Authors' conclusions

The review authors do not recommend prophylactic epidural blood patch over other treatments because there are too few trial participants to allow reliable conclusions to be drawn. However, therapeutic epidural blood patch showed a benefit over conservative treatment, based on the limited available evidence.

PLAIN LANGUAGE SUMMARY

Epidural blood patching for preventing and treating post-dural puncture headache

The role of epidural blood patching in the prevention or treatment of the headache that may follow dural puncture (usually lumbar puncture) is inconclusive. Dural puncture involves passing a needle into the fluid-filled space around the spinal cord and nerve roots. This procedure is used to obtain spinal fluid for laboratory tests or to give a spinal anaesthetic. However, leakage of fluid through the puncture created by the needle can cause headache. One suggestion for preventing or treating this headache is to inject some of the patient's own blood around the puncture to stop the leakage (epidural blood patch). However, this review showed that, according to current evidence, clear conclusions cannot be drawn about the advantage of preventative epidural blood patch over other treatments. The use of epidural blood patch after the onset of the headache, however, showed benefit over conservative treatment. There were too few participants in the included studies, however, to allow a reliable assessment of the potential benefits and harms of this technique.

BACKGROUND

This is an update of a Cochrane Review first published in Issue 2, 2002. Dural puncture (usually lumbar puncture) involves passing a needle through the dura mater into the cerebrospinal fluid (CSF)-filled subarachnoid space around the spinal cord, roots or both. The procedure may be performed:

1. for diagnostic purposes, to measure the CSF pressure or withdraw a CSF sample for laboratory analysis, or both;

2. for therapeutic purposes, to administer intrathecal chemotherapy;

3. in spinal anaesthesia, to introduce an anaesthetic agent (or agents) through the needle into the subarachnoid space;

4. inadvertently during epidural anaesthesia; and

5. in myelography, to instil radio-opaque material into the subarachnoid space prior to radiologic imaging.

Dural puncture is therefore a common procedure. Fortunately, serious, potentially life-threatening complications associated with the treatment, including spinal abscess or meningitis, subdural haematoma and cerebellar tonsillar herniation, are very rare (Evans 1998; van Crevel 2002; Domenicucci 2005; Horlocker 2008; Williams 2008). Headache following dural puncture is, however, much more common. Reported estimates of its frequency vary widely, from less than 1% to over 80%, depending on the types of patients studied, associated procedures such as the introduction of anaesthetic or radio-opaque material into the CSF, the definition of headache, and the method of follow up used (Turnbull 2003; Kuczkowski 2004; Ahmed 2006; Gaiser 2006; Simmons 2007; Reamy 2009). Post-dural puncture headache (PDPH) is classically postural in nature (i.e. worse on standing and improved by lying flat), and may be accompanied by nausea, vomiting, tinnitus and hearing impairment. The symptoms are thought to be due to leakage of CSF through the dural defect produced by the dural puncture, causing a reduction in CSF pressure and downward traction on the pain-sensitive intracranial veins and meninges, as well as the cranial nerves (Turnbull 2003; Gaiser 2006). Provided the patient stands up, the headache usually occurs within 48 hours of the procedure and resolves spontaneously within a few days. However, symptoms can last for a week or more, and may interfere with activities of daily living, causing disability and necessitating time off work (Tohmo 1998). If severe, the headache may necessitate hospital admission or readmission. Obstetric patients who suffer accidental dural puncture during epidural anaesthesia appear to be particularly at risk, in part because large diameter (usually 16 or 18 gauge) needles tend to be used for the procedure and so leave a larger defect if the dura is accidentally breached. Leakage of CSF may be exaggerated by rises in intra-abdominal pressure during labour (Reynolds1993; Kuczkowski 2004; Kuczkowski 2007; Simmons 2007; Thew 2008).

Both dural puncture and PDPH are common, therefore simple measures to reduce the occurrence of headache, and to reduce or abolish the symptoms should they occur, are well worth identify-

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ing. One such measure, the technique of epidural blood patching, is increasingly used in managing patients with persistent PDPH, as well as for its prevention. This involves the epidural injection of around 7.5 to 30 ml of autologous blood into the extradural space around the site where the dural puncture was performed (Turnbull 2003; Gaiser 2006; Thew 2008). Coagulation of the blood is thought to stop the leakage of CSF from the dural defect resulting from dural puncture. High success rates have established the epidural blood patch as the method of choice for the treatment of severe post-dural puncture headache (Turnbull 2003; Thew 2008). However, such 'success' rates cannot necessarily be attributed to the effects of blood patching because PDPH tends to resolve spontaneously in any case. Furthermore, there is a potential risk of epidural infection with epidural blood patching, and the procedure may also be associated with backache and lower limb paraesthesia (Candido 2003; Turnbull 2003; Gaiser 2006; Thew 2008). Randomised evidence is necessary to establish whether the apparent success of this technique is real, and whether the benefits outweigh the risks. As far as we are aware, the technique has never been reviewed systematically. This review therefore addresses the effectiveness of epidural blood patching for the prevention and treatment of PDPH.

OBJECTIVES

We aimed to assess the effectiveness of epidural blood patch in the prevention and treatment of post-dural puncture headache (PDPH) in patients who were undergoing dural puncture for any reason. We also aimed to assess the possibility of harm from this intervention, in particular any excess risk of infection, backache and lower limb paraesthesia.

METHODS

Criteria for considering studies for this review

Types of studies

We aimed to include only properly randomised controlled trials (RCTs), using a method of treatment allocation that precluded foreknowledge of the trial arm to which any participant would be assigned.

Types of participants

We included studies involving participants of any age and either sex.

Types of interventions

We included epidural blood patch versus no blood patch for the prevention (performed immediately after dural puncture) or treatment of post-dural puncture headache (PDPH).

Types of outcome measures

Primary outcomes

Our primary outcome was PDPH (headache after dural puncture that improves on lying flat) of any severity.

Secondary outcomes

Our secondary outcomes were severe PDPH (according to each trialist's definition of severe), all headache, backache and adverse effects of epidural blood patching.

Search methods for identification of studies

Electronic searches

For the original version of this review we searched the Cochrane Controlled Trials Register (*The Cochrane Library* 2000, Issue 4); MEDLINE (1994 to December 1998) and EMBASE (1980 to December 1998). For this updated review, we searched the Cochrane Pain, Palliative and Supportive Care (PaPaS) Group Trials Register (April 2009); the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, Issue 1); MEDLINE (1950 to April 2009) and EMBASE (1980 to April 2009). We developed a specific strategy for each database based on that developed for CENTRAL (Appendix 1). Please also see: Appendix 2 (MEDLINE); Appendix 3 (EMBASE); and Appendix 4 (PaPaS Trials Register).

Searching other resources

We searched the reference lists of all studies and review articles identified by electronic searching, and asked for information about any potentially relevant studies when we contacted trialists from the studies identified.

Data collection and analysis

Selection of studies

Two review authors (PB and SB) independently reviewed titles and abstracts identified from the literature searches for relevant studies

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and selected possibly relevant studies. We reviewed these studies using the full text and assessed them using the inclusion criteria detailed above. We (PB and SB) resolved any disagreement by consensus or, if necessary, by consulting a third review author (CW and CS). If we were not able to resolve differences then we intended to add the publication reference to those awaiting assessment and attempt to contact the study authors for clarification.

Data extraction and management

We used a data extraction form to obtain data from individual studies. This was performed by two review authors (PB and SB). We studied the reports of all possibly relevant trials identified and used a specially designed form to extract information on methods of randomisation and blinding, the comparison(s) of interest, the number of participants originally randomised in each arm of the study, any losses to follow up and the occurrence in each arm of the outcomes of interest. For all studies that fulfilled (or that might fulfil) the inclusion criteria (above), we attempted to contact the principal trialist (or, if necessary, one of the other authors) and asked them to check the information and data extracted and to provide any missing information that was available to them but not included in the trial report. We recorded the main reason (or reasons) for the exclusion of any potentially relevant studies, whether based on information extracted from published trial reports or received from trialists. Following data extraction, we performed double data entry and screened the database for inconsistencies as a quality assurance measure.

Assessment of risk of bias in included studies

A study was defined as: A (low risk of bias, all quality criteria met); B (moderate risk of bias, one or more of the quality criteria only partly met); and C (high risk of bias, one or more criteria not met). Any conflicts would be assessed through discussion and, if necessary, through evaluation by a third review author (CW and CS).

Data synthesis

We analysed the two questions (the role of epidural blood patching for the prevention, and for the treatment, of PDPH) separately using Review Manager (RevMan 5.0). We performed analysis on an intention-to-treat (ITT) basis, i.e. all participants randomised remained in their original trial arm, whether or not they had actually received the intervention allocated. In the main analyses we assumed that any patient lost to follow up did not experience the outcome being considered. Individual trial results and summary results for each outcome from a particular comparison were expressed as odds ratios (OR), calculated using the Peto O-E method.

Sensitivity analysis

We performed sensitivity analyses for missing data and study quality. Several sensitivity analyses were formulated *a priori.*

1. Where randomisation was mentioned but the method of treatment allocation remained unclear, even after contact with the trialists, we planned, where possible, to examine the effect on the primary outcome of excluding any such trials, and therefore of including only those studies that had used a method that should definitely ensure truly random treatment allocation.

2. Lack of blinding of patients or observers assessing patient outcomes may seriously bias trial results, particularly when the outcome is a subjective one, such as headache (Schulz 1995). For adequate patient blinding it was necessary for the trial participants to be unaware of their treatment allocation. In trials assessing epidural blood patch for the treatment of PDPH, this meant that patients allocated to the control group had to have undergone a sham procedure without epidural injection of blood. For adequate observer blinding we required someone other than the person performing the blood patch or sham procedure (who must inevitably be aware of the method being used) to have collected the outcome information. We aimed to examine the effect on the primary outcome of excluding trials with inadequate blinding of either trial participants or observers (or both) to the allocated intervention.

3. Bias in the results may also occur when follow up of all patients initially randomised is incomplete. To assess the robustness of our results to losses to follow up, we planned to adopt a 'penalty' system for each comparison. This would assess the effect on the summary result for the primary outcome of assuming that all patients lost to follow up in the arm which appeared superior had experienced the outcome, and all patients lost to follow up in the arm which appeared inferior had remained free of the outcome.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Searching all databases up to April 2009 identified 12 studies including those included for the first version of this review (Ackerman 1989; Seebacher 1989; Trivedi 1993) (see Figure 1). We excluded three of these for the reasons described in the 'Characteristics of excluded studies' table. We identified a total nine studies for possible inclusion in the review (Ackerman 1989;

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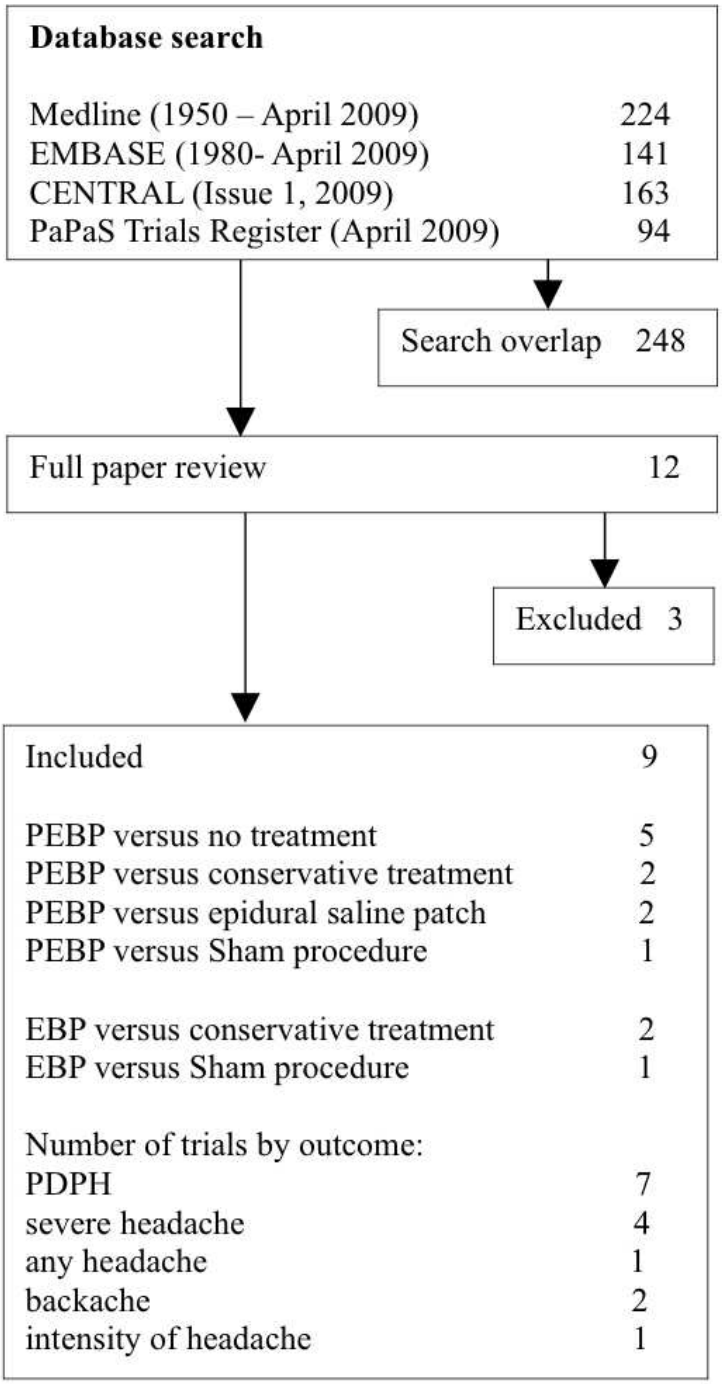
Colonna 1989; Lowenwirt 1998; Seebacher 1989; Sengupta 1989; Trivedi 1993; Scavone 2004; Sandesc 2005; van Kooten 2008).

Figure 1. Search results.



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Included studies

Six additional studies were added to this update which added a further 302 participants. Nine studies were included in total for this update involving 379 participants (see 'Characteristics of included studies' table). Ackerman 1989 compared prophylactic epidural blood patch versus no treatment among 21 participants. Three studies compared prophylactic epidural blood patch versus conservative treatment among 132 participants (Colonna 1989; Trivedi 1993; Lowenwirt 1998). Sengupta 1989 compared prophylactic epidural blood patch versus epidural saline patch among 48 participants. Scavone 2004 compared prophylactic epidural blood patch versus a sham procedure among 64 participants. Two studies compared blood patch versus conservative treatment in 72 participants (Sandesc 2005; van Kooten 2008). Seebacher 1989 compared epidural blood patch versus a sham procedure in 12 participants. We attempted to contact the principal trialist (Ackerman 1989; Seebacher 1989; Trivedi 1993) of the included studies but were able to obtain additional information from only one study (Seebacher 1989).

Excluded studies

We excluded three studies (see the 'Characteristics of excluded studies' table). Heide 1990 and Safa-Tisseront 2001 were both non-randomised trials. Loeser 1978 did not include the comparison of interest.

Risk of bias in included studies

Please see Figure 2 and Figure 3 for our assessment of the risk of bias in the included studies.

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Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

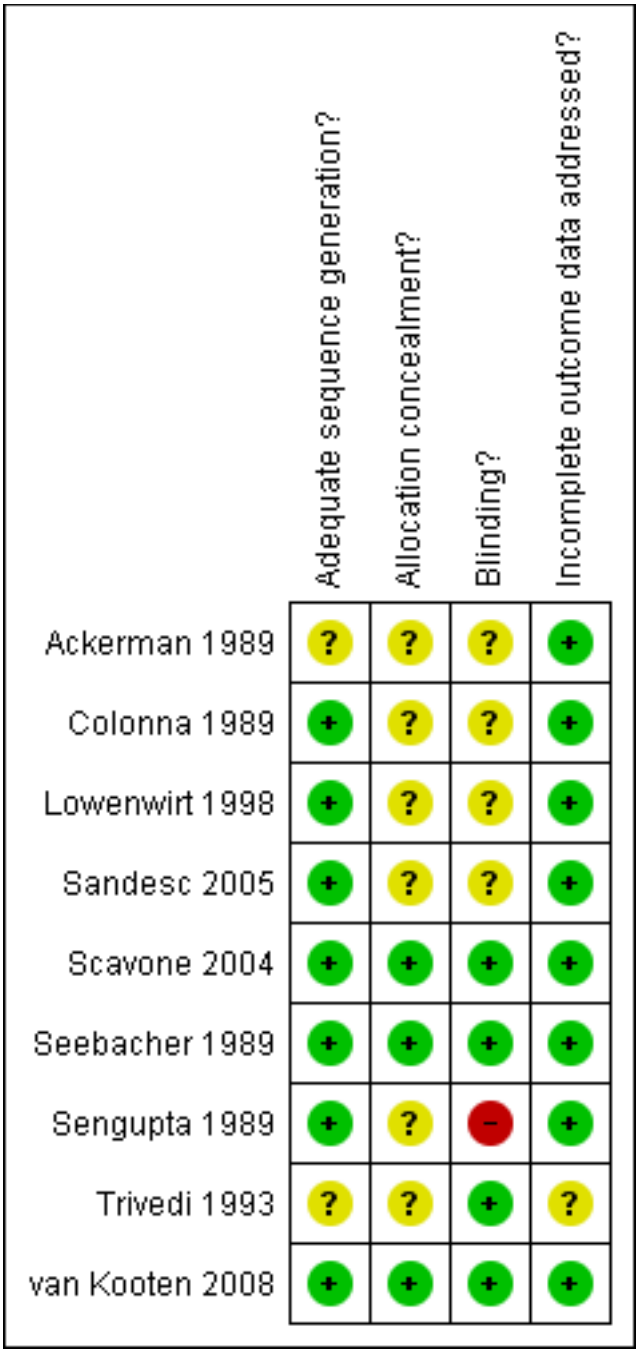

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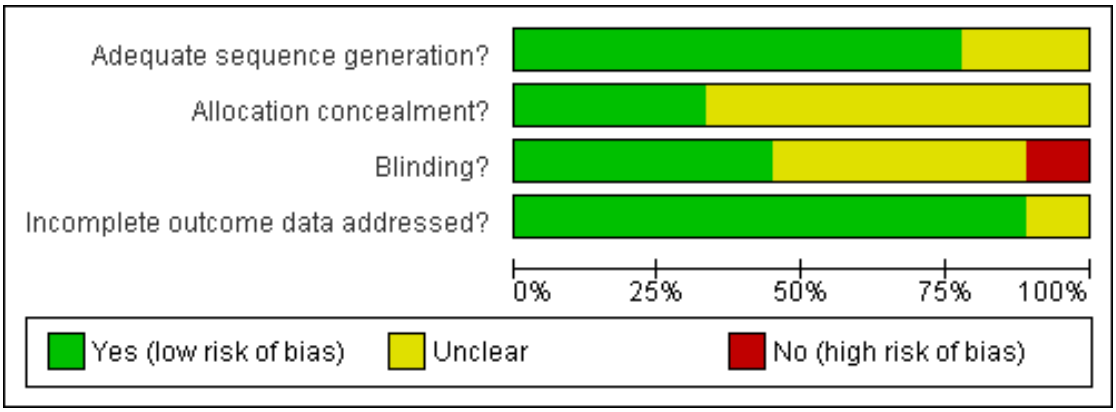
Figure 3. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

Three of the reports of the studies that assessed the effects of prophylactic epidural blood patch had adequate sequence generation and allocation concealment (Seebacher 1989; Scavone 2004; van Kooten 2008). Six of the studies did not describe the allocation concealment (Ackerman 1989; Colonna 1989; Sengupta 1989; Trivedi 1993; Lowenwirt 1998; Sandesc 2005).

Blinding

Four of the studies that assessed the effects of prophylactic epidural blood patch had adequate assessor blinding (Seebacher 1989; Trivedi 1993; Scavone 2004; van Kooten 2008). In two of the studies (Ackerman 1989; Sandesc 2005) outcome assessment was blinded. Participants were not clearly blinded in Colonna 1989, Sengupta 1989 or Lowenwirt 1998.

Incomplete outcome data

Five studies (Ackerman 1989; Colonna 1989; Sengupta 1989; Trivedi 1993; Lowenwirt 1998) assessed the effects of prophylactic epidural blood patch but described no missing data. Since follow up was for one to two days only, it is unlikely that many participants would have been lost to follow up. Scavone 2004 reported the missing data in both groups. Three studies (Seebacher 1989; Sandesc 2005; van Kooten 2008) assessed the effect of epidural blood patch and reported no missing data.

Effects of interventions

Prophylactic epidural blood patch

Please see Analysis 1.1, Analysis 1.2, Analysis 1.3 and Analysis 1.4 for further information.

Post-dural puncture headache (PDPH)

One study (Ackerman 1989) showed a significant difference in post-dural puncture headache (PDPH) between the prophylactic epidural blood patch and no blood patch groups (OR 0.11, 95% CI 0.02 to 0.64, 21 participants, Analysis 1.1: subgroup 1).
Two studies (Colonna 1989; Lowenwirt 1998) showed a significant difference in PDPH between the prophylactic epidural blood patch and conservative treatment groups (OR 0.06, 95% CI 0.03 to 0.14, 88 participants, Analysis 1.1: subgroup 2).
One study (Sengupta 1989) showed a significant difference in PDPH between the prophylactic epidural blood patch and epidural saline patch groups (OR 0.16, 95% CI 0.04 to 0.55, 48 participants, Analysis 1.1: subgroup 3).
One study (Scavone 2004) showed no significant difference in PDPH between the prophylactic epidural blood patch and sham procedure groups (64 participants, Analysis 1.1: subgroup 4).

Severe post-dural puncture headache

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One study (Ackerman 1989) showed no significant difference in severe PDPH between the prophylactic epidural blood patch and no blood patch groups (21 participants, Analysis 1.2: subgroup 1).
One study (Sengupta 1989) showed no significant difference in severe PDPH between the prophylactic epidural blood patch and epidural saline patch groups (48 participants, Analysis 1.2: subgroup 2).
One study (Scavone 2004) showed no significant difference in severe PDPH between the prophylactic epidural blood patch and sham procedure groups (64 participants, Analysis 1.2: subgroup 3).

Any headache

One study (Ackerman 1989) showed no significant difference in any headache between the prophylactic epidural blood patch and no blood patch groups (21 participants, Analysis 1.3: subgroup 1).
One study (Trivedi 1993) showed a significant difference in any headache between the prophylactic epidural blood patch and conservative treatment groups (OR 0.04, 95% CI 0.01 to 0.19, 44 participants, Analysis 1.3: subgroup 2).
One study (Trivedi 1993) showed a significant difference in any headache between the prophylactic epidural blood patch and epidural saline patch groups (OR 0.08, 95% CI 0.02 to 0.37, 50 participants, Analysis 1.3: subgroup 3).
One study (Scavone 2004) showed no significant difference in any headache between the prophylactic epidural blood patch and sham procedure groups (64 participants, Analysis 1.3: subgroup 4).

Backache

One study (Scavone 2004) showed no significant difference in headache between the prophylactic epidural blood patch and sham procedure groups (64 participants, Analysis 1.4).

Therapeutic epidural blood patch

Please see Analysis 2.1, Analysis 2.2, Analysis 2.3 and Analysis 2.4 for further information.

Post-dural puncture headache (PDPH)

One study (van Kooten 2008) showed a significant difference in PDPH between the therapeutic epidural blood patch and conservative treatment groups (OR 0.18, 95% CI 0.04 to 0.76, 40 participants, Analysis 2.1: subgroup 1).
One study (Seebacher 1989) showed a significant difference in PDPH between the therapeutic epidural blood patch and sham procedure groups (OR 0.04, 95% CI 0.00 to 0.39, 12 participants, Analysis 2.1: subgroup 2).

Severe post-dural puncture headache

One study (Seebacher 1989) showed a significant difference in severe PDPH between the therapeutic epidural blood patch and sham procedure groups (OR 0.03, 95% CI 0.00 to 0.22, 12 participants, Analysis 2.2).

Backache

One study (Seebacher 1989) showed a significant difference in backache between the therapeutic epidural blood patch and sham procedure groups (OR 23.17, 95% CI 2.57 to 208.60, 12 participants, Analysis 2.3).

Intensity of headache

One study (Sandesc 2005) showed a significant difference in intensity of headache between the therapeutic epidural blood patch and conservative treatment groups (MD -7.10, 95% CI -6.51 to -7.69, 32 participants, Analysis 2.4).
The small numbers of studies, patients and events included in these analyses meant that the planned sensitivity analyses could not be carried out.

DISCUSSION

Summary of main results

Prophylactic epidural blood patch decreased post-dural puncture headache (PDPH) compared to no treatment, conservative treatment and epidural saline patch. Severe PDPH was comparable between prophylactic epidural blood patch, no treatment and epidural saline patch groups. Prophylactic epidural blood patch resulted in less 'any headache' than conservative treatment and epidural saline patch. However, PDPH, severe PDPH, any headache and backache were comparable between prophylactic epidural blood patch and sham procedure groups. There were too few participants to draw reliable conclusions about the benefit of prophylactic epidural blood patch.
Therapeutic epidural blood patch decreased PDPH, severe PDPH and intensity of headache over a sham procedure. Epidural blood patch also decreased PDPH over conservative treatment. However, epidural blood patch resulted in more backache than a sham procedure. We could not draw clear conclusions because of too few studies.

Quality of the evidence

Five studies, with 221 participants, comparing prophylactic epidural blood patch with other treatment (Ackerman 1989; Colonna

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1989; Sengupta 1989; Lowenwirt 1998; Scavone 2004) were included in the review. However, lack of blinding, unclear allocation concealment and unclear missing data were found among these studies. Scavone 2004 compared prophylactic epidural blood patch with a sham procedure and had clear allocation concealment and blinding. This trial showed comparable benefits between prophylactic epidural blood patch and a sham procedure. The available studies which looked at the use of prophylactic epidural blood patch therefore had too few randomised participants to allow reliable conclusions to be drawn.

Therapeutic epidural blood patch showed benefit over both conservative treatment and a sham procedure. Three studies, involving 86 participants, had adequate allocation concealment and blinding techniques (Seebacher 1989; Sandesc 2005; van Kooten 2008) (Figure 2). However, again there were too few participants in the three studies to draw reliable conclusions.

Agreements and disagreements with other studies or reviews

Previous studies (Vasdev 2001; Turnbull 2003; Warwick 2007) did not recommend the routine use of prophylactic blood patch after dural puncture. A survey of anaesthesiologists also showed a decrease in the use of prophylactic blood patch, with a fall from 50% (Berger 1998) to 26% (Baraz 2005). Although our data showed an advantage of prophylactic epidural blood patch over no treatment and conservative treatment in reducing PDPH, it did not result in less PDPH than a sham procedure. We therefore cannot draw the same clear conclusions about the benefit of prophylactic epidural blood patch as in previous studies.

Therapeutic epidural blood patch after spinal anaesthesia with PDPH symptoms has shown benefit in many studies (Berger 1998; Turnbull 2003; Thew 2008). However, evidence from large RCTs comparing epidural blood patch with no blood patch is lacking. Epidural blood patch is favoured over conservative treatment (bed rest, oral and intravenous fluid, and caffeine), although most clinicians tend to use conservative treatment before epidural blood patch, which is often carried out when the conservative treatment has failed.

AUTHORS' CONCLUSIONS

Implications for practice

This is an updated review, the conclusions should be re-read as there is additional, but limited, evidence. Prophylactic epidural blood patch is not recommended as a routine preventative treatment. The studies found unclear benefit over other treatment in the incidence of post-dural puncture headache (PDPH). Prophylactic epidural blood patching should be reserved for exceptional cases only. However, therapeutic epidural blood patch for the treatment of PDPH has been accepted as a standard treatment. This review shows evidence that epidural blood patch could reduce PDPH compared to conservative treatment and sham procedures.

Implications for research

Although prophylactic epidural blood patch showed benefit over no treatment, conservative treatment and epidural saline patch, the data did not show a benefit over a sham procedure. The evidence from studies included in this review is therefore uncertain. Large trials of prophylactic epidural blood patch versus other treatments are required to allow reliable conclusions to be drawn. More trials of therapeutic epidural blood patch are also required to clarify the conclusions of benefit over conservative treatment and sham procedures.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Ackerman 1989

Methods	Randomisation and treatment allocation method: not stated Blinding of outcome assessment: yes Blinding of patients: unclear
Participants	21 obstetric patients, ASA Physical Status I - II, who sustained inadvertent dural tear during epidural anaesthesia for labour analgesia
Interventions	18 to 20 ml epidural autologous blood patch through epidural catheter on admission to recovery room after delivery versus no blood patch
Outcomes	Postural headache and severe postural headache up to 24 hours post-partum (requiring blood patch or further blood patch)
Notes	-

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Blinding of outcome assessment: yes Blinding of patients: unclear
Incomplete outcome data addressed? All outcomes	Yes	No missing data

Colonna 1989

Methods	Randomisation and treatment allocation method: yes Blinding of outcome assessment: not stated Blinding of patients: not stated
Participants	39 obstetric patients who receive epidural catheter placement with dural puncture
Interventions	Prophylactic epidural blood patch (injected 15 ml autologous blood) via epidural catheter within 2 to 14 hours versus conservative treatment (drinking fluids, avoiding ambulation)
Outcomes	PDPH, any headache
Notes	-

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Colonna 1989 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "Each patient was then randomly assigned to control group (CG) or to the study group (SG)."
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Not stated
Incomplete outcome data addressed? All outcomes	Yes	No missing data

Lowenwirt 1998

Methods	Randomisation and treatment allocation method: unclear Blinding of outcome assessment: not stated Blinding of patients: not stated
Participants	49 obstetric patients who had accidental dural puncture from 16 to 17-gauge needle
Interventions	Prophylactic epidural blood patch (injected 15 to 20 ml autologous blood) via epidural catheter versus conservative treatment (IV hydration, bed rest, theophylline or caffeine)
Outcomes	PDPH, any headache
Notes	Abstract only

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "... were randomized and allocated to two treatment group."
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Not stated
Incomplete outcome data addressed? All outcomes	Yes	No missing data

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Sandesc 2005

Methods	Randomisation and treatment allocation method: yes Blinding of outcome assessment: yes Blinding of patients: not stated
Participants	32 patients who had PDPH symptoms for less than 24 hours
Interventions	Epidural blood patch versus conservative treatment (oral and IV replacement, non steroidal anti-inflammatory drug, caffeine)
Outcomes	Intensity of headache (a visual analogue scale (VAS) from 0 to 10), intensity of PDPH
Notes	-

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "randomized, double-blinded manner"
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Not stated
Incomplete outcome data addressed? All outcomes	Yes	No missing data

Scavone 2004

Methods	Randomisation and treatment allocation method: yes Blinding of outcome assessment: yes Blinding of patients: yes
Participants	64 obstetric patients who incurred an inadvertent dural puncture with a 17-gauge epidural needle during initiation of neuraxial analgesia/anaesthesia, and subsequently had an epidural catheter placed successfully at the same or a different interspace, were eligible to participate
Interventions	Epidural blood patch (injected 20 ml autologous blood until have lower back pain/sacral pain) after resolution of analgesia/anaesthesia through the epidural catheter versus sham procedure
Outcomes	PDPH, headache severity (verbal rating pain score), severe headache (required epidural blood patch), backache
Notes	-

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Scavone 2004 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "...subjects were randomized (via a computer-generated random number table) to a treatment (PEBP) group or a control/sham (SHAM) group."
Allocation concealment?	Yes	Quote: "...subjects were randomized (via a computer-generated random number table) to a treatment (PEBP) group or a control/sham (SHAM) group."; "Group assignment was determined by opening an opaque envelope labelled with the study subject number."
Blinding? All outcomes	Yes	Quote: "Her family members, physicians, and nurses were blinded as to treatment group." and "An anesthesiologist investigator unaware of treatment group evaluated the subjects postpartum to ascertain the presence of PDPH."
Incomplete outcome data addressed? All outcomes	Yes	No missing data

Seebacher 1989

Methods	Randomisation and treatment allocation method: yes Blinding of outcome assessment: yes Blinding of patients: yes
Participants	12 patients with persistent (i.e. > 4 days) postural headache following dural puncture
Interventions	10 to 20 ml autologous blood patch versus placebo (sham procedure)
Outcomes	Persistent postural headache, persistent severe postural headache, backache, potential adverse effects up to 24 hours post blood patch
Notes	-

Risk of bias		
Item	**Authors' judgement**	**Description**

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Seebacher 1989 (*Continued*)

Adequate sequence generation?	Yes	Quote: "Randomisation and treatment allocation method: sealed envelopes (sequentially numbered and opaque)."
Allocation concealment?	Yes	Quote: "Randomisation and treatment allocation method: sealed envelopes (sequentially numbered and opaque)."
Blinding? All outcomes	Yes	Quote: "Blinding of outcome assessment and patients"
Incomplete outcome data addressed? All outcomes	Yes	No missing data

Sengupta 1989

Methods	Randomisation and treatment allocation method: yes Blinding of outcome assessment: no Blinding of patients: no
Participants	48 patients undergoing extracorporeal shock wave lithotripsy, ASA I-II, 18 to 60 years old, spinal anaesthesia
Interventions	10 ml of autologous blood into the epidural space versus 10 ml of normal saline into the epidural space after spinal anaesthesia
Outcomes	Headache, backache, loin pain
Notes	-

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "... were assigned randomly to receive either 10 ml of autologous blood or 10 ml of normal saline..."
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	No	Quote: "As the questions were put by one or other of the investigators, who were not blinded to the patients' grouping, some bias would be a possibility"
Incomplete outcome data addressed? All outcomes	Yes	No missing data

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Trivedi 1993

Methods	Randomisation and treatment allocation method: not stated Blinding of outcome assessment: yes Blinding of patients: no
Participants	74 obstetric patients who sustained inadvertent dural puncture during epidural anaesthesia for labour analgesia
Interventions	15 ml autologous epidural blood patch immediately after dural puncture versus 40 to 60 ml epidural saline versus no prophylactic treatment (epidural saline arm not included in analyses)
Outcomes	Any headache up to 2 days post-dural puncture
Notes	-

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Yes	Blinding of outcome assessment: yes Blinding of patients: no
Incomplete outcome data addressed? All outcomes	Unclear	Not stated

van Kooten 2008

Methods	Randomisation and treatment allocation method: yes Blinding of outcome assessment: yes Blinding of patients: no
Participants	42 patients who presented with PDPH (lasting 24 hours to 1 week)
Interventions	15 to 20 ml autologous epidural blood patch versus conservative treatment (24-hour bed rest, drink more than 2 litres of fluid/day)
Outcomes	Headache at 24 hours and at day 7, associated symptoms
Notes	-

Risk of bias

Item	Authors' judgement	Description

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van Kooten 2008 (*Continued*)

Adequate sequence generation?	Yes	Quote: "Patients with PDPH were randomised using a computer database which allocated the patient to active (EDBP) or control (conservative) treatment through a random number generator."
Allocation concealment?	Yes	Quote: "Patients with PDPH were randomised using a computer database which allocated the patient to active (EDBP) or control (conservative) treatment through a random number generator."
Blinding? All outcomes	Yes	Quote: "The research nurse was blinded to treatment allocation."
Incomplete outcome data addressed? All outcomes	Yes	No missing data

EDBP = epidural blood patch; IV = intravenous; PDPH = post-dural puncture headache; VAS = visual analogue scale

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

Heide 1990	Non-randomised (comparison of prophylactic epidural blood patch versus no blood patch)
Loeser 1978	Comparison not included within the scope of this review: epidural blood patch for treatment of post-dural puncture headache performed less than 24 hours versus more than 24 hours after dural puncture
Safa-Tisseront 2001	Prospective observational study

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DATA AND ANALYSES

Comparison 1. Prophylactic epidural blood patch (PEBP)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Post-dural puncture headache (PDPH)	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 PEBP versus no treatment	1	21	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.11 [0.02, 0.64]
1.2 PEBP versus conservative treatment	2	88	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.06 [0.03, 0.14]
1.3 PEBP versus epidural saline patch	1	48	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.16 [0.04, 0.55]
1.4 PEBP versus sham procedure	1	64	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.0 [0.38, 2.66]
2 Severe PDPH	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 PEBP versus no treatment	1	21	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.19 [0.03, 1.22]
2.2 PEBP versus epidural saline patch	1	48	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.34 [0.05, 2.61]
2.3 PEBP versus sham procedure	1	64	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.60 [0.22, 1.62]
3 Any headache	3		Peto Odds Ratio (Peto, Fixed, 99% CI)	Subtotals only
3.1 PEBP versus no treatment	1	21	Peto Odds Ratio (Peto, Fixed, 99% CI)	0.11 [0.01, 1.10]
3.2 PEBP versus conservative treatment	1	44	Peto Odds Ratio (Peto, Fixed, 99% CI)	0.04 [0.01, 0.19]
3.3 PEBP versus epidural saline patch	1	50	Peto Odds Ratio (Peto, Fixed, 99% CI)	0.08 [0.02, 0.37]
3.4 PEBP versus sham procedure	1	64	Peto Odds Ratio (Peto, Fixed, 99% CI)	0.87 [0.23, 3.31]
4 Backache	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 PEBP versus sham procedure	1	64	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.39, 3.52]

Comparison 2. Epidural blood patch (EBP)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PDPH	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 EBP versus conservative treatment	1	40	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.18 [0.04, 0.76]
1.2 EBP versus sham procedure	1	12	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.04 [0.00, 0.39]
2 Severe PDPH	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 EBP versus sham procedure	1	12	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.03 [0.00, 0.22]

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3 Backache	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 EBP versus sham procedure	1	12	Peto Odds Ratio (Peto, Fixed, 95% CI)	23.17 [2.57, 208.60]
4 Intensity of headache	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 EBP versus conservative treatment	1	32	Mean Difference (IV, Fixed, 95% CI)	-7.1 [-7.69, -6.51]

Analysis 1.1. Comparison 1 Prophylactic epidural blood patch (PEBP), Outcome 1 Post-dural puncture headache (PDPH).

Review: Epidural blood patching for preventing and treating post-dural puncture headache

Comparison: 1 Prophylactic epidural blood patch (PEBP)

Outcome: 1 Post-dural puncture headache (PDPH)

Study or subgroup	Prophylacitc EBP n/N	No blood patch n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 PEBP versus no treatment					
Ackerman 1989	1/10	7/11		100.0 %	0.11 [0.02, 0.64]
Subtotal (95% CI)	**10**	**11**		**100.0 %**	**0.11 [0.02, 0.64]**
Total events: 1 (Prophylacitc EBP), 7 (No blood patch)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.47 (P = 0.014)					
2 PEBP versus conservative treatment					
Colonna 1989	4/19	16/20		44.9 %	0.10 [0.03, 0.35]
Lowenwirt 1998	4/24	24/25		55.1 %	0.04 [0.01, 0.13]
Subtotal (95% CI)	**43**	**45**		**100.0 %**	**0.06 [0.03, 0.14]**
Total events: 8 (Prophylacitc EBP), 40 (No blood patch)					
Heterogeneity: Chi^2 = 1.05, df = 1 (P = 0.31); I^2 =5%					
Test for overall effect: Z = 6.56 (P < 0.00001)					
3 PEBP versus epidural saline patch					
Sengupta 1989	2/24	11/24		100.0 %	0.16 [0.04, 0.55]
Subtotal (95% CI)	**24**	**24**		**100.0 %**	**0.16 [0.04, 0.55]**
Total events: 2 (Prophylacitc EBP), 11 (No blood patch)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.89 (P = 0.0038)					
4 PEBP versus sham procedure					
Scavone 2004	18/32	18/32		100.0 %	1.00 [0.38, 2.66]
Subtotal (95% CI)	**32**	**32**		**100.0 %**	**1.00 [0.38, 2.66]**
Total events: 18 (Prophylacitc EBP), 18 (No blood patch)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
Test for subgroup differences: Chi^2 = 18.39, df = 3 (P = 0.00), I^2 =84%					

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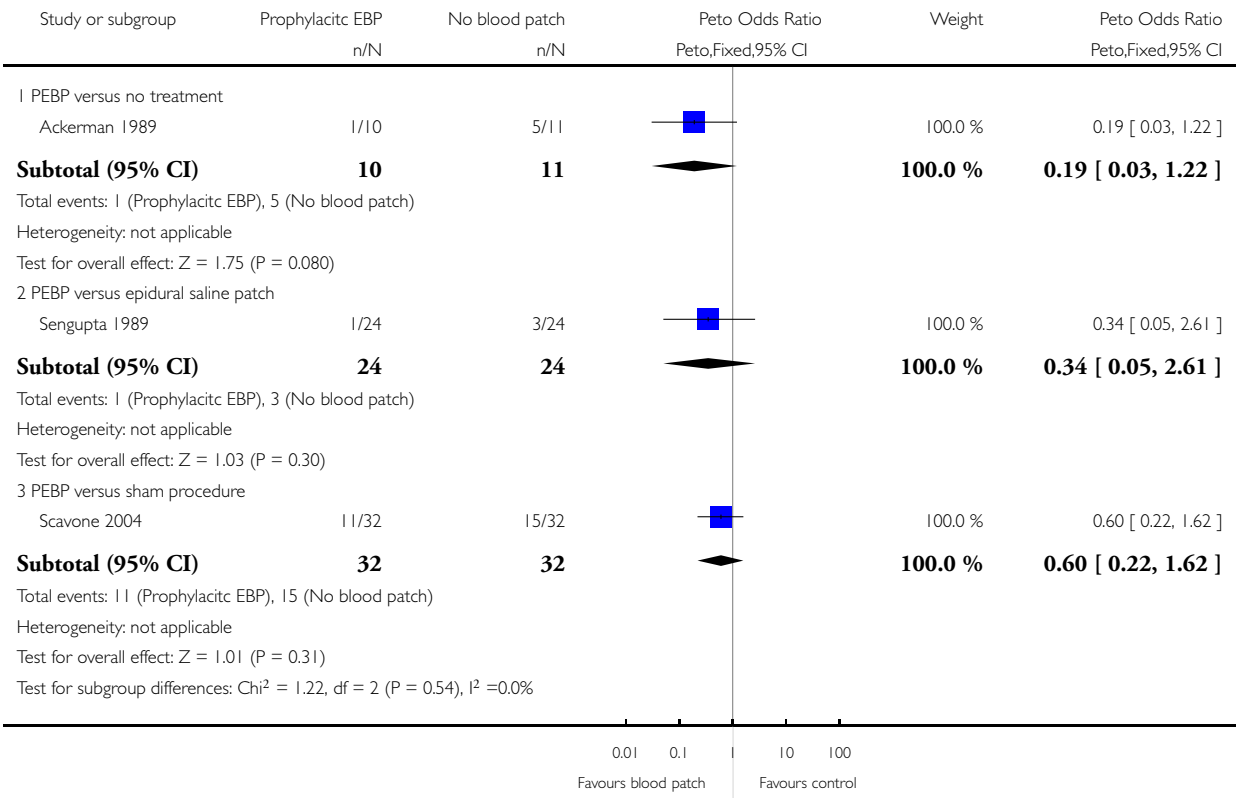
Analysis 1.2. Comparison 1 Prophylactic epidural blood patch (PEBP), Outcome 2 Severe PDPH.

Review: Epidural blood patching for preventing and treating post-dural puncture headache

Comparison: 1 Prophylactic epidural blood patch (PEBP)

Outcome: 2 Severe PDPH



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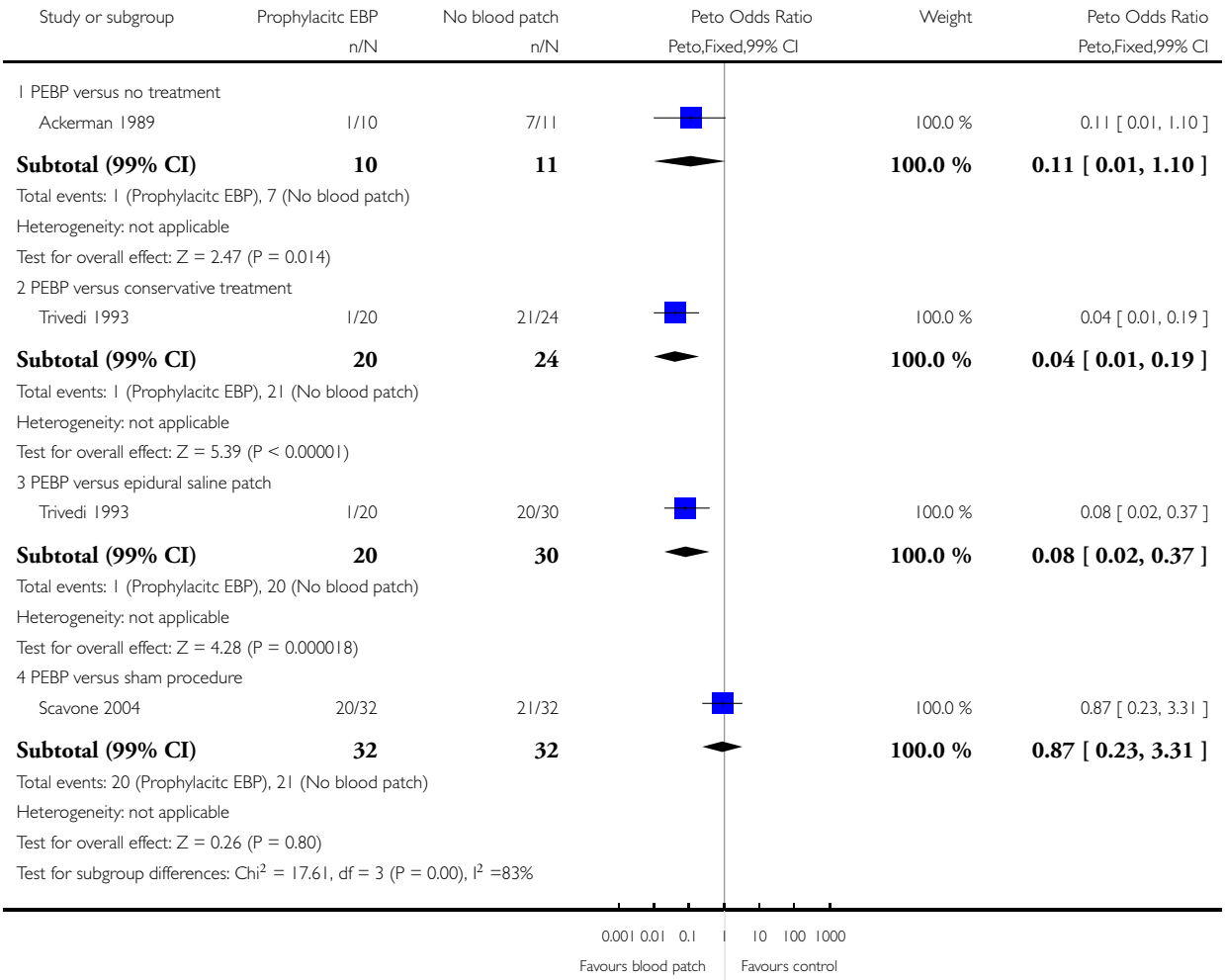
Analysis 1.3. Comparison 1 Prophylactic epidural blood patch (PEBP), Outcome 3 Any headache.

Review: Epidural blood patching for preventing and treating post-dural puncture headache

Comparison: 1 Prophylactic epidural blood patch (PEBP)

Outcome: 3 Any headache



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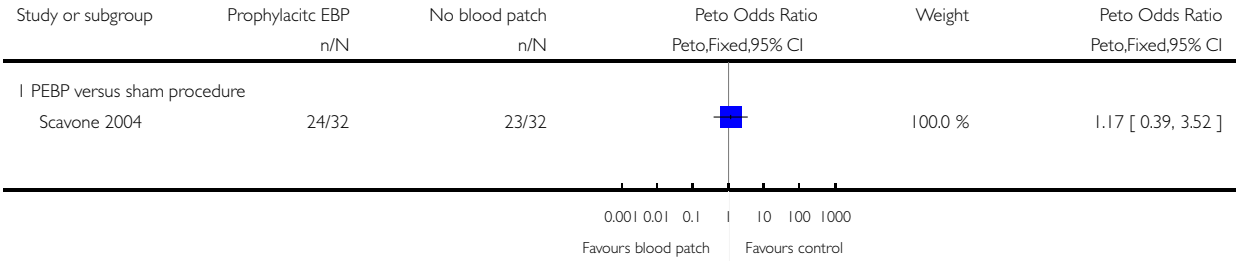
Analysis 1.4. Comparison 1 Prophylactic epidural blood patch (PEBP), Outcome 4 Backache.

Review: Epidural blood patching for preventing and treating post-dural puncture headache

Comparison: 1 Prophylactic epidural blood patch (PEBP)

Outcome: 4 Backache

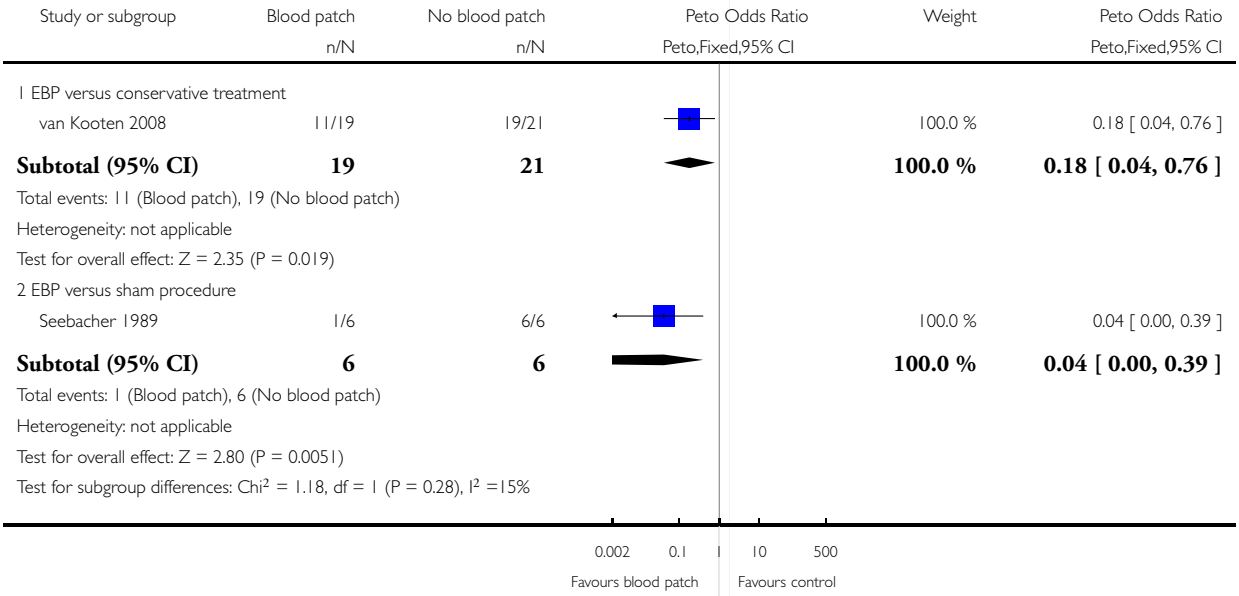


Analysis 2.1. Comparison 2 Epidural blood patch (EBP), Outcome 1 PDPH.

Review: Epidural blood patching for preventing and treating post-dural puncture headache

Comparison: 2 Epidural blood patch (EBP)

Outcome: 1 PDPH



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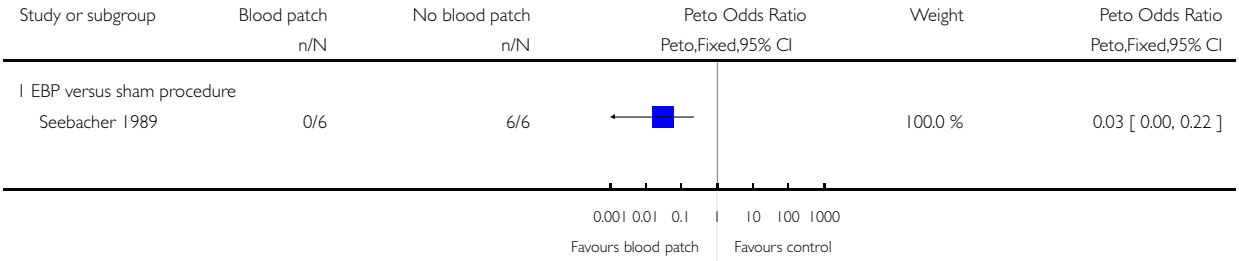
Analysis 2.2. Comparison 2 Epidural blood patch (EBP), Outcome 2 Severe PDPH.

Review: Epidural blood patching for preventing and treating post-dural puncture headache

Comparison: 2 Epidural blood patch (EBP)

Outcome: 2 Severe PDPH

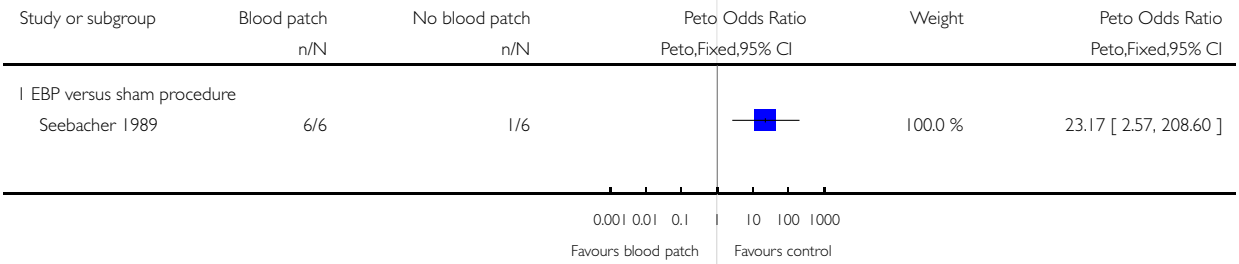


Analysis 2.3. Comparison 2 Epidural blood patch (EBP), Outcome 3 Backache.

Review: Epidural blood patching for preventing and treating post-dural puncture headache

Comparison: 2 Epidural blood patch (EBP)

Outcome: 3 Backache



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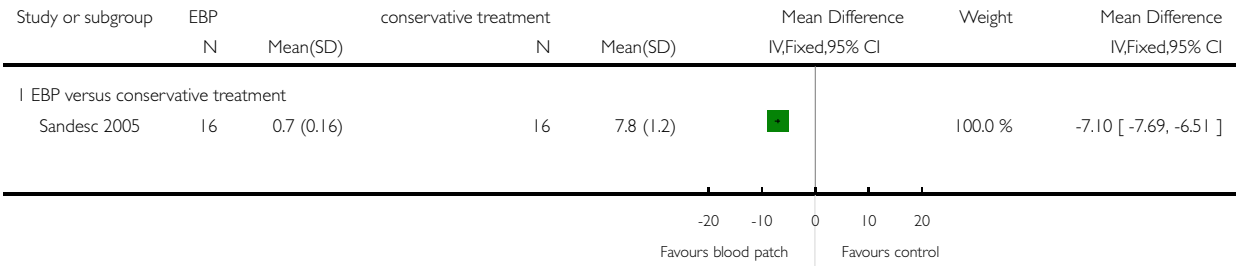
Analysis 2.4. Comparison 2 Epidural blood patch (EBP), Outcome 4 Intensity of headache.

Review: Epidural blood patching for preventing and treating post-dural puncture headache

Comparison: 2 Epidural blood patch (EBP)

Outcome: 4 Intensity of headache



APPENDICES

Appendix 1. CENTRAL

Search strategy for CENTRAL, The Cochrane Library 2009, Issue 1

Search number	Search terms
1	POST-DURAL PUNCTURE HEADACHE
2	(“post dural puncture headache*” or “postdural puncture headache*” or “post-dural puncture headache*”)
3	((dura* NEAR/3 puncture*) and headache*)
4	#1 or #2 or #3
5	randomized controlled trial.pt.
6	controlled clinical trial.pt.
7	randomized controlled trials.sh.
8	random allocation.sh.
9	double blind method.sh.

