS' CONCLUSIONS

Implications for practice

The clinical management of people with cyanotic congenital heart disease who developed a brain abscess has to rely on the results of retrospective studies and previous clinical experience other than that obtained through randomized controlled or controlled clinical trials.

Implications for research

As it is unlikely that a trial of treatment of brain abscess will be conducted owing to the rarity of the condition and concensus about the approach to choice of antibiotic regimens and indications for surgical drainage, future research may be best directed towards diagnosis and early detection of brain abscess, molecular methods to detect the infecting organism as an alternative to culture, and exploring more effective and practical drainage methods to improve quality of care.

POTENTIAL CONFLICT OF INTEREST

None known.

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- Khon Kaen University THAILAND

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TABLES

Characteristics of excluded studies

Study	Reason for exclusion
Abdullah 2001	Not a randomized controlled trial: reported on a case series of brain abscess (60 cases).
British Society 2000	Literature review on the antimicrobial treatment of brain abscess.
Gonzalez-Garcia 1999	Not a randomized controlled trial: reported on a case series of brain abscess (100 cases).
Hirsch 1983	Not a randomized controlled trial: reported on a case series of brain abscess in children (34 cases).
Jansson 2004	Not a randomized controlled trial: reported on a case series of brain abscess (66 cases).
Lu 2002	Not a randomized controlled trial: reported on a case series of brain abscess (125 cases).
Mampalum 1988	Not a randomized controlled trial: reported on a case series of brain abscess (102 cases).
Seneviratne Rde 2003	Not a randomized controlled trial: reported on a case series of brain abscess (41 cases).
Yang 1981	Not a randomized controlled trial: reported on a case series of brain abscess (400 cases).

ADDITIONAL TABLES

Table 01. MEDLINE search strategy

1 exp Heart Defects, Congenital/
2 Brain Abscess/
3 brain abscess$.tw.
4 cerebral abscess$.tw.

Table 01. MEDLINE search strategy (*Continued*)

5 cerebella$ abscess$.tw.
6 (tetralogy adj3 fallot$).tw.
7 (cyanotic adj3 heart).tw.
8 (congenital adj3 heart).tw.
9 (congenital adj3 cardiac).tw.
10 or/1-9
11 exp Antibiotics/
12 chloramphenicol$.tw.
13 penicillin$.tw.
14 cephalosporin$.tw.
15 metronidazole$.tw.
16 cephotaxime$.tw.
17 ceftriaxone$.tw.
18 ampicillin$.tw.
19 clindamycin$.tw.
20 ceftazidine$.tw.
21 Anti-Infective Agents/
22 anti-infective.tw.
23 antiinfective.tw.
24 antibiotic$.tw.
25 or/11-24
26 10 and 25
and RCT filter terms

Table 02. EMBASE search strategy

1 exp Congenital Heart Malformation/
2 Brain Abscess/
3 brain abscess$.tw.
4 cerebral abscess$.tw.
5 cerebella$ abscess$.tw.
6 (tetralogy adj3 fallot$).tw.
7 (cyanotic adj3 heart).tw.
8 (congenital adj3 heart).tw.
9 (congenital adj3 cardiac).tw.
10 or/1-9
11 exp Antibiotic Agent/
12 chloramphenicol$.tw.
13 penicillin$.tw.
14 cephalosporin$.tw.
15 metronidazole$.tw.
16 cephotaxime$.tw.
17 ceftriaxone$.tw.
18 ampicillin$.tw.
19 clindamycin$.tw.
20 ceftazidine$.tw.
21 Antiinfective Agent/
22 anti-infective.tw.
23 antiinfective.tw.

Table 02. EMBASE search strategy (*Continued*)

24 antibiotic$.tw.
25 or/11-24
26 10 and 25
27 clinical trial/
28 random$.tw.
29 randomized controlled trial/
30 trial$.tw.
31 follow-up.tw.
32 double blind procedure/
33 placebo$.tw.
34 placebo/
35 factorial$.ti,ab.
36 (crossover$ or cross-over$).ti,ab.
37 (double$ adj blind$).ti,ab.
38 (singl$ adj blind$).ti,ab.
39 assign$.ti,ab.
40 allocat$.ti,ab.
41 volunteer$.ti,ab.
42 Crossover Procedure/
43 Single Blind Procedure/
44 or/27-43
45 exp animal/
46 nonhuman/
47 exp animal experiment/
48 or/45-47
49 exp human/
50 48 not 49
51 44 not 50
52 51 and 26

GRAPHS AND OTHER TABLES

This review has no analyses.

COVER SHEET

Title	Antibiotics for brain abscesses in people with cyanotic congenital heart disease
Authors	Lumbiganon P, Chaikitpinyo A
Contribution of author(s)	PL searched for studies, reviewed the abstracts to assess for inclusion and drafted the review. AC assessed the studies independently, co-wrote the review and helped to revise the review.
Issue protocol first published	2003/4
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What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	01 June 2006
Date authors' conclusions section amended	Information not supplied by author
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Long versus short course treatment with Metformin and Clomiphene Citrate for ovulation induction in women with PCOS (Review)

Sinawat S, Buppasiri P, Lumbiganon P, Pattanittum P

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Long versus short course treatment with Metformin and Clomiphene Citrate for ovulation induction in women with PCOS (Review)

Sinawat S, Buppasiri P, Lumbiganon P, Pattanittum P

Status: *New*

This record should be cited as:
Sinawat S, Buppasiri P, Lumbiganon P, Pattanittum P. Long versus short course treatment with Metformin and Clomiphene Citrate for ovulation induction in women with PCOS. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD006226. DOI: 10.1002/14651858.CD006226.pub2.

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Date of most recent substantive amendment: 28 September 2007

ABSTRACT

Background
Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among reproductive-aged women. Apart from infertility, women with PCOS often have other endocrine disorders, including insulin resistance,hyperinsulinaemia and hyperandrogenism. Metformin,combined with clomiphene citrate (CC), has been shown to be more effective in ovulation induction when compared with clomiphene citrate alone. The optimal duration for metformin pretreatment before initiation of clomiphene citrate, however, is unknown.

Objectives
To determine the effectiveness of short-course (less than four weeks) metformin plus CC versus long-course (four weeks or more) metformin plus CC with regard to ovulation and achievement of pregnancy in infertile PCOS women.

Search strategy
We searched the Cochrane Menstrual Disorders and Subfertility Group Trials Register (December 2006), the Cochrane Central Register of Controlled Trials (The Cochrane Library 2006, 2006 issue 4), MEDLINE (1950 to 7 January 2007), CINAHL (1982 to December 2006) and EMBASE (1980 to 7 January 2007).

Selection criteria
Randomised controlled trials comparing short-course (less than four weeks) metformin plus CC versus long-course (four weeks or more) metformin plus CC for ovulation or achievement of pregnancy in infertile PCOS women.

Data collection and analysis
No trials were found that met the selection criteria.

Main results
No randomised controlled trials were identified.

Authors' conclusions
There are insufficient data to determine whether short-chouse metformin pretreatment is as effective as the conventional long-course metformin pretreatment before initiation of clomiphene citrate for ovulation induction in infertile PCOS patients. A well-designed randomised controlled trial is needed to answer this important clinical question.

PLAIN LANGUAGE SUMMARY

Long versus short course treatment with Metformin + Clomiphene Citrate for ovulation induction in women with PCOS

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among reproductive-aged women. Apart from infertility, women with PCOS often have other endocrine disorders, including insulin resistance, hyperinsulinaemia and hyperandrogenism. Metformin combined with clomiphene citrate (CC), has been shown to be more effective in ovulation induction when compared with clomiphene citrate alone. The optimal duration for metformin pretreatment before initiation of clomiphene citrate, however, is unknown. There have been no trials conducted to determine the effectiveness of short-course (less than four weeks) metformin plus clomiphene citrate as compared to the conventional long-course (four weeks or more) metformin plus clomiphene citrate with regard to ovulation and achievement of pregnancy in infertile women with polycystic ovary syndrome.

BACKGROUND

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among reproductive-aged women and affects approximately 5 to 10% of this population group (Hull 1987; Polson 1988). It is also the most common cause of anovulatory infertility.

Clomiphene citrate (CC) is currently the first-line, most widely used, oral medication to induce ovulation in women with PCOS (Kim 2000). However, only 70 to 85% of women with PCOS respond to clomiphene citrate, with a pregnancy rate of only 30 to 40% (Lobo 1982; Franks 1995). This could be attributed to the anti-estrogenic effect of clomiphene citrate on cervical mucous and endometrium (Randall 1991; Nakamura 1997).

PCOS is also associated with metabolic abnormalities, in part mediated through peripheral insulin resistance and subsequent hyperinsulinaemia. Metabolic abnormalities are more common in obese compared with lean PCOS women. Different techniques of measuring insulin resistance provide varying estimates of insulin resistance in PCOS. Up to 50-100% of obese and 22% of lean PCOS women may have insulin resistance (Dale 1992). Hyperinsulinaemia to lead to hyperandrogenism, which may adversely affect follicular development and ovulation (Barbieri 1986; Nestler 1998a). Metformin is a medication that has an insulin-sensitizing effect and is widely used in non-insulin dependent diabetes mellitus. Metformin could also ameliorate hyperandrogenism in PCOS women (Nestler 1998b; Pirwany 1999) and thus possibly correct the endocrinopathy. Several studies have demonstrated that treatment with metformin before administration of clomiphene citrate in women with PCOS may significantly increase ovulation and pregnancy rates (Velazquez 1994; Vandermolen 2001). The most recent research synthesis revealed that metformin was 50% better than placebo for increasing ovulation in infertile PCOS patients and that metformin plus clomiphene citrate may be three to four-fold superior to clomiphene citrate alone for producing ovulation and achievement of pregnancy (Kashyap 2004). The same study, however, showed that metformin-alone had no confirmed benefit over placebo for achievement of pregnancy.

Although it has become clear that the combination of metformin and clomiphene citrate is more effective in achieving pregnancy than clomiphene citrate (CC) alone (Kashyap 2004; Lord 2004), the optimal duration of metformin pretreatment before CC administration in women with PCOS is unknown. Previous studies usually used 4 to 12 weeks of metformin before beginning clomiphene citrate (Velazquez 1994; Vandermolen 2001), but many women found such duration of metformin pretreatment inconvenient. Long-term use of metformin may also be associated with several adverse effects such as lactic acidosis and gastrointestinal disturbances (Lord 2004). One study recently revealed that ultra-short (12 days) metformin pretreatment before administration of CC had significantly increased ovulation and pregnancy rates as compared to CC alone (Hwu 2005). It is of interest, therefore, to determine whether short-course (less than four weeks) metformin treatment in conjunction with CC is as effective as the conventional long-course (at least four weeks) metformin plus CC with regard to ovulation and achievement of pregnancy in infertile women diagnosed with polycystic ovary syndrome.

OBJECTIVES

To determine the effectiveness of short-course (less than four weeks) metformin plus CC versus long-course (four weeks or more) metformin plus CC with regard to ovulation and achievement of pregnancy in infertile women with PCOS.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomised controlled trials comparing short-course (less than four weeks) metformin plus CC versus long-course (four weeks or more) metformin plus CC to achieve ovulation or pregnancy in infertile women with PCOS.

Quasi-randomised controlled trials or crossover trials were not included in this review unless there were pre-crossover phase data.

Types of participants

Women of reproductive age (between 15 and 45 years) with anovulatory infertility attributed to PCOS.

Anovulation was defined as a lack of evidence of serum progesterone within the luteal range for the reference laboratory, menstrual cycles that were less frequent than every 35 days or fewer than six periods per year.

Infertility was defined as the inability to get pregnant after one year of unprotected sexual intercourse.

PCOS was defined according to the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) criteria (ESHRE/ASRM 2003). Two of the following three manifestations were required for diagnosis of PCOS: (1) oligo or anovulation (menstrual cycles less frequent than every 35 days or fewer than six periods per year); (2) clinical or biochemical signs of hyperandrogenism, or both (clinical hirsutism or acne; or biochemical elevated testosterone, dehydroepiandrosterone, or androstenedione levels); and, (3) polycystic ovary (ultrasound scanning showed enlarged ovary with peripheral cystic structures surrounded by an increased stromal mass)

Exclusion criteria

(1) Women with hyperprolactinaemia (greater than three times the upper limit of normal of the reporting laboratory's reference range), congenital adrenal hyperplasia (CAH) and Cushing's syndrome were excluded, since these conditions precluded the diagnosis of PCOS.
(2) Women diagnosed with hypogonadotropic hypogonadism (WHO group one anovulation) and ovarian failure (WHO group three anovulation) were also excluded from this review.

Types of intervention

The comparison between short-course (less than four weeks) metformin plus CC versus long-course (four weeks or more) metformin plus CC was looked for.

Types of outcome measures

Primary outcome
1. Livebirth rate.

Secondary outcomes
1. Clinical pregnancy rate. Clinical pregnancy rate was defined as ultrasound evidence of gestational sac.
2. Ovulation rate (per woman). Ovulation was defined as mid-luteal phase serum progesterone level greater than 3 ng/mL or in the luteal range for the reference laboratory or evidence of ovulation documented by ultrasound evaluation.
3. Multiple pregnancy rate.
4. Miscarriage rate (per pregnancy). Miscarriage was defined as the involuntary loss of pregnancy before 20 weeks of gestation.
5. Incidence of adverse effects (per woman). Adverse effects included gastro-intestinal disturbance, lactic acidosis, discontinuation of therapy, and other adverse effects described by the authors.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Menstrual Disorders and Subfertility Group methods used in reviews.

See: Cochrane Menstrual Disorders and Subfertility Group methods used in reviews.

This review followed the Cochrane Menstrual Disorders and Subfertility Group search strategy. The literature search aimed to locate randomised controlled trials reported in all languages.

(1) We searched the Cochrane Menstrual Disorders & Subfertility Group trials register (December 2006).

(2) We searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2006, issue 4) for keywords: Polycystic Ovary Syndrome (PCOS), metformin.

(3) We searched the following electronic databases for studies in all languages using following terms:

MEDLINE (1950 to 7 January 2007)
1) randomised controlled trial.pt
2) controlled clinical trial. pt
3) randomised controlled trial.pt
4) random allocation
5) double-blind method/
6) single-blind method/
7) or/1-6
8) clinical trial.pt
9) exp clinical trials/
10) (clin$ adj25 trial$).tw
11) ((singl$ or doubl$ or treb$ or tripl$) adj25 (blind$ or mask$)).tw
12) metformin/
13) metformin$.tw
14) random$.tw
15) research design/
16) or/8-15
17) animal/ not (human/ and animal/)
18) 7 or 16
19) 18 not 17
20) polycystic adj5 ovar$.tw
21) PCOS.tw
22) PCO.tw
23) Polycystic Ovary Syndrome/
24) or/20-23
25) anovul$.tw
26) infertil$.tw

27) subfertil$.tw
28) INFERTILITY/
29) or 25-28
30) 24 and 19
31) 7 or 19
31) 30 and 31

CINAHL (1982 to December 2006) database searched using comparable search terms to those used in MEDLINE.

EMBASE (1980 to 7 January 2007)
1) randomised controlled trial/
2) random allocation/
3) double-blind method/
4) single-blind method/
5) or/1-4
6) exp clinical trials/
7) (clin$ adj25 trial$).tw
8) ((singl$ or doubl$ or treb$ or trip$) adj25 (blind$ or mask$)).tw
9) metformin/
10) metformin$.tw
11) random$.tw
12) research design/
13) or/6-12
14) animal/ not(human/ and animal/)
15) 5 or 13
16) 15 not 14
17) polycystic adj5 ovar$.tw
18) PCOS.tw
19) PCO.tw
20) Polycystic Ovary Syndrome
21) or/17-20
22) anovu$.tw
23) infertil$.tw
24) subfertil$.tw
25) INFERTILITY
26) or/22-25
27) 21 and 26
28) 5 or 16
29) 27 and 28

(4) Reference lists of included studies, other relevant review articles and textbooks were checked.

(5) Pharmaceutical companies were contacted to locate any registered prospective clinical trials. Experts and specialists in the field were also contacted.

METHODS OF THE REVIEW

Selection of studies

Four review authors were involved. The search strategy described previously was employed to obtain titles, and where possible, abstracts of studies that were potentially relevant to the review. SS screened the titles and abstracts and discarded studies that were clearly ineligible but the aim was to be overly inclusive rather than risk losing relevant studies.

SS obtained copies of the full text articles and, after removing all information that could identify the authors, the publishers or the results of the study, the methods section were sent to the first review author (SS) and the second review author (BP). Both reviewers independently assessed whether the studies met the pre-stated inclusion criteria, with disagreement resolved by discussion and final arbitration by the third review author (LP). Further information was sought from the authors if papers contained insufficient information to make a decision about eligibility. The fourth review author (PP) was responsible for planning of analysis, data analysis, data interpretation and data presentation

Quality assessment

We had intended that two review authors would independently assess the quality of all studies that were eligible for the review with disagreement resolved by discussion or, if necessary, by the third review author. The quality of allocation concealment would be graded as adequate (A), unclear (B), or inadequate (C), following the detailed description of these categories provided by the Cochrane Menstrual Disorders and Subfertility Review Group as followed:

1. Assessment of methodological Quality

Rate each item as follows:
Clearly yes - rate A
Not sure - rate B (seek details from authors)
Clearly no - rate C

Section i: Internal Validity
1) Was the assigned treatment adequately concealed prior to allocation?
2) Were the outcomes of patients who withdrew or were excluded after allocation described and included in an "intention to treat" analysis?
3) Were the outcomes assessors blind to assignment status?
4) Were the treatment and control groups comparable at entry?
5) Were the subjects blind to assignment status following allocation?
6) Were the treatment providers blind to assignment status?
7) Were the care programs, other than the trial options, identical?
8) Were the withdrawals < 10% of study population?

Section ii: External Validity
9) Were the inclusion and exclusion criteria for entry clearly defined?
10) Were the outcome measures used clearly defined?
11) Were the accuracy, precision, and observer variation of the outcome measures adequate?
12) Was the timing of the outcome measures appropriate?

2. Allocation Score

Was the assigned treatment adequately concealed prior to allocation?

Clearly yes: Score A

- Some form of centralized randomization scheme, such as having to provide participant details by phone to receive treatment group allocation
- A scheme controlled by a pharmacy
- In a pharmaceutical study, sequential administration of pre-numbered or coded containers to enrolled participants
- An on-site computer system, given that allocations are in a locked unreadable file which can be accessed only after inputting participant details
- Assignment envelopes, provided that they are sequentially, sealed, and opaque
- Other combinations which appear to provide assurance of adequate concealment

Unclear: Score B

- Assignment envelopes, without description of adequate safeguards
- Use of a "list" or "table"
- Flip of coin
- A trial in which the description suggests adequate concealment, but other features are suspicious- for example, markedly unequal controls and trial groups
- Stated random, but unable to obtain further details

Clearly no: Score C

- Alteration
- Case record numbers, dates of birth, day of week, or any other such approach
- Any allocation procedure transparent before assignment, such as an open list random numbers

It was intended that this allocation score grading be used in investigation of any heterogeneity and in sensitivity analysis. Other aspects of study quality including the extent of blinding (if appropriate), whether groups were comparable at baseline, the extent of loses to follow-up, non-compliance, whether the outcome assessment was standardized and whether an "intention to treat" analysis was undertaken would provide a context for discussing the reliability of the results.

Data extraction

The following information was planned to be extracted from the studies included in the review

General information

(a) Title
(b) Publication status
(c) Authors
(d) Contact address
(e) Country
(f) Resource
(g) Publication year
(h) Publication language
(i) Duplication of publishing

Trial Characteristics

(a) Randomization
(b) Allocation concealment
(c) Trial design: multi-cent er or single cent er; single phase or crossover design
(d) Blinding
(e) Number of patients randomised, excluded and analysed
(f) Source of funding

Baseline characteristics of the studied groups

(a) Definition and duration of pre-existing infertility
(b) Age of the patients
(c) Body mass index (BMI) of the patients
(d) Investigative work-up
(e) Other causes of infertility
(f) Previous administered treatment(s)

Intervention

(a) Type of intervention
(b) Duration of treatment with metformin
(c) Dose regimen

Outcomes

(a) Outcomes reported
(b) How are outcomes defined?
(c) How are outcomes measured?
(d) Timing of outcome measurement?

Two of the authors (SS and BP) were going to independently extract all data using data extraction forms designed according to Cochrane guidelines. The form designed was pilot testing with a sample of the studies to ensure that it was understandable, easy to complete and comprehensive. Additional information was sought on trial methodology or actual trial data or both from the authors of the trials which appeared to meet eligible criteria but had aspects of methodology that were unclear or data in an unsuitable form for meta-analysis. Differences of opinion between the two review authors would be resolved by the third reviewer (LP). We had intended providing reasons for excluding any trial.

Statistical analysis

We planned entering data into Review Manager (RevMan 2002), and checking for accuracy by performing double data entry. Data analysis and graphical displays would be facilitated using RevMan 4.2.8 software distributed by the Cochrane Collaboration.

We planned to express all dichotomous outcomes and results as odds ratios (OR) with 95% confidence intervals (CI). In order to perform meta-analysis using dichotomous data, we planned to extract the number in each of the two categories in each of the intervention groups (the numbers needed to be filled in the 2 x 2 table).

The data extracted from different trials would be assessed for heterogeneity by using several methods as follows:
1. Inspection of individual 95% confidence interval (CI) in the forest plots.
2. Using the Cochrane Q statistic. P-value of less than 0.10 would be used to indicate significant heterogeneity.
3. Calculating the I^2 statistic (Higgins 2003). Value of I^2 greater than 50% was planned to be used to indicate heterogeneity.

If studies were clinically and statistically homogeneous, meta-analysis would be conducted using fixed-effect model.

If significant heterogeneity was found, pre-specified sub-group analysis would be done in order to determine the factors that could be responsible for such heterogeneity. If the studies demonstrating heterogeneous results were found to be comparable, we would undertake statistical synthesis of the results using the random-effects model.

Publication bias would be investigated by evaluating the Funnel plots.

We planned to perform sub-group analysis according to the body mass index (BMI) of study participants. The pre-specified sub-groups in this review included studies with participants' mean baseline BMI > 30 kg/m2 and those with participants' mean baseline BMI < 30 kg/m2.

We also intended performing sensitivity analysis in order to test the robustness of the review's conclusions by taking into account key decisions and assumptions that were made in the process of conducting the review. These approaches included the following.
1. Repeating the analysis excluding the trials most susceptible to bias based on the quality assessment (such as the trials with inadequate allocation concealment, high levels of post-randomization losses or exclusions).
2. Repeating the analysis, excluding the trials by using the following filters: publication language and country.

Timeline

Future update of this review is expected to be done within two years after it is published in *The Cochrane Library*.

DESCRIPTION OF STUDIES

The search identified no randomised controlled trials, no observational studies and no case series.

METHODOLOGICAL QUALITY

Not applicable

RESULTS

No randomised controlled trials were identified.

DISCUSSION

We did not identify any randomised controlled trials that compared the effectiveness of short-course (less than four weeks) metformin plus clomiphene citrate versus long-course (four weeks or more) metformin plus clomiphene citrate in infertile women with PCOS. We did not identify observational studies or case series assessing this comparison. Most studies used more than four weeks of metformin pretreatment before starting clomiphene citrate to induce ovulation in PCOS patients suffering from infertility. There were two studies (Hwu 2005; Khorram 2006) comparing short course metformin plus clomiphene citrate with clomiphene citrate alone. The study conducted by Khorram et al (Khorram 2006) used two weeks of metformin while the study reported by Hwu et al (Hwu 2005) gave 12 days of metformin pretreatment before beginning clomiphene citrate. Both studies revealed that short course metformin pretreatment resulted in improved response in relation to the control group (using clomiphene citrate alone) in terms of ovulation and pregnancy rates. Recent meta-analysis, however, revealed that addition of metformin to clomiphene citrate was effective in achieving live births while compared to clomiphene citrate alone only in women diagnosed with PCOS who were clomiphene-resistant (Moll 2007).

AUTHORS' CONCLUSIONS

Implications for practice

Combination of metformin to clomiphene citrate has been proved to be more effective in achieving live births than clomiphene citrate alone in infertile women diagnosed with PCOS who were clomiphene-resistant. The optimal duration of metformin use before starting clomiphene citrate, however, is unknown. Recent studies revealed that short course (less than four weeks) metformin in conjunction with clomiphene citrate is more effective than clomiphene citrate alone for ovulation induction in clomiphene-resistant infertile PCOS women. Prescribing short-course metformin before beginning clomiphene citrate should be beneficial to infertile PCOS women. There is, however, no data from randomised controlled trials or other types of studies to determine the effectiveness of short-course metformin as compared to the conventional long-course metformin pretreatment before initiation of clomiphene citrate.

Implications for research

Well-designed, randomised controlled trials are needed to evaluate the effectiveness of short-course metformin as compared to the

conventional long-course metformin pretreatment in conjunction with clomiphene citrate for achievement of ovulation and pregnancy in women diagnosed with PCOS who are clomiphene-resistant.

POTENTIAL CONFLICT OF INTEREST

None known.

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GRAPHS AND OTHER TABLES

This review has no analyses.

COVER SHEET

Title	Long versus short course treatment with Metformin and Clomiphene Citrate for ovulation induction in women with PCOS
Authors	Sinawat S, Buppasiri P, Lumbiganon P, Pattanittum P
Contribution of author(s)	Supat Sinawat: screened potentially relevant studies, obtained titles and abstracts of potentially relevant studies, assessed the eligibility of studies to be included in the review, and wrote the review. Pranom Buppasiri: assessed eligibility of studies to be included in the review, and approved the final version of the review. Pisake Lumbiganon: making final decision about eligibility of the studies to be included in the review and wrote the review. Porjai Pattanittum: commented and approved the final version of the review.
Issue protocol first published	/

Review first published	/
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Date of most recent SUBSTANTIVE amendment	28 September 2007
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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DOI	10.1002/14651858.CD006226.pub2
Cochrane Library number	CD006226
Editorial group	Cochrane Menstrual Disorders and Subfertility Group
Editorial group code	HM-MENSTR

Arthroscopic debridement for knee osteoarthritis (Review)

Laupattarakasem W, Laopaiboon M, Laupattarakasem P, Sumananont C

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2008, Issue 3

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Arthroscopic debridement for knee osteoarthritis (Review)

Laupattarakasem W, Laopaiboon M, Laupattarakasem P, Sumananont C

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ABSTRACT

Background
Knee osteoarthritis (OA) is a progressive disease that initially affects the articular cartilage. Observational studies have shown benefits for arthroscopic debridement (AD) on the osteoarthritic knee, but other recent studies have yielded conflicting results that suggest AD may not be effective.

Objectives
To identify the effectiveness of AD in knee OA on pain and function.

Search strategy
We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2006); MEDLINE (1966 to August, 2006); CINAHL (1982 to 2006); EMBASE (1988 to 2006) and Web of Science (1900 to 2006) and screened the bibliographies, reference lists and cited web sites of papers.

Selection criteria
We included randomised controlled trials (RCT) or controlled clinical trials (CCT) assessing effectiveness of AD compared to another surgical procedure, including sham or placebo surgery and other non-surgical interventions, in patients with a diagnosis of primary or secondary OA of the knees, who did not have other joint involvement or conditions requiring long term use of non-steroidal anti-inflammatory drugs (NSAIDs). The main outcomes were pain relief and improved function of the knee.

Data collection and analysis
Two review authors independently selected trials for inclusion, assessed trial quality and extracted the data. Results are presented using weighted mean difference (WMD) for continuous data and relative risk (RR) for dichotomous data, and the number needed to treat to benefit (NNTB) or harm (NNTH).

Main results
Three RCTs were included with a total of 271 patients. They had different comparison groups and a moderate risk of bias. One study compared AD with lavage and with sham surgery. Compared to lavage the study found no significant difference. Compared to sham surgery placebo, the study found worse outcomes for AD at two weeks (WMD for pain 8.7, 95% CI 1.7 to 15.8, and function 7.7, 95% CI 1.1 to 14.3; NNTH=5) and no significant difference at two years. The second trial, at higher risk of bias, compared AD and arthroscopic washout, and found that AD significantly reduced knee pain compared to washout at five years (RR 5.5, 95% CI 1.7 to 15.5; NNTB=3). The third trial, also at higher risk of bias, compared AD to closed-needle lavage, and found no significant difference.

Authors' conclusions
There is 'gold' level evidence that AD has no benefit for undiscriminated OA (mechanical or inflammatory causes).

PLAIN LANGUAGE SUMMARY

Arthroscopic debridement for osteoarthritis of the knee

This summary of a Cochrane review presents what we know from research about the effect of arthroscopic debridement (AD) for osteoarthritis (OA) of the knee.

The review shows that in people with OA, arthroscopic debridement:

- Probably does not improve pain or ability to function compared to placebo (sham surgery)
- Probably leads to little or no difference in pain or ability to function compared to lavage
- May improve pain compared to washout
- May not lead to any difference in pain or ability to function compared to closed needle joint lavage

We often do not have precise information about side effects and complications. This is particularly true for rare but serious side effects. Possible side effects may include a small risk of infection and of venous thromboembolism.

What is osteoarthritis and what is arthroscopic debridement?
Osteoarthritis (OA) is the most common form of arthritis that can affect the hands, hips, shoulders and knees. In OA, the cartilage that protects the ends of the bones breaks down and causes pain and swelling. OA can occur in different areas of the knee or the whole knee. When the cartilage breaks down, bits of tissue are left around the joint which can add to the inflammation and prevent the joint from working properly.

Arthroscopic debridement (AD) involves using instruments to remove damaged cartilage or bone. Often the doctor will start the procedure by using a tool to spray jets of fluid to wash and suck out all debris around the joint. This is called lavage or washout. Then, the parts of the joint bone that are loose or misshapen are removed.

Best estimate of what happens to people with OA who have arthroscopic debridement compared with washout:

Pain: 66 more people out of 100 reported being pain free after 1 year and 48 more people out of 100 reported being pain free after 2 years. These results are based on low quality evidence.

Best estimate of what happens to people with OA who have arthroscopic debridement compared with placebo:

Pain two weeks after treatment: Pain scores increased by 9 more points on a scale of 0-100.

Physical function two weeks after treatment: The ability to function improved 8 more points on a scale of 0-100 for the placebo group. These results are based on moderate quality evidence.

Physical function 12 months after treatment: The ability to function improved 7 more points on a 0-100 scale for the placebo group, indicating that the AD group experienced significantly more limited function. These results are based on low quality evidence.

The numbers given are our best estimate. When possible, we have also presented a range because there is a 95 percent chance that the true effect of the treatment lies somewhere between that range.

BACKGROUND

Knee osteoarthritis (OA) is a progressive disease that originally affects the articular cartilage. Certain mechanical and biological events may destabilise the normal degradation and repair processes of chondrocytes and extracellular matrix, causing deterioration of the articular cartilage (Dabov 2003). The cartilage breaks down resulting in fibrillation, fissures, ulceration and then full thickness loss of the joint surface. Ultimately, the subchondral bone and almost the entire joint become damaged with disabling deformities.

Knee OA has a worldwide distribution, though there is variation in the prevalence among different ethnic or cultural groups and genders (Zhang 2003). The elderly population has a higher risk of developing this condition. OA can be classified according to its aetiological factors as primary and secondary (Altman 2004). Although the end stage of both types may be the same, the progression of primary OA is usually slower and less relentless (Dabov 2003).

Patients with knee OA may seek medical treatment at different stages of the disease. Common complaints are pain exacerbated by knee motion or weight bearing, stiffness, swelling and deformity (genu varum, genu valgum or flexion contracture), and decreased walking distance. The objectives of management are to relieve pain, maintain or improve mobility, and minimise disability. Ini-

tial management of most patients is usually nonoperative (Pendleton 2000). This may combine analgesics with physical therapy, bracing, orthoses, ambulatory aids, nonsteroidal anti-inflammatory drugs (NSAIDs) and other novel medications (Lequesne 1994; Pelletier 2001), intra-articular injections of corticosteroids or chondroprotective agents. Changes in daily work and recreational activities may also be necessary. Obesity is a known risk factor for knee OA and weight loss has been shown to slow the progression of the disease (Messier 2004).

Because of the progressive nature of the condition, many patients with knee OA are eventually offered operative treatment. A variety of procedures have been described, ranging from arthroscopic lavage or debridement to corrective osteotomy or total knee arthroplasty. The choice of procedure depends on the severity of the disease and the patient's individual condition. For more localised articular lesion, current practices include microfracture, osteo-articular transplantation (Makino 2001; Nakaji 2006) and autologous chondrocyte implantation (Bentley 2003; Kish 2004; Knutsen 2004). Debridement for knee OA using an arthroscopic technique produces less postoperative pain and shorter rehabilitation time than the older open procedure (Dabov 2003). Arthroscopic debridement (AD) consists of tidal irrigation to wash out all debris. Unstable chondral flaps, redundant synovia, degenerated menisci and ligaments, loose bodies and osteophytes are shaved away or burred down by using mechanical instruments. AD can by no means stop the degenerative process inherent in the disease, and the full thickness chondral defect is not healed. AD is expected to remove chemical and mechanical components that contribute to the symptoms of OA (Smith 1997; Cameron 2004). Although pain and functions might be improved for a certain postoperative period, it is expected that the symptoms will return over time. Other techniques such as electrocautery, lasers or radiofrequency are also available for debridement.

Numerous retrospective and some prospective studies have suggested benefits of AD on the osteoarthritic knee at different stages of disease severity, although these studies are not as reliable as randomised controlled trials. This literature reports success rates of about 40% to 75% and favourable outcomes in reducing pain and improving function of the knee (Sprague 1981; Baumgaertner 1990; Timoney 1990; McLaren 1991; Hubbard 1996; Harwin 1999; McGinley 1999; Shannon 2001). These palliative effects were maintained for mostly two to five years (Baumgaertner 1990; Timoney 1990; McLaren 1991; Hubbard 1996; Shannon 2001), though possibly as long as 7 to 13 years (Harwin 1999; McGinley 1999). Most reports propose AD as a temporary treatment for knee OA, which is more effective in the early stages of the disease if malalignment of the joint has not developed. Moreover, patients with mechanical symptoms and symptoms of short duration tended to do well with this intervention.

However, results from recent studies suggest that AD may not be effective. Some studies have reported AD as having no clinically meaningful difference from placebo surgery (Moseley 1996; Moseley 2002). In comparison to arthroscopic lavage, some improvement in quadriceps isokinetic torque at 6 and 12 weeks was observed after joint lavage but not after AD (Gibson 1992). A systematic review was therefore needed to evaluate the effectiveness of this procedure.

OBJECTIVES

The main objective of this review was to estimate the effectiveness of AD on knee OA on pain reduction (reduced use of relevant medications) and/or functional improvement.

The secondary objectives were to observe:
1. The type or stage of severity of the OA in which AD is most effective.
2. The expected length of effectiveness until the patients need further intervention.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Any randomised controlled trials (RCT) or controlled clinical trials (CCT, trials using quasi- or pseudo-random process) which assess the effectiveness and persistence of the effects of the AD in osteoarthritic knees in reducing symptoms and/or reducing needs of non-steroidal anti-inflammatory drugs (NSAIDs) and/or analgesics and/or improving knee functions were considered.

Types of participants

Patients with diagnosis of primary or secondary OA of the knees, who did not have other joint involvement or conditions requiring long term use of NSAIDs, were included. Primary OA was any OA where a specific cause for the condition was not found. Secondary OA was where a definite cause could be found, such as trauma, joint instability, a metabolic disorder or other rheumatic disorder affecting the joint. The diagnosis should be established by pertinent history taking, physical examination and appropriate imaging.

Trials studying the following conditions were excluded from the review:
1. Other conditions in which prolonged use of NSAIDs was required.
2. Bed-ridden or wheel-chair-ridden conditions from any cause.
3. Combined surgery, such as combining AD with corrective osteotomy or AD with simultaneous operation on the other limb or the other joint(s) of the same limb.
4. Post-operative knee immobilisation (comparable with casting) for more than 2 weeks, which might compromise joint motion.

Types of intervention

The intervention for treated cases was arthroscopic, NOT open, debridement performed on the osteoarthritic knee. It was assumed that the procedure may also have included shaving, lavage, drilling, microfracture technique or abrasion arthroplasty, unless the study specifically stated that they were not used.

We recorded the method or modalities other than the common mechanical instruments (e.g., electrocautery, lasers, radiofrequency or coblation) used in the AD process if these were described in the studies.

The control could be any non-surgical intervention or comparative operation such as chondrocytes implantation, corrective osteotomy and replacement arthroplasty, including sham or placebo surgery.

Types of outcome measures

Primary outcomes included:
1. Reduction of knee pain.
2. Improvement of knee functions.

Knee pain and functions could be assessed and recorded as continuous data in scores. The scores could be measured directly (e.g. using visual analogue scales for pain), or using validated functional rating systems (e.g. Lysholm Knee Scores, International Knee Documentation Committee (IKDC) Scores, Hospital for Special Surgery (HSS) Scores or Western Ontario and McMaster Universities (WOMAC) OA Index). These outcomes could be affected by patients' use of NSAIDs and/or analgesics, which will also be measured.

Secondary outcomes included:
1. Time to next major intervention (e.g., TKA) indicating failure of the treatment or censoring due to end of the study or dropout.
2. Amount (doses, frequencies and types) of NSAIDs and/or analgesics used as rescue therapies in parallel with the treatment and control.
3. Post-operative morbidities or complications.
4. Other outcomes according to the authors' reports.

We recorded subsequent interventions. We counted use of topical drugs, injection of corticosteroids or any chondroprotective agents and taking of novel medications such as glucosamine sulfate and diacerein as co-interventions. When available, we also considered data on confounding factors (litigation, body weight, co-morbidity, etc) in the analysis.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Musculoskeletal Group methods used in reviews.

Studies were identified from the following electronic databases: The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2006); MEDLINE (1966 to August, 2006); CINAHL (1982 - 2006); EMBASE (1988 to 2006) and Web of Science (1900-2006). No language limitation was applied. In combination with search terms to identify randomised controlled trials, as defined by the Cochrane Collaboration and detailed in the Cochrane Reviewers' Handbook (Higgins 2005), we used the following search strategy to search MEDLINE:

1. exp osteoarthritis/
2. osteoarthrit$.tw.
3. osteoarthro$.tw.
4. oa.tw.
5. degenerative joint disease.tw.
6. degenerative arthritis.tw.
7. djd.tw.
8. gonarthro$.tw.
9. or/1-8
10. exp knee/
11. knee$.tw.
12. femorotibia$.tw.
13. or/10-12
14. exp Osteoarthritis, Knee/
15. 9 and 13
16. 14 or 15
17. debridement/ and Arthroscopy/
18. arthroscop$ debride$.tw.
19. 17 or 18
20. 16 and 19

The strategy was adapted for each database (see details in Additional Table 01). The bibliographies, reference lists and cited web sites of all papers identified by these strategies were searched. We also contacted the Cochrane Musculoskeletal Group for handsearching, but this could not be completed due to resource limitations.

METHODS OF THE REVIEW

Selection of trials

Two review authors (WL and ML) independently selected the trials, initially based on title, keywords and abstract of references identified by the search strategy. We assessed whether the study met the inclusion criteria regarding diagnosis, participants and intervention. We retrieved the full article of the selected trials, and trials that raised disagreement or doubt during the selection, for final assessment. Disagreements on inclusion were resolved by discussion and decided by consensus.

Quality assessment

We assessed the methodological quality of the selected trials using the criteria described in the Cochrane Handbook (Higgins 2005). Methods used for generation of the randomisation sequence were described for each trial.

(1) Selection bias (randomisation 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 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;
(D) concealment of allocation not used.

(2) Performance bias (blinding of participants, researchers and outcome assessment)
We assessed performance bias for each trial, using the following criteria:
(2.1) blinding of participants
yes: such as patients did not know which procedure they received
no: such as patients knew which procedure they received
unclear: no information
(2.2) blinding of outcome assessment
yes: such as investigators measured pain among the patients without awareness of the interventions they received;
no: such as pain was measured from the patients among the treatment groups
unclear: investigators measured pain among the patients similarly

(3) Attrition bias (loss of participants, for example, 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.

(4) Sample size calculation
(A) adequate explanation of sample size calculation: such as all information related to sample size calculation were available
(B) unclear whether the sample size was calculated or no available information
(C) inadequate explanation of sample size calculation: such as some information related to sample size calculation were 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.

The evidence of review was graded according to the Cochrane Musculoskeletal Group Method Guidelines (Maxwell 2006) as the following:

Platinum level
The Platinum ranking is given to evidence that comprises a published systematic review that has at least two individual controlled trials each satisfying the following:

- Sample sizes of at least 50 per group. If they do not find a statistically significant difference, they are adequately powered for a 20% relative difference in the relevant outcome.
- Blinding of patients and assessors for outcomes.
- Handling of withdrawals >80% follow up (imputations based on methods such as Last Observation Carried Forward (LOCF) acceptable).
- Concealment of treatment allocation.

Gold level
The Gold ranking is given to evidence if at least one randomised clinical trial meets all of the following criteria for the major outcome(s) as reported:

- Sample sizes of at least 50 per group. If they do not find a statistically significant difference, they are adequately powered for a 20% relative difference in the relevant outcome.
- Blinding of patients and assessors for outcomes.
- Handling of withdrawals > 80% follow up (imputations based on methods such as Last Observation Carried Forward (LOCF) acceptable).
- Concealment of treatment allocation.

Silver level
The Silver ranking is given to evidence if randomised trial does not meet the above criteria. Silver ranking would also include evidence from at least one study of non-randomised cohorts who did and did not receive the therapy or evidence from at least one high quality case-control study. A randomised trial with a 'head-to-head' comparison of agents is considered Silver level ranking unless a reference is provided to a comparison of one of the agents to placebo showing at least a 20% relative difference.

Bronze level
The bronze ranking is given to evidence if there is at least one high quality case series without controls (including simple before/after studies in which the patient acts as their own control) or if it is derived from expert opinion based on clinical experience without reference to any of the foregoing (for example, argument from physiology, bench research or first principles).

Data extraction
We modified data collection forms developed by the Cochrane Musculoskeletal Group for data inclusion or exclusion. Two review

authors (WL and ML) independently extracted the data. Extracted items included:

1. General information: publication, title, authors, contact address, country, resource, publication year, duplication of the publishing, sponsor.
2. Characteristics of the study: design, sample size calculation, research setting, inclusion/exclusion criteria, randomisation method, concealment, allocation procedure, blinding (patients, caregivers and outcome appraisers).
3. Intervention: treatment (AD) versus comparisons (placebo or sham operation or other types of therapy, e.g., NSAIDs, analgesics, non-pharmacological treatments and other surgeries).
4. Patients: characteristics (sex, age, ethnic group, side, location of lesions in the knee, diagnostic criteria, staging criteria of the OA, duration of disease, co-morbidities), total number or number in each study group.
5. Outcomes: Level of pain and functions measured at multiple points as continuous data. Length of the study and other outcomes reported in papers were also extracted.
6. Results: We paid particular attention to 'intention-to-treat' and dropout rate.

Analysis

Dichotomous outcomes were expressed as the relative risk (RR). Continuous outcomes were expressed as the weighted mean difference (WMD). We planned to meta-analyse the data using the statistical package in Review Manager software (Review Manager 2005). However, since the included trials measured different comparison groups, this was not appropriate. We will conduct a meta-analysis if more trials are found when updating our review in the future.

Clinical relevance tables

We compiled clinical relevance tables for primary outcomes under Additional Tables to improve the readability of the review. For dichotomous outcomes, we calculated the weighted absolute risk difference using the risk difference (RD) statistic in RevMan. RR-1 calculates the weighted relative percent change. We calculated the number needed to treat (NNT) to benefit (NNTB) or harm (NNTH) from the control group event rate (unless the population event rate was known) and the relative risk using the Visual Rx NNT calculator (Cates 2004). This was done for the primary outcomes measured.

For continuous outcome tables, *see* Additional Tables. We calculated weighted absolute change from the weighted mean difference (WMD) statistic in RevMan when trials using the same scale were pooled. For outcomes pooled on different scales, we multiplied the standardised mean difference (SMD) by the baseline standard deviation in the control group to obtain the weighted absolute change. We calculated relative percent change from baseline as the absolute benefit divided by the baseline mean of the control group. We calculated NNT using the Wells calculator available at the Cochrane Musculoskeletal Group editorial office. We determined the minimal clinically important difference (MCID) for each outcome for input into the calculator.

DESCRIPTION OF STUDIES

We initially identified 18 studies from multiple database searches. All were in English. After screening their titles and most available abstracts, we retrieved the full text of four studies (Chang 1993; Hubbard 1996; Moseley 2002; Forster 2003) for considering their potential eligibility. We finally excluded 15 studies for various reasons. Three of them were trials, twelve were not. Three studies were commentaries and one was a pilot study. Reasons for excluding individual studies are shown in the Table of Characteristics of Excluded Studies.

We included three trials (Chang 1993; Hubbard 1996; Moseley 2002). Details of each trial are shown in the Table of Characteristics of Included Studies.

Chang 1993 randomised 32 of 34 eligible patients stratified by each of the two study sites to receive either arthroscopic surgery (18) or closed-needle joint lavage (14). Two eligible patients were withdrawn before giving interventions due to concurrent medical problems. A single assessor for each site was blinded to the patient's treatment allocation when measuring all outcomes at 3 and 12 months follow-up. Pain and functional status were measured by the Arthritis Impact Measurement Scales (AIMS), from zero (best) to ten (worst), according to the patient's responses to the self-administered questionnaire. Baseline characteristics were similar in the two groups, except the mean initial AIMS Physical Activity score, which the authors attributed to random variation.