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(*Continued*)

10	single blind method.sh.
11	or/5-10
12	(ANIMALS not HUMAN).sh.
13	11 not 12
14	clinical trial.pt.
15	exp clinical trials/
16	(clin$ adj25 trial$).ti,ab.
17	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
18	placebos.sh.
19	placebo$.ti,ab.
20	random$.ti,ab.
21	research design.sh.
22	or/14-21
23	22 not 12
24	23 not 13
25	13 or 23
26	25 and 4

Appendix 2. MEDLINE

Search strategy for MEDLINE (OVID) (1950 to April 2009)

Search number	Search terms
1	Post-Dural Puncture Headache/
2	("post dural puncture headache$" or "postdural puncture headache$" or "post-dural puncture headache$").mp. [mp=title, original title, abstract, name of substance word, subject heading word]

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(*Continued*)

3	((dura$ adj2 puncture$) and headache$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4	or/1-3

Appendix 3. EMBASE

Search strategy for EMBASE (OVID) (1980 to April 2009)

Search number	Search terms
1	Post-Dural Puncture Headache/
2	("post dural puncture headache$" or "postdural puncture headache$" or "post-dural puncture headache$").mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3	((dura$ adj2 puncture$) and headache$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4	or/1-3
5	random$.ti,ab.
6	factorial$.ti,ab.
7	(crossover$ or cross over$ or cross-over$).ti,ab.
8	placebo$.ti,ab.
9	(doubl$ adj blind$).ti,ab.
10	(singl$ adj blind$).ti,ab.
11	assign$.ti,ab.
12	allocat$.ti,ab.
13	volunteer$.ti,ab.
14	CROSSOVER PROCEDURE.sh.
15	DOUBLE-BLIND PROCEDURE.sh.
16	RANDOMIZED CONTROLLED TRIAL.sh.

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(*Continued*)

17	SINGLE BLIND PROCEDURE.sh.
18	or/5-17
19	ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/
20	HUMAN/
21	19 and 20
22	19 not 21
23	18 not 22
24	23 and 4

Appendix 4. PaPaS register

Search strategy for PaPaS Trials Register (April 2009)

Search number	Search terms
1	(“post dural puncture headache*” or “postdural puncture headache*” or “post-dural puncture headache*” or ((“dura* puncture*”) and headache*))

WHAT'S NEW

Last assessed as up-to-date: 31 March 2009.

6 November 2009	New citation required and conclusions have changed	This review has been updated by two new review authors. The conclusions should be re-read as this update adds limited evidence to the previous review that therapeutic epidural blood patch showed a benefit over conservative treatment. However, the review authors still do not recommend prophylactic epidural blood patch over other treatments because there are too few trial participants to allow reliable conclusions to be drawn.
3 September 2009	New search has been performed	This review has been updated. Six additional studies (Colonna 1989; Lowenwirt 1998; Sandesc 2005; Scavone 2004; Sengupta 1989; van Kooten 2008) have

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(*Continued*)

		been included adding a further 302 participants.

HISTORY

Protocol first published: Issue 1, 2000

Review first published: Issue 2, 2002

3 November 2008	New search has been performed	Converted to new review format.
22 August 2002	Feedback has been incorporated	Feedback submitted and addressed by the authors.

CONTRIBUTIONS OF AUTHORS

Both review authors conceived the idea and methods for this review. In discussion with Charles Warlow, Cathie Sudlow, Polpun Boonmak and Suhattaya Boonmak developed and ran the search strategy for the update, identified studies for inclusion and exclusion, extracted and entered data, and ran the analyses. Cathie Sudlow wrote the original version of this review. Polpun Boonmak and Suhattaya Boonmak wrote the updated review. All review authors contributed to the published version.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Thai Cochrane Network, Thailand.

External sources

- No sources of support supplied

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INDEX TERMS

Medical Subject Headings (MeSH)

*Blood Patch, Epidural; Post-Dural Puncture Headache [prevention & control; *therapy]; Randomized Controlled Trials as Topic; Spinal Puncture [*adverse effects]

MeSH check words

Humans

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Haemostatic drugs for traumatic brain injury (Review)

Perel P, Roberts I, Shakur H, Thinkhamrop B, Phuenpathom N, Yutthakasemsunt S

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 1

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TABLE OF CONTENTS

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[Intervention Review]

Haemostatic drugs for traumatic brain injury

Pablo Perel[1], Ian Roberts[1], Haleema Shakur[1], Bandit Thinkhamrop[2], Nakornchai Phuenpathom[3], Surakrant Yutthakasemsunt[4]

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Editorial group: Cochrane Injuries Group.
Publication status and date: New, published in Issue 1, 2010.
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ABSTRACT

Background

Traumatic brain injury (TBI) is a leading cause of death and disability. Intracranial bleeding is a common complication of TBI, and intracranial bleeding can develop or worsen after hospital admission. Haemostatic drugs may reduce the occurrence or size of intracranial bleeds and consequently lower the morbidity and mortality associated with TBI.

Objectives

To assess the effects of haemostatic drugs on mortality, disability and thrombotic complications in patients with traumatic brain injury.

Search strategy

We searched the electronic databases: Cochrane Injuries Group Specialised Register (3 February 2009), CENTRAL (*The Cochrane Library* 2009, Issue 1), MEDLINE (1950 to Week 3 2009), PubMed (searched 3 February 2009 (last 180 days)), EMBASE (1980 to Week 4 2009), CINAHL (1982 to January 2009), ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to January 2009), ISI Web of Science: Conference Proceedings Citation Index - Science (CPCI-S) (1990 to January 2009).

Selection criteria

We included published and unpublished randomised controlled trials comparing haemostatic drugs (antifibrinolytics: aprotinin, tranexamic acid (TXA), aminocaproic acid or recombined activated factor VIIa (rFVIIa)) with placebo, no treatment, or other treatment in patients with acute traumatic brain injury.

Data collection and analysis

Two review authors independently examined all electronic records, and extracted the data. We judged that there was clinical heterogeneity between trials so we did not attempt to pool the results of the included trials. The results are reported separately.

Main results

We included two trials. One was a post-hoc analysis of 30 TBI patients from a randomised controlled trial of rFVIIa in blunt trauma patients. The risk ratio for mortality at 30 days was 0.64 (95% CI 0.25 to 1.63) for rFVIIa compared to placebo. This result should be considered with caution as the subgroup analysis was not pre-specified for the trial. The other trial evaluated the effect of rFVIIa in 97 TBI patients with evidence of intracerebral bleeding in a computed tomography (CT) scan. The corresponding risk ratio for mortality

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at the last follow up was 1.08 (95% CI 0.44 to 2.68). The quality of the reporting of both trials was poor so it was difficult to assess the risk of bias.

Authors' conclusions

There is no reliable evidence from randomised controlled trials to support the effectiveness of haemostatic drugs in reducing mortality or disability in patients with TBI. New randomised controlled trials assessing the effects of haemostatic drugs in TBI patients should be conducted. These trials should be large enough to detect clinically plausible treatment effects.

PLAIN LANGUAGE SUMMARY

Haemostatic drugs for traumatic brain injury

Injury (also called trauma) is a leading cause of death for children and young adults. Traumatic brain injury, such as from a blow to the head, is a frequent cause of death for patients with trauma who survive to reach hospital. Approximately half of patients with traumatic brain injury develop bleeding into the brain within the first 48 hours of hospital admission. If bleeding occurs, accumulating blood within the skull can put pressure on the brain and this may be fatal or result in serious long-term disability for the patient. Therefore, drugs that promote the production of clots or reduce the destruction of existing clots (known as haemostatic drugs) might reduce the bleeding into the brain after an injury and thereby reduce the risk of death or disability.

We searched for randomised clinical trials looking at the effectiveness of haemostatic drugs for reducing mortality and disability in patients with traumatic brain injury. We found two studies that evaluated the effects of a type of haemostatic drug called recombined activated factor VII. We reviewed the data presented in the reports of these trials. Both trials were too small to confirm or refute any plausible clinical effect, so we were unable to reach any conclusions regarding the effectiveness of haemostatic drugs for traumatic brain injury patients. More trials are needed to answer this question. Future trials should be large enough to detect plausible and important clinical effects.

BACKGROUND

Description of the condition

Traumatic brain injury is one of the main causes of death in patients with injuries, and is a leading cause of death and disability in young people (Ghajar 2000). Every year approximately 1.5 million people die and at least 10 million people are killed or hospitalised because of a traumatic brain injury (Langlois 2006). The incidence, fatality and disability rates are higher in low- and middle- income countries than in high income countries (Hyder 2007).

Although much of the damage to the brain occurs at the time of the injury, secondary brain damage due to ongoing intracranial bleeding and brain swelling is an important and potentially avoidable cause of morbidity and mortality. Intracranial bleeding is a common complication of traumatic brain injury. In the CRASH trial, which included patients with mild, moderate and severe traumatic brain injury, 56% of trial participants had at least one intracranial bleed that could have been epidural, subdural, subarachnoid or intra-parenchymal (CRASH Trial).

There is evidence that intracranial bleeding can develop or worsen after hospital admission. Prospective observational studies have shown that traumatic intracranial haemorrhage expansion occurs in up to 51% of patients with traumatic brain injury during the first 24 to 48 hours after hospital admission (Narayan 2008). Prognostic studies have shown that intracranial haemorrhage is associated with increased mortality and disability six months after injury (Maas 2007; Perel 2008). Intracranial bleeding exerts significant pressure on brain tissue (Bullock 2006), and prompt neurosurgical intervention is an important part of the therapeutic approach. However, not all intracranial haemorrhages can be controlled by surgical intervention and there is interest in pharmacological approaches that use haemostatic drugs to reduce the occurrence or size of intracranial bleeds (Ceylan 1992; Mandera 1999; Holcomb 2004).

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Description of the intervention

Haemostatic drugs have the potential to reduce bleeding by influencing the coagulation cascade. In the haemostatic process, coagulation occurs rapidly to build a tight net of fibrin at the site of the damaged vessel. At the same time, the fibrinolytic system removes fibrin deposits that could cause permanent occlusion of blood vessels once vascular repair has taken place (Prentice 1980). Thus, the coagulation and fibrinolytic systems are in a state of dynamic balance that maintains an intact vascular system.

The treatments that have been most extensively evaluated as haemostatic drugs include antifibrinolytics and pro-coagulant drugs such as recombinant activated factor VII (rFVIIa) (Mannucci 2007). Antifibrinolytic drugs maintain the stability of blood clots, whereas pro-coagulant drugs act directly on the coagulation cascade (Holcomb 2004).

The pro-coagulant rFVIIa acts locally at the site of tissue injury. It is believed that it binds to exposed tissue factor and generates thrombin, which activates the platelets. The activated platelet surface forms a template on which recombinant factor VIIa can directly or indirectly mediate further activation of coagulation, resulting in the generation of more thrombin and, ultimately, in the conversion of fibrinogen to fibrin.

Antifibrinolytic agents suppress fibrinolysis, thereby reducing excessive or recurrent bleeding. Antifibrinolytics can be divided into lysine analogues (tranexamic acid (TXA) and aminocaproic acid) and plasmin inhibitors (aprotinin). The former impairs endogenous fibrinolysis by blocking lysine binding sites on plasminogen molecules. In contrast, aprotinin directly inhibits the fibrinolytic enzyme plasmin, plasma and tissue kallikrein, trypsin and activated coagulation factor XII.

How the intervention might work

Haemostatic drugs have been used to prevent or reduce blood loss and the need for blood transfusion.

For example, antifibrinolytic drugs are widely used in general surgery to reduce bleeding and the need for transfusions (Slaughter 1997). A systematic review of the use of antifibrinolytic agents in surgical patients identified 211 randomised controlled trials that included 20,781 participants (Henry 2007). The results showed that TXA reduced the risk of blood transfusion by 39% (risk ratio (RR) 0.61, 95% confidence interval (CI) 0.54 to 0.69), while aprotinin lowered the risk by 34% (RR 0.66, 95% CI 0.61 to 0.71). Antifibrinolytic agents also reduced the need for blood transfusion and reoperation due to bleeding. There was a trend toward a decreased risk of death in patients treated with aprotinin (RR 0.90, 95% CI 0.67 to 1.20) and TXA (RR 0.60, 95% CI 0.32 to 1.12) but this was not statistically significant. There was no evidence of an increased risk of thrombotic events with either treatment.

The effects of haemostatic drugs in non-traumatic intracranial bleeding have also been evaluated. A systematic review of randomised controlled trials of antifibrinolytic drugs in patients with aneurysmal subarachnoid haemorrhage showed that antifibrinolytic drugs reduced the rate of re-bleeding by approximately 40% but, because of the associated increase in cerebral ischaemia, there was no overall benefit (Roos 2003). However, the length of treatment in these trials was six weeks. It is possible that a shorter treatment period might prevent re-bleeding without increasing the risk of ischaemia. The systematic review was conducted in 2003. Since then, a randomised controlled trial of early administration of a short course (three days) of TXA in patients with aneurysmal subarachnoid haemorrhage has found that TXA reduced the occurrence of re-bleeding from 10.8% to 2.4%, with no evidence of increased side effects (Astrup 2006).

A systematic review of haemostatic drugs in primary intracerebral haemorrhage (non-traumatic) found four phase II trials and reported that haemostatic drugs reduced the risk of death and dependence measured on the modified Rankin Scale (RR 0.79, 95% CI 0.67 to 0.93) and the Glasgow Outcome Scale (RR 0.90, 95% CI 0.81 to 1.01) (You 2006). A recent clinical trial, which was not included in that systematic review, showed that activated factor VIIa reduced intracerebral haemorrhage expansion but did not improve the survival or functional outcomes of patients (Mayer 2008).

Why it is important to do this review

If haemostatic agents reduce intracranial bleeding in patients with traumatic brain injury, they could substantially reduce the extent of secondary brain damage and subsequently lower the mortality and morbidity rates associated with brain injury. Given the number of cases of traumatic brain injury that occur each year, even a modest reduction in the risk of unfavourable outcomes could have major public health implications.

OBJECTIVES

To assess the effects of haemostatic drugs on mortality, disability and thrombotic complications in patients with traumatic brain injury.

METHODS

Criteria for considering studies for this review

Types of studies

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We included published and unpublished randomised controlled trials comparing haemostatic drugs with placebo, no treatment, or other treatment in patients with acute traumatic brain injury. Comparisons between different types of haemostatic drugs were also to be included.

Types of participants

Any patient with traumatic brain injury.

Types of interventions

Any of the systemic haemostatic drugs listed below compared with placebo, no treatment, or another haemostatic drug. For studies in which different doses of the intervention were compared with placebo, the intervention groups were combined and compared with the control group. For the purpose of this review, we considered the following haemostatic drugs.

- Antifibrinolytics: aprotinin, tranexamic acid (TXA), aminocaproic acid.
- Activated factor VIIa.

Types of outcome measures

Primary outcomes

1. Mortality
2. Disability (Glasgow Outcome Scale (GOS), Disability Rating Scale (DRS), or other measure of neurological function)
3. Thrombotic complications: deep venous thrombosis (DVT), pulmonary embolism (PE), stroke, and myocardial infarction (MI)

Secondary outcomes

1. Volume of intracranial bleeding
2. Brain ischaemic lesions
3. Need for neurosurgical operation or reoperation
4. Renal failure

Search methods for identification of studies

The searches were not restricted by date, language, or publication status.

Electronic searches

We searched the following electronic databases:

- Cochrane Injuries Group Specialised Register (searched 3 February 2009),
- CENTRAL (*The Cochrane Library* 2009, Issue 1),
- MEDLINE (1950 to Week 3 2009),
- PubMed (searched 3 February 2009 (last 180 days)),
- EMBASE (1980 to Week 4 2009),
- CINAHL (1982 to January 2009),
- ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to January 2009),
- ISI Web of Science: Conference Proceedings Citation Index - Science (CPCI-S) (1990 to January 2009).

The full search strategies can be found in Appendix 1.

Searching other resources

We searched the Internet for relevant information and conference abstracts. We also sought other potentially relevant published, unpublished, or ongoing studies by:

1. checking the reference lists of relevant papers and literature reviews,
2. communicating with relevant trial authors,
3. contacting the manufacturers of relevant drugs.

Data collection and analysis

Selection of studies

Two review authors (PP and IR) independently examined all electronic records and their abstracts to establish eligibility. They decided on whether or not to acquire the full report and, in cases of uncertainty, obtained the full report. We planned to resolve any disagreements through discussion and consultation with a third review author. Any duplicate trials were planned to be examined individually to verify that they presented unique sets of data. If we were unsure about whether a study should be included, because additional information was necessary, we allocated the study to the list of those awaiting assessment and contacted the study authors for clarification. The reasons for excluding studies are described in the 'Characteristics of excluded studies' table.

Data extraction and management

Two review authors (PP and IR) extracted the data from the included studies. We extracted data on the study methods, participants, interventions, and outcomes. We extracted data so that an intention-to-treat analysis could be performed. For binary outcomes, we determined the number of participants experiencing the outcome of interest in each group. For continuous outcomes, we used the mean change from baseline at final assessment, together with the number of participants and standard deviation for each group.

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Assessment of risk of bias in included studies

Two review authors (PP and IR) evaluated the risk of bias of the included studies with respect to six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. The risk of bias in each domain was rated as high risk, low risk, and unclear. Any disagreement between raters was resolved by consensus.

Measures of treatment effect

For dichotomous data, we calculated the risk ratio (RR) and 95% CI. We calculated the mean difference (MD) and 95% CI for continuous outcomes that were measured on the same scale, otherwise we planned to calculate the standardised mean difference.

Dealing with missing data

We attempted to contact study authors to obtain any missing information.

Assessment of heterogeneity

We planned to examine the participants, interventions, and outcomes of the trials for evidence of clinical heterogeneity. Statistical heterogeneity was planned to be examined with the I^2 statistic and Chi^2 test. The I^2 statistic describes the percentage of total variation across studies that is due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity; larger values show increasing heterogeneity. Substantial heterogeneity is considered to exist when I^2 is more than 50%. For the Chi^2 test, a P value of less than 0.10 was considered as indicating the presence of statistically significant heterogeneity. We planned that if there was any evidence of clinical or statistical heterogeneity, we would not conduct a meta-analysis and would report findings in a narrative form.

Assessment of reporting biases

We planned to assess reporting bias using a funnel plot.

Data synthesis

We planned to conduct a meta-analysis if the included trials were clinically homogeneous and there was no evidence of statistical heterogeneity. For dichotomous outcomes, we planned to use the Mantel-Haenszel method.

Subgroup analysis and investigation of heterogeneity

If significant heterogeneity was present, and the number of studies was sufficient, we planned to investigate heterogeneity using the following subgroups.

1. Severity of acute traumatic brain injury (mild, moderate, or severe).
2. Type of traumatic brain injury lesion (focal or diffuse).
3. Type of intervention (i.e. kind of haemostatic drug used).

Sensitivity analysis

We planned to perform a sensitivity analysis to investigate the effect of the methodological quality of the included studies on the results.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search

The search of the databases identified a total of 659 records. These were screened by two authors (PP and IR) and the full text of 12 potentially eligible reports were obtained for closer examination. Of these, only two studies met the inclusion criteria. A further study was identified by searching the reference lists of selected seminal papers.

Included studies

Two trials were included in this systematic review. Both evaluated the effects of recombinant factor VIIa (rFVIIa). The earlier of these trials (Kluger 2007) was a post-hoc analysis of traumatic brain injury (TBI) patients from a randomised controlled trial of rFVIIa in blunt trauma patients (Boffard 2005). The later paper evaluated the effects of rFVIIa in TBI patients with evidence of intracerebral bleeding of at least 2 ml on a baseline computed tomography (CT) scan obtained within six hours of the injury (Narayan 2008).
More details about the studies are reported in the 'Characteristics of included studies' table.

Excluded studies

We identified a trial that evaluated the effects of aprotinin in patients with severe TBI (Auer 1979). It was reported as a randomised controlled trial; however after randomly allocating the first 20 patients, five patients were added to the aprotinin group. It was not possible to separate the outcome data for the 20 randomised and the five non-randomised patients. Therefore, this study provided no useable outcome data and was excluded.

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Pending study results

Another trial that could contribute useful data to this systematic review was a phase 3 randomised controlled trial that evaluated the effect of rFVIIa in trauma patients. This trial planned to recruit 1502 patients but it was stopped by its sponsor after 550 patients because of futility (Novoseven Study). Although we contacted the sponsor of this trial, as of July 2009 we were not able to obtain any data.

Ongoing studies

There are three ongoing trials that could contribute to this systematic review. The CRASH-2 trial (CRASH-2 Trial) is an international study evaluating the effects of TXA in patients with trauma and significant bleeding; a subgroup analysis of TBI patients is planned. CRASH-2 aims to recruit 20,000 patients and will be finished by December 2009. An explanatory study, CRASH-2 IBS (Intracranial Bleeding Study) is also being conducted among a sample of 300 CRASH-2 participants. In patients recruited to CRASH-2 IBS, a second CT scan is obtained within 24-48 hours after randomisation to evaluate changes in the volume of intracranial bleeding. Another trial is being conducted in Thailand to evaluate the effectiveness and safety of TXA for adult patients with moderate to severe TBI. It was to recruit 240 patients and should have been finished by May 2009 (Tranexamic acid in TBI).

Risk of bias in included studies

The review authors' assessment of the risk of bias for each included study can be found in Figure 1 and Figure 2.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

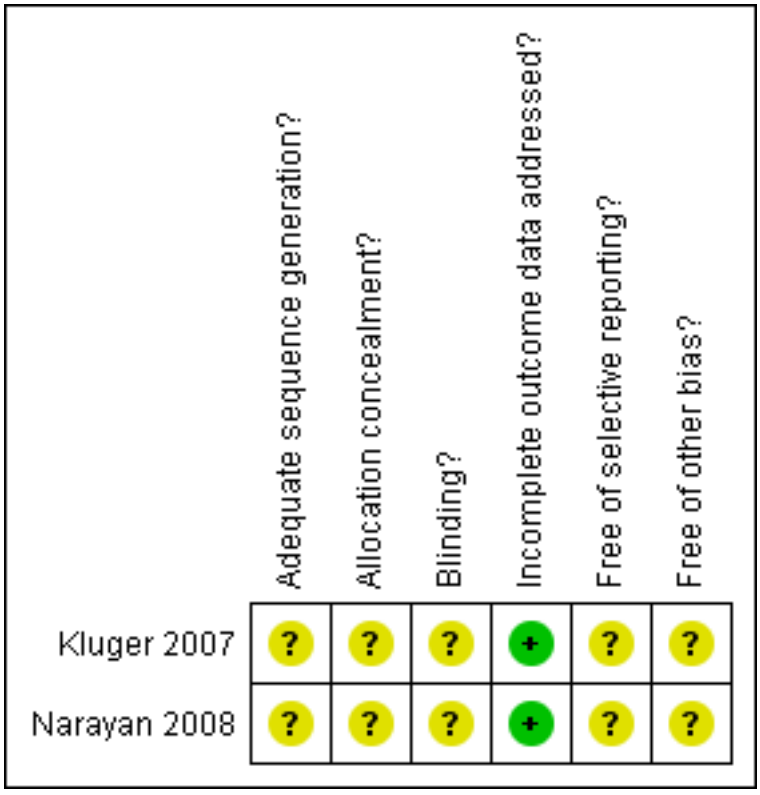

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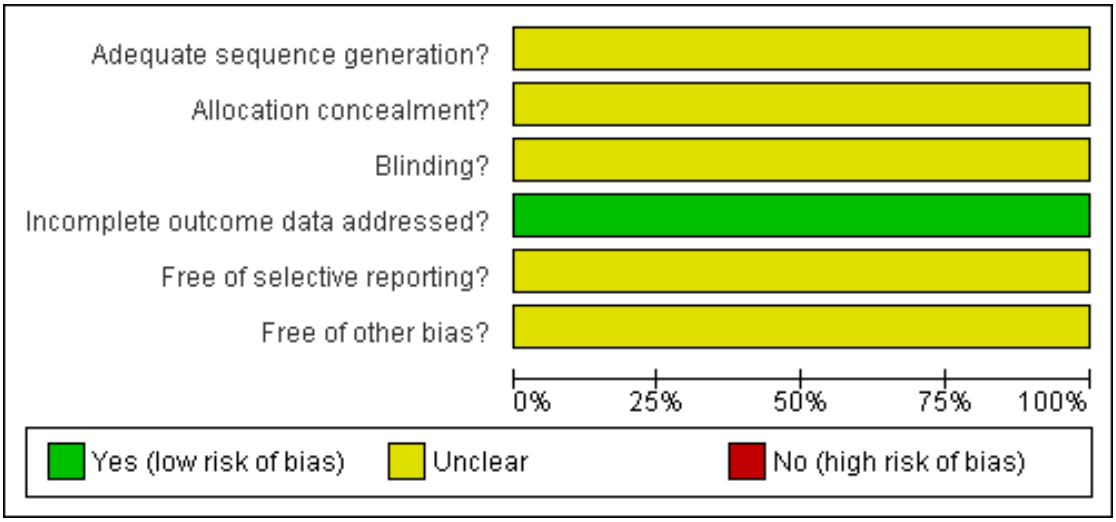
Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies. Two studies are included in this review.



Allocation

Method of allocation concealment was not reported in either of the included studies.

Blinding

Although both studies were reported to be 'double blind' they did not describe the method of blinding.

Incomplete outcome data

Both studies reported the pre-specified outcomes for all included patients. However, in the trial by Narayan and collaborators only mortality at 15 days was reported. They also reported in-hospital mortality after 15 days but it was not clear if this information was collected for all the patients.

Selective reporting

A protocol was not available for either of the included studies, so it was not possible to assess the presence of reporting bias.

Effects of interventions

We did not attempt to combine the results of the two included trials as we judged that they included two different populations. One study evaluated the effect of rFVIIa in trauma patients with extracranial bleeding who also had a TBI (Kluger 2007), and the other study only included patients with mild and moderate TBI and evidence of traumatic intracranial bleeding in the CT scan (Narayan 2008).

Primary outcomes

Mortality

Both studies reported on mortality.

Kluger 2007 reported a RR for mortality at 30 days of 0.64 (95% CI 0.25 to 1.63) for patients receiving rFVIIa in comparison to those receiving placebo.

Narayan 2008 reported a RR for mortality at the last follow-up time of 1.08 (95% CI 0.44 to 2.68) for patients receiving rFVIIa in comparison to those receiving placebo.

Disability

Kluger 2007 did not report the effect of rFVIIa on disability.

Narayan 2008 evaluated the effect on disability using the GOS and the Barthex Index (BI).

The BI was evaluated in only 71 (76%) patients. The authors reported that the median scores were 46.3 and 43.9 for the placebo and rFVIIa arms, respectively. However, their report did not provide enough data (SD and denominators) to estimate the mean difference between the two groups. Similarly, insufficient data were reported to evaluate the effect on GOS. It was reported that at 15 days, 17% of the patients in the placebo and 18% in the rFVIIa group had moderate to good recovery according to the GOS.

Thrombotic complications

Both studies reported the effect of rFVIIa on thrombotic complications.

Kluger 2007 followed the 'local diagnostic procedures' in the case of clinical symptoms of thromboembolic events. They reported two serious adverse thromboembolic events in the placebo arm

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and none in the rFVIIa arm (RR 0.16, 95% CI 0.01 to 2.99 for rFVIIa in comparison to placebo).

Narayan 2008 conducted a more intense follow up of patients to detect thromboembolic complications. An ultrasound screening of the lower extremities (USLE) was mandated by protocol at 72 ± 8 hours to detect the presence of DVT. A 12-lead electrocardiogram (ECG) and a centralised laboratory measurement of troponin I were mandated at baseline and 24 hours after trial drug administration. The authors reported that eight patients (13%) from the rFVIIa arm presented with a thromboembolic complication, while only two patients (6%) presented with such a complication in the placebo arm. The estimated RR for thrombotic complications in this study was 2.36 (95% CI 0.53 to 10.51).

Secondary outcomes

The secondary outcomes were only reported by Narayan 2008.

Intracranial bleeding volume

Narayan 2008 analysed the effect of rFVIIa on intracranial bleeding volume in different ways. For each arm, the investigators reported the: 1) mean volume at baseline, 24, and 72 hours; 2) mean volume change (defined as volume increase, no change, or decrease) at 24 and 72 hours; and 3) volume increase at 24 and 72 hours, only considering patients in whom an increase was reported. We reported the mean volume change at 72 hours as we considered this to be both the most relevant outcome and the most powerful analysis. The mean difference in volume change at 72 hours was -3.10 (95% CI -10.47 to 4.27) for patients receiving rFVIIa in comparison to patients receiving placebo.

For the other secondary outcomes there were too few events to obtain effect estimate measures.

Brain ischaemic lesions

Narayan 2008 reported one cerebral infarction in the placebo arm and no events in the rFVIIa arm.

Need for neurosurgical operation or reoperation

Narayan 2008 reported the need for emergency intracranial bleeding evacuation for three patients in the placebo group and for one in the rFVIIa group. Two of the three placebo-treated patients who underwent the emergency evacuation needed a reoperation, while a reoperation was not conducted for the rFVIIa-treated patients who underwent the emergency evacuation.

Renal failure

Neither of the studies reported on renal failure.

DISCUSSION

Summary of main results

There is no reliable evidence that haemostatic drugs are effective in reducing mortality or disability in patients with TBI. Only two studies evaluating the effects of rFVIIa were found. One of them was a post-hoc analysis of a trial including 30 bleeding trauma patients with a concomitant moderate or mild TBI. This result should be considered with caution as it was a post-hoc analysis of a subgroup of patients (with TBI) within a larger trial of trauma patients. Posteriori subgroup analyses are likely to be misleading as they can be the result of data dredging and chance. The other study included 97 TBI patients with evidence of intracerebral bleeding in the initial CT scan.

Both studies were too small to confirm or refute a clinically plausible effect in the TBI population. We did not find a single randomised controlled trial of an antifibrinolytic drug for TBI patients. The pending results of the Novoseven study and the results of the ongoing studies with tranexamic acid (TXA) will provide useful information about the effects of haemostatic drugs in TBI patients.

Quality of the evidence

Neither of the trial reports provided enough data to assess the risk of bias for sequence generation, allocation concealment, blinding, or selective reporting.

Potential biases in the review process

Although our search was comprehensive and we used validated search strategies, the possibility of publication bias cannot be ruled out. Because few studies were included in this review we were not able to conduct formal analysis of publication bias (a funnel plot). Full protocols of the included studies were not available so we could not assess the presence of selective reporting bias, however for our primary outcome (mortality) this type of bias is very unlikely. Finally, one of the included trials was a post-hoc subgroup analysis and its result should be considered with caution.

Agreements and disagreements with other studies or reviews

This is the first review to evaluate the effects of haemostatic drugs in TBI patients. However, other reviews related to this question have been published.

Stanworth and collaborators conducted a systematic review on rFVIIa for the prevention and treatment of bleeding in patients without haemophilia (Stanworth 2007). This review included the randomised controlled trial in trauma patients from which the post-hoc analysis reported in our systematic review was conducted (Boffard 2005). However, that review did not analyse the effect of rFVIIa in TBI patients.

Another Cochrane review evaluated the effects of antifibrinolytic agents in trauma patients (Coats 2004). That review included two studies, one of them (Auer 1979) is among the excluded studies for our review. The trial involved TBI patients and the intervention under study was aprotinin, but the report provided no useable

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outcome data. The other study reported in the review by Coats and collaborators did not include TBI patients.

A recent review of the clinical use of rFVIIa evaluated the effects of rFVIIa in different conditions usually treated in the emergency department (Fishman 2008). Among the outcomes, the effect on trauma patients was reported although TBI patients were not specifically included. The only included randomised controlled trial involving trauma patients was by Boffard 2005, which is included in this systematic review.

AUTHORS' CONCLUSIONS

Implications for practice

There is no reliable evidence to recommend the use of haemostatic drugs for TBI patients.

Implications for research

New randomised clinical trials assessing the effects of haemostatic drugs in TBI patients should be conducted. These trials should be large enough to detect clinically plausible effects.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Kluger 2007

Methods	Randomised clinical trial.
Participants	30 adult patients (between 16 and 65 years old) with severe blunt trauma and moderate or mild traumatic brain injury (based on CT scan results). Exclusion criteria were: cardiac arrest pre-hospital or in the emergency or operating room, prior to trial drug administration; gunshot wound to the head; base deficit of greater than 15 mEq/l or severe acidosis with pH of less than 7.00; transfusion of 8 or more units of RBCs prior to arrival at the trauma center; injury sustained greater than or equal to 12 hours before randomisation; and severe TBI, defined as a Glasgow Coma Scale (GCS) score of less than or equal to 8, unless in the presence of a normal head CT scan.
Interventions	Eligible patients were randomly assigned to treatment groups within a 4-hour period. Treatment arms were either three intravenous injections of rFVIIa (200, 100, and 100 μg/kg) or three placebo injections. The first dose of study drug was administered immediately after transfusion of the eighth unit of RBCs. The second and third doses followed 1 and 3 hours after the first dose, respectively.
Outcomes	Mortality was categorised as: early (<48 hours) or late (between 48 hours and 30 days).
Notes	This study was a post hoc analysis of patients with traumatic brain injury enrolled into a randomised, placebo-controlled study of patients with severe blunt trauma.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not described.
Allocation concealment?	Unclear	Not described.
Blinding? All outcomes	Unclear	Reported as "double blind" but method of blinding was not reported.
Incomplete outcome data addressed? All outcomes	Yes	Outcome reported for all included patients.
Free of selective reporting?	Unclear	The protocol is not available.
Free of other bias?	Unclear	-

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Narayan 2008

Methods	Randomised clinical trial.
Participants	97 adult patients (>18 years old) with traumatic brain injury, a Glasgow Coma Scale (GCS) score between 4 and 14, and evidence of traumatic intracerebral bleeding with a total volume of at least 2 ml on the baseline CT scan obtained within 6 hours of the injury. Exclusion criteria were: the presence of penetrating head or spinal cord injury; life expectancy of less than 24 hours after hospital admission; any planned surgical evacuation of intracerebral haematoma within 24 hours after dosing; isolated subarachnoid haemorrhage, intraventricular haemorrhage, epidural or subdural haematomas or sICH; significant cardiovascular disease or dysfunction; haemodynamic instability; known history of hypercoagulability or thromboembolism; current vitamin K antagonist use; and pregnancy.
Interventions	Five doses of rFVIIa (40, 80, 120, 160, and 200 μg/kg) were compared with placebo in escalating dose tiers. The first dose tier (40 μg/kg) was assigned in a 1:1 ratio to the treatment or placebo group. Subsequent dose tiers were assigned in a 2:1 ratio.
Outcomes	The primary objective of this study was to evaluate safety of the intervention. All adverse events, defined as deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, cerebral infarction, disseminated intravascular coagulation or coagulopathy were reported until day 15. Early mortality was defined as within 15 days of recruitment, and late mortality as any death after 15 days of recruitment. The effectiveness assessment focused on changes in haematoma volumes on CT scans between baseline, 24 hours, and 72 hours after the intervention.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not described.
Allocation concealment?	Unclear	Not described.
Blinding? All outcomes	Unclear	Reported as "double blind" but method of blinding was not reported.
Incomplete outcome data addressed? All outcomes	Yes	Outcome reported for all the patients included. The only exception was late mortality (more than 15 days) for which the authors stated that they did not record it systematically for all the patients but recorded only those in-hospital deaths reported by collaborators.
Free of selective reporting?	Unclear	Protocol not available.
Free of other bias?	Unclear	-

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

Auer 1979	This study is described as a randomised controlled trial of aprotinin versus placebo in patients with severe traumatic brain injury but, after randomly allocating the first 20 patients, five patients were added to the aprotinin group. Because it was not possible to separate the outcome data for the 20 randomised and the five non-randomised patients, this study provided no useable outcome data.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Novoseven Study

Methods	Randomised controlled trial.
Participants	550 severely injured trauma patients with bleeding refractory to standard treatment.
Interventions	Three single doses of rFVIIa (200 μg/kg + 100 μg/kg + 100 μg/kg) or placebo.
Outcomes	Mortality at 30 days.
Notes	This study planned to recruit 1502 patients but after recruiting 550 patients, in June 2008 the sponsor (Novo Nordisk) made the announcement that they were stopping this trial as it was futile. Some of the patients recruited in this trial had traumatic brain injury and could provide useful data for this systematic review. We contacted Novo Nordisk but we were unable to obtain any data.

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

CRASH-2 Trial

Trial name or title	CRASH-2.
Methods	Randomised clinical trial.
Participants	Adults with trauma who are within 8 hours of injury and have either significant haemorrhage or are considered to be at risk of significant haemorrhage. The trial will recruit 20,000 patients and is planned to finish in December 2009.
Interventions	2 g of tranexamic acid or placebo.
Outcomes	Primary outcome: death in hospital within four weeks of injury. Secondary outcome: receipt of a blood product transfusion, the number of units of blood products transfused, surgical intervention, and the occurrence of thromboembolic episodes.
Starting date	May 2005
Contact information	CRASH@lshtm.ac.uk

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CRASH-2 Trial (*Continued*)

Notes	

Tranexamic acid in TBI

Trial name or title	Tranexamic Acid for Preventing Progressive Intracranial Haemorrhage in Traumatic Brain Injury.
Methods	Randomised clinical trial.
Participants	Adult patients with moderate or severe TBI.
Interventions	2 g of tranexamic acid or placebo.
Outcomes	Primary outcome: progressive intracranial haemorrhage at 24 ± 8 hours confirmed by repeated CT of the brain. Secondary outcome: functional scale (GOS, DRS), mortality, operative treatment (later surgery for bleeding) , adverse effect and transfusion needed.
Starting date	October 2008
Contact information	surakrant@gmail.com
Notes	

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DATA AND ANALYSES

Comparison 1. Outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Thrombotic complication	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Change in volume of intracranial bleeding	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Outcomes, Outcome 1 Mortality.

Review: Haemostatic drugs for traumatic brain injury

Comparison: 1 Outcomes

Outcome: 1 Mortality

Study or subgroup	Factor VIIa n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Kluger 2007	5/17	6/13		0.64 [0.25, 1.63]
Narayan 2008	11/61	6/36		1.08 [0.44, 2.68]

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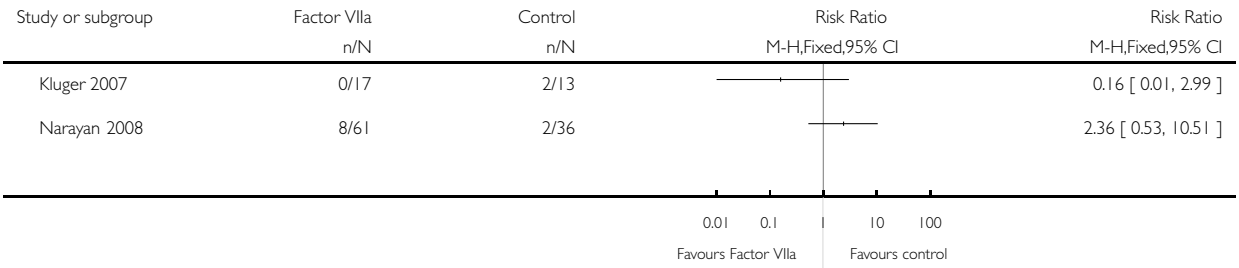
Analysis 1.2. Comparison 1 Outcomes, Outcome 2 Thrombotic complication.

Review: Haemostatic drugs for traumatic brain injury

Comparison: 1 Outcomes

Outcome: 2 Thrombotic complication

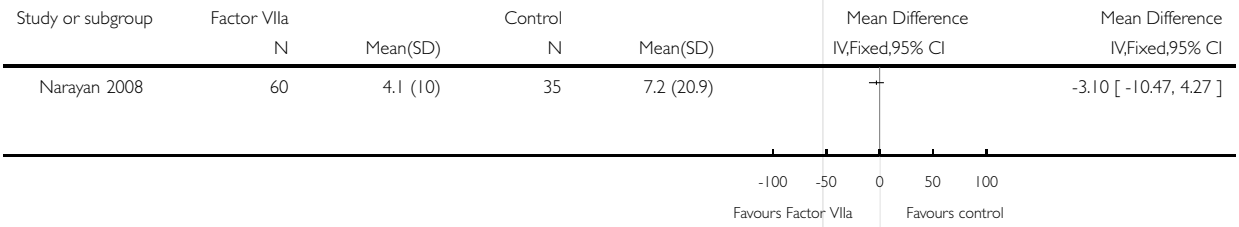


Analysis 1.3. Comparison 1 Outcomes, Outcome 3 Change in volume of intracranial bleeding.

Review: Haemostatic drugs for traumatic brain injury

Comparison: 1 Outcomes

Outcome: 3 Change in volume of intracranial bleeding



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APPENDICES

Appendix 1. Search strategy

Cochrane Injuries Group Specialised Register (searched 3 February 2009)

1. ((haemosta* or hemosta* or antihaemorrhag* or antihemorrhag*) and (drug* or agent* or treat* or therap*)) or ((coagulat* or clotting) and (factor*)) or ("Tranexamic Acid" or Antithrombins* or anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin* or "plasmin inhibitors" or "thrombin inhibitors" or "factor 7a" or "factor VIIa" or factor IXa)
2. ((head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) and (injur* or trauma* or damag* or wound* or fracture* or contusion*)) or ((head or crani* or cerebr* or brain* or intra-cran* or inter-cran*) and (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or pressure)) or ((brain or cerebral or intracranial) and (oedema or edema or swell*)) or ((unconscious* or coma* or concuss* or 'persistent vegetative state') and (injur* or trauma* or damag* or wound* or fracture*)) or ("Glasgow coma score") or ("Glasgow outcome score") or ("Glasgow coma scale") or ("Glasgow outcome scale") or ("diffuse axonal injury" or "diffuse axonal injuries")
3. 1 and 2

CENTRAL (*The Cochrane Library 2009, Issue 1)*

#1 MeSH descriptor Craniocerebral Trauma explode all trees
#2 MeSH descriptor Cerebrovascular Trauma explode all trees
#3 MeSH descriptor Brain Edema explode all trees
#4 (brain or cerebral or intracranial) next (oedema or edema or swell*)
#5 MeSH descriptor Glasgow Coma Scale explode all trees
#6 MeSH descriptor Glasgow Outcome Scale explode all trees
#7 MeSH descriptor Unconsciousness explode all trees
#8 glasgow next (coma or outcome) next (score or scale)
#9 (Unconscious* or coma* or concuss* or 'persistent vegetative state') near5 (injur* or trauma* or damag* or wound* or fracture*)
#10 "Rancho Los Amigos Scale"
#11 (head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) near3 (injur* or trauma* or damag* or wound* or fracture* or contusion*)
#12 Diffuse next axonal next injur*
#13 (head or crani* or cerebr* or brain* or intra-cran* or inter-cran*) near3 (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or pressure)
#14 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)
#15 MeSH descriptor Hemostatics explode all trees
#16 MeSH descriptor Blood Coagulation Factors explode all trees
#17 MeSH descriptor Hemostasis explode all trees with qualifier: DE
#18 MeSH descriptor Blood Coagulation explode all trees with qualifier: DE
#19 MeSH descriptor Fibrinolysis explode all trees with qualifier: DE
#20 MeSH descriptor Platelet Activation explode all trees with qualifier: DE
#21 MeSH descriptor Antithrombins explode all trees with qualifier: DE
#22 MeSH descriptor Thrombin explode all trees with qualifier: DE
#23 (haemosta* or hemosta* or antihaemorrhag* or antihemorrhag*) near5 (drug* or agent* or treat* or therap*):ab,ti
#24 (coagulat* or clotting) next (factor*):ab,ti
#25 MeSH descriptor Factor VIIa explode all trees
#26 (factor) next (7a or VIIa or VII):ab,ti
#27 MeSH descriptor Factor IXa explode all trees
#28 MeSH descriptor Estrogens, Conjugated (USP) explode all trees
#29 (conjugated next estrogen*) or (carentil or congest or dagynil or oestrofeminal or estro-feminal or oestro-feminal or prelestrin or premarin or climarest or climopax or presomen or progens or transannon or femavit):ab,ti
#30 MeSH descriptor Erythropoietin explode all trees
#31 MeSH descriptor Erythropoietin, Recombinant explode all trees
#32 erythropoietin or recormon or epoetin alfa or epogen or eprex:ti,ab
#33 MeSH descriptor Deamino Arginine Vasopressin explode all trees

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#34 (deamino next arginine) or (desmopressin or adiuretin or apo-desmopressin or ddavp or desmopressine or desmospray or desmotabs or octim or octostim or minirin or minurin or desmogalen or nocutil or stimate or Arginine or Vasopressins or DDVAP):ti
#35 MeSH descriptor Antifibrinolytic Agents explode all trees
#36 MeSH descriptor Aprotinin explode all trees
#37 MeSH descriptor Aminocaproic Acids explode all trees
#38 MeSH descriptor Tranexamic Acid explode all trees
#39 (aminocaproic or 6-aminohexanoic or epsilon-aminocaproic) next (acid*):ti
#40 (tranexamic acid or TXA or amcha or amca or cyklokapron or kabi-2161 or transamin or ugurol or t-amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid or EACA):ab,ti
#41 (amicar or caprocid or epsamon or epsikapron or aprotinin* or BPTI or antilysin or contrical or contrykal or dilmintal or iniprol or kontrikal or kontrykal or pulmin or trasylol or zymofren or argatroban):ab,ti
#42 (Basic or bovine or kunitz or kallikrein) next (trypsin inhibitor* or trypsin inactivator*):ab,ti
#43 (kallikrein-trypsin or bovine pancreatic trypsin or tranexamic or cyklokapron or pharmacia or t-amcha or amcha or ugurol or transamin or kabi or epsilon-aminocaproic acid or aminocaproic or lederle):ab,ti
#44 (anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin*) or (plasmin next inhibitor*) or (thrombin next inhibitor*):ab,ti
#45 (#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44)
#46 (#14 AND #45)

MEDLINE (Ovid SP) 1950 to week 3 January 2009

1. exp Craniocerebral Trauma/
2. exp Brain Edema/
3. exp Glasgow Coma Scale/
4. exp Glasgow Outcome Scale/
5. exp Unconsciousness/
6. exp Cerebrovascular Trauma/
7. ((head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) adj3 (injur* or trauma* or damag* or wound* or fracture* or contusion*)).ab,ti.
8. ((head or crani* or cerebr* or brain* or intra-cran* or inter-cran*) adj3 (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or pressure)).ti,ab.
9. (Glasgow adj (coma or outcome) adj (scale* or score*)).ab,ti.
10. "rancho los amigos scale".ti,ab.
11. ("diffuse axonal injury" or "diffuse axonal injuries").ti,ab.
12. ((brain or cerebral or intracranial) adj (oedema or edema or swell*)).ab,ti.
13. ((unconscious* or coma* or concuss* or 'persistent vegetative state') adj5 (injur* or trauma* or damag* or wound* or fracture*)).ti,ab.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. exp hemostatics/
16. exp blood coagulation factors/
17. hemostasis/de or blood coagulation/de or fibrinolysis/de or exp platelet activation/de or exp antithrombins/ or thrombin/ai
18. ((h?emosta* or antih?emorrhag*) adj5 (drug* or agent* or treat* or therap*)).ab,ti.
19. ((coagulat* or clotting) adj factor*).ab,ti.
20. exp Factor VIIa/
21. (factor adj (7a or VIIa or VII)).ab,ti.
22. exp factor ixa/
23. exp "Estrogens, Conjugated (USP)"/
24. ((conjugated adj3 estrogen*) or carentil or congest or dagynil or oestrofeminal or estro-feminal or oestro-feminal or prelestrin or premarin or climarest or climopax or presomen or progens or transannon or femavit).ab,ti.
25. exp Erythropoietin/ or exp Erythropoietin, Recombinant/ or exp Receptors, Erythropoietin/
26. (erythropoietin or recormon or epoetin alfa or epogen or eprex).ti,ab.
27. exp Deamino Arginine Vasopressin/
28. ((deamino adj arginine) or desmopressin or adiuretin or apo-desmopressin or ddavp or desmopressine or desmospray or desmotabs or octim or octostim or minirin or minurin or desmogalen or nocutil or stimate or Arginine or Vasopressins or DDVAP).ti.
29. exp Antifibrinolytic Agents/

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30. exp Aprotinin/
31. exp Aminocaproic Acids/
32. exp Tranexamic Acid/
33. ((aminocaproic or 6-aminohexanoic or epsilon-aminocaproic) adj acid*).ti,ab.
34. (tranexamic acid or TXA or amcha or amca or cyklokapron or kabi-2161 or transamin or ugurol or t-amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid or EACA).ab,ti.
35. (amicar or caprocid or epsamon or epsikapron or aprotinin* or BPTI or antilysin or contrical or contrykal or dilmintal or iniprol or kontrikal or kontrykal or pulmin or trasylol or zymofren or argatroban).ab,ti.
36. ((Basic or bovine or kunitz or kallikrein) adj (trypsin inhibitor* or trypsin inactivator*)).ab,ti.
37. (kallikrein-trypsin or bovine pancreatic trypsin or tranexamic or cyklokapron or pharmacia or t-amcha or amcha or ugurol or transamin or kabi or epsilon-aminocaproic acid or aminocaproic or lederle).ab,ti.
38. (anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin* or (plasmin adj inhibitor*) or (thrombin adj inhibitor*)).ab,ti.
39. 15 or 16 or 17 or 18 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40. 14 and 39
41. randomi?ed.ab,ti.
42. randomized controlled trial.pt.
43. controlled clinical trial.pt.
44. placebo.ab.
45. clinical trials as topic.sh.
46. randomly.ab.
47. trial.ti.
48. 41 or 42 or 43 or 44 or 45 or 46 or 47
49. (animals not (humans and animals)).sh.
50. 48 not 49
51. 40 and 50

PubMed (www.ncbi.nlm.nih.gov/sites/entrez/) (searched 3 Feb 2009: added to PubMed in the last 180 days)
#1((haemosta* or hemosta* or antihaemorrhag* or antihemorrhag*) and (drug or drugs or agent* or treatment* or therapy or therapies or therapeutic*)) or ((coagulat* or clotting) and (factor or factors)) or ("Tranexamic Acid" or Antithrombins* or anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin* or "plasmin inhibitors" or "thrombin inhibitors" or "factor 7a" or "factor VIIa" or factor IXa)
#2((head or craniu* or crania* or cerebra* or cerebru* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) and (injury or injuries or trauma or traumas or traumatic or damag* or wound* or fracture* or contusion*)) or ((head or craniu* or crania* or cerebra* or cerebru* or brain* or intra-cran* or inter-cran*) and (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or pressure)) or ((brain or cerebral or intracranial) and (oedema or edema or swell*)) or ((unconscious* or coma* or concuss* or 'persistent vegetative state') and (injury or injuries or trauma or traumas or traumatic or damag* or wound* or fracture*)) or ("Glasgow coma score") or ("Glasgow outcome score") or ("Glasgow coma scale") or ("Glasgow outcome scale") or ("diffuse axonal injury" or "diffuse axonal injuries")
#3((randomized controlled trial[pt] OR controlled clinical trial[pt]) OR (randomized OR randomised OR randomly OR placebo[tiab]) OR (trial[ti]) OR ("Clinical Trials as Topic"[MeSH Major Topic])) NOT (("Animals"[Mesh]) NOT ("Humans"[Mesh] AND "Animals"[Mesh]))
#4#1 and #2 and #3

EMBASE (Ovid SP) 1980 to week 4 January 2009
1.exp Brain Injury/
2.exp Brain Edema/
3.exp Glasgow Coma Scale/
4.exp Glasgow Outcome Scale/
5.exp Rancho Los Amigos Scale/
6.exp Unconsciousness/
7.((brain or cerebral or intracranial) adj5 (oedema or edema or swell$)).ab,ti.