Hubbard 1996 randomised 76 knees of eligible patients to receive either AD (40 knees) or washout (36 knees). Pain was measured as 'success' for its absence and 'failure' for its presence. Physical function was measured as a modified Lysholm score with a maximum of 70 points. Outcome assessors were neither independent nor blinded. The outcomes were measured at three months, 12 months and every year until five years after the intervention, but were only reported at one and five years. Baseline characteristics of the two groups were not reported.

In Moseley 2002, there were three treatment groups: AD, lavage and placebo surgery. Three hundred and twenty-four patients were eligible. Among them, 180 (56%) agreed to participate to the trial. Participants were younger than those who refused to participate (mean age 52.3 ± SD 11.3 years for participants versus 55.3 ± SD 12.4 years for those who refused), were more likely to be caucasian (62.2% versus 50.7%), and had more severe arthritis (25.0% versus 12.5 % with grade seven or eight arthritis). The 180 participants were randomly assigned to receive AD (59), arthroscopic lavage (61), or placebo surgery (60). Patients and assessors were blinded to the treatment group assignment. Pain and physical function were measured at two weeks, six weeks, three

months, six months, 12 months, 18 months and 24 months after the intervention. Pain was the primary outcome, assessed by a 12-item, self-reported Knee-Specific Pain Scale (KSPS, 0 to 100 scale, higher scores indicating more severe pain). Physical function was measured by two self-reported scales: the five-item walking-bending subscale from the AIMS2 tool (0 to 100 scale, higher scores indicating more limited function) and the ten-item physical-function subscale from the SF-36 tool (0 to 100 scale, higher scores indicating better function). Baseline characteristics were similar in the three study groups.

METHODOLOGICAL QUALITY

Allocation was adequately concealed in Hubbard 1996 and Moseley 2002. In Hubbard 1996, the sequence of numbers was computer-generated and kept in sealed envelopes. In Moseley 2002, a stratified randomisation process with fixed blocks of six was used. Sealed, sequentially numbered, stratum-specific envelopes containing treatment assignments were prepared and given to the research assistant. The allocation concealment was unclear in Chang 1993.

Participants were blinded to treatment allocation in two trials (Hubbard 1996; Moseley 2002), but not in Chang 1993. Outcome assessors were blinded to treatment allocation in Chang 1993 and Moseley 2002, but not blinded in Hubbard 1996.

In Chang 1993, 22% of participants withdrew from the arthroscopy group and 7% from the control group at 12 month follow-up. Sensitivity analysis was conducted for the missing data and no effect on the summary measures were found. In Hubbard 1996, 20% of patients were lost to follow-up in the debridement group and 28% in the wash-out group. Around 10% of patients in each group were lost to follow-up in Moseley 2002.

Sample size calculation was clearly explained only in Moseley 2002. However, this trial was originally designed to test for superiority of the arthroscopic procedures over the sham surgery, but the authors then changed their analysis to test for equivalence, after evidence of the superiority was not found. They also set the minimal important difference based on the trial data and available literature. These decisions may have led to bias in the interpretation of results.

Overall, Moseley 2002 was assessed to be at moderate risk of bias while the other two trials (Chang 1993; Hubbard 1996) were at high risk of bias.

RESULTS

Results of the three trials are individually described due to differences of the comparison groups and heterogeneity of the clinical and methodological aspects, which precluded meta-analysis of results.

Two trials (Chang 1993; Moseley 2002) compared AD to lavage. Their results were presented separately because the scales of pain scores and physical function were different.

AD versus closed-needle joint lavage

Chang 1993 found that after controlling for baseline differences, the adjusted mean AIMS pain scores were 5.0 in the AD group and 5.4 in the lavage group with no statistically significant difference (WMD -0.4, 95% CI -1.6 to 0.8) at three months of follow-up (see 'Analyses: Comparison 01, Outcome 01' and 'Additional Table 02'). The adjusted mean AIMS pain scores at 12 months of follow-up were 5.3 in the AD group and 5.0 in the lavage group with no statistically significant difference (WMD 0.3, 95% CI -1.1 to 1.8)(*see* 'Analyses: Comparison 01, Outcome 01' and 'Additional Table 02').

AD versus lavage

Moseley 2002 presented results from a total of 163 patients who completed the trial at 24 months. The pain scores showed quite a big decrease from the baseline of around 10 points in AD and lavage at two weeks after the intervention. The WMD for pain scores was 2.5 (95% CI -4.4 to 9.4) (*see* 'Analyses: Comparison 02, Outcome 01' and 'Additional Table 03'). After that the pain scores fluctuated less than 5 points at each measurement and the WMD was not statistically significant at any of the measurement points (up to 24 months after the intervention) (*see* 'Analyses: Comparison 02, Outcome 01' and 'Additional Table 03'). A similar pattern but smaller changes were seen in physical function. The WMD difference at 24 months was -0.6 (95% CI -8.3 to 7.1), with higher scores indicating more limited function (*see* 'Analyses: Comparison 02, Outcome 02' and 'Additional Table 03'). The authors reported that 79.7% of participants in the AD group and 88.5 % of patients in the lavage group used analgesics (prescribed and non-prescribed).

AD versus washout

Hubbard 1996 found a significant difference in pain relief with a relative risk of 5.76 (95% CI 2.52 to 13.18) between debridement and washout at one year follow-up (*see* 'Analyses: Comparison 03, Outcome 01'). A significant difference in pain relief of 5.15 (95% CI 1.71 to 15.49) between debridement and washout at five years follow-up was also found (*see* 'Analyses: Comparison 03, Outcome 01'), and the number needed to treat to benefit was 2 at one year and 3 at five year follow-up (*see* 'Additional Table 04'). Physical function measured as mean modified Lysholm scores were presented without standard deviations for each subgroup for pain relief (success or failure). The scores were similar for each comparable pain relief subgroup. The higher mean scores were seen in the success groups with 61 for debridement versus 63 for washout at one year follow-up, and 58 for debridement versus 59 for washout at five years follow-up. Lower mean scores were seen in

the failure groups, with 33 for debridement versus 35 for washout at one year and five year follow-up (data not shown).

AD versus placebo

Moseley 2002 found a large decrease of 19 points from the baseline in the placebo group at two weeks after the intervention. The WMD for pain was 8.7 (95% CI 1.7 to 15.8), indicating a statistically significant result in favour of the placebo group (that is, the AD group experienced more pain) (*see* 'Analyses: Comparison 04, Outcome 01'), and the number needed to treat to harm was 5 (*see* 'Additional Table 05). After that the pain scores fluctuated, and the WMD at each measurement point was not statistically significant at any of the other measurement points (up to 24 months after the intervention) (*see* Analyses: Comparison 04, Outcome 01'). A similar pattern of changing scores was seen for physical function. The WMD for function at two weeks was 7.7 (95% CI 1.1 to 14.3), indicating that the AD group experienced significantly more limited function (*see* 'Analyses: Comparison 04, Outcome 02'), and the number needed to treat to harm was 6 (*see* 'Additional Table 05'). A second statistically significant result was found at 12 months follow-up, finding a WMD of 6.9 (95% CI 0.4 to 13.4) (*see* 'Analyses: Comparison 04, Outcome 01'), and the number needed to treat to harm was 9 (*see* 'Additional Table 05'). The authors reported that 79.7% of participants in the AD group and 91.7% in the placebo group used analgesics.

The other outcomes of interest for this review were not measured by the included studies, including time to next major intervention; post-operative morbidities or complications; subsequent interventions; use of topical drugs; injection of corticosteroids or any chondroprotective agents; taking of novel medications such as glucosamine sulfate and diacerein; and data on confounding factors (litigation, body weight, co-morbidity, etc.).

DISCUSSION

Our systematic review includes three studies with different comparison groups. There is only one RCT of moderate quality (Moseley 2002) that shows the effect of AD in comparison to placebo. In this study, AD did not differ significantly from lavage or placebo surgery for pain and physical functions at two years, although results indicated that AD may in fact be worse over the short term. Of the two low quality trials, Chang 1993 found no significant difference between AD and closed-needle joint lavage, but Hubbard 1996 found that AD was significantly superior to arthroscopic washout. Hubbard 1996 included participants with degenerative lesions of grade three or four on the Outerbridge classification (Outerbridge 1961) and confined at the medial femoral condyle. This study gives some information on our secondary objective regarding the type or stage of severity of the OA in which AD is most effective. However, there is no study giving a solution to the expected length of effectiveness until the patients need further intervention.

It is interesting that there is only one RCT showing the effect of AD on knee OA in comparison with placebo. The limitation of such trials could be due to difficulty in conducting research on placebo effects for surgical intervention. This requires comparison with a sham operation, which is subject to comprehensive criticism about medical ethics. Although direct comparison with placebo is important, we feel that researchers investigating a similar research question should compare alternative treatment options to increase the number of options for people with knee OA who have not responded to conservative treatments.

The finding reported by Moseley et al (Moseley 2002) is striking because it is contrary to most of the previous literature, which indicated AD as the treatment of choice after failure of conservative therapies in controlling osteoarthritic symptoms of the knee, especially when there are intra-articular mechanical derangements (Sprague 1981; Baumgaertner 1990; McLaren 1991; Harwin 1999; McGinley 1999; Shannon 2001). However, these conclusions are mainly based on case series or observational studies, which do not provide strong evidence.

We agree with the other commentaries (Bernstein 2003; Gillespie 2003) that Moseley's trial (Moseley 2002) was well planned and the design was robust. The authors had properly described processes of the trial and the validity was strengthened by the concealed randomisation.

The authors reported that the study was based on 56% of eligible subjects who were younger, more likely to be white and had more severe arthritis than the 44% eligible subjects who refused to participate in the study. The findings are therefore limited in their generalisability to common clinical practice, such as for people with earlier stages of OA arising from a specific cause. In addition, those who did participate were more likely to trust and expect benefits from the arthroscopic interventions, which may have positively influenced the results for the placebo group. Future research should compare AD, placebo surgery and no intervention to evaluate this effect.

Although pain was one of the primary outcome measures for this review, it is a subjective outcome and tends to be modified by various confounding factors such as the use of rescue analgesics, NSAIDs and/or other concomitant therapies. The analgesic use reported in Moseley 2002 provided information on other agents that could be important confounders of the results. It would be important for future research in this area to measure these outcomes, as well as other objective end points such as length of time until subsequent interventions are required (e.g. osteotomy or replacement arthroplasty).

Although neither Moseley 2002 nor Chang 1993 identified a benefit for AD, debates continue about the procedure (Bernstein 2003;

Day 2005). The studies included in this review did not examine whether there are specific indications or levels of disease at which AD is more effective. For example, if the OA stage is too advanced (e.g., with significant deformities), then the patient might not be a good responder; while too early (e.g., with only minimal chondral lesions), the procedure may not be justifiable. Since the procedures affect only superficial structures, it is reasonable to believe that they might not be able to alleviate pain caused by the deeper subchondral bone.

The studies also did not compare the different techniques and components of AD. Chang 1993 compared AD with lavage, and found that the removal of soft tissue did not contribute to a better result over lavage alone, with the exception of a subgroup with particular meniscal tears. More evidence is required to identify the mechanical effects that are most important, and also to explain the positive effects found in the placebo participants in this review.

AUTHORS' CONCLUSIONS

Implications for practice

Based on the results of this review, we conclude that there is gold level evidence (Moseley 2002) that AD has no significant benefit for knee OA of undiscriminated cause. Debatable areas remain to be addressed, for example, there may be groups of patients or levels of severity of disease for which the intervention may be effective. Hubbard 1996 found that AD provides more successful results for localised lesion on the medial femoral condyle than arthroscopic washout, but the study was of lower methodological quality.

Implications for research

New, high quality research on larger numbers of participants should be conducted to investigate the effects of AD, in particular comparing groups of people with different levels of disease severity and other disease characteristics. Outcomes measured should include survival data on the time to subsequent interventions such as rescue NSAIDs or analgesics or other surgical interventions. Different techniques for AD should be compared. It would also be interesting to investigate the strength of placebo effects of sham surgery over no intervention or conservative treatments on pain and dysfunction of the knee.

POTENTIAL CONFLICT OF INTEREST

The review authors do not have any potential conflict of interest regarding internal or external financial support about this review or clinical practices.

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** Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Chang 1993
Methods	Method of allocation/randomisation: stratified randomisation by study site Setting: 2 sites, the Rheumatology-Orthopedic Knee Clinic of the Northwestern Medical Faculty Foundation and the Division of Rheumatology of the Lutheran General Medical Group, USA. Design: Randomised, controlled trial. Power of study: No information. Number of patients randomised: 32. Number of patients analysed: 32. Concealment of allocation: no information. Outcome assessor blinding: Clear; assessors of outcome were blinded to the treatment-group assignment. Dropout: No.

Characteristics of included studies (*Continued*)

	Source of funding: No information.
Participants	Patients > 20 years old and 1) persistent knee pain for longer than 3 months, 2) weight bearing knee radiographs showing grade 1,2 or 3 changes described by Kellgren and Lawrence and 3) willingness to attend followup visits at 3 and 12 months, and give written informed consent. For patients with bilateral disease, the more symptomatic knee was included. Exclusions: the patients with knee surgery within 6 months of study entry, total knee replacement, any concurrent illness having effect on knee functional assessments or precluding arthroscopic surgery.
Interventions	Arthroscopic surgery: 1) debridement of torn meniscus and removal of maniscal and cruciate ligament fragments, 2) removal of proliferative synovia, or 3) excision of loose articular cartilage fragments. During the procedure, the patients received continuous saline lavage. Closed-needle joint lavage: Giving non-narcotic analgesia and physical therapy identical to the arthroscopy group. Tidal knee lavage procedure using a total of 1 liter of saline injected into and aspirated from the knee in aliquots of 40-120 cc.
Outcomes	A single assessor at each site was blinded to the patient's treatment and assessed the outcomes at 3 and 12 months followup . Pain and functional status measured by the AIMS from 0 (best) to 10 (worst) according to the patient's responses to the self-administered questionnaire. A decrease of at least 1 point from the baseline was assessed for improvement. Clinical outcome of active and passive range of knee motion, knee joint swelling and tenderness. Global well being outcome measured as 10 cm visual analog scale. Economic outcome based on cost of all arthroscopic surgery.
Notes	
Allocation concealment	B – Unclear

Study	**Hubbard 1996**
Methods	Method of allocation/randomisation: Computer-generated random numbers. Setting: No information. Design: Randomised controlled trial. Power of study: No information. Number of knees randomised: 76. Number of patients analysed: 76. Concealment of allocation: Sealed, numbered, enveloped. Outcome assessor blinding: Patients and assessors of outcome were unblinded to the treatment group. Dropout: No. Source of funding: Research Committee of the Clwyd Area Health Authority.
Participants	Patients suffering unremitted symptoms in the knee for one year, no previous surgery to the knee, no laxity, no deformity, single medial femoral condyl degenerative lesion grade 3 or 4, no other intra-articular pathology, normal plain radiograph and modified Lysholm score < 38/70. Exclusions: knees with their radiographs showing a loss of joint space and all which had had a previous operation or steroid injection with any reason. Source of patients: No information. Location: No information.
Interventions	Debridement group: Resection of loose cartilage using a 4.5 mm, 90 degree angled punch through an anteromedial portal with the arthroscope in an anterolateral portal and was completed using straight and curved 3 mm punches with 3 litres of saline running through the knee afterward. Washout group: 3 litres of saline running through the knee in similar manner.
Outcomes	Pain was measured as 'success' for absence of pain and 'failure' for presence of pain. Physical function was measured as a modified Lysholm score with a maximum of 70 points. They were measured at three months, 12 months and every year until 5 years.

Notes	The authors reported without explanation that it had not been possible to use independent observers or blinded observation.
Allocation concealment	A – Adequate

Study	**Moseley 2002**
Methods	Method of allocation/randomisation: Stratified randomisation process with fixed blocks of six. Setting: 1 centre at the Houston Veterans Affairs Medical Center, USA. Design: Randomised blinded placebo controlled trial. Power of study: 90%. Number of patients randomised: 180. Number of patients analysed: 163. Concealment of allocation: Sealed, sequentially numbered, stratum-specific envelopes containing treatment assignments were prepared and given to the research assistant. Outcome assessor blinding: Clear; patients and assessors of outcome were blinded to the treatment-group assignment. Dropout: 17; 5 placebo, 6 lavage and 6 debridement, without detail of dropout reasons. Source of funding: Department of Veterans Affairs.
Participants	Patients 75 years old or younger, osteoarthritis of the knee as defined by the American College of Rheumatology, reported at least moderate knee pain on average (> 4 on a visual-analogue scale ranging from 0 to 10) despite maximal medical treatment for at least six months, and had not undergone arthroscopy of the knee during the previous two years. Exclusions: the patients with a severity grade of 9 or higher, severe deformity, and serious medical problems. Source of patients: Houston Veterans Affairs Medical Center Location: Texas, USA.
Interventions	Debridement: lavage with at least 10 litres of fluid, shaving of rough articular cartilage, removal of loose debris, and trimming of torn or degenerated meniscal fragments. No abrasion arthroplasty or microfracture performed. Lavage: the joint was lavaged with at least 10 litres of fluid. Anything that could be flushed out through arthroscopic cannulas was removed. Placebo surgery: received three 1 cm skin incisions under a short acting tranquiliser and an opioid and spontaneously breathed oxygen-enriched air. simulation of the operating atmospheres but no instrument was admitted into the knee joint.
Outcomes	Pain in the studied knees at 24 months (Knee-Specific Pain Scale, scores 0-100 [most severe]) Secondary outcomes: General arthritis pain (Arthritis Impact Measurement Scales [AIMS2]), body pain (pain subscale of the 36-item Short Form General Health Survey [SF-36]), and physical function (5-item walking bending subscale from the AIMS2 and the 10-item physical function score from the SF-36).
Notes	
Allocation concealment	A – Adequate

Characteristics of excluded studies

Study	**Reason for exclusion**
Dervin 2003	Cohort study
Felson 2002	Commentary
Forster 2003	Interventions were not associated with inclusion criteria
Gillespie 2003	Commentary

Characteristics of excluded studies (*Continued*)

Goldman 1997	Review
Grifka 1994	Interventions were not associated with inclusion criteria
Gunther 2001	Review
Hanssen 2001	Review
Knutsen 2004	Interventions were not associated with inclusion criteria
Lubowitz 1993	Descriptive study
Merchan 1993	Prospective studies
Mohtadi 2003	Commentary
Moseley 1996	Pilot study
Stein 2003	Diagnostic Images
Wai 2002	Descriptive study

ADDITIONAL TABLES

Table 01. Search strategy - additional detail

CINAHL	EMBASE	CENTRAL	Web of Science
1. exp osteoarthritis/ 2. osteoarthrit$.tw. 3. osteoarthro$.tw. 4. oa.tw. 5. degenerative joint disease.tw. 6. degenerative arthritis.tw. 7. djd.tw. 8. gonarthro$.tw. 9. or/1-8 10. exp KNEE/ 11. knee$.tw. 12. femorotibia$.tw. 13. or/10-12 14. 9 and 13 15. DEBRIDEMENT/ 16. ARTHROSCOPY/ 17. 15 and 16 18. arthroscop$ debride$.tw. 19. 17 or 18 20. 14 and 19	1. exp osteoarthritis/ 2. osteoarthrit$.tw. 3. osteoarthro$.tw. 4. oa.tw. 5. degenerative joint disease.tw. 6. degenerative arthritis.tw. 7. djd.tw. 8. gonarthro$.tw. 9. or/1-8 10. exp KNEE/ 11. knee$.tw. 12. femorotibia$.tw. 13. or/10-12 14. 9 and 13 15. exp Knee Osteoarthritis/ 16. 14 or 15 17. exp DEBRIDEMENT/ 18. exp ARTHROSCOPY/ 19. 17 and 18 20. arthroscop$ debride$.tw. 21.19 or 20 22.16 and 21	1. MeSH descriptor Osteoarthritis explode all trees in MeSH products 2. osteoarthrit* in All Fields, from 1800 to 2005 in all products 3. osteoarthro* in All Fields, from 1800 to 2005 in all products 4. oa in All Fields, from 1800 to 2005 in all products 5. “degenerative joint disease” in All Fields, from 1800 to 2005 in all products 6. degenerative arthritis in All Fields in all products 7. djd in All Fields in all products 8. gonarthro* in All Fields in all products 9. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8) 10. MeSH descriptor Knee explode all trees in MeSH products 11. knee* in All Fields, from 1800 to 2005 in all products 12. femorotibia* in All Fields, from 1800 to 2005 in all products	1 (arthroscop* debride*) and (osteoarthr* and knee*)

Table 01. Search strategy - additional detail (*Continued*)

CINAHL	EMBASE	CENTRAL	Web of Science
		13. (#10 OR #11 OR #12) 14. (#9 AND #13) 15. MeSH descriptor Osteoarthritis, Knee explode all trees in MeSH products 16. (#14 OR #15) 17. MeSH descriptor Debridement explode all trees in MeSH products 18. MeSH descriptor Arthroscopy explode all trees in MeSH products 19. (#17 AND #18) 20. arthroscop* next debride* in All Fields in all products 21. (#19 OR #20) 22. (#16 AND #21)	

Table 02. Clinical relevance table: AD versus closed-needle joint lavage

Outcome	#patients (#trials)	Control baseline m	Wt absolute change	Relative % change	NNT (B) or NNT (H)	Stat. significance	Quality of evidence
Pain at 3 months (AIMS scale, 0-10)	32 (1)	6.1	-4% (0 fewer points on a 0-10 scale)	-7% (I)	n/a	Not significant	Silver
95% CI			(-16%, 8%)	(-26% (I), 13% (W))			
Pain at 12 months (AIMS scale, 0-10)	32 (1)	6.1	3% (0 more points on a 0-10 scale)	5% (W)	n/a	Not significant	Silver
95% CI			(-11%, 17%)	(-19% (I), 28% (W))			
Physical function at 3 months (AIMS scale, 0-10)	32 (1)	1.7	-5% (0 fewer points on a 0-10 scale)	-30% (I)	n/a	Not significant	Silver
95% CI			(-12%, 2%)	(-71% (I), 29% (W))			
Physical function at 12 months (AIMS scale,	32 (1)	1.7	-3% (0 fewer points on a 0-10 scale)	-18% (I)	n/a	Not significant	Silver

Table 02. Clinical relevance table: AD versus closed-needle joint lavage (*Continued*)

Outcome	#patients (#trials)	Control baseline m	Wt absolute change	Relative % change	NNT (B) or NNT (H)	Stat. significance	Quality of evidence
0-10)							
95% CI			(-11%, 5%)	(-65% (I), 29% (W))			
Legend		m = mean	Wt = weighted	I = improvement W = worsening	NNT = number needed to treat B = benefit H = harm		

Table 03. Clinical relevance table: AD versus lavage

Outcome (scale)	#patients (#trials)	Control baseline m	Wt absolute change	Relative % change	NNT (B) or NNT (H)	Stat. significance	Quality of evidence
Pain at 2 weeks (KSPS scale, 0-100)	118 (1)	65.0	3% (3 more points on a 0-100 scale)	4% (W)	n/a	Not significant	Gold
95% CI			(-4%, 9%)	(-7% (I), 14% (W))			
Pain at 6 weeks (KSPS scale, 0-100)	116 (1)	65.0	-2% (2 fewer points on a 0-100 scale)	-3% (I)	n/a	Not significant	Gold
95% CI			(-10%, 6%)	(-15% (I), 9% (W))			
Pain at 3 months (KSPS scale, 0-100)	117 (1)	65.0	-4% (4 fewer points on a 0-100 scale)	-6% (I)	n/a	Not significant	Gold
95% CI			(-12%, 4%)	(-18% (I), 6% (W))			
Pain at 6 months (KSPS scale, 0-100)	115 (1)	65.0	-3% (3 fewer points on a 0-100 scale)	-5% (I)	n/a	Not significant	Gold
95% CI			(-11%, 5%)	(-17% (I), 7% (W))			
Pain at 12 months (KSPS scale, 0-100)	107 (1)	65.0	-3% (3 fewer points on a 0-100 scale)	-5% (I)	n/a	Not significant	Gold

Table 03. Clinical relevance table: AD versus lavage (*Continued*)

Outcome (scale)	#patients (#trials)	Control baseline m	Wt absolute change	Relative % change	NNT (B) or NNT (H)	Stat. significance	Quality of evidence
95% CI			(-11%, 5%)	(-17% (I), 8% (W))			
Pain at 18 months (KSPS scale, 0-100)	107 (1)	65.0	0% (0 fewer points on a 0-100 scale)	-1% (I)	n/a	Not significant	Gold
95% CI			(-10%, 9%)	(-15% (I), 13% (W))			
Pain at 24 months (KSPS scale, 0-100)	108 (1)	65.0	-2% (2 fewer points on a 0-100 scale)	-4% (I)	n/a	Not significant	Gold
95% CI			(-11%, 7%)	(-17% (I), 10% (W))			
Physical function at 2 weeks (AIMS scale, 0-100)	114 (1)	48.5	3% (3 more points on a 0-100 scale)	6% (W)	n/a	Not significant	Gold
95% CI			(-6%, 12%)	(-12% (I), 24% (W))			
Physical function at 6 weeks (AIMS scale, 0-100)	112 (1)	48.5	2% (2 more points on a 0-100 scale)	5% (W)	n/a	Not significant	Gold
95% CI			(-6%, 10%)	(-12% (I), 21% (W))			
Physical function at 3 months (AIMS scale, 0-100)	111 (1)	48.5	1% (1 more points on a 0-100 scale)	1% (W)	n/a	Not significant	Gold
95% CI			(-6%, 8%)	(-13% (I), 16% (W))			
Physical function at 6 months (AIMS scale, 0-100)	106 (1)	48.5	0% (0 more points on a 0-100 scale)	1% (W)	n/a	Not significant	Gold
95% CI			(-7%, 8%)	(-14% (I), 16% (W))			
Physical function at 12 months	101 (1)	48.5	2% (2 more points on a 0-	4% (W)	n/a	Not significant	Silver

Table 03. Clinical relevance table: AD versus lavage (*Continued*)

Outcome (scale)	#patients (#trials)	Control baseline m	Wt absolute change	Relative % change	NNT (B) or NNT (H)	Stat. significance	Quality of evidence
(AIMS scale, 0-100)			100 scale)				
95% CI			(-5%, 10%)	(-11% (I), 20% (W))			
Physical function at 18 months (AIMS scale, 0-100)	93 (1)	48.5	2% (2 more points on a 0-100 scale)	3% (W)	n/a	Not significant	Silver
95% CI			(-7%, 10%)	(-13% (I), 20% (W))			
Physical function at 24 months (AIMS scale, 0-100)	94 (1)	48.5	-1% (1 fewer points on a 0-100 scale)	-1% (I)	n/a	Not significant	Silver
95% CI			(-8%, 7%)	(-17% (I), 15% (W))			
Legend		m = mean	Wt = weighted	I = improvement W = worsening	NNT = number needed to treat B = benefit H = harm		

Table 04. Clinical relevance table: AD versus washout

Outcome	#patients (#trials)	Control event rate	Wt Absolute RD	Wt Rel % change	NNT(B) or NNT(H)	Stat. significance	Quality of evidence
Pain free at 1 year	76 (1)	13.9% 14 out of 100	66% 66 more out of 100	476% (I)	NNT (B) = 2	Significant	Silver
95% CI			(49, 83)	(152% (I), 1218% (I))	(2,5)		
Pain free at 5 years	58 (1)	11.5% 12 out of 100	48% 48 more out of 100	415% (I)	NNT (B) = 3	Significant	Silver
95% CI			(27, 69)	(71% (I), 1449% (I))	(2, 13)		
Legend			Wt = weighted RD = risk difference	Wt Rel = weight relative I = improvement	NNT = number needed to treat		

Table 04. Clinical relevance table: AD versus washout (*Continued*)

Outcome	#patients (#trials)	Control event rate	Wt Absolute RD	Wt Rel % change	NNT(B) or NNT(H)	Stat. significance	Quality of evidence
				W = worsening	B = benefit H = harm		

Table 05. Clinical relevance table: AD versus placebo

Outcome (scale)	#patients (#trials)	Control baseline m	Wt absolute change	Relative % change	NNT(B) or NNT(H)	Stat. significance	Quality of evidence
Pain at 2 weeks (KSPS scale, 0-100)	118 (1)	55.0	9% (9 more points on a 0 to 100 scale)	16% (W)	NNT(H) = 5	Significant	Gold
95% CI			(2%, 16%)	(3%(W), 29% (W))	(3, 27)		
Pain at 6 weeks (KSPS scale, 0-100)	116 (1)	55.0	4% (4 more points on a 0 to 100 scale)	7% (W)	n/a	Not significant	Gold
95% CI			(-5%, 12%)	(-8% (I), 21% (W))			
Pain at 3 months (KSPS scale, 0-100)	114 (1)	55.0	1% (1 more point on a 0 to 100 scale)	1% (W)	n/a	Not significant	Gold
95% CI			(-7%, 8%)	(-14% (I), 15% (W))			
Pain at 6 months (KSPS scale, 0-100)	113 (1)	55.0	2% (2 more points on a 0 to 100 scale)	4% (W)	n/a	Not significant	Gold
95% CI			(-5%, 10%)	(-10% (I), 18% (W))			
Pain at 12 months (KSPS scale, 0-100)	103 (1)	55.0	3% (3 more points on a 0 to 100 scale)	5% (W)	n/a	Not significant	Gold
95% CI			(-6%, 11%)	(-10% (I), 21% (W))			
Pain at 18 months (KSPS scale, 0-100)	103 (1)	55.0	-2% (2 fewer points on a 0 to 100 scale)	-3% (I)	n/a	Not significant	Gold
95% CI			(-11%, 8%)	(-20% (I),			

Table 05. Clinical relevance table: AD versus placebo (*Continued*)

Outcome (scale)	#patients (#trials)	Control baseline m	Wt absolute change	Relative % change	NNT(B) or NNT(H)	Stat. significance	Quality of evidence
				14% (W))			
Pain at 24 months (KSPS scale, 0-100)	108 (1)	55.0	0% (0 fewer points on a 0 to 100 scale)	0%	n/a	Not significant	Gold
95% CI			(-9%, 9%)	(-16% (I), 16% (W))			
Physical function at 2 weeks (AIMS scale, 0-100)	116 (1)	48.5	8% (8 more points on a 0-100 scale)	16% (W)	NNT(H) = 6	Significant	Gold
95% CI			(1%, 14%)	(2%, 30%)	(3, 45)		
Physical function at 6 weeks (AIMS scale, 0-100)	114 (1)	48.5	6% (6 more points on a 0-100 scale)	12% (W)	n/a	Not significant	Gold
95% CI			(-1%, 13%)	(-3% (I), 27% (W))			
Physical function at 3 months (AIMS scale, 0-100)	110 (1)	48.5	2% (2 more points on a 0-100 scale)	5% (W)	n/a	Not significant	Gold
95% CI			(-4%, 8%)	(-8% (I), 17% (W))			
Physical function at 6 months (AIMS scale, 0-100)	108 (1)	48.5	3% (3 more points on a 0-100 scale)	6% (W)	n/a	Not significant	Gold
95% CI			(-3%, 9%)	(-6% (I), 18% (W))			
Physical function at 12 months (AIMS scale, 0-100)	96 (1)	48.5	7% (7 more points on a 0-100 scale)	14% (W)	NNT(H) = 9	Significant	Silver
95% CI			(0%, 13%)	(1% (W), 28% (W))	(4, 199)		
Physical function at 18 months	90 (1)	48.5	4% (4 more points on a 0-	9% (W)	n/a	Not significant	Silver

Table 05. Clinical relevance table: AD versus placebo (*Continued*)

Outcome (scale)	#patients (#trials)	Control baseline m	Wt absolute change	Relative % change	NNT(B) or NNT(H)	Stat. significance	Quality of evidence
(AIMS scale, 0-100)			100 scale)				
95% CI			(-3%, 11%)	(-6% (I), 24% (W))			
Physical function at 24 months (AIMS scale, 0-100)	88 (1)	48.5	5% (5 more points on a 0-100 scale)	10% (W)	n/a	Not significant	Silver
95% CI			(-1%, 11%)	(-2% (I), 22% (W))			
Legend		m = mean	Wt = weighted	I = improvement W = worsening	NNT = number needed to treat B = benefit H = harm		

ANALYSES

Comparison 01. Debridement versus closed-needle joint lavage

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain in AIMS scale (scores from 0 (best) to 10 (worst))			Mean difference (Fixed) 95% CI	Totals not selected
02 Physical function in AIMS scale (scores from 0 (best) to 10 (worst))			Mean difference (Fixed) 95% CI	Totals not selected

Comparison 02. Debridement versus lavage

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain in KSPS scale (scores from 0 (best) to 100 (worst))			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
02 Physical function in AIMS scale (scores from 0 (best) to 100 (worst))			Weighted Mean Difference (Fixed) 95% CI	Totals not selected

Comparison 03. Debridement versus washout

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain free			Relative Risk (Fixed) 95% CI	Totals not selected

Comparison 04. Debridement versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain in KSPS scale (scores from 0 (best) to 100 (worst))			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
02 Physical function in AIMS scale (scores from 0 (best) to 100 (worst))			Weighted Mean Difference (Fixed) 95% CI	Totals not selected

INDEX TERMS

Medical Subject Headings (MeSH)

Arthroscopy [*methods]; Debridement [*methods]; Osteoarthritis, Knee [*surgery]; Randomized Controlled Trials as Topic

MeSH check words

Humans

COVER SHEET

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Authors	Laupattarakasem W, Laopaiboon M, Laupattarakasem P, Sumananont C
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Review: Arthroscopic debridement for knee osteoarthritis

Comparison: 01 Debridement versus closed-needle joint lavage

Outcome: 01 Pain in AIMS scale (scores from 0 (best) to 10 (worst))

Analysis 01.02. Comparison 01 Debridement versus closed-needle joint lavage, Outcome 02 Physical function in AIMS scale (scores from 0 (best) to 10 (worst))

Review: Arthroscopic debridement for knee osteoarthritis

Comparison: 01 Debridement versus closed-needle joint lavage

Outcome: 02 Physical function in AIMS scale (scores from 0 (best) to 10 (worst))

Study	Mean difference (SE)	Mean difference (Fixed) 95% CI	Mean difference (Fixed) 95% CI
01 at 3 months			
Chang 1993	-0.50 (0.36)		-0.50 [-1.20, 0.20]
02 at 12 months			
Chang 1993	-0.30 (0.41)		-0.30 [-1.10, 0.50]

Analysis 02.01. Comparison 02 Debridement versus lavage, Outcome 01 Pain in KSPS scale (scores from 0 (best) to 100 (worst))

Review: Arthroscopic debridement for knee osteoarthritis

Comparison: 02 Debridement versus lavage

Outcome: 01 Pain in KSPS scale (scores from 0 (best) to 100 (worst))

Study	Debridement N	Debridement Mean(SD)	Lavage N	Lavage Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weighted Mean Difference (Fixed) 95% CI
01 At 2 weeks						
Moseley 2002	59	54.60 (18.50)	59	52.10 (19.50)		2.50 [-4.36, 9.36]
02 At 6 weeks						
Moseley 2002	59	49.30 (23.00)	57	51.20 (20.40)		-1.90 [-9.81, 6.01]
03 At 3 months						
Moseley 2002	58	49.30 (22.00)	59	53.10 (20.70)		-3.80 [-11.54, 3.94]
04 At 6 months						
Moseley 2002	56	50.00 (21.00)	59	53.20 (22.60)		-3.20 [-11.17, 4.77]
05 At 12 months						
Moseley 2002	50	51.70 (22.40)	57	54.80 (19.80)		-3.10 [-11.16, 4.96]
06 At 18 months						
Moseley 2002	51	50.70 (25.30)	56	51.10 (22.70)		-0.40 [-9.54, 8.74]
07 At 24 months						
Moseley 2002	53	51.40 (23.20)	55	53.70 (23.70)		-2.30 [-11.15, 6.55]

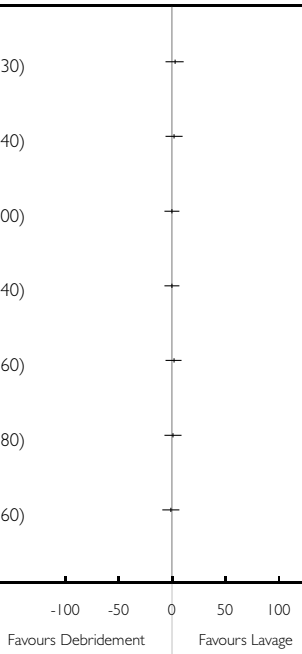
Analysis 02.02. Comparison 02 Debridement versus lavage, Outcome 02 Physical function in AIMS scale (scores from 0 (best) to 100 (worst))

Review: Arthroscopic debridement for knee osteoarthritis

Comparison: 02 Debridement versus lavage

Outcome: 02 Physical function in AIMS scale (scores from 0 (best) to 100 (worst))

Study	Debridement N	Mean(SD)	Lavage N	Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weighted Mean Difference (Fixed) 95% CI
01 At 2 weeks						
Moseley 2002	57	56.00 (21.80)	57	53.00 (25.30)		3.00 [-5.67, 11.67]
02 At 6 weeks						
Moseley 2002	58	51.70 (24.70)	54	49.50 (19.40)		2.20 [-6.00, 10.40]
03 At 3 months						
Moseley 2002	56	49.50 (17.40)	55	48.80 (21.00)		0.70 [-6.48, 7.88]
04 At 6 months						
Moseley 2002	54	49.80 (17.40)	52	49.40 (20.40)		0.40 [-6.83, 7.63]
05 At 12 months						
Moseley 2002	47	52.50 (20.30)	54	50.40 (17.60)		2.10 [-5.36, 9.56]
06 At 18 months						
Moseley 2002	44	52.80 (20.90)	49	51.20 (18.80)		1.60 [-6.51, 9.71]
07 At 24 months						
Moseley 2002	44	52.60 (16.40)	50	53.20 (21.60)		-0.60 [-8.30, 7.10]



Analysis 03.01. Comparison 03 Debridement versus washout, Outcome 01 Pain free

Review: Arthroscopic debridement for knee osteoarthritis

Comparison: 03 Debridement versus washout

Outcome: 01 Pain free

Study	Debridement n/N	Washout n/N	Relative Risk (Fixed) 95% CI	Relative Risk (Fixed) 95% CI
01 at 1 year				
Hubbard 1996	32/40	5/36		5.76 [2.52, 13.18]
02 at 5 years				
Hubbard 1996	19/32	3/26		5.15 [1.71, 15.49]

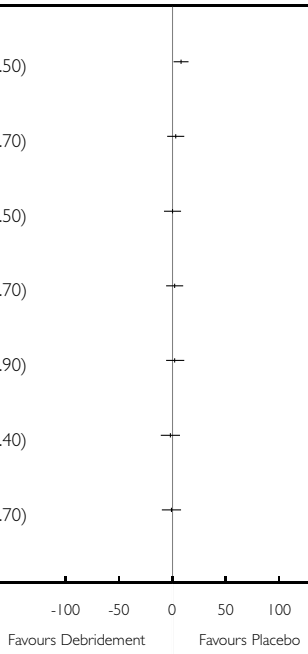
Analysis 04.01. Comparison 04 Debridement versus placebo, Outcome 01 Pain in KSPS scale (scores from 0 (best) to 100 (worst))

Review: Arthroscopic debridement for knee osteoarthritis

Comparison: 04 Debridement versus placebo

Outcome: 01 Pain in KSPS scale (scores from 0 (best) to 100 (worst))

Study	Debridement N	Mean(SD)	Placebo N	Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weighted Mean Difference (Fixed) 95% CI
01 At 2 weeks						
Moseley 2002	59	54.60 (18.50)	59	45.90 (20.50)		8.70 [1.65, 15.75]
02 At 6 weeks						
Moseley 2002	59	49.30 (23.00)	57	45.70 (21.70)		3.60 [-4.53, 11.73]
03 At 3 months						
Moseley 2002	58	49.30 (22.00)	56	48.80 (21.50)		0.50 [-7.49, 8.49]
04 At 6 months						
Moseley 2002	56	50.00 (21.00)	57	47.60 (20.70)		2.40 [-5.29, 10.09]
05 At 12 months						
Moseley 2002	50	51.70 (22.40)	53	48.90 (21.90)		2.80 [-5.76, 11.36]
06 At 18 months						
Moseley 2002	51	50.70 (25.30)	52	52.40 (22.40)		-1.70 [-10.93, 7.53]
07 At 24 months						
Moseley 2002	53	51.40 (23.20)	55	51.60 (23.70)		-0.20 [-9.05, 8.65]



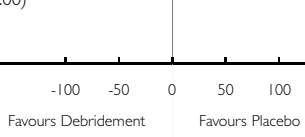
Analysis 04.02. Comparison 04 Debridement versus placebo, Outcome 02 Physical function in AIMS scale (scores from 0 (best) to 100 (worst))

Review: Arthroscopic debridement for knee osteoarthritis

Comparison: 04 Debridement versus placebo

Outcome: 02 Physical function in AIMS scale (scores from 0 (best) to 100 (worst))

Study	Debridement		Placebo		Weighted Mean Difference (Fixed)	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
01 At 2 weeks						
Moseley 2002	57	56.00 (21.80)	59	48.30 (13.40)		7.70 [1.09, 14.31]
02 At 6 weeks						
Moseley 2002	58	51.70 (24.70)	56	45.90 (12.00)		5.80 [-1.29, 12.89]
03 At 3 months						
Moseley 2002	56	49.50 (17.40)	54	47.30 (16.00)		2.20 [-4.04, 8.44]
04 At 6 months						
Moseley 2002	54	49.80 (17.40)	54	47.00 (13.00)		2.80 [-2.99, 8.59]
05 At 12 months						
Moseley 2002	47	52.50 (20.30)	49	45.60 (10.20)		6.90 [0.43, 13.37]
06 At 18 months						
Moseley 2002	44	52.80 (20.90)	46	48.50 (12.40)		4.30 [-2.84, 11.44]
07 At 24 months						
Moseley 2002	44	52.60 (16.40)	44	47.70 (12.00)		4.90 [-1.10, 10.90]



Azithromycin for acute lower respiratory tract infections (Review)

Panpanich R, Lerttrakarnnon P, Laopaiboon M

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2008, Issue 3

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Azithromycin for acute lower respiratory tract infections (Review)

Panpanich R, Lerttrakarnnon P, Laopaiboon M

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ABSTRACT

Background
Acute lower respiratory tract infections (LRTI) range from acute bronchitis and acute exacerbations of chronic bronchitis to pneumonia. Approximately five million people die of acute respiratory tract infections annually. Among these, pneumonia represents the most frequent cause of mortality, hospitalization and medical consultation. Azithromycin is a new macrolide antibiotic, structurally modified from erythromycin and noted for its activity against some gram-negative organisms associated with respiratory tract infections, particularly *Haemophilus influenzae* (*H. influenzae).*

Objectives
To compare the effectiveness of azithromycin to amoxycillin or amoxycillin/clavulanic acid (amoxyclav) in the treatment of LRTI, in terms of clinical failure, incidence of adverse events and microbial eradication.

Search strategy
We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007 Issue 2), MEDLINE (January 1966 to July 2007), and EMBASE (January 1974 to July 2007).

Selection criteria
Randomized and quasi-randomized controlled trials, comparing azithromycin to amoxycillin or amoxycillin/clavulanic acid in participants with clinical evidence of acute LRTI: acute bronchitis, pneumonia, and acute exacerbation of chronic bronchitis were studied.

Data collection and analysis
The criteria for assessing study quality were generation of allocation sequence, concealment of treatment allocation, blinding, and completeness of the trial. All types of acute LRTI were initially pooled in the meta-analyses. The heterogeneity of results was investigated by the forest plot and Chi-square test. Index of I-square (I^2) was also used to measure inconsistent results among trials. Subgroup and sensitivity analyses were conducted.

Main results
Fifteen trials were analysed. The pooled analysis of all trials showed that there was no significant difference in the incidence of clinical failure on about day 10 to 14 between the two groups (relative risk (RR), random-effects 1.09; 95% confidence interval (CI) 0.64 to 1.85). Sensitivity analysis showed a reduction of clinical failure in azithromycin-treated participants (RR 0.55; 95% CI 0.25 to 1.21) in three adequately concealed studies, compared to RR 1.32; 95% CI 0.70 to 2.49 in 12 studies with inadequate concealment. Twelve trials reported the incidence of microbial eradication and there was no significant difference between the two groups (RR 0.95; 95% CI 0.87 to 1.03). The reduction of adverse events in the azithromycin group was RR 0.76 (95% CI 0.57 to 1.00).

Authors' conclusions
There is unclear evidence that azithromycin is superior to amoxicillin or amoxyclav in treating acute LRTI. In patients with acute bronchitis of a suspected bacterial cause, azithromycin tends to be more effective in terms of lower incidence of treatment failure and adverse events than amoxicillin or amoxyclav. Future trials of high methodological quality are needed.

PLAIN LANGUAGE SUMMARY

Azithromycin is not better than amoxycillin or amoxyclav in the treatment of acute lower respiratory tract infections

Acute lower respiratory tract infections (LRTI) are one of the most common diagnoses in ambulatory settings. In general, people with LRTI present with cough and fever, which varies from mild to severe. Antibiotic therapy is considered in patients with a suspected bacterial cause. This review examines trials that compared azithromycin with amoxycillin or amoxyclav in the treatment of acute LRTI. We found that azithromycin was not more effective than amoxycillin or amoxyclav in terms of cure, improvement or failure.

BACKGROUND

The spectrum of acute lower respiratory tract infection (LRTI) ranges from acute bronchitis and acute exacerbations of chronic bronchitis to pneumonia. Annually approximately five million people die of acute respiratory tract infections. Among these, pneumonia represents the most frequent cause of mortality, hospitalization and medical consultation (Bariffi 1995).

Acute bronchitis is one of the most common diagnoses in ambulatory settings. The diagnosis of acute bronchitis is mainly based on symptom of cough, usually mild and self-limiting. Acute bronchitis with underlying pulmonary diseases or a prolonged cough of more than two weeks was considered for antibiotic therapy (Knutson 2002). A prospective multicenter study of 359 cases of community-acquired pneumonia in the United States reported that 58.5% had identifiable pathogens, 32.9% had unknown etiology, and 8.6% had aspiration-related and post-obstructive pneumonia. The most frequent aetiologic agent was *Streptococcus pneumoniae (Streptococcus pneumoniae (S. pneumoniae)* (15%), followed by *Haemophilus influenzae (H. influenzae)* (10.9%), Legionella spp (6.7%) and *Chlamydia pneumoniae (C. pneumoniae)* (6.1%) (Fang 1990). Recently, a study in The Netherlands of 145 adults with LRTI showed that bacterial cause was found in 43 (30%) and a viral cause in 57(39%). Influenza virus A was the most frequently diagnosed microorganism. The most frequently bacterial agents were *H. influenzae* (9%) and *Mycoplasma pneumoniae (M. pneumoniae)* (9%) followed by *S. pneumoniae* (6%) (Graffelman 2004).

Over the past 30 years, strains of *S. pneumoniae* with diminished susceptibility to penicillin, have emerged and spread worldwide (Austrian 1994). Cross-resistance to other antibiotics has also been reported in many strains of *S. pneumoniae* that have diminished susceptibility to penicillin and cephalosporin (Goldstein 1996). A number of studies indicated the importance of *Mycoplasma pneumoniae (M. pneumoniae)* as the main aetiologic agent in ambulatory patients with pneumonia (Berntsson 1986; Langille 1993; Marrie 1996). Co-infection by more than one pathogen was also reported, and ranged from less than 10% to 38.9% (Lieberman 1996). The value of routine microbial investigation in all patients with LRTI is uncertain (Woodhead 1991). A survey on the management of 2056 such infections obtained from general practitioners in France, Germany, Italy, Spain and the UK, reported that microbiological examination was performed in only 7% of cases compared to 22% for chest radiography (Woodhead 1996).

Antimicrobial treatment in LRTI has to be effective, partly because of the need to reduce the cost and also the problem of increasing resistance to the commonly used antibiotics (Legnani 1997). It has also been suggested that the start of therapy should not be delayed for longer than six hours for diagnostic studies (Brown 1998). The importance of early antimicrobial treatment was supported by a study in elderly patients with pneumonia, which showed that 30 day mortality was lower after administration of antibiotics within eight hours of arrival at hospital, than after delayed treatment (Meehan 1997). Compliance is also important, particularly in ambulatory patients. A study related to medical compliance for the out-patient management of infectious diseases, indicated that there was an inverse relationship between frequency of dose and compliance. A short-term regimen requiring administration once a day, was found to have the highest compliance rate - 80% compared to 69% and 38% for administration twice a day and three times a day, respectively (Sclar 1994).

Amoxycillin, an oral antibiotic, constitutes extended spectrum penicillin and is active against many aerobic gram-negative bacilli encountered in patients with pneumonia. By combining the beta-lactamase inhibitor, clavulanic acid with amoxycillin, the in-vitro spectrum of penicillin is expanded to include beta-lactamase producing organisms which would otherwise be resistant to this drug (Mandell 1994). Amoxycillin has been accepted to be one of the first choice antibiotics in patients with community-acquired LRTI. Amoxycillin-clavulanic acid is recommended particularly in the high prevalence area of beta-lactamase producing organisms, and also when an etiologic agent is not identified (Bartlett 1998; Huchon 1998).

Azithromycin is a new macrolide antibiotic structurally modified from erythromycin with an expanded spectrum of activity and improved tissue pharmacokinetic characteristics relative to erythromycin. The drug is noted for its activity against some gram-negative organisms associated with respiratory tract infections, particularly *H. influenzae*. Azithromycin has similar properties to other macrolides against *S. pneumoniae* and *Moraxella catarrhalis (M. catarrhalis)*, and is active against atypical pathogens such as *Legionella pneumophilae (L. pneumophilae)*, *C. pneumoniae* and *M. pneumoniae* (Dunn 1996).

This review compares the effects of azithromycin and amoxycillin or amoxycillin-clavulanic acid in treating acute LRTI: acute bronchitis, pneumonia and acute exacerbation of chronic bronchitis in terms of clinical failure, incidence of adverse events and microbial eradication.

OBJECTIVES

To compare the effectiveness of azithromycin to amoxycillin or amoxycillin/clavulanic acid (amoxyclav) in the treatment of LRTI, in terms of clinical failure, incidence of adverse events and microbial eradication.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomized and quasi-randomized controlled trials.

Types of participants

Participants of any age or gender, with clinical evidence of acute LRTI: acute bronchitis; pneumonia; and acute exacerbations of chronic bronchitis.

Types of intervention

Azithromycin with any dose regimens in comparison to amoxycillin or amoxycillin/clavulanic acid (amoxyclav).

Types of outcome measures

Primary outcome
Clinical failure (persistence or deterioration of symptoms, death, or relapse assessed at about 10 to 14 days after therapy started).

Secondary outcomes
Incidence of serious complications.
Adverse drug events.
Eradication of organism (causative micro-organism absent from the sputum culture after treatment).

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Acute Respiratory Infections Group methods used in reviews.

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007 Issue 2), MEDLINE (January 1966 to July 2007), and EMBASE (January 1974 to July 2007).

We combined the following search strategy with the Cochrane highly sensitive search strategy phases one and two as published in appendix 5c of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005). The search terms were also run over CENTRAL. The EMBASE search was adapted and is listed below.

MEDLINE (OVID)
1 exp Azithromycin/
2 (azithromycin or azithromicin).mp.
3 or/1-2
4 exp Amoxicillin/
5 exp Amoxicillin-Potassium Clavulanate Combination/
6 (amoxicillin or amoxycillin).mp.
7 amoxicillin clavula$.mp.
8 or/4-7
9 exp Pneumonia/
10 pneumonia.mp.
11 exp Bronchitis/
12 bronchitis.mp.
13 (lower respiratory tract infection$ or lower respiratory infection$ or LTRI$).mp.
14 or/9-13
15 and/3,8,14

EMBASE (WebSPIRS)
#1 explode 'azithromycin-' / all subheadings in DEM,DER,DRM,DRR
#2 (azithromycin or azithromicin) in ti
#3 (azithromycin or azithromicin) in ab
#4 #1 or #2 or #3
#5 explode 'amoxicillin-' / all subheadings in DEM,DER,DRM,DRR
#6 explode 'amoxicillin-plus-clavulanic-acid' / all subheadings in DEM,DER,DRM,DRR
#7 (amoxicillin or amoxycillin) in ti
#8 (amoxicillin or amoxycillin) in ab
#9 (amoxicillin clavula* in ti) or (amoxicillin clavula* in ab)
#10 #5 or #6 or #7 or #8 or #9
#11 explode 'pneumonia-' / all subheadings in DEM,DER,DRM,DRR
#12 (pneumonia in ti) or (pneumonia in ab)
#13 explode 'bronchitis-' / all subheadings in DEM,DER,DRM,DRR
#14 (bronchitis in ti) or (bronchitis in ab)
#15 explode 'lower-respiratory-tract-infection' / all subheadings in DEM,DER,DRM,DRR
#16 (lower respiratory tract infection$ or lower respiratory infection$ or LTRI$)in ti
#17 (lower respiratory tract infection$ or lower respiratory infection$ or LTRI$)in ab
#18 #11 or #12 or #13 or #14 or #15 or #16 or #17
#19 #4 and #10 and #18

We reviewed the citations in the trials identified by the above searches. We contacted the organizations and individual

researchers working in this field for unpublished data, and missing data of published trials. There were no language or publication restrictions.

METHODS OF THE REVIEW

Study selection

Two review authors (RP, PL) independently screened the results of the search strategy for potentially relevant studies. We used an eligibility form to assess these studies for inclusion in the review. Disagreements were resolved by discussion.

One review identified from the new search (Kogan 2003) is awaiting assessment. This trial was conduct on children with pneumonia and the results are not expected to have any effect or change the findings of this review.

Quality assessment

Three review authors (RP, PL, ML) independently assessed the quality of the included studies using an assessment form. The criteria were:

1. generation of allocation sequence;
2. concealment of treatment allocation;
3 blinding;
4 completeness of the trial.

Trials were assessed to have adequate concealment if randomization was administered by a central facility or the use of sealed opaque envelopes. Disagreements were resolved by discussion.

Data extraction

A data extraction form was used to collect information from included trials regarding participants, methods, interventions, and outcomes. Data were extracted by one review author (RP) and independently cross checked by another review author (PL). The data sources were checked to avoid multiple publication based on the same data. Data extraction included:

1. the time period and geographical location of the study;
2. baseline characteristics of participants;
3. inclusion/exclusion criteria;
4. preparation and dosing of treatment regime.

We extracted information on the main outcomes: clinical failure, microbial eradication, and adverse events.

Data synthesis

Two review authors analyzed data using Review Manager (Version 4.2). All types of acute LRTI were initially pooled in the meta-analyses. Event rates, RR, and their corresponding 95% CIs were calculated. We examined publication bias by using a funnel plot. The heterogeneity of results was investigated through visual examination of the forest plot, the Chi square test of heterogeneity using a 10% level of statistical significance, and the index of $I^2$was also used to measure inconsistency results among trials (Higgins 2003). Subgroup analysis was conducted for age and types of respiratory tract infections: acute bronchitis, acute exacerbation of chronic bronchitis, and pneumonia. Sensitivity analysis was conducted to recruit only trials with adequate concealment.

DESCRIPTION OF STUDIES

Study location

Fifteen trials met the inclusion criteria. Details of the included trials are provided in the 'Characteristics of included studies' table. Thirteen trials were published in English, one trial was in Italian and one was in Chinese. The studies were conducted between 1991 and 2002 in the following countries: France, Belgium, The Netherlands, The United States of America, Italy, and China.

Participants

Twelve out of 15 trials were conducted in adults. Four trials (Gris 1996; Hoepelman 1993; Hoepelman 1998; Zachariah 1996) recruited adult participants either with acute bacterial bronchitis or chronic bronchitis with acute exacerbation or pneumonia. Five trials (Beghi 1995; Mertens 1992; Sevieri 1993; Suping 2002; Whitlock 1995) recruited only participants with chronic bronchitis with acute exacerbation. Three trials (Ferwerda 2001; Harris 1998; Wubbel 1999) were conducted in children aged 6 months to 16 years with community-acquired pneumonia.

Interventions

Azithromycin was compared to amoxycillin-clavulanic acid in 13 trials (Balmes 1991; Beghi 1995; Biebuyck 1996; Ferwerda 2001; Gris 1996; Harris 1998; Hoepelman 1993; Hoepelman 1998; Sevieri 1993; Suping 2002; Whitlock 1995; Wubbel 1999; Zachariah 1996). Two trials (Daniel 1991; Mertens 1992) compared azithromycin to amoxycillin.

There were two regimens of azithromycin in adult trials:

1. azithromycin 500 mg single dose daily for three days (eight trials); and
2. azithromycin 500 mg single dose on day one followed by 250 mg single dose daily on day two to five (four trials).

The regimen of azithromycin in children in two trials (Harris 1998; Wubbel 1999) was 10 mg/kg single dose on day one and followed by 5 mg/kg once daily on day two to five, and the other trial (Ferwerda 2001), was 10 mg/kg/day once daily for three days.

Two trials in children (Harris 1998; Wubbel 1999) compared azithromycin to amoxycillin/clavulanic acid in children aged up to five years, and to erythromycin in those with older age. This review included the data only the comparison with amoxycillin/clavulanic acid.

Outcomes

All trials reported numbers of participants cure, improved, failure and relapse. Microbial eradication were reported in 11 trials (Balmes 1991; Beghi 1995; Daniel 1991; Gris 1996; Harris 1998;

Hoepelman 1993; Hoepelman 1998; Mertens 1992; Sevieri 1993; Whitlock 1995). No trial reported duration of fever. All trials reported failure at about 10 to 14 days after the therapy started.

METHODOLOGICAL QUALITY

All trials were randomized, but only three trials had adequately concealment of treatment allocation (Ferwerda 2001; Hoepelman 1998; Mertens 1992).

Seven trials (Ferwerda 2001; Gris 1996; Harris 1998; Hoepelman 1998; Mertens 1992; Whitlock 1995; Zachariah 1996) performed double-blinding, one trial (Hoepelman 1993) mentioned single blinding and seven trials (Balmes 1991; Beghi 1995; Biebuyck 1996; Daniel 1991; Sevieri 1993; Suping 2002; Wubbel 1999) had no descriptions of blinding.

Five trials reported the completeness of follow up, all randomized patients were included in the analysis. In two trials, 15% to 20% of participants were excluded from analysis. Most trials reported less than 15% of dropouts.

RESULTS

Fifteen trials enrolled 2601 participants; 2496 were recruited in the analysis. There were 1388 participants who received azithromycin and 1108 received amoxicillin or amoxyclav. All trials reported incidence of clinical failure (persistence or deterioration of symptoms or relapse). Eleven trials reported incidence of microbacterial eradication. There was no evidence of publication bias by using the funnel plot (Figure 01).

The pooled analysis of all trials showed that the incidence of clinical failure on day 10 to 14 in azithromycin group was 10.1% (140/1,388) compared to 10.3% (114/1,108) in amoxicillin or amoxyclav group. There was no statistical significance in the incidence of clinical failure between the two groups (RR, random-effects model 1.09; 95% CI 0.64 to 1.85). However, the heterogeneity between trials was significant with a degree of 65.3% (P value 0.0002).

Heterogeneity would be anticipated with a variation between age groups and types of diagnosis between trials. Subgroup analysis stratified by age groups showed no significant difference of treatment effects between the azithromycin group and the amoxycillin or amoxyclav group in either adults (RR, random-effects model 1.15; 95% CI 0.60 to 2.20) or children (RR 0.93; 95% CI 0.45 to 1.94).

In subgroup analysis of trials with acute bronchitis participants, the incidence of clinical failure was significantly lower in the azithromycin group compared to amoxycillin or amoxyclav (RR, random-effects model 0.63; 95% CI 0.45 to 0.88). In analysis of trials with acute exacerbation of chronic bronchitis participants, there was significant heterogeneity between trials with a degree of 75.5% (P value 0.0001) and the clinical failure was not significant different between the groups.

Sensitivity analysis was conducted to recruit three trials with adequate concealment. The reduction of clinical failure in azithromycin-treated participants was RR 0.55 (95% CI 0.25 to 1.21), compared to RR 1.32 (95% CI 0.70 to 2.49), restricted to 12 studies with inadequate concealment.

Sensitivity analysis was also performed by excluding the biggest trial (Biebuyck 1996). The result showed that the overall effect of azithromycin compared to amoxycillin or amoxyclav on reducing clinical failure was of RR 1.06 (95% CI 0.62 to 1.79). This figure was quite similar to the result of total of 15 trials (RR 1.09, 95% CI 0.64 to 1.85).

Twelve trials reported the incidence of microbial eradication. The pooled analysis showed that the incidence of microbial eradication in azithromycin group was 66.4% (326/491) compared to 67.6% (318/470) in azithromycin or amoxyclav group. There was no significant difference between the two groups (RR, fixed-effect model 0.95; 95% CI 0.87 to 1.03).

Twelve trials reported adverse events. The most frequent adverse events were mild to moderate gastrointestinal symptoms; nausea, vomiting, and diarrhea. The others reported were headache, insomnia, rash, and transient laboratory liver function changes. In one big trial (Biebuyck 1996) reported more number of participants receiving amoxyclav discontinued treatment because of adverse events than in azithromycin group; 7% compared to 1.2% respectively. The overall incidence of adverse events in azithromycin group was 17.9% (244/1,363) compared to 23.6% (246/1,043) in amoxicillin or amoxyclav group. The reduction of adverse events in azithromycin group was of RR 0.76 (95% CI 0.57 to 1.00).

No trials reported death.

DISCUSSION

There were some limitations that related to quality of studies included into this review. Adequately concealed treatment allocation was performed in only three trials and nearly half of the number of trials had no descriptions of blinding.

The results of this review showed that the incidence of clinical failure on about day 10 to 14 in the azithromycin group and amoxicillin or amoxyclav group was not statistically significantly different in terms of clinical failure, microbial eradication and adverse events. However, in a group of participants with acute bronchitis suspected bacterial cause, the incidence of clinical failure was significantly lower in azithromycin group.

The effect of azithromycin in reducing clinical failure was shown to be much stronger when compared to amoxycillin than to amoxy-

clav. The evidence was not clear because there were only two trials for the control group of amoxycillin. In the sensitivity analysis, we found a better trend in reduction of clinical failures in participants treated with azithromycin in three adequately concealed studies.

AUTHORS' CONCLUSIONS

Implications for practice

There is unclear evidence that azithromycin is superior to amoxicillin or amoxyclav in treating acute LRTI. In patients with acute bronchitis of a suspected bacterial cause, azithromycin tends to be more effective by the lower incidence of treatment failure than amoxicillin or amoxyclav. Azithromycin seems to have a lower incidence of adverse events than the amoxicillin or amoxyclav. In clinical practice, the choice between azithromycin and amoxicillin or amoxyclav could be based on other considerations such as the cost, convenience, and adherence to treatment.

Twelve trials reported adverse events. The most frequent adverse events were mild to moderate gastrointestinal symptoms - nausea, vomiting, and diarrhea. The other adverse events reported were headache, insomnia, rash, and transient laboratory liver function changes. One large trial (Biebuyck 1996) reported that the number of participants for whom treatment was discontinued prematurely due to adverse events was higher in the amoxyclav group (7%) compared to participants in the azithromycin group (1.2%). The overall incidence of adverse events in the azithromycin group was 17.9% (244/1363) compared to 23.6% (246/1043) in amoxicillin or amoxyclav group. The reduction of adverse events in the azithromycin group was of RR 0.76 (95% CI 0.57 to 1.00).

Implications for research

High methodological quality research is needed to clarify whether azithromycin is better than amoxicillin or amoxyclav in treating acute LRTI.

FEEDBACK

Less adverse events?

Summary

While informative, this systematic review leaves at least one unanswered question. Namely, with regards to the outcome of adverse events which seems to favor azithromycin, the severity of these complications are not well described. Another important consideration in the interpretation of this data is that the absence of difference between azithromycin and amoxi/clavulin is far more robust than with the comparison to Amoxil. As a result, clinicians might be tempted to equate all three drugs when reading this systematic review when in fact, the demonstration of equivalence is more convincing between azithromycin and amoxi/clavulin and not amoxycillin and azithromycin. It is also quite interesting to note that the authors conclude a possible benefit in acute bronchitis when a Cochrane review concludes that there is no net benefit associated with the use of antibiotics in acute bronchitis.

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Author's reply

I have revised the review and added details about adverse events in paragraph 6 of the RESULTS section.
There is information regarding this in the last sentence of paragraph 3 of the RESULTS section, reporting the risk ratios of two comparisons; azithromycin versus amoxyclav and azithromycin versus amoxycillin.

In the DISCUSSION section we stated that the effect of azithromycin in reducing clinical failure was shown to be much stronger when compared to amoxycillin than to amoxyclav. The evidence was not clear because there were only two trials for the control group of amoxycillin.

Acute bronchitis in this review refers to acute bronchitis with suspected bacterial cause. The review focuses on comparison of effects of azithromycin to amoxyclav or amoxycillin. I understand that the other Cochrane review you mentioned compared antibiotics with placebo. The conclusions of review could be different

Ratana Panpanich
Peerasak Lerttrakarnnon
Malinee Laopaiboon

Contributors

Eddy Lang
Comment posted 20/03/2005

POTENTIAL CONFLICT OF INTEREST

We certify that we have no affiliations with, or involvement in, any organisation or entity with a direct financial interest in the subject matter of the review (for example employment, consultancy, stock ownership, honoraria, expert testimony).

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** Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Balmes 1991**
Methods	Location: France Patients were randomly assigned to treatment. No description of blinding. Efficacy was evaluated at 10-15 days after the therapy started
Participants	110 adults with acute lower respiratory tract infection, either acute bacterial bronchitis or pneumonia. Acute bronchitis was defined to bacterial bronchial or bronchopulmonary infection accompanied by the production of purulent sputum. Patients with infectious mononucleosis, chronic or chronic obstructive pulmonary disease with out acute infection, had received antibiotics within 48 hours prior to the study were excluded Participants: azithromycin group N = 52 (acute bronchitis 48, pneumonia 4), amoxicillin/clavulanic acid group N = 58 (acute bronchitis 54, pneumonia 4)
Interventions	1. Azithromycin 500 mg single dose on day 1 followed by a single dose of 250 mg daily on day 2-5 2. Amoxicillin /clavulanic acid 625 mg (amoxycillin 500 mg, clavulanic 125 mg) three times daily for 10 days

Characteristics of included studies (*Continued*)

Outcomes	Cure Improvement Failure Adverse events Pathogen eradication
Notes	Of the bronchitis cases, 20/48 in the azithromycin group and 19/54 in the amoxycillin/clavulanic acid group were described as acute exacerbation of chronic bronchitis Of 110 randomized patients, 104 were assessed and included in analysis
Allocation concealment	B – Unclear

Study	**Beghi 1995**
Methods	Multicenter study, patients were randomized to receive either azithromycin or amoxicillin/clavulanic acid. No blinding. Efficacy was evaluated 10 days after the therapy started
Participants	142 hospitalized or out-patients aged 18 years or more with acute purulent exacerbation of chronic bronchitis. Exclusion criteria: patients were treated with other antibiotics 48 hours prior to the study, leucopenia, coagulation disorders, renal dysfunction, HIV/AIDS on immunosuppressive drugs, suspected pneumonia with lung abscess, pleuritis, empyema, or active tuberculosis, pregnancy and lactation. Participants: azithromycin group N = 62, amoxicillin/clavulanic acid group N = 73
Interventions	1. Azithromycin (Pfizer) 500 mg single dose daily for 3 days 2. Amoxycillin/clavulanic acid SmithKline Beecham (amoxycillin 875 mg +clavulanic acid 125 mg) twice daily for 8 days
Outcomes	Cure (disappearance of all signs and clinical symptoms of infection by day 10 Improvment (disappearance of only a few signs and/or clinical symptoms. Failure (persistence or worsening of signs and symptoms at days 4 and 10
Notes	Corticosteroids were allowed, provided not exceed 25 mg for prednisolone or its equivalent in both groups. Of the 142 patients, 2 patients were dropout and not included in analysis
Allocation concealment	B – Unclear

Study	**Biebuyck 1996**
Methods	Patients were randomized in a 2:1 ratio to receive either azithromycin or amoxicillin/clavulanic acid. No blinding. Efficacy was evaluated at 8-10 days after the therapy started
Participants	759 adult patients aged between 18-75 years, 620 had acute tracheobronchitis and 139 had acute exacerbations of chronic bronchitis were recruited. A diagnosis of acute tracheobronchitis was based on the presence of at least two of the following signs and symptoms: cough, fever 38 C or higher, purulent sputum and rhonchi/rales. Participants: azithromycin group N = 501, amoxicillin/clavulanic acid group N = 258
Interventions	1. Azithromycin 500 mg once daily for 3 days (two 250 capsules taken at least 1 hour before or 2 hours after meals) 2. Amoxicillin /clavulanic acid 625 mg (amoxycillin 500 mg + clavulanate 125 mg) three times daily for 5-10 days, taken during or shortly after meals
Outcomes	Cure Improvement Failure Adverse events
Notes	Of 759 patients, 31 patients with various reasons; adverse events, lack of efficacy, and lost to follow up discontinued treatment, 9 in the azithromycin group and 22 in the amoxycillin/clavulanate group. 26 out of 31 dropouts were followed and evaluated. In analysis, 754 patients were included
Allocation concealment	B – Unclear

Characteristics of included studies (*Continued*)

Study	**Daniel 1991**
Methods	Multicenter study, 9 study centers in four European countries (Belgium, Finland, FRG, and UK). Patients were allocated to either treatment group using a randomization list. No blinding. Efficacy was evaluated at 10-15 days after the therapy started
Participants	251 adult patients aged 18 years or older diagnosed by clinical criteria as acute bronchitis or pneumonia were recruited. Patients with life-threatening conditions, cystic fibrosis, had received antibiotics in the 48 hours preceding the study were excluded. Participants: azithromycin group N = 125, amoxicillin group N = 126
Interventions	1. Azithromycin 500 mg single dose on day 1 followed by a 250 mg daily on day 2-5 2. Amoxicillin 500 mg orally three times daily for 7 days
Outcomes	Cure Adverse events Pathogen eradication
Notes	Of 251 randomized patients, 241 were assessed and included in analysis
Allocation concealment	C – Inadequate

Study	**Ferwerda 2001**
Methods	Location: The Netherlands Multicentre, randomized, double blind, double dummy study. Randomization was done in block of six at research center. Blinding was maintained by match placebo. Clinical evaluation was done on days 3-5, days 10-13 and days 25-30
Participants	118 patients aged 3 months to 12 years with community acquired lower respiratory tract infection were recruited. The diagnosis was based on the presence of respiratory signs and symptoms in combination with a positive chest radiograph or clinical evidence of temperature 38 C or higher, cough, leucocytosis > 10000 cells/cu. mm. Patients with symptom longer than 1 week, weight > 40 kg, or need for parenteral therapy were excluded. Azithromycin group N = 56, co-amoxyclav N = 54
Interventions	1. Azithromycin suspension 10 mg/kg/day single dose for 3 days 2. Co-amoxyclav suspension 45/11.25 mg/kg/day three times a day for 10 days
Outcomes	Cure Improvement Failure Adverse events
Notes	Of 118 randomised patients, 110 were clinically evaluated. 8 were excluded; 7 of them did not meet the inclusion criteria, and one patients the informed consent was withdrawn. Compliance was measured by diary card, registered by parents
Allocation concealment	A – Adequate

Study	**Gris 1996**
Methods	Location: Belgium, multicenter study Patients were randomly assigned to receive either azithromycin or amoxicillin/clavulanic acid. Double blinding was performed with match placebo tablets. Efficacy was evaluated 14 days after the therapy started
Participants	78 adult patients aged 18 years or older with acute bronchitis, acute exacerbations of chronic bronchitis or pneumonia were recruited. Diagnosis was made on the clinical sign and symptoms and chest radiology. Patients who received antibiotics in the 48 hours preceding the study were excluded. Participants: azithromycin group N = 41, co-amoxyclav N = 37
Interventions	1. Azithromycin 500 mg (Pfizer) once daily for 3 days 2. Co-amoxyclav 625 mg (amoxycillin 500 mg + clavulanate 125 mg) three times daily for 10 days
Outcomes	Cure

Characteristics of included studies (*Continued*)

	Improvement Failure Adverse events Pathogen eradication
Notes	11 out of 78 patients were not clinically evaluated with reasons; failure to meet entry criteria, failure to strict with the protocol, and adverse events, 7 in the azithromycin group and 4 in the co-amoxyclav group
Allocation concealment	B – Unclear

Study	**Harris 1998**
Methods	Location: US, multicenter study Patients were randomized 2:1 to receive either azithromycin or amoxycillin/clavulanate in patients aged 6 months to 5 years, and erythromycin in children aged older than 5 years. Double blinding was performed. Patients were evaluated at four clinic visits: baseline, day 2-5, day 15-19, and 4-6 weeks after treatment
Participants	Patients with community-acquired pneumonia at 23 centers in the US, aged 6 months to 16 years. Pneumonia were diagnosed by chest X-ray of acute infiltration and the presence of tachypnea, with at least one of the following: fever, cough, white blood count 12,000/cu. mm. or more, and respiratory signs of suggestive of pneumonia. Patients with severe or multilobar pneumonia, with evidence of hematologic, renal, hepatic or cardiovascular disease, chronic steroid use or concomitant treatment with other drugs were excluded. Participants aged less than 5 years: azithromycin group N = 129, amoxy-clavulanic acid group N = 66
Interventions	1. Azithromycin oral suspension 10 mg/kg (maximum 500 mg) once on day 1, followed by 5 mg/kg (maximum 250 mg) once daily on day 2-5 2. Conventional therapy, three times daily for 10 days (amoxicillin/clavulanic acid 40 mg/kg/day for patients aged 6 months to 5 years, and erythromycin estorate 40 mg/kg/day for children aged 5-16 years)
Outcomes	Cure Improvement Failure Adverse events Eradication of pathogen
Notes	
Allocation concealment	B – Unclear

Study	**Hoepelman 1993**
Methods	Location: The Netherlands, multicenter study Patients were randomly assigned to treatment. Single blind was performed. All 99 randomized patients were clinically evaluated on day 3-7 and day 12-16
Participants	99 outpatients from 4 centers in the Netherlands, with clinical evidence of lower respiratory tract infection either pneumonia or purulent bronchitis or acute exacerbation of chronic bronchitis were recruited. Patients with terminal illness, concomitant with use of other antibiotics, with infectious mononucleosis, cystic fibrosis and gastrointestinal absorption abnormality were excluded. Azithromycin group N = 48, co-amoxyclav N = 51
Interventions	1. Azithromycin 500 mg once daily for three days 2. Co-amoxyclav 625 mg three times a day for 10 days
Outcomes	Cure Improvement Failure Adverse events Eradication of pathogen

Characteristics of included studies (*Continued*)

Notes	Medication (bronchodilators, adrenergic stimulators or corticosteroids) was given in addition to the study drug to 83% of patients in azithromycin group and 82% in Co-amoxyclav group. Compliance was measured by pill count. All 99 randomized patients were evaluated for clinical efficacy.
Allocation concealment	C – Inadequate

Study	**Hoepelman 1998**
Methods	Location: The Netherlands, multicenter study Patients were randomized to received either azithromycin or co-amoxyclav. Double blind was performed with match placebo tablets. Clinical outcomes were evaluated on day 12-16
Participants	144 outpatients were recruited. 123 of them had Type I acute exacerbation of chronic bronchitis, 18 had acute purulent bronchitis and 3 had pneumonia. Patients with terminal illness, pregnant or lactating, were receiving concomitant antibiotics or had used antibiotics within 48 hours prior to the study treatment, had infectious mononucleosis, cystic fibrosis, or gastrointestinal abnormality that could affect absorption, were excluded. Participants: azithromycin group N = 72, co-amoxyclav group N = 72
Interventions	1. Azithromycin 500 mg once daily for 3 days 2. Co-amoxyclav 625 mg three times daily for 10 days
Outcomes	Clinical: cure, improvement, failure, relapse Microbiological: eradication, persistence, recurrence
Notes	Medication (bronchodilators, adrenergic stimulators, corticosteroids was given to 94% of patients in azithromycin group and 97% in co-amoxyclav group. Of 144 randomized patients, only patients diagnosed Type I acute exacerbation of chronic bronchitis (N = 123) were analysed
Allocation concealment	A – Adequate

Study	**Mertens 1992**
Methods	Location: The Netherlands. This study was a part of unpublished international multicenter study Patients were randomized to receive either azithromycin or amoxicillin. Block randomization was done by Pfizer-Euroclin, Brussels, Belgium. Double blind was performed with match placebo tablets. Patients were clinically evaluated on day 5-7 and 12-15
Participants	50 in-and out-patients aged 18 years or older with acute exacerbation of chronic bronchitis were recruited. Chronic bronchitis was clinically defined as 3 levels of severity. Type I exacerbation (most severe grade), Type II exacerbation (less severe grade) and Type III exacerbation (lease severe grade) Patients with terminal illness, concomitant use of antibiotics with in 48 hours prior to treatment were excluded. Participants: azithromycin group N = 25, amoxycillin N = 25
Interventions	1. Azithromycin 500 mg once daily for three days 2. Amoxicillin 500 mg three times daily for 5 days
Outcomes	Cure Improvement Failure Pathogen eradication
Notes	All 50 randomized patients were analyzed
Allocation concealment	A – Adequate

Study	**Sevieri 1993**
Methods	Location: Italy Patients were randomly assigned to treatment. The actual randomization is not clear. No description of blinding

Characteristics of included studies (*Continued*)

Participants	50 adult patients with acute purulent exacerbation of chronic bronchitis caused by H. Influenzae were recruited. Participants: azithromycin group N = 25, amoxicillin/clavulanic acid group N = 25
Interventions	1. Azithromycin 500 mg once daily for 3 days 2. Amoxicillin /clavulanic acid 1 gm twice daily for 6 days
Outcomes	Cure Pathogen eradication
Notes	All 50 randomized patients were clinically and bacteriological evaluated
Allocation concealment	D – Not used

Study	**Suping 2002**
Methods	Location: China Patients were assigned to treatments. The information of randomization generation, allocation concealment and blinding is not clear
Participants	80 hospitalized patients with acute purulent exacerbation of chronic bronchitis and aged more than 30 years. The patients having antibiotic within 48 hours and with known allergy to beta-lactam antibiotics, beta-lactamase inhibitors, serum creatinine > 200 mg/L, and immunosuppressant users were excluded. Participants: azithromycin group N = 38, amoxicillin/clavulanic group N = 42
Interventions	1. Azithromycin i.v. administration for 5 days, day 1 500 mg and day 2-5 250 mg qd 2. Amoxicillin/clavulanic acid i.v. administration for 7 days with 1.2 bid
Outcomes	Cure Improved Failure Adverse effect
Notes	
Allocation concealment	B – Unclear

Study	**Whitlock 1995**
Methods	Location: United States of America, multicenter study Patients were randomly assigned to treatment. Investigator-blinded, parallel-group study. Clinical evaluation was performed at 3 visits, day 5-7, day 11-14 and day 26-30
Participants	70 outpatients aged between 35 and 75 years with a clinical diagnosis of acute bacterial exacerbation of chronic bronchitis were recruited. Patients with pneumonia, bronchitis with concurrent bronchiectasis or active bronchial asthma, uses of antibiotics within 72 hours of enrolment were excluded Participants: azithromycin group N = 39, amoxycillin/clavulanate N = 31
Interventions	1. Azithromycin 500 mg once on day 1, followed by 250 mg daily on day 2-5 2. Amoxycillin/clavulanate 500 mg three times a day for 10 days
Outcomes	Cure (complete resolution of resolution of acute exacerbation of COPD on day 11) Improvement (incomplete resolution) Failure Relapse (day 28) Adverse events Eradication of pathogen (day 11) Recurrence of pathogen (day 28)
Notes	14 patients were excluded from clinical outcome analysis. 8 of 14 with reason had a resistant pathogen (azithromycin 6, amoxycillin/clavulanate 2), 6 had protocol violations (azithromycin 4, amoxycillin/clavulanate 2). Bacteriologic evaluation were performed in 37 patients who had baseline pathogen reported

Characteristics of included studies (*Continued*)

Allocation concealment	B – Unclear

Study	**Wubbel 1999**
Methods	Location: The US, Randomized, non-blinded trial Patients were randomized to receive either azithromycin or amoxycillin/clavulanate in patients aged 6 months to 5 years, and erythromycin in children aged older than 5 years. Patients were evaluated at enrolment and again at 2-3 and 10-37 day after the treatment started
Participants	88 patients with community-acquired pneumonia at the Children's Medical Center of Dallas aged 6 months to 16 years were enrolled. Participants aged 6 months to 5 years: azithromycin group N = 39, amoxy-clavulanic acid group N = 49
Interventions	1. Azithromycin oral suspension 10 mg/kg (maximum 500 mg) once on day 1, followed by 5 mg/kg (maximum 250 mg) once daily for 4 days 2. Conventional therapy, three times daily for 10 days (amoxicillin/clavulanic acid 40 mg/kg/day for patients aged 6 months to 5 years, and erythromycin estorate 40 mg/kg/day for children aged 5-16 years)
Outcomes	Cure Improvement Failure Adverse events
Notes	
Allocation concealment	D – Not used

Study	**Zachariah 1996**
Methods	Multicenter, double blinded trial. Patients were randomly assigned to treatment. Matched placebo tablets were given. Patients were assessed clinically on days 5 and 14
Participants	369 Patients aged 18 years or more diagnosed acute bronchitis, or acute infectious exacerbation of chronic bronchitis, or community-acquired pneumonia were recruited. Acute bronchitis was defined as the presence of purulent sputum together with fever, leucocytosis, and/or symptoms suggestive of lower respiratory tract infection. Pregnant and lactating women, patients with terminal illness, gastrointestinal or hepatic disorders, infectious mononucleosis, or had received prior antimicrobial treatment were excluded. Participants: azithromycin group N = 186, co-amoxyclav N = 183
Interventions	1. Azithromycin (Pfizer) 500 mg once daily for 3 days 2. Co-amoxyclav (augmentin; Smithkline Beecham) 375 mg three times daily for 10 days
Outcomes	Cure Improvement Failure Relapse Adverse events Eradication of pathogen
Notes	Of 369 randomized patients, 346 were clinically evaluated; 173 were in azithromycin group and 173 were in co-amoxyclav group. 193 patients who had baseline pathogen were bacteriologic evaluated
Allocation concealment	B – Unclear

i.v.: intravenously
qd: four times a day
bid: three times a day

Characteristics of excluded studies

Study	Reason for exclusion
Berry 1998	The in vitro study compared efficacies of azithromycin and other macrolides with amoxycillin-clavulanate against Streptococcus pneumoniae and Haemophilus influenzae
Bohte 1995	The study compared azithromycin with benzyl penicillin or erythromycin in community-acquired pneumonia
Bradbury 1993	The study compared azithromycin with clarithromycin
Ficnar 1997	The study compared different doses of azithromycin in the treatment of upper and lower respiratory tract infections
Gomez 1996	The comparators were amoxycillin or erythromycin. The data was analysed in overall results that not be able to get the information specific to amoxycillin
Laurent 1996	The study compared azithromycin with roxithromycin
Lauvau 1997	The study included patients with upper respiratory infections
Morandini 1993	The study compared azithromycin with roxithromycin
Rahav 2004	The study compared azithromycin with other antibiotics
Roord 1996	The study compared azithromycin with erythromycin

ANALYSES

Comparison 01. Azithromycin versus amoxillin or amoxycillin-clavulanate

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Clinical failure	15	2496	Relative Risk (Random) 95% CI	1.09 [0.64, 1.85]
02 Clinical failure by diagnosis			Relative Risk (Random) 95% CI	Subtotals only
03 Clinical failure by age group			Relative Risk (Random) 95% CI	Subtotals only
04 Clinical failure by dose regimen of azithromycin	12	2112	Relative Risk (Random) 95% CI	1.15 [0.60, 2.20]
05 Clinical failure by type of antibiotic in control group	15	2496	Relative Risk (Random) 95% CI	1.09 [0.64, 1.85]
06 Sensitivity analysis with excluding one large trial	14	1742	Relative Risk (Random) 95% CI	1.20 [0.69, 2.09]
07 Sensitivity analysis with the condition of concealment	15	2496	Relative Risk (Random) 95% CI	1.09 [0.64, 1.85]
08 Microbial eradication	12	961	Relative Risk (Random) 95% CI	0.95 [0.85, 1.05]
09 Adverse events	12	2406	Relative Risk (Random) 95% CI	0.76 [0.57, 1.00]

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Amoxicillin [*therapeutic use]; Amoxicillin-Potassium Clavulanate Combination [*therapeutic use]; Anti-Bacterial Agents [*therapeutic use]; Azithromycin [*therapeutic use]; Bronchitis [*drug therapy]; Drug Therapy, Combination; Pneumonia [*drug therapy]; Randomized Controlled Trials as Topic; Respiratory Tract Infections [drug therapy]; Treatment Failure

MeSH check words

Humans

COVER SHEET

Title Azithromycin for acute lower respiratory tract infections

Authors	Panpanich R, Lerttrakarnnon P, Laopaiboon M
Contribution of author(s)	Ratana Panpanich (RP) designed the protocol, identified studies and extracted data from the included studies and co-wrote the review. Peerasak Lerttrakarnnon (PL) co-wrote the review and extracted data from the included studies. Malinee Luopaiboon (ML) helped analyse data and prepared the final draft of this review. All review authors contributed to this updated review.
Issue protocol first published	2000/1
Review first published	2004/4
Date of most recent amendment	12 November 2007
Date of most recent SUBSTANTIVE amendment	01 October 2007
What's New	A trial from China (Suping 2002) in patients with acute exacerbation of chronic bronchitis comparing azithromycin with amoxyclav was added to this 2007 update. The conclucions remain unchanged.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	17 July 2007
Date authors' conclusions section amended	Information not supplied by author
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DOI	10.1002/14651858.CD001954.pub3
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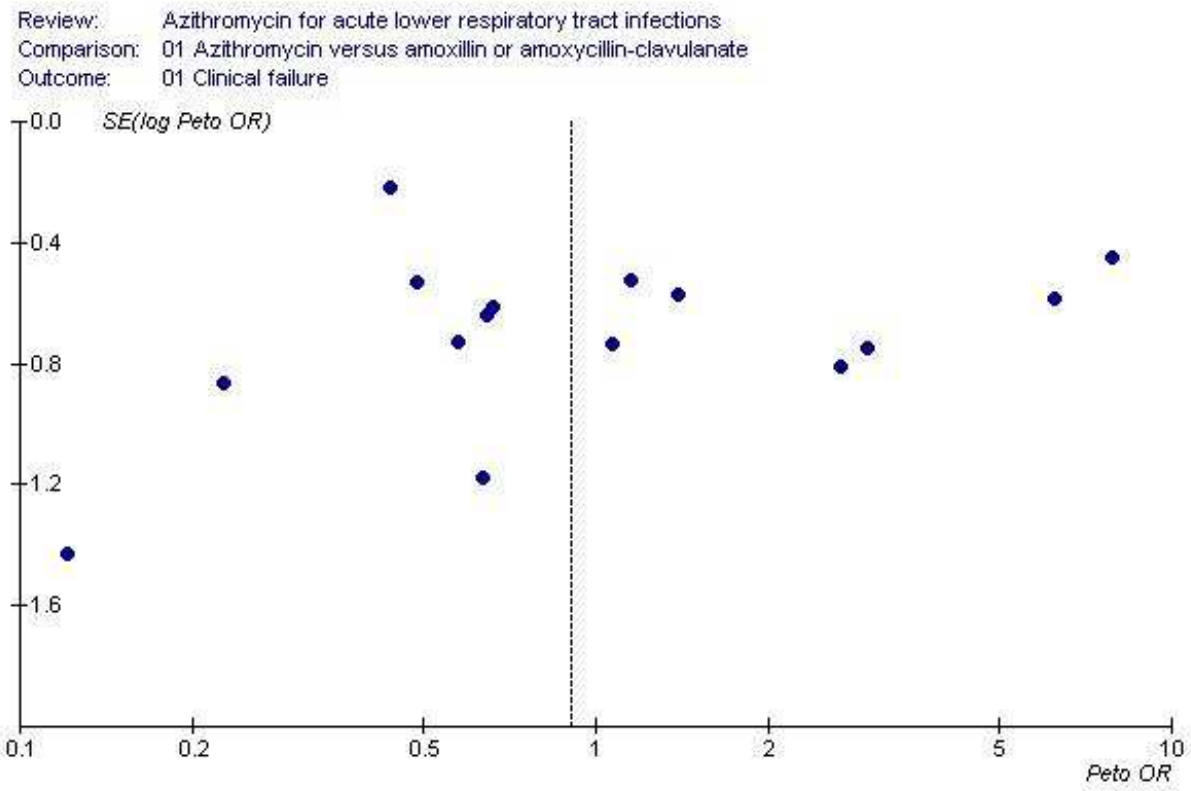
GRAPHS AND OTHER TABLES

Figure 01.