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8.((head or crani$ or cerebr$ or capitis or brain$ or forebrain$ or skull$ or hemispher$ or intra-cran$ or inter-cran$) adj5 (injur$ or trauma$ or damag$ or wound$ or fracture$ or contusion$)).ab,ti.
9.(Glasgow adj (coma or outcome) adj (scale$ or score$)).ab,ti.
10.Rancho Los Amigos Scale.ab,ti.
11.((unconscious$ or coma$ or concuss$ or 'persistent vegetative state') adj3 (injur$ or trauma$ or damag$ or wound$ or fracture$)).ti,ab.
12.Diffuse axonal injur$.ab,ti.
13.((head or crani$ or cerebr$ or brain$ or intra-cran$ or inter-cran$) adj3 (haematoma$ or hematoma$ or haemorrhag$ or hemorrhag$ or bleed$ or pressure)).ab,ti.
14.or/1-13
15.exp Randomized Controlled Trial/
16.exp controlled clinical trial/
17.randomi?ed.ab,ti.
18.placebo.ab.
19.*Clinical Trial/
20.randomly.ab.
21.trial.ti.
22.15 or 16 or 17 or 18 or 19 or 20 or 21
23.exp animal/ not (exp human/ and exp animal/)
24.22 not 23
25.14 and 24
26.exp Hemostatic Agent/
27.exp Blood Clotting Factor/
28.hemostasis/de or blood coagulation/de or fibrinolysis/de or exp platelet activation/de or exp antithrombins/ or thrombin/ai
29.((h?emosta* or antih?emorrhag*) adj5 (drug* or agent* or treat* or therap*)).ab,ti.
30.((coagulat* or clotting) adj factor*).ab,ti.
31.exp Blood Clotting Factor 7a/
32.(factor adj (7a or VIIa or VII)).ab,ti.
33.exp Blood Clotting Factor 9a/
34.exp "Estrogens, Conjugated (USP)"/
35.((conjugated adj3 estrogen*) or carentil or congest or dagynil or oestrofeminal or estro-feminal or oestro-feminal or prelestrin or premarin or climarest or climopax or presomen or progens or transannon or femavit).ab,ti.
36.exp Erythropoietin/ or exp Recombinant Erythropoietin/ or exp Erythropoietin Receptor/
37.(erythropoietin or recormon or epoetin alfa or epogen or eprex).ti,ab.
38.exp "Argipressin[1 Deamino]"/
39.((deamino adj arginine) or desmopressin or adiuretin or apo-desmopressin or ddavp or desmopressine or desmospray or desmotabs or octim or octostim or minirin or minurin or desmogalen or nocutil or stimate or Arginine or Vasopressins or DDVAP).ti.
40.exp Antifibrinolytic Agent/
41.exp Aprotinin/
42.exp Aminocaproic Acid/ or exp Aminocaproic Acid Derivative/
43.exp Tranexamic Acid/
44.((aminocaproic or 6-aminohexanoic or epsilon-aminocaproic) adj acid*).ti,ab.
45.(tranexamic acid or TXA or amcha or amca or cyklokapron or kabi-2161 or transamin or ugurol or t-amcha or trans-4-aminomethylcyclohexanecarboxylic acid or EACA).ab,ti.
46.(amicar or caprocid or epsamon or epsikapron or aprotinin* or BPTI or antilysin or contrical or contrykal or dilmintal or iniprol or kontrikal or kontrykal or pulmin or trasylol or zymofren or argatroban).ab,ti.
47.((Basic or bovine or kunitz or kallikrein) adj (trypsin inhibitor* or trypsin inactivator*)).ab,ti.
48.(kallikrein-trypsin or bovine pancreatic trypsin or tranexamic or cyklokapron or pharmacia or t-amcha or amcha or ugurol or transamin or kabi or epsilon-aminocaproic acid or aminocaproic or lederle).ab,ti.
49.(anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin* or (plasmin adj inhibitor*) or (thrombin adj inhibitor*)).ab,ti.
50.or/26-49
51.25 and 50

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CINAHL (EBSCO) 1982 to January 2009

1.S35 (S24 and S34)
2.S34 (S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33)
3.S33 TI (anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or
4.anti-fibrinolysin* or antiplasmin* or anti-plasmin*) or TI plasmin
5.inhibitor* or TI thrombin inhibitor*
6.S32 AB (anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or
7.anti-fibrinolysin* or antiplasmin* or anti-plasmin*) or AB plasmin
8.inhibitor* or AB thrombin inhibitor*
9.S31 AB (coagulat* or clotting) and AB factor*
10.S30 TI (coagulat* or clotting) and TI factor*
11.S29 TI (haemosta* or hemosta* or antihaemorrhag* or antihemorrhag*) and
12.TI (drug* or agent* or treat* or therap*)
13.S28 AB (haemosta* or hemosta* or antihaemorrhag* or antihemorrhag*) and
14.AB (drug* or agent* or treat* or therap*)
15.S27 (MH "Blood Coagulation+")
16.S26 (MH "Blood Coagulation Factors+")
17.S25 (MH "Hemostatics+") or (MH "Hemostatic Techniques+")
18.S24 (S11 and S23)
19.S23 (S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or
20.S22)
21.S22 AB singl* W3 blind* or AB doubl* W3 blind* or AB trebl* W3 blind* or
22.AB tripl* W3 blind*
23.S21 TI singl* W3 blind* or TI doubl* W3 blind* or TI trebl* W3 blind* or
24.TI tripl* W3 blind*
25.S20 MH quantitative studies
26.S19 TX random* N3 allocat*
27.S18 MH random assignment
28.S17 TX placebo*
29.S16 MH placebos
30.S15 TX randomi?ed N3 control* N3 trial*
31.S14 TX clinical N3 trial*
32.S13 PT clinical trial*
33.S12 MH clinical trials
34.S11 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10
35.S10 TI (head or crani* or cerebr* or brain* or intra-cran* or inter-cran*
36.) and AB (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed*
37.or pressure)
38.S9 AB (head or crani* or cerebr* or capitis or brain* or forebrain* or
39.skull* or hemispher* or intra-cran* or inter-cran*) and TI (injur* or
40.trauma* or damag* or wound* or fracture* or contusion*)
41.S8 TX Diffuse W1 axonal N3 injur*
42.S7 TX Rancho Los Amigos Scale
43.S6 AB (Unconscious* or coma* or concuss* or "persistent vegetative state"
44.) and TI (injur* or trauma* or damag* or wound* or fracture*)
45.S5 TX glasgow and TX (coma or outcome) and TX (score or scale)
46.S4 (MH "Unconsciousness+") or (MH "Brain Concussion+")
47.S3 (MH "Glasgow Coma Scale")
48.S2 (MH "Brain Injuries+")
49.S1 (MH "Head Injuries+")

ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to January 2009) and Conference Proceedings Citation Index- Science (CPCI-S) (1990 to January 2009)

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1.Topic=((haemosta* or hemosta* or antihaemorrhag* or antihemorrhag*) SAME (drug* or agent* or treat* or therap*)) OR Topic=((coagulat* or clotting) SAME (factor*)) OR Topic=((factor) SAME (7a or VIIa or VII OR IX)) OR Topic=((conjugated) SAME (estrogen* OR oestrogen*))
2.Topic=(carentil or congest or dagynil or oestrofeminal or estro-feminal or oestro-feminal or prelestrin or premarin or climarest or climopax or presomen or progens or transannon or femavit) OR Topic=(erythropoietin or recormon or epoetin alfa or epogen or eprex) AND Topic=(desmopressin or adiuretin or apo-desmopressin or ddavp or desmopressine or desmospray or desmotabs or octim or octostim or minirin or minurin or desmogalen or nocutil or stimate or Arginine or Vasopressins or DDVAP) AND Topic=(deamino SAME arginine)
3.Topic=(amicar or caprocid or epsamon or epsikapron or aprotinin* or BPTI or antilysin or contrical or contrykal or dilmintal or iniprol or kontrikal or kontrykal or pulmin or trasylol or zymofren or argatroban OR Aminocaproic Acid* OR Tranexamic Acid*) OR Topic=(anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin*) OR Topic=(plasmin SAME inhibitor*) OR Topic=(thrombin SAME inhibitor*)
4.Topic=(kallikrein-trypsin or bovine pancreatic trypsin or tranexamic or cyklokapron or pharmacia or t-amcha or amcha or ugurol or transamin or kabi or epsilon-aminocaproic acid or aminocaproic or lederle) OR Topic=((Basic or bovine or kunitz or kallikrein) SAME (trypsin inhibitor* or trypsin inactivator*))
5.1 or 2 or 3 or 4
6.Topic=(glasgow SAME (coma or outcome) SAME (score or scale)) OR Topic=((Unconscious* or coma* or concuss* or 'persistent vegetative state') SAME (injur* or trauma* or damag* or wound* or fracture*)) OR Topic=("Rancho Los Amigos Scale" OR diffuse axonal injur*) OR Topic=((head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) same (injur* or trauma* or damag* or wound* or fracture* or contusion*)) OR Topic=((head or crani* or cerebr* or brain* or intra-cran* or inter-cran*) SAME (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or pressure))
7.TS=((injur* or trauma* or lesion* or damage* or wound* or oedema* or edema* or fracture* or contusion* or concus* or commotion* or pressur*) SAME (head or crani* or capitis or brain* or forebrain* or skull* or hemisphere or intracran* or orbit*)) OR TS=(Craniocerebral Trauma OR Cerebrovascular Trauma OR Brain Edema) OR TS=((brain or cerebral or intracranial) SAME (oedema or edema or swell*))
8.6 or 7
9.Topic=((singl* OR doubl* OR trebl* OR tripl*) SAME (blind* OR mask*))
10.Topic=(randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial) OR Topic=(controlled clinical trial OR controlled trial OR clinical trial OR placebo)
11. 9 or 10
12. 5 and 8 and 11

HISTORY

Protocol first published: Issue 3, 2009

Review first published: Issue 1, 2010

CONTRIBUTIONS OF AUTHORS

PP and IR developed the search strategy, scanned the search results, extracted the data and drafted the first version of the review. SY drafted the first version of the protocol, which provides the foundation of the review.

All the authors edited and approved the review.

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DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Thai Cochrane Network, Thailand.
- Faculty of Medicine, Khon Kaen University, Thailand.
- Khon Kaen Hospital, Ministry of Public Health, Thailand.
- Cochrane Injuries Group, UK.
- London School of Hygiene & Tropical Medicine, UK.

External sources

- The Thailand Research Fund, Senior Research Scholar, Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We removed desmopressin, oestrogens, and activated factor IX from the interventions, and we focused on the most commonly used haemostatic drugs (antifibrinolytics, and rFVIIa).

INDEX TERMS

Medical Subject Headings (MeSH)

Cerebral Hemorrhage, Traumatic [*drug therapy]; Factor VIIa [*therapeutic use]; Head Injuries, Closed [*complications]; Hemostatics [*therapeutic use]; Randomized Controlled Trials as Topic; Recombinant Proteins [therapeutic use]

MeSH check words

Humans

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Roselle for hypertension in adults (Review)

Ngamjarus C, Pattanittum P, Somboonporn C

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 1

http://www.thecochranelibrary.com

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TABLE OF CONTENTS

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[Intervention Review]

Roselle for hypertension in adults

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ABSTRACT

Background

Hypertension is considered a serious health problem worldwide. Controlling and lowering blood pressure have a significant benefit to the hypertensive patients because hypertension is a risk factor for stroke, heart disease and cardiovascular disease. A tropical plant called Roselle, or Red Sorrel in English-speaking countries, has been used both as a thirst-quenching drink and for medical purposes.

Objectives

To explore the effect of Roselle on blood pressure in hypertensive adult patients.

Search strategy

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The following databases were searched (Date of most recent search was September 2009):

- Cochrane Database of Systematic Reviews (2nd Quarter 2009)

- DARE (2nd Quarter 2009)

- Ovid MEDLINE (1950 to Present with Daily Update)

- EMBASE (1980 to 2009 Week 22)

- AMED (1985 to May 2009)

- EBSCO CINAHL

- BIOSIS (1969 to 2008)

- AGRICOLA (1970 to May 2009)

- Food Science and Technology Abstract (1969 to 2009 June Week 1)

- International Pharmaceutical Abstracts

- International Bibliographic Information on Dietary Supplements

- Clinical Trials.gov and Current Controlled Trials

- OpenSIGLE

- Hand searching of journals

- ISI Web of Knowledge

Selection criteria

We sought randomised control trials (RCTs) evaluating use of any forms of Roselle with placebo or no treatment in hypertensive patients. Change in trough and/or peak systolic and diastolic blood pressure were primary outcomes. Secondary outcomes were withdrawals due to adverse effects, change of pulse pressure and change of heart rate.

Data collection and analysis

Two review authors (C Ngamjarus, CN and P Pattanittum, PP) independently scanned titles and abstracts, as well as independently screened the full reports of the potentially relevant studies. At each stage, the results were compared and disagreements were solved by discussion.

Main results

No studies were identified that met the inclusion criteria. However, one abstract of an ongoing study is likely to meet the inclusion criteria, when completed.

Authors' conclusions

There is insufficient evidence to support the benefit of Roselle for either controlling or lowering blood pressure in patients with hypertension. Based on the information of this review, there is a clear need to develop well-designed studies to assess the efficacy of Roselle on hypertensive patients.

PLAIN LANGUAGE SUMMARY

No evidence that red tea (Roselle) lowers blood pressure in adults

Hypertension is a serious health problems worldwide. Controlling and lowering blood pressure have a significant benefit to the hypertensive patients because hypertension is a risk factor for stroke, heart disease and cardiovascular disease. A tropical plant called Roselle or red tea has been used as a thirst-quenching drink and for medical purposes. We searched for evidence from clinical studies to evaluate the effectiveness of red tea compared with placebo or no treatment in hypertensive patients. There is a lack of evidence from

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randomised control trials to demonstrate a benefit of Roselle tea in reducing blood pressure. Rigorous studies need to be done in order to answer this question.

BACKGROUND

Description of the condition

The classification of hypertension in adults according to blood pressure values was recently described in the Australian 'Guide to management of hypertension 2008'. This guideline considers a patient as hypertensive when either systolic blood pressure ≥ 140 millimetres of mercury (mmHg) or diastolic blood pressure ≥ 90 mmHg. (National 2008)

Hypertension is considered a serious health problem worldwide. It is ranked among the top 20 global risk factors for mortality (Majid 2002). Between a fifth and a quarter of most adults would meet the classification of hypertension (MacMahon 2005).

Description of the intervention

Hibiscus Sabdariffa Linne, a member of the family Malvacae, known as Roselle or Red Sorrel in English-speaking countries, is a tropical plant, widely grown in Central and West Africa, South-East Asia, and elsewhere. Common names, besides Roselle, are Red Sorrel, Karkade, sour tea and red tea (Mozaffari-Khosravi 2009, Ali 2005). Various parts of Roselle (flower, leaves, calyx and corolla) are used in beverages in China, Taiwan and Thailand both as a thirst-quenching drink and for medical purposes (Wright 2007) and recently, for its alleged antihypertensive properties (Herrera-Arellano 2004). The chemical components contained in Roselle include anthocyanins, flavonoids and polyphenols (Lin 2007). The extracts of Roselle are also used in folk medicine against many complaints that include high blood pressure, liver disease and fever. The red anthocyanin pigments in the calyces are used as food colouring agents (Ali 2005).

How the intervention might work

Many studies investigated the capabilities of Roselle on blood pressure. In animal studies, it was found by Mojiminiyi 2007 that an aqueous extract of the calyx of Roselle possesses anti-hypertensive, hypotensive and negative chronotropic effects (Roselle was administered as dissolved in normal saline). Odigie 2003 conducted their study in renovascular hypertensive rats. They suggested that the aqueous extract of Roselle petal exhibited antihypertensive and cardioprotective properties, which supported the public belief that Roselle may be a useful antihypertensive agent. Onyenekwe 1999 reported that Roselle calyx infusion was found to lower significantly both systolic and diastolic pressure in spontaneously hypertensive and normotensive Wistar-Kyoto rats.

In humans, Herrera-Arellano 2007 assessed the effects of dried extract of Roselle calyxes on patients with stage I or II hypertension, aged 25-61 years. The results showed that the dried extract of Roselle calyxes decreased blood pressure from 146/98 to 130/86 mmHg. They concluded that Roselle exerted important antihypertensive effectiveness with a wide margin of tolerability and safety. Mckay 2007 reported in their research project that consuming Roselle tea lowered blood pressure in mildly hypertensive adults (Roselle tea compared with artificial flavouring and colour). The information from a non-Cochrane systematic review (Thavorn 2006) and a mini-review (Ernst 2005) confirmed the modest antihypertensive effects observed in the study of Herrera-Arellano 2004 (dry calyx from Roselle significantly decreased both systolic and diastolic blood pressure of hypertensive patients, aged 30-80 years) and found a marked effect (11% reduction) on both systolic and diastolic blood pressure in patients with moderate essential hypertension (Haji 1999).

Why it is important to do this review

As mentioned above, hypertension is a global risk factor for mortality and there are many people who suffer from hypertension. Lowering blood pressure level will likely decrease the risk of stroke and cardiovascular disease. Therefore, it is important to explore the effectiveness of Hibiscus Sabdariffa Linne for lowering blood pressure in hypertensive patients.

OBJECTIVES

To determine the effect of Roselle (Hibicus Sabdariffa Linne) on blood pressure in patients with primary hypertension.

METHODS

Criteria for considering studies for this review

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Types of studies

All randomised controlled trials (RCT) comparing the use of any forms of Roselle with placebo (or no intervention) in patients with hypertension. Minimum duration of study was 3 weeks and maximum duration was 12 weeks.

Types of participants

Adults (18 years or older) who had at least 140 mmHg systolic blood pressure or at least 90 mmHg diastolic blood pressure. At least two BP measurements were needed at baseline to qualify patients as being hypertensive. Pregnant women were excluded.

Types of interventions

Any forms of Roselle compared to placebo or no treatment.

Types of outcome measures

Primary outcomes

Change in trough (13 to 26 hours after the dose) and/or peak (1 to 12 hours after the dose) systolic (SBP) and diastolic blood pressure (DBP) compared to placebo or no treatment. If blood pressure measurements were available at more than one time within the acceptable window, the weighted means of blood pressures taken in the 3-12 week range were used.

Secondary outcomes

1. withdrawals due to adverse effects
2. change of pulse pressure (mm Hg)
3. change of heart rate (beats/min)

Search methods for identification of studies

Electronic searches

The Database of Abstracts of Reviews of Effectiveness (DARE) and the Cochrane Database of Systematic Reviews were searched for related reviews (see Appendix 1).

The following electronic databases were searched for primary studies in June 2009:

1. The Cochrane Central Register of Controlled Trials (CENTRAL) (see Appendix 2)

2. English language databases, including MEDLINE (2005-9) (see Appendix 3), EMBASE (2007-9) (see Appendix 4), AMED - Allied and Complementary Medicine Database (1985- May 2009) (see Appendix 5), CINAHL (1982-2009) (see Appendix 6), BIOSIS (1969-2008) (see Appendix 7), AGRICOLA (1970-May 2009) (see Appendix 8), Food Science and Technology Abstracts (1969 - June 2009 Week 1) (see Appendix 9), International Pharmaceutical Abstracts (1970 - May 2009) (see Appendix 10) and International Bibliographic Information on Dietary Supplements (IBID) (see Appendix 11).

Electronic databases were searched using a modified version of the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity-maximizing version (2008 revision) with selected MeSH terms and free text terms relating to Roselle and hypertension. No language restrictions were used. The MEDLINE search strategy (Appendix 3) was translated into the other databases using the appropriate controlled vocabulary as applicable.

Full strategies for English language databases have been included in the Appendices of the review.

Searching other resources

1. Clinical Trials.gov and Current Controlled Trials (see Appendix 12).
2. OpenSIGLE (System for Information on Grey Literature in Europe) (see Appendix 13).
3. Hand searching of those high-yield journals and conference proceedings which have not already been hand searched on behalf of the Cochrane Collaboration (see Appendix 14).
4. Reference lists of all papers and relevant reviews identified.
5. Authors of relevant papers were contacted regarding any further published or unpublished work.
6. Authors of trials reporting incomplete information were contacted to provide the missing information.
7. ISI Web of Science (see Appendix 15).

Data collection and analysis

We created and pilot test a data collection form. This form was used to collect the data from the potential studies that were selected by the review authors. We collected any data of the potential studies, including details of methods, participants, interventions, outcomes and results.

For selecting the studies, two review authors (CN and PP) independently screened the titles and abstracts that were obtained by the search strategies mentioned above. Any disagreement in screening resolved by discussion and consultation with the third review author (C Somboonporn, CS). We identified potential studies by applying the inclusion criteria before data extraction.

We found that there were no studies which met our criteria. Therefore, CN wrote reasons for exclusion of the excluded studies in tables of characteristics of excluded studies in the RevMan software (RevMan 2008). To addition, we contacted authors of the original studies to provide additional information when information from the potential studies was unclear. CN did not conduct the meta-

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analysis due to no studies were identified for inclusion in this review.

Although no studies were included in this reviews, the methods of data extraction, data management, assessment of risk of bias and data analysis will be applied in subsequent updates of this review when future studies meet our criteria (see Appendix 16).

RESULTS

Description of studies

See: Characteristics of excluded studies; Characteristics of studies awaiting classification.

No studies found met the inclusion criteria for this review. For the reasons of exclusion see Characteristics of excluded studies.

Results of the search

The search of 14 electronic databases and 3 hand searching of journals (see 'Appendix 1; to Appendix 15' for database name and search terms) resulted in 159 records. A total of 137 records were excluded after screening the titles and the abstracts by two review authors (CN and PP). Twenty-six records were considered relevant and were retrieved for further assessment. After 17 duplicates were removed, 9 articles were retrieved for the full text. There were 6 full texts available and for the other three only the abstracts could be obtained.

We excluded 2 articles after reviewing the full text because they were not done in hypertensive patients and one abstract was excluded because it was not an RCT.

Four of the full texts and two abstracts were comprehensively considered. For the two abstracts, we contacted the authors and were informed that McKay 2007 was an initial report of McKay 2008; therefore McKay 2007 was excluded, whereas McKay 2008 is in the process of publishing the full article (see 'Characteristics of studies awaiting classification' for further details). None of the remaining four full texts met our inclusion criteria (see 'Characteristics of excluded studies' for further details).

Included studies

No studies met the inclusion criteria for this review.

Excluded studies

Studies found through our literature search were excluded because they did not meet the inclusion criteria. The reasons for exclusion are reported in the Characteristics of excluded studies.

Risk of bias in included studies

No studies were included.

Effects of interventions

No data available for analysis because no studies were included.

DISCUSSION

No reliable conclusions can be drawn about the benefit of Roselle for either controlling or lowering blood pressure in patients with hypertension compared to placebo or no treatment.

Although the evidence does not exist to demonstrate the efficacy of Roselle for hypertension compared to placebo or no treatment, studies were conducted comparing Roselle with antihypertensive agents. Herrera-Arellano 2004 compared Roselle tea to captopril, an angiotensin converting enzyme (ACE) inhibitor that is used for the treatment of hypertension. In this study Roselle tea administered for 4 weeks decreased SBP and DBP of 53 mild and moderate hypertensive patients from 139 to 124 mmHg and 91 to 80 mmHg, respectively, and no side-effects or intolerability were detected. Herrera-Arellano 2007 studied the effect of Roselle compared to lisinopril (another ACE inhibitor) and reported that after one hundred hypertensive patients consumed Roselle for 4 weeks, the SBP and DBP dropped from 146 to 130 mmHg and 98 to 86 mmHg, respectively.

In addition, two studies showed an advantage of Roselle compared to ordinary tea and black tea. Haji 1999 evaluated the effect of Roselle tea and ordinary tea in essential hypertensive patients. The information from 31 patients in the Roselle group revealed that at 12 days SBP and DBP were reduced by 11.2% and 10.8% as compared to the first day. Mozaffari-Khosravi 2009 compared Roselle tea to black tea in hypertensive patients with type II diabetes. It was found that SBP of 27 patients before and after drinking Roselle tea for 15 and 30 days were 134, 123 and 113 mmHg, respectively. The DBP of those patients at days 0, 15 and 30 were 82, 83 and 81 mmHg, respectively.

At this time, there is a need for well-designed studies evaluating the advantages and adverse effects of Roselle compared with placebo or no treatment in both short- and long-term administration in hypertensive patients.

AUTHORS' CONCLUSIONS

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Implications for practice

There is no RCT evidence to indicate whether Roselle can control or lower blood pressure in hypertensive patients compared with placebo or no treatment.

Implications for research

A high quality study is needed to investigate the effects of Roselle compared with placebo or no treatment in hypertensive patients on controlling or lowering blood pressure in both short- and long-term administration of treatment.

ACKNOWLEDGEMENTS

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Haji Faraji M, Haji Tarkhani AH. The effect of sour tea (Hibiscus Sabdariffa) on essential hypertension. Journal of Ethnopharmacology 1999; Vol. 65, issue 3:231–6.

Herrera-Arellano 2004 *{published data only}*
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Herrera-Arellano 2007 *{published data only}*
Herrera-Arellano A, Miranda-Sanchez J, Avila-Castro P, Herrera-Alvarez S, Jimenez-Ferrer JE, Zamilpa A, et al.Clinical effects produced by a standardized herbal medicinal product of Hibiscus Sabdariffa on patients with hypertension. A randomized, double-blind, lisinopril-controlled clinical trial. Planta Medica 2007; Vol. 73, issue 1:6–12. [: 0032–0943]

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Mozaffari-Khosravi H, Jalali-Khanabadi BA, Afkhami-Ardekani M, Fatehi F, Noori-Shadkam M. The effects of sour tea (Hibiscus Sabdariffa) on hypertension in patients with type II diabetes. Journal of Human Hypertension 2009; Vol. 23, issue 1:48–54. [: 0950–9240]

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Mckay 2007
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National 2008

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Onyenekwe 1999

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Wright CI, Van-Buren L, Kroner CI, Koning MMG. Herbal medicines as diuretics: A review of the scientific evidence. Journal of Ethnopharmacology 2007; Vol. 114, issue 1:1–31. [: 0378–8741]

* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Haji 1999	Systolic and diastolic blood pressures were measured before and 15 days after the intervention, which does not meet our criteria in types of studies.
Herrera-Arellano 2004	This study compared the effectiveness and tolerability of a standardized extract from Roselle with captopril, which does not meet our criteria in types of interventions.
Herrera-Arellano 2007	This study compared therapeutic effectiveness, tolerability, and safety, as well as the effect on serum electrolytes and the angiotensin-converting enzyme inhibitory effect of a herbal medicinal product prepared from the dried extract of H. sabdariffa calyxes with those of lisinopril, which does not meet our criteria in types of interventions.
McKay 2007	This abstract presented the results from first 20 subjects, which were the preliminary data. It was only available as an abstract and was subsequently established that it is a sub-study of McKay 2008.
Mozaffari-Khosravi 2009	This study compared the antihypertensive effectiveness of sour tea (Rosselle) with black tea, which does not meet our criteria in types of interventions.

Characteristics of studies awaiting assessment *[ordered by study ID]*

McKay 2008

Methods	A double-blind, placebo-controlled clinical trial of 6 weeks duration
Participants	65 men and women, aged 30 - 70 years, with SBP 120 - 150 and DBP≤95 mm Hg, Subjects were not on BP lowering medications.
Interventions	Hibiscus sabdariffa tisane (3 c/d hibiscus tea) compared with placebo
Outcomes	Lowering of SBP and DBP
Notes	It claims that a standardized method was used to measure BP at 2 baseline visits, 1 week apart, and at weekly intervals thereafter. Treatment lowered SBP (mean±SEM) compared with placebo (-7.2±1.9 vs. -1.3±1.8 mmHg, p-value= 0.030). The change in DBP was not significantly different from placebo (-3.1±1.2 vs. -0.5±1.4 mmHg, p-value= 0.160). However only the abstract could be found. We contacted the first author via e-mail and the author replied that "the manuscript of our full study is still under review. We are not sure how long this review process will take. "

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DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Cochrane Database of Systematic Reviews search strategy (2nd Quarter 2009)

Searched on 05 June 2009

---

1. (hibiscus or rosella or roselle or ambary or anthocyanin$ or burao or chemparathampoo or erragogu or esculetin or gogu or karkad$ or kenaf or sorrel or red tea or sabdarifa or sabdariffa or sour tea or tellagogu or zobo).mp.
2. hypertens$.tw.
3. ((diastolic or systolic or arterial or blood) adj pressure).tw.
4. 1 and (2 or 3)

Appendix 2. DARE (2nd Quarter 2009) search strategy

Searched on 05 June 2009

---

1. (hibiscus or rosella or roselle or ambary or anthocyanin$ or burao or chemparathampoo or erragogu or esculetin or gogu or karkad$ or kenaf or sorrel or red tea or sabdarifa or sabdariffa or sour tea or tellagogu or zobo).mp.
2. hypertens$.tw.
3. ((diastolic or systolic or arterial or blood) adj pressure).tw.
4. 1 and (2 or 3)

Appendix 3. Ovid MEDLINE (1950 to Present with Daily Update) search strategy

Searched on 05 June 2009

---

1. Hibiscus/
2. (hibiscus or rosella or roselle or kenaf or red sorrel or karkade or sour tea or red tea).tw.
3. 1 or 2
4. Hypertension/
5. hypertens$.tw.
6. (blood adj pressure).tw.
7. or/4-6
8. 3 and 7
9. randomized controlled trial.pt.
10. controlled clinical trial.pt.
11. randomized.ab.
12. placebo.ab.
13. drug therapy.fs.
14. randomly.ab.
15. trial.ab.
16. groups.ab.
17. or/9-16
18. animals/ not (humans/ and animals/)

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19. 17 not 18
20. 8 and 19
21. limit 20 to yr="2005 - 2009"

Appendix 4. EMBASE (1980 to 2009 Week 22) search strategy

Searched on 05 June 2009

---

1. hibiscus/
2. hibiscus sabdariffa extract/
3. (hibiscus or rosella or roselle or ambary or anthocyanin$ or burao or chemparathampoo or erragogu or esculetin or gogu or karkad$ or kenaf or sorrel or red tea or sabdarifa or sabdariffa or sour tea or tellagogu or zobo).mp.
4. or/1-3
5. exp hypertension/
6. hypertens$.tw.
7. exp blood pressure/
8. blood pressure.mp.
9. bloodpressure.tw
10. ((diastolic or systolic or arterial) adj pressure).tw.
11. or/5-10
12. controlled clinical trial$.mp.
13. random$.mp.
14. placebo$.mp.
15. dt.fs.
16. trial.ab.
17. groups.ab.
18. (doubl$ adj3 blind$).mp.
19. or/12-18
20. animals/ not (humans/ and animals/)
21. 19 not 20
22. 4 and 11 and 21
23. limit 22 to yr="2007 - 2009"

Appendix 5. AMED (1985 to May 2009) search strategy

Searched on 05 June 2009

---

1. Hibiscus/
2. (hibiscus or rosella or roselle or ambary or anthocyanin$ or burao or chemparathampoo or erragogu or esculetin or gogu or karkad$ or kenaf or sorrel or red tea or sabdarifa or sabdariffa or sour tea or tellagogu or zobo).mp.
3. or/1-2
4. hypertension/
5. hypertens$.mp
6. blood pressure/
7. bloodpressure.tw.
8. ((diastolic or systolic or arterial or blood) adj pressure).mp.
9. or/4-8
10. controlled clinical trial.mp.
11. randomized controlled trials/
12. random$.mp.
13. placebo$.mp.
14. trial.ab.

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15. groups.ab.
16. (doubl$ adj3 blind$).mp.
17. or/10-16
18. 3 and 9 and 17

Appendix 6. EBSCO CINAHL search strategy

Searched on 05 June 2009

- S1 TX hypertens*
- S2 (MH "Blood Pressure+")
- S3 TX diastolic n1 pressure or TX systolic n1 pressure or TX arterial n1 pressure or TX blood n1 pressure
- S4 TX bloodpressure
- S5 (MH "Clinical Trials")
- S6 random*
- S7 placebo*
- S8 doubl* n3 blind*
- S9 TX trial
- S10 AB groups
- S11 (MH "Hibiscus")
- S12 TX hibiscus
- S13 TX (hibiscus or rosella or roselle or ambary or anthocyanin$ or burao or chemparathampoo or erragogu or esculetin or gogu or karkad$ or kenaf or sorrel or red tea or sabdarifa or sabdariffa or sour tea or tellagogu or zobo)
- S14 S1 or S2 or S3 or S4
- S15 S5 or S6 or S7 or S8 or S9 or S10
- S16 S11 or S12 or S13
- S17 S14 and S15 and S16

Appendix 7. BIOSIS (1969 to 2008) search strategy

Searched on 05 June 2009

---

1. (hibiscus or rosella or roselle or ambary or anthocyanin$ or burao or chemparathampoo or erragogu or esculetin or gogu or karkad$ or kenaf or sorrel or red tea or sabdarifa or sabdariffa or sour tea or tellagogu or zobo).tw.
2. hypertens$.tw.
3. bloodpressure.tw.
4. ((diastolic or systolic or arterial or blood) adj pressure).tw.
5. or/2-4
6. controlled clinical trial$.tw.
7. random$.tw.
8. placebo$.tw.
9. trial.ab.
10. groups.ab.
11. (doubl$ adj3 blind$).tw.
12. or/6-11
13. animals/ not (humans/ and animals/)
14. 12 not 13
15. 1 and 5 and 14

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Appendix 8. AGRICOLA (1970 to May 2009) search strategy

Searched on 05 June 2009

---

1. exp hibiscus/
2. (hibiscus or rosella or roselle or ambary or anthocyanin$ or burao or chemparathampoo or erragogu or esculetin or gogu or karkad$ or kenaf or sorrel or red tea or sabdarifa or sabdariffa or sour tea or tellagogu or zobo).mp.
3. or/1-2
4. exp hypertension/
5. hypertens$.tw.
6. exp blood pressure/
7. blood pressure.mp.
8. bloodpressure.tw.
9. ((diastolic or systolic or arterial) adj pressure).tw.
10. or/4-9
11. controlled clinical trial$.mp.
12. random$.mp.
13. placebo$.mp.
14. trial.ab.
15. groups.ab.
16. (doubl$ adj3 blind$).mp.
17. or/11-16
18. animals/ not (humans/ and animals/)
19. 17 not 18
20. 3 and 10 and 19
21. from 20 keep 1

Appendix 9. Food Science and Technology Abstract (1969 to 2009 June Week 1) search strategy

Searched on 05 June 2009

---

1. (hibiscus or rosella or roselle or ambary or anthocyanin$ or burao or chemparathampoo or erragogu or esculetin or gogu or karkad$ or kenaf or sorrel or red tea or sabdarifa or sabdariffa or sour tea or tellagogu or zobo).mp.
2. hypertens$.tw.
3. blood pressure.mp.
4. bloodpressure.tw.
5. ((diastolic or systolic or arterial) adj pressure).tw.
6. or/2-5
7. controlled clinical trial$.mp.
8. random$.mp.
9. placebo$.mp.
10. trial.ab.
11. groups.ab.
12. (doubl$ adj3 blind$).mp.
13. or/7-12
14. 1 and 6 and 13

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Appendix 10. International Pharmaceutical Abstracts search strategy (1970 to May 2009)

Searched on 05 June 2009

---

1. (hibiscus or rosella or roselle or ambary or anthocyanin$ or burao or chemparathampoo or erragogu or esculetin or gogu or karkad$ or kenaf or sorrel or red tea or sabdarifa or sabdariffa or sour tea or tellagogu or zobo).mp.
2. hypertens$.mp.
3. blood pressure.mp.
4. bloodpressure.tw.
5. ((diastolic or systolic or arterial) adj pressure).mp.
6. or/2-5
7. controlled clinical trial$.mp.
8. random$.mp.
9. placebo$.mp.
10. trial.ab.
11. groups.ab.
12. (doubl$ adj3 blind$).mp.
13. or/7-12
14. animals/ not (humans/ and animals/)
15. 13 not 14
16. 1 and 6 and 15

Appendix 11. International Bibliographic Information on Dietary Supplements search strategy

Searched on 17 September 2009

+(hibiscus rosella roselle karkade kardada karkadi kenaf sorrel sabdarifa sabdariffa "sour tea" "red tea") +(hypertens* blood pressure arterial pressure systolic pressure diastolic pressure) +(random* control* trial placebo double blind*)

Appendix 12. Clinical Trials.gov and Current Controlled Trials

Searched on 17 September 2009 (via http://www.controlled-trials.com/mrct/search.html)

---

hypertension AND (hibiscus OR roselle OR sour tea)

Appendix 13. OpenSIGLE

Searched on 17 September 2009 (via http://opensigle.inist.fr/)

((title:hibiscus) OR (title:roselle) OR (title:sabdarifa)) AND (hypertension)

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Appendix 14. Hand searching of journals

1. American Journal of Nursing - using search strategy: (hibiscus OR roselle OR sabdarifa) AND (hypertens*)
2. BMC -(hibiscus OR roselle OR sabdariffa) AND hypertension AND human AND randomized controlled trial
3. Journal of Urban Health- ti:(roselle) or ti:(hibiscus and sabdariffa)

Appendix 15. ISI Web of Knowledge search strategy

Searched on 16 September 2009

---

1. TI=(hibiscus)
2. TI=((hibiscus or rosella or roselle or kenaf or red sorrel or karkade or sour tea or red tea))
3. #2 OR #1
4. TI=(Hypertension)
5. TI=(hypertens*)
6. TI=((blood adj pressure))
7. #6 OR #5 OR #4
8. #7 AND #3
9. TS=(randomized controlled trial)
10. TS=(controlled clinical trial)
11. TS=(randomized)
12. TS=(placebo)
13. TS=(drug therapy)
14. TS=(randomly)
15. TS=(trial)
16. TS=(groups)
17. #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9
18. TS=(animals)
19. #17 NOT #18
20. #8 AND #19

Appendix 16. Methods of data extraction, data management, assessment of risk of bias and data analysis for subsequent updates of this review

Data extraction and management

Two review authors (CN and PP) will independently extract the data from all potential studies. Any disagreement in data extraction will be resolved by discussion and consultation with the third review author (CS).

We will try to contact authors of the original studies to provide additional information when information from the potential studies is unclear. All relevant data will be entered into Review Manager Software (RevMan 2008).

Assessment of risk of bias in included studies

Two review authors (CN and PP) will independently assess the risk of bias in the included studies according to the Cochrane Collaboration's tool for assessing risk of bias (Higgins 2008).

The result of assessing the risk of bias will be recorded in the data collection form. Any disagreements in the assessment of the risk of bias will be resolved by discussion and consultation with the third review author (CS). The assessment of the risk of bias in the included studies will be presented in the risk of bias tables, risk of bias graph and risk of bias summary.

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Measures of treatment effect

We will use mean difference (MD) with 95% confidence intervals (CI) for changes in blood pressure, heart rate and pulse pressure. We will use relative risk (RR) and risk difference (RD) with their 95% CI for withdrawals due to adverse effects.

Unit of analysis issues

Studies with multiple treatment groups

In the case of studies with multiple treatment groups, we will combine all relevant intervention groups into a single group, and all relevant control groups into a single control group (Higgins 2008).

Repeated observations on participants

We will select a single time point and analyse only data at this time for studies in which it is presented (Higgins 2008).

Dealing with missing data

We will try to contact the original investigators (using e-mail, letter and/or fax) to request missing data.
In the case of missing standard deviation of the change in blood pressure, the standard deviation will be imputed based on the information in the same study or from other studies using the same drug. The following hierarchy (listed from high to low preference) will be used to impute standard deviation values:

1. standard deviation of change in blood pressure taken in a different position than that of the blood pressure data used
2. standard deviation of blood pressure at the end of treatment
3. standard deviation of blood pressure at the end of treatment measured in a different position than that of the blood pressure data used
4. standard deviation of blood pressure at baseline (except if this measure is used for entry criteria)
5. mean standard deviation of change in blood pressure from other studies using the same drug

Assessment of heterogeneity

We will use the chi-squared test and I^2 to assess the heterogeneity of treatment effect among the studies.

Assessment of reporting biases

If the number of studies is enough (at least 10 studies included in the meta-analysis), we will use the funnel plot, the Egger's test and the Egger's plot to investigate publication bias. The Egger's test and the Egger's plot will be conducted in the STATA program (StataCorp 2007).

Data synthesis

Data synthesis and analyses will be done using the Cochrane Review Manager software, RevMan 5. We will use the fixed-effect model to pool the treatment effect from the studies if there is no significant heterogeneity. On the other hand, we will use the random-effects model to pool the treatment effect from the studies if there is significant heterogeneity.

Subgroup analysis and investigation of heterogeneity

If we find statistical heterogeneity between studies, we will investigate the source of heterogeneity by subgroup analysis using the following categories:

1. Type of Roselle's form
2. Underlining disease of the patients

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Sensitivity analysis

We will conduct a sensitivity analysis to explore the effect of study quality.

HISTORY

Protocol first published: Issue 3, 2009

Review first published: Issue 1, 2010

CONTRIBUTIONS OF AUTHORS

C Ngamjarus (CN) developed the protocol, did the literature searching, screened the studies from literature searching, and wrote the review.

P Pattanittum (PP) edited and commented on the protocol, screened the studies from literature searching, and commented on the review.

C Somboonporn (CS) commented on the protocol and the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Department of Biostatistics and Demography, Faculty of Public Health, Khon Kaen University, Thailand.
- Department of Radiology (Division of Nuclear Medicine), Faculty of Medicine, Khon Kaen University, Thailand.

External sources

- Thailand Research Fund (Senior Research Scholar), Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. CAMPAIN (Complementary and AlternativeMedicine and Pain Database) could not be accessed for searching the studies.
2. Chinese language databases were not searched because we could not access them.
3. The detail of measures of treatment effect and data synthesis were changed for a minor degree from the protocol (see Appendix 16).

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INDEX TERMS

Medical Subject Headings (MeSH)

*Rumex; Antihypertensive Agents [*pharmacology]; Blood Pressure [*drug effects]; Hypertension [*drug therapy]; Phytotherapy [*methods]

MeSH check words

Adult; Humans

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Interval debulking surgery for advanced epithelial ovarian cancer (Review)

Tangjitgamol S, Manusirivithaya S, Laopaiboon M, Lumbiganon P, Bryant A

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 10

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TABLE OF CONTENTS

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[Intervention Review]

Interval debulking surgery for advanced epithelial ovarian cancer

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ABSTRACT

Background

Interval debulking surgery (IDS), following induction or neoadjuvant chemotherapy, may have a possible role in treating advanced epithelial ovarian cancer (stage III to IV) where primary debulking surgery is not an option.

Objectives

To assess the effectiveness and complications of IDS for patients with advanced stage epithelial ovarian cancer.

Search strategy

We searched the Cochrane Gynaecological Cancer Group's Specialised Register to July 2009, the Cochrane Central Register of Controlled Trials (CENTRAL) Issue 2, 2009, MEDLINE from January 1966 to June week 4 2009, and EMBASE from January 1966 to week 27 2009.

Selection criteria

Randomised controlled trials (RCTs) comparing survival of women with advanced epithelial ovarian cancer, who had IDS performed between cycles of chemotherapy after primary surgery with survival of women who had conventional treatment (primary debulking surgery and adjuvant chemotherapy).

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. Searches for additional information from study authors were attempted. Meta-analysis of overall and progression-free survival (PFS) were performed using random-effects models.

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Main results

Three RCTs randomising 853 women, of whom 781 were evaluated, met the inclusion criteria. Meta-analysis of three trials for overall survival (OS) found no statistically significant difference between IDS and chemotherapy alone (hazard ratio (HR) = 0.80, 95% confidence interval (CI) 0.61 to 1.06, I^2 = 58%). Subgroup analysis for OS in two trials, where the primary surgery was not performed by gynaecologic oncologists or was less extensive, showed a benefit of IDS: HR = 0.68, 95% CI 0.53 to 0.87, I^2 = 0%). Meta-analysis of two trials for progression-free survival (PFS) found no statistically significant difference between IDS and chemotherapy alone (HR = 0.88, 95% CI 0.57 to 1.33, I^2 = 83%). Rates of toxic reactions to chemotherapy were similar in both arms (risk ratio = 1.19, 95% CI 0.53 to 2.66, I^2 = 0%), but little information was available for other adverse events or quality or life.

Authors' conclusions

No conclusive evidence was found to determine whether IDS between cycles of chemotherapy would improve or decrease the survival rates of women with advanced ovarian cancer, compared with conventional treatment of primary surgery followed by adjuvant chemotherapy. IDS appeared to yield benefit only in patients whose primary surgery was not performed by gynaecologic oncologists or was less extensive. Data on QoL and adverse events were inconclusive.

PLAIN LANGUAGE SUMMARY

Interval debulking surgery for advanced epithelial ovarian cancer

Ovarian cancer frequently presents at an advanced stage so it may not be possible to remove all tumours during surgery. Several cycles of chemotherapy are generally given after primary surgery. Secondary surgery, performed after a few cycles of chemotherapy before further cycles of chemotherapy, is called interval debulking surgery (IDS). This review compares the survival of patients with advanced epithelial ovarian cancer, who had IDS performed between cycles of chemotherapy after primary surgery with survival of patients who had conventional treatment (primary debulking surgery and adjuvant chemotherapy). It found similar survival rates in patients who did and did not receive IDS. No adequate information regarding adverse effects was available. Data on quality of life (QoL) of the patients were also inconclusive.

BACKGROUND

Ovarian cancer is the sixth most common cancer among women and the leading cause of death in women with gynaecological malignancies (GLOBOCAN 2002). A woman's risk of developing cancer of the ovaries by age 75 years varies between countries, ranging from 0.5% to 1.6% (IARC 2002). Primary surgery is the mainstay of treatment for ovarian cancer, followed by adjuvant chemotherapy to destroy any gross or microscopic residual tumour cells.

Primary ovarian cancer surgery is performed to achieve optimal cytoreduction as the amount of residual tumour is one of the most important prognostic factors for survival of women with epithelial ovarian cancer (Bristow 2002; Griffiths 1975; Hoskin 1994). An optimal surgical procedure, defined as a reduction of tumours to < 1 to 2 cm in size, required for advanced stage disease (III to IV) is not always possible especially in patients whose diseases are extensive. Such surgery can be complicated requiring extensive bowel resection and major blood loss, with a high risk of morbidity. Another obstacle to extensive primary surgery lies in the patients' medical condition, e.g. poor projected performance status or medical contraindications.

Induction chemotherapy can play an alternative role in these circumstances. The term induction chemotherapy generally describes the administration of chemotherapy to reduce tumour size, allowing further surgery. The term neoadjuvant chemotherapy (NAC) is more specific in that it describes the administration of chemotherapy when primary debulking surgery is not feasible, and only biopsy is done for histologic diagnosis. However, the two terms are sometimes used interchangeably. In this review, if chemotherapy administration does not fit the definition of NAC, we will use the term induction chemotherapy.

When a few cycles of chemotherapy are administered with some tumour response, secondary surgery may be possible before further chemotherapy is considered. This secondary surgery between the courses of chemotherapy is called interval debulking surgery

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(IDS). Although the optimal timing of IDS has not been agreed, it is usually performed after 2 to 4 cycles of chemotherapy. A longer interval between primary surgery and IDS (with more cycles of chemotherapy) could result in the chemotherapy selectively destroying chemosensitive tumour cells leaving chemoresistant clones. Many retrospective or prospective non-randomised trials report the beneficial effects of NAC or induction chemotherapy after inoperable advanced ovarian cancer or those with gross residual diseases, respectively. Chemotherapy may increase the number of patients suitable for secondary surgery (IDS); many authors reported the rates of optimal resection in IDS after induction chemotherapy ranging from 77% to 94% (Ansquer 2001; Chan 2003; Giannopoulos 2006; Jacob 1991; Kuhn 2001; Lawton 1989; Lee 2006; Morice 2003; Surwit 1996).

Another potential benefit of IDS after NAC or induction chemotherapy compared to aggressive primary debulking surgery, as reported in retrospective (Lawton 1989; Morice 2003) and prospective (Giannopoulos 2006) cohort studies, may be lower associated morbidity, e.g. less blood loss, requirement of intensive care unit admission, and duration of hospital stay due to the tumours being smaller. However, this was not found in another study (Kuhn 2001). The QoL of patients treated with IDS after NAC was also reported in one study to be better than those who had conventional treatment (primary debulking surgery followed by a complete and continual cycle of adjuvant chemotherapy) (Chan 2003). By removing the smaller size tumour masses induced by chemotherapy, IDS would facilitate the response of the residual tumours (if any) or the microscopic lesions to subsequent chemotherapy.

Unlike the advantage on the resectability and response rates which were demonstrated in most studies, there is still conflicting evidence from various studies regarding the survival benefit of IDS after chemotherapy compared to conventional treatment. Most studies of IDS after NAC or induction chemotherapy are non-randomised and retrospective in nature. Many of them show that the survival rates of patients who underwent IDS, after sub-optimal primary surgery followed by chemotherapy, were similar to those patients who had primary debulking surgery (Jacob 1991; Kayikçioglu 2001; Loizzi 2005; Morice 2003; Schwartz 1999; Shibata 2003; Surwit 1996). Only a few studies reported significantly longer median survival of patients who had IDS after chemotherapy than of those who had conventional treatment of primary surgery and adjuvant chemotherapy (Kuhn 2001; Vergote 1998), and even fewer studies showed an inferior result of IDS than optimal primary cytoreduction (Fanfani 2003). This conflicting result on the survival benefit of IDS may depend on various characteristics of the patients and their disease, e.g. extent of residual tumour after primary surgery or IDS, tumour response after induction chemotherapy and prior to IDS etc. (Fanfani 2003; Jacob 1991; Kuhn 2001; Mazzeo 2003; Vergote 1998).

We are aware of three major RCTs (Redman 1994; Rose 2004; Van der Burg 1995) which have been conducted to evaluate the survival benefit of IDS in ovarian cancer. These trials did not agree on the benefit of survival outcomes of patients with IDS. Redman 1994 and Rose 2004 showed similar survival rates between patients who had IDS and those who had conventional treatment, while Van der Burg 1995 showed significantly longer survival in the IDS group which was still present after a 10-year follow-up.

One previous meta-analytical study (Bristow 2006) and two systematic reviews (Bristow 2007; Morrison 2007) addressed the question of whether the advanced ovarian cancer patients should have primary surgery before or after chemotherapy. The first meta-analytical study reviewed the role of platinum-based NAC and IDS for advanced ovarian cancer, involving 835 patients from 51 studies (Bristow 2006). The result showed that survival of patients who had NAC after an attempt of primary surgery was inferior to those who had primary surgery. However, the review included only phase I to II and retrospective studies. The other systematic review of NAC or induction chemotherapy and IDS in advanced ovarian cancer was recently published in 2007 (Bristow 2007). The review included the three major RCTs, six non-randomised studies, and the other 26 retrospective and phase I/II studies. The authors categorized the studies into three groups according mainly to the survival outcomes of the patients in the NAC or induction chemotherapy/IDS arm compared to the conventional arm: inferior survival outcome by NAC; no significant difference; and those with limited validation of inclusion criteria for NAC. The results from these studies were simply described and tabulated without a meta-analysis for survival. The Cochrane systematic review (Morrison 2007) identified only one RCT (Liu 2004) of NAC given by intra-arterial route before IDS comparing conventional primary surgery and adjuvant chemotherapy. This study by Liu et al (Liu 2004) found no significant difference in overall survival between the two treatment arms. The objective of these systematic reviews and meta-analysis was to evaluate if NAC could be used in lieu of primary surgery, which was different from the aim of our review which focuses on the role of repeated surgery (IDS) after primary surgery which had been attempted but resulted in sub-optimal surgery.

We found only one previous meta-analytical study which reviewed the role of IDS after neoadjuvant chemotherapy in advanced ovarian cancer (Elit 1995). The two authors from that review identified 33 publications and included three RCTs and three historical cohort trials in their review (Elit 1995). Homogeneity testing was not statistically significant by the Breslow-Day method. Significant survival benefit from the IDS was identified by the Mantel-Haenszel method with odds ratio of 0.5 (P = 0.02) (Elit 1995).

Since there are potential intrinsic biases of patient selection and variations of several factors, such as chemotherapeutic agents or cycles of administration in many retrospective or phase I/II studies, together with conflicting data from the RCTs, a definite conclusion about the advantage of IDS after attempted primary surgery could not be made. Hence, a thorough systematic review in this subject

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focusing only on the high quality data or trials is warranted to give a better view of the use of IDS in advanced epithelial ovarian cancers.

OBJECTIVES

To assess the effectiveness and complications of IDS for patients with advanced stage epithelial ovarian cancer.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Patients with advanced stage epithelial ovarian cancer who have a confirmed pathological diagnosis from primary surgery which was sub-optimal, with residual tumours of more than 1 to 2 cm. Primary surgical procedures range from tumour biopsy, tumour removal, or standard surgical staging for epithelial ovarian cancer.

Types of interventions

Treatment: Interval debulking surgery (IDS), defined as secondary surgery which is performed after 2 to 4 cycles of neoadjuvant chemotherapy (NAC) or induction chemotherapy, to remove the bulk of the tumour, and followed by adjuvant chemotherapy of the same type.
Control: Adjuvant chemotherapy only.

Types of outcome measures

Primary outcomes

- Overall survival (OS): Survival until death from all causes. Survival was assessed from the time when women were enrolled in the study.

Secondary outcomes

- Progression-free survival (PFS).
- Adverse events.
- Quality of life (QoL), measured using a scale that had been validated through reporting of norms in a peer-reviewed publication.

Search methods for identification of studies

Papers in all languages were sought and translations carried out if necessary.

Electronic searches

See: Cochrane Gynaecological Cancer Group methods used in reviews.
Searches were run on the following databases: Cochrane Gynaecological Cancer Group's Specialised Register (CGCSR) to June 2008, the Cochrane Central Register of Controlled Trials (CENTRAL) Issue 2, 2008, MEDLINE from January 1966 to June 2008, and EMBASE from January 1966 to June 2008. For this update the searches were extended to: CGCSR to July 2009, CENTRAL Issue 2, 2009, MEDLINE Ovid to June week 4 2009, EMBASE to 2009 week 27 (see Appendix 1; Appendix 2; Appendix 3; Appendix 4).
All relevant articles found were identified on PubMed and using the 'related articles' feature, a further search was carried out for newly published articles.

Searching other resources

Unpublished and grey literature

We searched Metaregister, Physicians Data Query, www.controlled-trials.com/rct, www.clinicaltrials.gov and www.cancer.gov/clinicaltrials and Gynaecologic Oncologists of Canada (http://www.g-o-c.org) for ongoing trials. The main investigators of any relevant ongoing trials were contacted for further information, as were major co-operative trials groups active in this area.

Reference lists and correspondence

We checked the citation lists of included trials to identify further reports of trials. We also contacted authors of all trials and/or reviews relevant to the reviewed topic to request information on any similar trials. Colleagues, collaborators and other experts in the field were requested to identify missing or unreported trials.

Data collection and analysis

Selection of studies

All titles and abstracts retrieved by electronic searching were downloaded to a reference management database (Endnote), duplicates were removed and the remaining references were examined by two review authors (ST and SM) independently. Those studies which clearly did not meet the inclusion criteria were excluded and copies

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of the full text of potentially relevant references were obtained. The English abstracts of non-English studies were evaluated, and if eligible, the full text studies were obtained and translated. The eligibility of retrieved papers was assessed independently by ST and SM. Disagreements were resolved by discussion.

Data extraction and management

For included studies, we abstracted data as recommended in chapter 7 of the Cochrane Handbook (Higgins 2008).
We collected data on author, year of publication, journal citation, country, setting, inclusion and exclusion criteria, study design and methodology, study population (total number enrolled, patient characteristics, age, size and number of residual tumours after primary surgery, performance status, stage, histology, size and number of residual tumours before and after IDS), interventions (expertise of surgeons, type and schedule of chemotherapy, duration of the treatment), risk of bias, duration of follow-up and outcomes (OS, PFS, QoL and adverse events). We also recorded the following information for each outcome of interest:

- outcome definition;
- unit of measurement (if relevant);
- for scales: upper and lower limits, and whether high or low score is good;
- results: number of participants allocated to each intervention group;
- sample size; missing participants.

Data on outcomes were extracted as below:

- for time to event (OS) data, we extracted the log of the hazard ratio [log(HR)] and its standard error from trial reports; if these were not reported, we attempted to estimate them from other reported statistics using the methods of Parmar 1998;
- for dichotomous outcomes (e.g. adverse events), we extracted the number of patients in each group who experienced the outcome of interest and the number of patients assessed at endpoint, in order to estimate a risk ratio (RR).

Both unadjusted and adjusted statistics were extracted, if reported. Where possible, all data extracted were those relevant to an intention-to-treat (ITT) analysis, in which participants were analysed in groups to which they were assigned.
The time points at which outcomes were collected and reported were noted.
Data were abstracted independently by two review authors (ST, SM) onto a data abstraction form specially designed for the review. Disagreement between authors was resolved by discussion. If this failed a third author (PL) was consulted.

Assessment of risk of bias in included studies

The risk of bias in included RCTs was assessed using the Cochrane Collaboration's tool and the criteria specified in chapter 8 of the Cochrane Handbook (Higgins 2008). This included assessment of:

- sequence generation;
- allocation concealment;
- blinding (of outcome assessors since it was not possible to blind either patients or physicians to the patient's assigned treatment);
- incomplete outcome data: we coded the satisfactory level of loss to follow-up for each outcome as

    - Yes, if fewer than 20% of patients were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms;
    - No, if more than 20% of patients were lost to follow-up or reasons for loss to follow-up differed between treatment arms;
    - Unclear if loss to follow-up was not reported;

- selective reporting of outcomes;
- other possible sources of bias.

The risk of bias tool was applied independently by two review authors (ST, SM) and differences resolved by discussion or by appeal to a third reviewer (PL). Results are summarised in both a risk of bias graph and a risk of bias summary. Results of meta-analyses were interpreted in light of the findings with respect to risk of bias.

Measures of treatment effect

We used the following measures of the effect of treatment:

- for time to event data, we used the HR, where possible;
- for dichotomous outcomes, we used the RR.

Dealing with missing data

We attempted to extract data on the outcomes only among participants who were assessed at endpoint. We did not impute missing outcome data; if only imputed outcome data were reported, we contacted trial authors to request data on the outcomes only among participants who were assessed.

Assessment of heterogeneity

Heterogeneity between studies was assessed by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials which cannot be ascribed to sampling variation (Higgins 2003), by a formal statistical test of the significance of the heterogeneity (Deeks 2001), and, if possible, by subgroup analyses (see below). If there was evidence of substantial heterogeneity, the possible reasons for this were investigated and reported.

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Assessment of reporting biases

We were unable to assess reporting bias as only three trials met our inclusion criteria.

Data synthesis

If sufficient clinically similar trials were available, their results were pooled in meta-analyses. Adjusted summary statistics were used where available; otherwise unadjusted results were used.

- For time-to-event data, HRs were pooled using the generic inverse variance facility of RevMan 5.
- For any dichotomous outcomes, the RR was calculated for each study and these were then pooled.

Random-effects models with inverse variance weighting were used for all meta-analyses (DerSimonian 1986).

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were performed, where possible, grouping trials by:

- expertise of surgeons (gynaecological oncologist, gynaecologist, general surgeon).

Factors such as age, stage, type of intervention, length of follow-up, adjusted/unadjusted analysis were considered in interpretation of any heterogeneity.

Sensitivity analysis

Sensitivity analysis was not performed as there were insufficient trials in the review.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search

The original search identified 134 references whose titles and abstracts were examined. Eighteen studies were potentially relevant to this review. Two studies were readily excluded from the abstracts' data (Evdokimova 1982; Kumar 2007). Full text articles of 16 studies were obtained and were assessed for eligibility by two authors (ST, SM) independently. Thirteen studies were additionally excluded. The reasons for exclusion are presented in the Characteristics of excluded studies table. Three RCTs met all inclusion criteria and were included (Redman 1994; Rose 2004; Van der Burg 1995). The updated search identified 336 references, of which there were 17 possible relevant articles. Only two RCTs were identified; one was of a Japanese study that referred to a study that was excluded in the primary review. The other was an abstract of the EORTC 55971 trial, which was presented at the IGCS 2008 meeting in Bangkok and was also excluded.
We identified one study that is still awaiting classification (JCOG 0206).