Analysis 01.01. Comparison 01 Azithromycin versus amoxillin or amoxycillin-clavulanate, Outcome 01 Clinical failure

Review: Azithromycin for acute lower respiratory tract infections

Comparison: 01 Azithromycin versus amoxillin or amoxycillin-clavulanate

Outcome: 01 Clinical failure

Study	Azithromycin n/N	Amoxy or amoxy-clav n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Balmes 1991	4/48	7/56		7.6	0.67 [0.21, 2.14]
Beghi 1995	22/69	2/73		6.5	11.64 [2.84, 47.65]
Biebuyck 1996	53/497	53/257		11.5	0.52 [0.36, 0.73]
Daniel 1991	5/121	10/120		8.2	0.50 [0.17, 1.41]
Ferwerda 2001	5/55	7/53		8.0	0.69 [0.23, 2.03]
Gris 1996	6/34	2/33		6.0	2.91 [0.63, 13.41]
Harris 1998	11/125	4/63		7.9	1.39 [0.46, 4.18]
Hoepelman 1993	4/48	4/51		6.8	1.06 [0.28, 4.01]
Hoepelman 1998	3/62	5/61		6.6	0.59 [0.15, 2.36]
Mertens 1992	1/25	5/25		4.2	0.20 [0.03, 1.59]
Sevieri 1993	5/25	2/25		5.9	2.50 [0.53, 11.70]
Suping 2002	12/38	2/42		6.4	6.63 [1.59, 27.74]
Whitlock 1995	0/29	2/27		2.5	0.19 [0.01, 3.72]
Wubbel 1999	1/39	2/49		3.5	0.63 [0.06, 6.68]
Zachariah 1996	8/173	7/173		8.5	1.14 [0.42, 3.08]
Total (95% CI)	**1388**	**1108**		**100.0**	**1.09 [0.64, 1.85]**

Total events: 140 (Azithromycin), 114 (Amoxy or amoxy-clav)

Test for heterogeneity chi-square=40.35 df=14 p=0.0002 I^2 =65.3%

Test for overall effect z=0.32 p=0.8

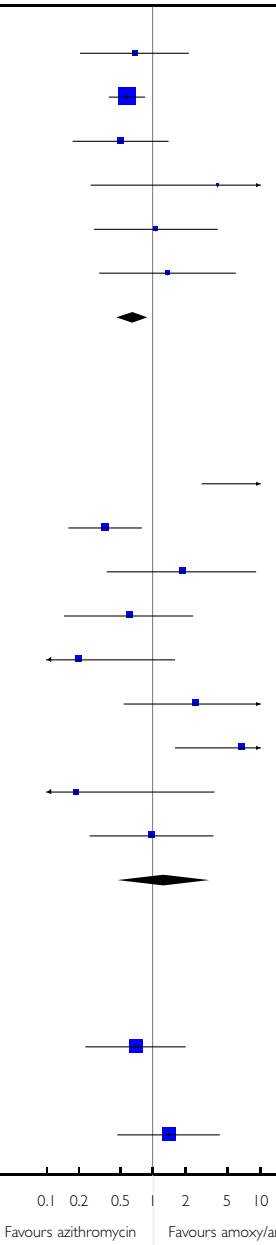
Analysis 01.02. Comparison 01 Azithromycin versus amoxillin or amoxycillin-clavulanate, Outcome 02 Clinical failure by diagnosis

Review: Azithromycin for acute lower respiratory tract infections

Comparison: 01 Azithromycin versus amoxillin or amoxycillin-clavulanate

Outcome: 02 Clinical failure by diagnosis

Study	Azithromycin n/N	Amoxy or amoxy-clav n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Acute bronchitis					
Balmes 1991	4/48	7/56		7.9	0.67 [0.21, 2.14]
Biebuyck 1996	44/404	41/213		69.8	0.57 [0.38, 0.84]
Daniel 1991	5/121	10/120		9.8	0.50 [0.17, 1.41]
Gris 1996	2/4	0/3		1.4	4.00 [0.26, 61.76]
Hoepelman 1993	4/48	4/51		6.1	1.06 [0.28, 4.01]
Zachariah 1996	4/113	3/115		4.9	1.36 [0.31, 5.93]
Subtotal (95% CI)	**738**	**558**		**100.0**	**0.63 [0.45, 0.88]**
Total events: 63 (Azithromycin), 65 (Amoxy or amoxy-clav)					
Test for heterogeneity chi-square=3.90 df=5 p=0.56 I^2 =0.0%					
Test for overall effect z=2.76 p=0.006					
02 Acute exacerbation of chronic bronchitis					
Beghi 1995	22/69	2/73		11.9	11.64 [2.84, 47.65]
Biebuyck 1996	9/93	12/44		14.3	0.35 [0.16, 0.78]
Gris 1996	4/28	2/26		11.0	1.86 [0.37, 9.30]
Hoepelman 1998	3/62	5/61		12.0	0.59 [0.15, 2.36]
Mertens 1992	1/25	5/25		9.2	0.20 [0.03, 1.59]
Sevieri 1993	5/25	2/25		11.3	2.50 [0.53, 11.70]
Suping 2002	12/38	2/42		11.8	6.63 [1.59, 27.74]
Whitlock 1995	0/29	2/27		6.4	0.19 [0.01, 3.72]
Zachariah 1996	4/59	4/57		12.2	0.97 [0.25, 3.68]
Subtotal (95% CI)	**428**	**380**		**100.0**	**1.24 [0.46, 3.32]**
Total events: 60 (Azithromycin), 36 (Amoxy or amoxy-clav)					
Test for heterogeneity chi-square=32.66 df=8 p=<0.0001 I^2 =75.5%					
Test for overall effect z=0.43 p=0.7					
03 Pneumonia					
Ferwerda 2001	5/55	7/53		46.0	0.69 [0.23, 2.03]
Gris 1996	0/2	0/4		0.0	Not estimable
Harris 1998	11/125	4/63		44.4	1.39 [0.46, 4.18]



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Study	Azithromycin n/N	Amoxy or amoxy-clav n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Wubbel 1999	1/39	2/49		9.7	0.63 [0.06, 6.68]
Zachariah 1996	0/1	0/1		0.0	Not estimable
Subtotal (95% CI)	**222**	**170**		**100.0**	**0.93 [0.45, 1.94]**
Total events: 17 (Azithromycin), 13 (Amoxy or amoxy-clav)					
Test for heterogeneity chi-square=0.91 df=2 p=0.64 I^2 =0.0%					
Test for overall effect z=0.19 p=0.8					

Analysis 01.03. Comparison 01 Azithromycin versus amoxillin or amoxycillin-clavulanate, Outcome 03 Clinical failure by age group

Review: Azithromycin for acute lower respiratory tract infections

Comparison: 01 Azithromycin versus amoxillin or amoxycillin-clavulanate

Outcome: 03 Clinical failure by age group

Study	Azithromycin n/N	Amoxy or amoxy-clav n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Adult					
Balmes 1991	4/48	7/56		9.3	0.67 [0.21, 2.14]
Beghi 1995	22/69	2/73		8.2	11.64 [2.84, 47.65]
Biebuyck 1996	53/497	53/257		12.9	0.52 [0.36, 0.73]
Daniel 1991	5/121	10/120		10.0	0.50 [0.17, 1.41]
Gris 1996	6/34	2/33		7.7	2.91 [0.63, 13.41]
Hoepelman 1993	4/48	4/51		8.6	1.06 [0.28, 4.01]
Hoepelman 1998	3/62	5/61		8.3	0.59 [0.15, 2.36]
Mertens 1992	1/25	5/25		5.6	0.20 [0.03, 1.59]
Sevieri 1993	5/25	2/25		7.6	2.50 [0.53, 11.70]
Suping 2002	12/38	2/42		8.1	6.63 [1.59, 27.74]
Whitlock 1995	0/29	2/27		3.5	0.19 [0.01, 3.72]
Zachariah 1996	8/173	7/173		10.2	1.14 [0.42, 3.08]
Subtotal (95% CI)	**1169**	**943**		**100.0**	**1.15 [0.60, 2.20]**
Total events: 123 (Azithromycin), 101 (Amoxy or amoxy-clav)					
Test for heterogeneity chi-square=39.39 df=11 p=<0.0001 I^2 =72.1%					
Test for overall effect z=0.42 p=0.7					

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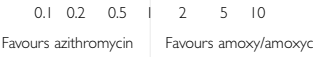
Study	Azithromycin n/N	Amoxy or amoxy-clav n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
02 Paediatric					
Ferwerda 2001	5/55	7/53		46.0	0.69 [0.23, 2.03]
Harris 1998	11/125	4/63		44.4	1.39 [0.46, 4.18]
Wubbel 1999	1/39	2/49		9.7	0.63 [0.06, 6.68]
Subtotal (95% CI)	**219**	**165**		**100.0**	**0.93 [0.45, 1.94]**
Total events: 17 (Azithromycin), 13 (Amoxy or amoxy-clav)					
Test for heterogeneity chi-square=0.91 df=2 p=0.64 I^2 =0.0%					
Test for overall effect z=0.19 p=0.8					



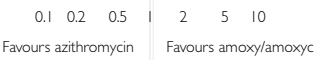
Analysis 01.04. Comparison 01 Azithromycin versus amoxillin or amoxycillin-clavulanate, Outcome 04 Clinical failure by dose regimen of azithromycin

Review: Azithromycin for acute lower respiratory tract infections

Comparison: 01 Azithromycin versus amoxillin or amoxycillin-clavulanate

Outcome: 04 Clinical failure by dose regimen of azithromycin

Study	Azithromycin n/N	Amoxy or amoxyclav n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 500 mg once daily x 3					
Beghi 1995	22/69	2/73		8.2	11.64 [2.84, 47.65]
Biebuyck 1996	53/497	53/257		12.9	0.52 [0.36, 0.73]
Gris 1996	6/34	2/33		7.7	2.91 [0.63, 13.41]
Hoepelman 1993	4/48	4/51		8.6	1.06 [0.28, 4.01]
Hoepelman 1998	3/62	5/61		8.3	0.59 [0.15, 2.36]
Mertens 1992	1/25	5/25		5.6	0.20 [0.03, 1.59]
Sevieri 1993	5/25	2/25		7.6	2.50 [0.53, 11.70]
Zachariah 1996	8/173	7/173		10.2	1.14 [0.42, 3.08]
Subtotal (95% CI)	**933**	**698**		**69.1**	**1.25 [0.55, 2.83]**
Total events: 102 (Azithromycin), 80 (Amoxy or amoxyclav)					
Test for heterogeneity chi-square=28.64 df=7 p=0.0002 I^2 =75.6%					
Test for overall effect z=0.54 p=0.6					
02 500 mg single dose followed by 250 mg on day 2-5					
Balmes 1991	4/48	7/56		9.3	0.67 [0.21, 2.14]



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Study	Azithromycin n/N	Amoxy or amoxyclav n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Daniel 1991	5/121	10/120		10.0	0.50 [0.17, 1.41]
Suping 2002	12/38	2/42		8.1	6.63 [1.59, 27.74]
Whitlock 1995	0/29	2/27		3.5	0.19 [0.01, 3.72]
Subtotal (95% CI)	**236**	**245**		**30.9**	**0.95 [0.25, 3.62]**
Total events: 21 (Azithromycin), 21 (Amoxy or amoxyclav)					
Test for heterogeneity chi-square=10.26 df=3 p=0.02 I^2 =70.8%					
Test for overall effect z=0.08 p=0.9					
Total (95% CI)	**1169**	**943**		**100.0**	**1.15 [0.60, 2.20]**
Total events: 123 (Azithromycin), 101 (Amoxy or amoxyclav)					
Test for heterogeneity chi-square=39.39 df=11 p=<0.0001 I^2 =72.1%					
Test for overall effect z=0.42 p=0.7					

Analysis 01.05. Comparison 01 Azithromycin versus amoxillin or amoxycillin-clavulanate, Outcome 05 Clinical failure by type of antibiotic in control group

Review: Azithromycin for acute lower respiratory tract infections

Comparison: 01 Azithromycin versus amoxillin or amoxycillin-clavulanate

Outcome: 05 Clinical failure by type of antibiotic in control group

Study	Azithromycin n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Amoxycillin					
Daniel 1991	5/121	10/120		8.2	0.50 [0.17, 1.41]
Mertens 1992	1/25	5/25		4.2	0.20 [0.03, 1.59]
Subtotal (95% CI)	**146**	**145**		**12.4**	**0.41 [0.16, 1.05]**
Total events: 6 (Azithromycin), 15 (Control)					
Test for heterogeneity chi-square=0.59 df=1 p=0.44 I^2 =0.0%					
Test for overall effect z=1.86 p=0.06					
02 Amoxyclav					
Balmes 1991	4/48	7/56		7.6	0.67 [0.21, 2.14]
Beghi 1995	22/69	2/73		6.5	11.64 [2.84, 47.65]
Biebuyck 1996	53/497	53/257		11.5	0.52 [0.36, 0.73]
Ferwerda 2001	5/55	7/53		8.0	0.69 [0.23, 2.03]
Gris 1996	6/34	2/33		6.0	2.91 [0.63, 13.41]

(*Continued* . . .)

(. . . *Continued*)

Study	Azithromycin n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Harris 1998	11/125	4/63		7.9	1.39 [0.46, 4.18]
Hoepelman 1993	4/48	4/51		6.8	1.06 [0.28, 4.01]
Hoepelman 1998	3/62	5/61		6.6	0.59 [0.15, 2.36]
Sevieri 1993	5/25	2/25		5.9	2.50 [0.53, 11.70]
Suping 2002	12/38	2/42		6.4	6.63 [1.59, 27.74]
Whitlock 1995	0/29	2/27		2.5	0.19 [0.01, 3.72]
Wubbel 1999	1/39	2/49		3.5	0.63 [0.06, 6.68]
Zachariah 1996	8/173	7/173		8.5	1.14 [0.42, 3.08]
Subtotal (95% CI)	**1242**	**963**		**87.6**	**1.28 [0.71, 2.30]**
Total events: 134 (Azithromycin), 99 (Control)					
Test for heterogeneity chi-square=38.22 df=12 p=0.0001 I^2 =68.6%					
Test for overall effect z=0.82 p=0.4					
Total (95% CI)	**1388**	**1108**		**100.0**	**1.09 [0.64, 1.85]**
Total events: 140 (Azithromycin), 114 (Control)					
Test for heterogeneity chi-square=40.35 df=14 p=0.0002 I^2 =65.3%					
Test for overall effect z=0.32 p=0.8					

Analysis 01.06. Comparison 01 Azithromycin versus amoxillin or amoxycillin-clavulanate, Outcome 06 Sensitivity analysis with excluding one large trial

Review: Azithromycin for acute lower respiratory tract infections

Comparison: 01 Azithromycin versus amoxillin or amoxycillin-clavulanate

Outcome: 06 Sensitivity analysis with excluding one large trial

Study	Azithromycin n/N	Amoxy or amoxyclav n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Balmes 1991	4/48	7/56		8.6	0.67 [0.21, 2.14]
Beghi 1995	22/69	2/73		7.3	11.64 [2.84, 47.65]
Daniel 1991	5/121	10/120		9.3	0.50 [0.17, 1.41]
Ferwerda 2001	5/55	7/53		9.1	0.69 [0.23, 2.03]
Gris 1996	6/34	2/33		6.8	2.91 [0.63, 13.41]
Harris 1998	11/125	4/63		8.9	1.39 [0.46, 4.18]
Hoepelman 1993	4/48	4/51		7.7	1.06 [0.28, 4.01]
Hoepelman 1998	3/62	5/61		7.4	0.59 [0.15, 2.36]
Mertens 1992	1/25	5/25		4.7	0.20 [0.03, 1.59]
Sevieri 1993	5/25	2/25		6.7	2.50 [0.53, 11.70]
Suping 2002	12/38	2/42		7.2	6.63 [1.59, 27.74]
Whitlock 1995	0/29	2/27		2.8	0.19 [0.01, 3.72]
Wubbel 1999	1/39	2/49		3.9	0.63 [0.06, 6.68]
Zachariah 1996	8/173	7/173		9.6	1.14 [0.42, 3.08]
Total (95% CI)	**891**	**851**		**100.0**	**1.20 [0.69, 2.09]**

Total events: 87 (Azithromycin), 61 (Amoxy or amoxyclav)

Test for heterogeneity chi-square=28.84 df=13 p=0.007 I^2 =54.9%

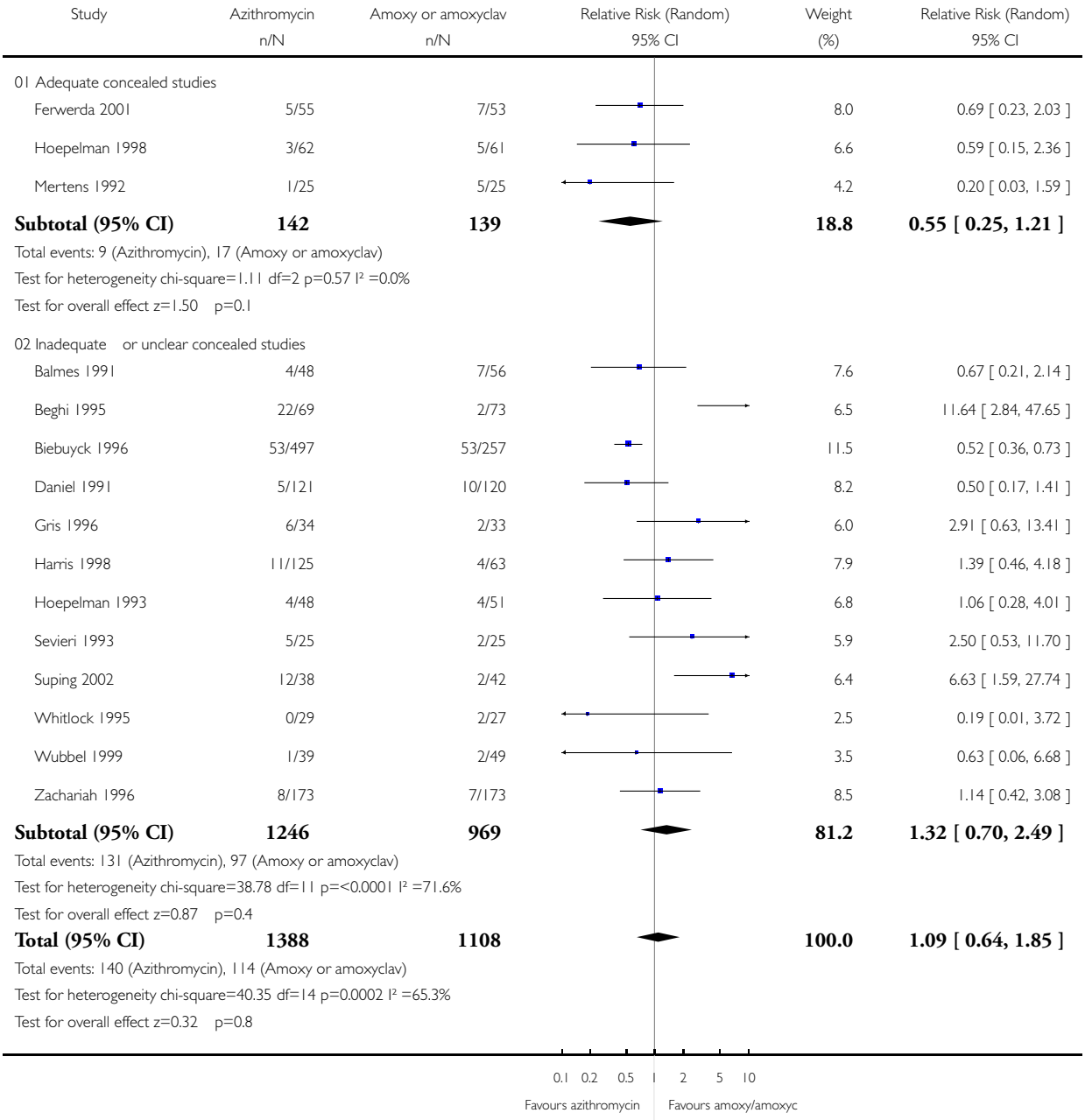
Test for overall effect z=0.64 p=0.5

Analysis 01.07. Comparison 01 Azithromycin versus amoxillin or amoxycillin-clavulanate, Outcome 07 Sensitivity analysis with the condition of concealment

Review: Azithromycin for acute lower respiratory tract infections

Comparison: 01 Azithromycin versus amoxillin or amoxycillin-clavulanate

Outcome: 07 Sensitivity analysis with the condition of concealment



Analysis 01.08. Comparison 01 Azithromycin versus amoxillin or amoxycillin-clavulanate, Outcome 08 Microbial eradication

Review: Azithromycin for acute lower respiratory tract infections

Comparison: 01 Azithromycin versus amoxillin or amoxycillin-clavulanate

Outcome: 08 Microbial eradication

Study	Azithromycin n/N	Amoxy or amoxy-clav n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Balmes 1991	29/32	25/28		11.6	1.02 [0.86, 1.20]
Beghi 1995	20/69	25/73		3.4	0.85 [0.52, 1.38]
Daniel 1991	31/41	39/46		9.8	0.89 [0.72, 1.10]
Gris 1996	9/10	16/16		10.0	0.90 [0.73, 1.11]
Harris 1998	35/40	16/19		9.2	1.04 [0.83, 1.30]
Hoepelman 1993	15/48	13/51		2.2	1.23 [0.65, 2.30]
Hoepelman 1998	26/60	26/59		4.5	0.98 [0.65, 1.48]
Mertens 1992	13/25	10/25		2.4	1.30 [0.71, 2.39]
Sevieri 1993	21/25	24/25		10.8	0.88 [0.72, 1.06]
Suping 2002	26/38	40/42		9.3	0.72 [0.57, 0.90]
Whitlock 1995	19/21	11/12		9.5	0.99 [0.79, 1.23]
Zachariah 1996	82/82	73/74		17.2	1.01 [0.99, 1.04]
Total (95% CI)	**491**	**470**		**100.0**	**0.95 [0.85, 1.05]**

Total events: 326 (Azithromycin), 318 (Amoxy or amoxy-clav)

Test for heterogeneity chi-square=30.91 df=11 p=0.001 I^2 =64.4%

Test for overall effect z=1.10 p=0.3

Analysis 01.09. Comparison 01 Azithromycin versus amoxillin or amoxycillin-clavulanate, Outcome 09 Adverse events

Review: Azithromycin for acute lower respiratory tract infections

Comparison: 01 Azithromycin versus amoxillin or amoxycillin-clavulanate

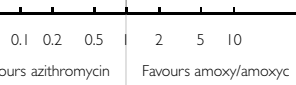
Outcome: 09 Adverse events

Study	Azithromycin n/N	Amoxy or amoxy-clav n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Balmes 1991	3/48	7/56		3.6	0.50 [0.14, 1.83]
Beghi 1995	1/69	1/69		1.0	1.00 [0.06, 15.67]
Biebuyck 1996	98/501	72/258		15.4	0.70 [0.54, 0.91]
Daniel 1991	18/125	28/126		10.7	0.65 [0.38, 1.11]
Ferwerda 2001	33/59	41/58		15.1	0.79 [0.60, 1.05]
Gris 1996	5/41	5/37		4.3	0.90 [0.28, 2.87]
Harris 1998	18/147	30/71		11.1	0.29 [0.17, 0.48]
Hoepelman 1993	16/48	6/51		6.6	2.83 [1.21, 6.64]
Hoepelman 1998	25/62	22/61		12.1	1.12 [0.71, 1.76]
Suping 2002	3/38	3/42		2.7	1.11 [0.24, 5.15]
Whitlock 1995	11/39	12/31		8.7	0.73 [0.37, 1.42]
Zachariah 1996	13/186	19/183		8.7	0.67 [0.34, 1.32]
Total (95% CI)	**1363**	**1043**		**100.0**	**0.76 [0.57, 1.00]**

Total events: 244 (Azithromycin), 246 (Amoxy or amoxy-clav)

Test for heterogeneity chi-square=27.16 df=11 p=0.004 I^2 =59.5%

Test for overall effect z=1.98 p=0.05



Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery (Review)

Swadpanich U, Lumbiganon P, Prasertcharoensook W, Laopaiboon M

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[Intervention review]

Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery

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ABSTRACT

Background

Preterm birth is birth before 37 weeks' gestation. Genital tract infection is one of the causes of preterm birth. Infection screening during pregnancy has been used to reduce preterm birth. However, infection screening may have some adverse effects, e.g. increased antibiotic drug resistance, increased costs of treatment.

Objectives

To assess the effectiveness and complications of antenatal lower genital tract infection screening and treatment programs in reducing preterm birth and subsequent morbidity.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (January 2008) and the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2007, Issue 2).

Selection criteria

We included all published and unpublished randomised controlled trials in any language that evaluated any described methods of antenatal lower genital tract infection screening compared with no screening. Preterm births have been reported as an outcome.

Data collection and analysis

Two review authors independently assessed eligibility, trial quality and extracted data.

Main results

One study (4155 women) met the inclusion criteria. This trial is of high methodological quality. In the intervention group (2058 women), the results of infection screening and treatment for bacterial vaginosis, trichomonas vaginalis and candidiasis were reported; in the control group (2097 women), the results of the screening program for the women allocated to receive routine antenatal care were

not reported. Preterm birth before 37 weeks was significantly lower in the intervention group (3% versus 5% in the control group) with a relative risk (RR) of 0.55 (95% confidence interval (CI) 0.41 to 0.75). The incidence of preterm birth for low birthweight preterm infants with a weight equal to or below 2500 g and very low birthweight infants with a weight equal to or below 1500 g were significantly lower in the intervention group than in the control group (RR 0.48, 95% CI 0.34 to 0.66 and RR 0.34; 95% CI 0.15 to 0.75, respectively).

Authors' conclusions

There is evidence that infection screening and treatment programs in pregnant women may reduce preterm birth and preterm low birthweights. Future trials should evaluate the effects of types of infection screening program, gestational ages at screening test and the costs of introducing an infection screening program.

PLAIN LANGUAGE SUMMARY

Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery

A genital tract infection during pregnancy can cross into the amniotic fluid and result in prelabour rupture of the membranes and preterm labour. Such infections include bacterial vaginosis; chlamydial, trichomonas and gonorrhoeal infections; syphilis and HIV, but not candida. Preterm birth (before 37 weeks of gestation) is associated with poor infant health and early deaths, admission of the newborn to neonatal intensive care in the first few weeks of life, prolonged hospital stay and long-term neurologic disability including cerebral palsy.

The present systematic review found that a simple infection screening and treatment program during routine antenatal care may reduce preterm births and preterm low (below 2500 g) and very low (below 1500 g) birthweights, from only one identified controlled study. The study was of high methodological quality and reported on 4155 women randomly assigned either to an intervention group where the results of infection screening were reported or a control group where the results of the vaginal smear test were not reported. The simple infection screening reduced preterm births from 5% of women in the control group to 3% in the intervention group. The number of low birthweight preterm infants and very low birthweight infants were significantly lower in the intervention group than in the control group. Neonatal morbidity or deaths in the hospitalisation period were not reported. No adverse effects were reported for the pregnant women during the treatment. Women in the intervention group who were found to have vaginal infection received standard treatment and blinding of the treatment was not possible. The obstetricians may, therefore, have provided a different level of care to women in whom an infection had been identified compared with the control group.

BACKGROUND

Preterm birth, defined as birth occurring prior to 37 weeks' gestation, occurs in 5% to 10% of all pregnancies and is the most common cause of perinatal morbidity and mortality in the world. Moreover, preterm birth is implicated in at least two-thirds of early infant deaths (Cunningham 1997) and causes 60% of perinatal mortality and nearly half of long-term neurologic disability, including cerebral palsy, and is associated with admission to neonatal intensive care, severe morbidity in the first weeks of life, prolonged hospital stay after birth, and readmission to hospital in the first year of life (Cunningham 2001; Goldenberg 1998; Roberts 2000; Wood 2000). Surviving infants, especially those born before 32 weeks, have a substantially increased risk of chronic lung disease, and major and minor impairments (Doyle 1996; Saigal 2000). Whatever the result, the emotional impact on the family can be enormous.

A wide spectrum of causes and demographic factors have been implicated in the birth of preterm infants. These can be categorized into four groups:

1. medical and obstetric complications: there are associations with placental hemorrhage and hypertensive disorders in about one-third of cases (Meis 1995);
2. lifestyle factors: there is an association with alcohol abuse, low maternal age, and occupational factors (Henriksen 1995; Holzman 1995; Satin 1994);
3. amniotic fluid infection caused by a variety of micro-organisms located in the genital tract: approximately one-third of preterm births are associated with chorioamniotic infection (Lettieri 1993); and
4. asymptomatic cervical dilatation (Papiernik 1986).

Many micro-organisms cause both symptomatic and asymptomatic infection and may result in preterm prelabour rupture of membranes, preterm labour, or both. For example,

bacterial vaginosis (including *Gardnerella vaginalis*, *Bacteroides* species, *Mobiluncus* species, Ureaplasma urealyticum, and Mycoplasma hominis) (Hillier 1995; McDonald 1994; McGregor 1990; Meis 1995), Chlamydia trachomatis (Gravett 1986), Trichomonas vaginalis (Cotch 1997), Neisseria gonorrhoeae (Elliott 1990), Group B streptococci (Regan 1981), Staphylococcus aureus (McGregor 1990), syphilis (McFarlin 1995), HIV (Temmerman 1994), enteropharyngeal bacteria and Peptostreptococcus species (McDonald 1994) have been associated with an increased risk of preterm birth. Candida species, however, has not been associated with preterm birth (Cotch 1998).

A possible mechanism for the link between infection and preterm birth is the bacterial stimulation of the biosynthesis of prostaglandins, either directly via phospholipase $A_2$and C (Bejar 1981) or bacterial endotoxin introduced into the amniotic fluid stimulating decidual cells to produce cytokines and prostaglandins that initiate labour (Cox 1989). Indirect links via substances such as interleukin-1, tumour necrosis factor and platelet activating factor, all of which may be found in infected amniotic fluid, have also been identified (Romero 1992; Yoon 2000).

A program of screening for and treating asymptomatic vaginal infections has been associated with a reduction in preterm birth (Kiss 2006). There are differences in the screening methods of different types of organisms. There is scant evidence that can be used to determine the optimal screening regimen appropriate for each organism in pregnancy. Therefore, it is unclear whether all women should be routinely screened, how often the screening should occur, and which tests should be used.

Chlamydia trachomatis has been identified by multiple tests from different specimen sources. The tests may be analysed by three types of DNA-based test: ligase chain reaction, polymerase chain reaction (PCR) and enzyme immuno-assay (Watson 2002). DNA amplification techniques are providing highly sensitive and specific tests (Black 1997). The screening test can detect Chlamydia on genital secretions, urine specimens, endocervical and vaginal or urethral samples (Domeika 1999; Shrier 2004). Nucleic acid amplification tests are more sensitive than cell culture (Jespersen 2005).

Trichomoniasis may be asymptomatic in up to 50% of infected women (Wolner-Hanssen 1989). The diagnosis is usually made on clinical findings and laboratory procedures (Petrin 1998) such as direct microscopy and culture. The gold standard for diagnosis of trichomoniasis is a culture (Borchardt 1991). Most frequently, the saline wet-mount preparation is used for observation of motile organisms under the light microscope. Wet-mount smear is a cheap and quick method but more sensitive techniques are culture, immunofluorescence and enzyme immunoassay (Lossick 1991). Different staining techniques include Gram stain, Giemsa stain, Papanicolaou smear, acridine orange (Borchardt 1991; Rein 1990), and diverse molecularly-based diagnostic methods (hybridization assay and PCR). These vary widely in sensitivities and specificities for screening Trichomoniasis (DeMeo 1996; Madico 1998; Mayta 2000; Muresu 1994).

Bacterial vaginosis is a clinical syndrome; the microbiology of bacterial vaginosis is complex and is composed of Gardnerella vaginalis, Mycoplasma hominis and anaerobic bacteria (Amsel 1983). The diagnosis is usually made on clinical Amsel criteria findings (Amsel 1983) and laboratory tests. Vaginal pH testing may be a valuable screening tool as it is a quick and inexpensive test (Gjerdingen 2000). Vaginal swab Gram stain with quantification of the microbial flora has high sensitivity and specificity and is accepted as an alternative method (Nugent 1991).

Screening tests for other organisms including syphilis have been identified by multiple tests. Screening tests such as Treponema pallidum hemagglutination assay, Treponema pallidum particle agglutination assay, and enzyme-linked immunosorbent assays (ELISAs) are more reliable than Venereal Disease Research Laboratory testing, the fluorescent treponemal antibody absorption test, and immunoblot assays (Muller 2006). The screening test for Neisseria gonorrhoeae, usually made from a culture, remains accurate when transport conditions are suitable. The tests could be used with cervical, urine and vaginal swabs. DNA amplification techniques provide highly sensitive and specific tests (Carroll 1998; Koumans 1998; Livengood 2001). Diagnosis of HIV infection can be obtained from enzyme-linked immunosorbent assay (ELISA), Western blot, and RNA PCR testing (Kleinman 1998). The HIV-p24 Ag was tested for early diagnosis of an acute HIV infection (Thies 1994). Strategies for the diagnosis of Group B streptococcus (GBS) include obtaining vaginal or both vaginal and anorectal GBS cultures (Quinlan 2000) and a rapid enrichment cum antigen detection test (Das 2003).

Other Cochrane protocols and reviews have addressed a number of issues regarding treatment of infection in pregnancy. Antibiotic treatment of chlamydial, trichomonas, bacterial vaginosis and gonorrhoeal infection in pregnancy appears to be effective to clear organisms (Brocklehurst 1998; Brocklehurst 2002; Gülmezoglu 2002; McDonald 2007) but it is not known whether treatment of trichomonas will have any effect on pregnancy outcomes (Gülmezoglu 2002). There is little evidence to show that screening and treatment in all asymptomatic pregnant women for bacterial vaginosis can prevent preterm birth (McDonald 2007). Antibiotic prophylaxis in pregnancies with a previous preterm birth associated with bacterial vaginosis can reduce preterm delivery (Thinkhamrop 2002). There is insufficient evidence to treat ureaplasmas to reduce preterm birth (Raynes-Greenow 2004). There is no evidence that antiretrovirals and the treatment of syphilis influence the incidence of premature delivery (Volmink 2007; Walker 2001). None of these reviews are concerned primarily with the screening program for antenatal lower genital tract infection. There is unclear evidence for the effectiveness of screening programs of lower genital tract infection to prevent preterm birth.

OBJECTIVES

To assess the effectiveness and complications of antenatal lower genital tract infection screening and treatment programs in reducing preterm birth and subsequent morbidity.

METHODS

Criteria for considering studies for this review

Types of studies

We included all published and unpublished randomised controlled trials evaluating any described method of antenatal lower genital tract infection screening.

Types of participants

Pregnant women with a gestational age of less than 37 weeks, who are not in labour, have no vaginal bleeding and are without symptoms of lower genital tract infection.

Types of interventions

Any lower genital tract infection screening and treatment programs compared with no screening. The infection screening programs are defined as screening tests such as wet mount, Gram stain and culture of vaginal secretions and are followed by appropriate treatment after a positive screening test, or a screening test followed by no treatment after a negative screening test. No screening is defined as pregnant women receiving routine antenatal care but without being given a screening program.

Types of outcome measures

Primary outcomes

1. Preterm birth (less than 37 weeks)

Secondary outcomes

1. Low birthweight (LBW) less than 2500 g
2. Very LBW less than 1500 g (not prespecified)
3. Neonatal morbidity: sepsis, respiratory distress syndrome, intraventricular haemorrhage, necrotizing enterocolitis, seizures
4. Duration of admission to neonatal intensive care unit or hospital
5. Death: stillbirth, neonatal mortality, infant mortality
6. Side-effects of treatment including drug resistance
7. Persistent infection
8. Recurrent infection
9. Failure of treatment
10. Economic analysis (cost effectiveness, cost utility)
11. False positive/negative result of the screening program
12. Women's 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 (January 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 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.

In addition, we searched the CENTRAL (*The Cochrane Library 2007,* Issue 2) using the search strategy detailed in Appendix 1

Searching other resources

We did not identify any additional or ongoing trials from personal communication. We searched the reference lists of trials and review articles identified.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Using the inclusion criteria, one review author, Ussanee Swadpanich (US),assessed all studies for inclusion in the review, and a second author, Witoon Prasertcharoensook (WP), independently duplicated the process. There were no disagreements.

Data extraction and management

We used the Cochrane Pregnancy and Childbirth Group's data extraction template to extract data. Both authors extracted the data

using the agreed form. There were no discrepancies. We used the Review Manager software (RevMan 2003) to enter the data.
If any of the information regarding any of the above was inadequate, we attempted to contact authors of the original reports to provide further details.

Assessment of methodological quality of included studies

We assessed the validity of each 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 randomisation sequence for the trial in the 'Characteristics of included studies' table.

(1) Selection bias (randomisation and allocation concealment)

We assigned 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) Attrition bias (loss of participants - for example, 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.
We will exclude the trials that have more than 20% loss of participants because of the risk of bias.

(3) Performance bias (blinding of participants, researchers and outcome assessment)

We assessed 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).
The one identified trial scored an A when rating selection bias and attrition bias.

Measures of treatment effect

We carried out statistical analysis using RevMan 2003. We presented dichotomous results as summary relative risks with 95% confidence intervals (CIs).

If we had identified more than one trial for continuous outcomes (such as duration of admission to neonatal intensive care unit or hospital), we would have presented weighted mean difference with 95% CIs if the outcomes were measured in the same way between trials. We would have used the standardised mean difference to combine trials that measured the same outcome, but used different methods. We would have conducted a fixed-effect meta-analysis for combining data in the absence of significant heterogeneity if trials were sufficiently similar. If heterogeneity had been found, we would have explored this by a sensitivity analysis followed by random-effects if required.
If we find more trials in the future, we will use the methods we prespecified in the published protocol: *see* Table 1.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
The searches identified three potential publications. Two trials (Gjerdingen 2000; McGregor 1995) were excluded due to the participants not meeting the inclusion criteria and not being randomised controlled trials (*see* table of 'Characteristics of excluded studies').
One included article (Kiss 2004) reported a randomised controlled trial designed to evaluate a vaginal infection screening strategy for prevention of preterm delivery in a general population of pregnant women. A total of 4155 pregnant women presenting for their routine prenatal visit without subjective complaints were randomised to either the intervention (n = 2058) or the control group (n = 2097). All women were screened by Gram stain for asymptomatic vaginal infection. For the intervention group, women found to have vaginal infection received standard treatment. For the control group, vaginal smear test results were not revealed so the standard antenatal care program could not be influenced.

Risk of bias in included studies

Of the 4429 pregnant women who were randomised, 274 were excluded (140 lost to follow up; 68 did not fulfil all the inclusion criteria; 66 had multiple pregnancies).
Blinding of the treatment was not possible in the intervention group, but the vaginal smears were diagnosed in a central laboratory using the Nugent scoring system (Nugent 1991). This method of blinding permitted the risk of detection bias; the obstetricians may have provided a different level of care to women in the intervention group in whom an infection had been identified.

Effects of interventions

We identified a single randomised controlled trial comparing antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery with no screening program. A total of 4429 women were randomised with 274 women excluded from the analysis. In the intervention group (2058 women), the results of infection screening and treatment for bacterial vaginosis, trichomonas vaginalis and candidiasis were reported; in the control group (2097 women), the results of the screening program for the women allocated to receive routine antenatal care were not reported. There was a statistically significant difference for preterm birth before 37 weeks between the two groups (relative risk (RR) 0.55, 95% confidence interval (CI) 0.41 to 0.75).

For secondary outcomes, preterm low birthweight infants (weight equal to or below 2500 g) and preterm very low birthweight infants (weight equal to or below 1500 g) were significantly lower in the intervention group than in the control group (RR 0.48, 95% CI 0.34 to 0.66 and RR 0.34, 95% CI 0.15 to 0.75, respectively). None of the women reported adverse effects during the treatment period.

DISCUSSION

There is currently only one trial that meets our inclusion criteria (Kiss 2004) The results indicate statistically significant lower preterm births in the intervention (screening and treatment) group. Low birthweight preterm births (below 2500 g) and very low birthweight (below 1500 g) were also significantly reduced in the intervention group. There was no information about adverse effects.

The results of this review are based on the evidence from one trial, assessed as being of high quality according to allocation concealment (see 'Methodological quality of included studies'). The strength of this review was that the included trial was a large multicentre prospective, randomized controlled trial. There was a clear sample-size calculation and an adequate number of participants were available for the analysis. However, around 3.2% of all randomized women (140/4429) were lost to follow up without the information of whether the loss to follow up rate was balance between the two groups. Not blinding participants and outcome assessors might create bias in providing different care between the two groups.

The included trial was conducted in a developed country (Austria) where characteristics of the population, e.g., incidences and pattern of lower genital tract infections and socioeconomic status, etc, might be different from other countries. Therefore, the results of this review might not be generalized to all pregnant women. Further trials in different population especially in developing countries are needed to confirm the results.

AUTHORS' CONCLUSIONS

Implications for practice

Integrating a simple infection screening and treatment program into routine antenatal care may reduce preterm births in a general population of pregnant women. However, based on the evidence reviewed, we are not able to determine the effects of recurrent or persistent infection on preterm birth. Healthcare providers should discuss the potential benefits and harms of infection screening and tailor them to meet the specific needs of each care setting and healthcare system, or both.

Implications for research

Further randomised controlled trials are needed to determine:

(1) the effects of infection screening programs (at different gestational ages, types of infection screening, number of screening test, in different population, e.g. developing countries);

(2) provide an economic analysis of infection screening programs.

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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), 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*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Kiss 2004

Methods	Randomised trial with allocation concealed according to computer-generated randomisation list. Participant blinding: control group only blinded to test results. Description of withdrawals: yes. Intention-to-treat analysis: not used.
Participants	4429 pregnant women (mean age 28.9, SD 5.6) presenting for routine prenatal visits between 15 and 19 weeks' gestation (mean 17, SD 1.6). Intervention group: 2058 pregnant women; control group: 2097 pregnant women. Inclusion criteria: gestational age 15-19 weeks without subjective complaints (e.g., contractions and vaginal bleeding). Exclusion criteria: clinical symptoms of vaginal infection, multiple pregnancies. Location: Vienna, Austria.
Interventions	Intervention group: vaginal smears (Gram stain and evaluated by the scoring criteria proposed by Nugent 1991) screening for Bacterial vaginosis, Trichomonas vaginalis and Candida species and received standard antibiotic treatment if positive screening test, i.e., 2% for six days local clindamycin for bacterial vaginosis, 300 mg twice daily for seven days oral clindamycin for recurrent bacterial vaginosis, 0.1 g for six days local clotrimazole for candidiasis, and 500 mg for seven days local metronidazole for trichomoniasis and included treatment of the partner. Control group: were smeared, but the results of testing were not made available to the women's care providers and did not have any effect on the standard clinical antenatal care program routine antenatal examination.
Outcomes	Primary outcome: spontaneous preterm delivery GA less than 37 weeks. Secondary outcomes: 1. low birthweight: preterm birth with birthweights below 2500 g; 2. very low birthweight: preterm birth with birthweight below 1500 g; 3. rates of miscarriage between 16-22 and 20-24 weeks; 4. intrauterine death;

Kiss 2004 (*Continued*)

5. prevalence of various forms of vaginal infections;
6. duration of sick leave and hospitalisation.

Notes	4429 randomised, 274 excluded from analysis, 140 lost to follow up, 68 did not fulfil all inclusion criteria, 66 multiple pregnancies. We have contacted the author and are waiting for a reply for our request for additional data (secondary outcomes e.g. neonatal necrotizing enterocolitis, neonatal sepsis, neonatal death, duration of neonatal admission to NICU/hospital) from the authors. We will incorporate these additional data, along with the economic data from a secondary report of this trial (Kiss 2006), in an update to the review.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

GA: gestational age
NICU: neonatal intensive care unit
SD: standard deviation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Gjerdingen 2000	Participants did not meet inclusion criteria. Study compared standard prenatal care including routine inquiry about vaginal symptoms versus standard care supplemented by vaginal pH testing. Both arms had pregnant women who were diagnosed with lower genital tract infection and all participants received vaginal pH screening. Participants: 121 pregnant women with or without vaginal infection symptoms. Intervention: vaginal pH testing. Outcomes: bacterial vaginosis detection rate, preterm deliveries.
McGregor 1995	Methods not clearly described, but seems likely that this was not a randomised controlled trial. Described as a prospective observational trial. Participants: 1260 women. Intervention: lower genital tract micro-organisms screening (vaginal fluid enzyme; nonspecific protease, sialidase, phospholipase C, phospholipase A2). Outcomes: preterm birth, early pregnancy loss.

DATA AND ANALYSES

Comparison 1. Lower genital tract infection screening versus no screening

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Preterm birth less than 37 weeks	1	4155	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.41, 0.75]
2 Preterm low birthweight (below or equal 2500 g)	1	4155	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.34, 0.66]
3 Preterm very low birthweight (below or equal 1500 g)	1	4155	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.15, 0.75]
4 Neonatal morbidity	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Duration of admission to neonatal intensive care unit/hospital	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
6 Neonatal death	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Side-effects of treatment (including drug resistance)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8 Persistent infection	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Recurrent infection	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Economic analysis	0		Economic analysis (Fixed, 95% CI)	Not estimable
11 Faise positive/negative of the screening program	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
12 Women's satisfaction	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable

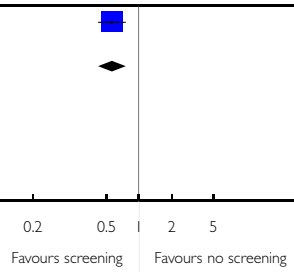
Analysis 1.1. Comparison 1 Lower genital tract infection screening versus no screening, Outcome 1 Preterm birth less than 37 weeks.

Review: Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery

Comparison: 1 Lower genital tract infection screening versus no screening

Outcome: 1 Preterm birth less than 37 weeks

Study or subgroup	Infection screening n/N	No screening n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kiss 2004	61/2058	112/2097		100.0 %	0.55 [0.41, 0.75]
Total (95% CI)	2058	2097		100.0 %	0.55 [0.41, 0.75]
Total events: 61 (Infection screening), 112 (No screening)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.77 (P = 0.00016)					



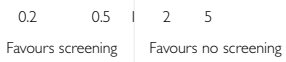
Analysis 1.2. Comparison 1 Lower genital tract infection screening versus no screening, Outcome 2 Preterm low birthweight (below or equal 2500 g).