Included studies

All three RCTs were multicentre studies: one from United Kingdom involved four institutions which were the referral centres for cancer care (Redman 1994); one by the European Organisation for Research and Treatment of Cancer (EORTC) involved 14 participating institutions in Europe (Van der Burg 1995) and one by the Gynecologic Oncology Group (GOG) from the United States involved more than 42 cancer centres (Rose 2004).
All of the trials (Redman 1994; Rose 2004; Van der Burg 1995) compared IDS and chemotherapy with chemotherapy only.
Median length of follow-up was reported in all three trials: 48 months (Redman 1994), 47 months (Rose 2004) and 42 months (Van der Burg 1995). Although Van de Burg et al. from the EORTC presented their long term follow-up (10 years) as an oral presentation in the European Society of Gynaecological Oncology annual meeting in 2005 (Van der Burg 2005), sufficient data were not available for meta-analysis.
The trial of Redman 1994 supplied data relating to non-assignment of treatment as: death, disease progression, pulmonary embolus, and patient refusal. The other two trials reported only the numbers or percentages of those not undergoing surgery but the reasons were not stated (Rose 2004; Van der Burg 1995).
All three trials reported HRs for OS (Redman 1994; Rose 2004; Van der Burg 1995). Two trials (Rose 2004; Van der Burg 1995) used Cox regression to assess the prognostic significance of numerous covariates (such as age, performance status, stage, tumour grade, response to induction chemotherapy, number of lesions, ascites, and residual diseases or size of tumours at three time points: after primary surgery, before IDS and after IDS). The definitions of optimal debulking or size of residual tumours after primary surgery varied between these trials. Optimal surgery was either defined as < 2 cm (Redman 1994) or < 1 cm (Rose 2004; Van der Burg 1995). OS was variously calculated from the day of induction chemotherapy initiation at enrolment (Van der Burg 1995), or date of randomisation, which was either after primary surgery but before chemotherapy in the Redman study (Redman 1994) or after three cycles of chemotherapy in the GOG trial (Rose 2004). Both the GOG and the EORTC trials reported HRs adjusted for prognostic factors; Redman 1994 also reported unadjusted HRs.
One included trial reported HR, adjusted for prognostic factors, for PFS data (Rose 2004) and one presented Kaplan-Meier disease-free survival curves (Van der Burg 1995), from which we used

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Parmar's method (Parmar 1998) to estimate the HR. The definitions of response and recurrence varied amongst these trials: Redman 1994 applied The International Union Against Cancer (UICC) criteria for response evaluation using physical examination, imaging studies, but not CA125; the EORTC trial used the World Health Organization (WHO) criteria allowing physical examination, imaging studies, and CA125; the GOG trial also used physical examination, imaging studies, and two CA125 levels two weeks apart - they defined progressive disease as an increase of at least 100 U/ml or doubling of the nadir in those whose level did not return to baseline.

Adverse events were reported in all three trials (Redman 1994; Rose 2004; Van der Burg 1995). However, Redman 1994 and Van der Burg 1995 described postoperative complications only in the IDS group while Rose 2004 compared general adverse effects between the IDS group and chemotherapy only group.

QoL was assessed only in the GOG trial and the results were reported subsequently by Wenzel et al. (Wenzel 2005). The assessment tool used was the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) questionnaire and treatment-specific supplemental questions at the third and sixth chemotherapy cycles and at 6 and 12 months after starting treatment.

Redman 1994

The trial of Redman 1994 from the UK is the first known RCT of IDS for the management of epithelial ovarian cancer. From April 1986 to February 1990, the authors randomised 86 patients with stage II to IV disease, who underwent primary surgery in 25 hospitals by 40 different surgeons and had residual disease > 2 cm. It was not clear how experienced the 40 surgeons were but the primary surgery had to be performed with an attempt to remove as much tumour as possible. Stage IV included only malignant pleural effusion without other evidence of distant spread or unresectable diseases. The patients received chemotherapy consisting of either a regimen of cisplatin and cyclophosphamide for eight cycles or a regimen of cisplatin, doxorubicin and bleomycin for three cycles followed by an escalated dose of cyclophosphamide for up to five cycles. Either regimen was given without detailed criteria for regimen selection. The control group had only chemotherapy after primary surgery. The intervention group had chemotherapy for one to four cycles and underwent IDS, which was performed by the primary surgeon, and then received further chemotherapy. Although our inclusion criteria for this review is IDS to be performed after chemotherapy for a minimum of two cycles, this study is included because only one out of 37 patients in the IDS group had only one cycle of chemotherapy before IDS. Interval debulking surgery was not performed if there was progressive disease, stable disease, or insufficient response after three cycles.

Seven of the 86 randomised patients were excluded after randomisation because primary surgery was not sub-optimal. Of the remaining 79 patients, 37 were in the IDS arm and 42 in the conventional arm. There were no significant differences between arms in patient or disease characteristics. Overall, 25 patients (68%) in the IDS arm actually underwent IDS. The reasons for not performing IDS in 12 patients (32%) were: death or progressive disease, pulmonary embolism, and patient refusal. In the conventional arm, one patient (2%) had IDS upon request.

Adverse effects of IDS were reported as perioperative death and significant postoperative complications including deep vein thrombosis, intestinal fistulae, chest or wound infections, or postoperative ileus. Adverse effects in the chemotherapy only group were not exhaustively reported. Toxicity was reported in both treatment groups.

Van der Burg 1995

The trial of Van der Burg 1995 enrolled 425 stage IIB to IV epithelial ovarian cancer patients between March 1987 to May 1993 who had undergone primary surgery and had residual disease > 1 cm. Neither the extent nor the aim of primary surgery nor the expertise of the surgeon were described in their primary report. However, the authors provided additional data from their reply to letter to the Editor (Kehoe 1995) and their subsequent review article (Van der Burg 2003) that the maximum effort to perform primary surgery was not attempted in all patients with different extents of debulking surgery, resulting in a high proportion of large residual tumours (> 5 cm) after primary surgery (Van der Burg 2003).

All patients received three cycles of chemotherapy consisting of intra-venous cisplatin and cyclophosphamide. Those who had response or stable diseases were randomised to undergo IDS or no IDS. Both groups would receive three more cycles of the same chemotherapy (continuation after six cycles based on institution policy).

Overall, 106 patients were not randomised; this number consisted of 39 patients with progressive disease who were removed from the study and also patients who had contraindications to surgery, died, declined to participate in the study, were ineligible, lost to follow-up, and those who were still receiving induction chemotherapy.

Of 319 patients who were randomised, 278 were evaluated (140 patients who underwent surgery and 138 patients who did not). The two groups were well balanced with respect to stage, histologic type and grade, number and size of lesions, peritoneal carcinomatosis, ascites, and response to induction chemotherapy. Rate of optimal debulking surgery (residual tumour < 1 cm) was 64%. The following adverse events were reported in the trial: bowel injury, urinary bladder injury, blood loss and postoperative fever, ileus, urinary tract infection, wound infection, deep vein thrombosis, lung embolism for peri- and postoperative adverse events, respectively.

Rose 2004

Rose 2004 enrolled 550 patients from June 1994 to January 2001,

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with stage III to IV (malignant pleural effusion or a resected anterior abdominal wall tumour) who underwent primary surgery to remove as much tumour as possible, but who still had residual disease > 1 cm. However, after March 1996 when the EORTC trial reported a greater benefit from secondary surgery after the exclusion of patients with stage IV diseases, only patients with stage III disease were included. The primary surgeons were either fellowship-trained or certified gynaecologic oncologists in 95% of patients. Patients whose disease had not progressed and who had residual extraperitoneal tumour of < 1 cm after three cycles of chemotherapy with paclitaxel and cisplatin were randomly assigned to secondary surgical cytoreduction (IDS) and further chemotherapy or chemotherapy alone. Overall, 102 patients were not randomised; the most common reasons were: progressive disease or death in 40 patients, the others were either medically contraindicated, declined, had extraperitoneal disease > 1 cm, experienced excessive delay before randomisation, or other reasons not specified.

A total of 448 patients were randomised: 226 patients to IDS and 222 to chemotherapy only. Patient characteristics were well balanced in the two groups. A considerable number of patients in both groups had protocol violations including: 7% in the IDS group did not have secondary surgery versus 3% in chemotherapy only arm had this surgery; 7% and 2% in the IDS and chemotherapy only arms, respectively, had fewer than three cycles of additional chemotherapy; and 10% and 13% in the IDS and chemotherapy only arms, respectively, had non-protocol consolidation therapy before progressive disease. All randomised patients were included in the analysis of OS and PFS and were counted in the group comparisons.

Cox regression for OS and PFS was performed to evaluate the prognostic importance of: the maximal diameter of residual tumour (2.0 cm or less, 2.1 to 5.0 cm, or 5.0 cm or more) after initial surgery, the patient's age, performance status, the presence or absence of measurable disease before chemotherapy, and the size of residual tumour after IDS (< 1 cm versus > 1 cm).

QoL of patients who did and did not undergo IDS in the GOG study were evaluated and subsequently reported by Wenzel et al (Wenzel 2005). The self-reported QoL was assessed in four settings, according to the Functional Assessment of Cancer Therapy-Ovarian (FACT-O), version 2-questionnaire which consists of 33 general questions for cancer patients and 12 questions specific to ovarian cancer patients. The first evaluation was at baseline after primary surgery and the third cycle of chemotherapy but before allocation to IDS or chemotherapy only. The three subsequent evaluations were at the sixth cycle of chemotherapy, at 6 and 12 months after starting treatment. Completion rates for these questionnaires declined from 90% for the first questionnaire to 83%, 83%, and 80% for the second, third, and fourth questionnaires, respectively. Nevertheless, lower completion rates were noted in the IDS group compared to chemotherapy only group especially at the second assessment, 77% and 89%, respectively (P < 0.001).

The included trials are described in detail below and in the table of Characteristics of included studies.

Excluded studies

Fifteen references were excluded, after obtaining the full text, for the following reasons:

- eight references reported data on non-comparable controlled trials or non-randomised studies (Angioli 2006; Chan 2003; Fuso 2006; Giannopoulos 2006; Ikeba 2004; Kuhn 2001; Lee 2006; Recchia 2001);
- IDS was allowed in both arms of the trial in two trials (EORTC 55971; Park-Simon 2006);
- in one trial survival outcomes were not analysed (Dutta 2005);
- IDS was selectively performed in subset of patients in one trial (Solomon 1988);
- in one trial (Evdokimova 1982), women with ascites were not randomly assigned to interventions;
- either histology or cytology was allowed for a pathologic diagnosis of ovarian cancer in one trial (Kumar 2007);
- one RCT (Liu 2004) was considered ineligible because NAC was given for only 1 cycle via intra-arterial route before the IDS.

For further details of all the excluded studies see the table Characteristics of excluded studies.

Risk of bias in included studies

Two trials (Redman 1994; Van der Burg 1995) were at moderate risk of bias: they satisfied three of the criteria that we used to assess risk of bias. The trial of Rose 2004 was at high risk of bias as it satisfied only one of the criteria (see Figure 1; Figure 2).

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Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

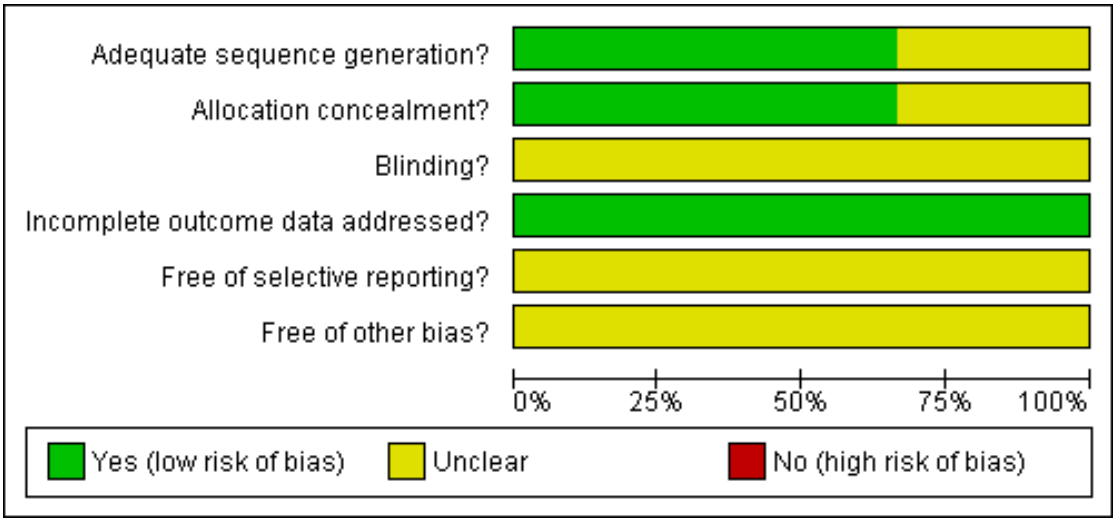

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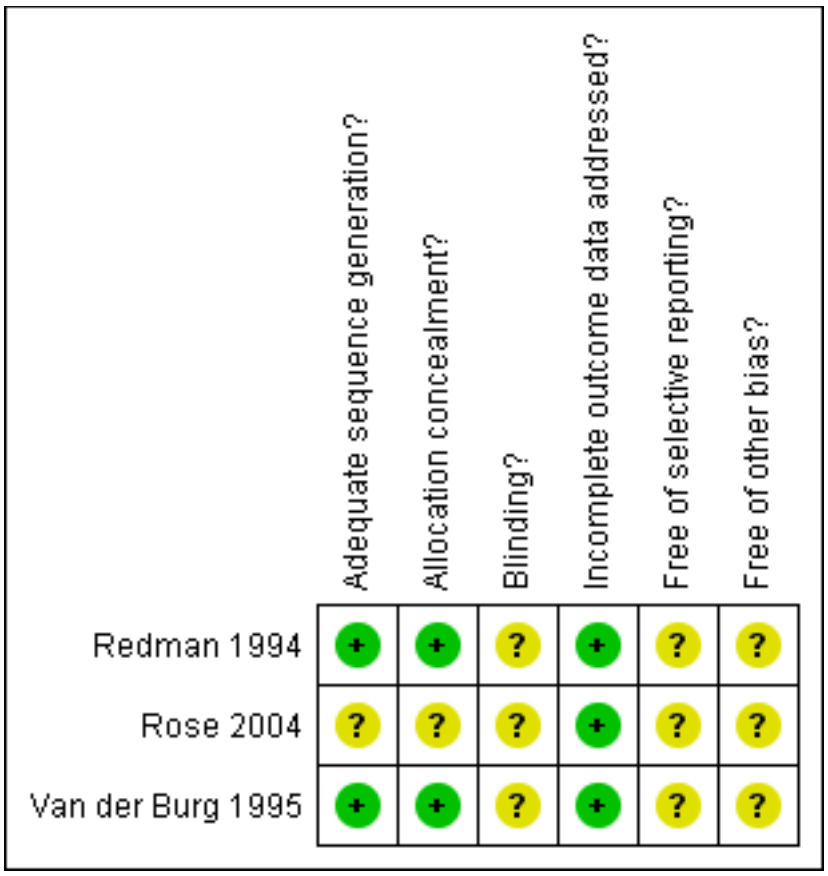
Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Two trials (Redman 1994; Van der Burg 1995) reported the method of generation of the sequence of random numbers used to allocate women to treatment arms. These trials also reported concealment of this allocation sequence from patients and healthcare professionals involved in the trial. The other trial (Rose 2004) did not report on either the method of sequence generation or concealment of allocation. None of the trials reported whether the outcome assessors were blinded. It was not certain whether all trials reported all the outcomes that they assessed and it was unclear whether any other bias may have been present. At least 87% of women who were enrolled were assessed at endpoint in the three trials (Redman 1994; Rose 2004; Van der Burg 1995).

Effects of interventions

Since only a small number of trials were included in meta-analyses, funnel plots were not examined.

IDS versus chemotherapy only

Survival

Overall survival (Analysis 1.1)

Meta-analysis of three trials (Redman 1994; Rose 2004; Van der Burg 1995), assessing 781 participants, found no statistically significant difference in the risk of death between IDS with chemotherapy and chemotherapy alone (HR = 0.80, 95% CI 0.61 to 1.06). The percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) may represent substantial heterogeneity (I^2 = 58%). Hence, we explored the sources of heterogeneity from the clinical factor of expertise of surgeon in the primary surgery and subsequently performed subgroup meta-analysis for OS based on this factor.

The conclusions above were not robust to subgroup analyses examining patients who received surgery from general surgeons (or had less extensive primary surgery) or gynaecologic oncologists separately. Meta-analysis of two trials (Redman 1994; Van der Burg

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1995) assessing 357 women who received surgery by a general surgeon found that IDS with chemotherapy was associated with a statistically significant decrease in the risk of death compared with chemotherapy alone (HR = 0.68, 95% CI 0.53 to 0.87, I^2 = 0%). The trial of Rose 2004, assessing 424 participants, found no statistically significant difference in the risk of death between IDS with chemotherapy and chemotherapy alone (HR = 0.99, 95% CI 0.79 to 1.24). Analysis 1.1

Progression-free survival (Analysis 1.2)

Meta-analysis of two trials (Rose 2004; Van der Burg 1995), assessing 781 participants, found no statistically significant difference in the risk of disease progression between IDS with chemotherapy and chemotherapy alone (HR = 0.88, 95% CI 0.57 to 1.33). The percentage of the variability in effect estimates that is due to heterogeneity rather than chance may represent considerable heterogeneity (I^2 = 83%). Analysis 1.2

Adverse events

Toxic reactions were the only adverse events which could be meta-analysed. They were reported in both treatment groups in Redman 1994 and Van der Burg 1995. It was not possible to meta-analyse other adverse events as they were not reported in sufficient detail for both treatment arms.

Toxic reactions to chemotherapy (Analysis 1.3)

Meta-analysis of two trials (Redman 1994; Van der Burg 1995), assessing 357 participants, found no statistically significant difference in the risk of disease progression between IDS with chemotherapy and chemotherapy alone (HR = 1.19, 95% CI 0.53 to 2.66). The percentage of the variability in effect estimates that is due to heterogeneity rather than by chance is not important (I^2 = 0%).

The following adverse events were reported in the trial of Rose 2004: Analysis 1.3

Peripheral neuropathy of grade 2 or higher (Analysis 1.4)

Women who received IDS with chemotherapy for treatment of advanced epithelial ovarian cancer had a significantly higher risk of high grade peripheral neuropathy than women who received chemotherapy alone (RR = 0.62, 95% CI 0.43 to 0.91). Analysis 1.4

Grade 3 or 4 gastrointestinal adverse events (Analysis 1.5)

There was no statistically significant difference in the risk of a high grade gastrointestinal adverse event between IDS with chemotherapy and chemotherapy alone (RR = 1.81, 95% CI 0.78 to 4.17). Analysis 1.5

Grade 4 pulmonary adverse events (Analysis 1.6)

There was no statistically significant difference in the risk of a grade 4 pulmonary adverse event between IDS with chemotherapy and chemotherapy alone. There were only two observed events in the IDS group and no events in the chemotherapy only group. Analysis 1.6

Grade 4 cardiovascular adverse events (Analysis 1.7)

There was no statistically significant difference in the risk of a grade 4 cardiovascular adverse event between IDS with chemotherapy and chemotherapy alone (RR = 2.89, 95% CI 0.30 to 27.55). Analysis 1.7

Quality of life (QoL)

Only Rose 2004 evaluated QoL, which was subsequently reported by Wenzel (Wenzel 2005). At six months after starting treatment, significantly more patients who had only chemotherapy experienced persistent numbness or tingling than those who had IDS, 54% versus 38% (P = 0.01). Otherwise, QoL was not significantly different in the two treatment groups at any time point.

DISCUSSION

Our systematic review included three RCTs, which evaluated 781 patients out of 853 randomised and a further RCT in abstract form which randomised 718 women, but it was unclear how many of these were evaluated. These four RCTs provided inconclusive evidence as to whether IDS improves or worsens the overall survival rate of patients. The random-effects model showed substantial heterogeneity between the results of the three trials. Likewise, meta-analysis of two RCTs, which evaluated 702 patients out of 767 randomised, provided inconclusive evidence about whether IDS improves or worsens progression-free survival; again, there was substantial heterogeneity between the trials.

Potential reasons for the inconclusive evidence are explained. Firstly, the small number of included studies, evaluating 781 patients, may not have had adequate statistical power to detect a small effect. Furthermore, the studies had different characteristics which may explain the heterogeneity in their results.

A major difference between these trials was the expertise and/or the level of effort given by the surgeons performing the primary debulking surgical procedures in the participating institutions in each study, which may partly explain the heterogeneity between trials. The majority of operations in the GOG trial were performed by the gynaecologic oncologists or fellowship-trained surgeons in various cancer centres (Rose 2004) while the surgical procedures in the Redman trial were performed mostly by general

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surgeons or gynaecologists in various hospitals (Redman 1994). In the EORTC trial where the expertise of the surgeon was not specified (Van der Burg 1995) but was subsequently revealed in other publications (Kehoe 1995; Van der Burg 2003), the maximum effort to perform primary surgery was not attempted in all patients with different extents of debulking surgery. Since there is substantial evidence from many retrospective studies that the extent of optimal surgery affects the survival of patients with epithelial ovarian cancer (Bristow 2002; Griffiths 1975; Hoskin 1994), the maximum primary surgical efforts in the optimal surgical setting in the GOG trial might indicate that their primary surgery was sufficient and subsequent surgical attempts would not affect the survival further. Compared to Redman 1994 and Van der Burg 1995, in which primary surgery was performed in sub-optimal settings, when most of the operations were not performed by gynaecologic oncologists (Redman 1994), without maximum effort (with less extensive primary debulking surgery) resulting in a high proportion of large residual tumours (Kehoe 1995; Van der Burg 1995; Van der Burg 2003), so the secondary surgery (IDS) after the tumours were down-sized by chemotherapy appeared worthwhile, although significant only in the EORTC trial. Our subgroup meta-analysis confirmed that IDS had benefits in this particular subgroup of patients. Nevertheless, this should be interpreted with caution because our subgroup analysis was based on only two trials (Redman 1994; Van der Burg 1995).

The second minor difference between these trials is the timing of randomisation. Redman was the only trial which randomised patients into two groups (to have or not to have IDS) at the start of the trial (Redman 1994) and only 67% of patients in the IDS group actually underwent surgery because the other assigned patients had disease progression or died precluding IDS. The other two larger trials of GOG and EORTC randomised only the patients who showed some response to induction chemotherapy (Rose 2004; Van der Burg 1995): this resulted in a high percentage of the patients (approximately 93% in both trials) who were randomised to undergo IDS. This difference may affect the result from each trial, based on the intention-to-treat analysis in all of these trials.

We explored the patients or their disease characteristics as the other potential reason for different effects of IDS on survival outcomes from the three trials: Redman 1994 and Rose 2004 did not show any advantage of IDS while Van der Burg 1995 showed significant survival improvement with IDS. Redman 1994 evaluated only 79 of the total of 86 patients included in the meta-analysis of OS and, therefore, did not have much influence on the results of the meta-analysis. The difference in outcomes from Rose 2004 and Van der Burg 1995 may be due to the different proportion of patients who had poor response to induction chemotherapy (who generally had poorer prognosis than those who showed some response): approximately 52% of patients in the GOG trial had residual diseases of > 1 cm after induction chemotherapy (Rose 2004) compared to 44% in the EORTC trial (van der Burg 1995). This might be interpreted that the GOG trial had a higher proportion of patients who had more aggressive tumours and so would not have a survival benefit from any treatment, even the optimal IDS. However, this mechanism of tumour aggressiveness and prognosis may not solely explain the ultimate outcome of the patients because the patients in the EORTC trial (Van der Burg 1995) who had tumour > 1 cm after induction chemotherapy but were removed to < 1 cm had better survival benefit than any other group of women in the trial. This might suggest that the IDS may play some role in survival improvement.

To emphasize the importance of the sensitivity of response to chemotherapy before IDS, we would like to point out the findings from the GOG and EORTC trials which showed that the patients whose tumour masses were reduced by chemotherapy to < 1 cm before the IDS (Rose 2004; Van der Burg 1995) had superior survival than the other groups. This response to chemotherapy might be used as a selective criterion for the patients who are likely to gain survival benefit from an IDS.

As we have mentioned in the results, meta-analysis of adverse events was not possible due to different formats of presentation of data in each RCT. The only obvious advantage appears to be fewer neurologic complications in the IDS group than in the chemotherapy only group in the GOG trial (Rose 2004). However, this adverse effect may be related to a particular drug and might not be experienced in the other settings using other chemotherapeutic regimens.

For the QoL comparison, which was only assessed in the GOG trial (Wenzel 2005), patients in the chemotherapy only arm had a higher rate of neurotoxicity than those in the IDS arm at one of the four time points when they were assessed, despite a similar total dose of chemotherapy exposures. The authors ascribed this finding to intermission from chemotherapy exposure allowing a certain degree of recovery, but it may be a chance finding as 48 tests of possible differences in QoL were made. Although other aspects of QoL were similar in the two groups of patients at every time point of assessment, definitive conclusions cannot be made because a significantly lower proportion of patients in the IDS group completed the QoL questionnaires in the second assessment compared to those in the chemotherapy only group, and it is possible that this lower questionnaire completion rate may be associated with QoL.

AUTHORS' CONCLUSIONS

Implications for practice

The heterogeneity of the results in our review precludes any definitive guidance or recommendations for clinical practice. Without strong evidence to support the superior advantages of IDS in combination with chemotherapy over the conventional primary

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surgery and chemotherapy, a clinician may remain unconvinced of the benefit of IDS instead of aggressive primary surgery for a patient with advanced ovarian cancer. The choice of extensive primary surgery or upfront chemotherapy followed by IDS in a patient must be individualized. Since we found the benefit of IDS in the subgroup of patients whose primary surgery had not been performed under the optimum condition by the oncologic surgeons or without maximum surgical effort, we would like to make a comment that IDS may improve patient survival in this setting. However, if the primary surgery has already been performed by the oncologic surgeons or with maximal surgical effort, IDS may not yield any further benefit to survival. Nevertheless, in a situation when there is evidence that primary surgery would be impossible or the morbidity from surgery would outweigh the benefit, induction chemotherapy followed by IDS may have a certain role.

Implications for research

This theoretical advantage of IDS needs further well designed RCTs to generate evidence to resolve the equivocal findings of this review.

These studies should focus on a comparison of current conventional primary surgery with adjuvant chemotherapy versus neoadjuvant chemotherapy (without any attempt to remove the bulk of tumours except a biopsy for histologic diagnosis) followed by IDS and then by further chemotherapy.

The level and expertise of the surgeon or the effort in performing the primary surgery should be standardized as far as possible, in order to obtain the best surgical outcome. The particular subgroup of patients with their specific disease characteristics should be a set criteria for IDS, e.g. patients with only small tumours after induction or neoadjuvant chemotherapy.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Redman 1994

Methods	Study duration: April 1986 to February 1990 Type of trial: Multicentre RCT, intention-to-treat analysis
Participants	Stage II-IV (except unresectable stage IV diseases) Performance status ECOG: at least 2 Histology proven, with exclusion of borderline tumour Primary surgery must be performed through an appropriate incision/ a maximal attempt to remove tumours Residual disease status > 2 cm No evidences of progressive disease, extraperitoneal tumour > 1 cm, or had excessive delay after induction chemotherapy and before randomisation Baseline characteristics: 24 women were under the age of 50, 25 between 50-60 and 30 were over 60 years 50 women had performance status 0 or 1, 20 status 2 and 9 women had status 3 or 4 6 women were diagnosed with FIGO stage IIB, 62 stage III and 11 had stage IV disease 39 women had residual disease between 2-5 cm, 29 between 5-10 cm and 11 more than 10 cm Histology type was as follows: Serous 32, mucinous 6, endometroid 13, clear cell 4, undifferentiated 6 and unspecified 20 Histology differentiation was as follows: Poor 37, moderate 27, well 6 and unspecified 9
Interventions	**Intervention:** **IDS:** after 1-4 cycles of induction chemotherapy composing of IV cisplatin 75 mg/m^2 + cyclophosphamide 750 mg/m^2 or cisplatin 75 mg/m^2 + doxorubicin 50 mg/m^2 + bleomycin 50 mg/m^2 followed by escalated dose of cyclophosphamide (0.5 g/m^2-2.5 g/m^2) up to 5 cycles. Chemotherapy cycles were repeated very 3 weeks. **Control:** **No IDS:** the same regimen of chemotherapy were given in a row every 3 weeks.
Outcomes	Overall survival Perioperative complications: primary haemorrhage, blood transfusion, deep vein thrombosis, intestinal fistula, postoperative febrile morbidity, postoperative ileus
Notes	Randomised at entry (within 4 weeks after primary surgery) Number ineligible: 7 (primary surgery was not sub-optimal) Only 9% of primary surgeons were gynaecologic oncologists IDS performed by the primary surgeon Response evaluation by physical examination, imaging studies (CA125 not used) OS was measured from the date of entry Rate of complications were described only in the IDS group
Risk of bias	

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Redman 1994 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"Randomisation sheets were produced by the random permuted blocks methods utilising the NAG Fortran Library subroutine to generate random numbers"
Allocation concealment?	Yes	"These preprinted sheets were kept at the trial's office and medical personnel were given no access to them"
Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed? All outcomes	Yes	% analysed: 79/86 (92%)
Free of selective reporting?	Unclear	Insufficient information to permit judgement
Free of other bias?	Unclear	Insufficient information to assess whether an important risk of bias exists

Rose 2004

Methods	Study duration: June 1994 to January 2001 Type of trial: Multicentre RCT, intention-to-treat basis
Participants	Stage III-IV (malignant pleural effusion or a resected anterior abdominal wall tumour) (exclusion of stage IV after March 1996 after EORTC reported a greater benefit from secondary surgery after the exclusion of such patients from the analyses) Age < 75 years Performance status ACOG: 0-2 with life expectancy of at least 8 weeks Primary surgery performed within 6 weeks before chemotherapy Primary surgery were aimed to remove as much as possible Histology proven, with central pathologic review Residual disease status > 1 cm Had no delay of chemotherapy treatment > 2 weeks The median age was 58.1 (Range: 25.4-81.6 years) in the IDS group and 57 (Range: 27-81.6 years) in the no IDS group 166 women had GOG performance status 0, 227 had status 1 and 31 women had status 2 400 women were diagnosed with FIGO stage III and 24 had stage IV disease 297 women had measurable disease 53 women had residual disease between 1-2 cm, 183 between 2.1-5 cm, 150 between 5.1-10 cm and 38 more than 10 cm Histology type was as follows: Serous 324, mucinous 3, endometroid 28, clear cell 7, mixed epithelial 37, adenocarcinoma (unspecified) 12 and undifferentiated or other 13

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Rose 2004 (*Continued*)

	Histology grade was as follows: 1: 40, 2: 167, 3 or clear cell: 217
Interventions	**Intervention:** **IDS:** after 3 cycles of chemotherapy composing of IV paclitaxel 135 mg/m^2 + cisplatin 75 mg/m^2 every 3 weeks. Three more cycles of the same chemotherapy regimen were given after IDS **No IDS:** the same regimen of chemotherapy was given in a row every 3 weeks for 6 cycles
Outcomes	Overall survival Progression-free survival Adverse effects: peripheral neuropathy, haematologic effects, gastrointestinal events, pulmonary events, cardiovascular events, and cause of death Quality of life
Notes	Randomised after 3 cycles of chemotherapy Number ineligible: 24 Majority of surgeons for primary and secondary surgery (IDS) were gynaecologic oncologists Response evaluation by physical examination, imaging studies, and CA125 Consolidation chemotherapy were allowed OS and progression-free survival were measured from the date of randomisation and also from the date of enrolment

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed? All outcomes	Yes	% analysed: 424/448 (95%)
Free of selective reporting?	Unclear	Insufficient information to permit judgement
Free of other bias?	Unclear	Insufficient information to assess whether an important risk of bias exists

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Van der Burg 1995

Methods	Study duration: March 1987 to May 1993 Type of trial: Multicentre RCT, intention-to-treat analysis
Participants	Stage IIB-IV Age of patients < 75 years Performance status WHO: 0-2 Primary surgery performed within 6 weeks before induction chemotherapy Histology proven, with central pathologic review Residual disease status > 1 cm Have some response or stable disease after induction chemotherapy without evidences of progressive diseases or had contraindication to surgery The median age in the trial was 59 years in both groups (Range: 32-74) 68 women had performance status 0, 99 status 2 and 33 women had status 2 10 women were diagnosed with FIGO stage IIB, 146 stage III and 44 had stage IV disease 10 women had residual disease between 1-2 cm, 45 between 2-5 cm, 44 between 5-10cm, 60 more than 10 cm and unknown but > 2 cm: 41 Histology type was as follows: Serous 115, mucinous 12, endometroid 17, clear cell 5, and unclassified 51 Histology grade was as follows: 1: 17, 2: 59, 3: 105 and unknown: 9
Interventions	**Intervention:** **IDS:** after 3 cycles of induction chemotherapy composing of IV cyclophosphamide 750 mg/m^2 + IV cisplatin 75 mg/m^2 every 3 weeks. Three more cycles of the same chemotherapy regimen were given after IDS **No IDS:** the same regimen of chemotherapy was given in a row every 3 weeks for 6 cycles
Outcomes	Overall survival Progression-free survival Perioperative complications: bowel injury, urinary bladder injury, blood loss, postoperative fever, ileus, urinary tract infection, wound infection, deep vein thrombosis, lung embolism Clinical response rate after 6 cycles of chemotherapy
Notes	Randomized after 3 cycles of induction chemotherapy at Central EORTC data centre, after stratification with a minimization technique to account for institution, performance status, and clinical response Number ineligible: 4 Response evaluation by WHO response criteria Consolidation chemotherapy after 6 cycles was allowed based on institutions policy Survivals were measured from the first date of chemotherapy (after enrolment) Rate of complications were detailed only in the IDS group

Risk of bias

Item	Authors' judgement	Description

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Van der Burg 1995 (*Continued*)

Adequate sequence generation?	Yes	"Randomization was done ... after stratification with a minimization technique to account for institution, performance status, and clinical response"
Allocation concealment?	Yes	"Randomization was done centrally at the EORTC Data Center"
Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed? All outcomes	Yes	% analysed: 278/319 (87%)
Free of selective reporting?	Unclear	Insufficient information to permit judgement
Free of other bias?	Unclear	Insufficient information to assess whether an important risk of bias exists

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

Study	Reason for exclusion
Angioli 2006	This study was evaluated as non-comparable controlled clinical trial. Neoadjuvant chemotherapy followed by IDS was selectively given to the patients based on initial laparoscopic findings of inoperability.
Chan 2003	This study was evaluated as uncontrolled clinical trial. Neoadjuvant chemotherapy was given to the studied patients without control group. The patients were selected by their inoperability based on CT scan without primary operation being attempted. Either histology or only cytology was allowed for a pathologic diagnosis of ovarian cancer.
Dutta 2005	This was an RCT of ovarian cancer patients to have either 3 cycles of NAC followed by IDS and further chemotherapy versus 6 cycles of NAC before surgery. Main objective was to study proapoptotic and antiapoptotic proteins in ovarian cancer tissue without survival outcome evaluation.
EORTC 55971	This study did not focus on IDS, but on NAC versus primary surgery. IDS was primarily allowed in the primary surgery arm too (upon the discretion of the physician).
Evdokimova 1982	This was an RCT comparing survival of patients with ovarian carcinoma patients who had NAC/IDS versus conventional treatment of surgery then chemotherapy. However, patients without ascites were selected to have primary surgery followed by chemotherapy while those with ascites had either NAC/IDS or conventional treatment.

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(*Continued*)

Fuso 2006	This uncontrolled prospective study was to assess the feasibility of triple chemotherapy composing of gemcitabine, carboplatin, and paclitaxel as first line drug in advanced ovarian cancer. The patients were selectively assigned to have 2 different types of treatment. After laparoscopic biopsy in all patients, those who were judged to be operable underwent primary surgery followed by chemotherapy while the inoperable patients were given NAC followed by IDS. However, few patients who had primary surgery also had IDS.
Giannopoulos 2006	This study was evaluated as a non-comparable controlled clinical trial. Neoadjuvant chemotherapy and IDS was selectively given to the patients who were determined to be inoperable based on CT scan and initial laparoscopic findings. Either histology or cytology was allowed for a pathologic diagnosis of ovarian cancer.
Ikeba 2004	This study was evaluated as an uncontrolled clinical trial. Neoadjuvant chemotherapy were given to the studied patients without control group.
Kuhn 2001	This study was evaluated as a non-comparable controlled clinical trial. Neoadjuvant chemotherapy was selectively given to the patients who had poor general health for primary surgery. Patients in the control group were those who did not agree to the study protocol or were incompatible with the trial because of psychological reasons.
Kumar 2007	This was an RCT presented as a conference abstract. The patients were randomised to have upfront debulking surgery followed by chemotherapy versus having NAC followed by IDS and further chemotherapy. No randomisation details were provided. Either histology or cytology was allowed for a pathologic diagnosis of ovarian cancer.
Lee 2006	This study was evaluated as a non-comparable controlled clinical trial. Neoadjuvant chemotherapy was selectively given to the patients who agreed to undergo the NAC treatment protocol. NAC cycles ranged from 3 cycles to 6 cycles. Some patients had secondary surgery which was not in an interval setting.
Liu 2004	This RCT was considered as ineligible because NAC was given only for 1 cycle via intra-arterial route before the IDS.
Park-Simon 2006	This RCT compared survivals of ovarian cancer patients who had ascites > 500 cc who were given NAC for either 2 versus 3 cycles, however, followed by IDS in both arms.
Recchia 2001	This study was evaluated as an uncontrolled clinical trial. Neoadjuvant chemotherapy was given to the studied patients without control group. Either histology or only cytology was allowed for a pathologic diagnosis of ovarian cancer.
Solomon 1988	This study was presented in conjunction with the prior RCT comparing combination versus sequential chlorambucil and cisplatin. IDS in this study was selectively performed only in the subset of patients who had not been debulked at primary surgery. Second-look surgery or surgical re-exploration were also performed in those with clinical complete remission or in those with complications requiring surgery, respectively.

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Characteristics of studies awaiting assessment *[ordered by study ID]*

JCOG 0206

Methods	
Participants	56 patients with stage III/IV mullerian carcinomas such as ovarian, tubal and peritoneal carcinomas Diagnosed by pre-laparoscopic clinical findings including imaging studies (CT, MRI or ultrasonography) and cytology of ascites, pleural effusions or fluids obtained by tumour centesis Malignancies of other origins, such as breast and digestive tract, should be excluded by endoscopy, opaque enema or ultrasonography (if suspected from symptoms, physical examination or imagings) To rule out malignancy of digestive tract , CA125 must be > 200 U/ml and CEA must be < 20 ng/ml
Interventions	- Diagnostic laparoscopy to confirm diagnosis, histology and stage - Biopsy from the main tumour or metastatic tumours - Resection of any organs or tumours attempting to reduce tumour volume not allowed. - Neoadjuvant chemotherapy (NAC) as paclitaxel (175 mg/m^2, day 1) and carboplatin (AUC = 6, day 1) for 4 cycles. - Interval cytoreductive surgery performed after the 4th cycle of NAC (unless PD) - An additional 4 cycles of the same chemotherapy regimen after surgery
Outcomes	Primary endpoint: clinical complete remission after protocol completion Secondary endpoints regarding NAC: response rate to NAC among patients whose clinical diagnosis is confirmed by laparoscopy proportion of patients who received ICS among patients whose clinical diagnosis is confirmed by laparoscopy Overall survival Progression-free survival Operative morbidity Adverse events
Notes	Plan for subsequent phase III study, comparing NAC therapy with current standard procedure

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DATA AND ANALYSES

Comparison 1. IDS vs chemotherapy only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	3	781	Hazard Ratio (Random, 95% CI)	0.80 [0.61, 1.06]
1.1 General Surgeons or less extensive primary surgery	2	357	Hazard Ratio (Random, 95% CI)	0.68 [0.53, 0.87]
1.2 Gynaecologic oncologists	1	424	Hazard Ratio (Random, 95% CI)	0.99 [0.79, 1.24]
2 Progression-free survival	2	702	Hazard Ratio (Random, 95% CI)	0.88 [0.57, 1.33]
3 Toxic reactions to chemotherapy	2	357	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.53, 2.66]
4 Peripheral neuropathy of grade 2 or higher	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5 Grade 3 or 4 gastrointestinal adverse events	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
6 Grade 4 pulmonary adverse events	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
7 Grade 4 cardiovascular adverse events	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

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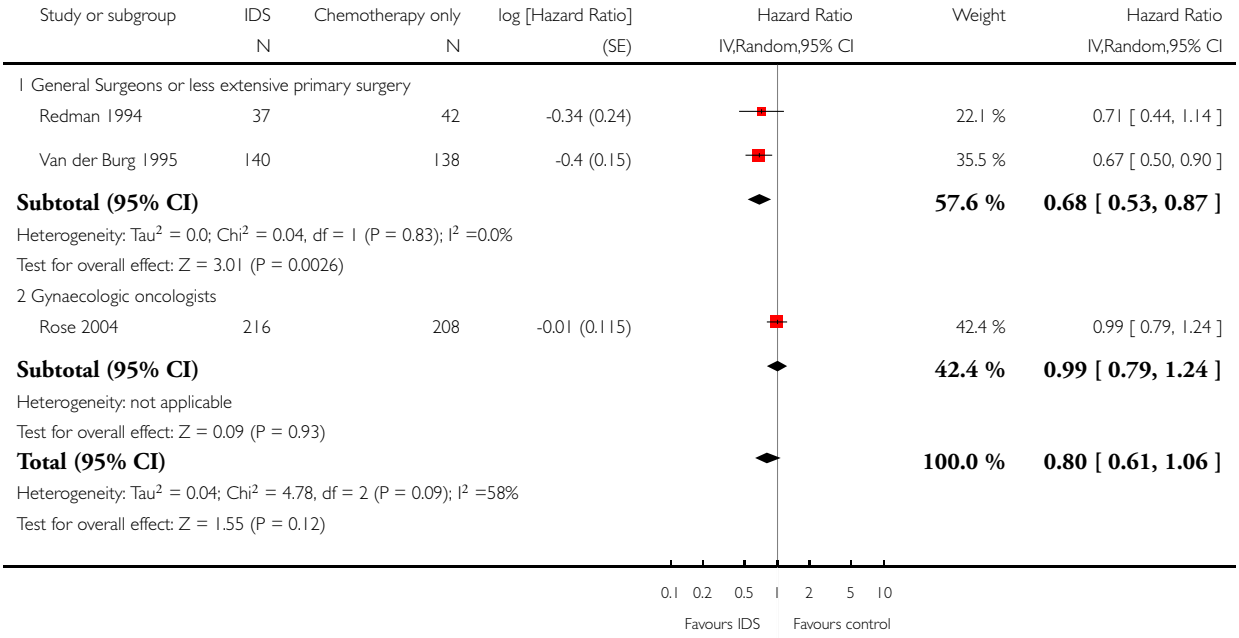
Analysis 1.1. Comparison 1 IDS vs chemotherapy only, Outcome 1 Overall survival.

Review: Interval debulking surgery for advanced epithelial ovarian cancer

Comparison: 1 IDS vs chemotherapy only

Outcome: 1 Overall survival

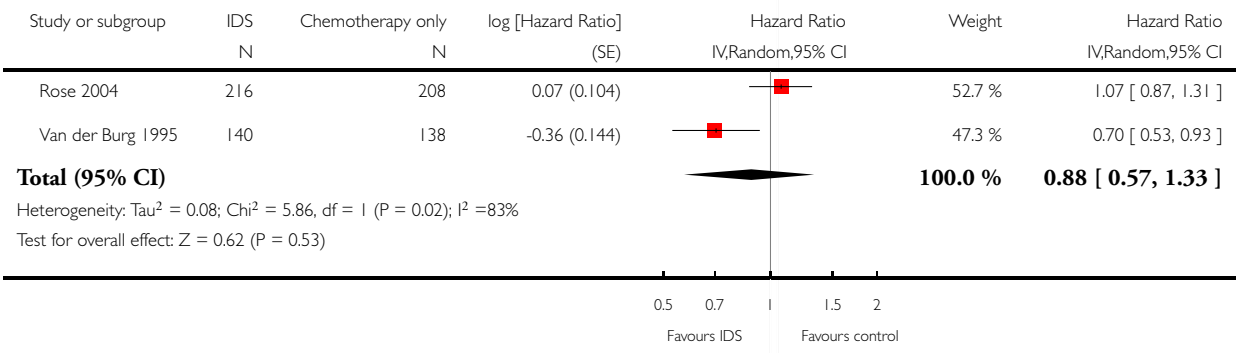


Analysis 1.2. Comparison 1 IDS vs chemotherapy only, Outcome 2 Progression-free survival.

Review: Interval debulking surgery for advanced epithelial ovarian cancer

Comparison: 1 IDS vs chemotherapy only

Outcome: 2 Progression-free survival



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Analysis 1.3. Comparison 1 IDS vs chemotherapy only, Outcome 3 Toxic reactions to chemotherapy.

Review: Interval debulking surgery for advanced epithelial ovarian cancer

Comparison: 1 IDS vs chemotherapy only

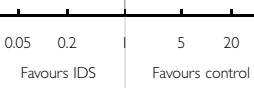
Outcome: 3 Toxic reactions to chemotherapy

Study or subgroup	IDS n/N	Chemotherapy only n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Redman 1994	7/37	7/42		68.5 %	1.14 [0.44, 2.93]
Van der Burg 1995	4/140	3/138		31.5 %	1.31 [0.30, 5.76]
Total (95% CI)	**177**	**180**		**100.0 %**	**1.19 [0.53, 2.66]**

Total events: 11 (IDS), 10 (Chemotherapy only)

Heterogeneity: $Chi^2 = 0.03$, df = 1 (P = 0.87); $I^2 = 0.0\%$

Test for overall effect: Z = 0.43 (P = 0.67)



Analysis 1.4. Comparison 1 IDS vs chemotherapy only, Outcome 4 Peripheral neuropathy of grade 2 or higher.

Review: Interval debulking surgery for advanced epithelial ovarian cancer

Comparison: 1 IDS vs chemotherapy only

Outcome: 4 Peripheral neuropathy of grade 2 or higher

Study or subgroup	IDS n/N	Chemotherapy only n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
Rose 2004	35/216	54/208		0.62 [0.43, 0.91]

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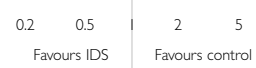
Analysis 1.5. Comparison 1 IDS vs chemotherapy only, Outcome 5 Grade 3 or 4 gastrointestinal adverse events.

Review: Interval debulking surgery for advanced epithelial ovarian cancer

Comparison: 1 IDS vs chemotherapy only

Outcome: 5 Grade 3 or 4 gastrointestinal adverse events

Study or subgroup	IDS n/N	Chemotherapy only n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
Rose 2004	15/216	8/208		1.81 [0.78, 4.17]



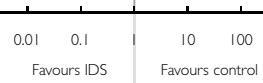
Analysis 1.6. Comparison 1 IDS vs chemotherapy only, Outcome 6 Grade 4 pulmonary adverse events.

Review: Interval debulking surgery for advanced epithelial ovarian cancer

Comparison: 1 IDS vs chemotherapy only

Outcome: 6 Grade 4 pulmonary adverse events

Study or subgroup	IDS n/N	Chemotherapy only n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
Rose 2004	2/216	0/208		4.82 [0.23, 99.71]



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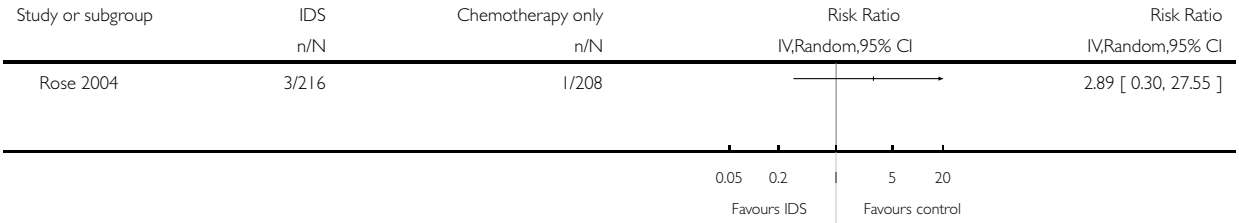
Analysis 1.7. Comparison 1 IDS vs chemotherapy only, Outcome 7 Grade 4 cardiovascular adverse events.

Review: Interval debulking surgery for advanced epithelial ovarian cancer

Comparison: 1 IDS vs chemotherapy only

Outcome: 7 Grade 4 cardiovascular adverse events



APPENDICES

Appendix 1. MEDLINE Ovid

1 exp Ovarian Neoplasms/
2 (ovar* adj5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).mp.
3 1 or 2
4 exp Surgical Procedures, Operative/
5 surg*.mp.
6 surgery.fs.
7 4 or 5 or 6
8 (interval or debulk* or cytoreduc* or secondary).mp.
9 3 and 7 and 8
10 randomized controlled trial.pt.
11 controlled clinical trial.pt.
12 randomized.ab.
13 randomly.ab.
14 trial.ab.
15 groups.ab.
16 10 or 11 or 12 or 13 or 14 or 15
17 9 and 16
18 limit 17 to yr="2008 - 2009"
19 (animals not (humans and animals)).sh.
20 18 not 19
key:
mp = title, original title, abstract, name of substance word, subject heading word
fs = floating subheading
pt = publication type
ab = abstract
sh = subject heading

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Appendix 2. EMBASE

1 exp ovary tumor/
2 (ovar* adj5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).mp.
3 1 or 2
4 exp surgery/
5 surg*.mp.
6 su.fs.
7 4 or 5 or 6
8 (interval or debulk* or cytoreduc* or secondary).mp.
9 7 and 8
10 exp cytoreductive surgery/
11 9 or 10
12 3 and 11
13 exp controlled clinical trial/
14 randomized.ab.
15 randomly.ab.
16 trial.ab.
17 groups.ab.
18 13 or 14 or 15 or 16 or 17
19 12 and 18
20 limit 19 to yr="2008 - 2009"
21 exp animal/
22 human/
23 21 not (21 and 22)
24 20 not 23
key:
mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name
fs = floating subheading
ab = abstract

Appendix 3. CENTRAL

#1 MeSH descriptor Ovarian Neoplasms explode all trees
#2 ovar* near/5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)
#3 (#1 OR #2)
#4 MeSH descriptor Surgical Procedures, Operative explode all trees
#5 surg*
#6 Any MeSH descriptor with qualifier: SU
#7 (#4 OR #5 OR #6)
#8 interval or debulk* or cytoreduc* or secondary
#9 (#3 AND #7 AND #8)
#10 (#9), from 2008 to 2009

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Appendix 4. Cochrane Gynaecological Cancer Review Group's Specialised Register

#8=OVY AND #11=SU AND #11= CT AND (#4=ADVANCED OR #4=RECURRENT OR #4=REFRACTORY OR #43=ADVANCED OR #43=RECURRENT OR #43=REFRACTORY)

WHAT'S NEW

Last assessed as up-to-date: 18 August 2010.

Date	Event	Description
19 August 2010	New citation required but conclusions have not changed	Searches re-run in July 2009. Seventeen possible relevant articles were identified. Only two RCTs were found; one RCT of a Japanese study and the EORTC 55971 trial. However, the Japanese study referred to a study that was excluded in our primary review and EORTC 55971 trial allowed IDS in both arms at discretion of physician.

HISTORY

Protocol first published: Issue 2, 2006

Review first published: Issue 4, 2008

Date	Event	Description
10 February 2009	Feedback has been incorporated	Feedback regarding new trial incorporated.
10 November 2008	New citation required but conclusions have not changed	Errors in reporting HR and RR corrected. Explanation regarding surgical expertise included.
20 March 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

ST and SM: protocol development, search for and determine the relevance of trials for the review, assess their methodological quality, extract data, and review development. ML: protocol development, data analysis, and review development. PL: protocol development, provide methodological advice throughout the review, arbitrate over any disagreements, advise over the content and presentation of the review. AB: methodological and statistical support.

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DECLARATIONS OF INTEREST

There is no conflict of interest amongst the authors of this review.

SOURCES OF SUPPORT

Internal sources

- Bangkok Metropolitan Administration Medical College and Vajira Hospital, Thailand.
- Faculty of Medicine, Khon Kaen University, Thailand.
- Faculty of Public Health, Khon Kaen University, Thailand.

External sources

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None of the trials reported continuous outcomes such as quality of life or had multiple treatment groups. We had originally specified the following in various sections of the protocol.

- For continuous outcomes (e.g. QoL measures), we will extract the final value and standard deviation of the outcome of interest and the number of patients assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference (if trials measured outcomes on the same scale) or standardised mean differences (if trials measured outcomes on different scales) between treatment arms and its standard error.

- For continuous outcomes, we will use the mean difference between treatment arms.

- For continuous outcomes, the mean differences between the treatment arms at the end of follow-up will be pooled if all trials measured the outcome on the same scale, otherwise standardised mean differences were pooled.

- If any trials had multiple treatment groups, the 'shared' comparison group will be divided into the number of treatment groups and comparisons between each treatment group and the split comparison group will be treated as independent comparisons.

- Where possible, indirect comparisons, using the methods of Bucher 1997 will be used to compare competing interventions that have not been compared directly with each other.

We had planned to compute funnel plots but this was not possible due to an insufficient number of included trials in the review. The protocol stated the following:

Funnel plots corresponding to meta-analysis of the primary outcome will be examined for evidence of small study effects. If such evidence exists, publication bias and other possible explanations will be considered. If funnel plots suggest that treatment effects may not be sampled from a symmetric distribution, as assumed by the random-effects model, sensitivity analyses will be performed using fixed-effect models.

We planned to perform sensitivity analyses to evaluate whether the pooled effect sizes were robust across components of methodological quality. However, only one trial reported adequate concealment of allocation (Redman 1994) and other components of quality were similar across studies, so these sensitivity analyses were not performed.

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INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [therapeutic use]; Chemotherapy, Adjuvant; Ovarian Neoplasms [drug therapy; mortality; pathology; *surgery]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans

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Meditation therapies for attention-deficit/hyperactivity disorder (ADHD) (Review)

Krisanaprakornkit T, Ngamjarus C, Witoonchart C, Piyavhatkul N

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 6

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TABLE OF CONTENTS

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[Intervention Review]

Meditation therapies for attention-deficit/hyperactivity disorder (ADHD)

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ABSTRACT

Background

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common developmental disorders experienced in childhood and can persist into adulthood. The disorder has early onset and is characterized by a combination of overactive, poorly modulated behavior with marked inattention. In the long term it can impair academic performance, vocational success and social-emotional development. Meditation is increasingly used for psychological conditions and could be used as a tool for attentional training in the ADHD population.

Objectives

To assess the effectiveness of meditation therapies as a treatment for ADHD.

Search strategy

Our extensive search included: CENTRAL, MEDLINE, EMBASE, CINAHL, ERIC, PsycINFO, C2-SPECTR, dissertation abstracts, LILACS, Virtual Health Library (VHL) in BIREME, Complementary and Alternative Medicine specific databases, HSTAT, Informit, JST, Thai Psychiatric databases and ISI Proceedings, plus grey literature and trial registries from inception to January 2010.

Selection criteria

Randomized controlled trials that investigated the efficacy of meditation therapy in children or adults diagnosed with ADHD.

Data collection and analysis

Two authors extracted data independently using a pre-designed data extraction form. We contacted study authors for additional information required. We analyzed data using mean difference (MD) to calculate the treatment effect. The results are presented in tables, figures and narrative form.

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Main results

Four studies, including 83 participants, are included in this review. Two studies used mantra meditation while the other two used yoga compared with drugs, relaxation training, non-specific exercises and standard treatment control. Design limitations caused high risk of bias across the studies. Only one out of four studies provided data appropriate for analysis. For this study there was no statistically significant difference between the meditation therapy group and the drug therapy group on the teacher rating ADHD scale (MD -2.72, 95% CI -8.49 to 3.05, 15 patients). Likewise, there was no statistically significant difference between the meditation therapy group and the standard therapy group on the teacher rating ADHD scale (MD -0.52, 95% CI -5.88 to 4.84, 17 patients). There was also no statistically significant difference between the meditation therapy group and the standard therapy group in the distraction test (MD -8.34, 95% CI -107.05 to 90.37, 17 patients).

Authors' conclusions

As a result of the limited number of included studies, the small sample sizes and the high risk of bias, we are unable to draw any conclusions regarding the effectiveness of meditation therapy for ADHD. The adverse effects of meditation have not been reported. More trials are needed.

PLAIN LANGUAGE SUMMARY

Meditation therapies for attention-deficit/hyperactivity disorder (ADHD)

Attention-deficit/hyperactivity disorder (ADHD) is a disorder that affects a significant number of children and adults in a variety of ways. It is characterized by chronic levels of inattention, impulsiveness and hyperactivity. Meditation therapy could be a beneficial treatment for those diagnosed with ADHD. The objective of this review was to assess the efficacy of this treatment. As a result of the small number of studies that we were able to include in this review and the limitations of those studies, we were unable to draw any conclusions regarding the effectiveness of meditation therapy for ADHD. No adverse effects of meditation in children have been reported. More trials are needed on meditation therapies for ADHD so that conclusions can be drawn regarding its effectiveness.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Meditation therapy versus drug therapy for attention deficit /hyperactivity disorder

Patient or population: patients with attention deficit /hyperactivity disorder
Settings:
Intervention: meditation therapy versus drug therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	meditation therapy versus drug therapy				
Teacher rating ADHD overall scale The Abbreviated Parent-Teacher Questionnaire (Conners, 1973) Follow-up: mean 4 weeks	The mean teacher rating adhd overall scale in the control groups was **14.83**	The mean Teacher rating ADHD overall scale in the intervention groups was **2.72 lower** (8.49 lower to 3.05 higher)		15 (1 study[4])	⊕◯◯◯ **very low**[1,2,3]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Unclear randomization method, unclear allocation concealment, no blinding, unclear attrition rate, other biases presented
[2] Wide confidence interval, small sample size
[3] Only one study(since 1987) presented for this outcome
[4] Study Moretti-Altuna, 1987

BACKGROUND

Description of the condition

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common developmental problems experienced in childhood and can persist into adulthood. The major symptoms are inconsistent development and chronic levels of inattention, impulsiveness and hyperactivity (Scahill 2000).

Prevalence estimates vary according to the diagnostic criteria used and the population sampled. These estimates can be further affected by influences on the diagnosis, such as the cultural environment and the differing attitudes of parents, clinicians and society towards acceptable children's behavior (Dwivedi 2005). According to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) (APA 2000), prevalence estimates among school children in the US are between 3% and 7% (APA 2000), but other estimates range from 1.7% to 16.0% (Pritchard 2005). Boys are diagnosed with ADHD three times more often than girls. Evidence attests to the strong influence of genetic factors on the expression of symptoms, however psychosocial, environmental and cultural factors also play a role (Swanson 2001).

An independent diagnostic test for ADHD does not exist, thus the diagnosis of ADHD is clinically based. The essential criteria for a diagnosis of ADHD are a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequently displayed and more severe than is typically observed in individuals at a comparable level of development, and is not better explained by the presence of another mental disorder. Symptoms evolve over time. In adolescence, signs of excessive gross motor activity (e.g. excessive running and climbing, not remaining seated) are less common, and hyperactivity symptoms may be confined to fidgeting or an inner feeling of jitteriness or restlessness. In adulthood, restlessness may lead to difficulty in participating in sedentary activities and to avoiding pastimes or occupations that provide limited opportunity for spontaneous movement (e.g. desk jobs) (APA 2000). Other adults may retain only some of the symptoms, in which case the diagnosis should be ADHD in partial remission.

In order to qualify for a diagnosis of ADHD, hyperactive-impulsive or inattentive symptoms must have presented before the age of seven, with some impairment from the symptoms present in at least two settings (e.g. at home and at school). There must be clear evidence of interference with developmentally appropriate social, academic or occupational functioning. Care must be taken to ensure that the disturbance does not occur exclusively during the course of a pervasive developmental disorder, schizophrenia or other psychotic disorder and is not better accounted for by another mental disorder (APA 2000).

The DSM-IV-TR provides subtypes for specifying the predominant symptom presentation: predominantly inattentive type, predominantly hyperactive/impulsive type and combined type. In the International Classification of Diseases (ICD-10) (WHO 1992) the disorders are defined under the category of 'Hyperkinetic Disorders' and are characterized by early onset, a combination of overactive, poorly modulated behavior with marked inattention and lack of persistent task involvement, pervasiveness across situations and persistence over time (WHO 1992).

Children with ADHD have pronounced impairments and can experience enduring adverse effects in their academic performance, vocational success and social-emotional development. These impairments, in turn, can have a profound impact on individuals, families, schools and society (NIH 1998). Moreover, studies indicate that children diagnosed as having ADHD and a comorbid anxiety or depressive disorder have higher levels of coexisting life stresses and parental symptoms than children who have the single diagnosis of ADHD (Jensen 1993).

Description of the intervention

Non-pharmacological treatment of ADHD in childhood can be divided into three categories: parent- or family-focused strategies, child-directed interventions and school-based interventions (ICSI 2005). Psychostimulant medications are considered first-line therapy as they are effective in 70% to 80% of children with ADHD, although their use may be limited both by tolerability and acceptability (AAP 2001). Augmentation of psychostimulant treatment with psychosocial interventions provides no advantage over medication alone for the core symptoms of ADHD, but appears to have an advantage for associated problems such as anxiety disorders, social skills difficulties, consumer satisfaction and possibly academic achievement (MTA 1999).

Due to an increase in scientific evidence, clinical experience and community attitudes are encouraging a shift towards more natural and holistic forms of therapy as alternatives or adjuncts to pharmacological approaches in a variety of conditions (Arias 2006; Krisanaprakornkit 2006; Mansky 2006).

Meditation is becoming increasingly popular as a treatment for psychological conditions and has a wide range of applications. A psychologically-oriented definition states that "meditation is a set of attentional practices leading to an altered state or trait of consciousness characterized by expanded awareness, greater presence, and a more integrated sense of self" (Davis 1998), which suggests that meditation might be a useful tool for attentional training in the ADHD population. In addition to increased attention, meditation may produce a state of calmness and contentment which is generally lacking in the ADHD population (Jensen 2004). Adequately trained practitioners who have first-hand experience can easily adapt meditation to the general medical setting (Hassed 1996).

Meditation originated in India more than three thousand years ago and has played a prominent role in the ritual practice of major religions and secular organizations alike. Meditation can be divided into two general types: concentrative meditation and mindfulness meditation (Barrows 2002).

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Concentrative meditation is best represented in modern medicine by two programs: Transcendental Meditation® (TM®) which was introduced to the West during 1960s and the 'Relaxation Response' developed subsequently by Benson (Benson 1975). Concentrative meditation involves focusing attention on an object and sustaining attention until the mind achieves stillness. A diverse range of items could be chosen as the focal object, for example words, light, colors, geometric forms, ideas etc. Continuous practice should result in relaxation, clarity of mind and calmness.

Mindfulness meditation emphasizes an open awareness to any contents of the mind that are emerging. After a period of practice the patient should develop a sustainable attentive observational capability, without reacting to their own thoughts and emotions. Achieving this state of mindfulness and equanimity helps to retrain or decondition previous patterns of reaction which are usually poorly adapted to external reality. This form of meditation is commonly represented by mindfulness-based stress reduction programs (Kabat-Zinn 1992). The techniques of mindfulness meditation, with their emphasis on developing detached observation and awareness of the contents of consciousness, may represent a powerful cognitive behavioral coping strategy for transforming the ways in which we respond to life events (Astin 1997).

Meditation, either concentrative or mindfulness, is able to enhance the attentional ability of the practitioners. Whilst concentrative meditation emphasizes sustained attention, mindfulness meditation aims to improve self-control and inhibitions to various internal and external stimuli, thereby helping to relieve the core symptoms of ADHD. However, any single meditation program will usually use both concentrative and mindfulness together.

Recently, five broad categories of meditation practices were identified by a group of experts using modified Delphi methodology (Ospina 2007).

- Mantra meditation (comprising the Transcendental Meditation® technique (TM®), Relaxation Response (RR) and Clinically Standardized Meditation (CSM)).
- Mindfulness meditation (comprising Vipassana, Zen Buddhist meditation, Mindfulness-based Stress Reduction (MBSR) and Mindfulness-based Cognitive Therapy (MBCT)).
- Yoga (various yogic meditative techniques).
- Tai Chi (encompassing Chinese traditional exercises that promote posture, flexibility, relaxation, well-being and mental concentration).
- Qi Gong (a category of 'energy healing', including Reiki, therapeutic touch and the Korean practice of Chundosunbup).

However, in this review we adhere to the old classification since it is generally well accepted and commonly used in the literature, although both classifications substantially overlap.

Thus, the operational definitions of meditation are the specific techniques of mind training which have two fundamental attentional strategies (Barrows 2002).

1. Concentrative meditation entails sustained attention directed towards a single object or point of focus. The aim is one-pointed attention to a single perception without distraction in order to produce concentration or a one-minded state.
2. Mindfulness meditation (opening-up, insight meditation) involves the continual maintenance of a specific perceptual-cognitive mind set towards objects as they spontaneously arise in ones awareness with a non-reactive attitude. The salient features are full awareness or mindfulness of any contents of consciousness with equanimity.

There are many methods which represent meditation in the above definitions, i.e. insight meditation, mindfulness-based meditation, Vipassana, Qiqong therapy, yoga (Asana, Pranayama, Raja yoga, Asthanga yoga, Laya yoga, Sahaj Marg etc), Tai Chi, Transcendental Meditation, Kundalini yoga, Anapanasathi (Buddhist breathing meditation), Zen and ChunDoSupBup. It is noted that Asana yoga (yoga of posture) and Tai Chi are also considered to be dynamic aspects of concentrative meditation.

Although historically meditation is associated with religious or spiritual movements, this is no longer always the case. It is now necessary to confirm the effectiveness of these meditation techniques by using non-cult, faith-free and specifically designed methods to treat patients. Nowadays there are increasing numbers of organizations which use scientific-based, less mystical terms to identify their techniques (Krisanaprakornkit 2006).

How the intervention might work

Some reports exist which detail the usefulness of meditation for children with ADHD. Grosswald (reported in Micucci 2005) conducted a study in April 2004 at Chelsea School in Silver Spring, Maryland, a private school for children with learning disabilities. The study compared ten students with ADHD before and after they learned and practiced Transcendental Meditation for ten minutes twice daily for three months. Participants reported being calmer, less distracted, less stressed and better able to control their anger and frustration. However, there was no control/comparison group in this study.

Preliminary bibliographic searching has not identified many studies using meditation therapy for ADHD. Jensen et al conducted a randomized controlled trial of the effect of yoga on boys with ADHD (n = 11) (Jensen 2004). This program consisted of respiratory training, postural training, relaxation training and concentration training and involved a technique called Trataka where participants focused on a word or shape, followed by seeing the image with their eyes closed and continuing to see the image on a blank piece of paper. The results only slightly supported the use of yoga for ADHD and there were some limitations of this study, such as low statistical power and inconsistency of home practices.

Hassasiri et al (Hassasiri 2002) developed a meditation program for children with ADHD in Thailand based on neo-humanist concepts which comprised meditation and imagery. The program was

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tested in a before-after design and found a statistically significant difference in change scores (P < 0.05).

In terms of adverse effects, reports exist suggesting that meditation can cause temporary depersonalization and derealization (Castillo 1990), and there are several reports of a possible association between meditation and psychotic state (Chan-Ob 1999; French 1975; Lazarus 1976; Walsh 1979). Studies of meditation in pediatric populations are still limited. It is not considered advisable for children to sit for extended lengths of time with closed eyes, which might in any case 'go against the grain' of the active nature of children. Different meditation techniques have different recommended practices for children, e.g. Sahaj Marg Meditation, a system of Raja yoga, recommends a minimum age of 18 before beginning the practice of meditation, implying that this technique is not suitable for younger people. In Transcendental Meditation, it is recommended that children of five years old meditate twice a day for five minutes at a time and thereafter add one minute for each year of their age until reaching 20-minute sessions when aged 20 and above. Reports of adverse effects of meditation in children are lacking.

Why it is important to do this review

To our knowledge no systematic review has been carried out specifically considering the effectiveness of meditation for ADHD, although several clinical trials have been conducted. This review aims to address that evidence gap.

OBJECTIVES

To assess the effects of concentrative and mindfulness meditation therapies for treating attention-deficit/hyperactivity disorders (ADHD) in children, adolescents and adults.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials comparing meditation therapy alone or in combination with conventional treatment (consisting of drugs or any other psychological interventions) to i) conventional treatment or ii) no intervention/waiting list control.

We excluded studies where meditation therapy was not a well-organized program (i.e. no structure, no schedule of practice, no formal setting).

Types of participants

Participants of any age diagnosed with attention-deficit/hyperactivity disorder (ADHD) or hyperkinetic disorders (HKD) according to established diagnostic criteria.

Types of interventions

Meditation therapy, consisting of concentrative meditation, mindfulness meditation or a combination of both, provided as the main intervention in the case of multi-component therapy.

Comparison conditions could be one or a combination of the following:

1. pharmacological therapy;
2. no intervention or waiting list;
3. other psychological treatment: cognitive behavioral therapy, parent training program, counseling etc.

Types of outcome measures

Primary outcomes

A. Symptoms of ADHD

Incidence/severity of the core symptoms (inattention, impulsivity, hyperactivity) measured by a validated symptoms rating scale ;

- The revised Conners' Parent Rating Scale (CPRS-R) (Conners 1997; Conners 1998).
- Conners' Teacher Rating Scale (CTRS-R) (Conners 1998/2).
- ADHD Rating Scale IV (Zhang 2005).
- Attention-Deficit Disorder Evaluation Scale (ADDES) (Adesman 1991).
- Conners' Continuous Performance Test (Conners 1995).
- Yale Children's Inventory (Shaywitz 1988).
- The ADD/H Adolescent Self-Report Scale (Robin 1996).
- The Internal Restlessness Scale (Weyandt 2003).

B. Quantitative laboratory assessment measures of ADHD symptoms

1. Psychological test

- Continuous Performance Test (CPT).
- The Gordon Diagnostic System (GDS).
- The Children's Checking Task (CCT).
- Test of Variable of Attention (TOVA) (Greenberg 1999).
- Delay of Gratification Tasks.
- The Choice-Delay Task (C-DT).
- The Stop Signal Task (SST) (Nichols 2004).
- The Auditory Continuous Performance Test (Riccio 1996).

2. Psychophysiological measures

- Electroencephalography (EEG).

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- Actograph pedometer which uses devices to monitor a child's movements and displays these as an actograph which provides an objective indicator of general motor activity.

C. Overall incidence/severity of the problem behaviors

- Child Behavior Checklist (CBCL) (Achenbach 2000).
- The Adolescent Behavior Checklist (Adams 1997).
- Children's Aggression Scale - Parent Version (Halperin 2002).
- Children's Aggression Scale - Teacher Version (Halperin 2003).
- Swanson Kotkin Atkins M-Flynn Pelham Scale (SKAMP) (Wigal 1998).
- Behavior Assessment System for Children (BASC) (Reynolds 1992).

Secondary outcomes

A. Intelligence

Standardized measures, including these intelligence scales.

- Wechsler Intelligence Scale for Children-III (Wechsler 1991).
- Stanford-Binet Intelligence Scales (Becker 2003).
- Tower of London Test (Shallice 1988).

B. School/academic performance

Measured by scale, grades or teacher reports, including:

- Wechsler Individual Achievement Test (WIAT) (Wechsler 1992);
- The Peabody Individual Achievement Test (Klinge 1974).

C. Psychopathology outcomes

Depression/anxiety-related outcome including:

- The Diagnostic Inventory for Depression (Zimmerman 2004);
- Multidimensional Anxiety Scale for Children (MASC) (March 1997).

Conduct/oppositional disorder outcomes, including:

- The Oppositional Defiant Behavior Inventory (Harada 2004).

D. Family and social outcomes

- Parenting Stress Index (Loyd 1985).
- Parenting Scale for Parents of Children with ADHD (Harvey 2001).
- Social Adjustment Inventory for Children and Adolescents (SAICA) (Biederman 1993).

E. Quality of life scales

- The ADHD Impact Module (Landgraf 2002).
- Adult Attention-Deficit/Hyperactivity Disorder Quality-of-Life Scale (AAQoL) (Brod 2006).
- Clinical Global Impression score changes (NIMH 1985).
- Children's Global Assessment Scale (CGAS) (Shaffer 1983).

F. Any adverse effects of meditation reported in the trials

Search methods for identification of studies

To determine whether meditation is the main intervention in multi-component therapy, the authors of the studies must specify meditation or related words in the title or keywords of the articles. Operational definitions of meditation are mentioned in the background section.

The following searches were conducted without language restriction.

Electronic searches

We searched the following electronic databases with the help of the Trials Search Co-ordinator of the Cochrane Developmental, Psychosocial and Learning Problems Group (CDPLPG).

- Cochrane Central Register of Controlled Trials (CENTRAL) (2010, Issue 1);
- MEDLINE (from 1966 to Jan 2010);
- OLDMEDLINE (pre 1966);
- EMBASE from 1980 to 2010 week 5;
- CINAHL from 1982 to Jan 2010;
- the Campbell Collaboration SPECTR (C2-SPECTR) database to Jan 2010;
- Educational Resources Information Center (ERIC) to Jan 2010;
- Virtual Health Library (VHL) in BIREME: Pan American Health Organization (PAHO) Specialized Center;
- LILACS (Latin American Health Sciences Literature) to Jan 2010;
- PsycINFO (psychological literature) to Feb 2010 week 2; and
- UMI Dissertation Express.

We searched the following complementary and alternative medicine specific databases to January 2010:

- CAM on PubMed;
- Cochrane Complementary and Alternative Medicine field;
- Complementary Medicine Resources for Health Professionals and Researchers;
- Complementary and Alternative Medicine Specialist Library in the National Library for Health (supported by the NHS); and

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- Complementary and Alternative Therapies databases of Bandolier.

We also searched the following sources to January 2010:

- OpenSIGLE - System for Information on Grey Literature in Europe;
- Health Services/Technology Assessment Text (HSTAT) database;
- Informit Databases: Humanities and Social Sciences Collection, Australia;
- English Databases of the Japan Science and Technology Agency (JST); and
- Research database of Thailand psychiatry and mental health and Thai Thesis Online.

The search strategies for these databases are shown in the appendices two to seven (see Appendices).

Searching other resources

We carried out a search of conference proceedings at ISI Proceedings from 1990 to January 2010 and searched for relevant studies cited in book chapters on the treatment of ADHD.

Personal communication

We consulted the authors of the included studies and experts in the fields to find out whether they knew of any published or unpublished RCTs/ CCTs of meditation therapy and ADHD, which have not yet been identified. We contacted persons and organizations whose work relates to meditation (i.e. Associacion de Medicinas Complementarias (AMC), the National Center for Complementary and Alternative Medicine (NCCAM), Sat Bir Sinah Khalas). We contacted religious/spiritual organizations around the world (internet web sites were extensively searched) to find out whether they had conducted or knew of the application of meditation in ADHD.

We also contacted worldwide organizations with resources for ADHD: Attention-Deficit Disorder Association, Attention-Deficit Disorder Resources; ADHD Support, Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD), the National Resource Center on AD/HD (NRC), Children and Adults with Attention-Deficit Disorders, Learning Disabilities Association of America, the Attention-Deficit Resource Network (ADRN) and the National Center for Girls and Women with AD/HD.

Ongoing trials

We sought ongoing trials by searching the *meta*Register of Controlled Trials (*m*RCT) ; Health Services Research Projects in Progress (HSRProj); the National Centre for Complementary and Alternative Medicine sponsored trials; www.ClinicalTrials.gov; UKCRN Clinical Research Portfolio and the Trials Register of Promoting Health Interventions (TRoPHI). All trial registry were search to January 2010.

We checked the reference lists of all relevant studies for further references.

Data collection and analysis

Selection of studies

KT and WC independently screened the titles and abstracts obtained by the search strategies against the eligibility criteria stated above. KT and WC verified study eligibility before data extraction with no disagreement on inclusion/exclusion decisions. For articles that appeared to be eligible RCTs, we obtained the full articles and inspected these to assess their relevance, based on the pre-defined inclusion criteria.

Data extraction and management

Two authors independently extracted data using a pre-designed data collection form, which was saved electronically. Any unpublished information, if used, was recorded and coded with a specific remark. We contacted authors either by e-mail or telephone call to obtain any missing data. KT entered all relevant data into RevMan 5 (RevMan 2008) and NC checked data for correctness. The reliability of data extraction and data entry were examined throughout the process.

For cross-over designs, we extracted all data but, because of the strong carry-over effect of meditation, we used only data from the first phase of study in our analyses. The data from the second phase after crossing over were described in the 'Characteristics of included studies' table and recorded in an additional table.

Assessment of risk of bias in included studies

We assessed risk of bias in the included studies using The Cochrane Collaboration's tool, which is based on multiple domain evaluation (Higgins 2008). There are six domains as follows:

1. Sequence generation
Was the allocation sequence adequately generated?
2. Allocation concealment
Was allocation adequately concealed?
3. Blinding of participants, personnel, outcome assessors
Was knowledge of the allocated intervention adequately prevented during the study?
4. Incomplete outcome data
Were incomplete outcome data adequately addressed?
5. Selective outcome reporting
Are reports of the study free of suggestion of selective outcome reporting?
6. Others sources of bias

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Was the study apparently free of other problems that could put it at a high risk of bias?

The review authors' judgments involved answering these questions for each entry, i.e. 'Yes' indicates low risk of bias; 'No' indicates high risk of bias; 'Unclear' indicates insufficient detail is reported or the risk of bias is unknown.

The risk of bias is presented in the 'Risk of bias' table with two additional figures: a 'Risk of bias graph' (Figure 1) and a 'Risk of bias summary' (Figure 2).

Figure 1. Methodological quality graph: review authors' judgments about each methodological quality item presented as percentages across all included studies.

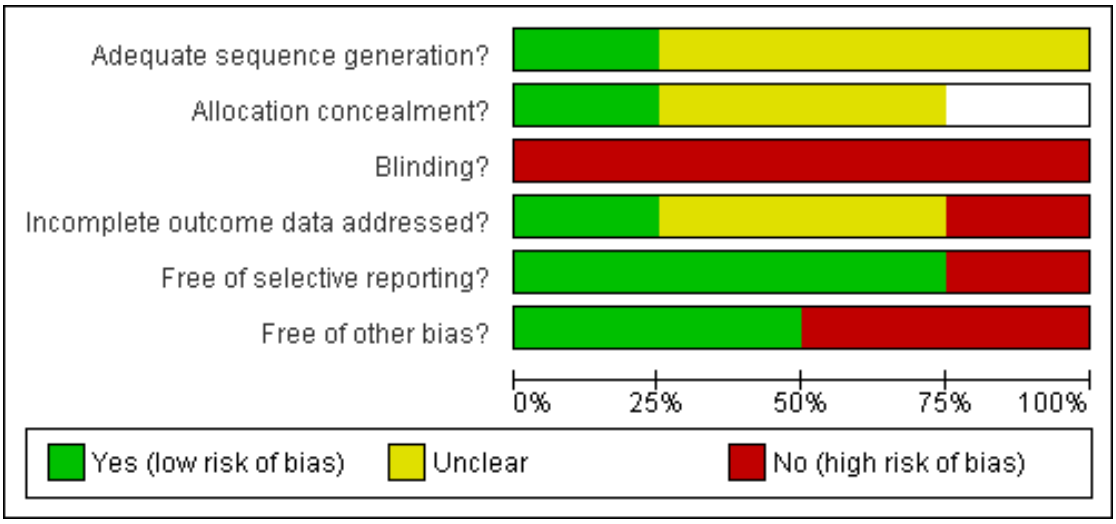

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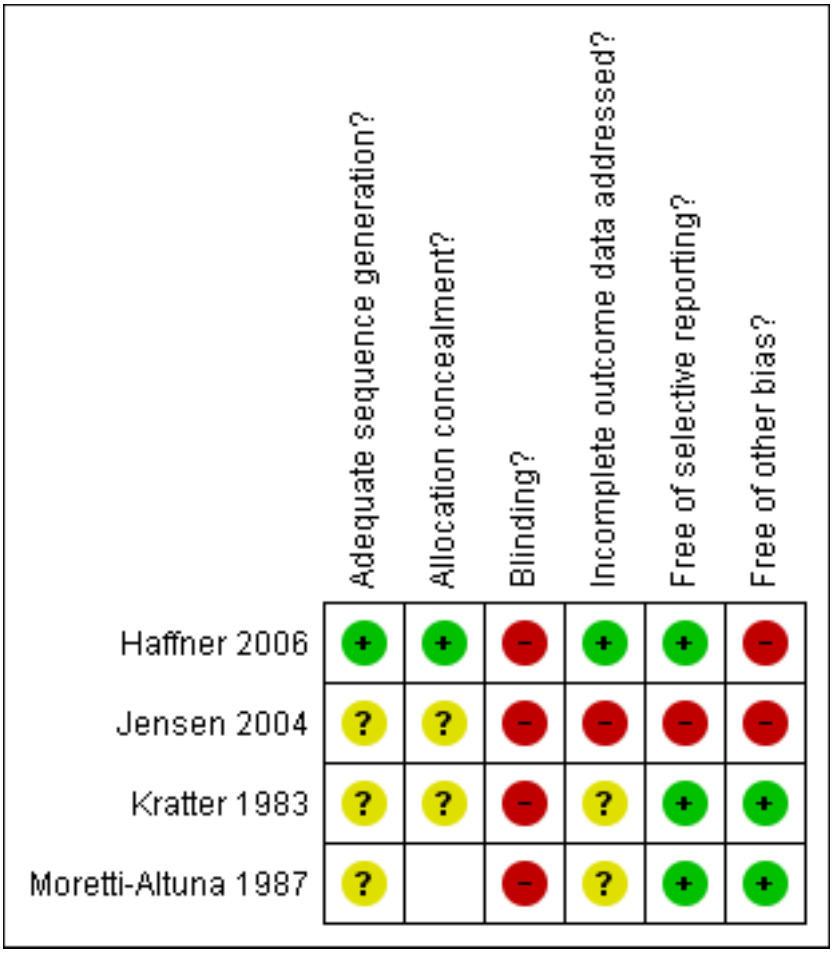
Figure 2. Methodological quality summary: review authors' judgments about each methodological quality item for each included study.



To determine selective outcome reporting we planned to compare the study with its protocol, which might be registered in trial registries, however no included studies were registered in any trial registries. Two out of four included studies, however, came from PhD dissertations which had an extensive published report which could be used to determine the completeness of reporting indirectly (Kratter 1983; Moretti-Altuna 1987).

The summary assessment of risk of bias used the authors' judgment for primary outcomes (symptoms of ADHD, quantitative laboratory assessment measures of ADHD symptoms, overall incidence/severity of the problem behaviors) both within and across studies.

Disagreements were discussed with a third author (WC) and resolved through consensus.

Measures of treatment effect

Dichotomous outcomes

Dichotomous outcomes were not presented in any of the included studies.

Continuous outcomes

We analyzed the endpoint score (because the change score data were not reported in the included studies) in RevMan 5 using mean differences (MD) and their 95% confidence intervals (CI). When considering the skewed data, we compared the mean to the standard deviation. If the mean was smaller than twice the

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standard deviation the data were probably skewed (Altman 1996). We present the skewed data in Additional table.

Unit of analysis issues

In trials of cross-over design (two included studies), because of the strong carry-over effect of meditation, we only used the data from phase one before crossing over in meta-analysis. The additional data were described in the 'Characteristics of included studies' table.

In a study with multiple treatment groups (meditation versus drug versus standard treatment control), we carried out the analysis for each pair between meditation and other treatments.

No cluster-randomized trials were identified.

Dealing with missing data

All of the included studies for this review used per protocol analysis. The reasons for missing data were clarified by the study authors and were described in the Notes sections of the 'Characteristics of included studies' table.

Assessment of heterogeneity

This review included one trial for each comparison. We therefore did not conduct assessment of heterogeneity. We have provided full methods for assessment of heterogeneity for future updates of this review in Appendix 1.

Assessment of reporting biases

If possible, we will use a funnel plot (Egger 1997; Light 1984) to determine potential publication bias.

The authors dealt with selective outcome reporting by searching for the original protocols for each included study in trial registries and comparing these (where available) with the list of outcomes in the methods section of the final report. In cases where there is a suspicion of selective outcome reporting, we contacted the study authors. The assessment of risk of bias due to selective reporting of outcome was made for each study as a whole.

This review included one trial for each comparison. We therefore did not create funnel plots to assess publication bias. For future updates of this review, we have provided full methods for assessment of reporting biases in Appendix 1.

Any other types of bias encountered in each study are reported in the Results and Discussion.

Data synthesis

Each comparison had only one included trial and had continuous outcomes. We therefore calculated MDs with their 95% CIs.

Subgroup analysis and investigation of heterogeneity

We did not conduct subgroup analysis because there was only one included trial for each comparison.

Sensitivity analysis

We did not conduct sensitivity analysis due to the limited number of included studies in the review.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

We carried out extensive searches, as described in 'Search methods for identification of studies'. We searched the electronic databases from their inception without language restrictions. We checked the titles from the preliminary search results and there were 17 potentially relevant studies at this stage. After checking the abstracts, we excluded 7 studies that were obviously irrelevant to the review. We obtained the full text of the 11 potentially relevant studies which required further clarification. Four studies met the eligibility criteria while 7 studies were put into the excluded studies category. All included studies were carried out by different research teams between 1983 and 2006. We contacted the first authors of three of the included studies to ask for additional data and details of their studies. One author (Kratter 1983) could not be contacted. One author (Haffner 2006) sent an original article in German and an English translated version.

Included studies

Settings

Two of the four studies included in this review were carried out in the USA. Both studies were dissertations submitted to the faculty of the Department of Psychology at St. John's University, New York (Kratter 1983; Moretti-Altuna 1987). Haffner 2006 was carried out in Germany and Jensen 2004 was carried out in Australia. Only one study (Kratter 1983) mentioned the meditation room, which was a quiet room with low lighting and comfortable chairs. Both studies of mind-based meditation (Kratter 1983; Moretti-Altuna 1987) used a padded, straight-back chair. Haffner 2006 and Jensen 2004 did not give details about their settings. None of the studies reported the time of year of the study, therefore it is

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unclear whether participants were in school or on holiday/vacation during the trials.

Participants

All participants were children with ADHD, with an age range between six and 13 years old. Three of the studies indicated that participants must be boys in the inclusion criteria; only (Haffner 2006) included girls. Three studies reported that they used the DSM diagnostic system (DSM-III, DSM-IV). One study, which was carried out in Germany (Haffner 2006), used the Diagnostic System for Psychic Disorders in Childhood and Adolescence, which corresponded to ICD-10 diagnosis. Jensen 2004 used Conners' Parent Rating Scales: Long (CPRS: R (L)) that demonstrated scores (over 70 t-score) to confirm the diagnosis of ADHD in all participants. Moretti-Altuna 1987 used a multidisciplinary intake committee to confirm the diagnosis. In the other two studies (Haffner 2006; Kratter 1983) no diagnostic re-confirmation procedures were used.

Interventions

Two studies used mantra meditation, which is mind-based. Kratter 1983 used the word "Ahnam", a Sanskrit word which means "nameless". Moretti-Altuna 1987 used "One", with the aim that by repeating the word the participants would learn to focus and re-focus their attention. These techniques were adapted from the well-known concentrative meditation developed by Benson 1975 and Carrington 1975, which has some roots in the Hindu religion. Apart from the different mantra used in their studies, other aspects of the intervention (duration, frequency, sitting position, passive attitude) were almost the same.

Haffner 2006 and Jensen 2004 used Hatha yoga, which is more physical-based. However, Jensen 2004 also used a visualization technique to accompany Hatha yoga and Haffner 2006 used breathing meditation combined with postures. They claimed that their yoga program was a standardized program and developed by a yoga instructor. The yoga program consisted of multiple components (respiratory, postural, relaxation concentration training). The details of each program are described below.

Concerning the qualification and skills of the meditation instructors, only Haffner 2006 used a well-trained yoga teacher while in the other three included studies the subjects were taught by the investigators themselves.

The intervention program ranged from four weeks (Kratter 1983; Moretti-Altuna 1987), to eight weeks (Haffner 2006) to 20 weeks (Jensen 2004). The frequency of visits varied from one session per week (Jensen 2004) to three sessions per week (Haffner 2006; Kratter 1983; Moretti-Altuna 1987). Some studies used the parents to assist and supervise their children while practicing meditation at home (Jensen 2004; Kratter 1983; Moretti-Altuna 1987), while Haffner 2006 just let the children practice yoga freely on their own at home or at school during the intervention period.

The intensity of meditation is determined from the duration of practice. Haffner 2006 and Jensen 2004 used a one-hour training session but do not mention the exact time spent in meditation. Kratter 1983 and Moretti-Altuna 1987 state that the actual meditation duration was gradually increased from one minute to eight minutes by the end of the four-week training period.

Comparator/control group

Haffner 2006 and Jensen 2004 compared yoga versus co-operative games/activities. Medicated participants were unevenly distributed between intervention groups. In Haffner 2006 five out of nine of the yoga group were medicated while three out of 11 of the control group were medicated.

Kratter 1983 compared three intervention groups: meditation training versus relaxation training versus waiting list control. The medicated participants were distributed evenly between treatment groups using a modified randomization method.

Moretti-Altuna 1987 compared meditation training versus drug therapy versus standard therapy control. Only participants in the drug therapy group received medication.

Outcome measures

The reported outcomes were:

1. Validated outcome scales rated by parents/teacher, which reflected the core symptoms of ADHD.
   - Fremdbeurteilungsbogen für hyperkinetische Störungen (FBB-HKS), used in Haffner 2006.
   - Conners' Parent (CPRS-R:L) Teacher (CTRS-R:L) Rating Scales - Revised: Long (Conners 1997), used in Jensen 2004.
   - Abbreviated Parent-Teacher Questionnaire (PTQ) (Conners 1973), used in Kratter 1983 and Moretti-Altuna 1987.
   - Werry-Weiss-Peters Activity Scale (WWPAS) (Werry 1968), used in Kratter 1983 and Moretti-Altuna 1987.
   - Nowicki-Strickland Locus of Control Scale (LCS), used in Kratter 1983.

2. Psychological testing to measure the symptoms profile of ADHD.
   - Dortmund Attention Test (DAT), used in Haffner 2006.
   - Test of Variables of Attention (TOVA) (Greenburg 1991), used in Jensen 2004.
   - Matching Familiar Figure Test (MFFT) (Kagan 1996), used in Kratter 1983 and Moretti-Altuna 1987.
   - Fruit Distraction Test (FDT) (Santostefano 1978), used in Kratter 1983 and Moretti-Altuna 1987.
   - The Children's Embedded Figures Test (CEFT) (Karp 1963), used in Moretti-Altuna 1987.

3. Psychophysiological measurements.
   - Motion logger - Actigraph, used in Jensen 2004.

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Study design

Haffner 2006 used a cross-over design in which the participants in the yoga group and the control (motor exercise) group crossed over to the other treatment after eight weeks, with a six-week break (wash-out period). As stated earlier, to prevent carry-over effects, we have only included the data from the first phase of each study in the analysis. Data from the second phase after cross-over are recorded in Tables. Jensen 2004 also stated that the study had a "randomized cross-over design", but only the participants in the control group were allowed to move to the yoga group; the yoga group did not cross over to the control group. This design cannot therefore be described as cross-over. The study is downgraded from RCT to only a before-after design when the study authors pooled all data together.

Excluded studies

There were 7 excluded studies. Four were carried out in the USA (Evans 2007; Kratter 1982; Peck 2005; Zylowska 2008), one was from Australia (Harrison 2004) one from Thailand (Hassasiri 2002) and one was carried out in Iran but get published in India (Abadi 2008) . One of the excluded studies involved development of an audio program for the treatment of adult ADHD and used a group of experts to give opinions about the program (Evans 2007). Three used a before-after design which did not have a control group (Harrison 2004; Hassasiri 2002; Zylowska 2008). One study (Peck 2005) was excluded due to the participants not having been diagnosed with ADHD. We also excluded one duplicate report (Kratter 1982). One study(Abadi 2008) have a control group but did not mention about the randomization.

Risk of bias in included studies

Systematic biases directly affected the validity of the included studies. See also the 'Risk of bias' graph (Figure 1) and 'Risk of bias' summary (Figure 2).

Allocation

Only one of the four included studies reported the method of randomization which was the use of drawing lots (Haffner 2006). The other three studies just mentioned randomization without giving any details in their methods. The method of allocation concealment was not reported in any trial but because Haffner 2006 used the drawing of lots we have assumed that allocation concealment automatically occurred because the sequence cannot be known in advance. In one trial (Jensen 2004) the process of randomization was terminated when five participants from the control group were allowed to move to the treatment group after 20 weeks. Allocation concealment was therefore not carried out in this trial. In Kratter 1983 the randomization method was modified to equalize the medicated children evenly between each group. This modification made the study potentially more susceptible to bias, as randomization could not guarantee the distribution of confounding factors and allocation concealment was not adequate. Moretti-Altuna 1987 did not give details of randomization methods and we therefore judged the adequacy of randomization and allocation concealment to be 'Unclear'.

Blinding

Only the blinding of of raters/assessors is possible in such trials. However, no trials reported blinding of the raters/assessors.

Incomplete outcome data

No studies in the included studies carried out an intention-to-treat analysis. Only patients who completed the entire trial were analyzed by per-protocol analysis.

In Haffner 2006 one nine-year old boy left the study because of a change of residence during the 21st week. The reason why the child left the study was adequately described and it would not have had a clinically relevant impact on the observed effect size.

Jensen 2004 reported the number of boys who began the trial (n = 16) but only data for 14 boys were used in analysis. No reasons for drop-outs were described.

Kratter 1983 reported that 24 boys participated the study but did not mention the attrition of participants at the end of the study. Moreover, the analysis table did not give the number of participants left in each group, therefore the data were not used in meta-analysis but are shown in Table 1.

Table 1. Data from Kratter 1983

Outcome	Meditation			Relaxation			Waiting list Control		
	Mean	SD	n	Mean	SD	n	Mean	SD	n
MFFT latency scores	12.412	6.675	-	10.462	3.986	-	10.962	5.125	-

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Table 1. Data from Kratter 1983 (*Continued*)

FDT card 1 Latency	40.312	9.051	-	41.687	8.062	-	42.375	10.905	-
FDT card 2 Latency	44.812	10.261	-	49.500	14.310	-	49.687	13.905	-
FDT card 3 Latency	45.687	8.856	-	46.625	8.895	-	53.375	16.153	-
FDT card 4 Latency	70.750	8.912	-	83.250	24.036	-	83.437	20.576	-
LCS scores	14.000	3.295	-	18.875	4.824	-	16.000	5.555	-
TRS scores	15.625	8.141	-	16.625	8.158	-	13.500	6.024	-
PTQ scores	14.250	6.840	-	15.375	2.774	-	18.625	1.061	-
WWPAS	25.000	7.709	-	26.375	10.169	-	28.125	7.827	-

No N in each group provided.
FDT = Fruit Distraction Test
LCS = Nowicki-Strickland Locus of Control Scale
MFFT = Matching Familiar Figure Test
PTQ = Parent-Teacher Questionnaire
TRS = Teacher Rating Scale
WWPAS = Werry-Weiss-Peters Activity Scale

In Moretti-Altuna 1987 there was no mention of the number of enrolled participants at the beginning of the trial. The authors reported that 23 boys participated in the trial and used this number in the final analysis. Completeness of outcome data is therefore doubtful.

Selective reporting

None of the four included studies appeared in trial registries and therefore we were not able to obtain protocols for these studies. Pre-specified outcomes were therefore not known and it is difficult to determine whether outcomes were omitted from reporting.
Haffner 2006, Kratter 1983 and Moretti-Altuna 1987 reported all the outcomes specified in their Methods section. Moreover, Kratter 1983 and Moretti-Altuna 1987 were dissertations which should guarantee the completeness of reporting.
Jensen 2004 used an Actigraph motion logger (a portable electronic activity monitor designed to be worn on the wrist, waist or ankle) and reported that "there were many technical problems encountered mainly due to their use in a naturalistic setting. On occasions they were damaged, stopped recording data, or failed to be activated at set times. As a consequence an incomplete set of data was collected. Due to these problems, data were deemed unreliable and were discarded." Even though the study authors had addressed the reason for non-reported outcomes, we still judged that this outcome was selectively reported.

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Other potential sources of bias

In Haffner 2006 more boys in the yoga group received medication (five of nine) than in the exercise group (three of 11). This unequal co-intervention could have substantial effects. Using a cross-over design in a trial of an intervention which needs practicing by the participants means it is difficult to discard the carry-over effect during phase two of the trial. Even during phase one (before crossing over) participants in both intervention arms might have some expectations of the treatment effects of the next intervention.
In Jensen 2004 there were significant differences between the control and yoga groups' pretest sub-scale scores
on almost all Conners' Rating Scales for both parents and teachers.

Effects of interventions

See: **Summary of findings for the main comparison** Meditation therapy versus drug therapy for attention deficit /hyperactivity disorder; **Summary of findings 2** meditation therapy versus standard treatment without drug for attention deficit /hyperactivity disorder
We collected data for three comparisons from the included studies which were non-skewed outcome data to put into the analyses and present in the 'Summary of Findings' table: this was the teacher rating ADHD overall scale . The distraction test was considered to be the intermediate outcomes which reflected psychological state but might not directly related to behavior of the child.
The effects of interventions are compared in a pair-wise manner as follows.

Meditation therapy versus drug therapy for ADHD

One study (Moretti-Altuna 1987) compared mantra meditation and drug therapy for ADHD. There were six outcomes which are considered to be the primary outcomes in this review. The study provided both endpoint scores with standard deviations (SD) and change scores with SD for each outcome after four weeks of treatment. The endpoint scores were selected for use in analysis. There was no statistically significant difference between the meditation therapy group and the drug therapy group in the teacher rating ADHD overall scale (MD -2.72, 95% CI -8.49 to 3.05, 15 patients, see Figure 3). In addition, we found that five outcomes had skewed data (see Table 2).

Table 2. Meditation therapy versus drug therapy (skewed data) (Moretti-Altuna 1987)

Outcome	Study	Meditation			Drug		
		Mean	SD	Total	Mean	SD	Total
1. Parent rating ADHD overall scale	Moretti-Altuna 1987	15.78	8.74	9	18.17	7.39	6
2. Parent rating activity level scale	Moretti-Altuna 1987	28.0	16.87	9	30.83	22.31	6
3. Impulsivity test (error scores)	Moretti-Altuna 1987	12.22	8.03	9	17.00	4.98	6
4. Distraction test	Moretti-Altuna 1987	247.72	117.77	9	238.25	123.07	6
5. Attention test	Moretti-Altuna 1987	14.11	6.09	9	11.0	5.76	6

Meditation therapy versus standard treatment without drugs for ADHD

Moretti-Altuna 1987 also compared mantra meditation and standard treatment without drugs for ADHD using the same outcome measures as the above comparison. The analysis was done by calculating the endpoint scores after four weeks of treatment. There was no statistically significant difference between the meditation

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therapy group and the standard therapy group in the teacher rating ADHD scale (MD -0.52, 95% CI -5.88 to 4.84, 17 patients, see Figure 4). In the same way there was no statistically significant difference between the meditation therapy group and the standard therapy group in the distraction test (MD -8.34, 95% CI -107.05 to 90.37, 17 patients, see Figure 5). Skewed data for this comparison are shown in Table 3.

Table 3. Meditation therapy versus standard treatment without drug (Moretti-Altuna 1987)

Outcome	Study	Meditation			Standard therapy control		
		Mean	SD	Total	Mean	SD	Total
1. Parent rating ADHD scale	Moretti-Altuna 1987	15.78	8.74	9	19.0	7.29	8
2. Parent rating activity level scale	Moretti-Altuna 1987	28.0	16.87	9	30.75	14.25	8
3. Attention test	Moretti-Altuna 1987	14.11	6.09	9	12.13	7.36	8
4. Impulsivity test (error scores)	Moretti-Altuna 1987	12.22	8.03	9	17.50	9.78	8

Meditation therapy versus relaxation training versus waiting list controls with drugs for ADHD

In Kratter 1983 there were three intervention groups. Mantra meditation was compared to relaxation training and to waiting list controls with drugs. The three groups had an equal number of medicated participants. There were five outcomes which are considered to be the primary outcomes in this review. The study provided both endpoint scores with SD and change scores with SD for each outcome. The data are shown in Table 1. From the published report, the authors used ANOVA to analyze the treatment effects. The findings were that mantra meditation as well as relaxation training significantly decreased impulsivity and improved behavior at home when rated by the parents. Only the meditation group improved in the selective deployment of attention, which was claimed as an essential aspect of meditation training. The sense of internal control and classroom behavior were not improved in any treatment group.

Hatha yoga versus non-specific physical exercise for ADHD

There were two studies which compared Hatha yoga and non-specific physical exercise for ADHD (Haffner 2006; Jensen 2004). However, only Haffner 2006 provided data for this comparison. In the study by Jensen 2004, the authors did not provide the data from truly randomized participants. In the published report analysis the authors combine the data from true randomized participants with data from the control group who moved to the treatment group. Mixing the participants from the two groups together ruined the randomization effects. We decided to discard these data from analysis, but the data are shown in Table 4.

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Table 4. Yoga versus control for ADHD (Jensen 2004)

Conners' Parent Rating Scales - Revised: Long (Conners 1997) (Figure 6)
Conners' Teacher Rating Scale - Revised: Long (Conners 1997) (Figure 7)
Test of Variables of Attention (TOV) (Greenburg 1991) (Figure 8)

To eliminate the carry-over effect in Haffner 2006 only the data from the first phase of trial were extracted and put into the comparison for meta-analysis. There were five outcomes for this comparison but their data were skewed (see Table 5). The data from phase two of the trial (after crossing over) are shown in Table 6.

Table 5. Hatha yoga versus non-specific physical exercise (skewed data)

Outcome	Study	Hatha yoga			Non-specific exercises		
		Mean	SD	Total	Mean	SD	Total
1. Parent rating ADHD overall scale	Haffner 2006	0.93	0.53	8	1.47	0.7	11
2. Parent rating attention-deficit	Haffner 2006	0.92	0.5	8	1.65	0.65	11
3. Parent rating hyperactivity	Haffner 2006	0.75	0.57	8	1.29	0.84	11
4. Parent rating impulsivity	Haffner 2006	1.26	0.67	8	1.39	0.88	11
5. Attention test	Haffner 2006	8.37	1.8	8	4.36	3.1	11

Table 6. Hatha yoga versus non-specific exercise for ADHD (phase 2: after crossing over) (Haffner 2006)

Measurements	Hatha Yoga N = 11 Mean (SD)	Exercise N = 8 Mean (SD)
DAT	9.81(1.5)	7.0(2.7)
FBB-HKS	-	-

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Table 6. Hatha yoga versus non-specific exercise for ADHD (phase 2: after crossing over) (Haffner 2006) (*Continued*)

Total scale	1.18(0.76)	1.03(0.65)
Attention-deficit	1.34(0.73)	0.9(0.6)
Hyperactivity	1.07(0.82)	0.86(0.72)
Impulsiveness	1.02(0.88)	1.61(0.79)

DAT = Dortmund Attention Test
FBB-HKS = Fremdbeurteilungsbogen für hyperkinetische Störungen (FBB-HKS): a rating scale for parents, teachers and educators

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ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

meditation therapy versus standard treatment without drug for attention deficit /hyperactivity disorder

Patient or population: patients with attention deficit /hyperactivity disorder
Settings:
Intervention: meditation therapy versus standard treatment without drug

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	meditation therapy versus standard treatment without drug				
Teacher rating ADHD overall scale Abbreviated Parent-Teacher Questionnaire (Conner, 1973) Follow-up: mean 4 weeks	The mean teacher rating adhd overall scale in the control groups was **12.63**	The mean Teacher rating ADHD overall scale in the intervention groups was **0.52 lower** (5.88 lower to 4.84 higher)		17 (1 study[4])	⊕○○○ **very low**[1,2,3]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Unclear randomization, unclear allocation concealment, no blinding, unclear attrition rate, other biases presented
[2] Wide confidence interval, small sample size
[3] Only one study(since 1987) present for this outcome
[4] Study Moretti-Altuna, 1987

DISCUSSION

Summary of main results

Four studies were included in this review. Two studies were dissertations submitted to the faculty of the Department of Psychology at St. John's University, New York in 1983 and 1987 (Kratter 1983; Moretti-Altuna 1987). One study was carried out in Sydney, Australia (Jensen 2004) and the other in Heidelburg, Germany (Haffner 2006). The first randomized controlled trial using meditation for ADHD was the study of Kratter 1983, which took place 25 years ago. Further studies have followed Kratter's trial but many of these have used a before-after design which has several methodological limitations. These studies were excluded from the review (Harrison 2004; Hassasiri 2002; Zylowska 2008). Haffner 2006, Jensen 2004 and Moretti-Altuna 1987 were randomized controlled trials with different comparators: 1) meditation therapy versus drug therapy, 2) meditation therapy versus standard treatment without drugs, 3) meditation therapy versus relaxation training versus waiting list controls with drugs and 4) Hatha yoga versus non-specific physical exercise.

The type of meditation used in these trials can be differentiated into two groups according to the different characteristics of meditation. Mind-based meditation (mantra meditation) was used in the Kratter 1983 and Moretti-Altuna 1987 studies. Physical-based meditation was used in Jensen 2004 and Haffner 2006. Mind-based meditation emphasizes the cognitive process which focuses on the use of selective deployment of attention: the participants learned to focus and re-focus their attention (Kratter 1983). Physical-based meditation (Hatha yoga, moving meditation) focuses on behavioral control. However, due to the complexity of body-mind interaction, and the concept of holistic approach, it is hard to differentiate body and mind and each meditation technique usually incorporates both components together. Due to the variety of theories and practices of meditation the inclusion of different techniques under the same umbrella of meditation is inappropriate. Five broad categories of meditation practice were identified by a group of experts using modified Delphi methodology: mantra meditation (comprising the Transcendental Meditation® technique (TM®), Relaxation Response (RR) and Clinically Standardized Meditation (CSM)), mindfulness meditation (comprising Vipassana, Zen Buddhist meditation, Mindfulness-based Stress Reduction (MBSR) and Mindfulness-based Cognitive Therapy (MBCT)), yoga, Tai Chi and Qi Gong (Ospina 2007)). The classifications in this system are more suited to defining the broad range and variety of meditation than the previously used classification (concentrative meditation and mindfulness meditation). The four included studies in this review fell into the categories of mantra meditation and yoga by this classification.

Only Haffner 2006 used a well-trained yoga teacher while participants in Jensen 2004, Kratter 1983 and Moretti-Altuna 1987 were taught by the investigators themselves. Qualification and experience in teaching meditation are important to guarantee proper teaching. When applying meditation therapy in clinical settings, the knowledge, attitude and skill of the therapist should be considered (Krisanaprakornkit 2006).

There were only two studies from which the data were appropriate for meta-analysis. Due to the limited number of studies, small sample size in each trial, apparent risk of bias and skew-ness of data we found no consistent evidence that meditation (either mind-based or physical-based) had a significant effect on core ADHD symptoms or psychological tests of attention, impulsivity and distraction. Mind-based meditation did not yield any significantly different effects compared to drugs and standard therapy controls. While physical-based meditation (Hatha yoga) showed some positive effects (parent rating attention-deficit, attention test), it did not show consistent results.

All of the included studies had differences in the number of meditation sessions and the amount and quality of home practice, which could affect the treatment effects. Some studies used the parents to assist and supervise their children while practicing meditation at home (Jensen 2004; Kratter 1983; Moretti-Altuna 1987). Haffner 2006 just let the children practice yoga freely on their own at home, at school and during lessons. Therefore the intensity of practice differed widely among participants and studies. There were no descriptions of monitoring of practice at home in any studies, therefore the quality and quantity of self-practice could not be guaranteed. This might be affected the results of each studies.

Data for the side effects of meditation and quality of life were not reported in any trials. Randomized trials usually focus on intended effects and focus less on possible adverse effects. Data on adverse effects are often sparse but the absence of information does not mean that the intervention is safe (Higgins 2008). The issue of side effects should therefore be addressed in any future meditation trials.

There is insufficient evidence to support the effectiveness of any types of meditation for ADHD at present given that only four randomized controlled trials have been carried out, and all were relatively small in size and limited in design, with inconsistent results across the outcomes.

Overall completeness and applicability of evidence

We considered the parent rating, teacher rating and self-rating ADHD symptoms scales to be the most important outcomes for patients. Quantitative laboratory assessment measures of ADHD symptoms, psychological testing etc. are surrogate outcomes which are less important. In the included studies all the participants were children with ADHD, therefore a self-rating scale is not necessary to measure outcomes because it is difficult for school-age children to rate their symptoms accurately.

No studies gave details of adverse effects, but this is an important outcome to be considered in every study, especially in trials in children. Despite this, a well-structured meditation program is

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considered safe and is promoted for children in many settings, including schools (Helen 2004).

In our protocol for this review we defined 'Overall severity of problem behaviors' and 'Quality of life' as outcome measures because these outcomes provide a broader perspective on the patient's life rather than merely focusing on symptoms. Meditation can not only improve attention but also the quality of mind (calmness, equanimity, contentment), all of which can affect the life of a patient as a whole (Ospina 2007). Outcomes which are measured at the end of a program cannot detect intermediate-term and long-term changes in personality profile. Data will be more complete if trials can follow up outcomes for six months to 12 months afterwards.

Due to the lack of consistent evidence to support the use of meditation for ADHD in the present review, we cannot comment on applicability and generalizability at this time. In some countries, for example Thailand, meditation is accepted as a means to improve attention, temperament, discipline, school performance, character, morals and for religious purposes (Krisanaprakornkit 2006). The included studies were carried out in the USA, Germany and Australia. As the effects of globalization and the holistic view of health expand, meditation may become more accepted and widely used in the clinical setting. Therefore, if the effectiveness of meditation can be established, it may be used more widely as a therapy in the future.

Quality of the evidence

In a Cochrane Review the quality of evidence reflects the extent to which we are confident that an estimate of the effect is correct. We therefore rate the quality of evidence for each outcome separately. Two included studies were dissertations submitted to the faculty of the Department of Psychology at St. John's University, New York in 1983 and 1987 (Kratter 1983; Moretti-Altuna 1987). We have assumed that the dissertations were generally supervised and verified by the committee. The inclusion of dissertations may mean more balanced results as they are less likely to overestimate treatment effects, as can occur in published trials (McLeod 2004). Trial quality is discussed in the 'Assessment of risk of bias in included studies' section, with graphical presentations in Figure 1 and Figure 2. We then assessed the risk of bias for an outcome across studies using the GRADE system. We judged the quality of the evidence by assessing limitations in design, inconsistency, indirectness, imprecision and publication bias.