Review: Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery

Comparison: 1 Lower genital tract infection screening versus no screening

Outcome: 2 Preterm low birthweight (below or equal 2500 g)

Study or subgroup	infection screening n/N	No screening n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kiss 2004	50/2058	107/2097		100.0 %	0.48 [0.34, 0.66]
Total (95% CI)	2058	2097		100.0 %	0.48 [0.34, 0.66]
Total events: 50 (infection screening), 107 (No screening)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.40 (P = 0.000011)					



Analysis 1.3. Comparison 1 Lower genital tract infection screening versus no screening, Outcome 3 Preterm very low birthweight (below or equal 1500 g).

Review: Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery

Comparison: 1 Lower genital tract infection screening versus no screening

Outcome: 3 Preterm very low birthweight (below or equal 1500 g)

Study or subgroup	Infection screening n/N	No screening n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kiss 2004	8/2058	24/2097		100.0 %	0.34 [0.15, 0.75]
Total (95% CI)	2058	2097		100.0 %	0.34 [0.15, 0.75]
Total events: 8 (Infection screening), 24 (No screening)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.65 (P = 0.0080)					

APPENDICES

Appendix 1. CENTRAL search strategy

#1 Pregnancy (explode MeSH)
#2 Pregnancy Complications (explode MeSH)
#3 pregnan*
#4 (preterm or premature) near (labour or labor)
#5 Infection (explode MeSH)
#6 infect*
#7 Mass Screening (explode MeSH)
#8 screen*

#9 (#1 or #2 or #3 or #4)
#10 (#5 or #6)
#11 (7 or #8)
#12 (#9 and #10 and #11)

Appendix 2. Methods to be used

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials, in which the unit of randomisation was a group of participants rather than individual participants, 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 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-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.

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-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

If we have a large number of trials included, we will conduct planned subgroup analyses classifying whole trials by interaction tests as described by Deeks 2001. We are aware of different screening methods and treatment practices for the same micro-organisms. If we have a large number of included trials, we will do subgroup analyses related to the same screening method following the same treatment practice for each type of organism. However, if we have a small number of trials, we will describe each trial with different screening and treatment practices separately.We plan to carry out the following subgroup analyses:
(a) studies which screened and treated the same infection, e.g. bacterial vaginosis;
(b) types of abnormal vaginal flora compared with each other;
(c) recurrent infection versus persistent infection;
(d) singleton versus multiple pregnancy;
(e) gestational age at screening (less than 12, 13 to 27, 28 to 36 weeks);
(f) effect of treatment of various abnormal vaginal flora on preterm birth rate;
(g) low-income and high-income settings;
(h) screening following with treatment versus screening following without treatment.

Sensitivity analyses

We will carry out sensitivity analyses to explore the effect of trial quality. This will involve analyses based on an A, B, C, or D rating of selection bias and attrition bias. We will exclude studies of poor quality from the analyses (those rated B, C, or D) in order to assess any substantive difference to the overall result. We will then analyse the impact the inclusion of quasi-controlled trials has had on trial

quality. 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.

WHAT'S NEW

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Date	Event	Description
15 February 2008	Minor change that doesn't fit any of the other events	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

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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 Medicine, Khon Kaen, Thailand.
- Khon Kaen University, Faculty of Public Health, Thailand.

External sources

- Thai Cochrane Network, Thailand.
- Thailand Research Fund (Senior Research Scholar), Thailand.

รายชื่อกลุ่มวิจัยเก่า

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หมายเหตุ

สังกัด ให้ใส่รายละเอียดที่อยู่ต้นสังกัด เช่น ภาควิชา / คณะ / มหาวิทยาลัย

สถานภาพปัจจุบัน - ยังอยู่ในโครงการหรือไม่ หากไม่อยู่ในโครงการแล้ว ให้ระบุหน่วยงานใหม่ด้วย

- หากเริ่มเข้าโครงการเป็นนักศึกษาปริญญาเอก ปริญญาโท หรือปริญญาตรี ให้ระบุปัจจุบันสำเร็จการศึกษาหรือยังไม่สำเร็จการศึกษา

รายชื่อกลุ่มวิจัยใหม่

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18. พญ. เกศนี บุณยวัฒนางกุล	พยาบาลชำนาญการ	โรงพยาบาลศรีนครินทร์ คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	พยาบาลชำนาญการ	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
19. พญ.ฐิติพร สิริวชิรชัย	พยาบาลชำนาญการ	กลุ่มงานสูตินรีเวชกรรม โรงพยาบาลขอนแก่น	ผู้ร่วมวิจัย	พยาบาลชำนาญการ	โรงพยาบาลขอนแก่น	ยังอยู่ในโครงการ
20. พญ.รัตนา คำวิลัยศักดิ์	พยาบาล	ภาควิชาสูติฯ คณะแพทยศาสตร์ มข.	ผู้ร่วมวิจัย	พยาบาล	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
21. ทพญ. มุขดา ศิริเทพทวี	รองศาสตราจารย์	ภาควิชาวินิจฉัยโรคช่องปาก คณะทันตแพทยศาสตร์	ผู้ร่วมวิจัย	รองศาสตราจารย์	มหาวิทยาลัยขอนแก่น	ยังอยู่ในโครงการ
22. นพ.ธนนิตย์ สังคมคำแหง	นายแพทย์	ภาควิชาออโธปิดิก โรงพยาบาลขอนแก่น	ผู้ร่วมวิจัย	นายแพทย์	โรงพยาบาลขอนแก่น	ยังอยู่ในโครงการ

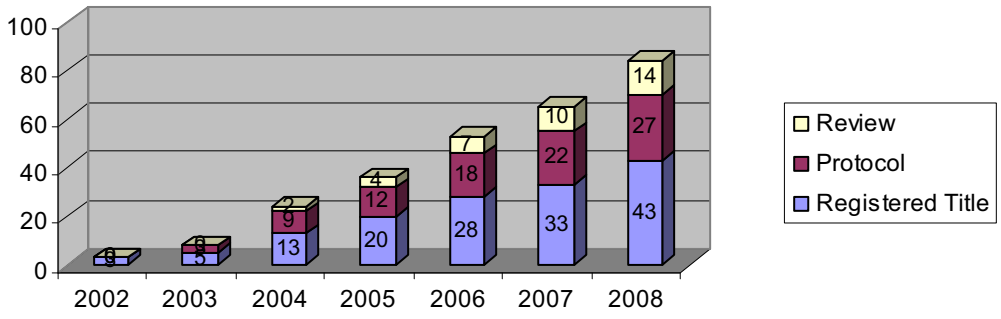
หมายเหตุ

สังกัด ให้ใส่รายละเอียดที่อยู่ต้นสังกัด เช่น ภาควิชา / คณะ / มหาวิทยาลัย

สถานภาพปัจจุบัน - ยังอยู่ในโครงการหรือไม่ หากไม่อยู่ในโครงการแล้ว ให้ระบุหน่วยงานใหม่ด้วย

- หากเริ่มเข้าโครงการเป็นนักศึกษาปริญญาเอก ปริญญาโท หรือปริญญตรี ให้ระบุปัจจุบันสำเร็จการศึกษาหรือยังไม่สำเร็จการศึกษา

Cumulative Cochrane review of Thai reviewers supported by Thailand Research Fund since 2002



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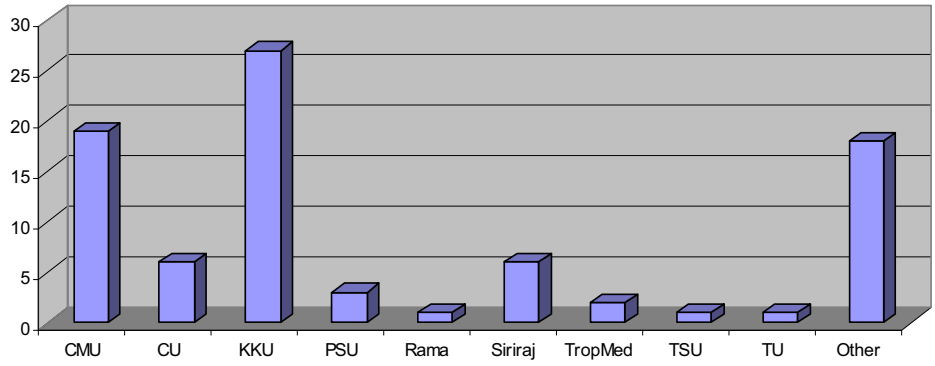

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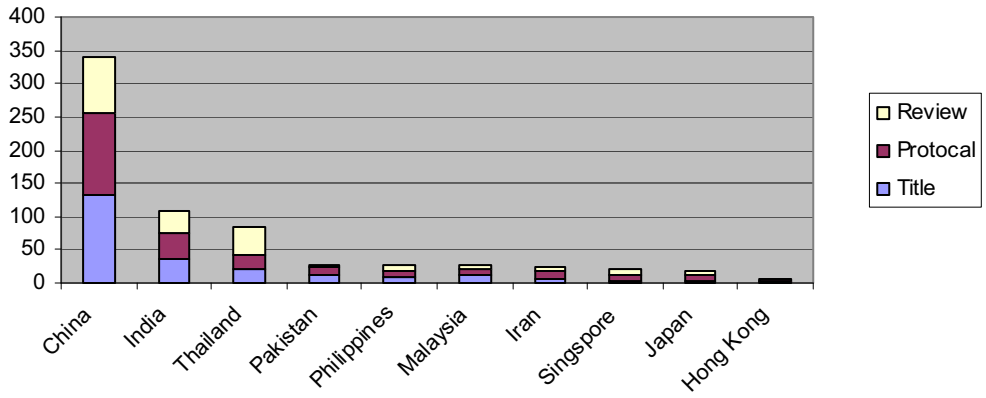

Follicular flushing during oocyte retrieval in assisted reproductive techniques (Protocol)

Wongtra-ngan S, Edi-Osagie EC, Vutyavanich T

This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2007, Issue 4

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Follicular flushing during oocyte retrieval in assisted reproductive techniques (Protocol)

Wongtra-ngan S, Edi-Osagie EC, Vutyavanich T

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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 whether follicular flushing impacts on numbers of live birth/ongoing pregnancy in women undergoing in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI).
(2) To compare different methods of follicular flushing (such as single versus multiple flush, different flushing media, and different volumes) in terms of live births/ongoing in women undergoing IVF and ICSI.

BACKGROUND

Assisted reproductive technique (ART) requires the handling of oocytes/embryos outside the body. The technique involves ovarian stimulation, monitoring of follicular growth, oocyte recovery, sperm preparation and insemination, embryo culture, embryo transfer, and luteal support.

Once maturity of the follicles is achieved, human chorionic gonadotropin (hCG) or recombinant luteinizing hormone (rLH) is used to trigger ovulation. Oocyte pickup is performed approximately 36 hours later, just prior to the actual rupture of the follicles. The technical details of oocyte recovery vary between centres especially with regard to the type of anaesthesia (local, sedation or general), type of aspiration needle (wide or narrow bore, single or double channel), route of retrieval (transvaginal or abdominal), aspiration alone or aspiration with follicular flushing, type of flushing media and collecting system.

The number of embryos obtained is dependent on the number of oocytes retrieved (Wood 2000). To maximize the number of oocytes recovered, follicular aspiration followed by one 2-ml flushing was suggested (el Hussein 1992). Waterstone and Parson (1992) reported that the use of double-lumen needles with flushing gave 20% more oocytes (Waterstone 1992). On the contrary, other studies found no difference in the number of oocytes collected, fertilization rates, embryo quality or pregnancy rates (Lenz 1987; Kingsland 1991; Tan 1992; Knight 2001). It has been suggested that aspiration without flushing reduced the operative time and decreased the amount of anaesthetics required (Tan 1992).

The place of follicular flushing during the oocyte recovery for assisted reproductive technology (ART) is still uncertain. The pros of flushing include the possibility of obtaining more oocytes, and subsequently more embryos. Whether this will translate into a higher pregnancy rate and live birth remains unknown. The cons of flushing are longer operative time and larger amount of anaesthetics required. From patient's perspectives, it could also mean a higher cost to them. Moreover, anaesthetics such as propofol could have detrimental effects on embryos, at least in the mouse model. Flushing could also remove some of the follicular cells that might have an important endocrine luteal support function.

The prevalence of infertility and the significant costs of assisted conception make it imperative to assess ART techniques to establish which are more effective and cost-beneficial with a view to improving treatment outcomes. This review will help provide information for women and clinicians as well as identifying other aspects for future study.

OBJECTIVES

(1) To determine whether follicular flushing impacts on numbers

of live birth/ongoing pregnancy in women undergoing in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI).

(2) To compare different methods of follicular flushing (such as single versus multiple flush, different flushing media, and different volumes) in terms of live births/ongoing in women undergoing IVF and ICSI.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Trials will be eligible for inclusion if they state that allocation was randomised (or they described an appropriate method of randomisation) to a group undergoing follicular aspiration and flushing or a control group undergoing follicular aspiration alone, during the process of oocyte retrieval for IVF or ICSI.

Crossover trials will be included. However, only the pre-crossover data will be used for analysis. Trials will be excluded if the comparison of flushing method is confounded by comparison of other methods, such as type of anaesthesia, route of oocyte retrieval, type of aspiration needles, type of flushing media and embryo transfer technique.

For the trial to be included in the meta-analysis all recruited women would have undergone only one cycle of treatment within the context of the trial and had embryos replaced in the uterine cavity in fresh or frozen/thawed cycles. Women will not be excluded if embryo replacement did not take place because of a failure of fertilisation or embryo failed to divide further (cleavage arrest).

Types of participants

The participants will be women who were due to undergo assisted conception by IVF or ICSI using their own gametes and participated in a trial of follicular flushing during oocyte retrieval.

Types of intervention

Trials will be included if they investigate any form of follicular flushing during oocyte retrieval, irrespective of the type of anaesthetic, aspiration needle and culture medium utilised. The effects of follicular flushing would have been compared to a control group in which flushing was not performed.

Trials replacing embryos resulting from oocytes that were derived from mixed groups of flushed and unflushed follicles in the same woman will be included. Sensitivity analysis of inclusion/exclusion of these trials will be performed.

Trials directly comparing different methods of follicular flushing (without a no-flushing control group) will also be included but they will be analysed and reported separately.

Types of outcome measures

Primary outcomes:

- Live birth rate - defined as the number of live offspring per woman randomised following follicular flushing
- Ongoing pregnancy - defined as the number of clinical pregnancy that is still ongoing at the end of the study

Secondary outcomes:

- Oocyte yield - defined as the number of oocytes retrieved per woman randomised
- Fertilisation rate - defined as the percentage of retrieved oocytes that fertilise after insemination
- Clinical pregnancy rate - defined as the number of sonologically detected fetal heart pulsations per woman randomised
- Miscarriage rate - defined as the number of miscarriages per clinical pregnancy
- Rates of embryo cleavage - defined as the number of embryos that proceed to the 2-cell stage or beyond divided by the number of 2-pronucleate embryos
- Number of embryo cryopreserved
- Rates of congenital and chromosomal abnormalities
- Duration of oocyte retrieval
- Amount of anaesthetic required
- Complication rate of the surgical procedure for flushing during the flushing procedure
- Volume of culture medium used to flush
- Cost per oocyte-retrieval procedure

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

All reports which describe (or might describe) randomised controlled trials of follicular flushing will be obtained using the following search strategy.

(1) The Menstrual Disorders & Subfertility Group's Specialised Register of controlled trials will be searched for any trials with follicular flushing in the title, abstract or keywords sections. See the Review Group for more details on the make-up of the Specialised Register.

(2) The following electronic databases will be searched using Ovid software;
MEDLINE - 1966 to current
EMBASE - 1980 to current
Biological Abstracts - 1980 to current

The MEDLINE and Biological Abstracts databases will be searched using the following subject headings and keywords:
1. randomised controlled trial.pt.
2. controlled clinical trial.pt.
3. randomised controlled trials/
4. random allocation/
5. double-blind method/
6. single-blind method/
7. or/1-6
8. clinical trial.pt.
9. exp clinical trials/
10. (clin$ adj25 trial$).tw.
11. ((singl$ or doubl$ or treb$ or tripl$) adj25 (blind$ or mask$)).tw.
12. placebos/
13. placebo$.tw.
14. random$.tw.
15. research design/
16. or/8-15
17. animal/ not (human/ and animal/)
18. (follic$ adj5 flush$).tw.
19. (follic$ adj5 wash$).tw.
20. 18 or 19
21. 17 and 20

The EMBASE database will be searched using the following subject headings and keywords:
1. Controlled study/ or Randomised Controlled Trial/
2. Double Blind Procedure/
3. Single Blind Procedure/
4. Crossover Procedure/
5. Drug Comparison/
6. Placebo/
7. Random$.tw.
8. latin square.tw.
9. crossover.tw.
10. cross-over.tw.
11. placebo$.tw.
12. ((doubl$ or singl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
13. (comparativ$ adj5 trial$).tw.
14. (clinical adj5 trial$).tw.
15. animal/ not (human/ and animal)
16. or/1-14
17. 16 not 15
18. (follic$adj5 flush$).tw.
19. (folic$ adj5 wash$).tw.
20. 18 or 19
21. 17 and 20

(3) The Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library Issue 4, 2003 will also be searched in all fields using the following words: follicular flushing or follicular washing.

(4) Other databases listing ongoing or recently completed trials, such as CentreWatch and National Research Register, will also be searched for any trials on follicular flushing.

(5) The citation lists of relevant publications, review articles, abstracts of scientific meetings and included studies will also searched.

(6) Letters will be sent to experts within the field, pharmaceutical companies producing the products being reviewed, and authors of unpublished abstracts to identify unpublished trials of follicular flushing.

(7) The MDSG Specialised Register also hand searches the following relevant journals for RCTs, so these results will be searched for any trials on follicular flushing.
Acta Eur Fertil. 1969-1989 Infertility RCT's only, 1990 - ongoing
Am J Reprod Immunol Microbiol. 1980-1990
Andrologia. 1980-1990 Searched for Infertility RCT's only, 1991 - ongoing
Arch Androl. 1978-1992 Searched for Infertility RCT's only, 1993 - ongoing
Climacteric. 1998 ongoing
Epidemiology. 1990-1995
Fertil Steril. 1950 - ongoing
Gynecol Endocrinol. 1987 - ongoing
Gynaecol Endosc. 1991 - ongoing
Hum Reprod. 1986 - ongoing
Int J Androl. 1978-1992 Searched for Infertility RCTs only, 1993 - ongoing
Int J Fertil Womens Med (previously Int J Fertil Menopausal Stud and Int J Fertil). 1968 - ongoing
J Androl. 1980-1990 Searched for Infertility RCTs only, 1991 - ongoing
J Assist Reprod Genet (formerly J In Vitro Fertil Embryo Transfer 1984-1991). 1984-1992 Searched for Infertility RCT's only, 1993 - ongoing.
J Reprod Fertil. 1966-1990 Searched for Infertility RCTs only, 1992 - ongoing.
Maturitas. 1978 - ongoing
Mol Reprod Dev. (Formerly Gamete Res 1978-1990). 1978-1992 Infertility RCTs only, 1993 - ongoing.
Pediatr Perinatal Epidemiology, 1987 - 1995
Reprod Fertil Dev. (Formerly Clin Reprod Fertil 1982-1990) 1982-1993 Searched for Infertility RCTs only, 1982 - ongoing

METHODS OF THE REVIEW

Two reviewers (SW, TV) will independently scan titles and abstracts from the searches. Trials that appear relevant will be selected and independently assessed for inclusion by these reviewers using an inclusion/exclusion form. Disagreements will

be resolved by consensus or through arbitration by a third reviewer (EE).

All assessments of trial quality and data extraction will be performed independently by two reviewers (SW, TV), using forms that will be designed for the review to assess the following characteristics:

TRIAL QUALITY CHARACTERISTICS
(1) Method of randomisation:
(a) randomised allocation - method of randomisation clearly stated and correct
(b) randomised allocation - method of randomisation not stated or unclear
(2) Allocation concealment:
(a) randomisation sequence adequately concealed
(b) allocation concealment unclear
(c) allocation concealment inadequate
(3) Blinding:
(a) presence or absence of blinding of participants
(b) presence or absence of blinding of outcome assessors
(4) Prospective power calculation reported
(5) Intention to treat analysis stated or implied
(6) Publication as full paper or abstract only

TRIAL DESIGN & FLOW
(7) Trial flow:
(a) numbers of women recruited
(b) numbers of women randomised
(c) numbers of women excluded
(d) numbers of women analysed
(e) numbers of women lost to follow-up
(8) Study setting:
(a) single- or multi-centre
(b) location
(c) timing
(9) Indications for follicular flushing:
(a) previous poor response to ovarian stimulation
(b) routine

TRIAL PARTICIPANTS
(10) Baseline characteristics
(a) age (mean and standard deviation in each study arm)
(b) primary or secondary infertility
(c) cause and duration of infertility
(d) previous treatment
(11) Other subgroup criteria
(a) women undergoing IVF only
(b) women undergoing ICSI only
(c) women over the age of 37 undergoing IVF and/or ICSI
(d) women with high early proliferative phase FSH levels undergoing IVF and/or ICSI
(e) women with repeated implantation failure undergoing IVF and/or ICSI
(f) women with poor response to ovarian stimulation for IVF and/or ICSI

INTERVENTIONS
(12) Follicular flushing
(a) flushing performed
(b) flushing not performed
(13) Number of flushes
(a) 1 flush
(b) 2 flushes
(c) >2 flushes
(14) Volume of flushing medium used
(15) Types of flushing medium used

OUTCOMES
(16) Primary
(a) Live birth/ongoing pregnancy (per woman randomised)
(17) Secondary
(a) oocyte yield (per woman randomised)
(b) fertilisation (per oocyte yield and per oocyte inseminated)
(c) clinical pregnancy (per woman randomised)
(d) miscarriage (per clinical pregnancy)
(e) embryo cleavage (per fertilised oocyte)
(f) number of embryo cryopreserved
(g) congenital and chromosomal abnormalities (per clinical pregnancy)
(h) duration of oocyte retrieval
(i) amount of anaesthetic used
(j) complications
(k) amount of culture medium used
(l) cost of procedure

Any discrepancies in quality assessment or data extraction will be resolved by consensus during discussions with the third reviewer (EE).

Additional information on trial methodology and/or actual original trial data will be sought from the authors of trials which appear to meet the eligibility criteria but have aspects of methodology that are unclear, or where the data are in a form unsuitable for meta-analysis.

Statistical analysis will be performed in accordance with the guidelines for statistical analysis developed by the Menstrual Disorders and Subfertility Group. For dichotomous data (e.g. live birth), results for each trial will be expressed as an odds ratio with 95% confidence intervals and these will then be combined for meta-analysis on RevMan 4.1 software using random effects methodology. Heterogeneity between the results of different trials will be examined using Cochran's test (assuming statistical significance at $p<0.1$). Methodological criteria such as concealment of allocation and high loss to follow-up will be investigated as possible causes of heterogeneity.

Other differences in trial design would be investigated through the following sub-groupings:

(a) Age - women below or over the age of 37 years
(b) FSH levels - women with normal or high early proliferative phase FSH levels. If individual data are reported, a cut-off value of 10 iu/l or more will be used for sub grouping.
(c) Repeated implantation failure - following the first or multiple cycles of IVF and/or ICSI
(d) Poor response to ovarian stimulation - when less than 3 mature follicles develop following controlled ovarian stimulation for IVF or ICSI
(e) Number of follicular flushing - single or multiple

Where possible, data on these sub-groupings will be extracted directly from included trials, but where not reported, the mean trial data (for example, the mean trial FSH level) will be used to place the whole trial in one of the subgroups.

Sensitivity analysis will be undertaken to examine the stability of results in relation to:
(a) adequacy of allocation concealment, by removing those trials with unclear or inadequate allocation concealment
(b) adequacy of the randomisation process, by removing those trials with no stated method of randomisation or where the method was unclear
The analyses will only be performed if there are more than five trials in each group.

Although all potential trials might be statistically homogeneous, differences in clinical parameters might be considerable (clinical heterogeneity). These differences will be taken into account when analysing and interpreting the pooled results. Clinical heterogeneity in subfertility cannot be avoided because most centres use their own "materials and methods", which can vary along a number of parameters. When trials meet the inclusion criteria and they have performed the same intervention, we consider it appropriate to pool their results.

Live births, ongoing pregnancies, clinical pregnancies, higher oocyte yield and rates of oocyte fertilisation and embryo cleavage, higher number of cryopreserved embryos will be considered positive consequences of treatment. Therefore it would be considered a benefit if a higher proportion of women achieved these. Miscarriage and chromosomal and congenital abnormalities will be considered negative consequences of treatment and it would be considered detrimental if higher numbers of women had such conditions. This will need to be taken into consideration when viewing the summary graphs.

Completion of the full review is anticipated within one year of publication of the protocol on the Cochrane Library. It is the intention of the reviewers that a new search for RCTs will be performed every other year and the review updated accordingly.

POTENTIAL CONFLICT OF INTEREST

None known.

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- No sources of support supplied

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Additional references

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COVER SHEET

Title	Follicular flushing during oocyte retrieval in assisted reproductive techniques
Authors	Wongtra-ngan S, Edi-Osagie EC, Vutyavanich T
Contribution of author(s)	S Wongtra-ngan: Involved in preparing all sections of the protocol EC Edi-Osagie: Involved in preparing all sections of the protocol T Vutyavanich: Involved in preparing all sections of the protocol
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Paracervical local anaesthesia for cervical dilatation and uterine intervention (Protocol)

Tangsiriwatthana T, Lumbiganon P, Sawadpanich U, Laopaiboon M

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Date of most recent substantive amendment: 27 May 2004

ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:
1. To determine the effectiveness of paracervical local anaesthesia versus general anaesthesia or analgesia for cervical dilatation and uterine intervention and the incidences of adverse events after each.
2. To determine the effectiveness of paracervical anaesthesia versus systemic analgesia for postoperative pain and the incidences of adverse events after each.
Our review primary and secondary hypotheses are:
Hypothesis 1A: There is no difference in the level of pain experienced by women during cervical dilatation and uterine intervention under paracervical local anaesthesia or systemic analgesia.
Hypothesis 1B: There is no difference in the level of pain experienced (or systemic analgesia received) by patients after cervical dilatation and uterine intervention that has been performed with either paracervical local anaesthesia, general anaesthesia or systemic analgesia.
Hypothesis 1C: The pain experienced after cervical dilatation and uterine intervention that has been performed under general anaesthesia is reduced as much by paracervical local anaesthesia as it is by systemic analgesia.
Hypothesis 2: The incidences of nausea or vomiting (separate or combined) are lower following cervical dilatation and uterine intervention performed under paracervical local anaesthesia than under general anaesthesia or systemic analgesia.
Hypothesis 3: The incidence of patient dissatisfaction is less following cervical dilatation and uterine intervention performed under paracervical local anaesthesia than under general anaesthesia or systemic analgesia.
Hypothesis 4: The efficacy of paracervical local anaesthesia on the incidence of outcomes following cervical dilatation and uterine intervention is less for women before the menopause than for women after the menopause.
Hypothesis 5: The efficacy of paracervical local anaesthesia on the incidence of outcomes following cervical dilatation and uterine intervention is different for women having the operation for gynaecological reasons than it is for women having the operation for obstetric reasons.

BACKGROUND

Indications for cervical dilatation and uterine intervention include abnormal uterine bleeding, which does not respond to medical treatment, postmenopausal bleeding, abortion, etc. General anaesthesia provides adequate operating conditions for cervical dilatation and uterine intervention. However, there are some situations when general anaesthesia is more hazardous, for example when the patient is in a poor medical condition or when no anaesthesiologist is available.

Paracervical local anaesthesia offers an alternative to general anaesthesia for cervical dilatation and uterine intervention in these patients (Garfield 1998). Injection of local anaesthetic around the cervix at the three O' clock and nine O'clock positions achieves paracervical anaesthesia of the 2nd to 4th sacral nerve roots as they pass through Frankenhauser's plexus at a depth of two to four millimetres (Piyamongkol 1998). The advantages of paracervical

local anaesthesia compared to general anaesthesia are that one does not need either general anaesthetic equipment nor the personnel trained to give it. However, paracervical local anaesthetic should be administered by trained staff and resuscitation facilities should be available. Many gynaecologists are still performing paracervical local anaesthesia 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. This review will compare the effectiveness of paracervical local anaesthesia for cervical dilatation and uterine intervention between premenopausal and postmenopausal as well as pregnant and non-pregnant women. The incidences of nausea and vomiting are high after general anaesthesia. We will therefore compare these incidences with those that occur after paracervical anaesthesia.

OBJECTIVES

1. To determine the effectiveness of paracervical local anaesthesia versus general anaesthesia or analgesia for cervical dilatation and uterine intervention and the incidences of adverse events after each.
2. To determine the effectiveness of paracervical anaesthesia versus systemic analgesia for postoperative pain and the incidences of adverse events after each.

Our review primary and secondary hypotheses are:

Hypothesis 1A: There is no difference in the level of pain experienced by women during cervical dilatation and uterine intervention under paracervical local anaesthesia or systemic analgesia.

Hypothesis 1B: There is no difference in the level of pain experienced (or systemic analgesia received) by patients after cervical dilatation and uterine intervention that has been performed with either paracervical local anaesthesia, general anaesthesia or systemic analgesia.

Hypothesis 1C: The pain experienced after cervical dilatation and uterine intervention that has been performed under general anaesthesia is reduced as much by paracervical local anaesthesia as it is by systemic analgesia.

Hypothesis 2: The incidences of nausea or vomiting (separate or combined) are lower following cervical dilatation and uterine intervention performed under paracervical local anaesthesia than under general anaesthesia or systemic analgesia.

Hypothesis 3: The incidence of patient dissatisfaction is less following cervical dilatation and uterine intervention performed under paracervical local anaesthesia than under general anaesthesia or systemic analgesia.

Hypothesis 4: The efficacy of paracervical local anaesthesia on the incidence of outcomes following cervical dilatation and uterine intervention is less for women before the menopause than for women after the menopause.

Hypothesis 5: The efficacy of paracervical local anaesthesia on the incidence of outcomes following cervical dilatation and uterine intervention is different for women having the operation for gynaecological reasons than it is for women having the operation for obstetric reasons.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Inclusion criteria for this review will be prospective randomized controlled trials in which allocation was achieved in a randomized or pseudo-randomized fashion (alternate days, weeks, odd and even hospital numbers). Concurrent cohort and observational studies will be excluded.

Types of participants

The population group will be women of any age who underwent cervical dilatation and uterine intervention for any indication.

Types of intervention

Included studies will have at least one arm in which paracervical local anaesthesia was used to provide pain control during and,or after, cervical dilatation and uterine intervention. We will not compare one type of paracervical local anaesthesia with another.

Types of outcome measures

1) Primary outcome measures:
a) Pain during and/or after cervical dilatation and uterine intervention, which were measured as categorical or continuous data (visual analogue scale (VAS), requirement for additional analgesia).
b) Adverse effects (nausea, vomiting, hypotension).

2) Secondary outcome measures:
a) Patients satisfaction (variously defined by the authors).

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We will search the Cochrane Anaesthesia Review Group trials register and CENTRAL (the current issue of *The Cochrane Library*) using the following strategy:
#1 PARACERV*
#2 DILAT* OR intervention OR VACUUM intervention: ME
#3 NERV* NEAR BLOCK* OR LIDOCAINE OR LIGNOCAINE OR BUPIVACAINE OR MARCAIN* OR LEVOBUPIVACAINE OR PRILOCAINE OR

CHLORPROCAINE OR PROCAINE OR XYLOCAINE OR ROPIVACAINE OR TETRACAINE OR AMETHOCAINE OR MEPIVACAINE
#4 OBSTETR* OR GYNAE* OR GYNE*
#5 ANAES* OR ANES*
#6 POSTOP* AND PAIN
#7 #2 AND #3
#8 #7 NOT #1
#9 #1 OR #8

We will search MEDLINE on Silver Platter (1966 to present) using the following strategy:
#1 PARACERV*
#2 DILAT* OR intervention
#3 NERV* AND BLOCK*
#4 LIDOCAINE OR LIGNOCAINE OR BUPIVACAINE OR MARCAIN* OR LEVOBUPIVACAINE OR PRILOCAINE OR CHLORPROCAINE OR PROCAINE OR XYLOCAINE OR ROPIVACAINE OR TETRACAINE OR AMETHOCAINE OR MEPIVACAINE
#5 "LOCAL ANAESTH* " OR "LOCAL ANESTH* "
#6 #4 or #5
#7 "Anesthesia, Local " [MESH] OR "Anesthetics, Local" [MESH]
#8 #6 OR #7
#9 #3 OR #8
#10 #2 AND #9
#11 #1 OR #10
To identify randomized controlled trials (RCTs), this search will be combined with the Cochrane Highly Sensitive Search Strategy phase one and two as contained in the Cochrane Reviewers' Handbook (Alderson 2004).

We will also search EMBASE Silver Platter (1980 to present) using the following strategy:
#1 PARACERV*
#2 DILAT* OR CURETT*
#3 NERV* AND BLOCK*
#4 LIDOCAINE OR LIGNOCAINE OR BUPIVACAINE OR MARCAIN* OR LEVOBUPIVACAINE OR PRILOCAINE OR CHLORPROCAINE OR PROCAINE OR XYLOCAINE OR ROPIVACAINE OR TETRACAINE OR AMETHOCAINE OR MEPIVACAINE
#5 (LOCAL ANAESTH*) OR (LOCAL ANESTH*)
#6 explode LOCAL- ANAESTHETIC/subheadings#4 or#5
#7 #4 or #5 or #6
#8 #3 or #7
#9 #2 and #8
#10 #1 or #9

To identify randomized controlled trials, this search will be combined with a search similar to the Cochrane Highly Sensitive Search Strategy used for MEDLINE.

We will search for ongoing or recently published studies using www.controlled-trials.com.
No language restrictions will be applied.

METHODS OF THE REVIEW

Eligibility
The reviewers will not be blinded to authors, institutions, journal of publication, or study results. Two reviewers (TT and US) will independently evaluate the titles and abstracts of trials that have been published in full as well as only abstracts identified in the literature search for their eligibility. The RCTs will be selected, analysed and considered for inclusion and graded for their methodological quality using concealment of randomizations, blinding of intervention, completeness of follow up and blinding of outcome assessment. We will use the Cochrane method of stratifying qualitative aspects of each study, using the four categories, A for adequate, B for unclear, C for inadequate and D for not used (Alderson 2004). Disagreement will be resolved through discussion. If this is unsuccessful, the third reviewer (PL) will evaluate the disputed trial to obtain a tiebreaker.

Data extraction
The standard methods of the Cochrane Anaesthesia Review Group will be used. All titles and abstracts of research identified from the search strategy will be scrutinized by at least two reviewers for their suitability and relevance to this review. Data will be extracted independently by at least two reviewers. The data will be checked and entered into Review Manager 4.2 by one reviewer (TT). Any missing information or data inconsistencies will be checked where necessary with the authors of the study.

Statistical analyses
Where appropriate, meta-analysis will be undertaken to pool trial data using RevMan 4.2.3. The method of meta-analysis will be dependent on the nature of the outcomes. For categorical data (for example, proportion of participants with a specific adverse effect), we will relate the numbers reporting an outcome to the numbers at risk in each group to derive a relative risk (RR) and 95% confidence interval. Continuous differences between groups in the meta-analysis (for example, pain relief on a visual analogue scale) will be shown as a weighted mean difference (WMD) and 95% confidence interval. As a general rule, a fixed effect model will be used for calculations of summary estimates and their 95% confidence intervals. When important heterogeneity is suspected from the I^2statistics for heterogeneity (Higgins 2003) or from visual inspection of the results, this will be investigated by looking for differences of clinical and methodological factors between the trials that may be the explanation. When concern about heterogeneity persists, consideration will be given to using a random effects model. We will examine funnel plots (Light 1984) for asymmetry and we will explore potential causes of any asymmetry found. When asymmetry is observed, the Trim and Fill

method will be used to assess the effect of this asymmetry on the conclusions. The sensitivity analysis will also be done for assessing the effect of quality of trials on the conclusions. We will assess the clinical significance of statistically significant differences between groups. We anticipate that a clinically significant difference in the incidences of adverse events or need for pain relief will be a difference of 50%. When meta-analysis is inappropriate, conclusions will be drawn by: the trials' descriptive elements, methodologic quality, number of trials with consistent findings, plausibility of the results, the strength of the associations in the primary trials as well as consensus among reviewers.

Summarizing the results:
Evidence tables will be used to summarize patient populations, methods and methodological quality, interventions, and reported outcomes and adverse events. Expressions of central tendency and distribution within trials have already been described under the 'Data extraction' section above. Meta-analysis will be conducted if sufficient data exist from two or more studies. Heterogeneity testing will be performed using the Breslow-Day method (Breslow 1980). If heterogeneity is present, the random effects model of DerSimonian and Laird (DerSimonian 1986) will be used. If heterogeneity is not detected, the fixed effect model will be utilized. Continuous data with normal distributions will be summarized as weighted mean difference with 95% confidence limits. For continuous data with non-normal distribution, meta-regression may be employed. Dichotomous data will be summarized as odds ratios and NNTs with their respective 95% confidence intervals. Graphical representation of continuous data will use the MetaView program integral to Review Manager 4.2
We anticipate that meta-analyses will be conducted on the following comparisons:
1. Paracervical analgesia versus general anaesthesia.
2. Paracervical analgesia versus systemic analgesia.
Sensitivity analyses will be performed assessing the effects of methodological quality.
Funnel plots will be performed to assess for publication bias (Egger 1997).

NOTES

second draft

POTENTIAL CONFLICT OF INTEREST

None known.

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Review Manager 4.2

The Cochrane Collaboration. Review Manager (RevMan). 4.2 for Windows. Oxford, England: The Cochrane Collaboration, 2004.

COVER SHEET

Title	Paracervical local anaesthesia for cervical dilatation and uterine intervention
Authors	Tangsiriwatthana T, Lumbiganon P, Sawadpanich U, Laopaiboon M
Contribution of author(s)	Thumwadee Tangsiriwatthana (TT) and Pisake Lumbiganon (PL): early development of title and question TT, PL and Usanee Sawadpanich (US): development and authorship of protocol Malinee Laopaiboon (ML) works on statistical problems inherent in data PL: advice on problems with expected data and the protocol development process and will act as external reviewer to check data allocation performed by other reviewers. TT and US will independently appraise the literature. TT, PL and ML will do the literature search. ML will analyse the data. TT, PL, US and ML will interpret the data. TT will draft the review. TT, PL, US and ML will approve the final version of the review
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Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media (Protocol)

Thanaviratananich S, Watanasapt P, Laopaiboon M

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Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media (Protocol)

Thanaviratananich S, Watanasapt P, Laopaiboon M

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:
(1) To compare the effectiveness of amoxicillin with or without clavulanate between once or twice daily doses, with three or four times daily doses for the treatment of acute otitis media in children.
(2) To compare the complication rates between once or twice daily doses with three or four times daily doses.
(3) To compare the adverse reactions between the dosing intervals.

BACKGROUND

Acute otitis media is one of the most common diseases in children. During the first six months of life about 48% of infants have an episode of acute otitis media (AOM) or otitis media with effusion (OME) and about 20% have two or more episodes (Daly 1999). The peak incidence of AOM occurs between six and 12 months of age. It had been found that by the first year of life 62.4% of infants have one or more episodes of AOM and 17.3% have 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 microbiology of acute otitis media was found to be *Streptococcal pneumoniae (S. pneumoniae), Haemophilus influenzae (H. influenzae)* and *Moraxella catarrhalis (M. catarrhalis)* (Jacobs 1998). These three most common bacterial causes of AOM are becoming increasingly resistant to antibiotics (Barnett 1995; Faden 1994; Henderson 1988; Johnson 1996; Kaplan 1995). Systematic reviews demonstrated that in uncomplicated 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). 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 United States of America (USA) (Froom 1997; Glasziou 2004). AOM was the most frequent disease that antibiotics were used to treat in outpatients in the USA (McCaig 1995). In contrast, the national Dutch guideline recommends that children be treated for symptoms but not receive antibiotics unless fever or pain persists (Froom 1997). Children in Britain also usually receive antibiotics (Appelman 1990). Due to growing bacterial resistance, the Centers for Disease Control and the American Academy of Pediatrics promote 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, 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 its an-

timicrobial activity against the suspected pathogens, but also on characteristics such as dosage; appropriate dosing intervals; and tolerability and palatability that promote compliance and adherence. A convenient once- or twice-daily dosing schedule increases the likelihood of compliance with the 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 at a daycare centres which necessitates the involvement and co-operation of a third person. The duration of time that serum levels of antibiotics are above the Minimal Inhibitory Concentration (MIC) or time above the MIC was demonstrated to be a major determinant in predicting successful clinical outcome 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 amount of each dose with comparable total daily dose in order to maximize time above the MIC. By this practice it will enhance compliance over three-times-daily dosing (Grob 1992; Urquhart 1992). It is reasonable to assess the effectiveness of clinical trials comparing reduced dosing intervals with traditional dosing intervals.

OBJECTIVES

(1) To compare the effectiveness of amoxicillin with or without clavulanate between once or twice daily doses, with three or four times daily doses for the treatment of acute otitis media in children.
(2) To compare the complication rates between once or twice daily doses with three or four times daily doses.
(3) To compare the adverse reactions between the dosing intervals.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomized controlled trials comparing two different dosing intervals of the same intervention, amoxicillin with or without clavulanate.

Types of participants

Patients aged 12 years or younger, with acute otitis media diagnosed by explicit criteria: acute ear pain (otalgia), inflamed ear drum (confirmed by positive tympanocentesis or tympanogram) of type B or C or not. (Tympanogram is the printout 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. Type B suggests fluid in the middle ear; type C suggests that the pressure within the middle ear is below atmospheric pressure.

Types of intervention

Amoxicillin with or without clavulanate comparing between once or twice daily with three or four times daily

Types of outcome measures

(1) Clinical cure rate will be assessed during therapy (days two to three), at the end of antibiotics therapy (days seven to 14) and post-treatment (one to three months):
1.1 resolution of otalgia (ear pain)
1.2 resolution of fever
1.3 resolution of middle ear effusion as determined by tympanometry, assessed only in those who do not have recurrences of AOM after completion of therapy
1.4 Bacteriological cure rate if the data is provided
(2) AOM complications: recurrent AOM (after completion of therapy), acute mastoiditis
(3) Medication adverse reactions.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

Multiple strategies will be used to identify as many trials as possible that meet the inclusion criteria, regardless of language or publication status. Electronic searches of the following databases will be conducted:
(1) The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, latest issue)
(2) MEDLINE (January 1966 to present)
(3) EMBASE (January 1990 to present)
(4) Science Citation Index (SCI)
(5) NLM Gateway which searches Health Services Research Meetings and HSRProj
(6) Health Services/Technology Assessment Texts (HSTAT)

The following search terms will be used, with appropriate modifications where necessary, on all databases listed above:
exp Otitis Media/ OR otitis media
AND
exp Amoxicillin/ OR exp Amoxicillin-Potassium Clavulanate Combination/ OR amoxycillin OR amoxicillin OR amoxicillin clavulanate

These search terms will be used in combination with parts I and II of the highly sensitive search strategy designed by the Cochrane Collaboration (the Cochrane Handbook version 4.2, Appendix 5b) (Dickersin 1994). This filter will be adapted for searching the other databases listed.

We will check the reference lists of identified clinical trials and any relevant reviews or meta-analyses. We will contact the major pharmaceutical companies that manufacture antibiotics and the relevant experts in the field for additional trial information. We

intend to contact the first author of relevant trials if any questions arise. We will also undertake handsearching with the help of the Cochrane Collaboration.

METHODS OF THE REVIEW

Data extraction

After retrieval of titles and abstracts from the literature search, two physician reviewers (ST & PW) will review the abstracts against the inclusion/exclusion criteria to determine eligibility for inclusion in the evidence synthesis. we will record reviews on a pre-designed screening form. The screening results for each title/abstract will be matched between the two reviewers by the third reviewer (ML). Disagreements on inclusion or exclusion will be solved in the meeting among the three reviewers. The articles which pass the screening criteria and those that fail will be summarized with the reasons for exclusion. The titles/abstracts identified as requiring further review will be requested from the librarian for full article retrieval with the help of Cochrane Acute Respiratory Infections Group. Two physician reviewers will then independently review each article and fill out the data extraction forms. We will resolve disagreements between reviewers on inclusion/exclusion through group discussion.

Quality assessment

The criteria for the assessment of study quality will include (1) random allocation concealment; (2) blinding; and (3) follow-up. Risk of bias will be graded 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).

Statistical analyses

Where appropriate we will perform meta-analyses to pool trial data using the Review Manager (RevMan 4.2.7) software. The method of meta-analysis 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 relative risk (RR) and 95% confidence interval. We will show continuous differences between groups in the meta-analysis (for example, pain relief on a visual analogue scale) as a weighted mean difference (WMD) and 95% confidence interval. As a general rule, a fixed effect model will be used for calculations of summary estimates and their 95% confidence intervals.