As such a limited number of trials was found, we suspect the possibility of publication bias. Concentrative meditation (mantra meditation) was introduced to the West during the 1960s and many pioneers in the field have developed modified forms of meditation suitable for use in the clinical setting, for example the 'relaxation response' of Herbert Benson (Bensonian meditation) (Benson 1975). Mindfulness meditation has emerged as a new approach to stress reduction and is an important innovation in the treatment of psychiatric disorders (Baer 2003). The Mindfulness-based Stress Reduction Program (Kabat-Zinn 1992) has subsequently been researched in ADHD adults and adolescents (Zylowska 2008). A Google search results in more than 1,170,000 hits for "meditation AND ADHD". This issue has also appeared in the news (e.g. 'Meditation helps kids with ADHD' (Helen 2004)) and meditation has gained acceptability in many primary and junior school in England (Eliaz 2008). Another reason for the small number of studies might be that meditation trials are less supported than medication trials, which may be funded by drug companies.

The graphical risk of bias presentations (Figure 1; Figure 2) show the serious limitations in design (high risk of bias) in the included studies overall. Randomization methods are not mentioned, therefore we cannot assess the adequacy of allocation concealment. Only the study of Kratter 1983 described the use of the drawing of lots, which automatically concealed the allocation. There was no mention of blinding. In Haffner 2006, the yoga instructors themselves carried out the assessment of the participants in both the yoga and control group; detection bias was therefore inevitable. Only Haffner 2006 described the reason for drop-out of one participant (moved home). The attrition rate of the other three studies was unclear or not described. The drop-out rate might be related to adverse effects or to some discomfort with meditation.

The consistency of results across studies could not be determined because there was only one study to provide data for each comparison. However, when checking the direction of the result in any one study the inconsistency of outcomes in each study was obvious. Each study measured many outcomes. Some outcomes were considered to be important, while others were surrogate outcomes (e.g. attention test, distractibility test). When many outcomes are used in one study this will increase the possibility of a significant difference which occurred by chance. The authors may also selectively accentuate the significance of positive outcomes while omitting to clarify the negative outcomes (reporting bias).

Most of the means differences had wide confidence intervals reflecting the small sample size, differences in baseline characteristics of study samples and different treatment effects in individuals.

No studies had problems of indirectness of evidence.

We therefore summarized quality for each comparison as follows.

Meditation therapy compared to drug therapy for attention-deficit/hyperactivity disorder

The quality of evidence was "very low" according to the GRADE classification for 'Teacher rating ADHD overall scale' (see Summary of findings table 1).

Meditation therapy compared to standard treatment without drug for attention-deficit/hyperactivity disorder

The quality of evidence was "very low" according to the GRADE classification for 'Teacher rating ADHD overall scale' (see Summary of findings table 2).

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Potential biases in the review process

Due to limited access our literature searching could not cover some sources, such as literature in Chinese.

Agreements and disagreements with other studies or reviews

Meditation for ADHD has been reviewed as a psychological treatment along with other psychosocial interventions. At this time there is no specific systematic review of meditation for ADHD only. Arnold 2001 was a narrative review on alternative treatment for adults with ADHD. This review included the two studies of Kratter 1983 and Moretti-Altuna 1987, which were carried out in children with ADHD. The authors concluded that meditation showed some benefit and warrants further study for both children and adults. The recent narrative review by Greydanus 2007 emphasized medication and meditation was only mentioned under the heading of psychological management, which included many types of psychological interventions (psychotherapy, cognitive behavioral therapy, support groups, parent training, educator/teacher training, biofeedback, meditation and social skills training). The authors stated that empirical evidence regarding these interventions was inconsistent (Greydanus 2007). These narrative reviews commonly failed to assess the methodological quality of the primary studies, therefore the results tend to overestimate the effects.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to draw conclusions about the effectiveness of any types of meditation for attention-deficit/hyperactivity disorder (ADHD). The adverse effects of meditation in children with ADHD are unknown.

Implications for research

There is a lack of evidence to support the effectiveness of meditation for ADHD. This review has highlighted the need for further research. Meditation therapy research protocols need to be rigorous in design and delivery, and use standardized meditation therapy programs which can be replicated by other researchers. The operational definition of meditation techniques used should be specified and relate to ADHD core symptoms. The trainers should be skilled or be experts in the meditation methods used. The monitoring of meditation practice at home in addition to the therapy sessions is a crucial element of adherence. The involvement of parents in practice should be considered and controlled. The concomitant use of medication should be distributed evenly between comparison groups. All the outcomes should be validated and described, including adverse effects. We plan to update this review within 24 months to incorporate any new studies and respond to any comments or criticisms.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Haffner 2006

Methods	Randomized controlled trial 2 x 2 cross-over design using the drawing of lots Analyzed by means of an analysis of variance for repeated measurements
Participants	20 grade school age children (13 boys and 7 girls) diagnosed with ADHD (Diagnostic System for Psychic Disorders in childhood and adolescence according to ICD-10 and DSM-IV (DISYPS-KJ)) Trial was conducted in the University Hospital in Heidelberg, Germany between May 2000 and March 2001 Yoga group (n = 9 ; 8 boys + 1 girl) Exercise group (n = 11; 5 boys + 6 girls) One 9-year old boy in the yoga group left the study because of a change of residence during the 21st week Exclusion criteria: severe developmental disturbances, low intelligence level (IQ < 70) , and extreme behavioral disturbances which would be incompatible with participation in a group
Interventions	Intervention 1: body-oriented yoga exercise program A standardized program consisting of elements of Hatha yoga (postures, breathing exercises, meditative exercises) especially developed for children with ADHD, consisting of 16 exercise units for children and documented in a therapy manual Individual practice of yoga at home or school was carried out by each participant independently, without schedule Intervention 2: conventional motor training exercises A program of various well-known active games was put together. These contained all the elements that occur in normal grade school and leisure-sport activities (running games, throwing and catching games, agility games, ball games, concentration games, social games) and are thus fundamentally different from the yoga exercises. Using a cross-over study design, both groups received 2 consecutive 8-week intervention/ training sessions (each with 2 training sessions of 1 hour per week), separated by a training break of 6 weeks
Outcomes	1. Fremdbeurteilungsbogen für hyperkinetische Störungen (FBB-HKS) Döpfner 2000, Brühl 2000: 20 items each with 4 levels (0 = not at all, 1 = a little, 2 = to a large extent, 3 = especially), summarized in 3 symptom groups: attention-deficit, hyperactivity and impulsiveness. Categorized severity scores: 0 to -0.5 = not at all, 0.5 to 1.5 = a little, 1.5 to 2.5 = quite/to a large extent, 2.5 to 3.0 = very much/especially 2. Dortmund Attention Test (DAT) Lauth 1993 : comparison of differed pictures to determine the response latency and rate of error, which reflects attention-deficit Measurements: first baseline (baseline 1 / period of 6 weeks with parents ratings of ADHD symptoms, 1 measurement per week, using a standardized rating scale for parents, teachers and educators: FBB-HKS). A second baseline was taken after the 8-week intervention (baseline 2 / period of 6 weeks with standardized parent ratings of ADHD symptoms) by means of weekly measurements. Following the program, a third baseline was measured (baseline 3 / period of 6 weeks), with one assessment done per week.

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Haffner 2006 (*Continued*)

	During both training phases weekly assessments were made. The Dortmund Attention Test was carried out in all 3 baseline time periods.
Notes	Data were abstracted from the translated original German paper (translation was done by the investigator) 8 received medication (in 7 cases methylphenidate, in 1 case pipamperone) 7 received complementary therapy (in 3 cases ergotherapy, in 2 cases dyslexia therapy and in 2 cases behavioral therapy) Only the data from the first phase of the study (before cross over) were included in the analysis

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "the children were randomly (by drawing lots) assigned" Comment: probably done
Allocation concealment?	Yes	Comment: automatically done by drawing lots for each participant at the time of sequence generation
Blinding? All outcomes	No	Comment: the intervention cannot be blinded
Incomplete outcome data addressed? All outcomes	Yes	Quote: "one 9-year-old boy left the study because of a change of residence during the 21st week" Comment: the drop-out case would not have had a clinically relevant impact on the observed effect size
Free of selective reporting?	Yes	Comment: the outcomes were reported as mentioned in the methods section. The study author was contacted and completeness of outcome reporting was confirmed.
Free of other bias?	No	Comment: co-intervention - more boys in the yoga group received medication (5 of 9) than the exercise group (3 of 11)

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Jensen 2004

Methods	Randomized controlled trial Initially a 20-week program. After 20 weeks, 5 of the control group moved to the treatment group
Participants	16 boys aged 8 to 13 years. Mean age for boys in the yoga group 10.63 years (SD = 1.78 years) and for boys in the control group 9.35 years (SD = 1.70 years). Participants diagnosed with ADHD according to DSM-IV criteria by experienced pediatricians and diagnosis confirmed by the results of pre-test Conners' Parent Rating Scales: Long (CPRS: R (L)). All medicated participants were stabilized after appropriate periods of titration on dexamphetamine and/or methylphenidate. All participants were Caucasian except one (Chinese) and were assessed as having average or high intelligence Participants were also required to be fluent in English and free from serious family pathology (e.g. parental clinical depression or substance abuse, criminality in one or both parents, or domestic violence). Families with these characteristics were excluded because they were unlikely to be compliant with the extensive time commitment required. Participants were excluded if they were receiving other forms of treatment (except medication for ADHD). Participants had to be able to attend weekly classes for the 20-week duration of the yoga program. Yoga group: 11 boys (6 originally randomized to yoga group, 5 crossed over from control group) Control group: 8 boys
Interventions	1. Yoga program Nagendra 1988, Saraswati 1990 which incorporated standard yogic practices and comprised: - Respiratory training: selective use of oral and nasal passages for respiratory flow intended to increase the child's breath awareness as well as train him to breathe naturally through both nares. All exercises were repeated several times during each session and in a regulated rhythmical manner. - Postural training: involved stretching, load bearing, backward, forward, lateral flexion, and extensions and inversions performed in sitting, standing, supine and prone positions. These were performed in combination with respiratory exercises in static and dynamic positions. - Relaxation training: involved becoming progressively aware of and relaxing body parts and tensing and relaxing muscles - Concentration training: involved a technique called Trataka where participants focused on a word or shape, followed by seeing the image with eyes closed and continuing to see the image on a blank piece of paper 20 1-hour weekly instructional group sessions took place at Westmead Hospital, New South Wales, Australia. Parents were encouraged to assist with daily practice sessions at home. 2. Control group: engaged in co-operative games and activities. These groups were conducted for 1 hour, once a month and at the same location as the yoga groups
Outcomes	1. Conners' Parent (CPRS-R:L) Teacher (CTRS-R:L) Rating Scales - Revised: Long (Conners 1997) 2. Test of Variables of Attention (TOVA) Greenberg 1991: a continuous performance test designed to avoid confounding attention with language processing skills or short-term memory problems

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	3. Motion Logger - Actigraph. The Actigraph is a portable electronic activity monitor designed to be worn on the wrist, waist or ankle.
Notes	Of the 14 boys who completed the trials, 6 participated in the yoga group only, 5 who were originally in the control group moved from the control group to the yoga group, and 3 were in the control group only. This gave a total of 11 boys who completed the yoga training and 8 boys who acted as controls.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "boys who were randomly allocated to the control group in the first allocation"
Allocation concealment?	Unclear	Comment: not mentioned in the report
Blinding? All outcomes	No	Comment: the intervention cannot be blinded. Probably not done.
Incomplete outcome data addressed? All outcomes	No	Quote "Letters were sent to 80 parents with eligible sons. Of the 25 who responded, 16 began the trials and completed them." Comment: the attrition rate and reason for drop-out were not reported in each intervention group
Free of selective reporting?	No	Quote: "On the Actigraph motion logger, many technical problems were encountered ... Due to these problems, data were deemed unreliable and were discarded." Comment: not all of the pre-specified outcomes were reported
Free of other bias?	No	Quote: "there were significant differences between the control and yoga groups on pretest sub-scale scores on almost all Conners' Rating Scales for both parents and teachers." Comment: significant baseline differences.

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Kratter 1983

Methods	Randomized controlled trial, but used a modified randomization method to ensure the medicated subjects were equally distributed between the 3 groups Dissertation submitted to the faculty of the Department of Psychology at St. John's University, New York in 1983
Participants	24 boys from the Five Towns area of Lang Island, New York, USA diagnosed with ADHD (DSM-III) based on parent and child interviews Age range 93 to 142 months (mean = 120.63 months) Participants had a minimum score of 15 on the Abbreviated Parent-Teacher Questionnaire and were free from neurological disease or psychosis. The participants who received stimulants were equally assigned into each group
Interventions	Three intervention groups: 1. Meditation training (MT): individual sessions twice weekly for 4 weeks. Meditation technique was modified from Benson 1975 and Carrington 1975: repeating the word "Ahnam" out loud and progressively more softly until the word was repeated silently. The actual meditation duration was gradually increased from 2 minutes to 8 minutes by the end of the 4-week training period. Practice was at least 3 times per week at home. 2. Relaxation training (RT): individual sessions twice weekly for 4 weeks, using modified progressive muscle relaxation by reduction in the number of muscle groups when compare to the standard progressive muscle relaxation, deep and slowing breathing phase before and after the tension-relaxation cycles and 5-second tension periods. The actual relaxation training duration was gradually increased from 2 minutes to 8 minutes by the end of 4 weeks. Practice was at least 3 times per week at home. 3. Waiting list controls (WLC): received no experimental manipulation
Outcomes	1. Matching Familiar Figure Test (MFFT) Kagan 1966 which measures the dimension of reflection-impulsivity by participants choosing identical pictures from an array of 6 variants. Errors reflect impulsivity. 2. Fruit Distraction Test (FDT) Santostefano 1978 which tests the selective deployment of attention between relevant and irrelevant stimuli by naming the color with and without distraction and contradictions 3. Nowicki-Strickland Locus of Control Scale (LCS) which is used in the identification of hyperactive children and to evaluate treatment effectiveness (consists of 39-items; 4-point scale) 4. Abbreviated Parent -Teacher Questionnaire (PTQ)Conners 1973 consisted of 10 overlapping items from the Conners' Teacher Rating Scale and the Parent Symptoms Questionnaire 5. Werry-Weiss-Peters Activity Scale (WWPAS) Werry 1968: a rating scale which assesses activity level in specific situations
Notes	Parents were to be included in the training sessions Results table did not show number in each group. Data cannot be used in meta-analysis.

Risk of bias

Item	Authors' judgement	Description

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Kratter 1983 (*Continued*)

Adequate sequence generation?	Unclear	Quote: "were randomly assigned to one of three conditions" Quote: "subjects who received stimulant medication... were assigned in a modified random fashion such that they were represented in approximately equal numbers" Comment: the randomization was not adequately done
Allocation concealment?	Unclear	Comment: No mention about allocation concealment.
Blinding? All outcomes	No	Comment: the intervention cannot be blinded. No description of blinding of the assessors.
Incomplete outcome data addressed? All outcomes	Unclear	Comment: no mention of attrition
Free of selective reporting?	Yes	Comment: all outcomes were reported as mentioned in the method section
Free of other bias?	Yes	

Moretti-Altuna 1987

Methods	Randomized controlled trial Conducted in New York, USA Dissertation submitted to the faculty of the Department of Psychology at St. John's University, New York in 1987. This study has many similar characteristics to Kratter 1983, which was also a dissertation from the same university.
Participants	23 boys, age range 6 to 10 years, 5 black, 5 white, 13 Hispanic Participants diagnosed with ADHD (DSM-III), confirmed by an intake committee (administrative team leader, a psychiatrist, multidisciplinary staff member). The participants had to be free from psychosis, neurological disease and not currently on psychoactive medication.
Interventions	1) Drug therapy (DT): medication + conventional treatment 2) Meditation-relaxation training (MT): individual sessions, 30 minutes twice weekly for 4 weeks. Meditation technique was modified from Benson 1975: participants repeated the word "One" out loud and progressively more softly until the word was repeated silently. The actual meditation duration was gradually increased from 1 minute to 8 minutes by the end of the 4-week training period. Practice was at least 3 times per week at home. 3) Standard therapy control (STC): conventional treatment without medication, i.e. milieu, individual, group and/or family therapy

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Moretti-Altuna 1987 (*Continued*)

Outcomes	1. Matching Familiar Figure Test (MFFT) Kagan 1966, which measures the dimension of reflection-impulsivity by participants choosing identical pictures from array of 6 variants. Errors reflected impulsivity. 2. Fruit Distraction Test(FDT) Santostefano 1978, which tests the selective deployment of attention between relevant and irrelevant stimuli by naming the color with and without distraction and contradictions 3. The Children's Embedded Figures Test (CEFT) Karp 1963, which measures the extent to which perception of part of a stimulus field is influenced by the entire field and requires the subject to find a simple form in a complex one 4. Abbreviated Parent-Teacher Questionnaire (PTQ) Conners 1973, which consists of 10 overlapping items from the Conners' Teacher Rating Scale and the Parent Symptoms Questionnaire 5. Werry-Weiss-Peters Activity Scale (WWPAS) Werry 1968: a rating scale which assesses activity level in specific situations
Notes	Parents were to be included in the training sessions

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "Subjects were randomly assigned to one of three conditions"
Blinding? All outcomes	No	Comment: the intervention cannot be blinded. No description of blinding of the assessors.
Incomplete outcome data addressed? All outcomes	Unclear	Comment: no mention of attrition rate
Free of selective reporting?	Yes	Comment: all outcome were reported as mentioned in the methods section
Free of other bias?	Yes	

ADHD = attention-deficit/hyperactivity disorder

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

Study	Reason for exclusion
Abadi 2008	No randomization
Evans 2007	Not a clinical trial
Harrison 2004	Before-after design in 2 sequential groups, no true control group
Hassasiri 2002	Before-after design, no control group
Kratter 1982	Duplicate publication, less detailed than Kratter 1983
Peck 2005	Not diagnosed with ADHD
Zylowska 2008	Before-after design, no control group

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

Krisanaprakornkit 2008

Trial name or title	Breathing meditation with methylphenidate for the treatment of attention-deficit/hyperactivity disorder children: a randomized controlled trial
Methods	Randomized controlled trial
Participants	Inclusion criteria: - Children diagnosed with ADHD by a child psychiatrist using DSM-IV-TR criteria - Any religious background - Aged between 7 and 12 years Exclusion criteria: - Autistic spectrum disorders - Mental retardation
Interventions	Breathing meditation versus standard treatment control
Outcomes	1. Conners' Abbreviated Parent Questionnaire (continuous outcome) assessed by the parents at baseline, at the end of 4 weeks, at 8 weeks and at 12 weeks 2. Child Attention Problems (CAP) Rating Scale assessed at the same time
Starting date	April 2006
Contact information	Associate Professor Thawatchai Krisanaprakornkit Department of Psychiatry, Faculty of Medicine, Khon Kaen University, Thailand
Notes	Registered at www.ClinicalTrials.gov

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DATA AND ANALYSES

Comparison 1. Meditation therapy versus drug therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Teacher rating ADHD overall scale	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 2. Meditation therapy versus standard treatment without drug

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Teacher rating ADHD scale	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Distraction test	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Meditation therapy versus drug therapy, Outcome 1 Teacher rating ADHD overall scale.

Review: Meditation therapies for attention-deficit/hyperactivity disorder (ADHD)

Comparison: 1 Meditation therapy versus drug therapy

Outcome: 1 Teacher rating ADHD overall scale

Study or subgroup	Meditation N	Mean(SD)	Drug N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Moretti-Altuna 1987	9	12.11 (5.51)	6	14.83 (5.64)		-2.72 [-8.49, 3.05]

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Analysis 2.1. Comparison 2 Meditation therapy versus standard treatment without drug, Outcome 1 Teacher rating ADHD scale.

Review: Meditation therapies for attention-deficit/hyperactivity disorder (ADHD)

Comparison: 2 Meditation therapy versus standard treatment without drug

Outcome: 1 Teacher rating ADHD scale

Study or subgroup	Meditation N	Mean(SD)	Standard therapy control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Moretti-Altuna 1987	9	12.11 (5.51)	8	12.63 (5.73)		-0.52 [-5.88, 4.84]

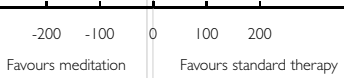
Analysis 2.2. Comparison 2 Meditation therapy versus standard treatment without drug, Outcome 2 Distraction test.

Review: Meditation therapies for attention-deficit/hyperactivity disorder (ADHD)

Comparison: 2 Meditation therapy versus standard treatment without drug

Outcome: 2 Distraction test

Study or subgroup	Meditation N	Mean(SD)	Standard therapy control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Moretti-Altuna 1987	9	247.72 (117.77)	8	256.06 (89.23)		-8.34 [-107.05, 90.37]



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APPENDICES

Appendix 1. Methods for data analysis in future updates of this review

Data analysis

Measures of treatment effect

Dichotomous outcomes

We will pool dichotomous outcomes using the risk ratio (RR) as the summary statistic. In cases where the numbers of participants and numbers of events are not available, but results calculated from them are (risk ratio, odds ratio, adjusted odds ratio), we will include the data in meta-analyses only if they are accompanied by measures of uncertainty such as 95% confidence intervals or exact P values. We will then pool the study-specific effect sizes using the generic inverse variance method in RevMan 5.0 (RevMan 2008).

Continuous outcomes

We will analyze data for continuous outcomes in RevMan 5.0 using either mean differences (MD) or standardized mean differences (SMD) if continuous outcomes are measured with similar, but not identical, instruments across studies. If the studies provide another statistic other than means and standard deviations (e.g. standard error, t-value, P value) we will perform the proper mathematical transformation to obtain standard deviations.

To ensure the appropriateness of meta-analysis, the following standards will be applied to all data before inclusion. To check for skewed data we will compare the mean to the standard deviation. If the mean is smaller than twice the standard deviation the data is probably skewed (Altman 1996). For data with finite limits, such as endpoint data, the observed mean minus the lowest possible value (or the highest possible value minus the observed mean), and dividing by the standard deviation. If the ratio is less than 1 there is strong evidence of a skewed distribution (Altman 1996). We will reveal the skewed data in additional tables. The endpoint score with standard deviation will be considered first in analysis if both endpoint score and change score are available. In cases where only change score is reported, we will contact authors of studies for endpoint figures. If only the change score is available, standard deviation of change score is needed for analysis and, if available, we will combine the data with endpoint scores (unless the standardized mean difference is used). If the available data cannot be managed by the above methods, we will present the data in 'other data' tables and use a narrative approach to synthesis.

If adjusted estimates of mean differences are presented from multiple regression analyses and analyses of covariance, the process of data extraction and analysis using the generic inverse variance method will be performed.

Unit of analysis issues

For cross-over studies, to exclude the potential additive effect in the second or further stages of these trials, we will only use data from the first stage in analysis. In studies with multiple treatment groups, we will carry out the analysis for each pair between meditation and other treatments. In studies with cluster-randomization (e.g. randomization by clinician or treatment settings), unless the cluster effect was accounted for, analysis and pooling of clustered data will result in unit of analysis error and overestimate statistical significance. In these cases, we will contact the authors of studies will be contacted to obtain intra-class correlation coefficients (ICC) of their clustered data and adjust by using accepted methods after consulting the Cochrane Developmental, Psychosocial and Learning Problems Group. Where clustering has been incorporated into the analysis of primary studies, we will also present these data as if from a non-clustered randomized study. If the cluster effect was not accounted for in primary studies and the ICC was not available, we will present the data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. The imputation of appropriate effect will be done by using the 'design effect' to calculate effective sample size. The design effect is 1+(m - 1)r, where m is the average cluster size and r is the intra-cluster correlation coefficient. If the ICC was not reported it will be assumed to be 0.05 (Higgins 2008).

In studies with repeated measures, we will carry out the analysis by separating the outcomes into short-term (up to three months), intermediate-term (three to 12 months) and long-term (more than 12 months).

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Dealing with missing data

For included studies which used an intention-to-treat analysis by filling in or imputation of data for missing cases (such as last observation carried forward method or assumed no changes), we will contact authors for available data.

Assessment of heterogeneity

We will carry out a test for homogeneity and calculate the I^2statistic, which provides an estimate of the percentage of variability due to heterogeneity, using Review Manager 5.0 (RevMan 2008).
Heterogeneity can occur from many sources. An important aspect of every meta-analysis is to consider and emphasize the existence of heterogeneity and to take account of this in the interpretation of results. Sources of heterogeneity (clinical heterogeneity) can be divided in to two groups: clinical data and type of meditation.
Clinical data:

- Subtypes of attention deficit/hyperactivity disorders, etc.
- Disorder severity and chronicity: mild, moderate, severe.
- Comorbidity of emotional/psychiatric problems, speech /language problems, learning problems, psychosocial problems, conduct disorder.

Type of meditation:
(a) Techniques:

- Concentrative, mindfulness meditation or combination.
- Combination of different techniques of meditation (physical and mental practice, such as yoga).
- Other ingredients of treatment: group activities, prayer, recreational activities, etc.

(b) Intensity and frequency of practice: duration of meditation per treatment session, frequency of practice, duration of practice.

- Different follow-up periods: at the end of trial, any specified period after trial, repeated follow-up measures.
- Multi-component intervention: drugs, counseling, biofeedback, parent training, psychotherapy, family therapy, etc.

Data synthesis

Meta-analysis should only be considered when a group of trials is sufficiently homogeneous in terms of participants, interventions and outcomes to provide a meaningful summary. We will use a fixed-effect model for all analyses if there is no statistical heterogeneity. We may use a random-effects meta-analysis to incorporate heterogeneity among trials only after exploring the causes of heterogeneity or when heterogeneity cannot readily be explained.
The data analysis will seek to answer the following questions.

1. What is the direction of effect of meditation?
2. What is the size of the effect of meditation?
3. Is the effect of meditation consistent across studies?
4. What is the strength of evidence for the effect of meditation?

Any meta-analysis will consider the following.

1. Different types of outcome (dichotomous, continuous, survival data).
2. Study design.
3. Follow up length (short-term, intermediate, long-term).

Subgroup analysis and investigation of heterogeneity

Due to clear differences in characteristics, rather than undertaking an overall pooled analysis, we will analyze the data in subgroups according to the following categories.

- Childhood (under 13 years).
- Adolescence (13 to 18 years).
- Adult ADHD (age more than 18 years).

We will only undertake subgroup analyses if a sufficient number of studies is identified.

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Sensitivity analysis

We will use a sensitivity analysis to test the robustness of effects of assumptions by examining the influence of the following on the results of the statistical analyses:

- the effect of the quality criteria (determine the effect of studies with high risk of bias on the overall effect); and
- blinding (masking) of raters.

Appendix 2. PubMed search strategy

("meditation"[mh] OR meditation[tw] OR "mindfulness-based"[tw] OR vipassana[tw] OR Zen[tw] OR yoga[tw] OR yogic[tw] OR pranayama[tw] OR Sudarshan[tw] OR Qi-gong[tw] OR Qigong [tw] OR "Chi kung "[tw] OR Kundalini[tw] OR ChunDoSunBup[tw] OR Reiki[tw] OR Tai Chi[tw]) AND ("Attention Deficit Disorder with Hyperactivity" [mh] OR "attention deficit/hyperactivity"[tw] OR attention def* [tw] OR ADHD [tw] OR ADD [tw] OR ADDH [tw] OR ADHS [tw] OR hyperactiv*[tw] OR hyperkin*[tw] OR "brain dysfunction"[tw]) AND (randomised controlled trial [pt] OR controlled clinical trial [pt] OR randomised controlled trials[mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR "clinical trial" [tw] OR singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw] OR mask* [tw] OR blind* [tw] OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT human [mh]).

Appendix 3. EMBASE search strategy

1 meditation/
2 meditation.tw.
3 mindfulness-based.tw.
4 vipassana.tw.
5 zen.tw.
6 yoga/
7 yoga.tw.
8 yogic.tw.
9 pranayama.tw.
10 sudarshan.tw.
11 qi-gong.tw.
12 qigong.tw.
13 chi kung.tw.
14 kundalini.tw.
15 ChunDoSunBup.tw.
16 reiki.tw.
17 tai chi.tw.
18 or/1-17
19 Attention Deficit Disorder/
20 (attention adj3 deficit$).tw.
21 adhd.tw.
22 addh.tw.
23 adhs.tw.
24 hyperactiv$.tw.
25 hyperkin$.tw.
26 minimal brain dysfunction$.tw.
27 or/19-26
28 18 and 27
29 clin$.tw.
30 trial$.tw.
31 (clin$ adj3 trial$).tw.

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32 singl$.tw.
33 doubl$.tw.
34 trebl$.tw.
35 tripl$.tw.
36 blind$.tw.
37 mask$.tw.
38 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
39 randomi$.tw.
40 random$.tw.
41 allocat$.tw.
42 assign$.tw.
43 (random$ adj3 (allocat$ or assign$)).tw.
44 crossover.tw.
45 44 or 43 or 39 or 38 or 31[M1]
46 exp Randomized Controlled Trial/
47 exp Double Blind Procedure/
48 exp Crossover Procedure/
49 exp Single Blind Procedure/
50 exp RANDOMIZATION/
51 46 or 47 or 48 or 49 or 50 or 45
52 51 and 28

Appendix 4. PSYCInfo Search Strategy

1. meditation/
2 meditation.tw.
3 mindfulness-based.tw.
4 vipassana.tw.
5 zen.tw.
6 yoga/
7 yoga.tw.
8 yogic.tw.
9 pranayama.tw.
10 sudarshan.tw.
11 qi-gong.tw.
12 qigong.tw.
13 chi kung.tw.
14 kundalini.tw.
15 ChunDoSunBup.tw.
16 reiki.tw.
17 tai chi.tw.
18 or/1-17
19 Attention Deficit Disorder/
20 (attention adj3 deficit$).tw.
21 adhd.tw.
22 addh.tw.
23 adhs.tw.
24 hyperactiv$.tw.
25 hyperkin$.tw.
26 minimal brain dysfunction$.tw.
27 or/19-26
28 18 and 27

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29 Treatment Effectiveness Evaluation/
30 exp Treatment Outcomes/
31 Psychotherapeutic Outcomes/
32 PLACEBO/
33 exp Followup Studies/
34 placebo$.tw.
35 random$.tw.
36 comparative stud$.tw.
37 randomi#ed controlled trial$.tw.
38 (clinical adj3 trial$).tw.
39 (research adj3 design).tw.
40 (evaluat$ adj3 stud$).tw.
41 (prospectiv$ adj3 stud$).tw.
42 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
43 control$.tw.
44 43 or 35 or 33 or 41 or 40 or 36 or 29 or 34 or 30 or 42 or 38 or 32 or 31 or 39 or 37
45 28 and 44

Appendix 5. CINAHL Search Strategy

1 meditation/
2 meditation.tw.
3 mindfulness-based.tw.
4 vipassana.tw.
5 zen.tw.
6 yoga/
7 yoga.tw.
8 yogic.tw.
9 pranayama.tw.
10 sudarshan.tw.
11 qi-gong.tw.
12 qigong.tw.
13 chi kung.tw.
14 kundalini.tw.
15 ChunDoSunBup.tw.
16 reiki.tw.
17 tai chi.tw.
18 or/1-17
19 Attention Deficit Disorder/
20 (attention adj3 deficit$).tw.
21 adhd.tw.
22 addh.tw.
23 adhs.tw.
24 hyperactiv$.tw.
25 hyperkin$.tw.
26 minimal brain dysfunction$.tw.
27 or/19-26
28 18 and 27
29 randomi$.mp.
30 clin$.mp.
31 trial$.mp.
32 (clin$ adj3 trial$).mp.

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33 singl$.mp.
34 doubl$.mp.
35 tripl$.mp.
36 trebl$.mp.
37 mask$.mp.
38 blind$.mp.
39 (33 or 34 or 35 or 36) and (37 or 38)
40 crossover.mp.
41 random$.mp.
42 allocate$.mp.
43 assign$.mp.
44 (random$ adj3 (allocate$ or assign$)).mp.
45 Random Assignment/
46 exp Clinical Trials/
47 exp Meta Analysis/
48 44 or 40 or 39 or 32 or 29 or 45 or 46 or 47
49 28 and 48

Appendix 6. LILACS search strategy

mediation or yoga or tai chi or reiki or mindfulness-based [Palavras] and attention deficit or adhd or addh or adhs

Appendix 7. OPENSIGLE search strategy

((meditation or yoga or reiki or tai chi or zen or mindfulness or vipassana or yogic or qigong or chi kung or kundalini or ChunDoSunBup))
AND
((attention deficit or adhd or addh or adhs or hyperactiv* or hyperkin* or minimal brain))

HISTORY

Protocol first published: Issue 2, 2007

Review first published: Issue 6, 2010

CONTRIBUTIONS OF AUTHORS

TK: protocol development, searching, data extraction, quality assessment and analysis.

CN: data extraction, quality assessment and statistical analysis.

CW: screening the potential included studies.

NP: quality assessment.

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DECLARATIONS OF INTEREST

TK runs the Meditation Therapy Clinic for various types of patients at the Department of Psychiatry, Faculty of Medicine, Khon Kaen University, Thailand.

TK is conducting a randomized controlled trial 'Breathing meditation with methylphenidate for the treatment of attention-deficit/hyperactivity disorder children', which is registered at www.ClinicalTrials.gov (Krisanaprakornkit 2008).

There are no potential conflict of interest for the other authors.

SOURCES OF SUPPORT

Internal sources

- Thai Cochrane Network, Thailand.
- Faculty of Medicine, Khon Kaen University, Thailand.
- Cochrane Developmental, Psychosocial and Learning Problems Group (CDPLPG), UK.

External sources

- Thailand Research Fund, Senior Research Scholar, Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed some sources of databases to be searched. We searched LILACS through the Virtual Health Library (VHL) in BIREME: Pan American Health Organization (PAHO), which incorporates many bibliographic databases in general health science (LILACS, MEDLINE, *The Cochrane Library*, SciELO), specialized areas (ADOLEC, BBO, BDENF, DESASTRES, HISA, HOMEOINDEX, LEYES, MEDCARIB, REPIDISCA) and international agencies (PAHO, WHOLIS).

The CISCOM database of The Research Council for Complementary Medicine was closed, therefore we searched other complementary and alternative medicine databases, i.e. CAM on PubMed, the web-site of the Cochrane Complementary and Alternative Health field, the Complementary Medicine Resources for Health Professionals and Researchers, and the Complementary and Alternative Therapies databases of Bandolier.

INDEX TERMS

Medical Subject Headings (MeSH)

*Yoga; Adolescent; Attention Deficit Disorder with Hyperactivity [drug therapy; * therapy]; Meditation [*methods]; Relaxation Therapy [methods]

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MeSH check words

Child; Female; Humans; Male

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Antibiotic prophylaxis for third- and fourth-degree perineal tear during vaginal birth (Review)

Buppasiri P, Lumbiganon P, Thinkhamrop J, Thinkhamrop B

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TABLE OF CONTENTS

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[Intervention Review]

Antibiotic prophylaxis for third- and fourth-degree perineal tear during vaginal birth

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ABSTRACT

Background

One to eight per cent of women suffer third-degree perineal tear (anal sphincter injury) and fourth-degree perineal tear (rectal mucosa injury) during vaginal birth, and these tears are more common after forceps delivery (28%) and midline episiotomies. Third- and fourth-degree tears can become contaminated with bacteria from the rectum and this significantly increases in the chance of perineal wound infection. Prophylactic antibiotics might have a role in preventing this infection.

Objectives

To assess the effectiveness of antibiotic prophylaxis for reducing maternal morbidity and side effects in third- and fourth-degree perineal tear during vaginal birth.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 August 2010) and the reference lists of retrieved articles.

Selection criteria

Randomised controlled trials comparing outcomes of prophylactic antibiotics versus placebo or no antibiotics in third- and fourth-degree perineal tear during vaginal birth.

Data collection and analysis

Two review authors independently assessed the reports and extracted data.

Main results

We identified and included one trial (147 participants) that compared the effect of prophylactic antibiotic (single-dose, second generation cephalosporin, intravenously) on postpartum perineal wound complications in third- or fourth-degree perineal tears. Perineal wound complications (wound disruption and purulent discharge) at the two-week postpartum check up were 8.20% and 24.10% in the treatment and the control groups respectively (risk ratio 0.34, 95% confidence interval 0.12 to 0.96).

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Authors' conclusions

Although the data suggest that prophylactic antibiotics help to prevent perineal wound complications following third- or fourth-degree perineal tear, loss to follow-up was very high. The results should be interpreted with caution as they are based on one small trial.

PLAIN LANGUAGE SUMMARY

Antibiotic prophylaxis for third- and fourth-degree perineal tear during vaginal birth

Most women are able to give birth without serious damage to their perineum. However, severe perineal trauma, which affects the muscle or tissue in the back passage, occurs in 1% to 8% of women giving birth and is common when forceps are used. There is an increased chance of infection when this happens, and antibiotics are often prescribed. The review of routine antibiotics for women with severe perineal tears identified one trial, involving 147 participants. This trial was conducted to explore the benefit of routine prophylactic antibiotics for women with severe perineal tears. The result showed fewer perineal wound complications when prescribing prophylactic antibiotic. However, the results are based on one small trial and there was a high loss to follow-up. More research is needed.

BACKGROUND

Episiotomy is the incision in the perineal area to enlarge the vaginal orifice for easier vaginal birth. It consists of two types: midline or median and mediolateral style. Many studies have shown that routine episiotomy can cause such problems as persistent perineal pain, unsatisfied postpartum sexual function, and increasing anal sphincter injury leading to faecal or flatus incontinence (Christianson 2003; Jones 2000; Labrecque 1997; Nager 2001; Signorello 2001). Pain in this area can impact not only on a woman's daily activity but also on her relationship with her baby and her partner. A restrictive episiotomy policy (strict criteria to perform episiotomy only in proper cases such as short stature mother with short perineum, large size baby, or imminent severe laceration of perineum) has been in place for many years and is strongly supported by a Cochrane systematic review (Carroli 1999). In addition, prenatal perineal massage has also been introduced into practice to prevent perineal tears (Davidson 2000; Eason 2000; Johanson 2000; Labrecque 1999). One randomised controlled trial failed to show the effectiveness of perineal massage but concluded that it did no harm (Stamp 2001).

Most women are able to give birth without serious damage to the perineum, but 1% to 8% of women suffer severe perineal tears (anal sphincter injury with or without rectal mucosa injury) during vaginal birth (De Leeuw 2001; Riskin-Mashiah 2002; Samuelsson 2000; Samuelsson 2002; Sultan 1994). These tears are more common after operative vaginal birth, especially when forceps are used. The incidence of severe perineal lacerations after the use of forceps has been reported as 21% for third-degree and 7% for fourth-degree tears (Bofill 1996). Other risk factors include race (Asian women have the highest risk, perhaps due to small size mother and short perineum), midline episiotomy (short distance to anal sphincter), nulliparity (lesser elasticity than a multiparous mother), and high birthweight baby (De Leeuw 2001; Goldberg 2003; Homsi 1994; Jones 2000; Labrecque 1997; Nager 2001; Sultan 1994).

When a woman has a severe perineal tear during vaginal birth, there is thought to be an increased risk of infection. Laceration of the vagina and perineum during vaginal birth are classified as first, second, third and fourth degree. First-degree tears involve the vaginal mucosa and connective tissue. Second-degree tears involve the vaginal mucosa, connective tissue and underlying muscles. Third-degree tears involve a complete transection of anal sphincter and fourth-degree tears involve the rectal mucosa (Cunningham 2001; WHO 2003). When the rectal mucosa is ruptured, the wound is classified as contaminated (Waddell 1994) or clean-contaminated (Mangram 1999). Antibiotic prophylaxis is generally used where wounds have become, or are likely to become, contaminated, such as in colorectal surgery (Oates 1986; Song 1998). A Cochrane review has also shown antibiotic prophylaxis to be effective in reducing puerperal morbidity after cesarean section (Smaill 2002). On the other hand, a Cochrane review on antibiotic prophylaxis after operative vaginal birth could not conclude its effectiveness (Liabsuetrakul 2004).

A woman contracting infection after a severe perineal tear may also be at risk of other morbidities as a result of the tear, such as haematoma, dyspareunia, incontinence and recto-vaginal fistula (Crawford 1993; Homsi 1994; Labrecque 1997; Nager 2001; Signorello 2001; Sorensen 1988; Sultan 2002; WHO 2003).

While some authorities recommend that prophylactic antibiotics

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be used for severe perineal tears (WHO 2003), others have recommended against this course of action (Whitfield 1995). As widespread use of antibiotics may contribute to antibiotic-resistant bacteria (Towers 1998; Weinstein 1996), the over-use of antibiotics is being discouraged by many groups. However, antibiotic prophylaxis is a low-cost, accessible intervention which may prevent considerable maternal morbidity. It is therefore, important to establish the benefits of prophylactic antibiotics for infection after severe perineal tears, and also to assess whether there are any adverse effects on mother or infant, by systematically reviewing the evidence.

OBJECTIVES

To assess the effectiveness of antibiotic prophylaxis for reducing maternal morbidity and side effects in third- and fourth-degree perineal tear during vaginal birth.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials. We did not plan to include quasi-randomised controlled, crossover trials or include studies that were presented only as abstracts.

Types of participants

Mothers with third- and fourth-degree perineal tears as a result of vaginal birth.

Types of interventions

Antibiotic regimens used to prevent perineal wound infection compared either to placebo, or to no treatment, antibiotic treatment in women who get infection only, and comparisons between different antibiotic regimens.

Types of outcome measures

Primary outcomes

1. Fever or puerperal febrile morbidity (body temperature of 38ºC or higher occurring on any two occasions in the first 10 days postpartum, exclusive of the first 24 hours).
2. Perineal wound complications, including infection (edematous, erythematous, wound edge with pain, serosanguinous or frankly purulent material), or wound dehiscence (wound separation).

Secondary outcomes

1. Serious infectious complications (such as bacteraemia, septic shock, septic thrombophlebitis, necrotising fasciitis, or death attributed to infection).
2. Pain (wound pain score or variously measured by authors).
3. Woman's comfort (unable to sit down or breast feed) while in hospital and six weeks postpartum.
4. Length of hospital stay for mother.
5. Adverse reaction (such as allergic reaction, anaphylaxis, diarrhoea).
6. Maternal-infant interactions including breastfeeding.
7. Sexual function including dyspareunia (pain on sexual intercourse), sexual satisfaction, sexual sensation, time to resuming sexual intercourse.
8. Woman's satisfaction.
9. Recto-vaginal fistula (hole between the vagina and rectum).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group Trials Register by contacting the Trials Search Co-ordinator (31 August 2010).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

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For details of additional searching carried out by authors for the initial version of the review, *see:* Appendix 1.

Searching other resources

We checked the references of retrieved articles to locate other relevant trials.
We did not apply any language restrictions.

Data collection and analysis

For this update we used the following methods when assessing the one trial identified by the updated search (Duggal 2008).

Selection of studies

Two review authors independently assessed for inclusion the report we identified as a result of the updated search. There were no disagreements.

Data extraction and management

We designed a form to extract data. For the eligible study, two review authors extracted the data using the agreed form. We would have resolved discrepancies through discussion or consulted a third person. We entered data into Review Manager software (RevMan 2008) and checked them for accuracy.
We contacted the contact author of the original report who provided additional data.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for the study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009). We would have resolved any disagreement by discussion or by involving a third assessor.

(1) Sequence generation (checking for possible selection bias)

We described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We assessed the method as:

- adequate (any truly random process, e.g. random number table; computer random number generator);
- inadequate (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear.

(2) Allocation concealment (checking for possible selection bias)

We described the method used to conceal the allocation sequence and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We assessed the methods as:

- adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear.

(3) Blinding (checking for possible performance bias)

We described the methods used, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding could not have affected the results. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed the methods as:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We described for the included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we re-included missing data in the analyses which we undertook. We assessed methods as:

- adequate; lost follow-up rate was 20% or less;
- inadequate; lost follow-up rate more than 20%;
- unclear; no information.

(5) Selective reporting bias

We described how we investigated the possibility of selective outcome reporting bias and what we found.
We assessed the methods as:

- adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were

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not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);

- unclear.

(6) Other sources of bias

We described any important concerns we have about other possible sources of bias, such as the trial stopped early due to some data-dependent process, extreme baseline imbalance, the study been claimed to be fraudulent:

- yes;
- no;
- unclear.

(7) Overall risk of bias

We made explicit judgements about whether the study was at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2009). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we used the mean difference if outcomes are measured in the same way between trials. We used the standardised mean difference to combine trials that measure the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials

We planned to include cluster-randomised trials in the analyses along with individually randomised trials. We planned to adjust their sample size using the methods described in the *Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we planned to report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we planned to synthesise the relevant information. We planned to consider it reasonable to combine the results from both if there was little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit was considered to be unlikely.

We planned to acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Dealing with missing data

For included studies, we noted levels of attrition. We explored the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and to analyse all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial would be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if T^2 was greater than zero and either I^2 was greater than 30% or there was a low P-value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there were 10 or more studies in the meta-analysis, we planned to investigate reporting biases (such as publication bias) using funnel plots. We planned to assess funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry. For continuous outcomes, we planned to use the test proposed by Egger 1997, and for dichotomous outcomes we planned to use the test proposed by Harbord 2006. If asymmetry was detected in any of these tests or was suggested by a visual assessment, we planned to perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2008). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. If there was clinical

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heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary if an average treatment effect across trials was considered clinically meaningful. We would treat the random-effects summary as the average range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we would not combine trials.

If we used random-effects analyses, we planned to present the results as the average treatment effect with its 95% confidence interval, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we had identified substantial heterogeneity, we planned to investigate it using subgroup analyses and sensitivity analyses. We planned to consider whether an overall summary was meaningful, and if it was, use random-effects analysis to produce it.

We planned to carry out the following subgroup analyses.

1. Immunocompromised versus not immunocompromised pregnant women, such as HIV infection, chronic steroid use.
2. Women with prolonged prelabour rupture membranes versus women not.
3. Women with preterm preterm prelabour rupture membranes versus not.
4. Third degree tears compared with fourth degree tears.

We would restrict subgroup analysis to the following outcomes:

1. Fever or puerperal febrile morbidity.
2. Perineal wound infection.

For fixed-effect inverse variance meta-analyses we would assess differences between subgroups by interaction tests. For random-effects and fixed-effect meta-analyses using methods other than inverse variance, we would assess differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis

We would perform sensitivity analyses for aspects of the review that might affect primary outcomes (fever or puerperal febrile morbidity and perineal wound infection), such as where there was risk of bias associated with the quality of some of the included trials. We planned to carry out sensitivity analysis to explore the effects of fixed-effect or random-effects analyses for primary outcomes with statistical heterogeneity and the effects of any assumptions made, such as the value of the ICC used for cluster-randomised trials.

RESULTS

Description of studies

See: Characteristics of included studies.

Results of the search

The updated search in December 2009 identified two reports of one study (Duggal 2008) - *see* Characteristics of included studies for details.

Risk of bias in included studies

The one included study was terminated before it reached the preplanned sample size and had a high rate of loss to follow-up (Duggal 2008).

Effects of interventions

Single dose, second generation cephalosporin intravenously (cefotetan or cefoxitin, 1 g, intravenously, or clindamycin, 900 mg intravenously if allergic to penicillin, in 100 ml of saline) was used as the intervention to prevent perineal wound infection or disruption in the third- or fourth-degree perineal tear compared with placebo (100 ml of normal saline intravenously) .

The primary outcome of the included study was gross disruption or purulent discharge at the site of perineal repair by two weeks postpartum.

Perineal wound complications at two weeks postpartum in treatment and control groups were four of 49 (8.20%) and 14 of 58 (24.10%) respectively (P = 0.037, risk ratio (RR) 0.34, 95% confidence interval (CI) 0.12 to 0.96).

Perineal wound infection before discharge and at six weeks postpartum was also reported. There were no perineal wound complications before hospital discharge in both groups. One hundred and twenty-eight participants were checked at six weeks postpartum (19 of 147 (12.9%) did not come for follow-up at six-weeks). There were perineal wound complications in four out of 55 (7.3%) and 14 out of 73 (19.2%) women in the treatment and control groups respectively, (P = 0.07, RR 0.38, 95% CI 0.13 to 1.09).

DISCUSSION

Summary of main results

There were marginally significantly fewer perineal wound complications at two weeks postpartum in the intervention group. There was no statistically significant difference in perineal wound complications before discharge and at six weeks postpartum. However,

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loss to follow-up was 27.2% and 12.9 % at two and six weeks postpartum respectively.

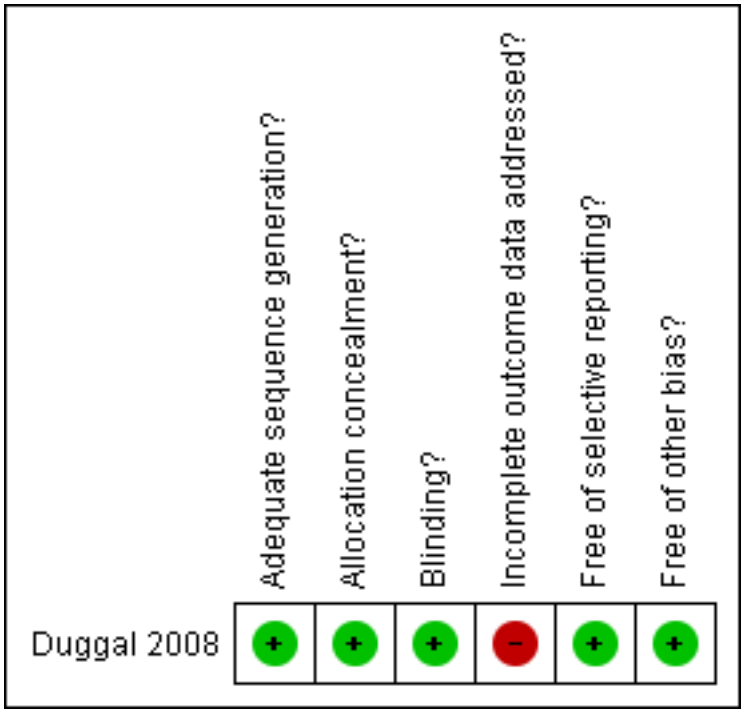
Overall completeness and applicability of evidence

The one included study, conducted in a developed country, with a relatively high loss of follow-up, provides insufficient data to address the objectives of this review.

Quality of the evidence

The risk of bias for the one included study in this review is high - *see* Figure 1. Inadequate sample size and high loss to follow-up rate do not allow us to draw a firm conclusion about the benefit of antibiotic prophylaxis in third- or fourth-degree perineal tear after vaginal birth.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Potential biases in the review process

We adhered to the Cochrane Pregnancy and Childbirth Group search strategies and review process. We are not aware of any potential bias in the review process.

Agreements and disagreements with other studies or reviews

There are no other studies or reviews addressing this clinical question.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence from the one included study is not strong enough to recommend prophylactic antibiotics for third- or fourth-degree perineal tear after delivery.

Implications for research

Well-designed, multicentre, randomised controlled trials are

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needed before prophylactic antibiotics for third- and fourth-degree perineal tear after vaginal birth can be recommended.

ACKNOWLEDGEMENTS

The review authors would like to thank the authors of Duggal 2008 for providing additional data which will be incorporated into the next update of this review. The review authors would also like to thank the editorial board for their comments, members of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

REFERENCES

References to studies included in this review

Duggal 2008 ***{published data only}***

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Duggal 2008

Methods	Type of study: prospective, randomised, placebo-controlled trial. Method: randomisation was done by using a random-numbers table. Women were randomly assigned to a single dose of antibiotic (cefotetan or cefoxitin, 1 g, intravenously, or clindamycin, 900 mg intravenously if allergic to penicillin, in 100 ml of saline) or placebo (100 ml of normal saline intravenously). The nurse was instructed to open the envelope and administer the medication or placebo. The log book was kept in a secure location in medication room. Placebo: yes, normal saline was used. Sample size: to demonstrate a 75% reduction in perineal infection rate with an alpha of 0.05 and a power of 80%, 310 participants (155 on each arm) were needed. Only 147 participants (83 in placebo group, 64 in treatment group) were enrolled in a 3-year period. Intention-to-treat basis: yes. Loss to follow-up: 27.2% (40 of 147) participants lost at 2-week postpartum check up. 107 participants visited at 2-week postpartum check up. 23.4% (15 of 64) were missed in treatment group, and 30.1% (25 of 83) in control group. 19 of 147 (12.9%) participants were lost to follow-up at the 6-week postpartum check up.
Participants	Location: Santa Clara Valley Medical Center and Stanford University Medical Center's Lucile Parkard Children's Hospital. California, San Francisco, USA. Time frame: September 2003-June 2006. Eligible criteria: women who sustained third- or fourth-degree perineal laceration after vaginal deliveries. Exclusion: age < 18 years, group B streptococcus positive, human immunodeficiency virus positive, had chorioamnionitis or history of inflammation bowel disease, or were already on antibiotics for any reason. Total recruited: 147 participants. Treatment group: 64 participants, control group = 83 participants.
Interventions	Treatment group: 64 participants. Control group: 83 participants.
Outcomes	Perineal wound infection rate (gross disruption or purulent discharge at site of perineal repair) by 2 weeks postpartum.
Notes	There were 310 preplanned participants (155 in each arm). The authors decided to terminated the study after 3 years of enrolment because they could not achieve the preplanned number of participants within a reasonable time period. Many women refused to participate and many missed enrolment due to busy labour and delivery wards. Only 147 participants were recruited: 64 cases in intervention group and 83 in the control group.
Risk of bias	

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Duggal 2008 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation was done by using a random numbers table.
Allocation concealment?	Yes	The nurse from another ward was instructed to open the randomisation envelope and administer the medication or placebo. The logbook was kept in a secure location in the medication room.
Blinding? All outcomes	Yes	No physician was involved in preparing the study medication, and obstetricians did not in practice prepare or retrieve medication from the medication room. The registered nurse providing postpartum care was on another floor and did not have access to the log book.The clinician evaluating the women postpartum did not have access to the log book and did not have a way of determining which arm a woman had been randomised to.
Incomplete outcome data addressed? All outcomes	No	107 of 147 participants visited for the 2-week postpartum check up, then 27.2 % were lost to follow-up; 15 of 64 (23.4%) in intervention group and 25 of 83 (30.1%) in the control group.
Free of selective reporting?	Yes	The authors reported perineal wound complication rates before discharge, and at the 2- and 6-week postpartum check ups.
Free of other bias?	Yes	It is unlikely to have other bias.

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DATA AND ANALYSES

Comparison 1. Antibiotic prophylaxis versus no treatment for perineal tear

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Infection rate at 2 weeks postpartum	1	107	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.12, 0.96]
1.1 Perineal wound infection in third- or fourth-degree tear	1	107	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.12, 0.96]
1.2 Perineal wound infection in third-degree tear	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3 Perineal wound infection in fourth-degree tear	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Infection rate at 6 weeks postpartum	1	128	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.13, 1.09]
2.1 Perineal wound infection in third- or fourth-degree tear	1	128	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.13, 1.09]
2.2 Perineal wound infection in third-degree tear	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.3 Perineal wound infection in fourth-degree tear	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

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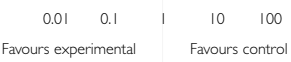
Analysis 1.1. Comparison 1 Antibiotic prophylaxis versus no treatment for perineal tear, Outcome 1 Infection rate at 2 weeks postpartum.

Review: Antibiotic prophylaxis for third- and fourth-degree perineal tear during vaginal birth

Comparison: 1 Antibiotic prophylaxis versus no treatment for perineal tear

Outcome: 1 Infection rate at 2 weeks postpartum

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Perineal wound infection in third- or fourth-degree tear					
Duggal 2008	4/49	14/58		100.0 %	0.34 [0.12, 0.96]
Subtotal (95% CI)	**49**	**58**		**100.0 %**	**0.34 [0.12, 0.96]**
Total events: 4 (Experimental), 14 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.04 (P = 0.042)					
2 Perineal wound infection in third-degree tear					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Perineal wound infection in fourth-degree tear					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**49**	**58**		**100.0 %**	**0.34 [0.12, 0.96]**
Total events: 4 (Experimental), 14 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.04 (P = 0.042)					



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Analysis 1.2. Comparison 1 Antibiotic prophylaxis versus no treatment for perineal tear, Outcome 2 Infection rate at 6 weeks postpartum.