When important heterogeneity is suspected from the chi squared test for heterogeneity (at 10%) or from visual inspection of the results, this will be investigated by looking for differences of clinical and methodological factors between the trials that may be the explanation. When concern about heterogeneity persists, consideration will be given to using a random effects model. The I^2 statistics will also be calculated to estimate degree of the heterogeneity. We will examine for publication bias using funnel plots (Light 1984). When asymmetry is observed, the Trim and Fill method will be used to assess the effect of this asymmetry on the conclusions. The sensitivity analysis will also be done for assessing the effect of quality of trials on the conclusions. When meta-analysis is inappropriate, conclusions will be drawn by the trials' descriptive elements, methodological quality, number of trials with consistent findings, plausibility of the results, the strength of the associations in the primary trials as well as consensus among reviewers.

Subgroup analysis will be performed according to the total dosages of antibiotics: equal and unequal.

POTENTIAL CONFLICT OF INTEREST

None known.

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Internal sources of support

- Faculty of Medicine, Khon Kaen THAILAND

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COVER SHEET

Title Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media

Authors	Thanaviratananich S, Watanasapt P, Laopaiboon M
Contribution of author(s)	Sanguansak Thanaviratananich (ST) contributions: responsible for conceiving, designing and co-ordinating the protocol. Also developed the search strategy, entered text into RevMan and wrote the protocol. Patravoot Watanasapt (PW) contributions: responsible for designing and co-ordinating the protocol. Also developed the search strategy, entered text into RevMan and provided general advice on the protocol. Malinee Laopaiboon (ML) contributions: responsible for entering text into RevMan and provided general advice on the protocol.
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Non-clinical interventions for reducing unnecessary caesarean section (Protocol)

Khunpradit S, Lumbiganon P, Jaipukdee J, Laopaiboon M

This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2007, Issue 4

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Non-clinical interventions for reducing unnecessary caesarean section (Protocol)

Khunpradit S, Lumbiganon P, Jaipukdee J, Laopaiboon M

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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 effectiveness and safety of non-clinical interventions for reducing unnecessary caesarean section. Non-clinical interventions refer to those that are applied independent of patient care in a clinical encounter between a particular provider and a particular patient.

BACKGROUND

Medical technology and public health measures have been introduced to reduce childbirth complications and mortality. One intervention is caesarean section. Nevertheless, this procedure may lead to increased maternal morbidities such as infections, hemorrhage, transfusion, other organs injury, anaesthetic complications, psychological complications and maternal mortality has been reported to be two to four times greater than that of vaginal birth in some settings (ICAN 2002).

Reported rates of caesarean sections have varied, especially between developed and developing countries. In England, Scotland, Norway, Finland, Sweden and Denmark the rate of caesarean section has consistently risen from around 4-5% to 20-22% between 1970 and 2001 (GSS 2001; Macfarlane 2000; Mayor 2002; Norton 1987; Notzon 1994; Thomas 2001). In low- to middle-income countries rates have also increased significantly during this period. Rates above 15% are reported in more than half of Latin American countries (Belizan 1999). Chile had the highest rate - 40% in 1997 (Murray 2000). In Brazil, caesarean section rates increased from 15% in 1970 to 31% in 1980 (BEMFAM 1997). Data from Asia reports similar trends - in one Chinese hospital, the caesarean section rate increased from 11% in 1990 to 30% in 1997 (Wu 2000). A population-based survey conduct in Shanghai, China showed that caesarean section rate increased from 4.7% between 1960-1979 to 22.5% in 1988-1993 (Cai 1998). In Thailand, the rate has increased steadily from 15.2% in 1990 to 22.4% in 1996 (Teerawattananon 2003).

Clinical, demographic, socioeconomic and health service reasons for the rising rates have been extensively studied, and there is a growing consensus that clinical factors alone cannot explain the observed increases. In 1985, WHO issued a consensus statement suggesting there were unlikely to be any additional health benefits associated with caesarean section rates above 10 to 15% (WHO 1985).

Clinical interventions that could help to reduce caesarean section rates include external cephalic version at 36 weeks (NICE 2004), continuous support during labour (Hodnett 2003), induction of labour for pregnancies beyond 41 weeks (NICE 2004), use of a partogram with a 4-hour action line in labour , fetal blood sampling before caesarean section for abnormal cardiotocograph in labour, and support for women who choose vaginal birth after caesarean section (NICE 2004).

However, caesarean section rates may also be reduced by policy-related interventions such as requirements for second opinions by an obstetrician on caesarean section decisions (Althabe 2004), education of health professionals (Zwarenstein 2004), education of patients/community, feedback and audit mechanisms (Jamtvedt 2004), clinical practice guidelines, quality improvement strategies and financial incentives (Walker 2002). A review is needed to de-

termine the effectiveness of the various policy options on reducing caesarean section rates.

Within this review we will evaluate the effectiveness of non-clinical intervention for reducing unnecessary caesarean section.

OBJECTIVES

To determine the effectiveness and safety of non-clinical interventions for reducing unnecessary caesarean section. Non-clinical interventions refer to those that are applied independent of patient care in a clinical encounter between a particular provider and a particular patient.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised controlled trials (RCTs) or well designed quasi-experimental studies, controlled clinical trials (CCT), controlled before after studies (CBAs) and interrupted time series analyses (ITS) where there is a clearly defined point in time when the intervention occurred and at least three data points before and three after the intervention (EPOC 2002).

No language restrictions will be applied.

Types of participants

Pregnant women and their families, health-care providers who work with expectant mothers, communities, and advocacy groups.

Types of intervention

Non-clinical interventions applied to eligible participants aimed at reducing unnecessary caesarean section, grouped as follows:

1. Professional - including education, audit & feedback
2. Organisational - eg practice guidelines, quality improvement strategies
3. Financial - e.g. incentives for certain procedures
4. Regulatory - e.g. mandatory second opinions

Types of outcome measures

1.Rate of cesarean section;
2.Rate of unnecessary caesarean section;
3.Maternal and fetal or neonatal complications, for example: maternal and neonatal mortality, postpartum anemia, postpartum infection, birth asphyxia, admission to neonatal intensive care unit.
4.Costs and financial benefits noted from the change in procedure rates.

Patient and provider satisfaction will be recorded and included in this review as useful secondary information. However, studies that only report patient or provider satisfaction, or both, will not be included in this review.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

The following electronic databases will be searched:
a.The EPOC Register (and the database of studies awaiting assessment) was reviewed (see SPECIALISED REGISTER under GROUP DETAILS)
b.The Cochrane Pregnancy and Childbirth Group Register
c.The Cochrane Central Register of Controlled Trials (CENTRAL)
d.Bibliographic databases include MEDLINE and CINAHL

Other sources
e.Hand searching of those high-yield journals and conference proceedings which have not already been hand searched on behalf of the Cochrane Collaboration.
f.Reference lists of all papers and relevant reviews identified.
g.Authors of relevant papers will be contacted regarding any further published or unpublished work.
h.Authors of other reviews in the field of effective professional practice will be contacted regarding relevant studies that they may be aware of.

Electronic databases will be searched using a strategy developed incorporating the methodological component of the EPOC search strategy combined with selected MeSH terms and free text terms relating to caesarean section. “Caesarian section” will be used as a term in the MEDLINE search strategy. This search strategy will be translated into the other databases using the appropriate controlled vocabulary as applicable.

In addition, we will search MEDLINE from 1966 to date using the following search strategy:
1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. intervention studies/
4. experiment$.tw.
5. (time adj series).tw.
6. (pre test or pretest or (posttest or post test)).tw.
7. random allocation/
8. impact.tw.
9. intervention?.tw.
10. chang$.tw.
11. evaluation studies/
12. evaluat$.tw.
13. effect?.tw.
14. comparative studies/
15. animal/
16. human/

17. 15 not 16
18. or/1-14

METHODS OF THE REVIEW

Selection of studies

Two reviewers will assess for inclusion all potential studies we identify as a result of the search strategy. For included studies, two reviewers will extract the data independently using an agreed data extraction form. Discrepancies between reviewers will be resolved by discussion and consensus reached by all reviewers.

Assessment of study quality

The quality of all eligible studies will be assessed by two independent reviewers using criteria described in the EPOC module (see ADDITIONAL INFORMATION, ASSESSMENT OF METHODOLOGICAL QUALITY under GROUP DETAILS). Any discrepancies in quality ratings will be resolved by discussion and involvement of an arbitrator where necessary.

When information regarding any of the above is unclear or incomplete, we will attempt to contact authors of the original reports to provide further details.

Reporting

For each study, data will be reported in natural units. Where baseline results are available from RCT, CCTs and CBAs, pre-intervention and post-intervention means or proportions will be reported for both study and control groups and the unadjusted and adjusted (for any baseline imbalance) absolute change from baseline will be calculated with 95% confidence limits.

For ITS we will report the main outcomes in natural units and two effect sizes: the change in the level of outcome immediately after the introduction of the intervention and the change in the slopes of the regression lines. Both of these estimates are necessary for interpreting the results of each comparison. For example, there could have been no change in the level immediately after the intervention, but there could have been a significant change in slope.

Analytical approach

Primary analyses

Primary analyses will be based upon consideration of dichotomous process measures (for example, proportion of patients managed according to evidence based recommendations). Where studies report more than one measure for each endpoint, the primary measure will be abstracted (as defined by the authors of the study) or the median measure identified.

The results for all comparisons will be presented using a standard method of presentation where possible. For comparisons of RCTs, CCTs, CBAs we will report (separately for each study design):

a. Median effect size across included studies
b. Inter-quartile ranges of effect sizes across included studies
c. Range of effect sizes across included studies.

Methods for reanalysis of RCTs, CCTs and CBAs with potential unit of analysis errors

Comparisons that randomise or allocate clusters (professionals or health care organisations) but do not account for clustering during analysis have 'potential unit of analysis errors' resulting in artificially extreme p-values and over narrow confidence intervals (Ukoumunne 1999). We will attempt to reanalyse studies with potential unit of analysis errors where possible. If a comparison is re-analysed then the p-value will be quoted and annotated with 'reanalysed'. If this is not possible, we will report only the point estimate.

Methods for reanalysis of ITS comparisons with inappropriate analysis

Time series regression will be used to reanalyse each comparison (where possible). The best fit pre-intervention and post-intervention lines will be estimated using linear regression and autocorrelation adjusted for using the Cochrane-Orcutt method where appropriate (Draper 1981). First order autocorrelation will be tested for statistically using the Durbin-Watson statistic and higher order autocorrelations will be investigated using the autocorrelation and partial autocorrelation function.

Secondary analyses

Secondary analyses will explore consistency of primary analyses with other types of endpoints (for example continuous process of care measures; dichotomous outcome of care measures and continuous outcome of care measures). Standardised effect sizes will be calculated for continuous measures by dividing the difference in mean scores between the intervention and comparison group in each study by an estimate of the (pooled) standard deviation. This results in a "scale free" estimate of the effect for each study, which can be interpreted and pooled across studies regardless of the original scale of measurement used in each study (Laird 1990).

Grouping of studies and heterogeneity

We will prepare tables and bubble plots comparing effect sizes of studies grouped according to potential effect modifiers (baseline caesarian section rates, specific population groups, low income versus high income countries, and types of treatment comparisons).

Analytic approach

It is anticipated that a wide range of study designs and interventions will be identified, conducted in a variety of settings. If this is the case, it is not sensible to use meta-analysis to pool the results of studies. Instead, we will present the results of studies in tabular form and make a qualitative assessment of the effects of studies, based upon the quality, the size and direction of effect observed and the statistical significance of the studies. We will report the following data (where available): pre intervention study and control data in natural units and statistical significance across

groups, post intervention study and control data in natural units and statistical significance across groups, absolute and relative percentage improvement. If a unit of analysis error is present, we will attempt to re-analyse the study using data provided in the original paper. If this is not possible, we present the point estimates of effects without p-values or 95% confidence intervals. If the study authors state the hypothesised direction of effect for any outcome variable, we will note whether the result favours the study or control groups.

Only if the number of included randomised trials and their data are sufficient and similar enough to be quantitatively analysed, we will carry out meta-analysis using the Review Manager software (RevMan 2004). For the included trials with dichotomous outcome, we will use relative risks (RR) with 95% confidence intervals as summary data. For continuous outcome, we will use weighted mean differences (WMD) with 95% confidence intervals. However, due to clinical diversity, it is expectable that the scale of some continuous outcome measures may not be identical. To combine data in this case, we will use standardised mean differences (SMD) with 95% confidence intervals.

We will perform sensitivity analyses based on the following characteristics:
(a) methodological quality: Analysis will be repeated excluding poor quality trials in order to test the robustness of the results,
(b) methods of meta-analysis: random and fixed effects models will be compared if there is unexplained heterogeneity between studies, and
(c) comparison of outcomes from cluster and individually randomised trials,
We will investigate the robustness of the conclusions, especially of the effect of varying assumptions about the magnitude of the Intracluster Coefficient (ICC). We will also enter data from all identified and selected trials into a funnel graph (trial effects versus inverse standard errors of the effects) in an attempt to investigate the likelihood of overt publication bias. If an asymmetry will be seen, possible causes will be considered. When suspected publication bias is observed, we will use Trim and Fill method to estimate missing data. Further we will use a sensitivity analysis to detect the effect of publication bias in the conclusions.

POTENTIAL CONFLICT OF INTEREST

None known.

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COVER SHEET

Title	Non-clinical interventions for reducing unnecessary caesarean section
Authors	Khunpradit S, Lumbiganon P, Jaipukdee J, Laopaiboon M
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Interval debulking surgery for advanced epithelial ovarian cancer (Protocol)

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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 complications of IDS for patients with advanced stage epithelial ovarian cancer.

BACKGROUND

Primary ovarian cancer surgery is performed to achieve optimal cytoreduction as the amount of residual tumor is one of the most important prognostic factors for survival of epithelial ovarian cancer (Bristow 2002; Griffiths 1975; Hoskin 1994). However, the surgical procedure required for advanced stage disease (III-IV) is not always possible especially in patients where the disease is extensive or involves multiple nearby viscera. The procedures can be complicated requiring extensive bowel resection with or without opening of the intestine through the abdominal wall (ostomy) or massive blood transfusion, with a high risk of morbidity. Another obstacle to extensive primary surgery lies in the patients' medical condition eg. poor projected performance status or medical contraindications.

Induction chemotherapy (IC) can play an alternative role in these circumstances. The term IC describes the administration of chemotherapy to reduce tumor size, allowing further surgery. The term neoadjuvant chemotherapy (NAC) describes the administration of chemotherapy when primary surgery is not possible. In this review, if chemotherapy administration does not fit the definition of NAC, we will use the term IC.

When a few cycles of chemotherapy is administered with some tumor 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 tumor cells leaving chemoresistant clones. Many retrospective or prospective non-randomized trials report the beneficial effects of NAC or IC after inoperable advanced ovarian cancer or those with gross residual diseases respectively. The IC may induce the possibility of secondary surgery (IDS); many authors reported the rates of optimal resection in IDS after IC ranging from 77% to 94% (Ansquer 2001; Chan 2003; Jacob 1991; Lawton 1989; Morice 2003; Surwit 1996).

Another benefit of IDS after NAC or IC is a lesser associated morbidity than the aggressive primary debulking surgery due to the tumours being of smaller size (Lawton 1989; Morice 2003). The quality of life (QOL) in 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). IDS, by removal of the smaller size tumor masses induced by chemotherapy, would facilitate the response of the residual tumors (if any) or the microscopic lesions to subsequent chemotherapy. However, unlike the advantage on the resectability and response rates which were demonstrated in most studies, there are still conflicting data from various studies regarding the survival benefit of IDS after chemotherapy in comparison to conventional treatment. Most studies of IDS after NAC or IC are non-randomized and retrospective in nature. Many of them show that the survival rates of patients who underwent IDS, after suboptimal primary surgery followed by chemotherapy, were similar to those patients who had

primary debulking surgery (Jacob 1991; Kayikciog 2001; Loizzi 2005; Morice 2003; Schwartz 1999; Shibata 2003; Surwit 1996). Only a few studies reported significantly longer median survival of the patients who had IDS after chemotherapy than 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).

We are aware of three randomized controlled trials (RCTs) (Redman 1994; Rose 2004; van der Burg 1995) and three controlled clinical trials (Chan 2003; Kuhn 2001; Lawton 1989) which were 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. The first randomized trial on IDS from the West Midlands Cancer Research Campaign Clinical Trials in the UK (Redman 1994) and the latest and larger trial from the Gynecologic Oncology Group (GOG) in the USA (Rose 2004) showed similar survival rates between patients who had IDS and those who had conventional treatment. While one small study from the UK (Kuhn 2001) and another large randomized multicenter trial by the Gynaecological Cancer Cooperative Group (GCCG) of the European Organization of Research and Treatment of Cancer (EORTC) showed significantly longer survival in the IDS group (Kuhn 2001; van der Burg 1995). The survival benefit yielded by the IDS, from the report of the GCCG of the EORTC, was still evidenced after a 10-year follow-up; the data of which has been recently presented in the International Meeting of the European Society of Gynecologic Oncology in 2005 (van der Burg 2005).

The positive role of IDS in certain cases of ovarian cancer is generally accepted. However, as mentioned earlier its survival benefit is still a subject of debate. The distinctive characteristics of the patients and their diseases in each study may be responsible for the different results. Some of these influencing factors included residual tumors after primary surgery, tumor response after IC and prior to IDS, or residual tumors after IDS etc. (Jacob 1991; Mazzeo 2003; Rose 2004; van der Burg 1995). These may make the conclusion on the survival benefit of IDS in such patients questionable. A thorough systematic review in this subject is therefore 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.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

RCTs and if there are insufficient RCTs for analyses then controlled clinical trials will be considered.

Types of participants

Patients with advanced stage epithelial ovarian cancer who have confirmed pathological diagnoses from primary surgery which was suboptimal, with residual tumors of more than 1 to 2cm.

The primary surgical procedures range from tumor biopsy, tumor removal, or standard surgical staging for epithelial ovarian cancer.

Types of intervention

Main intervention in the study group: interval debulking surgery (IDS)
IDS is defined as a secondary surgery which is performed after 2 to 4 cycles of neoadjuvant chemotherapy (NAC) or induction chemotherapy (IC), to remove the bulk of the tumor, and followed by adjuvant chemotherapy of the same type.

Patients in the control group receive only adjuvant chemotherapy after primary surgery.

Types of outcome measures

Primary outcomes:

- Progression-free survival
- Overall survival

Secondary outcomes:

- Adverse effects
- Quality of life (QOL)
- Patient satisfaction

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

1. Electronic search:
Searches will be made using the following databases:
MEDLINE from 1966 to 2005. The Cochrane Central Register of Controlled Trials (CENTRAL) "SR-GYNAECA", Issue 2, 2005
The subject search will use a combination of vocabulary (Mesh Terms) and free text terms based on the following search strategy:
1. Ovarian cancer or neoplasm
2. Chemotherapy neoadjuvant
3. Induction chemotherapy
4. Preoperative chemotherapy

5. Interval debulking surgery
6. Secondary surgery
7.# 1 AND 2
8.# 1 AND 3
9.# 1 AND 4
10.# 6 OR #7 OR # 8 AND # 5 or #6

This search strategy in each of the above mentioned databases will be complemented with other terms in order to focus the results on chemotherapy for epithelial ovarian cancer prior to surgery.
2. Identification of additional studies in the citations of each report relevant to the subject.
3. Contact the authors of all trials and/or reviews relevant to the reviewed topic to request information on any similar trials which they may be aware, remain unpublished, or not yet in CENTRAL.
4. Colleagues, collaborators and other experts in the field were requested to identify missing or unreported trials.

METHODS OF THE REVIEW

Study selection
All titles and abstracts retrieved by electronic searching will be downloaded to a reference management database (e.g. Reference Manager or Endnote), duplicates will be removed and the remaining references will be examined by two reviewers independently. Those studies which clearly do not meet the inclusion criteria will be excluded and copies of the full text of potentially relevant references will be obtained. The eligibility of retrieved papers will be assessed independently by two authors.

Data on characteristics of patients and interventions, study quality and endpoints will be abstracted independently by two authors onto a data abstraction form specially developed for the review. Differences between authors will be resolved by discussion or by appeal to a third author of necessary.

Data extraction
Two authors (ST and SM) working independently will assess the quality of included studies found, to select trials that meet the inclusion criteria, and will extract data onto predesigned data extraction forms. Disagreement will be resolved by discussion between the authors. If there is failure to resolve the disagreement in this way a third author (PL) will be involved.

We will extract characteristics of the patients included (e.g. age, size and number of residual tumors after primary surgery, performance status, stage, size and number of residual tumors after IDS), type and duration of the treatment (the details to be abstracted should be specified in detail, e.g. type of NAC?) and length of follow-up.

For time to event data (overall survival and progression-free survival) we will abstract the log hazard ratio and its variance from trial reports; if these are not presented, we will attempt to abstract the data required to estimate them using Parmar's methods (Parmar 1998) e.g. number of events in each arm and the log-rank p-value comparing the relevant outcomes in each arm, or relevant data from Kaplan-Meier survival curves. If it is not possible to estimate the log hazard ratio , we will abstract the number of patients in each treatment arm who experienced the outcome of interest, in order to estimate an odds ratio.

For dichotomous outcomes (e.g. adverse events) we will abstract the number of patients in each treatment arm who experienced the outcome of interest, in order to estimate an odds ratio.

For continuous outcomes (e.g. quality of life measures) the final value of the outcome of interest in each treatment arms at the end of follow-up will be abstracted for each study.

Where possible, all data abstracted will be those relevant to an intention to treat analysis.

Assessment of methodological quality
Methodological quality will be evaluated considering the method of randomization, prognostic balance between the treatment arms , blinding of the outcome measurement, completeness of follow-up and intention to treat analysis . Quality of concealment will be used according to the scale reported in the Cochrane Reviewers' Handbook (Higgins 2005) where:
A. Indicates adequate concealment of the allocation (eg. by telephone randomization, or use of consecutively numbered, sealed, opaque envelopes).
B. Indicates uncertainty about whether the allocation was adequately concealed (eg. where the method of concealment is not known).
C. Indicates that the allocation was definitely not adequately concealed (eg. open random number lists or quasi randomization such as alternate days, odd/even date of birth, or hospital number).

Statistical analyses
If appropriate , a meta-analysis will be carried out using the RevMan statistical package and will be done by one author (ML).

If possible, the primary outcomes of interest (overall survival and progression-free survival) will be assessed using hazard ratios (HR). The log HR and its variance will be abstracted from trial reports. Where possible, the log HRs from the various trials will be combined in a meta-analysis using the Generic Inverse Variance facility of RevMan.

Dichotomous outcomes (e.g. adverse events, and numbers of patients who relapse or die, if it is not possible to analyse these using HRs) will be assessed using odds ratios (ORs). These odds ratios will be pooled in a meta-analysis using Mantel-Haenszel methods, to estimate an overall Complications and patients' satisfaction, the secondary outcomes, will be expressed as odds ratios (OR) and their its 95 % CIs.

For continuous outcomes (e.g. QOL measures) the mean difference between the treatment arms at the end of follow-up will be calculated for each study. These will be pooled using the mean difference method if all trials have measured the outcome on the same scale, or using the standardised mean difference method otherwise.

Heterogeneity between studies will be assessed by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials which cannot be ascribed to sampling variation , and by a formal statistical test of the significance of the heterogeneity (Deeks 2001). If there is evidence of substantial heterogeneity, the possible reasons for this will be investigated and reported. Fixed effect models will be used to estimate overall treatment effects and their 95% CIs if the heterogeneity is low or moderate (the I^2statistic (Higgins 2003) is less than 50%). If $I^2 > 50\%$, sources of heterogeneity from clinical and methodological aspects will be explored in subgroup analyses. Some prior potential factors including size or number of residual tumors after primary surgery, performance status, stage, size or number of residual tumors after IDS are planned for the investigation.

If the number of included trials is so small, the results of subgroup analysis may be not convincing. Thus, random effects model will be used to estimate overall effects. If the number of included trials is big enough, potential publication bias will be examined from the funnel plots (Egger 1997) of primary outcomes. Potential causes will be explored if asymmetry plots are detected.

Sensitivity analysis will be performed according to the detected biases and methodological quality of trials included.

When meta-analysis is inappropriate, conclusions will be drawn by: the trials' descriptive elements, methodologic quality, plausibility of the results, the strength of the associations in the primary trials as well as consensus amongst authors.

POTENTIAL CONFLICT OF INTEREST

None known.

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COVER SHEET

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Antenatal breastfeeding education for increasing breastfeeding duration (Protocol)

Lumbigannon P, Martis R, Laopaiboon M, Festin MR, Ho JJ, Hakimi M

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:
(1) To assess the effectiveness of antenatal breastfeeding education for increasing breastfeeding duration.
(2) To compare the effectiveness of various forms of antenatal education; for example, peer support, educational programme, didactic teaching session, workshop, booklets, etc, or a combination of these interventions for increasing breastfeeding duration.

BACKGROUND

Advantages of breastfeeding for infants

Breastfeeding is well recognised as the best food source for infants (Simard 2005). Complementary foods offered before six months of age tend to displace breast milk and do not confer any health advantage over exclusive breastfeeding (Kramer 2002). Breastfeeding has been advocated to improve child health, mother's health and mother-infant bonding (Ball 2001; Hanson 2002). Breastfeeding has been associated with lower rates of gastrointestinal and respiratory diseases, otitis media and allergies, better visual acuity, and speech and cognitive development (Anderson 1999; Blaymore Bier 2002; Duffy 1997; Innis 2001; Wold 2000). It is also cost effective (Riordan 1997). Infants who are breastfed have a lower risk of developing insulin-dependent diabetes in childhood (Fava 1994; Verge 1994), sudden infant death syndrome (Mitchell 1991) and childhood cancer (Davis 1988). Recent research indicates that infant feeding may contribute to children becoming overweight and obese in early and late childhood. Breastfeeding has been shown to protect against child obesity and cardiovascular risk outcomes and is dose related - the longer the infant breastfed, the lower the risk (Arenz 2004; Harder 2005; Owen 2005).

Advantages of breastfeeding for mothers and families

Delay in fertility has been associated with frequent and long periods of exclusive breastfeeding, as well as a lower risk of developing premenopausal breast cancer (Newcomb 1994). Women who had not breastfed their babies were four times more likely to have osteoporosis than women who had breastfed (Blaauw 1994). Better emotional health has also been attributed to women who breastfed. Virden 1988 found that, at one month postpartum, women who breastfed their infants had scores indicating less anxiety than women who had bottle fed their infants. The review by Acheson 1995 showed not only less child abuse but also less physical and sexual abuse of the mother. This was a small review, the results of which warrant further study. A recent published study found that women who breastfed for at least one year were less likely to develop Type 2 diabetes than women who did not breastfeed (Stuebe 2005). Some literature has shown a benefit of breastfeeding in enhancing the couple and family relationships (Cohen 2002; Falceto 2004; Jordan 1993; Li 2004; Sullivan 2004) .

Breastfeeding terminology

In 1988, the WHO and UNICEF proposed the following standard terminology for the collection and description of data on breastfeeding behaviour, which were updated in 1991, and are now widely used (Dettwyler 1992).

Exclusive breastfeeding

Defined as an infant being fed only breast milk, with the possible exception of vitamin D in certain populations and iron in infants of relatively low birthweight (Dewey 2001).

Predominant breastfeeding

When the infant receives breast milk as the predominant source of nourishment. It allows the infant to receive liquids (water and water-based drinks, fruit juice, oral dehydration solutions) and drops or syrups (vitamins, minerals, medicines) but does not allow the infant to receive anything else (in particular, non-human milk and food-based fluids).

Complementary breastfeeding
When the infant receives breast milk and solid or semi-solid foods and allows the infant to receive any food or liquid including non-human milk.

Breastfeeding
When the infant receives breast milk but allows the infant to receive any food or liquid including non-human milk.

Breastfeeding statistics and trends
Despite the many advantages and extensive promotion of breastfeeding, Susin 1999 reports that the trend towards breastfeeding in many countries is increasing slowly. However, according to the recent UNICEF report (UNICEF 2005), six million lives a year are being saved by exclusive breastfeeding and global breastfeeding initiation rates have risen by at least 15% since 1990. Women breastfeed for a shorter time than they intended or wished to (Adams 2001; Wagner 2002). The World Health Organization (WHO) recommends that infants should be exclusively breastfed from birth to six months and then breastfed alongside age-appropriate, complementary feeding for two years and beyond (WHO 2001).

Rationale for using educational interventions
Another Cochrane systematic review provides evidence that various forms of breastfeeding education are effective at increasing rates of breastfeeding initiation among women on low incomes in the USA and will, therefore, not be discussed in this review (Dyson 2005). The impact of antenatal breastfeeding education on the duration of breastfeeding, however, has not been widely reported. In Australia, more than 90% of mothers initiate breastfeeding; however, only 48% of mothers are breastfeeding at one month postpartum and only 23% maintain any form of breastfeeding at six months (Lund-Adams 1996). Similar breastfeeding duration rates have been reported in the USA (Raj 1998) and Britain (Griffiths 2005; Hoddinott 2000), as well as in developing countries (UNICEF 1998). A variety of breastfeeding promotion methods including educational programmes have been trialled to support the trend to increase breastfeeding duration. It is generally believed that, by improving the mothers' knowledge of breastfeeding antenatally, the rates and duration of breastfeeding would increase (McLeod 2002). Lack of antenatal information and education about breastfeeding has been one factor attributed by New Zealand mothers interviewed about discontinuing breastfeeding (McLeod 2002).

Educational interventions
Antenatal breastfeeding education is defined as breastfeeding information being imparted during the pregnancy in a variety of forms. This could be on an individual or group basis, could include home visiting programmes, peer education programmes or clinic appointments specifically aimed at imparting breastfeeding knowledge and could involve prospective fathers or not. Breastfeeding education is usually a formalised, defined, descriptive and goal-orientated programme with a specific purpose and target audience.

Breastfeeding education differs from breastfeeding support. Breastfeeding support is usually aimed at the individual person as the need arises and is defined as a person, a group or an organisation providing support in many ways. This could be psychological support (affirming and encouraging the mother), physical support (providing meals, caring for her other children, house cleaning and gardening), financial support or breastfeeding information services available to be tapped into when a breastfeeding question arises. Breastfeeding support usually starts in the postnatal period, not antenatally.

Support for breastfeeding mothers is the subject of another Cochrane systematic review and will, therefore, not be the subject of this review (Sikorski 2002).

OBJECTIVES

(1) To assess the effectiveness of antenatal breastfeeding education for increasing breastfeeding duration.
(2) To compare the effectiveness of various forms of antenatal education; for example, peer support, educational programme, didactic teaching session, workshop, booklets, etc, or a combination of these interventions for increasing breastfeeding duration.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All identified published, unpublished and ongoing randomised controlled trials comparing two different methods of antenatal breastfeeding education programmes, with or without formal antenatal breastfeeding education, on duration of breastfeeding. The randomised units can be clustered; for example, hospitals, communities or groups of pregnant women or individual women.

Types of participants

Pregnant women.

Types of intervention

Any type of antenatal education with breastfeeding components. Antenatal breastfeeding education is defined as breastfeeding information being imparted during pregnancy in a variety of forms.

This could be on an individual or group basis, include home visiting programmes; peer education programmes or clinic appointments specifically aimed at imparting breastfeeding knowledge; brochures or booklets; electronic education programmes; or a combination of these, and could involve prospective fathers or not.

Types of outcome measures

Primary outcomes
Duration of any breastfeeding
Duration of exclusive breastfeeding
Proportion of mothers breastfeeding at three and six months
Proportion of mothers exclusively breastfeeding at three and six months
Initiation rate of breastfeeding

Secondary outcomes
Maternal satisfaction
Breastfeeding complications such as mastitis and breast abscess
Infant growth by weight and head circumference
Neonatal sepsis
Taking child to doctor
Hospital admission for child

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

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) monthly searches of MEDLINE;
(3) handsearches of 30 journals and the proceedings of major conferences;
(4) weekly current awareness search of a further 37 journals.

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 'Search strategies for identification of studies' 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 the Cochrane Central Register of Controlled Trials (*The Cochrane Library*) using the following terms:
#1 antenatal (MeSH)
#2 prenatal (MeSH)
#3 education*
#4 breastfeeding
#5 (breast next feeding)
#6 breast-feeding
#7 lactation*
#8 nursing
#9 (#1 or #2)
#10 (#4 or #5 or #6 or #7 or #8)
#11 (#9 and #3 and #10)

We will also adapt the search strategy to search MEDLINE (January 1966 to current) and EMBASE (January 1985 to current) by selecting appropriate MeSH and/or keywords from their respective thesauri. We will contact investigators (in the retrieved articles) and other content experts known to us for unpublished trials. Furthermore, we will look for relevant trials in the references of the retrieved articles.

We will not apply any language restrictions.

METHODS OF THE REVIEW

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). 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) 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 breastfeeding duration among the pregnant women without awareness of the interventions they received;
(B) unclear blinding explanation: such as study does not report if outcome assessor blinded;
(C) inadequate blinding explanation: such as outcome assessors measured breastfeeding duration among women with knowledge of their randomised 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 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 2003) 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
We will carry out statistical analysis using the Review Manager software (RevMan 2003). We will report breastfeeding duration and other continuous outcomes using mean difference with 95% confidence intervals (CI) if the 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. For the outcomes measured in dichotomous data, we will present relative risks with 95% CIs.

We plan to evaluate the following comparisons by subgroup analysis:
(1) an education programme versus no formal education;
(2) one form of education programme versus other form of education programme;
(3) programs involving multiple methods of providing education compared to those using a single method;
(4) different combinations of multiple methods of providing education.

We will assess heterogeneity by viewing the forest plots from the data from the trials' outcomes and by using the I^2 statistic (Higgins 2005) with 95% CI. If we find statistical heterogeneity among the trials, inconsistent forest plots and I^2 exceeding 50%, we will look for an explanation using subgroup analyses. The analyses will be conducted where sufficient data are available according to the following specified factors: type of intervention, trial setting, maternal education and maternal occupation. If trials in individual subgroups of the potential factors are thought to be comparable by interaction test as described by Deeks (Deeks 2001), we will use a random-effects meta-analysis for estimating an overall summary. Alternatively we will use a fixed-effect meta-analysis for combining data.

We are aware of potential variations in units of analysis across trials. 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 include cluster-randomised trials in the analyses along with individually-randomised trials. Their sample sizes will be adjusted using the methods described by 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.

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.

We will carry out sensitivity analyses to explore the effect of trial quality and, where appropriate, cluster-randomised trials on the meta-analysis conclusion. The trial quality will involve an 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. 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.

POTENTIAL CONFLICT OF INTEREST

None known.

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COVER SHEET

Title	Antenatal breastfeeding education for increasing breastfeeding duration
Authors	Lumbigannon P, Martis R, Laopaiboon M, Festin MR, Ho JJ, Hakimi M
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Meditation therapies for attention deficit /hyperactivity disorder (Protocol)

Krisanaprakornkit T, Witoonchart C, Krisanaprakornkit W

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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 concentrative and mindfulness meditation therapies for treating attention deficit /hyperactivity disorders in children, adolescents and adults.

BACKGROUND

The essential feature of attention-deficit hyperactivity disorder (ADHD) is 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. Prevalence estimates of ADHD vary according to the diagnostic criteria used and the population sampled. Cultural environment and the differing attitudes of parents, clinicians and society towards acceptable child's behaviour may influence diagnosis (Dwivedi 2005). DSM-IV prevalence estimates among school children in the US are 3-7%DSM-IV-TR 2000, but other estimates range from 1.7% to 16.0% (Pritchard 2005). Boys are diagnosed with ADHD three times more often than girls. An independent diagnostic test for ADHD does not exist, and thus the diagnoses of ADHD is clinically based. Evidence attests to the strong influence of genetic factors on the expression of symptoms (Swanson 2001) .

The major symptoms of this disorder are developmentally inconsistent and chronic levels of inattention, impulsiveness, and hyperactivity (Scahill L 2000). The essential feature of attention-deficit hyperactivity disorder is 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. Hyperactive-impulsive or inattentive symptoms that cause impairment must have been present before the age of seven in order for children to qualify for a diagnosis of ADHD. Furthermore, some impairment from the symptoms must be present in at least two settings (e.g., at home and at school or work). There must be clear evidence of interference with developmentally appropriate social, academic, or occupational functioning. To accurately diagnose ADHD, it must be ensured 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. The Diagnostic and Statistical Manual of Mental Disorders- 4^{th}edition-Text Revision(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 Disease-10 (ICD-10), the disorders are defined under the category of " Hyperkinetic Disorders " which is characterized by : early onset; a combination of overactive, poorly modulated behaviour with marked inattention and lack of persistent task involvement , and pervasiveness over situations and persistence over time of these behavioural characteristics (WHO 1992).

Children with ADHD have pronounced impairments and can experience long-term adverse effects on academic performance, vocational success, and social-emotional development which have a profound impact on individuals, families, schools, and society (NIH 1998). Studies have indicated that children diagnosed as having attention deficit disorder with hyperactivity plus a comorbid anxiety or depressive disorder had higher levels of coexisting

life stresses and parental symptoms than did children who had the single diagnosis of attention deficit disorder with hyperactivity (Jensen 1993).

Symptoms of ADHD evolve over the 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 fidgetiness 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) (DSM-IV-TR 2000). Other adults may retain only some of the symptoms, in which case the diagnosis of Attention-Deficit/Hyperactivity Disorder, In Partial Remission, should be used.

Non-pharmacological treatment of ADHD in childhood can be divided into three categories which are: parent- / family- focused strategies, child-directed interventions and school interventions (ICSI 2005). Psychostimulant medications are considered first-line therapy as they are effective in 70-80% of children with ADHD, although their use may be limited both by tolerability and acceptability. Augmentation of psychostimulant treatment with psychosocial interventions provides no advantage over medication alone for the core symptoms of ADHD, but does have an advantage for associated problems such as anxiety disorders, social skills difficulties, consumer satisfaction, and possibly academic achievement (MTA 1999).

Growing scientific evidence, clinical experience and community attitudes are encouraging a shift to more natural and holistic forms of therapy as alternatives or adjuncts to pharmacological approaches in a variety of conditions (Arias 2006; Mansky 2006; Krisanaprakornit 06).

Meditation is a growing treatment of 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). From this definition, meditation might be used as a tool for attentional training in the ADHD population. Apart from increased attention, meditation may produce state of calmness and contentment which are generally lacking in ADHD (Jensen 2004). Meditation is easily adapted to the general medical setting by adequately trained practitioners who have first hand experience of this form of therapy (Hassed 1996). Meditation originated in India more than 3,000 years ago, long before the advent of contemporary psychological treatments and has existed in the ritual practice of major religions and in many secular organisations. There are two general types of meditation: '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 which was developed subsequently (Benson 1975). Concentrative meditation emphasises focusing the attention onto an object and sustaining attention until the mind achieves stillness. The objects of focusing could be varied from words, light, colours, geometric forms, ideas etc. Relaxation, clarity of mind, calmness are intended to result from continuous practice.

Mindfulness meditation is another kind of meditation which emphasizes an open awareness to any contents of the mind that are emerging. After a period of practice, the patient is supposed to develop a sustainable attentive observational capability, without reacting to their own thoughts and emotions. Mindful state with equanimity helps to retrain or decondition the previous pattern of reaction which is usually poorly adapted to external reality. It is represented by mindfulness-based stress reduction programs (Kabat-Zinn 1992). The techniques of mindfulness meditation which focus on awareness to develop a detached observation of the contents of consciousness may represent a powerful cognitive behavioural coping strategy for transforming the ways in which we respond to life events (Astin 1997).

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 toward a single object or point of focus. The aim is one-pointed attention to a single perception without distraction in order to produce the concentration or one-mindedness state.
2. Mindfulness meditation (opening-up, insight meditation) involves the continual maintenance of a specific perceptual-cognitive set toward objects as they spontaneously arise in awareness with a nonreactive 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 definition i.e. insight meditation, mindfulness-based meditation, Vipassana, Qiqong therapy, Pranayama (Hindu breathing meditation), Yoga (Asana, Raja Yoga, Asthanga Yoga, Laya Yoga, Sahaj Marg etc), Tai Chi, Transcendental Meditation, Kundalini Yoga, Anapanasathi (Buddhist breathing meditation), Zen, ChunDo-SupBup(Korean style meditation) . Noted that Asana Yoga (yoga of posture) and Tai Chi are also considered to be dynamic aspects of concentrative meditation . Although meditation was historically associated with religious or spiritual movements, this is no longer always the case. It is now very 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 organisations which use more scientific-based, less mystical terms to identify their techniques (Krisanaprakornit 06).

Some reports exist of 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, Marylan, 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. Pauline et al conducted a randomized controlled trial of the effect of yoga on boys with ADHD(n=11) (Jensen 2004). The program consist of respiratory training, postural training, relaxation training and concentration training involved a technique called Trataka where participants focused on a word or shape, followed by seeing the image with eye 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 under statistical powered and inconsistency of home practice among participants.

Hassasiri et al (Hassasiri 2002) developed a meditation program for children with ADHD in Thailand based on Neo-humanist concept which comprised of meditation and imagery . The program was tested in pre-post test design with purposive sampling and yielded the statistical significance different of change scores ($p<0.05$).

In terms of the adverse effects of meditation, reports exist suggesting that meditation can cause temporary depersonalisation and derealisation (Castillo 1990), and there exist several reports of a possible association between meditation and psychotic state (French 1975; Lazarus 1976; Walsh 1979; Chan-Ob 1999). Studies of meditation in pediatric populations are still limited. For young children, 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 recommendations of meditation practice for children i.e. Sahaj Marg Meditation, a system of Raja Yoga. Sahaj Marg guru recommends a minimum age of 18 before beginning the practice of meditation, implying this technique is not suitable for younger people . Regarding 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 .

To our knowledge, no systematic review has been carried out specifically on the effectiveness of meditation for ADHD, although several clinical trials have been conducted and this review aims to address that gap.

OBJECTIVES

To assess the effects of concentrative and mindfulness meditation therapies for treating attention deficit /hyperactivity disorders in children, adolescents and adults.

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.

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 intervention

Meditation therapy, consisting of concentrative meditation, mindfulness meditation or combination of both, provided as the main intervention in the case of multi-component therapy.

Exclusion criteria
Meditation therapy that was not a well-organized program i.e. no structure, no schedule of practice, no formal setting.

Comparison conditions: may be one or combination of
1) Pharmacological therapy.
2) No intervention or waiting list.
3) Other psychological treatment : cognitive-behavioural therapy, parent training program, counseling etc.

Types of outcome measures

Trials reporting at least one of the following outcome measures will be included.
Primary outcomes;
A. Symptoms of ADHD
- Incidence/severity of the core symptoms (inattention, impulsivity, hyperactivity) measured by validated symptoms rating scale : including:
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)
Test of Variable of Attention (TOVA) (Greenberg 1999)
Connors Continuous Performance Test (Connors 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)
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. Psychophysiologic measures :

Electroencephalography(EEG)
Actograph pedometer by using devices monitor child's movements and displayed as actograph which provides an objective indicator of general motor activity.

C. Overall incidence/severity of the problem behaviours :

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

Standardised measures including the intelligence scale, including:
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 Scale:

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

See: methods used in reviews.

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 titles or key words of the articles. Operational definitions of meditation are mentioned in the background section, above.

The following sources will be searched:

1. Electronic databases: these will be searched with the help of the Trials Search Co-ordinator of The Cochrane Developmental, Psychosocial and Learning Problems Group (CDPLPG)
1.1 The Cochrane Central Register of Controlled Trials (CENTRAL)
1.2 MEDLINE (from 1966) and OLDMEDLINE(pre 1966) will be searched via PubMed
1.3 EMBASE
1.4 Campbell Collaboration SPECTR(C2-SPECTR)
1.5 ERIC. Educational Resources Information Center (ERIC)
1.6 LILACS (Latin American Health Sciences Literature)
1.7 CINAHL (Nursing and Allied Health)
1.8 PsycINFO (Psychological literature)
1.9 International Dissertation Abstracts (http://wwwlib.umi.com/dxweb)
1.10 Complementary and Alternative Medicine specific databases will be searched:
CISCOM- Centralized Information Service for Complementary Medicine (CISCOM)
1.11System for Information on Grey Literature in Europe(SIGLE)
1.12 Health Services/Technology Assessment Text (HSTAT) database
1.13 The Australasian Medical Index.
1.14 The Chinese Biomedical Literature Database
1.15 The Gale Directory of Online (http://www.dialog.com)
1.16 The Japan Information Centre of Science and Technology File on Science, Technology and Medicine (JICST-E)
1.17 Research database of psychiatric and mental health of Jittavej KhonKaen Hospital (www.jvkk.go.th) , Thai Thesis, Thailand.

The search terms for PubMed will be :
("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 (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized 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]).

This search strategy will be modified where necessary to search the other databases listed.

2. Searching of relevant conference proceedings.
3. Search for the relevant studies cited in book chapters on the treatment of attention deficit/hyperactivity disorder.

4. Personal communication:
4.1 The authors of the included studies and experts in the fields will be consulted to find out whether they know about any published or unpublished RCTs/ CCTs of meditation therapy and ADHD, which have not yet been identified. The organisation/personal contact will be made with persons whose work relates to meditation (i.e. Associacion de Medicinas Complementarias(AMC), The National Center for Complementary and Alternative Medicine (NCCAM)).
4.2 Religious/spiritual organizations around the world (Internet web sites were extensively searched including Internet mailing lists) to find out whether they have conducted or know of the application of meditation in ADHD .
4.3 Organizations with resources for ADHD worldwide : Children and Adults with Attention Deficit Disorders(http://www.chadd.org) , The Council for Exceptional Children(http://www.cec.sped.org) , Parent Advocacy for Children 's
Educational Rights(http:www.pacer.org) etc.

5. Ongoing trials will be sought by searching:
metaRegister of Controlled Trials (mRCT)
Current Controlled Trials (http://www.controlled-trials.com/)
Health Services Research Projects in Progress(HSRProj)
National center for Complementary and Alternative Medicine under NIH
ClinicalTrials.gov
TrialsCentral^{TM}The National Research Register (NRR) Trials Register of Promoting Health Interventions (TRoPHI).

6. Checking reference lists found in 1-3.

SciSearch and Science Citation Index of included and excluded studies will be searched for further relevant studies.

METHODS OF THE REVIEW

Selection of studies
Two reviewers (KT and WC) will independently screen the titles and abstracts obtained by the search strategies against the eligibility criteria stated above.
Verification of study eligibility will be done by KT and WC before data abstraction.
For articles that appear to be eligible RCTs, the full articles will be obtained and inspected to assess their relevance, based on the pre-planned criteria for inclusion.

Data extraction and management
Data will be independently extracted by two reviewers (KT and WC) using a predesigned data collection form, and saved electronically with appropriate version control. The data collection form will be pilot tested for clarity, relevance to the study questions and completeness. The instruction for codings and meanings will be placed adjacent or near to the data field that is to be coded. The coding of the form with a revision date or version number will be applied to ensure ease of update. Any unpublished information if used will be written and coded with a specified remark. The comparison of extracted data will be done by each author independently. Any disagreements will be discussed with a third reviewer (KW), and the decisions documented.

Where there are missing data, and where no information is provided about adverse events, we will contact the authors using every means available (e-mail, formal letter, facsimile, telephone call).

All relevant data will be entered into RevMan 4.2.9 by KT and re-checked by WC for correctness. The reliability of data extraction and data entry will be examined throughout the process.

In case of trials using a crossover design, all data will be abstracted. Data of the first phase of study will only be used for analysis. The data of the second phase after crossing over will be described in the characteristics of included study table, but not in the comparisons and data table .

Assessment of methodological quality
According to the evidence of a strong relationship between the potential for bias in the results and allocation concealment , adequacy of allocation concealment will be judged (Higgins 2006).
A: Adequate
B: Unclear
C: Inadequate
D: Not used

The methodological quality of the selected trials will be assessed independently by two reviewers (KT and WC), using the approach

described in the Cochrane Handbook for Systematic Reviews of Interventions 4.2.5. The criteria are based on and are defined below:
1. Was the randomness of the allocation procedure adequate?
2. Was the allocation concealment properly done?
3. Were treatment programmes, other than the interventions, identical?
4. Were important baseline characteristics reported and comparable?
5. Were the outcomes of patients who withdrew described and included in the analysis?
6. Were the outcome measurements clearly defined and done by blind assessors?
Each question may be answered Met, Partly Met, Not Met.

Three quality categories are set:
A. Low risk of bias - all of the criteria met.
B. Moderate risk of bias - one or more criteria partly met.
C. High risk of bias- one or more criteria not met .

Disagreements will be resolved through consensus, or referred for arbitration by the editorial base of the CDPLPG if needed.

Data analysis
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?

For cross-over studies, to exclude the potential additive effect in the second or more stages on these trials, only data from the first stage will be use in analysis.

In studies with multiple treatment groups, the analysis will be done for each pair between meditation and other treatments.

In studies with cluster randomised trials (e.g. randomisation by clinician or treatment settings), unless the cluster effect was not accounted, analysis and pooling of clustered data will result in unit of analysis error and overestimate of statistical significant. In these cases, the authors of studies will be contacted to obtain intra-class correlation coefficients (ICC) of their clustered data and to adjust by using accepted methods after consulting CDPLPG. Where clustering has been incorporated into the analysis of primary studies, we will also present these data as if from a non-cluster randomised 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 accounting of '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 intracluster correlation coefficient. If the ICC was not reported it will be assumed to be 0.05 (Higgins 2006).

In studies with repeated measures, the analysis will be done by separating the outcome into short term (up to 3 months); intermediate term (3-12 months) and long term (more than 12 months).

Any meta-analysis will consider:
1. different types of outcome (dichotomous, continuous, survival data)
2. Study design
3. Follow-up length (short term, intermediate, long term).

Dichotomous outcomes
Dichotomous outcomes will be pooled using the risk ratio as the summary statistic. When overall results are significant, risk differences will be calculated using absolute effect measures then the number needed to treat (NNT) will be calculated (where no clinical, methodological or statistical heterogeneity are evident).
In case of the numbers of participants and numbers of events are not available, but results calculated from them are risk ratio, odds ratio, adjusted odds ratio, the data will be included in meta-analyses only if they are accompanied by measures of uncertainty such as a 95% confidence interval or an exact P-value. Then the study-specific effect sizes will be pooled using the generic inverse variance method in RevMan 4.2.9.

Continuous outcomes
Data on continuous outcomes will be analysed in RevMan 4.2.9 using either mean differences or standardised mean differences if continuous outcomes are measured with similar, but not identical, instruments across studies. If the studies provide another statistics other than means and standard deviations (e.g. standard error, t-value, p-value) the proper mathematical transformation will be performed to obtain standard deviation.

Statistics for meta-analysis are thought to be able to cope with some skew, but are formulated for parametric data. To ensure the appropriateness of meta-analysis, the following standards will be applied to all data before inclusion:
1. Standard deviations and means were reported, calculated or obtained from authors.
2. For data with finite limits, such as the 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) .
3. 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 are reported, authors of studies will be contacted for endpoint figures. If only the change score is available, standard deviation of change score is needed for analysis, and if available, the data will be combined with endpoint scores (unless the standardised mean difference is used).
If the available data can not be managed by the above criteria, the data will be put into the 'other data' tables and narrative approach to synthesis will be used.

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.

Intention-to-treat analyses
For the included studies which used the 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). The authors will be contacted for available data.

The statistical model of meta-analysis
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. A fixed effect model will be used for all analyses if there is no statistical heterogeniety. A random effects meta-analysis may be used to incorporate heterogeneity among trials and will be applied only after exploring the causes of heterogeneity or when heterogeneity cannot readily be explained.

Analysis of Heterogeneity
A test for homogeneity and I-square which provides an estimate of the percentage of variability due to heterogeneity will be done using Review Manager 4.2.9 .
Heterogeneity can occur from many sources. An important aspect of every meta-analysis is to consider and emphasise the existence of heterogeneity and to take account of this in the interpretation of results. Sources of heterogeneity (clinical heterogeneity) can be divided in to two groups: biologic and methodologic .
Biological :
1. Characteristic of patients: age, sex, socioeconomic status, education.
2. Subtype of attention deficit/hyperactivity disorders etc.
3. Disorder severity and chronicity: mild, moderate, severe.
4. Comorbidity of emotional/psychiatric problems, speech /language problems, learning problems, psychosocial problems, conduct disorder.

Methodological :
1. Type of meditation
(a) Techniques:

- concentrative, mindfulness meditation or combination
- combination of different techniques of meditations (physical and mental practice, such as Yoga)
- other ingredients of treatment ; group activities, pray , recreational activities, etc.

(b) Intensity and frequency of practice: duration of meditation per treatment session, frequency of practice , duration of practice .

2. Different follow up period: at the end of trial, any specified period after trial, repeated follow up measure.

3. Multi-component intervention: drugs, counselling, biofeedback, parent training, psychotherapy, family therapy etc.

Strategies for exploring heterogeneity:
1. Identification of the methodological differences between studies.
2. Identification of the biological differences in study sample.
3. Subgroup analysis
4. Meta-regression if enough data are available(Meta-regression should generally not be considered when there are fewer than 10 trials in a meta-analysis) (Higgins 2006).

Subgroup analysis
Due to clear differences in characteristics, rather than undertaking an overall pooled analysis, the data will be analysed in subgroups according to the following categories:
- childhood (under 13 years)
- adolescence (13-18 years)
- adult ADHD(age more than 18 years).

Subgroup analyses will only be undertaken if a sufficient number of studies are identified.

Sensitivity analysis:
A sensitivity analysis will be used to test the robustness of effects of assumptions by examining the influence of the following on the results of the statistical analyses:
1. the effect of the quality criteria (determine the effect of studies with high risk of bias to the overall effect).
2. blinding(masking) of raters.

Assessment of bias
If possible, a funnel plot (Light 1984; Egger 1997) will be used to determine potential publication bias, by plotting the effect size against sample size. Publication bias may result when trials with negative results are under-represented.

Any other types of bias of each studies (e.g. selection, measurement, attrition bias) will be reported in the results and discussion.

POTENTIAL CONFLICT OF INTEREST

TK runs the Meditation Therapy Clinic for various types of patients at the Department of Psychiatry, Faculty of Medicine, KhonKaen University, Thailand.
No potential conflict of interest for other authors.

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Pars plana vitrectomy for diabetic macular edema (Protocol)

Yospaiboon Y, Ratanapakorn T

This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2007, Issue 4

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:
The objective of this review is to assess the effects of pars plana vitrectomy, with or without peeling of the internal limiting membrane, in patients with refractory diabetic macular edema who have had one or more laser treatments.

BACKGROUND

Description of the condition

Diabetic macular edema (DME) is an important cause of severe vision loss in patients with diabetic retinopathy. Diabetic macular edema results from leakage of intraretinal fluid from both microaneurysms and abnormal retinal capillaries. Thickening of the basement membrane and reduction in the number of pericytes is believed to lead to increased permeability and incompetence of the retinal vasculature. The pathogenesis of DME is multifactorial including increased diastolic blood pressure, duration of diabetes, age at diagnosis, female sex, use of insulin, level of glycosylated hemoglobin, degree of proteinuria, cardiac decompensation and more severe diabetic retinopathy. These factors presumably lead to a breakdown in the blood-retina barrier, causing macular edema (Klein 1995).

The World Health Organization estimates that 15 million people in the USA and more than 150 million people worldwide have diabetes and if untreated, there is a 25% to 30% risk of developing clinically significant macular edema with moderate visual loss. Data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) estimate that after 15 years of known diabetes, the prevalence of it is approximately 20% in patients with type 1 diabetes mellitus (DM), 25% in patients with type 2 DM who are taking insulin, and 14% in patients with type 2 DM who do not take insulin (Klein 1995).

Clinically, DME is best detected by slit-lamp biomicroscopy with a contact lens or by a hand held lens. The Early Treatment Diabetic Retinopathy Study (ETDRS) defined clinically significant macular edema as retinal edema located at or within 500 μm of the center of the macula, hard exudates at or within 500 μm of the center if associated with thickening of the adjacent retina and a zone of thickening larger than one disc area if located within one disc diameter of the center of the macula (ETDRS 1985).

Description of the intervention

Several approaches to the treatment of DME have been attempted with a variable degree of success. These include topical and systemic steroids, topical and oral non-steroidal anti-inflammatory agents and laser photocoagulation treatment. The ETDRS demonstrated that eyes with DME benefited from focal argon laser photocoagulation treatment when compared with untreated eyes. Laser treatment reduced the risk of moderate visual loss and increased the chance of visual recovery (ETDRS 1985). More recently other therapeutic modalities, including immunomodulators, intravitreal injection of triamcinolone and pars plana vitrectomy, have also been employed.

How the intervention might work

Vitrectomy, with or without internal limiting membrane peeling, can be beneficial for the treatment of DME that is resistant to laser photocoagulation (Gandorfer 2000; Otani 2002; Stolba 2005; Yamamoto 2003; Yanyali 2005). Visual improvement has been reported in approximately 40% to 90% of patients with approximately 85% to 100% experiencing either improvement or stabilization of vision (Grigorian 2003). Macular edema decreases or resolves in approximately 70% to 100% of patients (Grigorian 2003). Complications range in severity with approximately 5%

to 20% of patients developing peripheral retinal breaks, approximately 1% to 2% developing retinal detachment, approximately 2% developing macular hole and approximately 10% to 60% developing cataract (Grigorian 2003). Severe complications such as rubeosis iridis and the fibrinoid syndrome have also been reported.

Why is it important to do this review

Several clinical studies have demonstrated that vitrectomy, with or without internal limiting membrane peeling, leads to macular edema resolution and visual improvement of two or more lines in 38% to 92% of the eyes. However, the majority of these studies are retrospective and some are small case series.

OBJECTIVES

The objective of this review is to assess the effects of pars plana vitrectomy, with or without peeling of the internal limiting membrane, in patients with refractory diabetic macular edema who have had one or more laser treatments.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

We will include relevant randomized controlled trials and quasi-randomized trials.

Types of participants

The participants will be diabetic patients who had clinically significant macular edema as defined by ETDRS, despite previous macular laser treatments.

Types of intervention

We will include trials that compare pars plana vitrectomy with or without internal limiting membrane peeling to laser treatment in patients with refractory diabetic macular edema.

Types of outcome measures

Primary outcome

Change in best-corrected visual acuity at six months. We will define visual improvement as the difference between baseline and six-month best-corrected visual acuity and classify vision as improved when there is a two or more line improvement in Snellen acuity. We will note the percentage of patients with improved vision at six months.

Secondary outcomes

(a) Change in central macular thickness at six months. We will note the reduction in mean central macular thickness measured by optical coherence tomography (OCT) or other relevant retinal thickness analyzer devices at baseline and six months.

(b) Adverse effects. We will report any sight-threatening complications resulting from pars plana vitrectomy with or without internal limiting membrane peeling, such as cataract progression, retinal breaks, retinal detachment, rubeosis iridis and neovascular glaucoma. In addition, we will include any adverse events from laser macular treatments.

(c) We will include vision related quality of life measured by the Visual Function Index (VF-14) and National Eye Institute Visual Function Questionnaire (NEI-VFQ).

(d) We will also consider economic data comparing the cost and effectiveness of both pars plana vitrectomy and laser macular treatment.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

Electronic searches

We will search the Cochrane Central Register of Controlled Trials - CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) in *The Cochrane Library*, MEDLINE, EMBASE and LILACS. We will not apply any date or language restrictions in the electronic searches for trials.

We will use the following strategy to search CENTRAL:
#1 MeSH descriptor Diabetic Retinopathy
#2 macular edema cystoid
#3 macular degeneration
#4 macula* near edema
#5 macula* near oedema
#6 DME
#7 DMO
#8 CME
#9 CSME
#10 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11 MeSH descriptor Vitrectomy
#12 par* near plana near vitrectom*
#13 PPV
#14 (#11 OR #12 OR #13)
#15 (#10 AND #14)

We will use the following strategy to search MEDLINE:
1 exp clinical trial/ [publication type]
2 (randomized or randomised).ab,ti.
3 placebo.ab,ti.
4 dt.fs.
5 randomly.ab,ti.
6 trial.ab,ti.
7 groups.ab,ti.
8 or/1-7
9 exp animals/

10 exp humans/
11 9 not (9 and 10)
12 8 not 11
13 exp diabetic retinopathy/
14 exp macular edema cystoid/
15 exp macular degeneration/
16 (macula$ adj2 edema).tw.
17 (macula$ adj2 oedema).tw.
18 DME.tw.
19 DMO.tw.
20 CME.tw.
21 CSME.tw.
22 or/13-21
23 exp vitrectomy/
24 (par$ adj2 plana adj2 vitrectom$).tw.
25 PPV.tw.
26 PPV$.tw.
27 or/23-26
28 22 and 27
29 12 and 28

The search strategy at the beginning of the MEDLINE search is from the published paper by Glanville et al (Glanville 2006).

We will use the following strategy to search EMBASE:
1 exp randomized controlled trial/
2 exp randomization/
3 exp double blind procedure/
4 exp single blind procedure/
5 random$.tw.
6 or/1-5
7 (animal or animal experiment).sh.
8 human.sh.
9 7 and 8
10 7 not 9
11 6 not 10
12 exp clinical trial/
13 (clin$ adj3 trial$).tw.
14 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15 exp placebo/
16 placebo$.tw.
17 random$.tw.
18 exp experimental design/
19 exp crossover procedure/
20 exp control group/
21 exp latin square design/
22 or/12-21
23 22 not 10
24 23 not 11
25 exp comparative study/
26 exp evaluation/
27 exp prospective study/
28 (control$ or prospectiv$ or volunteer$).tw.
29 or/25-28
30 29 not 10
31 30 not (11 or 23)
32 11 or 24 or 31
33 exp diabetic retinopathy/
34 exp retina macula cystoid edema/
35 exp retina macula degeneration/
36 (macula$ adj2 edema).tw.
37 (macula$ adj2 oedema).tw.
38 DME.tw.
39 DMO.tw.
40 CME.tw.
41 CSME.tw.
42 or/33-41
43 exp vitrectomy/
44 (par$ adj2 plana adj2 vitrectom$).tw.
45 PPV.tw.
46 PPV$.tw.
47 or/43-46
48 42 and 47
49 32 and 48

We will search LILACS using the string (macula$ edema or macula$ oedema) and (PPV or vitrectom$).

Other sources
We will search the reference lists of identified articles and contact investigators to locate additional published and unpublished studies. We will not handsearch conference proceedings or journals specifically for this review.

METHODS OF THE REVIEW

Selection of studies
Both authors will independently review the abstracts of studies identified by the searches and select relevant papers according to the definitions in 'Criteria for considering studies for this review'. We will obtain full copies of all reports referring to possible trials to assess their relevance to the review. We will document in the excluded studies table those reports that we exclude after obtaining full copies.

Assessment of methodological quality of included studies
Both authors will assess trial quality according to the methods set out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2006). We will consider four parameters: allocation concealment; method of allocation; documentation of exclusions and completeness of follow up. We will grade each parameter of trial quality: A adequate; B unclear; C inadequate. We will resolve discrepancies by discussion. We will not be masked to any trial details during the assessment. We will contact study authors for further information on any item graded B.

Data extraction and management

Both authors will independently extract the data for the primary and secondary outcomes on to a form developed by the Cochrane Eyes and Vision Group. One author will enter data into RevMan and the second author will re-enter the data using the double-data entry facility to check for errors. The authors will resolve any differences by discussion. If there is any doubt about the data of the trial, the review authors will contact the authors of the trial.

Measures of treatment effect

We will conduct the data analysis using Section 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2006). For change in best-corrected visual acuity, we will express the percentage of patients achieving improved vision between two groups as relative risk and 95% confidence interval. For change in central macular thickness, we will compare the mean difference and standard deviation between two groups.

Dealing with missing data

When needed, we will always seek missing information and clarification about the statistics presented from the trial report authors. However, for several of the measures of variation there is an approximate or direct algebraic relationship with standard deviations, so it may be possible to obtain the required statistic even if it is not published directly in the paper.

Assessment of heterogeneity

We will assess clinical and methodological diversity by review of the papers. We will also check for heterogeneity using a statistic for quantifying inconsistency, I^2= [(Q - df)/Q] x 100%, where Q is the chi-squared statistic and df is its degrees of freedom (Higgins 2002; Higgins 2003). This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). A value greater than 50% may be considered substantial heterogeneity.

Data synthesis (meta-analysis)

We will use the fixed-effect model when there are fewer than three trials in a comparison. If considerable heterogeneity is detected we will not perform a meta-analysis but will give a descriptive summary of the results.

We will use the fixed-effect model if there are fewer than three trials in a comparison. If considerable heterogeneity is detected, we will not perform a meta-analysis but will give a descriptive summary of the results.

Sensitivity analysis

We will conduct a sensitivity analysis to assess the effect of excluding trials graded C on any aspect of trial quality and changing the cut-off point for inclusion and exclusion criteria.

POTENTIAL CONFLICT OF INTEREST

None known.

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COVER SHEET

Title	Pars plana vitrectomy for diabetic macular edema
Authors	Yospaiboon Y, Ratanapakorn T
Contribution of author(s)	Conceiving the review: YY Designing the review: YY Co-ordinating the review: YY Undertaking manual searches: YY, TR Screening search results: YY, TR Organising retrieval of papers: YY Screening retrieved papers against inclusion criteria: YY,TR Appraising quality of papers: YY, TR Abstracting data from papers: YY, TR Writing to authors of papers for additional information: YY Obtaining and screening data on unpublished studies: YY, TR Data management for the review: YY, TR Entering data into RevMan: YY, TR Analysis of data: YY,TR Interpretation of data: YY, TR Writing the review: YY Securing funding for the review: YY, TR Guarantor for the review: YY

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What's New	Information not supplied by author
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Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery (Protocol)

Suwannachat B, Lumbiganon P, Laopaiboon M

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TABLE OF CONTENTS

Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery (Protocol)

Suwannachat B, Lumbiganon P, Laopaiboon M

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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 rapid versus stepwise negative pressure application for assisted vaginal delivery by vacuum extraction.

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 to 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 (Miksovsky 2001). Rates of vacuum extraction vary around 10% in the Middle East and Canada (Shihadeh 2001; Cargill 2004), 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 labor, suspicion of actual or potential fetal compromise, and to shorten the second stage of labor 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/cm^2 every two minutes, to reach 0.8 kg/cm^2 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) - that an 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/cm^2 in as little as one minute (Kuit 1993). Potential adverse effects of rapid application of vacuum extraction include cup detachment, 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 will systematically evaluate 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.

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 intervention

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

- Success/failure rate of vacuum procedure
- Detachment rate
- Duration of vacuum extraction procedure
- Birth passage injury including degree of perineal tears, cervical and uterine tears
- Actual mode of delivery

(2) Fetal

- Birth asphyxia (according to trialists' definition)
- Fetal injury including scalp abrasions or lacerations, caput succedaneum, cephalhematoma, subgaleal hemorrhage, intracranial injury (rely on trialists' definition)
- Hyperbilirubinemia

Secondary outcomes

(1) Maternal

- Perineal pain after delivery
- Perineal wound infection
- Rectovaginal fistula
- Postpartum haemorrhage

(2) Fetal

- Retinal hemorrhage
- Breastfeeding failure
- Perinatal death

(3) Obstetrician Satisfaction

(4) Maternal Satisfaction

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

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) monthly searches of MEDLINE;
(3) handsearches of 30 journals and the proceedings of major conferences;
(4) weekly current awareness search of a further 36 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 'Search strategies for identification of studies' 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.

We will not apply any language restrictions.

METHODS OF THE REVIEW

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). Methods used for generation of the randomization sequence will be described for each trial.

(1) Selection bias (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.

(2) Attrition bias (loss of participants, e.g. discharge very soon after birth, 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 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.
High-quality trials will be defined as those receiving an A rating for selection bias and detection bias.

Data extraction and management
We will 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 2003) 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
We will carry out statistical analysis using the Review Manager software (RevMan 2003). We will report birth passage injury, postpartum haemorrhage, birth asphyxia, fetal injury and other binary outcomes using relative risk with 95% confidence intervals (CI). For the continuous outcomes, such as duration of second stage of labor, we will present mean difference with 95% CIs if the outcomes are measured in the same way between trials. We will use the standardized 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^2 statistic (Higgins 2005) with 95% CI. If we find statistical heterogeneity among the trials, inconsistent forest plots and I^2 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.

POTENTIAL CONFLICT OF INTEREST

None known.

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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COVER SHEET

Title	Rapid versus stepwise negative pressure application for vacuum extraction assisted vaginal delivery
Authors	Suwannachat B, Lumbiganon P, Laopaiboon M
Contribution of author(s)	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.
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Deliberate hypotension with propofol under anaesthesia for functional endoscopic sinus surgery (FESS) (Protocol)

Boonmak S, Boonmak P, Laopaiboon M

This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2007, Issue 4

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Deliberate hypotension with propofol under anaesthesia for functional endoscopic sinus surgery (FESS) (Protocol)

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:
We aim to compare the use of propofol versus other techniques for deliberate intra-operative hypotension during FESS procedures with regard to blood loss and operative conditions.

BACKGROUND

Chronic sinusitis is a common disease in any age group and may be defined as inflammation of the mucous membrane in the paranasal sinuses and fluid within the sinus cavity that lasts more than 12 weeks. The primary treatments for chronic sinusitis are antibiotics and topical nasal steroids. If these measures are not successful then sinus surgery is usually considered (Kennedy 2001; Yanez 2003). The most common procedure is functional endoscopic sinus surgery (FESS). FESS is a minimally invasive technique in which the sinus air cells and ostia are opened under direct visualization using an endoscopic technique (Khalil 2006), thereby restoring sinus ventilation (Stammberger 1991).

The use of FESS as a sinus surgical method has now become widely accepted (Khalil 2006). The number of FESS procedures that are performed has grown (Dalziel 2003; Dalziel 2006; Danielsen 2003). Compared to other more traditional methods, endoscopic sinus surgery is associated with fewer complications and greater symptomatic improvement (Dalziel 2006) including less postoperative pain, no external scars, and more rapid recovery. Complications related to FESS include bleeding, orbital haematoma, damage to intraorbital structures, epiphora, loss of vision, cerebrospinal fluid leak, damage to intracranial structures and death (Maniglia 1991; May 1994; Reinhart 1993; Stankiewicz 2001). The main problem in practice is intraoperative bleeding because of small areas of bleeding sites that can reduce visibility during FESS. This can result in abandonment of the procedure or unintentional destruction of surrounding structures.

Deliberate hypotension can reduce blood loss in many operations for example orthopedic surgery, maxillofacial surgery, and neurosurgery (Dutton 2004; Tobias 2002). A technique of deliberate hypotension during general anaesthesia may be employed where the aim is to lower the mean arterial blood pressure (MAP), to values between 50 and 65 mm Hg in normotensive patients, in order to significantly reduce blood loss (Clincikas 2003).While the precise mechanism cannot be defined, it is likely to be the result of either a reduction in cardiac output, blood pressure, or a combination of these factors (Aken 2000). This technique can reduce blood loss in FESS by between 80 to 141 millilitres (Clincikas 2003; Elsharnouby 2006). However, deliberate hypotension is not without potential complications which include permanent cerebral damage, delayed awakening, cerebral thrombosis, brain ischemias, and death (Aken 2000).

Techniques for deliberate hypotension include controlling venous return (for example through positioning of the patient) and a number of pharmacological interventions including volatile anaesthetics (halothane, isoflurane, sevoflurane, desflurane); direct-acting vasodilator drugs (sodium nitroprusside, nitroglycerine, hydralazine); trimethaphan; alpha-adrenergic receptor blocking drugs (phentolamine, urapidil); beta-adrenergic receptor blocking drugs (propranolol, esmolol); combined alpha and beta adrenergic receptor blocking drugs (labetalol); calcium channel block-

ers (nicardipine); and prostaglandin E1(Aken 2000; Dodds 2001; Morgan 2002). There are disadvantages with each of these approaches. For example, the use of nitroprusside or nitroglycerine may require escalating doses because of tachyphylaxis (Aken 2000); nitroprusside in large doses may result in cyanide intoxication (Bendo 2001); and both require invasive monitoring of the arterial blood pressure (Aken 2000). Volatile anaesthetics can prolong recovery and delay discharge (Aken 2000).

More recently, deliberate hypotension using the anaesthetic agent propofol has become popular. Propofol is commonly used during anaesthesia as both an induction agent and for maintenance of anaesthesia. It induces a state of general anaesthesia by involve facilitation of inhibitory neurotransmission mediated by gamma-amino butyric acid (GABA). Propofol has a rapid onset and recovery time with a short half-life and duration of action (Reves 2005). Disadvantages of propofol are that it is painful on injection and administration can decrease arterial blood pressure and cardiac output. The changes in blood pressure can be rapidly achieved in response to either bolus doses or infusion, as required (Reves 2005). For deliberate hypotension, many studies found that propofol seemed to be more effective in reducing blood loss than volatile anaesthetics (Aken 2000; Blackwell 1993; Dodds 2001; Eberhart 2003; Morgan 2002; Pavlin 1999). If propofol is superior to alternative agents in the conduct of deliberate hypotension for FESS then this would be important information for the anaesthetist in choosing the more appropriate technique. If, on the other hand, there are any clear disadvantages associated with propofol the information is equally important to the clinical practitioner.

OBJECTIVES

We aim to compare the use of propofol versus other techniques for deliberate intra-operative hypotension during FESS procedures with regard to blood loss and operative conditions.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

We will include all published and unpublished, randomized controlled trials (RCTs) comparing propofol versus other drugs for deliberate hypotension under general anaesthesia for FESS.

Types of participants

We will include patients of any age who received general anaesthesia for FESS with various deliberate hypotension techniques.

Types of intervention

We will compare propofol for deliberate hypotension (MAP lowered to values between 50 and 65 mm Hg) to other deliberate hypotension techniques during FESS under general anaesthesia.

Types of outcome measures

Our primary outcomes are the following.
1. total blood loss (blood loss during surgery as assessed, in millilitres; total blood loss will be measured as that collected in the suction apparatus and by weight of the nasal swabs);
2. mortality.

Our secondary outcomes are:
3. Operator assessment of quality of surgical field:

Good: slight bleeding, no suctioning required, occasional suctioning required or slight bleeding, frequent suctioning required and bleeding threatens surgical field a few seconds after suction is removed.
Fair: moderate bleeding, frequent suctioning required and bleeding threatens surgical field directly after suction is removed.
Poor: severe bleeding, constant suctioning required, bleeding appears faster than can be removed by suction, surgical field severely threatened and surgery usually not possible.

4. Operation time as assessed in minutes (from start until end of operation)
5. Complications from the deliberate hypotension technique as reported in a trial (such as mortality rate, permanent cerebral damage, delayed awakening, cerebral thrombosis, and brain ischemia).
6. Incidence of failed deliberate hypotension (defined as failure to reduce MAP to values between 50 and 65 mm Hg)
7. Need for re-operation
8. Need for admission to intensive care or ahigh dependency area postoperatively

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We will search the current issue of the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*), MEDLINE (1950 to present), EMBASE (1980 to present) and LILACS (1982 to present).

We will develop a specific strategy for each database. We will base each search strategy on that developed for MEDLINE (Additional Table 01) (please see: Additional Table 02 (CENTRAL); Table 03 (EMBASE); and Table 04 (LILACS)).

We will also identify trials by:
1. searching specialist journals i.e. *Anesthesia and Analgesia, Anesthesiology, Anaesthesia, Acta Anesthesiologica Scandinavica, British Journal of Anaesthesia, Canadian Journal of Anaesthesia, European Journal of Anaesthesia, Laryngoscope, American Journal of Otolaryngology, European Archives of Oto-rhino-laryngology;*
2. searching conference proceedings and abstracts (The American Society of Anesthesiologists (ASA), International Anaesthesia

Research Society (IARS), European Society of Anaesthesiologists (ESA));
3. contacting known trialists, experts and medical or pharmaceutical companies for unpublished trials;
4. searching grey literature (such as SIGLE);
5. checking the reference list of relevant articles.

We will not apply any language restriction.

METHODS OF THE REVIEW

We will use the standardized methods for conducting a systematic review as described by The Cochrane Collaboration in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005).

Selection of trials

Two authors (BS and BP) will independently scan the titles and abstracts of reports identified by electronic database and hand-searching of journals. We will obtain and assess the full article of any possibly and definitely relevant trials according to the definitions provided in the criteria for considering studies for this review. We (BS and BP) will resolve any disagreement by consensus, or if necessary, by consulting a third author (LM). If we cannot resolve differences then we will add the publication reference to those awaiting assessment and contact the study authors for clarification of study details. One author (BS) will summarize data from all included trials on a standardized data extraction form; that data will be checked by a second author (BP).

Assessing quality of trials

Two authors (BS and BP) will assess the methodological quality of each trial following the guidelines described by The Cochrane Collaboration in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005).

Our assessment criteria are:
1. randomization and allocation concealment: adequate, unclear, or inadequate, not used;
2. blinding of treatment: adequate, unclear, or inadequate;
3. blinded outcome assessment: adequate, unclear, or inadequate;
4. description of dropouts and withdrawals: adequate, unclear, or inadequate;
5. use of intention-to-treat analysis: yes, no, no information.

We will independently evaluate and rank the quality of each trial.

We will address any major differences in methodological quality by sensitivity analysis.

We will resolve any conflicts in assessment through discussion and, if necessary, through evaluation by a third author (LM).

Statistical analysis

We will useReview Manager 4.2 software (RevMan 4.2) for data analysis. We propose using a fixed-effect model where there is no evidence of significant heterogeneity between studies, and a random-effects model when such heterogeneity is likely (DerSimonian 1986). We will give consideration to the appropriateness of meta-analysis in the presence of significant clinical or statistical heterogeneity.

For proportions (that isdichotomous outcomes mortality, complications, incidence of failed deliberate hypotension, need for re-operation, need for postoperative admission to intensive care or a high dependency area), we will use relative risk (RR). We will convert continuous data (that is blood loss during surgery, operation time) to mean difference (MD) using the inverse variance method and calculate an overall MD. If trials use different scales or measures of the same outcome, we will calculate standardized mean difference (SMD). The data on quality of surgical field, which is an ordinal outcome, will be converted to a dichotomous outcome; good and fair will be defined as positive and poor will be defined as negative.

We will assess statistical heterogeneity using the I-squared (I^2) statistic (Higgins 2002) and give consideration to the appropriateness of pooling and meta-analysis. We will explore heterogeneity and perform subgroup analyses, if appropriate.

We will perform subgroup analysis where appropriate by calculation of RR or MD in each subgroup and by examination of the 95% confidence intervals. No overlap in the intervals will be taken to indicate a statistically significant difference between subgroups.
Where appropriate data exist, we will consider subgroup analyses based on:
1. age group (less than 15, 15 to 65, more than 65 years old);
2. MAP level;
3. anaesthetic technique (inhalation maintenance anaesthesia, intravenous maintenance anaesthesia);
4. hypotensive drug combination.

All analyses are to be made on an intention-to-treat basis where possible and using a fixed-effects model. We will calculate out tests of interaction to determine if the results for subgroups are significantly different. We will assume statistical heterogeneity to be significant if the I^2analysis suggests that more than 30% of the variability in an analysis was due to differences between trials. We will then give consideration to the appropriateness of pooling and meta-analysis; when analysis is undertaken in the face of statistical or clinical heterogeneity we will use a random-effects model.

We will test for publication bias using funnel plots or other corrective analytical methods, depending on the number of clinical trials included in the systematic review.

We intend to perform sensitivity analyses for missing data and study quality. In the case of missing data, we will employ sensitivity analyses using different approaches to imputing missing data. The best-case scenario will assume that none of the originally enrolled patients that were missing from the primary analysis in

the treatment group had the negative outcome of interest whilst all those missing from the control group did. The worst-case scenario will be the reverse. If appropriate, we will also conduct sensitivity analysis by study quality based on the presence or absence of a reliable random allocation method, concealment of allocation, and blinding of participants or outcome assessors.

POTENTIAL CONFLICT OF INTEREST

None known.

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ADDITIONAL TABLES

Table 01. Search strategy for SilverPlatter MEDLINE (WebSPIRS) (1950 to date)

search number	search terms
1	explode "Propofol-" / all SUBHEADINGS in MIME,MJME,PT
2	explode "Hypotension-" / all SUBHEADINGS in MIME,MJME,PT
3	hypoten*
4	explode Anesthesia, General/ all subheadings
5	"Anesthesia-Inhalation-+" / all SUBHEADINGS in MIME,MJME,PT
6	an?esthesia
7	propofol or diprivan or disoprofol or pofol

8	#1 or #2 or #3 or #4 or #5 or #6 or #7
9	explode “Paranasal-Sinus-Diseases” / all SUBHEADINGS in MIME,MJME,PT
10	explode “Paranasal-Sinuses” / all SUBHEADINGS in MIME,MJME,PT
11	“Endoscopy-” / all SUBHEADINGS in MIME,MJME,PT
12	surg* near (paranas* or endoscop* or microscop*)
13	nasal
14	sinus* near (maxilliary or frontal or ethmoid or sphenoid)
15	explode “Ethmoid-Sinus” / all SUBHEADINGS in MIME,MJME,PT
16	explode “Frontal-Sinus” / all SUBHEADINGS in MIME,MJME,PT
17	explode “Maxillary-Sinus” / all SUBHEADINGS in MIME,MJME,PT
18	explode “Sphenoid-Sinus” / all SUBHEADINGS in MIME,MJME,PT
19	(“Paranasal-Sinus-Neoplasms-+” / all SUBHEADINGS in MIME,MJME,PT) or (“Sinusitis-+” / all SUBHEADINGS in MIME,MJME,PT)
20	intranasal or paranasal or endonasal
21	“Nasal-Cavity” / all SUBHEADINGS in MIME,MJME,PT
22	explode “Otorhinolaryngologic-Surgical-Procedures” / all SUBHEADINGS in MIME,MJME,PT
23	(surg* (paranas* or endoscop* or microscop*)) and (nasal or endonas* or intranas* or paranas*)
24	sinus* and (maxilliary or frontal or ethmoid or sphenoid)
25	rhin* not rhinoceros
26	#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25
27	#8 and #26
28	RANDOMIZED-CONTROLLED-TRIAL in PT
29	CONTROLLED-CLINICAL-TRIAL in PT
30	RANDOMIZED-CONTROLLED-TRIALS
31	RANDOM-ALLOCATION
32	DOUBLE-BLIND-METHOD
33	SINGLE-BLIND-METHOD
34	#28 or #29 or #30 or #31 or #32 or #33
35	(TG=ANIMALS) not ((TG=HUMAN) and (TG=ANIMALS))
36	#34 not #35
37	CLINICAL-TRIAL in PT
38	explode CLINICAL-TRIALS / all subheadings
39	(clin* near trial*) in TI

Table 01. Search strategy for SilverPlatter MEDLINE (WebSPIRS) (1950 to date) (*Continued*)

search number	search terms
40	(clin* near trial*) in AB
41	(singl* or doubl* or trebl* or tripl*) near (blind* or mask*)
42	(#41 in TI) or (#41 in AB)
43	PLACEBOS
44	placebo* in TI
45	placebo* in AB
46	random* in TI
47	random* in AB
48	RESEARCH-DESIGN
49	#37 or #38 or #39 or #40 or #42 or #43 or #44 or #45 or #46 or #47 or #48
50	(TG=ANIMALS) not ((TG=HUMAN) and (TG=ANIMALS))
51	#49 not #50
52	#51 not #36
53	#36 or #52
54	#27 and #53

Table 02. Search strategy for CENTRAL

Search number	Search terms
1	MeSH descriptor Propofol explode all trees
2	MeSH descriptor Hypotension explode all trees
3	hypoten* in All Text
4	MeSH descriptor Anesthesia, General explode all trees
5	MeSH descriptor Anesthesia, Inhalation explode all trees
6	an?esthesia in All Text
7	(propofol in All Text or diprivan in All Text or disoprofol in All Text or pofol in All Text)
8	(#1 or #2 or #3 or #4 or #5 or #6 or #7)
9	MeSH descriptor Paranasal Sinus Diseases explode all trees
10	MeSH descriptor Paranasal Sinuses explode all trees
11	MeSH descriptor Endoscopy explode all trees
12	(surg* in All Text near/6 paranas* in All Text)
13	(surg* in All Text near/6 endoscop* in All Text)

Table 02. Search strategy for CENTRAL (*Continued*)

Search number	Search terms
14	(surg* in All Text near/6 microscop* in All Text)
15	nasal in All Text
16	(sphenoid in All Text and sinus* in All Text)
17	(ethmoid in All Text and sinus* in All Text)
18	(frontal in All Text and sinus* in All Text)
19	MeSH descriptor Ethmoid Sinus explode all trees
20	MeSH descriptor Frontal Sinus explode all trees
21	MeSH descriptor Maxillary Sinus explode all trees
22	MeSH descriptor Sphenoid Sinus explode all trees
23	MeSH descriptor Paranasal Sinus Neoplasms explode all trees
24	(ntranasal in All Text or paranasal in All Text or endonasal in All Text)
25	MeSH descriptor Nasal Cavity explode all trees
26	MeSH descriptor Otorhinolaryngologic Surgical Procedures explode all trees
27	(sinus* in All Text and (maxillary in All Text or frontal in All Text or ethmoid in All Text or sphenoid in All Text))
28	rhin* in All Text
29	(#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25) (#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25)
30	(#8 and #26)

Table 03. Search strategy for SilverPlatter EMBASE (WebSPIRS) (1980 to date)

search number	search terms
1	explode “propofol-” / all SUBHEADINGS in DEM,DER,DRM,DRR
2	explode “hypotension-” / all SUBHEADINGS in DEM,DER,DRM,DRR
3	“general-anesthesia” / all SUBHEADINGS in DEM,DER,DRM,DRR
4	“inhalation-anesthesia” / all SUBHEADINGS in DEM,DER,DRM,DRR
5	an?esthesia
6	hypoten*
7	propofol or diprivan or disoprofol or pofol
8	#1 or #2 or #3 or #4 or #5 or #6 or #7
9	“paranasal-sinus-disease” / all SUBHEADINGS in DEM,DER,DRM,DRR
10	explode “paranasal-sinus” / all SUBHEADINGS in DEM,DER,DRM,DRR
11	“endoscopy-” / all SUBHEADINGS in DEM,DER,DRM,DRR

12	explode “ethmoid-sinus” / all SUBHEADINGS in DEM,DER,DRM,DRR
13	explode “ethmoid-sinus” / all SUBHEADINGS in DEM,DER,DRM,DRR
14	explode “maxillary-sinus” / all SUBHEADINGS in DEM,DER,DRM,DRR
15	explode “sphenoid-sinus” / all SUBHEADINGS in DEM,DER,DRM,DRR
16	“paranasal-sinus-tumor” / all SUBHEADINGS in DEM,DER,DRM,DRR
17	“paranasal-sinusitis” / all SUBHEADINGS in DEM,DER,DRM,DRR
18	explode “nose-cavity” / all SUBHEADINGS in DEM,DER,DRM,DRR
19	“ear-nose-throat-surgery” / all SUBHEADINGS in DEM,DER,DRM,DRR
20	surg* near (paranas* or endoscop* or microscop*)
21	nasal
22	sinus* near (maxilliary or frontal or ethmoid or sphenoid)
23	intranasal or paranasal or endonasal
24	(surg* (paranas* or endoscop* or microscop*)) and (nasal or endonas* or intranas* or paranas*)
25	sinus* and (maxilliary or frontal or ethmoid or sphenoid)
26	rhin* not rhinoceros
27	#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
28	#8 and #27
29	explode “randomized-controlled-trial” / all SUBHEADINGS in DEM,DER,DRM,DRR
30	(randomi?ed controlled trial*) in TI, AB
31	random*
32	explode “randomization-” / all SUBHEADINGS in DEM,DER,DRM,DRR
33	randomi?ation
34	explode “clinical-trial” / all SUBHEADINGS in DEM,DER,DRM,DRR
35	clinical near trial*
36	explode multicenter-study / all subheadings
37	multi?cent*
38	explode phase-4-clinical-trial / all subheadings or explode double-blind-procedure / all subheadings or explode single-blind-procedure / all subheadings
39	(RANDOM* or CROSS?OVER* or FACTORIAL* or PLACEBO* or VOLUNTEER*) in TI, AB, TW
40	((SINGL* or DOUBL* or TREBL* or TRIPL*) near (BLIND* or MASK*)) in TI,AB
41	#29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40
42	(human) in DER
43	(animal or nonhuman) in DER

Table 03. Search strategy for SilverPlatter EMBASE (WebSPIRS) (1980 to date) (*Continued*)

search number	search terms
44	#42 and #43
45	#43 not #44
46	#41 not #45
47	#28 and #46

Table 04. Search strategy for LILACS (1982 to date)

search number	search terms
1	"PROPOFOL" or "PROPOFOL/"
2	"HYPOTENSION" or "HYPOTENSION, CONTROLLED/"
3	"ANAESTHESIA" or "ANAESTHESIC" or "ANAETHESIA" or "ANAETHESIC" or "ANESTHESIA" or "ANESTHESIA AND ANALGESIA" or "ANESTHESIA, CLOSED-CIRCUIT/" [Words]
4	rhinosinusal or paranasal or nasal or intranasal or endonasal or "NASAL CAVITY/" or "PARANASALE" or "PARANASALES" or "PARANASALS" or "ETHMOID SINUS" or "ETHMOID SINUS/" or "SPHENOID SINUS" or "SPHENOID SINUS/" or "SPHENOID SINUSITIS/" or "FRONTAL SINUS" or "FRONTAL SINUS/" or "FRONTAL SINUSITIS/" or nasal or Endoscopy or sinus [Words]
5	#1 or #2 or#3
6	#4 AND #5

COVER SHEET

Title	Deliberate hypotension with propofol under anaesthesia for functional endoscopic sinus surgery (FESS)
Authors	Boonmak S, Boonmak P, Laopaiboon M
Contribution of author(s)	Conceiving the review: Suhattaya Boonmak (SUBO) Co-ordinating the review: SUBO, Polpun Boonmak (POBO), Malinee Laopaiboon (MALI) Undertaking manual searches: SUBO, POBO Screening search results: SUBO, POBO Organizing retrieval of papers: SUBO, POBO Screening retrieved papers against inclusion criteria: SUBO, POBO Appraising quality of papers: SUBO, POBO Abstracting data from papers: SUBO, POBO Writing to authors of papers for additional information: SUBO Providing additional data about papers: SUBO Obtaining and screening data on unpublished studies: POBO Data management for the review: SUBO, POBO, MALI Entering data into Review Manager (RevMan 4.2): SUBO RevMan statistical data: MALI Other statistical analysis not using RevMan: MALI Double entry of data: (data entered by person one: SUBO; data entered by person two: POBO) Interpretation of data: MALI Statistical inferences: MALI

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Pharmacological management for prevention of phantom limb pain (Protocol)

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Pharmacological management for prevention of phantom limb pain (Protocol)

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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 pharmacological management (regional anesthesia, NMDA receptor antagonist, clonidine, opioid, calcitonin, etc.) for prevention of phantom limb pain, stump pain and phantom sensation after limb amputation.