Review: Antibiotic prophylaxis for third- and fourth-degree perineal tear during vaginal birth

Comparison: 1 Antibiotic prophylaxis versus no treatment for perineal tear

Outcome: 2 Infection rate at 6 weeks postpartum

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Perineal wound infection in third- or fourth-degree tear					
Duggal 2008	4/55	14/73		100.0 %	0.38 [0.13, 1.09]
Subtotal (95% CI)	**55**	**73**		**100.0 %**	**0.38 [0.13, 1.09]**
Total events: 4 (Experimental), 14 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.80 (P = 0.072)					
2 Perineal wound infection in third-degree tear					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Perineal wound infection in fourth-degree tear					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**55**	**73**		**100.0 %**	**0.38 [0.13, 1.09]**
Total events: 4 (Experimental), 14 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.80 (P = 0.072)					

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APPENDICES

Appendix 1. Search strategy

For the initial version of the review, authors searched CENTRAL (*The Cochrane Library* 2005, Issue 2), MEDLINE (1966 to 15 July 2005) using the strategy below:
#1 PERINEUM single term (MeSH)
#2 perine*
#3 (tear* or injur* or lacerat* or trauma or damage*)
#4 (#2 and #3)
#5 (anal near sphincter) or (rectal mucosa) or rectum or (anal epithelium) or anus or (recto-vaginal fistulae) or (anorectal mucosa) or (anal skin)
#6 (tear* or injur* or damage* or lacerat* or rupture* or trauma)
#7 (#5 and #6)
#8 (obstetric* near tear*) or (obstetric near lacerat*)
#9 EPISIOTOMY single term (MeSH)
#10 episiotom* or postepisiotom*
#11 EXTRACTION OBSTETRICAL explode tree 1 (MeSH)
#12 vacuum or ventouse or forcep*
#13 deliver*
#14 (birth or childbirth or child-birth or (child next birth))
#15 antibio*
#16 ANTIBIOTICS explode all trees (MeSH)
#17 (#1 or #4 or #7 or #8)
#18 (#9 or #10 or #11 or #12 or #13 or #14)
#19 (#15 or #16)
#20 (#17 and #18 and #19)

WHAT'S NEW

Last assessed as up-to-date: 3 October 2010.

Date	Event	Description
31 August 2010	New search has been performed	Search updated, no new studies identified. One trial identified in the previous updated search has now been included (Duggal 2008). The methods have been updated to reflect the latest Cochrane Handbook. A note about the next update of this review has been added to Published notes.
31 August 2010	New citation required and conclusions have changed	The scope of the review has changed to include both 3rd and 4th degree perineal tears.

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HISTORY

Protocol first published: Issue 1, 2005

Review first published: Issue 4, 2005

Date	Event	Description
1 December 2009	Amended	Search updated. Two new reports identified.
13 February 2009	Amended	Contact details updated.
1 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Pranom Buppasiri (PB) and Pisake Lumbiganon (PL) formulated the review question. PB drafted the protocol. PB, PL, Jadsada Thinkhamrop (JT) and Bandit Thinkhamrop (BT) revised and approved the final version of the protocol. PB drafted the review. PL, JT and BT revised and approved the final version of the review. All authors approved the final version of the update review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Faculty of Medicine, Khon Kaen University, Thailand.

External sources

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have broadened the inclusion criteria to include women with third-degree tears and divided the outcomes into primary and secondary.

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NOTES

The review authors have contacted the trialists of the one included trial (Duggal 2008) in order to obtain the data separated by degree of perineal tear (3rd or 4th degree). These data will be added to the next update of this review, and we plan to carry out subgroup analysis by degree of perineal tear.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antibiotic Prophylaxis; Anal Canal [injuries]; Delivery, Obstetric [*adverse effects]; Rectum [*injuries]; Rupture [etiology]; Wound Infection [*prevention & control]

MeSH check words

Female; Humans; Pregnancy

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Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections (Review)

Siriwachirachai T, Sangkomkamhang US, Lumbiganon P, Laopaiboon M

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 12

http://www.thecochranelibrary.com

Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections (Review)
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TABLE OF CONTENTS

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[Intervention Review]

Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections

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ABSTRACT

Background

Chorioamnionitis is more likely to occur when meconium-stained amniotic fluid (MSAF) is present. Meconium may enhance the growth of bacteria in amniotic fluid by serving as a growth factor, inhibiting bacteriostatic properties of amniotic fluid. Many adverse neonatal outcomes related to MSAF result from Meconium Aspiration Syndrome (MAS). MSAF is associated with both maternal and newborn infections. Antibiotics may be an effective option to reduce such morbidity.

Objectives

The objective of this review is to assess the efficacy and side effects of prophylactic antibiotics for MSAF during labour in preventing maternal and neonatal infections.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 September 2010).

Selection criteria

Randomized controlled trials (RCTs) comparing prophylactic antibiotics with placebo or no treatment during labour for women with MSAF.

Data collection and analysis

Two review authors independently assessed the results of the only available trial and extracted data on maternal and neonatal outcomes.

Main results

We included one study with 120 pregnant women. It compared ampicillin-salbactam (N = 60) versus normal saline (N = 60) in pregnant women with MSAF. Prophylactic antibiotics appeared to have no statistically significant reduction in the incidence of neonatal sepsis (risk ratio (RR) 1.00, 95% CI 0.21 to 4.76), neonatal intensive care unit (NICU) admission (RR 0.83, 95% CI 0.39 to 1.78) and postpartum endometritis (RR 0.50, 95% CI 0.18 to 1.38). However, significant decrease in the risk of chorioamnionitis (RR 0.29, 95% CI 0.10 to 0.82). No serious adverse effects were reported.

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Authors' conclusions

Current evidence indicates that compared to placebo, antibiotics for MSAF in labour may reduce chorioamnionitis. There was no evidence that antibiotics could reduce postpartum endometritis, neonatal sepsis and NICU admission. This systematic review identifies the need for more well-designed, adequately powered RCTs to assess the effect of prophylactic antibiotics in the incidence of maternal and neonatal complications.

PLAIN LANGUAGE SUMMARY

Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections

Meconium-stained amniotic fluid (MSAF) is the result of waste maternal from the fetal colon passing into the mother's amniotic cavity. Its incidence increases in post-term pregnancies. Pregnant women with MSAF are more likely to develop maternal complications including inflammation of the fetal membranes caused by a bacterial infection (chorioamnionitis), postpartum inflammation of the lining of the uterus (endometritis) and neonatal complications such as neonatal sepsis and need for admission to a neonatal intensive care unit (NICU) . Fetal stress or hypoxia may trigger gasping fetal respirations, which results in the aspiration of meconium.

Our review was based on one identified randomized controlled study (involving 120 women) and found that prophylactic antibiotics may reduce the risk of intra-amniotic infection in women with MSAF. Antibiotics use did not clearly reduce neonatal sepsis, NICU admission or postpartum endometritis. Studies with much larger numbers of pregnant women with MSAF would be needed to examine these issues.

BACKGROUND

Description of the condition

Meconium-stained amniotic fluid (MSAF), as a result of the passage of fetal colonic contents into the amniotic cavity, occurs in approximately 12% of all deliveries (Cleary 1998). The incidence of intrapartum MSAF ranges from 7% to 22% for a term pregnancy but this figure increases to up to 40% in a post-term pregnancy (Katz 1992). The composition of meconium from a term fetus is primarily water (70% to 80%). Other constituents include mucopolysaccharides, cholesterol and its precursors, proteins, lipids, bile acids and salts (giving the characteristic green colour), pancreatic enzymes, interleukin-8, phospholipase A2, squamous cells, and vernix caseosa (Cleary 1998; Usta 2000).

MSAF may act directly and indirectly on exposed tissue. Its effects depend on the concentration of meconium, duration of exposure, and the presence of associated stress factors (hypoxia, infection). MSAF has long been associated with potentially adverse fetal outcomes including meconium aspiration syndrome (MAS), admission to neonatal intensive care unit (NICU), neonatal sepsis, cerebral palsy, seizure and pulmonary diseases (Berkus 1994; Katz 1992; Nathan 1994). Many adverse neonatal outcomes related to MSAF result from MAS. MAS occurs in 5% of the cases of MSAF and more than 4% of infants with MAS die, accounting for 2% of all perinatal deaths (Cleary 1998; Wiswell 1990). Hypoxia is the key factor that triggers gasping fetal respirations, which results in the aspiration of meconium. Most cases of MAS probably result from in utero aspiration rather than aspiration at the time of delivery. In addition to possibly contributing to respiratory distress in the neonate, MSAF has been associated with a higher risk of neonatal infection (Romero 1991). Chorioamnionitis is a risk factor for neonatal sepsis, which results in NICU admissions and potential fetal morbidity and death (Alexander 1999). Fetal microbial invasion has been proposed to cause inflammatory brain damage through the effects of elevated cytokines (e.g. TNF alpha, IL-1 beta,and IL-6) (Hoskins 1987).

Chorioamnionitis is also more likely to occur when MSAF is present (Mazor 1995; Romero 1991; Usta 2000). The risk of clinical chorioamnionitis and histological chorioamnionitis in patients with intrapartum MSAF is significantly higher than those with clear fluid. The risk for clinically diagnosed endometritis is twofold (Markovitch 1993; Mazor 1995). Intrapartum chorioamnionitis is associated with dystocia and increased risk for operative delivery (Casey 1997; Mark 2000). Unrecognized or undertreated chorioamnionitis can lead to postpartum endomyometritis which can result in further maternal morbidity, and increased length of stay in hospital and hospital costs. MSAF is the risk factor for microbial invasion of the amniotic cavity in patients

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with intact membranes and preterm labour (Romero 1991). Maternal infection is also more likely in the presence of MSAF. Patients with MSAF were almost two and a half times as likely to develop postoperative endometritis (Josephson 1984). There are statistically significant associations between MSAF and puerperal infection in term deliveries (Piper 1998). Puerperal infection rates are associated with the degree of meconium staining, with rates rising as meconium thickness increases (Tran 2003). There is a three-fold increase in positive amniotic fluid cultures in patients with MSAF compared to those with clear amniotic fluid (Mazor 1995; Romero 1991).The most common amniotic fluid isolates in MSAF are anaerobes, *Ureaplasma urealyticum, Streptococci, Escherichia coli, Candida albicans* and *Listeria monocytogenes* (Mazor 1995; Romero 1991).

Meconium may enhance the growth of bacteria in amniotic fluid by serving as a growth factor, inhibiting bacteriostatic properties of amniotic fluid, or antagonizing host defence systems, thus increasing the risk of chorioamnionitis. Generally, amniotic fluid is a poor culture medium for *Escherichia coli, Listeria monocytogenes* and *Staphylococcus aureus;* however, with enough meconium, amniotic fluid becomes an excellent culture medium (Florman 1969). Meconium may alter the zinc-to-phosphorous ratio in amniotic fluid and facilitate bacterial growth and decrease host defences (Hoskins 1987). Light and very light MSAF significantly impair mechanisms for intracellular microbial killing. Phagocytic ability of neutrophils was also significantly diminished in the presence of moderate MSAF (Clark 1995). Mechanisms of meconium associated puerperal infections include altering the antibacterial properties of amniotic fluid and enhancing bacterial growth, impairing the host immune response through the inhibition of phagocytosis and neutrophil oxidative burst (Clark 1995; Katz 1992).

Description of the intervention

One study has shown a significant reduction in the rate of clinical chorioamnionitis when the intervention ampicillin-sulbactam was administered prophylactically for the indication of MSAF (Edwards 1999).

How the intervention might work

Antibiotics can be bacteriostatic (they stop bacteria from multiplying) or bactericidal (they kill the bacteria). To perform either of these functions, antibiotics must be brought into contact with the bacteria. Antibiotics are thought to interfere with the surfactant of bacteria cells, causing a change in their ability to reproduce (Heizmann 2007). Gentamicin is an aminoglycoside antibiotic with bactericidal activity that acts at the 30S bacterial ribosomal subunit, inhibiting the synthesis of bacterial proteins (Ward 2008).

Why it is important to do this review

Cochrane reviews have addressed a number of issues about MAS including steroid therapy, endotracheal intubation, surfactant and antibiotics for neonates (Halliday 2001; Shivananda 2006; Ward 2003). Other interventions include amnioinfusion for MSAF in labour (Hofmeyr 2002). Prophylactic intravenous intrapartum ampicillin-sulbactam therapy or cefazolin infusion into the amniotic cavity during amnioinfusion in mothers with MSAF did not show any benefit in reducing chorioamnionitis, endometritis and neonatal sepsis (Adair 1996; Edwards 1999). However, the role of antibiotics for MSAF during labour has not been systematically evaluated.

OBJECTIVES

The objective of this review is to assess the efficacy and side effects of prophylactic antibiotics for meconium-stained amniotic fluid during labour in preventing maternal and neonatal infections.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomized controlled trials (RCTs) of prophylactic antibiotic administration during labour for women with MSAF. We excluded quasi-RCTs.

Types of participants

Pregnant women with a gestational age of more than 22 weeks who were in labour and had MSAF.

Types of interventions

Systemic prophylactic antibiotics started during labour in women with MSAF compared with no treatment or placebo.

Types of outcome measures

The primary outcomes were the most clinically important for the neonate, whereas the secondary outcomes also included maternal and neonatal complications.

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Primary outcomes

1. Early onset neonatal sepsis (symptomatic before 72 hours of age).
2. Late onset neonatal sepsis (symptomatic after 72 hours of age).

(Definition of sepsis as defined by authors)

Secondary outcomes

Maternal

1. Intrapartum chorioamnionitis.
2. Postpartum endometritis.
3. Side effects of treatment, e.g. drug allergy, anaphylactic shock.
4. Drug resistance.

Neonatal

1. Mortality and morbidity prior to discharge, e.g. birth asphyxia, intracranial haemorrhage, intraventricular haemorrhage, necrotizing enterocolitis and admission to neonatal intensive care unit.
2. Duration of mechanical ventilation (days).
3. Duration of admission to neonatal intensive care unit/ hospital.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (30 September 2010).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Thitiporn Siriwachirachai (TS) and Ussanee Sangkomkamhang (US) independently assessed trials for inclusion and methodological; quality. There were no disagreements.

Data extraction and management

We designed a form to extract data. For eligible studies, TS and US independently extracted the data using the agreed form. There were no discrepancies. We entered the data into Review Manager software (RevMan 2008) and checked for accuracy. We did not contact the original study authors because the reported information was sufficient in the report.

Assessment of risk of bias in included studies

TS and US independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009).

(1) Sequence generation (checking for possible selection bias)

We described for included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- adequate (any truly random process, e.g. random number table; computer random number generator);
- inadequate (any non random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear.

(2) Allocation concealment (checking for possible selection bias)

We described for included study the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

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- adequate (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear.

(3) Blinding (checking for possible performance bias)

We described for included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We judged studies at low risk of bias if they were blinded, or if we judged that the lack of blinding could not have affected the results. We assessed blinding separately for different outcomes or classes of outcomes. We assessed the methods as:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors;

where 'adequate' is when there was blinding or where we assess that the outcome or the outcome measurement is not likely to have been influenced by lack of blinding.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We described for included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, we assessed methods as:

- adequate;
- inadequate;
- unclear.

We discussed whether missing data greater than 20% might (a) be reasonably expected (acknowledging that complete data are difficult to attain), and (b) impact on outcomes.

(5) Selective reporting bias

We described for the included trial how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- adequate (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear.

(6) Other sources of bias

We described for the included study any important concerns we have about other possible sources of bias. We assessed whether study was free of other problems that could put it at risk of bias:

- yes;
- no;
- unclear.

(7) Overall risk of bias

We made explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We did not explore the impact of the level of bias through undertaking sensitivity analyses because we included only one study.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratios (RR) with 95% confidence intervals (CIs) .

Continuous data

For continuous data, we used the mean difference if outcomes were measured in the same way between trials. We used the standardized mean difference to combine trials that measure the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomized trials

We included only one RCTs. In future updates, if we identify cluster-randomized trials, we will include these in the analyses along with individually randomized trials. We will adjust their sample sizes using the methods described in the *Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population (Higgins 2009). If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both

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cluster-randomized trials and individually-randomized trials, we plan to synthesize the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and we consider the interaction between the effect of intervention and the choice of randomization unit to be unlikely.
We will also acknowledge heterogeneity in the randomization unit and perform a subgroup analysis to investigate the effects of the randomization unit.

Dealing with missing data

For the included study, we noted levels of attrition. We explored the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.
For all outcomes, we have carried out analyses, as far as possible, on an intention-to-treat basis; i.e. we attempted to include all participants randomized to each group in the analyses, and analyze all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial is the number randomized minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

This review did not include meta-analysis. In future updates, as more data become available, we will assess statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if T^2 is greater than zero and either I^2 is greater than 30% or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

In subsequent updates of this review, if there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry. For continuous outcomes we will use the test proposed by Egger 1997, and for dichotomous outcomes we will use the test proposed by Harbord 2006. If asymmetry is detected in any of these tests or is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2008). This review only included one RCT so we did not pool any data. In future updates, if more data become available, we will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials is considered clinically meaningful. We will treat the random-effects summary as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful we will not combine trials.
If we use random-effects analyses, we will present the results as the average treatment effect with its 95% confidence interval, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

In future updates of this review, when sufficient data become available, we plan to carry out the following subgroup analyses:

1. intact versus rupture membrane;
2. single versus combine antibiotic regimens;
3. duration of antibiotics less than 24 hours versus more than 24 hours.

We will use the following outcomes in subgroup analysis:

- early onset neonatal sepsis (symptomatic before 72 hours of age);
- late onset neonatal sepsis (symptomatic after 72 hours of age).

For fixed-effect inverse variance meta-analyses we will assess differences between subgroups by interaction tests. For random-effects and fixed-effect meta-analyses using methods other than inverse variance, we will assess differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis

In subsequent updates we also plan to conduct a sensitivity analysis comparing the results using all studies and using only those of high methodological quality.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

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Results of the search

We identified four publications as potentially eligible for inclusion in this review.

Included studies

This review includes one RCT (Adair 1996) in which 120 pregnancies were randomized and analyzed; *see* Characteristics of included studies.

Excluded studies

We assessed and excluded two retrospective cohort studies (Adair 1998; Edwards 1999) and one conference abstract (Adair 1999); *see* Characteristics of excluded studies.

Risk of bias in included studies

We have summarized the risk of bias of the included study (Adair 1996) in Figure 1 and Figure 2. We classified it as a trial with low risk of bias because it had 'clear' allocation concealment, blinding and no withdrawal.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

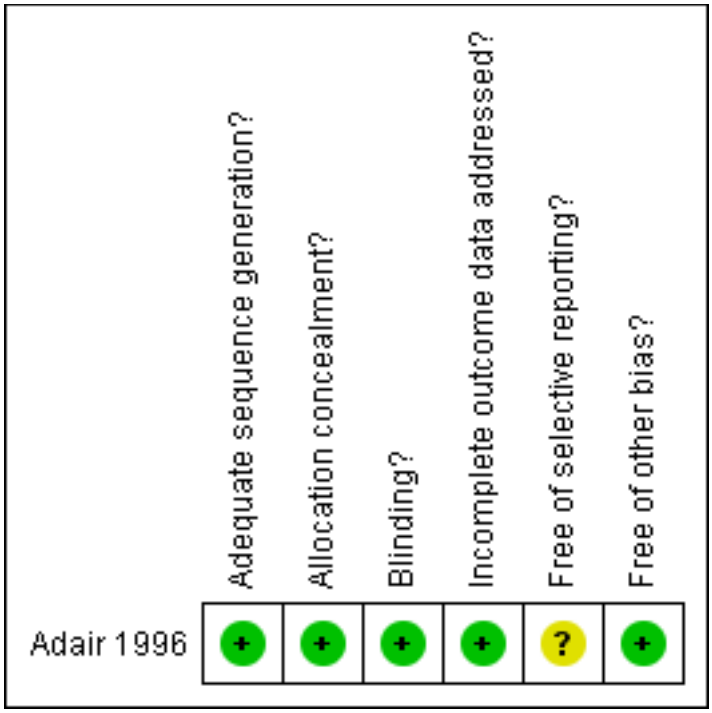

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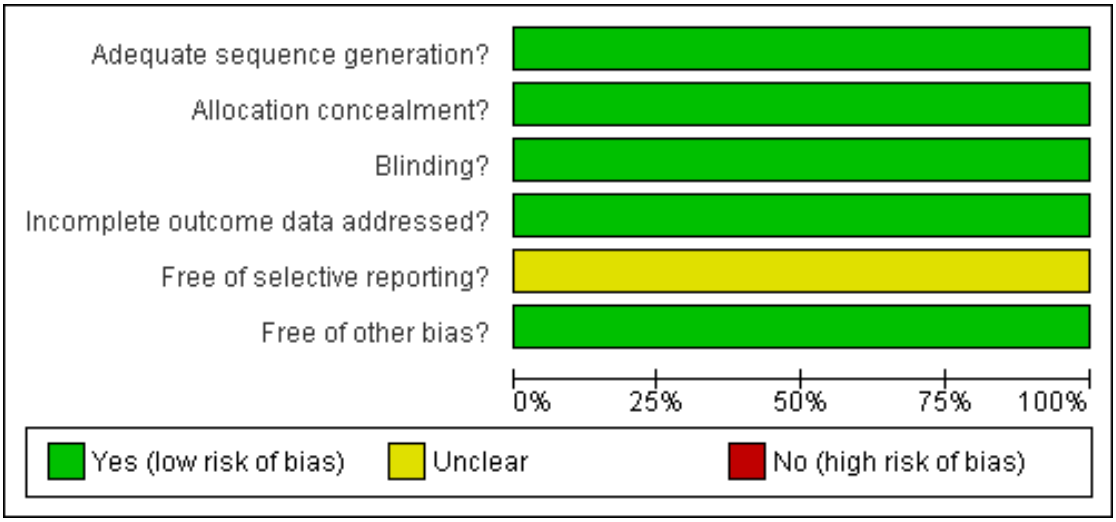
Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

The trial reported clear information of allocation concealment. The randomization schedule was generated and kept in an area away from the clinical area and was unavailable to caregivers (Adair 1996).

Blinding

Participants and all caregivers were thoroughly blinded until the study was completed. Interventions were identically prepared in 100 ml fluid bags and issued by one of two research nurses, independent to the trial investigators. The outcome assessors were also blinded to the randomization status**.**

Incomplete outcome data

No withdrawals occurred and analysis could be done based on intention-to-treat basis.

Selective reporting

We do not have access to this study protocol; therefore we could not evaluate this risk of bias..

Other potential sources of bias

None.

Effects of interventions

Results are based on one RCT (120 pregnancies/120 newborns).

Antibiotic versus placebo

Primary outcomes

There was no significant reduction in the incidence of neonatal sepsis (RR 1.00, 95% CI 0.21 to 4.76), *see* Analysis 1.1. The authors (Adair 1996) did not report their results in terms of early and late onset neonatal sepsis.

Secondary outcomes

There was a significant reduction in the incidence of chorioamnionitis in the ampicillin-sulbactam group compared with placebo (RR 0.29, 95% CI 0.10 to 0.82), *see* Analysis 1.2. There was no significant reduction in the incidence of endometritis (RR 0.50, 95% CI 0.18 to 1.38), *see* Analysis 1.3 or neonatal intensive care unit admission (RR 0.83, 95% CI 0.39 to 1.78), *see* Analysis 1.4. No serious adverse effects were reported.

DISCUSSION

Summary of main results

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There was a significant reduction in the incidence of chorioamnionitis in mothers who received ampiciline-sulbactam compared to placebo. Neonatal sepsis was not differentiated into 'early' or 'late' onset but there was no difference in the incidence of neonatal sepsis between the two groups. Endometritis was not statistically reduced. There was no information about adverse effects.

Overall completeness and applicability of evidence

Only one RCT from a developed country was found by this review and it did not report the primary outcome 'neonatal sepsis' in terms of early or late onset. The evidence may be insufficient to evaluate the efficacy and side effects of prophylactic antibiotics for meconium-stained amniotic fluid in labour for preventing neonatal sepsis.

Quality of the evidence

The included trial is of high methodological quality based on adequate random allocation concealment. However, the sample size was not adequate to make any firm conclusion.

Potential biases in the review process

We followed the process of review as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* Higgins 2009. We also did an exhaustive search which included many clinical trial registries.

Agreements and disagreements with other studies or reviews

There are no other reviews and studies related to the efficacy and side effects of prophylactic antibiotics for MSAF during labour in preventing maternal and neonatal infections.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to support the use of prophylactic antibiotics in women with MSAF during labour because the rates of neonatal sepsis were not different in the two groups.

Implications for research

This systematic review has identified the need for more well-designed, adequately powered RCTs to assess the benefits and harms of antibiotic prophylactic in MSAF during labour for preventing neonatal sepsis. The trials should include clinical outcomes of neonatal sepsis.

ACKNOWLEDGEMENTS

As part of the pre-publication editorial process, this review has been commented on by two peers (an editor and referee who is external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Adair 1996

Methods	Randomized trial with allocation concealment using computer-generated randomization list. All participants, caregivers and outcome assessors were blinded to the treatment regimen.
Participants	Intervention group: 60 pregnant women (mean age 24.5, SD 6.3) with gestational age more than 24 weeks (mean 39.8, SD 1.0). Control group: 60 pregnant women (mean age 25.9, SD 6.3), (mean gestational age 39.9, SD 1.2). Inclusion criteria: gestational age more than 24 weeks with MSAF complicating the intrapartum. Exclusion criteria: patients with penicillin and/or cephalosporin allergy, evidence of active infection, presence of intrauterine death, GA < 24 weeks, or history of antibiotics use in 7 days. Location: North Carolina, United States.
Interventions	**Intervention**: ampicillin-sulbactam 3.0 g intravenous prepared in 100 ml fluid bags, and was repeated every 6 hours until delivery. **Control**: normal saline infused as an IV bolus.
Outcomes	**Mother** Chorioamnionitis. Postpartum endometritis. **Neonatal** Number of NICU admissions. Incidence of sepsis (not defined), and adverse outcomes including enterocolitis and respiratory distress.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomization was performed by a computer-generated list.
Allocation concealment?	Yes	Adequate: there was randomization by computer-generated list and both IV preparations were prepared by 1 of 2 research nurses who were not involved in this study.

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Adair 1996 (*Continued*)

Blinding? All outcomes	Yes	Adequate: there was blinding of participants, caregivers and outcome assessor.
Incomplete outcome data addressed? All outcomes	Yes	Adequate: there was no withdrawal.
Free of selective reporting?	Unclear	Unclear, because we don't have access to this trial's outcomes.
Free of other bias?	Yes	Study appeared to be free of other sources.

GA: gestational age
IV: intravenous
MSAF: meconium-stained amniotic fluid
NICU: neonatal intensive care unit
RCT: randomized controlled trial
SD: standard deviation

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

Study	Reason for exclusion
Adair 1998	Not a RCT, this was a retrospective cohort study.
Adair 1999	This is a conference abstract.
Edwards 1999	Intervention not of interest to systematic review, it is not systematic prophylactic antibiotics.

RCT: randomized controlled trial

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DATA AND ANALYSES

Comparison 1. Antibiotic versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal sepsis	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.21, 4.76]
2 Chorioamnionitis	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.10, 0.82]
3 Postpartum endometritis	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.18, 1.38]
4 Neonatal intensive care admissions	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.39, 1.78]

Analysis 1.1. Comparison 1 Antibiotic versus placebo, Outcome 1 Neonatal sepsis.

Review: Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections

Comparison: 1 Antibiotic versus placebo

Outcome: 1 Neonatal sepsis

Study or subgroup	Antibiotic n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Adair 1996	3/60	3/60		100.0 %	1.00 [0.21, 4.76]
Total (95% CI)	**60**	**60**		**100.0 %**	**1.00 [0.21, 4.76]**
Total events: 3 (Antibiotic), 3 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					

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Analysis 1.2. Comparison 1 Antibiotic versus placebo, Outcome 2 Chorioamnionitis.

Review: Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections

Comparison: 1 Antibiotic versus placebo

Outcome: 2 Chorioamnionitis

Study or subgroup	Antibiotic n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Adair 1996	4/60	14/60		100.0 %	0.29 [0.10, 0.82]
Total (95% CI)	**60**	**60**		**100.0 %**	**0.29 [0.10, 0.82]**
Total events: 4 (Antibiotic), 14 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.33 (P = 0.020)					

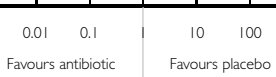
Analysis 1.3. Comparison 1 Antibiotic versus placebo, Outcome 3 Postpartum endometritis.

Review: Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections

Comparison: 1 Antibiotic versus placebo

Outcome: 3 Postpartum endometritis

Study or subgroup	Antibiotic n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Adair 1996	5/60	10/60		100.0 %	0.50 [0.18, 1.38]
Total (95% CI)	**60**	**60**		**100.0 %**	**0.50 [0.18, 1.38]**
Total events: 5 (Antibiotic), 10 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.34 (P = 0.18)					



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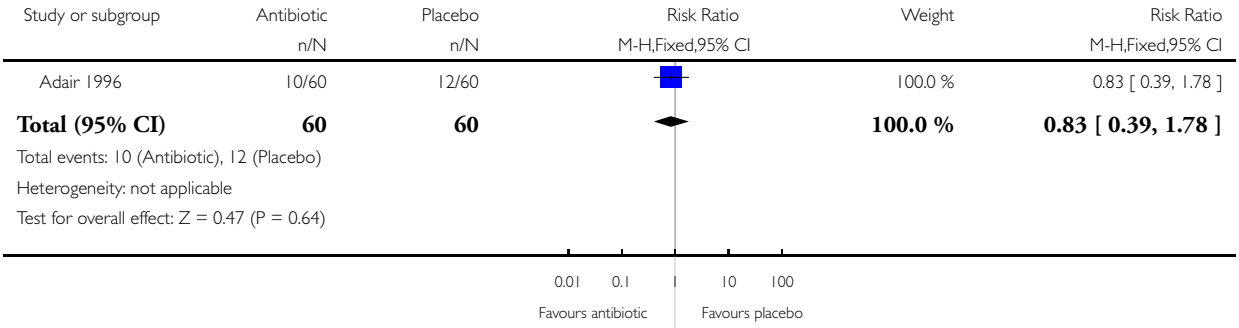
Analysis 1.4. Comparison 1 Antibiotic versus placebo, Outcome 4 Neonatal intensive care admissions.

Review: Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections

Comparison: 1 Antibiotic versus placebo

Outcome: 4 Neonatal intensive care admissions



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CONTRIBUTIONS OF AUTHORS

Thitiporn Siriwachirachai and Ussanee Sangkomkamhang drafted the review, Pisake Lumbiganon and Malinee Laopaiboon revised and approved the final version of the review.

DECLARATIONS OF INTEREST

None known.

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External sources

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- Thai Cochrane Network, Thailand.

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ภาคผนวกที่ 3

มีนักวิจัยเข้าร่วมในโครงการจำนวน 43 คน จาก 11 สถาบัน

รายชื่อกลุ่มวิจัยเก่า

ชื่อ-นามสกุล	เริ่มเข้าโครงการ			ปัจจุบัน		
	ตำแหน่งวิชาการ	สังกัด	ตำแหน่งในโครงการ	ตำแหน่งวิชาการ	สังกัด	สถานภาพปัจจุบัน
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หมายเหตุ

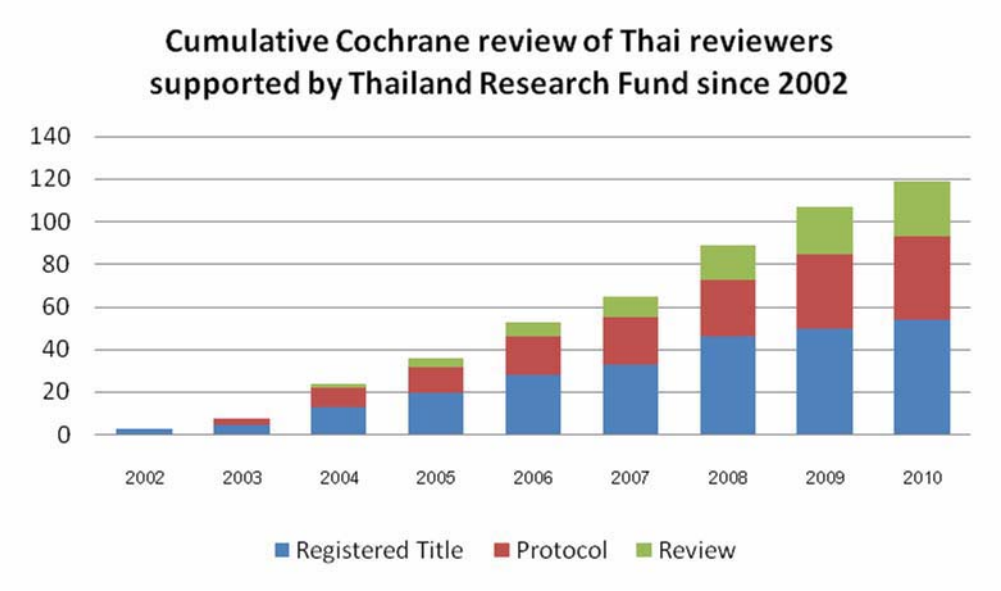
สังกัด ให้ใส่รายละเอียดที่อยู่ต้นสังกัด เช่น ภาควิชา / คณะ / มหาวิทยาลัย

สถานภาพปัจจุบัน - ยังอยู่ในโครงการหรือไม่ หากไม่อยู่ในโครงการแล้ว ให้ระบุหน่วยงานใหม่ด้วย

- หากเริ่มเข้าโครงการเป็นนักศึกษาปริญญาเอก ปริญญาโท หรือปริญญตรี ให้ระบุปัจจุบันสำเร็จการศึกษาหรือยังไม่สำเร็จการศึกษา

ภาคผนวกที่ 4

ประเทศไทยมีโครงการวิจัยเชิงสังเคราะห์ที่ทำร่วมกับ Cochrane Collaboration มากขึ้นอย่างรวดเร็วและปัจจุบันเป็นอันดับที่ 3 ใน Asia รองจากจีน และอินเดีย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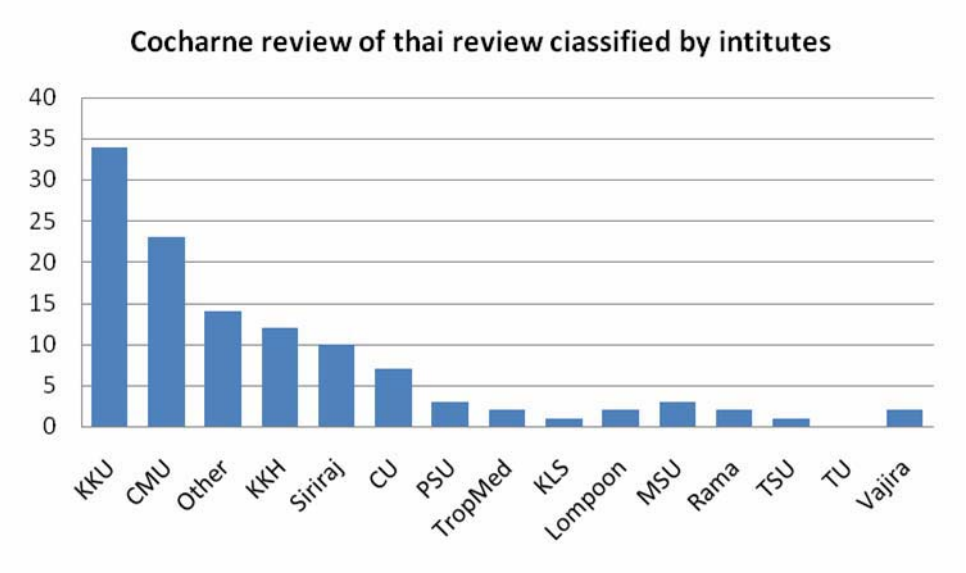
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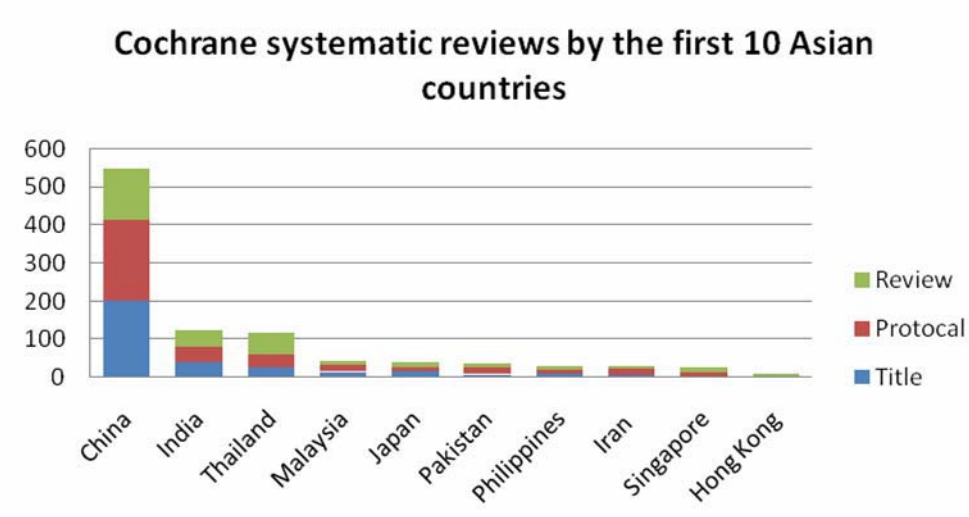
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ภาคผนวกที่ 5

ตีพิมพ์ Protocols for Cochrane reviews ใน Cochrane Library จำนวน 9 เรื่อง

Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes (Protocol)

Buppasiri P, Lumbiganon P, Thinkhamrop J, Ngamjarus C

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TABLE OF CONTENTS

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[**Intervention Protocol**]

Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

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Editorial group: Cochrane Pregnancy and Childbirth Group.
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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To determine the effect of calcium supplementation on maternal, fetal and neonatal outcome as well as on possible side effects (other than for preventing or treating hypertension).

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BACKGROUND

Calcium metabolism

Calcium is an essential mineral for many of the body's processes (Trichopoulou 1990). Calcium is a key and important intracellular component for maintaining cell membranes in nerve, muscle contraction, enzyme and hormone actions. Bone formation is also dependent on calcium levels. Maternal nutrition during pregnancy is known to have a significant effect on fetal growth and development (Luke 1994; Susser 1991). Pregnancy and lactation are the periods when the mother needs to consume a great amount of calcium (Cross 1995; Prentice 1995; Ritchie 1998). Calcium is transported to the fetus by an active transport process across the placenta. The mother has to maintain her calcium levels to keep normal balance and reduce the risk of osteoporosis in later life (Bonner 1994). The fetus needs calcium for skeletal development as well (Thomas 2006). During pregnancy and lactation, maternal bone mineral density (BMD) decreases in multiple sites of body such as the lumbar spine, femoral neck, total hip, and radius wrist. After weaning this is relatively quickly reversed (Cross 1995; Kalkwarf 1997; Laskey 1999; Prentice 1995; Sowers 1993; Sowers 1995). Inadequate intake of calcium may harm both mother and her fetus. Risks include osteopenia, osteoporosis, tremor, paresthesia, muscle cramp, tetany, delayed fetal growth, low birth weight, and poor fetal mineralization (Inzucchi 1999; Koo 1999). Recommendation for calcium intake during pregnancy and lactation differ around the world from 600 to 1425 mg per day, 400 to 600 mg per day higher than nonpregnant or nonlactating women (Prentice 1994; Prentice 1995). A breastfeeding mother secretes 200 mg calcium into breast milk every day (Prentice 1995).

Calcium supplementation

Calcium supplementation to the daily diet has been recommended to meet the body's demands during pregnancy and lactation to benefit the mother and fetus. The recommended dosages in the literature vary from 300 to 2000 mg/d of elemental calcium (Jarjou 2006; Kalkwarf 1997; Prentice 1995; Villar 1990). Providing extra calcium tablets is attractive because it is cheap, readily available with few side effects, such as difficult swallowing, increase in urinary stones, increase in urinary tract infection, and reduced absorption of other minerals such as iron, zinc and magnesium that could harm the pregnant women (Hallberg 1992).

Current approach to calcium supplementation

Currently, there is no consensus on the role of routine calcium supplementation for pregnant women. Extra calcium tablets are not routinely prescribed for pregnant women because the real benefit is still questionable. In a recent Cochrane meta-analysis of calcium supplementation for hypertension, a significant beneficial effect in reducing the risk of pregnancy-induced hypertension was found (Hofmeyr 2006). For maternal bone mineral density and fetal mineralization, there is still conflicting data. Many studies show that fetal femur length, fetal weight and fetal mineralization are significantly better in calcium-supplemented mothers (Chang 2003; Chan 2006; Janakiraman 2003; Merialdi 2003; Raman 1978). This is in contrast with other studies that suggest that calcium supplementation has no additional effects (Jarjou 2006; Prentice 1995). The effectiveness of calcium supplementation in reducing preterm birth is also uncertain; some studies show a protective effect (Carroli 1994; Villar 1990) while others do not (Belizan 1991; Lopez-Jaramillo 1989; Villar 1998). Leg cramps are the most common symptom of calcium deficiency, particularly in pregnant women (Hammar 1981). The role of calcium supplementation in reducing leg cramps remains unclear (Hammar 1981; Hammar 1987; Young 2002). Possible explanations for differences in the results of these studies include differences in baseline calcium intake, socioeconomic status, dosage and duration of calcium supplementation, etc.

There is need for a systematic review to evaluate the effectiveness of calcium supplementation during pregnancy for improving maternal, fetal and neonatal outcomes other than preventing or treating hypertension because of the varying results reported in the literature.

OBJECTIVES

To determine the effect of calcium supplementation on maternal, fetal and neonatal outcome as well as on possible side effects (other than for preventing or treating hypertension).

METHODS

Criteria for considering studies for this review

Types of studies

All published, unpublished and ongoing simple and cluster-randomized controlled trials comparing maternal, fetal, and neonatal outcomes in calcium supplementation versus placebo or no treatment in pregnant women. We will include studies reported only in abstract form in the "Studies awaiting classification" category and will include them in the analysis when they are published as full reports. We will exclude quasi- and pseudo-randomized controlled trials.

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Types of participants

Pregnant women who received any calcium supplementation compared with placebo or no treatment.

Types of interventions

Calcium supplementation during pregnancy and placebo or no treatment.

Types of outcome measures

Primary outcomes

Maternal outcomes

1. Preterm delivery

(a) Birth prior to 37 weeks
(b) Birth prior to 34 weeks

Infant outcomes

1. Low birth weight (< 2,500 gm)

Secondary outcomes

Maternal outcomes

1. Maternal weight gain
2. Maternal bone mineral density (BMD)
3. Leg cramps
4. Backache
5. Tetany (muscle spasm and twitching)
6. Osteopenia
7. Osteoporosis
8. Incidence of fracture
9. Duration of breastfeeding
10. Tremor
11. Paresthesia
12. Mother need to admit intensive care unit
13. Maternal death

Fetal and neonatal outcomes

1. Stillbirth
2. Fetal death
3. Neonatal death
4. Perinatal mortality
5. Admission to neonatal intensive care unit
6. Birth weight
7. Birth length
8. Head circumference
9. Intrauterine growth restriction
10. Neonatal BMD
11. Osteopenia
12. Limb pain
13. Ricket
14. Fracture

Adverse outcomes

1. Side effects of calcium supplementation
2. Compliance
3. Satisfaction
4. Urinary stones
5. Urinary tract infection
6. Nephrocalcinosis
7. Impair renal function
8. Maternal anemia

Search methods for identification of studies

Electronic searches

We will contact the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register.
The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.
Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.
We will not apply any language restrictions.

Data collection and analysis

Selection of studies

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Two review authors (P Buppasiri (PB) and J Thinkhamrop (JT)) will independently assess for inclusion all potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or by involving the third review author (P Lumbiganon (PL)). The fourth review author (C Ngamjarus (CN)) will be responsible for the planning of the data analysis.

Assessment of methodological quality of included studies

Two review authors (PB and JT) will assess the validity of each study independently using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2006). We will use only the criteria of selection bias and detection bias that are feasible for our review. Methods used for generation of the randomisation sequence will be described for each trial.

(1) Selection bias (randomisation and allocation concealment)

We will assign a quality score for each trial, using the following criteria:
(A) adequate concealment of allocation: such as telephone randomisation, consecutively numbered, sealed opaque envelopes;
(B) unclear whether adequate concealment of allocation: such as list or table used, sealed envelopes, or study does not report any concealment approach;
(C) inadequate concealment of allocation: such as open list of random-number tables, use of case record numbers, dates of birth or days of the week.

(2) Attribution bias (loss of participants, eg, withdrawal, dropouts, protocol deviation)

We will assess completeness to follow up using the following criteria:
(A) less than 5% loss of participants;
(B) 5% to 9.9 % loss of participants;
(C) 10% to 19.9 loss of participants;
(D) more than 20% loss of participants.

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

We will assess blinding using the following criteria:

1. blinding of participants (yes /no /unclear);
2. blinding of caregiver (yes /no /unclear);
3. blinding of outcome assessment (yes/no /unclear).

Data extraction and management

We will adapt the Cochrane Pregnancy and Childbirth Group's data extraction form template to extract data. At least two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion. We will use the Review Manager software (RevMan 2007) to double enter all the data or a subsample.
When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually randomised trials. Their sample sizes will be adjusted using the methods described in Gates 2005 using an estimate of the 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.

Data analysis

Measures of treatment effect

We will compare categorical data using relative risks and their 95% confidence intervals. For continuous data, we will calculate mean difference with 95% confidence intervals (CI) if the outcomes are measured in the same way among trials. We will use the standardized mean difference to combine trials that measure the same outcome, but use different methods. We will test for statistical heterogeneity between trials using the I-squared statistic, with values greater than 50% indicating significant heterogeneity. In the absence of significant heterogeneity, we will pool data using a fixed-effect model. If there is significant heterogeneity, a random-effects model will be used and an attempt made to identify potential sources of heterogeneity based on subgroup analyses by baseline dietary calcium intake.

Dealing with missing data

We will analyse data on all participants with available data in the group to which they are allocated, regardless of whether or not they received the allocated intervention. If in the original reports participants are not analysed in the group to which they were

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randomised, and there is sufficient information in the trial report, we will attempt to restore them to the correct group.

Assessment of publication bias

Where sufficient trials are included, we will consider publication bias using funnel plots of between-treatment effect and its precision on individual trials. If we find asymmetry funnel plots with statistical publication bias, we will further examine the effect of the bias on the meta-analysis conclusion using sensitivity analyses.

Sensitivity analyses

We will carry out sensitivity analyses to explore the effect of trial quality. The trial quality will involve an analysis based on concealment of allocation. Trials with clearly inadequate allocation of concealment will be excluded in order to assess for any substantive difference to the overall result.

Subgroup analyses

We will conduct the following subgroup analysis:
1. Total dose per day of calcium supplementation: high/low (< 1,000 and $\geq$ 1,000 mg).
2. Time of supplementation taken from: first half of pregnancy (< 20 weeks); and second half of pregnancy ($\geq$ 20 weeks).
3. Type of calcium supplementation preparation: calcium carbonate, lactate, gluconate.

ACKNOWLEDGEMENTS

The authors would like to thank Professor Caroline Crowther, Phillippa Middleton, Ruth Martis and the SEA-ORCHID project for supporting a fellowship for PB enabling her to complete this systematic review.

As part of the pre-publication editorial process, this protocol has been commented on by three peers (an editor and two referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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* *Indicates the major publication for the study*

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HISTORY

Protocol first published: Issue 2, 2008

CONTRIBUTIONS OF AUTHORS

P Buppasiri developed the protocol.

P Lumbiganon and J Thinkhamrop edited and commented on the protocol.

C Ngamjarus commented on the protocol.

DECLARATIONS OF INTEREST

None known.

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Interventions for preventing excessive weight gain during pregnancy (Protocol)

Muktabhant B, Lumbiganon P, Ngamjarus C

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TABLE OF CONTENTS

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[Intervention Protocol]

Interventions for preventing excessive weight gain during pregnancy

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the effectiveness of interventions for preventing excessive weight gain during pregnancy.

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BACKGROUND

Appropriate gestational weight gain may be important for achieving healthy pregnancies and deliveries, and birth outcomes, as well as long-term health for childbearing women.

In 1990, the Institute of Medicines (IOM) in the United States advised underweight women (body mass index (BMI) less than 19.8 kg/m^2) to gain 12.5 to 18 kg and normal weight women (BMI 19.8 to 25.9 kg/m^2) to gain 11.5 to 16.0 kg; whereas overweight women (BMI 26 to 29 kg/m^2) were advised to gain between 7 to 11.5 kg and obese women (BMI at least 30 kg/m^2) to gain approximately 7 kg with no upper limit proposed (Medicine 1990). These guidelines were widely adopted but not universally accepted. However, a substantial review examined fetal and maternal outcomes according to the IOM's weight-gain recommendations in women with a normal prepregnancy weight (Abrams 2000). These studies showed that pregnancy weight gain within the IOM's recommended ranges is associated with the best outcome for both mothers and infants. Abrams 2000 also stated that there was no published scientific evidence to support the concept that weight gain within the IOM's recommended ranges is harmful for either mothers or their infants.

Different countries have differing recommendations on weight gain. There are currently no official recommendations for weight gain during pregnancy in the UK. The UK also does not have clinical guidelines for gestational weight gain. It is the responsibility of health professionals such as general practitioners, midwives and obstetricians to monitor normal pregnancies by preventing abnormal weight gain, yet typically in the UK, women are weighed only once, i.e. at the antenatal booking appointment, which is primarily undertaken for the interpretation of screening tests (Ford 2001). Recently, gestational weight gain limits for BMI categories based on significant risk estimates of adverse maternal and fetal outcome determined by a large population-based cohort study was published from Swedish Medical Registers. The optimal gestational weight gain in Swedish women was 4 to 10 kg for BMI less than 20; 5 and 2 to 10 kg for BMI 20 to 24.9. For women with a BMI of 25 to 29.9, a weight gain of less than 9 kg was recommended and pregnant women with a BMI of 30 or more were recommended to gain less than 6 kg in weight (Cedergren 2007). Pregnant Asian women in general had lower weight gains (Abrams 1995; Siega-Riz 1993). Hence, maternal weight gain recommendations based on data compiled from white women may be not applicable to Asian females. A study to produce ethnic-specific maternal weight gain recommendations was performed in China. A maternal weight gain chart and recommendations for the total weight gain of Chinese women were derived from the distribution of weight gained in women with a good pregnancy outcome. The recommended total weight gain was 13 to 16.7 kg, 11 to 16.4 kg, and 7.1 to 14.4 kg respectively for women of low (BMI less than 19), moderate (BMI 19 to 23.5), and high (BMI greater than 23.5) BMI. Women who did not achieve the lower quartile range had more than twice the risk of having a low-birthweight infant. Those with excessive weight gain were at risk of needing an assisted delivery (Wong 2000).

Although the IOM guidelines have been promoted for over a decade, only 30% to 40% of pregnant women in the United States gain gestational weight within the IOM recommended ranges (Abrams 2000; Cogswell 1999; Medicine 1990; Olson 2003). Furthermore, gestational weight gain above the guidelines is more common than gestational weight gain below (Stotland 2006). Several studies on gestational weight gain in the USA and Europe indicate that about 20% to 40% of women are gaining weight above the recommendations (Cedergren 2006; Medicine 1990; Olson 2003) and the prevalence of excessive gestational weight gain is increasing (Abrams 2000; Rhodes 2003; Schieve 1998). In an investigation of over 120,000 women enrolled in women, infants, and children (WIC) clinics over a six-year period (from 1990 to 1996), Schieve 1998 found that the percentage of women reporting a pregnancy weight gain greater than the IOM recommendation significantly increased from 41.5% to 43.7%. Two studies examined trends in excess gestational weight gain which was classified by using upper limits of the IOM recommendations (more than 18 kg) due to lack of prepregnancy BMI data. A study by Rhodes 2003, examining trends in excess gestational weight gain (more than 18 kg) by analysing US Natality Files of birth certificate data, found that between 1990 and 2000, excess weight gain (more than 18 kg) rose steadily from 18.6% to 24.2%. A retrospective cohort study was undertaken to examine the trend in weight gain during pregnancy of 1,463,936 women over 16 years in North Carolina and found that the proportion of women gaining excessive gestational weight (more than 18 kg) increased from 15.5% in 1988 to 19.5% in 2003; an additional 40 women per 1000 gained excessive weight by 2003 (Helms 2006).

Several studies indicated that the incidence of weight gain during pregnancy varied by prepregnancy weight category. Obese women tend to gain the least weight and normal weight women tend to gain the most weight (Abrams 1989; Bianco 1998; Edwards 1996; Walling 2006). Two large population-based studies in the United States and in Sweden reported similar findings. They found that approximately 30% of average and overweight women had high gestational weight gain, whereas approximately 20% of obese women had high gestational weight gain (Cedergren 2006; Cogswell 1995). A descriptive study of over 4000 pregnant women from the University of California, San Francisco Perinatal Database, found that total gestational weight gain exceeded the guidelines for 23% of the underweight women, 49% of the normal-weight women, 70% of the overweight women, and 57% of the obese women (Carmichael 1997). Similarly, in a prospective cohort study of 622 women in prenatal care in a 10-county area of upstate New York, 11% of underweight women, 37% of normal-weight women, 70% of overweight women, and 41% of obese women exceeded the weight gain recommendations (Olson

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2003).

It is well known that excessive weight gain during pregnancy is associated with multiple maternal and neonatal complications. A retrospective cohort study of 20,465 non-diabetic, term, singleton births was undertaken to examine the relationship between gestational weight gain and adverse neonatal outcomes among infants born at term (37 weeks or more). Through a multivariate analyses it was established that gestational weight gain above the upper limit of the IOM guideline (more than 18 kg) was associated with multiple adverse neonatal outcomes such as a low five-minute Apgar score (adjusted odds ratio (AOR) 1.33, 95% confidence interval (CI) 1.01 to 1.76), seizure (AOR 6.50, 95% CI 1.43 to 29.65), hypoglycemia (AOR 1.52, 95% CI 1.06 to 2.16), polycythemia (AOR 1.44, 95% CI 1.06 to 1.94), meconium aspiration syndrome (AOR 1.79, 95% CI 1.12 to 2.86), and large-for-gestational age (AOR 1.98, 95% CI 1.74 to 2.25) compared with women within weight gain guidelines (Stotland 2006). Similar results were found in a cohort of 45,245 women who delivered singletons at Kaiser Permanente Medical Care Program Northern California in 1996 to 1998. It was found that women who gained more weight than was recommended by the IOM were three times more likely to have an infant with macrosomia (odds ratio (OR) 3.05, 95% confidence interval (CI) 2.19 to 4.26), and nearly 1.5 times as likely to have an infant with hypoglycemia (OR 1.38, 95% CI 1.01 to 1.89), or hyperbilirubinemia (OR 1.43, 95% CI 1.06 to 1.93) than women whose weight gain was in the recommended range. Women who gained less than the IOM recommendations were less likely than women in the recommended range to have an infant with macrosomia (OR 0.38, 95% CI 0.20 to 0.70), but equally likely to have an infant with hypoglycemia or hyperbilirubinemia (Hedderson 2006). A prospective population-based cohort study of 245,526 singleton term pregnancies was studied in Sweden to estimate the effects of gestational weight gain on obstetric outcome. Women were grouped in five categories of BMI and in three gestational weight gain categories; less than 8 kg (low weight gain), 8 to 16 kg and greater than 16 kg (high weight gain). Obese women with low gestational weight gain had a decreased risk for the following outcomes: pre-eclampsia (AOR 0.52, 95% CI 0.42 to 0.62), cesarean section (AOR 0.81, 95% CI 0.73 to 0.90), instrumental delivery (AOR 0.75, 95% CI 0.63 to 0.88), and large-for-gestational age births (AOR 0.66, 95% CI 0.59 to 0.75). There was a two-fold increased risk for pre-eclampsia and large-for -gestational age infants among average and overweight women with excessive weight gain. High gestational weight gain increased the risk for cesarean delivery in all maternal BMI classes (Cedergren 2006). The relationship between the incidence of high birthweight and weight gain during pregnancy varied by pregnancy weight categories. Average-weight women who gained more than 18 kg were more than three times likely to deliver a large infant as were women in the reference group. Overweight women who gained more than 18 kg were more than four times as likely to deliver a large infant as were women in the reference group. Very overweight women who gain more than 18 kg were more than twice as likely to deliver a large infant as were women in the reference group (Cogswell 1995). Kabali and Werler studied the combined effects of prepregnant women's BMI and weight gain in relation to macrosomia in offspring of 815 non-diabetic women, using data collected from a retrospective study. Compared to mothers with a normal prepregnancy BMI and pregnancy weight gain, risk of macrosomia in offspring was significantly elevated only in overweight women with excess weight gain (AOR 2.6, 95% CI 1.2 to 5.4) but not among normal weight mothers with excess gain (AOR 1.1, 95% CI 0.5 to 2.4) or overweight mothers with normal or low gain (AOR 1.1, 95% CI 0.4 to 3.1). It was concluded that given the complications that are associated with delivering large babies, overweight women may benefit from not gaining excess weight in pregnancy (Kabali 2007). There have been a number of studies which conclude that excessive gestational weight gain increases postpartum weight retention (Gunderson 2000; Keppel 1993; Polley 2002; Rooney 2002; Rossner 1997; Scholl 1995) and is related to a two- to three-fold increase in the risk of becoming overweight after delivery (Gunderson 2000). Moreover, mothers who gained more weight during pregnancy had children at higher risk of being overweight in early childhood (Oken 2007).