BACKGROUND

Phantom limb pain, a pain often described in a surgically removed limb or portion thereof, is commonly experienced after amputation (Merskey 1994). This type of pain is a significant problem among amputees since it often delays rehabilitation, limits use of prosthetic devices and has a profound influence on the quality of life (van der Schans 2002). Phantom limb sensations are reported by 70 to 100% of amputees and phantom limb pain occurs in 60 to 85% of these cases (Montoya 1997). Though phantom limb pain is less frequent in young children, the occurrence seems to be independent of age in adults. There also appears to be no relation between patient's gender, previous health status, or level of amputation (upper or lower limb), or side and cause of amputation (Nikolajsen 2001). The incidence of phantom limb pain is increased with the presence of acute or chronic pain in that limb before amputation (Houghton 1994).

Onset of phantom limb pain is unpredictable. About 75% of patients develop pain within the first few days after amputation but the pain can be delayed for months or years (Nikolajsen 2001). Phantom limb pain varies in character, duration, frequency and intensity. Phantom limb pain has been described as sharp, dull, burning, squeezing, cramping, shooting or a shock-like electrical sensation in the missing limb.

Amputees may experience other sensations in the missing limb or in the residual limb after amputation which should be differentiated from phantom limb pain. Phantom sensation is any sensation of the missing limb, except pain, while residual limb pain or stump pain is pain at the site of an extremity amputation. Stump pain is often described as sharp and is usually aggravated by pressure or infection in the stump. Stump pain is a common occurrence in the early postamputation period and can develop after several weeks or months afterwards, or persist indefinitely if untreated.(Merskey 1994)

There is a significant positive relationship between the occurrence and intensity of stump pain and phantom limb pain (Montoya 1997). Approximately two-thirds of amputees experience phantom limb pain in conjunction with stump pain, as well as this, it is exacerbated by episodes of stump pain (Sherman 1992). The long term course of phantom pain is unclear depending on the type and time of assessment. However, about 60% of patients still have significant phantom pain two years after surgery (Jensen 1985). It seems that phantom pain persisting six months after amputation is difficult to treat (Davis 1993).

While the peripheral nervous system is the main underlying mechanism of stump pain, the proposed mechanism for phantom limb pain remains unclear. There is now evidence for both peripheral and central contribution to phantom limb pain (Flor 2002). Pe-

ripheral nerve damage during an amputation initiates regenerative nerve sprouting of the injured axon leading to formation of a mass that arises from nerve tissue which is called a neuroma. Such neuromas show spontaneous and abnormal evoked activity following mechanical or electrical stimulation. Mechanical and chemical stimulation e.g. noradrenaline increase the rate of ectopic discharge from the neuroma and dorsal root ganglion. An afferent nociceptive barrage then initiates spinal cord hyperexcitability and expansion of the receptive field. Spinal sensitization involves an increased activity in the N-methyl-D-aspartate (NMDA) receptor-operating system as many aspects of central sensitization can be reduced by NMDA receptor antagonists. As well as the functional changes, reorganization at both spinal and supraspinal level have been described. Substantial degeneration of afferent C-fibre terminals in laminar II reduces the number of synaptic contacts with second order neurons. As a result, the central terminal of A beta fibres which normally terminate in deeper laminae, sprout into laminar II and may form synaptic contacts with vacant nociceptive second order neurons. At supraspinal level, a change in the neuromatrix or network of neurons in several brain areas including the thalamus, somatosensory cortex, reticular formation and limbic system form abnormal input results in abnormal signature patterns which are interpreted as painful sensations (Melzack 1990). The demonstrable influence on central activities implicates several preventive and therapeutic modalities, i.e. absolute analgesia before amputation for a longer period of time and reduction of cortical reorganization by drugs, behaviour interventions or treatments such as hypnosis, or both.

On being considered a neuropathic type of pain, treatment for phantom limb pain needs a multimodal and multidisciplinary approach. Multimodal analgesia involves the use of more than one method or modality of controlling pain (e.g., drugs from two or more classes, or drug plus non drug treatment to obtain additive beneficial effects, reduce side effects, or both) (Wilson 1997). Psychological approaches such as sensory discrimination training, cognitive behavioral therapy, biofeedback and hypnosis have been used for treatment of this chronic pain condition as well as other treatment modalities such as transcutaneous electrical nerve stimulation (TENS), massage, acupuncture and ultrasound (Flor 2002). However, treatment of phantom limb pain is difficult and has generally been unsuccessful. Results from large surveys in the 1980s have shown that most treatments at that time were ineffective (Sherman 1980). Even then, despite much research in this area, there is only a little evidence from randomized trials to guide clinicians on treatment (Manchikanti 2004). The preventive model may be a better approach for this well-recognized sequela and epidemic pain after amputation.

To prevent phantom limb pain after amputation, the mechanism underlying the development of central sensitization should be targeted. Attempts to control pre-amputation pain, reduce noxious intraoperative input and minimize acute postoperative pain by various pharmacological management techniques have yielded inconsistent results (Schug 1995; Nikolajsen 1997; Lambert 2001). Epidural anesthesia given three days before amputation has been shown to reduce the rate of phantom limb pain at six months after amputation (Bach 1988). However, perioperative epidural anesthesia introduced at a median of 18 hours before the amputation and continued into the postoperative period has not been shown to prevent phantom limb pain (Nikolajsen 1997). Regional nerve block, with perineural or intraneural analgesia, introduced either at the time of or immediately after surgery found only short term pain relief with no significant long term benefits (Elizaga 1994; Pinzur 1996). Intravenous ketamine, an NMDA receptor antagonist, given after induction of anesthesia and continued for 48 to 72 hours postoperatively found conflicting results (Dertwinkel 2002; Hayes 2004). Due to the primary analgesic effect through the receptor mediated modulation of serotonergic neuronal activity of the pain pathway in the central nervous system, salmon calcitonin was found to produce prolonged and rapid analgesia in acute phantom limb pain (Jaeger 1992). Recently clonidine and memantine were combined with regional anesthesia for amputation in order to prevent phantom limb pain (Reuben 2006; Schley 2006). Nonpharmacological pain management such as hypnosis attempting to control preamputation pain or to prepare patient for amputation including an awareness of concern about disposition of the limb has been shown to be beneficial (Solomon 1978).

As there is uncertainty of evidence to support current treatment used in the prevention of phantom limb pain, a systematic review was conducted by Halbert et al (Halbert 2002). In this review, searching MEDLINE from 1966 to 1999 and searching only English-language articles, a narrative summary of the evidence was provided due partly to the quality of trials included and the heterogeneity of phantom limb pain outcomes and follow-up periods. The major conclusion was regarding research and suggested the need for further, adequately designed studies of therapeutic regimen for phantom limb pain (Halbert 2002).

There has been a growing scientific evidence for prevention of phantom limb pain during the last five years. Multimodal pain management has been used in practice for patients undergoing limb amputation for some time. It is necessary now to do a systematic review with an extensive search for the current evidence and to try to find ways of preventing phantom limb pain. As stump pain and phantom sensation are closely related to phantom pain, they will also be included in this review. This review will not include treatment as there is already underway another Cochrane protocol covering that topic (Alviar 2007).

OBJECTIVES

To assess the effectiveness of pharmacological management (regional anesthesia, NMDA receptor antagonist, clonidine, opioid, calcitonin, etc.) for prevention of phantom limb pain, stump pain and phantom sensation after limb amputation.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All relevant randomized controlled trials (RCTs) comparing pharmacological management alone, or in combination with non pharmacological management, compared to placebo or non pharmacological management or no intervention that aimed to prevent phantom limb pain will be included.

Types of participants

Participants of any age undergoing either upper or lower limb amputation will be included.

Types of intervention

All pharmacological management (regional anesthesia, NMDA receptor antagonist, clonidine, opioid, calcitonin, etc.), singly or in combination, given alone or in combination with non pharmacological management in a preoperative, intra-operative and early post operative period (< 2 weeks) of limb amputation that aims to prevent phantom limb pain, phantom sensation and stump pain compared to placebo, non pharmacological management or no treatment will be included. For the pharmacological management in the early postoperative period, only the intervention that aims to prevent (before the symptoms of phantom limb pain exist) will be included.

Traumatic amputation with be excluded.

Types of outcome measures

Primary outcome

- Incidence of phantom limb pain (diagnosed by a physician according to the IASP definition) at 72 hours, one week, six months and one year after amputation.

Secondary outcome

- Phantom limb pain intensity
- Incidence of stump pain
- Stump pain intensity
- Incidence of phantom sensation
- Quality of life as measured on a commonly used scale such as the SF-36 (Aaronson 1992)
- Adverse effects

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

The Following data sources will be searched:

1. Cochrane Pain, Palliative & Supportive Care Register
2. The Cochrane Central Register of Controlled Trials (CENTRAL)
3. MEDLINE and OLD MEDLINE
4. EMBASE
5. LILACS (Latin American Health Sciences Literature)
6. CINAHL (Nursing and Allied Health)
7. PsycINFO (Psychological literature)
8. International Dissertation Abstracts (http://wwwlib.umi.com/dxweb)
9. CISCOM- (Centralized Information Service for Complementary Medicine)
10. SIGLE (System for Information on Grey Literature in Europe)
11. Health Services/Technology Assessment Text (HSTAT) database.
12. The Australasian Medical Index.
13. The Japan Information Centre of Science and Technology File on Science, Technology and Medicine (JICST-E)

To identify studies for inclusion in this review, detailed search strategies will be developed for each electronic database searched. These will be based on the search strategy developed for MEDLINE but revised appropriately for each database. This search will combine the subject search with phases 1 and 2 of the Cochrane Sensitive Search Strategy for RCTs (as published in Appendix 5c in the Cochrane Handbook) (Higgins 2006).

MEDLINE Pubmed search strategy

Phase 1

(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized 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]) AND (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 humans [mh])

Phase 2

Search strategy for searching *The Cochrane Library*

#1 PHANTOM LIMB
#2 phantom or fantom
#3 #2 and limb*
#4 #1 or #3
#5 Explode PAIN
#6 pain* or discomfort* or sensation* or sore* or ache* or tender*
#7 stump near pain*
#8 (("phantom pain*" or fantom pain*") and amput*

#9 #5 or #6 or #7 or #8
#10 #4 and #9]

The Boolean operator OR will be used to combine the terms in phase 2. Then the Boolean operator AND will be used to combine the two phases.

As well as searching the electronic databases, we will:
1. hand search conference proceeding relating to pain management;
2. search for relevant studies cited in book chapters on phantom limb;
3. identify personal communication with the authors of included studies and experts in the field to find out whether they know about any published or unpublished RCTs/CCTs of prevention of phantom limb pain, which have not yet been identified;
4. search ongoing trials from:
- metaRegister of Controlled Trials (mRCT)
- Current Controlled Trials (http://www.controlled-trials.com/)
- ClinicalTrials.gov
- TrialsCentralTM
- The National Research Register (NRR)
- Trials Register of Promoting Health Interventions (TRoPHI)

METHODS OF THE REVIEW

Selection of studies
Two review authors (KW and KT) will screen the abstracts of all publications obtained by the search strategies. The reasons for eligibility will be noted and inserted into RevMan. For trials that appear to be eligible RCTs, the full articles will be obtained and inspected to assess their relevance, based on the pre-planned criteria for inclusion.

Quality assessment
In order to ensure that variation is not caused by systematic errors in the design of a study, the methodological quality of the selected trials will be assessed by two independent review authors (KW and KT), using the simple approach described in the Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 (Higgins 2006). The criteria are defined below:
1. were the inclusion and exclusion criteria clearly defined?
2. was the allocation concealment properly performed?
3. were treatments, other than the interventions, identical?
4. were important baseline characteristics reported and compared?
5. were the outcomes of patients who withdrew described and included in the analysis?
6. were the outcome measures clearly defined, and valid?
Each question may be answered 'met', 'partly met', 'not met'.

Three quality categories were set:
A. low risk of bias - all of the criteria met;
B. moderate risk of bias - one or more criteria partly met;
C. high risk of bias - one or more criteria not met.

According to the presence of evidence of a strong relationship between the potential for bias in the results and allocation concealment, adequacy of allocation concealment will be judged (Higgins 2006):
A: adequate,
B: unclear,
C: inadequate,
D: not used.

Disagreements will be resolved through consensus, or referred for arbitration by the PaPaS editorial base if needed.

Data extraction and management
Data will be independently extracted by two review authors (KW and KT) using a predesigned data collection form. Data extracted will be: name of the study, design, sample size, study duration (including follow-up period), participant characteristics (age, gender, type of amputation i.e. upper extremity or lower extremity and cause of amputation i.e. traumatic or amputation due to other causes, presence of preamputation pain), inclusion and exclusion criteria, intervention including dosage, route of administration, treatment duration, technique of anesthesia for amputation, outcomes, number of patient drop-outs, withdrawals, and number of patients analyzed in the different treatment groups. All exclusion/drop outs will be identified. In the case of no data about adverse effects being reported in the included studies, the authors will be contacted for unpublished data.

Any unpublished information if used will be written and coded with a specified remark. The comparison of data extracted will be done by each author separately. Any disagreements will be discussed with a third review author (ST), the decisions documented and where necessary, the author will be contacted for additional information on the study.

All relevant data when a consensus is reached will be put into RevMan 4.2.10 by KW and re-checked by KT for accuracy. The reliability of data extraction and data entry will be examined throughout the project.

Data analysis
The analysis will be performed for included studies both narrative or quantitative, or both, when feasible and sensible. The general framework for synthesis will be focused on:
1. what is the direction of effect of intervention in the included studies?
2. what is the effect size?
3. is the effect of intervention consistent across studies?
4. what is the strength of evidence for the effect of intervention?

Comparisons will be made between interventions and placebo, non pharmacologic pain management or no treatment. Quantitative analysis will be done on an intention-to-treat basis. For studies where authors have used intention-to-treat analysis by imputation of data for missing cases (such as last observation carried forward method or assumed no changes), the authors will

be contacted for available case analysis. If it's not possible to get available data from the authors, those studies will not be included in a meta-analysis.

Statistical methods

Dichotomous outcomes (presence or absence of phantom limb pain, adverse effects) from each study will be pooled using risk ratio as the summary statistic. When overall results are significant, risk difference will be calculated using the absolute effect measure then the number needed to treat (NNT) will be calculated (where no clinical, methodological or statistical heterogeneity are identified).

In the case where the numbers of participants and numbers of events are not available, but results calculated from them are risk ratio, odds ratio and adjusted odds ratio, the data will be included in meta-analyses only if they are accompanied by measures of uncertainty such as a 95% confidence interval (CI) or an exact P-value. The numbers will be analysed using the generic inverse variance method in RevMan.

For continuous outcomes, mean differences in the outcome measures with their 95% CI will be used to quantify the effects of the intervention (difference in pain intensity, quality of life scores). The mean difference is the difference in the magnitude of effect in the treatment and control groups. To combine and summarize these measures across the studies, the weighted mean difference (WMD) for each outcome measure will be calculated including the 95% CI. Trials with different types of outcomes such as different scales measuring pain severity and standardized mean difference (SMD) will be used.

Meta-analysis will be performed only when a group of trials is sufficiently homogeneous in terms of participants, interventions and outcomes. A random effects meta-analysis will be used to incorporate heterogeneity among trials and will be applied only after exploring the causes of heterogeneity or when heterogeneity cannot readily be explained. To assess the amount of heterogeneity among the studies the I^2 statistic will be used where an I^2 value greater than 50% will mean that a significant amount of heterogeneity exists among the studies. A fixed effect model will be used for all analyses if there is no statistical heterogeneity.

Sources of clinical heterogeneity will be explored by qualitative assessment. Biological heterogeneity may come from different characteristics of patients: age, type and cause of amputation, presence of preamputation pain while methodological heterogeneity may come from:
1. different types of management: single, combination with other intervention, combination with non pharmacologic management;
2. different dosage, duration of administering intervention, and
3. different follow up period.

If heterogeneity is detected, the effect of some factors such as preamputation pain, combination of non pharmacologic management that influence the outcomes will be explored in subgroup analysis according to the following categories:
1. presence or absence of preamputation pain in the patients enrolled;
2. intervention with and without non pharmacologic management.

Subgroup analyses will only be undertaken if a sufficient number of studies are identified.

Sensitivity analysis will be performed to confirm robustness of the result by determining the effect of studies with a high risk of bias by using the Oxford Quality Scale score (Jadad 1996) to assess the overall effect.

POTENTIAL CONFLICT OF INTEREST

None known.

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COVER SHEET

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Contribution of author(s)	WK: developed protocol, has a role for understanding statistical methods and will search and assess the literature, analyse the data, report the results and write the final review. TK: developed the protocol, will search and assess the literature and analyse the data. PR: will search and assess the literature. ST: will search and assess the literature and assess the review for English language usage. MW: analyse the data and report the results.
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High concentration versus low concentration sevoflurane for anaesthesia induction (Protocol)

Boonmak P, Boonmak S, Krisanaprakornkit W, Pattanittum P

This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2007, Issue 4

http://www.thecochranelibrary.com

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High concentration versus low concentration sevoflurane for anaesthesia induction (Protocol)

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:
We aim to compare the induction time and complication rates between high and low concentration sevoflurane anaesthetic induction techniques in patients who received gas induction for general anaesthesia.

BACKGROUND

General anaesthesia (GA) may be induced either by intravenous injection (IV induction) or by breathing in a volatile anaesthetic agent along with oxygen through a mask (inhalational induction). Inhalational anaesthetic induction may be the preferred method in children and in some adult patients who refuse intravenous cannulation (Eger II 2003) or have poor venous access. One of the commonly used volatile anaesthetic agents for inhalational induction of anaesthesia is sevoflurane (Ulthane™, Sevorane™). Sevoflurane (2, 2, 2 -trifluoro-1-[trifluoromethyl] ethyl fluoromethyl ether) was first introduced into clinical practice in Japan in 1990 and is sweet-smelling, non-flammable and less irritating to mucous membranes.

Induction of anaesthesia with sevoflurane has been reported to be safe, reliable and well accepted by patients (van den Berg 2005). Its characteristics are: inherent stability; low flammability; non-pungent odour; limited irritation to airways; low blood or gas anaesthetic solubility, which allows rapid induction of, and emergence from, anaesthesia; minimal cardiovascular and respiratory side effects; and minimal end-organ effects (Delgado-Herrera 2001). Sevoflurane's muscle relaxation properties allow the insertion of a laryngeal mask airway (LMA) or endotracheal intubation (Aantaa 2001) without a muscle relaxant.

Inhalational induction of anaesthesia with sevoflurane uses either low or high concentrations of sevoflurane. The low concentration technique involves initially administering a low concentration of sevoflurane, then increasing the concentration until the patient is anaesthetized (Eger II 2003). The high concentration technique involves administering high concentrations of sevoflurane (from 6% to 8 %) from the beginning, continuing until the patient is anaesthetized (Eger II 2003). Both techniques can be carried out using different breathing patterns, either vital capacity or tidal volume breathing. The vital capacity method consists of breathing out the residual volume then taking a maximal breath and holding as long as is comfortable followed by spontaneous respiration; and the tidal volume method involves normal breathing and respiratory rate.

Other interventions or medications can be used to improve the quality of induction of anaesthesia (for example inspiratory pressure support at 15 cm H_2O using an anaesthetic ventilator (Banchereau 2005)); priming of the breathing circuit with high concentration sevoflurane in oxygen, with or without nitrous oxide prior induction of anaesthesia (Yurino 1995); use of nitrous oxide with sevoflurane and oxygen (Dubois 1999; O'Shea 2001); use of sufentanil (Meaudre 2004), midazolam (Nishiyama 2002) or clonidine (Watanabe 2006) before induction of anaesthesia. Induction time, the time to loss of eyelash reflex (LOER), is measured

to compare the efficacy of the different methods. However, complications during the induction of anaesthesia such as coughing, salivation, failed induction at the first attempt, laryngospasm, breath holding, apnea, severe movement or panic reaction, hypotension, an epileptiform electroencephalogram (EEG) and bradycardia can increase the morbidity (Epstein 1998; Kaisti 1999; Martin-Larrauri 2004; Roodman 2003; Vakkuri 2001; Yurino 1995).

High concentration volatile anaesthetic induction has been reported to result in a shorter (faster) induction time (Epstein 1998; Martin-Larrauri 2004). A shorter induction time is the preferred choice. But this may be accompanied by a number of complications such as breath holding, laryngospasm, severe movement and hypotension (Dubois 1999; Epstein 1998; Martin-Larrauri 2004). More frequent and longer duration apnea after induction (Pancaro 2005) with a high concentration of sevoflurane and a higher incidence of bradycardia (Green 2000) and epileptiform EEG (Constant 2005; Vakkuri 2001) have been reported.

We aim to compare the induction times and the risk of complications between two the induction methods, low concentration and high concentration of sevoflurane induction of anaesthesia. A technique having a shorter induction time and lower complication rate may help us to choose the optimum volatile anaesthetic induction technique using sevoflurane.

OBJECTIVES

We aim to compare the induction time and complication rates between high and low concentration sevoflurane anaesthetic induction techniques in patients who received gas induction for general anaesthesia.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

We will include all published and unpublished randomized controlled trials (RCTs) comparing high concentration gas induction versus low concentration gas induction. Any studies reported only in abstract form will be included in the studies awaiting assessment category.

Types of participants

We will include patients of all ages receiving an sevoflurane induction technique for general anaesthesia.

Types of intervention

We will include two sevoflurane induction techniques for general anaesthesia.
1. High concentration sevoflurane (control): equal to or more than a 4% concentration of sevoflurane, including vital capacity and tidal volume breath induction.
2. Low concentration sevoflurane induction (experimental): starting concentration less than 4% sevoflurane.

Types of outcome measures

Our primary outcome is: induction time (time to loss of eyelash reflex (LOER), assessed in seconds (beginning from inhalation of gas until loss of eyelash reflex); or time to drop a weighted object, assessed in seconds (beginning from inhalation of gas until weighted object dropped, for example a syringe).

Our secondary outcomes are:
1. patient satisfaction (numeric rating scale);
2. failed gas induction in the first attempt (yes or no);
3. complications

We will define complications as:

- cough during induction period;
- laryngospasm;
- breath-holding;
- apnea;
- severe movement or panic reaction during induction (such as grabbing the mask, trying to slip off the operating table etc.);
- hypotension (more than 20% of baseline blood pressure);
- other rare complications (epileptiform EEG, bradycardia (below 20% of baseline heart rate)).

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We will search the current issue of the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*), MEDLINE (1950 to present), EMBASE (1980 to present) and LILACS (1982 to present).

We will develop a specific strategy for each database on that developed for MEDLINE (Table 01). (Please see: Table 02 (CENTRAL); Table 03 (EMBASE); Table 04 (LILACS)).

We will also identify trials by:
1. searching specialist journals such as *Anaesthesia and Analgesia;Anesthesiology;Anaesthesia;Acta Anesthesiologica Scandinavica*; *British Journal of Anaesthesia*; *Canadian Journal of Anaesthesia*; *European Journal of Anaesthesia*;
2. searching conference proceedings and abstracts. (The American Society of Anesthesiologists (ASA); International Anaesthesia Research Society (IARS); European Society of Anaesthesiologists (ESA));
3. contacting known trialists, experts and medical or pharmaceutical companies for unpublished trials;

4. searching grey literature (such as SIGLE);
5. checking the reference list of relevant articles.
We will not apply a language restriction.

METHODS OF THE REVIEW

We will use the standardized methods for conducting a systematic review as described by The Cochrane Collaboration in the Cochrane Handbook for Systematic Reviews of Interventions. (Higgins 2005).

Selection of trials
Two authors (PB and SB) will independently scan the titles and abstracts of reports identified by searching the electronic databases and hand searching journals. We will obtain and assess the full article of any possibly and definitely relevant trials according to the definitions provided in the criteria for considering studies for this review. We (PB and SB) will resolve any disagreement by consensus or, if necessary, by consulting a third author (WK or PP). If we can not resolve differences then we will add the publication reference to those awaiting assessment and contact the study authors for clarification.

Assessing quality of trials
Two authors (PB and SB) will assess the methodological quality of each trial following the guidelines described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005). Our assessment criteria are:
1. randomizations and allocation concealment: adequate, unclear, or inadequate, not used;
2. blinding of treatment: adequate, unclear, or inadequate;
3. blinded outcome assessment: adequate, unclear, or inadequate;
4. description of dropouts and withdrawals: adequate, unclear, or inadequate;
5. use of intention-to-treat analysis: yes, no, no information.

We will define a trial 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).
We will resolve any conflicts in assessment through discussion and, if necessary, through evaluation by a third author (WK or PP).

Data extraction
We will use a data extraction form to obtain data from individual studies. This will be performed by two authors (PB and SB). We will use five studies previously chosen as fulfilling the review selection criteria to pilot the form to ensure the data obtained is adequate for the review's purposes. We will obtain or clarify missing or unclear data by contacting authors.
We will obtain data as follows: study characteristics (study authors; authors of the report; MEDLINE journal ID; year of publication; language; country where study performed; source of funding; study design; method of allocation; study population inclusion or exclusion criteria; blinding of patients, operator and assessor; participants (number of participants recruited, completing trial and withdrawing, gender, age, overall sample size); intervention description; statistical methods; use of intention-to-treat analysis), outcomes (LOER, time to drop a weighted object, patient satisfaction, failed gas induction in the first attempt, complications (cough during induction period, laryngospasm, breath holding, apnea, severe movement, hypotension, other rare complications). Following data extraction, we will perform double data entry and the database will be screened for inconsistencies as a quality assurance measure.

Statistical analysis
We will analyse data and display it using Review Manager (RevMan 4.2) software distributed by The Cochrane Collaboration.

We will analyse continuous data results, time to LOER, time to drop a weighted object and patient satisfaction as weighted mean differences. We will analyse dichotomous data of failed gas induction in the first attempt and complications (cough, laryngospasm, breath holding, apnea, severe movement, hypotension, bradycardia and epileptiform EEG) as relative risk. We will review the data from included studies qualitatively and then, if possible, combine the data quantitatively by population, intervention and outcome.

We will assess heterogeneity among studies by:
1. inspection of individual 95% confidence interval in the forest plot;
2. I^2 statistic (Higgins 2002); heterogeneity is suspected if it is more than 50%.

If we cannot detect the sources of heterogeneity then we will use the random-effects method of DerSimonian and Laird (DerSimonian 1986) to estimate an overall effect of the treatment. If heterogeneity among the trial results is not be detected we will conduct meta-analysis using the fixed-effect model.

If heterogeneity is detected the effect of factors that may influence the outcome will be investigated. Subgroup analysis will be performed, where data are available in each subgroup, and the 95% confidence intervals will be examined. Non-overlap of the intervals will be taken to indicate a statistically significant difference between subgroups. We will compare:
1. breathing technique (vital capacity, tidal volume);
2. supplement drug (fentanyl, morphine, lidocaine, midazolam, nitrous oxide);
3. anaesthetic circuit type (Mapleson system, circle circuit);
4. different age groups (infant or toddler (0 to 2 years), child (3 to 12 years) and adolescent (more than 13 years).

We will perform sensitivity analyses for missing data and study quality. In the case of missing data, we will employ sensitivity analysis using different approaches to imputing missing data. The best-case scenario will assume that none of the originally enrolled patients missing from the primary analysis in the treatment group

had the negative outcome of interest whilst all those missing from the control group did. The worst-case scenario will be the reverse. We will also conduct sensitivity analysis by study quality based on the risk of bias (presence or absence of a reliable random allocation method, concealment of allocation and blinding of participants or outcome assessors).

We will test publication bias using funnel plots.

POTENTIAL CONFLICT OF INTEREST

None known.

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ADDITIONAL TABLES

Table 01. Search strategy for SilverPlatter MEDLINE (WebSPIRS) (1950-2006/11/wk1)

search number	search terms
1	Sevofluran* or Sevorane or Ultane
2	CLINICAL-TRIAL in PT
3	randomized in AB
4	placebo in AB
5	(clinical trials) in MESH
6	randomly in AB
7	trial in TI

Table 01. Search strategy for SilverPlatter MEDLINE (WebSPIRS) (1950-2006/11/wk1) (*Continued*)

search number	search terms
8	#2 or #3 or #4 or #5 or #6 or #7
9	TG=animals
10	TG=humans
11	#9 not (#9 and #10)
12	#8 not #11
13	#1 and #12

Table 02. Search strategy for CENTRAL, The Cochrane Library 2006, Issue 4

Search number	Search terms
1	sevofluran* or sevorane or ultane
2	MeSH descriptor Anesthesia explode all trees
3	MeSH descriptor Laryngeal Masks explode all trees
4	MeSH descriptor Intubation, Intratracheal, this term only
5	intubat* or LMA endotracheal
6	laryngeal near mask*
7	an?esthesia near general
8	(#2 OR #3 OR #4 OR #5 OR #6 OR #7)
9	(#1 AND #8)

Table 03. Search strategy for SilverPlatter EMBASE (WebSPIRS) (1980-2006/11/wk1)

search number	search terms
1	explode "sevoflurane-" / all SUBHEADINGS in DEM,DER,DRM,DRR
2	sevofluran* or sevorane or ultane
3	#1 or #2
4	explode "general-anesthesia" / all SUBHEADINGS in DEM,DER,DRM,DRR
5	explode "laryngeal-mask" / all SUBHEADINGS in DEM,DER,DRM,DRR
6	explode "endotracheal-intubation" / all SUBHEADINGS in DEM,DER,DRM,DRR
7	an?esthesia near general
8	laryngeal near mask*(
9	intubat* or LMA or endotracheal
10	#4 or #5 or #6 or #8 or #9

Table 03. Search strategy for SilverPlatter EMBASE (WebSPIRS) (1980-2006/11/wk1) (*Continued*)

search number	search terms
11	#3 and #10
12	"RANDOMIZED-CONTROLLED-TRIAL"/ all subheadings
13	"RANDOMIZATION"/ all subheadings
14	"CONTROLLED-STUDY"/ all subheadings
15	"MULTICENTER-STUDY"/ all subheadings
16	"PHASE-3-CLINICAL-TRIAL"/ all subheadings
17	"PHASE-4-CLINICAL-TRIAL"/ all subheadings
18	"DOUBLE-BLIND-PROCEDURE"/ all subheadings
19	"SINGLE-BLIND-PROCEDURE"/ all subheadings
20	#12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
21	(RANDOM* or CROSS?OVER* or FACTORIAL* or PLACEBO* or VOLUNTEER*) in TI,AB
22	(SINGL* or DOUBL* or TREBL* or TRIPL*) near ((BLIND* or MASK*) in TI,AB)
23	#20 or #21 or #22
24	HUMAN in DER
25	(ANIMAL or NONHUMAN) in DER
26	#24 and #25
27	#25 not #26
28	#23 not #27
29	#11 and #28

Table 04. Search strategy for LILACS (1982 - 2006)

search number	search terms
1	"sevofluran$" or "ultane" or "SEVOFLURANE" or "SEVOFLURANO" or "SEVOFLURANOA" or "SEVORANE" or "SEVORANO" [Words]

COVER SHEET

Title	High concentration versus low concentration sevoflurane for anaesthesia induction
Authors	Boonmak P, Boonmak S, Krisanaprakornkit W, Pattanittum P
Contribution of author(s)	Conceiving the review: Polpun Boonmak (PB) Co-ordinating the review: Suhattaya Boonmak (SB) Undertaking manual searches: PB, SB Screening search results: PB, SB Organizing retrieval of papers: PB Screening retrieved papers against inclusion criteria: PB, SB Appraising quality of papers: PB, SB, Wimonrat Krisanaprakornkit (WK)

	Abstracting data from papers: PB, SB, WK Writing to authors of papers for additional information: PB Providing additional data about papers: PB Obtaining and screening data on unpublished studies: PB Data management for the review: PB, Porjai Pattanittum (PP) Entering data into Review Manager (RevMan 4.2): PB RevMan statistical data: PB, PP Other statistical analysis not using RevMan: PP Double entry of data: data entered by person one PB, data entered by person two SB Interpretation of data: PB, PP Statistical analysis: PP Writing the review: PB, SB Securing funding for the review: PB Performing previous work that was the foundation of the present study: PB Guarantor for the review (one author): PB Person responsible for reading and checking review before submission: PB
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Music during caesarean section under regional anesthesia for improving maternal and infant outcomes (Protocol)

Laopaiboon M, Lumbiganon P, Martis R, Vatanasapt P, Somchiwong B

This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2008, Issue 1

http://www.thecochranelibrary.com

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Music during caesarean section under regional anesthesia for improving maternal and infant outcomes (Protocol)

Laopaiboon M, Lumbiganon P, Martis R, Vatanasapt P, Somchiwong B

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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 music during caesarean section under regional anesthesia on improving clinical and psychological outcomes for mothers and infants.

BACKGROUND

Caesarean section is a surgical procedure for delivering a baby through incisions made on the mother's abdominal wall and uterus. Caesarean section can be a life-saving operation if it is performed for certain medical indications such as placenta praevia (placenta lying over the opening of the cervix) or transverse lie (the baby lying across the uterus) or for fetal distress (the baby does not have adequate oxygen supply) (Neilson 2003). Pregnant mothers undergoing caesarean section often experience anxiety in anticipation of the event that will be unfamiliar, uncomfortable, or have undesirable results. The anxiety can increase the risk of psychological and physiological complications and postoperative recovery (Good 1996; Mok 2003). The anxiety, however, could be reduced by various means including support by their surgeons, nurses and maybe music in the operative rooms.

There is evidence to suggest that there are increased maternal risks associated with the 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). A caesarean section may also increase the chances of women experiencing problems in subsequent pregnancies related to the uterine scar (Hemminki 1996). Furthermore, new, unexpected, long-term risks of caesarean section continue to be reported; these include abnormal 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 the baby 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 in the next pregnancy (Smith 2003).

Music is an intentional auditory stimulus with organized 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. Music was found to enhance wellbeing in a randomized crossover trial (McCraty 1998), reduce stress and distract patients from unpleasant symptoms in a systematic review of randomized controlled trials (Evans 2002) and a quasi-experiment

study (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 randomized repeated experimental study (White 1999) and two quasi-experimental studies (Umemura 1998; Urakawa 2005) show that listening to classical music may increase the heart rate variability whereas listening to noise or rock music may decrease the heart rate variability (reflecting greater stress). It also has indirect effects by modifying caregiver behaviour. A randomized controlled trial (Lepage 2001) and two quasi-experimental studies (Haun 2001; Yung 2002) show that music can reduce anxiety effectively and improves 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 had methodologic problems, such as small sample size, lack of random assignment, and lack of control for patient anesthesia (Kemper 2005). A systematic review of randomized controlled trials on music for pain relief (Cepeda 2006) also found that the beneficial effect of music on pain intensity levels and opioid requirements is unclear. In a randomized controlled trial, music was found to improve the quality of life for patients receiving palliative care (Hilliard 2003). It enhances a sense of comfort and relaxation in a pre and post study (Burns 2001) and two randomized controlled trials (Cassileth 2003; Smith 2001). A quasi-experimental study (Allen 1994) and a randomized controlled trial (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 technical aspects of care.

Music's ability to slow respiratory rates and decrease the stress response is beneficial during labour. It has been shown to have the ability to shorten labour in an observational study (Winokur 1984). Even when the course of labour does not speed up when music is utilized, the perceived length of labour decreases, as shown in a quasi-experimental study (Clark 1981). Other studies of a review (McKinney 1990) and a self-controlled experiment (Hanser 1983) have shown that when music is played, pain is decreased. The efficacy of music therapy for premature infants was found in a nonsystematic review of literature (Standley 2002). Their findings suggest that music is clinically useful for the care of this group. One cohort study describes the use of medical resonant music therapy as preoperative preparation for caesarean section. Compared with a control group of women who received sedatives for preoperative preparation the experimental group receiving music therapy had lower cortisol levels and noted better sleep and less need for analgesics postoperatively (Sidorenko 2000).

Music may be particularly useful during caesarean sections. Most anaesthesia for caesarean sections are performed under epidural or spinal block. The pregnant mother is anaesthetized from the waist down. There is often some degree of discomfort for the mother before the baby is born, when the uterus is manipulated. Music may be an effective way to decrease the discomfort here (Schwartz 1997). There is, however, no evidence of a systematic review discussing the benefit of music during caesarean section. Its effects on controlling clinical outcomes and promotion of psychological outcomes of mothers and infants during caesarean section could contribute to important clinical practice change.

OBJECTIVES

To assess the effectiveness of music during caesarean section under regional anesthesia on improving clinical and psychological outcomes for mothers and infants.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

We will consider all identified published, unpublished and ongoing randomized controlled trials (RCT) and quasi-RCTs for inclusion. It will not be possible to blind the participants to the treatment (music therapy). The randomized units can be individual or clustered like hospitals.

Types of participants

Pregnant women scheduled to receive caesarean sections under regional anesthesia.

Types of intervention

Adjunct 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 (SpO_2)
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

See: Cochrane Pregnancy and Childbirth Group methods used in reviews.

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) monthly searches of MEDLINE;
(3) handsearches of 30 journals and the proceedings of major conferences;
(4) weekly current awareness search of a further 36 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 'Search strategies for identification of studies' 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.

We will not apply any language restrictions.

METHODS OF THE REVIEW

Selection of studies

Two review authors will independently assess for inclusion all potential studies we identify as a result of the search strategy. We will resolve any disagreement, if required, through discussion with a third review author.

Assessment of methodological quality of included studies
Two review authors will assess the validity of each study independently using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005). We will use only the criteria for selection bias and detection bias that are feasible for our review. We will describe 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, pre-numbered or coded identical containers, 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) Detection bias (blinding of outcome assessment)
We will assess detection bias using the following criteria:
(A) adequate blinding explanation: such as investigators measured blood pressure among the women without awareness of the interventions they received;
(B) unclear blinding explanation: such as investigators measured blood pressure among the women similarly;
(C) inadequate blinding explanation: such as blood pressure was assessed by clinicians involved in the caesarean operation.

High-quality trials will be defined as those receiving an A rating for selection bias and detection bias.

Data extraction and management
We will design a form, based on the Cochrane Pregnancy and Childbirth Group's 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 2003) 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 2003). We will report continuous outcomes such as maternal blood pressures, pain and infant Apgar scores

using weighted 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. If there is evidence of skewness, this will be reported. We will report binary outcomes such as analgesic requirement, etc, using relative risk with 95% CI and the corresponding number needed-to-treat.

Assessment of heterogeneity
We will evaluate whether the music effect size was similar in the included studies, if appropriate, using the I-squared 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) which were found to relate to music choices, 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. Alternatively, we will use fixed-effect meta-analysis for combining data.

Cluster-randomized trials
We are aware of potential variations in units of analysis across trials. We will include cluster-randomized trials in the analyses along with individually randomized trials. Their sample sizes will be adjusted 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 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. 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 analyses to explore the effect of trial quality and, where appropriate, cluster-randomized trials on the meta-analysis conclusion. 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. 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.

POTENTIAL CONFLICT OF INTEREST

None known.

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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), 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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Extracorporeal shock wave lithotripsy (ESWL) for kidney stones (Protocol)

Srisubat A, Potisat S, Lojanapiwat B, Setthawong V, Laopaiboon M

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:
This review aims to assess the effectiveness and complications of ESWL for kidney stones compare with other modalities.

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 which disintegrates stones in the kidney and upper urinary tract through the use of shock waves. However, there are several factors which will alter the treatment options 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 mm to 10 mm), 23% to 56% (11 mm to 20 mm) and 14% to 33% (21 mm to 30 mm) (Albala 2001; Alken 2003). The success rate of ESWL also depends on stone composition. ESWL for uric acid and calcium oxalate dihydrate 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 to 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 predominance in 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, 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 mm to 20 mm, 93% treated with PCNL were stone-free, compared to only 23% of those treated with ESWL. Finally, for patients with stones 21 mm to 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 comorbidities. 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).

In summary, we will assess the effectiveness, safety and complications of ESWL compared with other modalities for the treatment of kidney stones.

OBJECTIVES

This review aims to assess the effectiveness and complications of ESWL for kidney stones compare with other modalities.

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 shall also 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 will be excluded.

Types of intervention

Any patients with kidney stones treated using ESWL compared to PCNL or RIRS.

Types of outcome measures

Primary outcomes

- Success rate: Stone-free, clinically insignificant residual fragments (CIRF) (residual fragment less than 4 mm).
- Re-treatment rate.
- Auxiliary procedures.
- Efficacy quotient (EQ).

Secondary outcomes

- Mean procedural time.
- Mean hospital stay.
- Complications after treatment.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Renal Group methods used in reviews.

1). The Cochrane Renal Groups specialised register and the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, (most recent) which will be searched using the following terms:-
#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)

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 2007). Therefore we will 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 2007).

2). MEDLINE (1966 to most recent) using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs (Dickersin 1994) with the following specific search strategy developed with input from the Cochrane Renal Groups Trial Search Co-ordinator.
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
22. and/16,21

3). EMBASE (1980 to most recent) using a search strategy adapted from that developed for the Cochrane Collaboration for the identification of RCTs (Lefebvre 1996) together with the following specific search strategy developed with input from the Cochrane Renal Groups Trial Search Co-ordinator.
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$.tw.
11. pcnl.tw.
12. retrograde intrarenal surgery.tw.
13. rirs.tw.
14. flexible ureteroscop$.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

4). Reference lists of nephrology textbooks, review articles and relevant studies.
5). Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

METHODS OF THE REVIEW

Included and excluded studies

The review will be undertaken by five authors (AS, SP, BL, VS, ML). The search strategy described will be used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts will be screened independently by AS, SP and VS, who will discard studies that are not applicable, however studies and reviews that might include relevant data or information on studies will be retained initially. Reviewers BL and VS who are urologists will independently assess retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfy the inclusion criteria. Data extraction will be carried out independently by the same authors using standard data extraction forms. Studies reported in non-English language journals will be translated before assessment. Where more than one publication of one study exists, reports will be grouped together and the most recent or most complete dataset will be used. Any discrepancy between published versions will be highlighted. Any further information required from the original author will be requested by written correspondence and any relevant information obtained in this manner will be included in the review. Disagreements will be resolved by discussion. Data entry and analysis will be performed by ML.

Study quality

The quality of studies to be included will be assessed independently by AS and SP without blinding to authorship or journal using the checklist developed for the Cochrane Renal Group. Discrepancies will be resolved by discussion. The quality items to be assessed are allocation concealment, blinding (participants, investigators, outcome assessors and data analysis), intention-to-treat analysis and completeness of follow-up.

Quality checklist

Allocation concealment

- Adequate (A): Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study.
- Unclear (B): Randomisation stated but no information on method used is available.
- Inadequate (C): 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/no/not stated.
- Blinding of data analysis: Yes/no/not stated.

Intention-to-treat

- Yes: Specifically reported by authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment.
- Yes: Not stated but confirmed on study assessment.
- No: Not reported and lack of intention-to-treat analysis confirmed on study assessment. (Patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation).
- No: Stated but not confirmed upon study assessment.
- Not stated.

Completeness of follow-up

Per cent of participants excluded or lost to follow-up.

Data analysis

Measures of treatment effect

The mean procedural time and mean hospital stay will be assessed using mean difference (WMD) with 95% confidence intervals (CI) if the outcomes are measured in the same way among studies. The standardized mean difference (SMD) will be used to combine studies that measure the same outcome, but by different methods. If there is evidence of skewness, this will be reported. For stone-free rate, CIRF, re-treatment rate, use of auxiliary procedures, and complications after treatment the relative risk (RR) with 95% CI, and the corresponding number needed-to-treat (NNT) will be calculated. Data will be pooled using the random-effects model but the fixed-effect model will also be analysed to ensure robustness of the model chosen and susceptibility to outliers

Assessment of heterogeneity

We will evaluate whether ESWL and other modalities effect sizes were similar in the included studies. If appropriate, the I^2 statistic will be used (Higgins 2003) and if high levels of heterogeneity among the studies can be identified (exceeding 50%), we will explore using subgroup analyses.

Subgroup analyses

We will conduct subgroup analyses where sufficient data are available for kidney stone sizes (less than 10 mm, 10 to 20 mm, more than 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.

Dealing with missing data

Participants with be analysed according to the group to which they were randomised, regardless of whether or not they received the allocated intervention. If in the original reports participants are not analysed in the allocated group, and if there is sufficient information in the study report, we will attempt to restore them to the correct group.

Assessment of publication bias

Where sufficient studies are identified, we will consider publication bias using funnel plots of between-treatment effect and its precision on individual studies. If asymmetric funnel plots with statistically significant publication bias are found, we will examine its effect on the meta-analysis conclusion using sensitivity analyses.

Sensitivity analyses

Sensitivity analyses will be conducted to explore the effect of study quality and, where appropriate on the meta-analysis conclusion. The study quality will involve an analysis based on concealment of allocation. Studies with inadequate allocation of concealment will be excluded in order to assess for any substantive difference to the overall result.

POTENTIAL CONFLICT OF INTEREST

None known.

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COVER SHEET

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