However, too strict a weight gain restriction might result in adverse birth outcomes. A systematic review was undertaken to assess the effects of advice to increase or reduce energy or protein intake during pregnancy on gestational weight gain, and the outcome of pregnancy. It was established that in three trials involving 384 women, energy or protein restriction of pregnant women who were overweight or exhibited high weight gain significantly reduced weekly maternal weight gain and reduced mean birthweight but had no effect on pregnancy-induced hypertension or pre-eclampsia. It concluded that protein or energy restriction of pregnant women is unlikely to be beneficial and may be harmful to the infant (Kramer 2003). There is some evidence that too low a weight gain is associated with preterm deliveries (Medicine 1990). A study of low-income women in Alabama used the lower limit of the IOM's recommended range to define low weight gain during the third trimester in non-obese women (Hickey 2005). After a variety of other risk factors were controlled for, women with a low rate of weight gain during the third trimester had a statistically significant higher risk of spontaneous preterm delivery than did women without a low weight gain in the third trimester (odds ratio 2.46, 95% CI 1.53 to 3.92). A similar relation between low weight gain and preterm birth was reported in a primarily Hispanic cohort in Los Angeles (Siega-Riz 1994). Weight gain in pregnancy is also related to fetal growth. Too low a weight gain is associated with reduced fetal growth, ie, low birthweight (less than 2500 g) or small-for-gestational-age infants (less than the 10th percentile of weight for a given gestation). A retrospective cohort study found that mothers who gained lower than the IOM's guideline had increased rates of small-for-gestational-age infants, seizure, meconium aspiration syndrome, and prolonged hospital

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stay (Stotland 2006). Thus, either low or excessive weight gain during pregnancy should be avoided to optimize birth outcome.

Given the increasing prevalence and negative consequences of excessive gestational weight gain, preventing excessive weight gain during pregnancy is potentially important. The best intervention is to help pregnant women to achieve the recommended weight gain, with the objective of ensuring the best possible outcome for their infants and themselves. Dietary control, exercise and eating behavior modification are the main elements for controlling weight. Pregnancy may be an optimal time to inform and challenge women to change their eating habits and physical activities, and thereby prevent excessive weight gain. There are systematic reviews which aimed to assess the effect of dietary advice, exercise intervention and psychosocial intervention for achieving weight loss in overweight and obese adults. The results of the review on exercise for overweight or obesity support the use of exercise as a weight loss intervention, particularly when combined with dietary change (Shaw 2006). People who are overweight or obese benefit from psychological interventions, particularly behavioral and cognitive-behavioural strategies, to enhance weight reduction. These measures are predominantly useful when combined with dietary and exercise strategies (Shaw 2005). In addition, overall, weight loss strategies using dietary, physical activity, or behavioral interventions produced significant improvement in weight among people with prediabetes (Norris 2005).

The aim of this review is to identify and systematically review all randomized controlled trials of interventions for limiting weight gain during pregnancy to provide the best available evidence for clinical decision-making and to stimulate further research about preventing excessive weight gain during pregnancy.

OBJECTIVES

To evaluate the effectiveness of interventions for preventing excessive weight gain during pregnancy.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomized controlled trials and quasi-randomized controlled trials of interventions aimed at preventing excessive weight gain during pregnancy, irrespective of their country of origin or language.

Types of participants

Pregnant women.

Types of interventions

Any intervention (e.g., nutrition intervention, exercise intervention, health education or counseling) for preventing excessive weight gain compared with routine care.

Types of outcome measures

Primary outcomes

Excessive weight gain as defined by triallists.

Secondary outcomes

For the mothers

1. Behaviour change: physical activity, diet
2. Weight gain
3. Low-weight gain as defined by triallists
4. Preterm birth
5. Preterm premature rupture of membranes
6. Pre-eclampsia or eclampsia
7. Need for and indication for induction of labour
8. Postpartum complication including postpartum haemorrhage, wound infection, endometritis, need for antibiotics, perineal trauma, thromboembolic disease, maternal death
9. Cesarean delivery rate

For the newborns

1. Birthweight greater than 4000 grams and greater than the 90th centile for gestational age and infant sex
2. Birthweight less than 2500 grams and less than the 10th centile for gestational age and infant sex
3. Complication related to macrosomia including hypoglycaemia, hyperbilirunaemia, infant birth trauma (palsy, fracture, shoulder dystocia

Long-term health outcomes

1. Maternal weight retention postpartum
2. Childhood weight

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Search methods for identification of studies

Electronic searches

We will contact the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register.
The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.
Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords.
In addition, we will search MEDLINE (1966 to current) using the search strategy given in Appendix 1
We will not apply any language restrictions.

Data collection and analysis

Selection of studies

We will assess for inclusion all potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, consult an outside person.

Assessment of methodological quality of included studies

We will assess the validity of each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005). We will describe the methods used for generation of the randomization sequence for each trial.

(1) Selection bias (randomization and allocation concealment)

We will assign a quality score for each trial, using the following criteria:
(A) adequate concealment of allocation: such as telephone randomization, consecutively numbered, sealed opaque envelopes;
(B) unclear whether adequate concealment of allocation: such as list or table used, sealed envelopes, or study does not report any concealment approach;
(C) inadequate concealment of allocation: such as open list of random-number tables, use of case record numbers, dates of birth or days of the week.
if we identify and include quasi-randomized controlled trials, we will perform a sensitivity analysis by trial quality.

(2) Attrition bias (loss of participants, for example, withdrawals, dropouts, protocol deviations)

We will assess completeness to follow up using the following criteria:
(A) less than 5% loss of participants;
(B) 5% to 9.9% loss of participants;
(C) 10% to 19.9% loss of participants;
(D) more than 20% loss of participants.

(3) Detection bias (blinding of outcome assessment)

We will assess detection bias using the following criteria:
(A) adequate blinding explanation: such as outcome assessors measured weight of the pregnant women without awareness of the intervention they received;
(B) unclear blinding explanation: such as study does not report if outcome assessors blinded;
(C) inadequate blinding explanation: such as outcome assessors measured weight of the pregnant women with knowledge of their randomized group.
High-quality trials will be defined as those receiving an A rating for selection bias, attrition bias and detection bias.

Data extraction and management

We will adapt for our use the Cochrane Pregnancy and Childbirth data extraction form template to extract data. At least two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion. We will use the Review Manager software (RevMan 2007) to double enter all the data or a subsample.
When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Data analysis

Measures of treatment effect

We will carry out statistical analysis using the Review Manager software (RevMan 2007). We will use fixed-effect meta-analysis

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for combining data in the absence of significant heterogeneity if trials are sufficiently similar. If heterogeneity is found, this will be explored by sensitivity analysis followed by random-effects if required. For dichotomous data, we will present results as summary relative risk with 95% confidence intervals. For continuous data, we will use the weighted mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods. If there is evidence of skewness, this will be reported.

Assessment of heterogeneity

We will apply tests of heterogeneity between trials, if appropriate, using the I-squared statistic. If we identify high levels of heterogeneity among the trials (exceeding 50%), we will explore it by prespecified subgroup analysis and perform sensitivity analysis. A random-effects meta-analysis will be used as an overall summary if this is considered appropriate.

Subgroup analyses

We will conduct planned subgroup analyses classifying whole trials by interaction tests as described by Deeks 2001.
If sufficient data are available, we plan to carry out the subgroup analyses according to:

1. criteria of excessive weight gain as defined by triallists. Different trials may use different criteria to categorize weight gain of pregnant women. There are classified in two ways. The first is classified according to the Institute of Medicine of USA guidelines, excess weight gain is any amount over 'normal' gain, adequate weight gain is any amount within 'normal' gain and low weight gain is any amount under 'normal' gain of each body mass index (BMI) categories. The second classification split weight gain into less than the lower or greater than upper limits of recommended.
2. prepregnancy BMI: (1) underweight (2) normal weight (3) overweight (4) obese. These BMI categories as defined by triallists. Each trial may use difference classification of BMI. Some trials may categorize BMI using cut-off point of industrial criteria and some using Asian criteria.
3. types of intervention.
4. gestational age at first visit prenatal clinic: (1) 20 weeks or lower (2) more than 20 weeks. Gestational age at 20 weeks is the middle age of gestation.
5. gestational age at first visit prenatal clinic: (1) 28 weeks or lower (2) more than 28 weeks. Gestational age at 28 weeks is early of the 3rd trimester which weight gain is rapidly increasing.

Cluster-randomized trials

We will include cluster-randomized trials in the analyses along with individually randomized trials. Their sample sizes will be 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 synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomization unit is considered to be unlikely.
We will also acknowledge heterogeneity in the randomization unit and perform a separate meta-analysis; therefore the meta-analysis will be performed in two parts as well.

Dealing with missing data

We will analyse data on all participants with available data in the group to which they are allocated, regardless of whether or not they received the allocated intervention. If in the original reports participants are not analysed in the group to which they were randomized, and there is sufficient information in the trial report, we will attempt to restore them to the correct group.

Assessment of publication bias

Where sufficient trials are included, we will consider publication bias using funnel plots of between-treatment effect and its precision on individual trials, and Egger's test (Egger 1997). If we find asymmetry funnel plots with statistical publication bias, we will further examine the effect of the bias on the meta-analysis conclusion using sensitivity analyses.

Sensitivity analyses

We will carry out sensitivity analysis to explore the effect of trial quality. This will involve analysis based on an A, B, C, or D rating of selection bias and attrition bias. Studies of poor quality will be excluded in the analysis (those rating B, C, or D) in order to assess for any substantive difference to the overall result. For clustering effect, we will perform a sensitivity analysis to see what the effect of different values of the ICC on the results of the analysis would be.

ACKNOWLEDGEMENTS

As part of the pre-publication editorial process, this protocol has been commented on by three peers (an editor and two referees who are external to the editorial team), one or more members of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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* *Indicates the major publication for the study*

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APPENDICES

Appendix 1. MEDLINE search strategy

1 exp Pregnancy/
2 Pregnant Women/
3 1 or 2
4 Weight Gain/
5 exp Obesity/pc [Prevention & Control]
6 exp Clinical Trial/
7 randomized.ti,ab.
8 placebo.ti,ab.
9 dt.fs.
10 randomly.ti,ab.
11 trial.ti,ab.
12 groups.ti,ab.
13 or/6-12
14 Animals/
15 Humans/
16 14 not (14 and 15)
17 13 not 16
18 4 or 5
19 17 and 18 and 3

HISTORY

Protocol first published: Issue 2, 2008

CONTRIBUTIONS OF AUTHORS

B Muktabhant conceived and designed the draft protocol. P Lumpiganon and C Ngamjarus reviewed and commented on the revisions of the protocol.

DECLARATIONS OF INTEREST

None known.

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Cyclo-oxygenase (COX) inhibitors for preventing preterm labour (Protocol)

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Cyclo-oxygenase (COX) inhibitors for preventing preterm labour (Protocol)
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TABLE OF CONTENTS

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[**Intervention Protocol**]

Cyclo-oxygenase (COX) inhibitors for preventing preterm labour

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effectiveness and safety of COX inhibitors for preventing preterm labour in high-risk women.

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BACKGROUND

Description of the condition

Preterm birth is defined as delivery before 37 completed weeks (Cunningham 2005). Incidence of preterm birth among Swedish during 1973 - 2001 was around 5.6% (Morken 2005).

Preterm labour is documented by three criteria (Cunningham 2005): uterine contractions of four in 20 minutes or eight in 60 minutes plus progressive change in the cervix; cervical dilatation greater than 1 cm; and cervical effacement of 80% or greater.

If preterm labour is not managed properly, active labour can occur and result in preterm birth. Preterm birth is one of the major complications in obstetrics. The mortality rate of preterm infants has continued to decline over the past 60 years, but infant mortality associated with preterm birth or low birthweight has not declined (Arias 2003). Preterm birth is also the leading cause of perinatal morbidities such as low birthweight, respiratory distress syndrome, intraventricular haemorrhage, anaemia, etc. Moreover, these complications may cause both major and minor consequences for these newborn infants (Kliegman 2007).

Factors associated with preterm birth include: medical and obstetric complications (Meis 1995); multiple pregnancy (Blondel 2006; Kurdi 2004; Murphy 2007); threatened abortion (Weiss 2004); cigarette smoking (Tsai 2008); short stature; low pre-pregnancy body mass index (BMI); inadequate weight gain (Kramer 1995; Schieve 2000); young or advanced maternal age (Morken 2005); prolonged walking or standing; strenuous working conditions; long weekly work hours (Luke 1995); stress (Hobel 2003); genetic factors (Hoffman 1999); chorioamnionitis (Ustun 2001); lower genital tract infections (Kiss 2004); history of previous abortion; socioeconomic status and nulliparity (Meis 1995).

Description of the intervention

Prevention of preterm labour is the most important step for preventing preterm birth. Prostaglandins have been proposed as playing an important role in parturition (Gibb 2002; Olson 1995). Prostaglandins have a diverse effect on the uterus (Narumiya 1999). They are commonly considered as uterotonics (which increase myometrial tone) (Olson 2007) but can sometimes act as smooth muscle relaxants (Toppozada 1975).

Cyclo-oxygenase (COX) is a type of enzyme in the pathway of prostaglandins synthesis. This pathway can be obstructed by COX inhibitors resulting in the hindrance of prostaglandin production.

How the intervention might work

Prostaglandins are produced from plasma arachidonic acid, which is usually released by the action of enzymes called phospholipases A2 or C. Arachidonic acid can act as substrate for cyclo-oxygenase-1 and -2 (COX-1 and -2) (Smith 1996). These enzymes are the target of many nonsteroidal anti-inflammatory drugs (NSAIDs) (Vane 1998).

The effect of prostaglandins on tissue targets is complicated by prostaglandin receptors. The prostaglandin family of receptors is classified according to the specificity of binding of a given receptor to a particular prostaglandin. These receptors are thromboxane A2(TP), PGD2(DP), prostacyclin or PGI2(IP), PGF2alpha(FP), and EP1 to EP4 (PGE2) (Narumiya 1999). PGE2 and PGI2 have been shown to cause relaxation of vascular smooth muscle and vasodilatation in many circumstances (Henry 2005; Williams 1994). Thus, either the generation of specific prostaglandins or the relative expression of the various prostaglandin receptors may determine the responses of human myometrium to prostaglandins (Myatt 2004). In addition to changes with gestation, several studies show that there may be regional changes in the upper and lower uterine segments (Brodt-Eppley 1999; Grigsby 2006). Thus, it is entirely possible that prostanoids contribute to myometrial relaxation at one stage of pregnancy and to regional myometrial contraction of the fundus after the initiation of parturition. In the process of labour, many investigators have accepted and fostered the view that prostaglandins, particularly PGF2alpha and PGE2, are involved. The following evidence may support the role of COX inhibitors in preventing preterm labour.

1. The levels of prostaglandins in amniotic fluid, maternal plasma, and the uterus increase during labour (Gibb 1998).
2. Prostaglandins cause abortion or labour (Novy 1980).
3. An observational study by Loudon found that COX-2 inhibitors was effective in treating preterm labour (Loudon 2003).
4. Prostaglandin treatment of myometrial smooth muscle tissues in vitro sometimes causes contraction, dependent on the prostanoid tested and the physiological status of the tissue treated (Myatt 2004).

However, like oxytocin, prostaglandins produced directly in or adjacent to myometrial tissue are likely to play a major role in the effectiveness of myometrial contractions of active labour once labour is initiated. Based on the evidence that during the parturition process prostaglandins play an important role in labour, COXinhibitors may help to relieve myometrial tone (tocolytic effect) and result in cessation of labour (Dawood 1993; Olson 2003). COX-2 progressively increases expression while gestational age increases, so there is a potential role for COX-2 in normal parturition (Vermillion 2005). Thus, selective COX-2 inhibitors may be more effective in preventing uterine contraction than non-selective COX inhibitors.

Why it is important to do this review

There is no Cochrane review addressing the effectiveness and safety of COX inhibitors in preventing preterm labour. A previous Cochrane review on COX inhibitors found insufficient data

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to draw conclusions about its role in treating preterm labour and there was limited information on serious maternal outcomes such as death, cardiac arrest, respiratory arrest and admission to intensive care unit (King 2005). There is no Cochrane review on the effectiveness and safety of antenatal COX inhibitors for preventing preterm labour in high risk women.

OBJECTIVES

To assess the effectiveness and safety of COX inhibitors for preventing preterm labour in high-risk women.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all published and unpublished randomised trials evaluating administration of any COX inhibitors for preventing preterm labour. We will exclude quasi-randomised trials and studies with crossover designs. We will include cluster-randomised trials.

Types of participants

Pregnant women at 22 to 36 weeks' gestation, at risk for but not experiencing preterm labour.

Types of interventions

Administration of COX inhibitors compared with placebo or any other interventions (including conservative management) for preventing preterm labour.

Types of outcome measures

Primary outcomes

1. Preterm labour (less than 37 completed weeks)
2. Preterm birth (less than 37 completed weeks)

Secondary outcomes

Maternal outcomes

1. Preterm labour at gestational age of 34 - < 37 completed weeks
2. Preterm labour at gestational age of 28 - < 34 completed weeks
3. Preterm labour at gestational age of 22 - < 28 completed weeks
4. Labour-free interval
5. Preterm birth < 34 weeks
6. Adverse effects
7. Length of hospital stay
8. Pregnant women's satisfaction

Neonatal outcome

1. Birthweight
1.1 Low birthweight (LBW): birthweight less than 2500 grams
1.2 Very low birthweight (VLBW): birthweight less than 1500 grams
1.3 Extremely low birthweight (ELBW): birthweight less than 1000 grams
2. Neonatal morbidity index (the presence of one or more of the following conditions: premature closure of ductus arteriosus; patent ductus arteriosus; sepsis; necrotising enterocolitis; intraventricular haemorrhage; respiratory distress syndrome)
3. Admission to NICU
4. Perinatal mortality
5. Long-term outcomes e.g. developmental delay, cerebral palsy, educational attainment etc.

Search methods for identification of studies

Electronic searches

We will contact the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register.
The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and

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the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.
Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.
We will not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors will independently assess for inclusion all potential studies identified as a result of the search strategy. We will resolve any disagreement through discussion, or if required, consult the third reviewer.

Data extraction and management

We will design a form for data extraction. At least two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion. We will use the Review Manager software (RevMan 2008) to double enter all the data.
When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). We will resolve any disagreement by discussion or by involving a third assessor.

(1) Sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We will assess the method as:

- adequate (any truly random process e.g. random number table; computer random number generator);
- inadequate (any non random process e.g. odd or even date of birth; hospital or clinic record number); or
- unclear.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We will assess the methods as:

- adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear.

(3) Blinding (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will judge studies at low risk of bias if they were blinded, or if we judge that the lack of blinding could not have affected the results. We will assess blinding separately for different outcomes or classes of outcomes.
We will assess the methods as:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors; or
- partial for some situations e.g. data from unblinded participant been recorded by blinded personnel.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported; the numbers included in the analysis at each stage (compared with the total randomised participants); reasons for attrition or exclusion where reported; and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake. We will assess methods as:

- adequate;
- inadequate;
- unclear.

We will discuss whether missing data greater than 20% might (a) be reasonably expected (acknowledging that with long-term follow up, complete data are difficult to attain), and (b) impact on outcomes.

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(5) Selective reporting bias

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:

- adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear.

(6) Other sources of bias

We will describe for each included study any important concerns we have about other possible sources of bias.
We will assess whether each study was free of other problems that could put it at risk of bias:

- yes;
- no;
- unclear.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the Handbook (Higgins 2008). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - *see* 'Sensitivity analysis'.

Measures of treatment effect

We will carry out statistical analysis using the Review Manager software (RevMan 2008). We will use fixed-effect meta-analysis for combining data in the absence of significant heterogeneity if trials are sufficiently similar. If heterogeneity is found, we will explore this by sensitivity analysis followed by random-effects if required.

Dichotomous data

For dichotomous data, we will present results as summary risk ratio (RR) with 95% confidence intervals (CI).

Continuous data

For continuous data, we will use the mean difference (MD) if outcomes are measured in the same way between trials. We will use the standardised mean difference (SMD) to combine trials that measure the same outcome, but use different methods. If there is evidence of skewness, we will report this.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually randomised trials. We will adjust their sample sizes using the methods described in the *Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources are used, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.
We will also acknowledge heterogeneity in the randomisation unit and perform a separate meta-analysis.

Dealing with missing data

We will analyse data on all participants with available data in the group to which they are allocated, regardless of whether or not they received the allocated intervention. If in the original reports participants are not analysed in the group to which they were randomised, and there is sufficient information in the trial report, we will attempt to restore them to the correct group.

Assessment of heterogeneity

We will apply tests of heterogeneity between trials, if appropriate, using the I^2 statistic. If we identify high levels of heterogeneity among the trials (exceeding 50%), we will explore it by prespecified subgroup analysis and perform sensitivity analysis. A random-effects meta-analysis will be used as an overall summary if this is considered appropriate.

Assessment of reporting biases

Where we suspect reporting bias (*see* 'Selective reporting bias', above), we will attempt to contact study authors asking them to provide missing outcome data. Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

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Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2008). We will use fixed-effect inverse variance meta-analysis for combining data where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. Where we suspect clinical or methodological heterogeneity between studies sufficient to suggest that treatment effects may differ between trials, we will use random-effects meta-analysis.

If we identify substantial heterogeneity in a fixed effect meta-analysis, we will note this and repeat the analysis, using a random-effects method.

Subgroup analysis and investigation of heterogeneity

We will conduct planned subgroup analyses classifying whole trials by interaction tests as described by Deeks 2001.

We plan to carry out the following subgroup analyses:

1. Nonselective COX inhibitors versus selective COX-2 inhibitors
2. Singleton versus multiple pregnancies

Sensitivity analysis

We will carry out sensitivity analysis to explore the effect of trial quality, only including studies which have been assessed as having adequate control of the potential for bias.

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As part of the pre-publication editorial process, this protocol has been commented on by three peers (an editor and two referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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* *Indicates the major publication for the study*

HISTORY

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CONTRIBUTIONS OF AUTHORS

Thirawut Khanprakob (TK) registered the review title and drafted the protocol. Ussanee Swadpanich (US), Pisake Lumbiganon (PL) and Malinee Laopaiboon (ML) revised and approved the final version of the protocol. TK will draft the review. US, PL and ML will revise and approve the final version of the review.

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DECLARATIONS OF INTEREST

None known.

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Hepatitis B vaccination during pregnancy for preventing infant infection (Protocol)

Sangkomkamhang US, Lumbiganon P, Laopaiboon M

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TABLE OF CONTENTS

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[Intervention Protocol]

Hepatitis B vaccination during pregnancy for preventing infant infection

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effectiveness and adverse effects of hepatitis B vaccine administered to pregnant women for preventing HBV infection in infants.

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BACKGROUND

Description of the condition

Hepatitis B virus (HBV) is an enveloped, double-stranded DNA virus. Hepatitis B is an infection caused by the HBV and occurs worldwide. The highest rates of HBV carriers are found in developing countries with limited medical facilities. In highly endemic areas of Asia, Africa, and the Pacific, approximately 75% of hepatitis B carriers usually acquire the virus perinatally or in childhood (Safary 2000). Whereas in western and northern European countries and North America, HBV infection is relatively rare and acquired primarily in adulthood. HBV infections result in 500,000 to 1.2 million deaths per year caused by chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) (Lavanchy 2004). Globally, HBV causes 60% to 80% of the worlds primary liver cancers (Parkin 2001).

Diagnosis of hepatitis is made by biochemical assessment of liver function and coagulation studies (Hollinger 2001). Diagnosis is confirmed by demonstration of specific antigens and/or antibodies. Three clinically useful antigen antibody systems have been identified for hepatitis B: (1) hepatitis B surface antigen (HBsAg) and antibody to HBsAg (anti-HBs IgG); (2) antibody (anti-HBc IgM) and anti-HBc IgG) to hepatitis B core antigen (HBcAg); and (3) hepatitis B e antigen (HBeAg) and antibody to HBeAg (anti-HBe) to determine infectivity.

For infants and children, the two primary sources of HBV infection are perinatal transmission from infected mothers and horizontal transmission from infected household contacts. Perinatal transmission is common in hyperendemics areas, especially when HBsAg carrier mothers are also HBeAg positive (Hollinger 2001; Mahoney 1999). For a newborn infant whose mother is positive for both HBsAg and HBeAg, the risk for chronic HBV infection is 70% to 90% by age six months in the absence of postexposure immunoprophylaxis (Wong 1984). By comparison, the infant risk for chronic infection is less than 10% in the mother with HBeAg negative (Stevens 1985). Of persons who are infected with HBV as infants or young children, 25% to 90% become chronic carriers, and approximately 25% of those with chronic infection die prematurely from cirrhosis or liver cancer (hepatocellular carcinoma) (Gitlin 1997; McMahon 1990). Development of chronic HBV infection at an early age increases the risk of HCC more than infection at older age (Hsieh 1992). Nearly 100% of HCC children were hepatitis B surface antigen seropositive (Chang 1998). Breastfeeding by an HBsAg positive mother does not increase the risk for acquisition of HBV infection in the infant (Beasley 1975).

Description of the intervention

Hepatitis B vaccines are composed of the surface antigen of HBV (HBsAg), and are produced by two different methods: plasma derived or recombinant DNA (Assad 1999). Plasma-derived vaccines, derived from the plasma of HBsAg-positive donors, consist of highly purified, formalin-inactivated and/or heat-inactivated, alum-adsorbed, hepatitis B subvirion particles (22 nm) of HBsAg that are free of detectable nucleic acid, and, therefore, non-infectious. Recombinant DNA yeast-derived or mammalian cell-derived vaccines, the S gene (pre-S1, pre-S2, S), is cloned and isolated, inserted into an expression plasmid and introduced into yeast or mammalian cells. The desired protein is expressed and assembled into 22 nm antigenic particles. As on natural HBsAg particles, the epitope that elicits the most important immune response is exposed on the surface of artificial particles. Vaccines used for primary prevention have effectively reduced risk of infection in most populations (Mahoney 1993). Completion of hepatitis B vaccine programmes induces protection in about 95% of recipients (Jackson 2007). Vaccination during pregnancy is safe and provides passive transfer of antibodies to the newborn (Anonymous 1991; Gupta 2003; Levy 1991).There are no known side effects from vaccination, in either pregnant women or their offspring (Grosheide 1993). The most common side effects from hepatitis B vaccination are pain at the injection site and mild to moderate fever (Andre 1989; Greenberg 1993).

Hepatitis B vaccine is given into the deltoid intramuscularly in a series of three doses (de Lalla 1988; Krugman 1981). The first shot is given at the elected date; the second dose a month later; and the third dose six months after the first dose. Vaccine batches should be stored at 2° to 8°C. Freezing destroys the potency of the vaccine. Factors that may reduce the immunogenicity of hepatitis vaccines include age (greater than 40 years), weight, genetics, haemodialysis, HIV infection, immunosuppression, tobacco smoking, subcutaneous injection, injection into the buttocks, and accelerated schedule (Ingardia 1999).

How the intervention might work

The mechanism of hepatitis B vaccination during pregnancy for preventing neonatal infection is the production of maternal antibodies that can be transferred across the placenta and provide the neonate with high antibody titers. This could protect the neonate from horizontal infection until active immunization after birth is protective (Reddy 1994).

Why it is important to do this review

Complex HBV epidemiology makes it difficult to evaluate and compare the effectiveness of different immunization policies. HBV infection rates vary in different parts of the world according to the pattern of hepatitis B transmission. In high endemic populations, perinatal transmission has been documented to result in a high rate of hepatitis B infection (Beasley 1983). Many countries have implemented universal hepatitis B immunization at birth, which provides long-term protection against infection in more than 90%

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of healthy people (Shepard 2006). Despite this, some infants who are born to HBV sero-positive mothers have become infected by HBV despite having received passive-active immunoprophylaxis (Ngui 1998). Maternal hepatitis B vaccine immunization may be a way of preventing hepatitis B infection in infants before hepatitis B vaccine can be administered and provide protection. However, the ideal plan for hepatitis B vaccine administration during pregnancy, taking into consideration risk factors (high risk of HBV infection or the general population); endemic populations (high or low); and cost effectiveness, is not known.

OBJECTIVES

To assess the effectiveness and adverse effects of hepatitis B vaccine administered to pregnant women for preventing HBV infection in infants.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomized controlled trials (RCTs) of hepatitis B vaccination during pregnancy for preventing infant infection. The randomized units could be individual or clustered (e.g. hospitals). We will exclude cross-over trials and quasi-randomized trials.

Types of participants

All pregnant women unaware of marker results of hepatitis B virus serology.

Types of interventions

Hepatitis B vaccine compared with placebo or no treatment.

Types of outcome measures

Primary outcomes

Incidence of hepatitis B virus infection in infants.

Secondary outcomes

1. Hepatitis B antibody for hepatitis B virus (HBs Ab) in newborns up to six months after birth.
2. Maternal antibody for hepatitis B virus (HBs Ab).
3. Adverse maternal effects such as local reactions at injection site (soreness, swelling, erythema); fatigue; fever; headache.

Search methods for identification of studies

Electronic searches

We will contact the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register.
The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.
Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.
We will not apply any language restrictions.

Data collection and analysis

The methodology for data collection and analysis is based on the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2008).

Selection of studies

Two review authors, Ussanee S Sangkomkamhang (US) and Pisake Lumbiganon (PL) will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult an additional review author.

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Data extraction and management

We will design a form to extract data. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult an additional review author. We will enter data into Review Manager software (RevMan 2008) and check for accuracy. When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). We will resolve any disagreement by discussion or by involving an additional assessor.

(1) Sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We will assess the method as:

- adequate (any truly random process, e.g. random number table; computer random number generator);
- inadequate (any non random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We will assess the methods as:

- adequate (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear.

(3) Blinding (checking for possible performance bias)

We will describe for each included study all the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will also provide information on whether the intended blinding was effective.
We will assess the methods as:

- adequate, inadequate, or unclear for participants;
- adequate, inadequate, or unclear for personnel;
- adequate, inadequate, or unclear for outcome assessors;

where 'adequate' is when there was blinding or where we assess that the outcome or the outcome measurement is not likely to have been influenced by lack of blinding.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We will describe for each included trial, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake. We will assess methods as:

- adequate;
- inadequate:
- unclear.

We will discuss whether missing data greater than 20% might (a) be reasonably expected (acknowledging that with long-term follow up, complete data are difficult to attain); and (b) impact on outcomes.

(5) Selective reporting bias

We will describe for each included trial how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:

- adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear.

(6) Other sources of bias

We will describe for each included study any important concerns we have about other possible sources of bias.
We will assess whether each study was free of other problems that could put it at risk of bias:

- yes;

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- no;
- unclear.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - *see* 'Sensitivity analysis'.

When information regarding any of the above (1) to (6) is unclear, we will attempt to contact authors of the original reports to provide further details.

Measures of treatment effect

Dichotomous data

For dichotomous data, such as the incidence of hepatitis B virus infection in infants, we will present results as summary risk ratio with 95% confidence interval.

Continuous data

For continuous data, such as maternal antibody levels, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomized trials in the analyses, along with individually randomized trials. We will adjust their sample sizes using the methods described in the *Handbook,* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources are used, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomized trials and individually-randomized trials, we plan to synthesize the relevant information. We will consider it reasonable to combine the results from both, if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomization unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomization unit and perform a separate meta-analysis.

Dealing with missing data

For included trials, we will note levels of attrition. We will explore the impact of including trials with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. For all outcomes we will carry out analyses, as far as possible, on an intention-to-treat basis: i.e. we will attempt to include all participants randomized to each group in the analyses. The denominator for each outcome in each trial will be the number randomized minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity (I^2 greater than 50%), we will explore it by prespecified subgroup analysis.

Assessment of reporting biases

Where we suspect reporting bias (*see* selective reporting bias above), we will attempt to contact study authors, asking them to provide missing outcome data. Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such trials in the overall assessment of results by a sensitivity analysis.

Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2008). We will use fixed-effect inverse variance meta-analysis for combining data where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. Where we cannot explain heterogeneity between trials' treatment effects, we will use random-effects meta-analysis.

Subgroup analysis and investigation of heterogeneity

If we can include a number of trials, we plan to carry out subgroup analyses for the primary outcome of incidence of hepatitis B virus infection in infant as following:

1. low risk of hepatitis B virus (HBV) infection versus high risk (as defined by authors e.g. injection drug users, healthcare workers) of HBV infection;
2. low endemic setting versus high endemic setting of HBV infection;
3. vaccination schedule (e.g. three doses versus two doses regimen);
4. maternal negative versus positive for marker of hepatitis B virus serology.

For fixed-effect meta-analyses we will conduct planned subgroup analyses classifying whole trials by interaction tests as described by

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(Deeks 2001). For random-effects meta-analyses we will assess differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis

We will perform sensitivity analysis based on trial quality, separating high-quality trials from trials of lower quality. For the purposes of this sensitivity analysis, we will define 'high quality' as a trial having adequate allocation concealment, and classify an 'unreasonably expected loss to follow up' as less than 20%, given the stated importance of attrition as a quality measure (Tierney 2005). If we include any cluster-randomized trials, other sensitivity analysis may also be desirable. If cluster trials have been incorporated with an estimate of the ICC borrowed from a different trial, we will perform a sensitivity analysis to see what the effect of different values of the ICC on the results of the analysis would be.

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As part of the pre-publication editorial process, this protocol has been commented on by three peers (an editor and two referees who are external to the editorial team) and the Group's Statistical Adviser.

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* *Indicates the major publication for the study*

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HISTORY

Protocol first published: Issue 3, 2009

CONTRIBUTIONS OF AUTHORS

Ussanee S Sangkomkamhang selected the topic from vacant list and drafted the protocol. Pisake Lumbiganon and Malinee Laopaiboon revised and approved the protocol.

DECLARATIONS OF INTEREST

None known.

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

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Antibiotics for chronic rhinosinusitis in adults (Protocol)

Piromchai P, Thanaviratananich S, Laopaiboon M

This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 1

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Antibiotics for chronic rhinosinusitis in adults (Protocol)
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TABLE OF CONTENTS

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[Intervention Protocol]

Antibiotics for chronic rhinosinusitis in adults

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

1. To determine the effectiveness of systemic antibiotic therapy for chronic rhinosinusitis in adults.
2. To determine the adverse reactions associated with systemic antibiotic therapy for chronic rhinosinusitis in adults.

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BACKGROUND

Description of the condition

Rhinosinusitis is the inflammation of the paranasal sinus mucosa. It is defined as chronic when it has lasted longer than three months without complete resolution of symptoms (EPOS 2007; Rosenfeld 2007). Symptoms may consist of purulent nasal discharge, nasal obstruction, facial pain/pressure/fullness or decreased sense of smell, in addition to evidence of inflammation, including purulent discharge or oedema of the middle meatus or ethmoid region, polyps in the nasal cavity or the middle meatus and/or radiographic imaging showing inflammation of the paranasal sinuses. Rhinosinusitis is categorised as with or without nasal polyps. Although various infective and non-infective inflammatory processes are involved in the pathogenesis of chronic rhinosinusitis, bacterial infection is believed to play an important role. A study by Merino et al demonstrated bacterial growth in 98% of aspirates from 510 patients with chronic rhinosinusitis; most were mixed aerobic and anaerobic bacteria (Merino 2003). The bacteriology of chronic rhinosinusitis study by Brook also demonstrated 41% mixed organisms, 34% anaerobes and 25% aerobes (Brook 2006). Chronic rhinosinusitis is a common health problem which significantly affects quality of life (Gliklich 1995; van Agthoven 2001; Wang 2003). According to a national health interview survey of the prevalence of chronic conditions, chronic rhinosinusitis has been estimated to affect 12.5% to 15.5% of the total population, making it the second most common chronic condition in the United States (Adams 1999; Collins 1997). However, the prevalence of doctor diagnosed chronic rhinosinusitis is much lower; a prevalence of 2% was found using ICD-9 codes as an identifier (Shashy 2004). The prevalence rate is substantially higher in females with a female/male ratio of 6/4 (Collins 1997) and increases with age, with a mean of 2.7% and 6.6% in the age groups of 20 to 29 and 50 to 59 years, respectively, and levelling off at 4.7% after 60 years (Bonfils 2005).

Description of the intervention

A wide range of medical and surgical therapies have been used to treat chronic rhinosinusitis. Medical therapy includes antibiotics, corticosteroids, decongestants, antihistamines, mast cell stabilisers, anti-leukotrienes, nasal douching, immunotherapy and reduction of environmental factors (EPOS 2007). A recent Cochrane Review found nasal saline irrigation, both as a sole modality and as an adjunct to medical treatment for chronic rhinosinusitis, to be beneficial (Harvey 2007). Surgical treatment by functional endoscopic sinus surgery (FESS) has also become a well-established strategy for the treatment of chronic rhinosinusitis refractory to medical treatment. However, a Cochrane Review has suggested that FESS has not been demonstrated to confer additional benefit to that obtained by medical treatment (Khalil 2006).

How the intervention might work

Systemic and topical antibiotics are used in chronic rhinosinusitis with the aim of eliminating infection and inflammation (Inamura 2000; Miyanohara 2000; Wallwork 2006), altering bacterial biofilm formation (Wozniak 2004), reversing ostial occlusion and improving symptoms. However, unnecessary antibiotic prescriptions should be avoided. Some adverse effects have been reported, including allergy (MacLaughlin 2000), diarrhoea and abdominal pain (Bucher 2004). Overuse is associated with increasing resistance to antibiotics among community acquired pathogens. There is evidence of conflict in the definition of chronic rhinosinusitis and this makes evaluation of the effectiveness of antibiotic treatment difficult. In recent clinical practice guidelines (EPOS 2007; Rosenfeld 2007), it was proposed that chronic rhinosinusitis diagnosis requires appropriate signs/symptoms for more than 12 weeks and documented inflammation. The definition of chronic rhinosinusitis in this systematic review is based primarily on these guidelines.

Why it is important to do this review

Various groups of systemic antibiotics have been studied in the treatment of chronic rhinosinusitis, including penicillins (Huck 1993; Legent 1994; Namyslowski 2002), cephalosporins (Huck 1993; Namyslowski 2002), quinolones (Legent 1994) and macrolides (Ragab 2004; Wallwork 2006). The duration of antibiotic course in these studies has ranged from nine days (Legent 1994) to 12 weeks (Ragab 2004; Wallwork 2006), and types of study design varied from descriptive studies to randomised controlled trials. Clinical cure rates reported in the studies are inconsistent and range from as low as 50% (Legent 1994) to 95% (Namyslowski 2002).

Topical antibiotics have also been used to treat chronic rhinosinusitis with the theoretical advantage of acting directly on the site of infection and producing a higher concentration of antibiotic at the target site (Desrosiers 2007). However, a systematic review of topical treatment of rhinosinusitis in children found no evidence of effectiveness (Fiocchi 2007). A systematic review of topical antibiotics for chronic rhinosinusitis (Lim 2008) and antibiotic nasal washes in chronic rhinosinusitis (Elliott 2006) also demonstrated low-level corroborative evidence.

There are systematic reviews which support the use of systemic antibiotics in acute rhinosinusitis (Ahovuo-Saloranta 2008; González 2006). However, the evidence for systemic antibiotics in chronic rhinosinusitis is still in question.

The recent European practice guideline states that while there are randomised controlled studies on the efficacy/effectiveness of short-term oral antibiotics for chronic rhinosinusitis, the results show a negative outcome, while long-term oral antibiotic use has been shown to be beneficial (EPOS 2007). Although at present the US Food and Drug Administration has not approved any medica-

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tions for the treatment of chronic rhinosinusitis, oral antibiotics and nasal corticosteroids are the two most commonly used medications in most cases (Dubin 2007; Kaszuba 2006).
To our knowledge, no meta-analysis of randomised controlled trials of systemic antibiotics for chronic rhinosinusitis is currently available. A Cochrane Review assessing the effects of antibiotics in the treatment of chronic rhinosinusitis is therefore warranted.

OBJECTIVES

1. To determine the effectiveness of systemic antibiotic therapy for chronic rhinosinusitis in adults.

2. To determine the adverse reactions associated with systemic antibiotic therapy for chronic rhinosinusitis in adults.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

Chronic rhinosinusitis defined by at least 12 weeks of two or more of the following signs and symptoms:

- mucopurulent drainage (anterior/posterior nasal drip);
- nasal blockage/obstruction/congestion;
- facial pain/pressure/fullness; or
- decrease or loss of smell.

Inflammation is also documented by one or more of the following findings:

- purulent (not clear) mucus or oedema in the middle meatus or ethmoid region;
- polyps in nasal cavity or the middle meatus; and/or
- radiographic imaging showing inflammation of the paranasal sinuses.

Inclusion criteria:
Patients aged at least 18 years with chronic rhinosinusitis without nasal polyps.
We will exclude patients with the following conditions:

1. cystic fibrosis, based on positive sweat test or DNA alleles;
2. gross immunodeficiency (congenital or acquired);
3. congenital mucociliary problems, e.g. primary ciliary dyskinesia (PCD);
4. fungal rhinosinusitis;
5. systemic vasculitis and granulomatous diseases;
6. cocaine abuse;
7. neoplasia;
8. acute exacerbation on chronic rhinosinusitis at the time of study entry;
9. using topical or systemic corticosteroids within four weeks before entering the study;
10. aspirin hypersensitivity;
11. receiving antibiotics within two weeks before entering the study.

Types of interventions

Systemic antibiotics versus placebo.

Types of outcome measures

Primary outcomes

- Clinical cure rate post-treatment; cure defined as no clinical symptoms or signs, or substantially improved.

Secondary outcomes

- Bacteriological cure rate.
- Radiographic response rate.
- Relapse rate: new episodes of sinusitis after 60 days from the start of the initial treatment.
- Adverse effects.

Search methods for identification of studies

We will conduct systematic searches for randomised controlled trials. There will be no language, publication year or publication status restrictions. We may contact original authors for clarification and further data if trial reports are unclear and we will arrange translations of papers where necessary.

Electronic searches

Published, unpublished and ongoing studies will be identified by searching the following databases from their inception: the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library,* current issue); PubMed; EMBASE; CINAHL; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts; Web of Science; BIOSIS Previews; CNKI; *m*RCT (Current Controlled Trials); ClinicalTrials.gov; ICTRP (International Clinical Trials Registry Platform) and Google.

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Subject strategies for databases will be modelled on the search strategy designed for CENTRAL shown in Appendix 1. Where appropriate, we will combine subject strategies with adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in *The Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.1, Box 6.4.b. (Handbook 2008)).

Searching other resources

We will scan reference lists of identified publications for additional trials and contact authors if necessary. PubMed; TRIPdatabase; NHS Evidence ENT & Audiology; and Google will be searched to retrieve existing systematic reviews possibly relevant to this systematic review, so that we can scan their reference lists for additional trials.

Data collection and analysis

Selection of studies

Papers that appear loosely to meet the inclusion criteria (based on title and abstract) will be selected by one author. If the information relevant to the inclusion criteria is not available in the abstract, or if the title is relevant but the abstract is not available, we will obtain the full text of the report. Papers that pass this initial review will be assessed by two authors. We will resolve disagreements between authors by discussion until a consensus is reached.

Data extraction and management

Two authors will extract data independently, using a paper data extraction form. We will compare results and resolve disagreements by discussion until a consensus is reached. Data will be entered into RevMan (RevMan 2008) and pooled where appropriate.

We will extract the following information relating to the study methodology or quality: randomisation concealment as described in the study, blinding, timing of follow up, percentage of drop-outs during follow up and baseline comparability of the groups.

We will extract the following characteristics relating to methods: criteria for accepting participants into the study (diagnosis on clinical/radiography/culture basis), definition of cure/failure and treatment compliance.

We will extract the following characteristics relating to participants: number of participants in treatment and control groups at start, mean age of participants (plus age range), gender, year study published and study setting.

We will extract the following characteristics of the intervention: intervention comparisons, courses of antibiotics and information about co-interventions.

We will extract information on clinical, bacteriological and radiographic outcomes and adverse event rates. We will mainly extract outcome information as numbers of participants with cure rate by study group. We will classify relapse within 60 days from the onset of the treatment will be classified as a clinical failure. In some studies, the results may be reported at more than one period of follow up. We will extract the data for all periods. We will carry out meta-analyses based on the available data.

Assessment of risk of bias in included studies

Two review authors will independently carry out the assessment of risk of bias in the included studies. We will resolve any disagreements between the authors by consensus. We will assess the risk of bias of included studies using the suggested six domains of sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias (Higgins 2008).

We will base the overall 'Risk of bias' table on the *Cochrane Handbook for Systematic Reviews of Interventions* 5.0.1 (section 8.5 (Higgins 2008)) and the domains outlined in the previous paragraph. Overall risk of bias will be classified as low, unclear or high.

Measures of treatment effect

We will assess treatment effect by calculating the risk ratio (RR) (and 95% confidence intervals (CI)) of cure at a specific time point (dichotomous variable) for each trial. We will use mean difference (MD) and 95% CI for continuous variables (severity scores, duration of symptoms, etc.).

When trials are sufficiently homogeneous, we will pool intervention effects.

Unit of analysis issues

For cross-over studies, we will calculate the mean treatment differences between the periods where possible and enter these using the fixed-effect generic inverse variance (GIV) analysis in RevMan (RevMan 2008), to provide summary mean differences and 95% CIs. In cross-over studies, if we believe there is a carry-over effect which will outlast any washout period included in the study, we will include only data from the first period in the meta-analysis. In studies with multiple treatment groups we will combine similar groups if possible to create a single pair-wise comparison.

Dealing with missing data

In assessing the influence of missing data on the overall results of the placebo controlled studies (primary outcome measures only), we will use three ways of imputing data: assuming the outcomes of participants for whom no outcome was recorded a) as failures, b) as non-failures or c) according to the event rate observed in the control group.

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Assessment of heterogeneity

We will assess the significance of any discrepancies in the estimates of the treatment effects from the different trials by means of Cochran's Q test for heterogeneity and by a measure of the I^2 statistic. The I^2 statistic describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. A value greater than 50% may be considered to represent substantial heterogeneity. We will also use the forest plot to assess heterogeneity visually.

Assessment of reporting biases

We will assess publication bias by means of a funnel plot if there are a sufficient number of trials.

Data synthesis

We will conduct meta-analyses for trials with similar characteristics using RevMan (RevMan 2008). We will use fixed-effect inverse variance meta-analysis for combining data where trials are judged sufficiently similar. Where there is clinical or methodological heterogeneity between studies sufficient to suggest that treatment effects may differ between trials, we will use random-effects meta-analysis. Where the heterogeneity between studies cannot be explained by any potential factor, we will use random-effects meta-analysis to pool the treatment effects.

Subgroup analysis and investigation of heterogeneity

The following conditions will be considered for subgroup analysis if heterogeneity of treatment effect is found:

1. short-term versus long-term treatment;
2. asthma/bronchial hyper-reactivity/chronic obstructive pulmonary disease (COPD)/bronchiectases based on symptoms, respiratory function tests;
3. allergy based on specific serum IgE or skin prick tests (SPTs).

Sensitivity analysis

To test the robustness of results, we plan to use sensitivity analyses to examine the effect of chronic rhinosinusitis diagnostic criteria (signs/symptoms, presence of inflammation and/or radiograph), and the classification of the risk of bias, on the overall estimates of effect for important outcomes.

ACKNOWLEDGEMENTS

We would like to thank Thai Cochrane Network and the Cochrane Ear, Nose and Throat Disorders Group for their support.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategy

CENTRAL search strategy

#1 MeSH descriptor Sinusitis explode all trees
#2 rhinosinusitis OR nasosinusitis OR sinusitis OR pansinusitis OR ethmoiditis OR antritis OR sphenoiditis
#3 (kartagener* near syndrome)
#4 (inflamm* near sinus*)
#5 (#1 OR #2 OR #3 OR #4)
#6 MeSH descriptor Chronic Disease explode all trees
#7 MeSH descriptor Recurrence explode all trees
#8 (chronic* OR persist* OR recur*)
#9 (#6 OR #7 OR #8)
#10 (#5 AND #9)
#11 MeSH descriptor Anti-Bacterial Agents explode all trees
#12 MeSH descriptor Antibiotic Prophylaxis explode all trees
#13 MeSH descriptor Lactams explode all trees
#14 MeSH descriptor Quinolones explode all trees
#15 MeSH descriptor Macrolides explode all trees
#16 ANTIBIOT* OR ANTI NEXT BIOT* OR ANTIMICROBIAL* OR ANTI NEXT MICROBIAL* OR BACTERIOCID* OR ANTIBACTERIAL* OR ANTI NEXT BACTERIAL*
#17 PENICILLIN* OR AMOXICILLIN OR AMPICILLIN OR CLAVULANIC NEXT ACID OR AMOXICLAV OR AUGMENTIN OR TICARCILLIN OR TIMENTIN OR FLUCLOXACILLIN OR FLUAMPICIL OR MAGNAPEN OR PIPERACILLIN OR TAZOCIN OR CEPHALOSPORIN* OR CEFACLOR OR DISTACLOR OR CEFADROXIL OR BAXAN OR CEFALEXIN OR CEPOREX OR KEFLEX OR CEFAMANDOLE OR KEFADOL OR CEFAZOLIN* OR KEFZOL OR CEFIXIME OR SUPRAX OR CEFOTAXIME OR CLAFORAN OR CEFOXITIN OR MEFOXIN OR CEFPIROME OR CEFROM OR CEFPODOXIME OR ORELOX OR CEFPROZIL OR CEFZIL OR CEFRADINE OR VELOSEL OR CEFTAZIDIM OR FORTUM OR KEFADIM OR CEFTRIAXONE OR ROCEPHIN OR CEFUROXIME OR ZINACEF OR ZINNAT OR CEFONICID OR AZTREONAM OR AZACTAM OR IMIPENEM OR CILASTATIN OR PRIMAXIN OR MEROPENEM OR TETRACYCLINE* OR DETECLO OR DEMECLEOCYCLIN OR LEDERMYCIN OR DOXYCYCLINE OR VIBRAMYCIN OR MINOCYCLINE OR MINOCINE OR OXYTETRACYCLINE OR TERRAMYCIN OR MACROLIDE* OR ERYTHROMYCIN OR ERYMAX OR ERYTHROCIN OR ERYTHROPED OR AZITHROMYCIN OR ZITHROMAX OR CLARITHROMYCIN OR KLARICID OR TELITHROMYCIN OR KETEK OR TRIMOXAZOLE OR SEPTRIN OR TRIMETHOPRIM OR MONOTRIM OR TRIMOPAN OR METRONIDAZOLE OR FLAGYL OR METROLYL OR PHENOXYMETHYLPENICILLIN OR SULFAMETHOXAZOLE OR OXACILLIN OR CEPHALOTHIN OR SULBACTAM OR OFLOXACIN OR CLINDAMYCIN OR GENTAMYCIN OR VANCOMYCIN

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#18 (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)
#19 (#10 AND #18)

HISTORY

Protocol first published: Issue 1, 2010

CONTRIBUTIONS OF AUTHORS

Patorn Piromchai wrote the first draft of protocol and will be responsible for study selection, data extraction and analysis, and writing the review.

Sanguansak Thanaviratananich commented on the draft and will be responsible for study selection, data extraction and analysis, and writing the review.

Malinee Laopaiboon drafted the analysis plan in the protocol, reviewed the protocol, and will carry out data analysis and presentation.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Thai Cochrane Network, Thailand.

External sources

- No sources of support supplied

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Vitamin K for the prevention and treatment of osteoporosis in post-menopausal women (Protocol)

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Vitamin K for the prevention and treatment of osteoporosis in post-menopausal women (Protocol)
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TABLE OF CONTENTS

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[Intervention Protocol]

Vitamin K for the prevention and treatment of osteoporosis in post-menopausal women

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess efficacy and safety of vitamin K1 or vitamin K2 for prevention and treatment of postmenopausal osteoporosis.

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BACKGROUND

Description of the condition

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength primarily reflects the integration of bone density and bone quality. Bone density is expressed as grams of mineral per area or volume, and in any given individual is determined by peak bone mass and amount of bone loss. Bone quality refers to architecture, turnover, damage accumulation (e.g., microfractures), and mineralization (NIH 2001). The most common clinical manifestations of osteoporosis are fractures of the hip, vertebrae or wrist.

Approximately 30% of postmenopausal females have osteoporosis according to the World Health Organization (WHO) definition of osteoporosis (WHO 1994). In the USA, approximately 1.5 million fractures annually are attributable to osteoporosis. These include 700,000 vertebral fractures, 250,000 distal forearm (Colles') fractures, 250,000 hip fractures, and 300,000 fractures of other limb sites (Riggs 1995). Hip fracture is a significant cause of morbidity and mortality worldwide, the risk of death is increased in patients with osteoporotic fractures and that the highest risk is found immediately after the fracture event (Johnell 2004a; Johnell 2004b). Following a hip fracture, there is a 10% to 20% mortality over the subsequent 6 months, 50% of sufferers will be unable to walk without assistance, and 25% will require long term domiciliary care (Riggs 1995). For 2005, total costs in the United States including prevalent fractures are more than $19 billion (Burge 2007).

Treatments for osteoporosis includes both non pharmacological and pharmacological methods. Five classes of osteoporosis drugs were studied in osteoporotic fractures: hormone replacement therapy (HRT), bisphosphonates (BSP), calcitonin, selective estrogen receptor modulators (SERMs) and vitamin D derivative (Rocaltrol). Comparing between the treated and untreated patients, mortality is significantly lower in the treated group, the lower mortality in the treated group, combined with the knowledge that antiresorptive drugs reduce fractures and increase bone density (Cree 2003). However, bisphosphonate groups have higher cost and gastrointestinal side effect than other drugs. Hormonal therapy also has uncommon side effects after long-time use such as increased risks of mammary cancer (CGHF 1997). Other Cochrane reviews have addressed a number of issues regarding prevention and treatment of postmenopausal osteoporosis. Exercise therapy appears to be effective in increasing bone density at the lumbar spine and hip in postmenopausal women but no prevention fractures (Bonaiuti 2002). Alendronate (Wells 2008a), Risedronate (Wells 2008c) and Strontium ranelate (O'Donnell 2006) demonstrate benefit in the secondary prevention of vertebral and non-vertebral fractures. Etidronate (Wells 2008b) demonstrate benefit in the secondary prevention of vertebral fractures but no reductions in non-vertebral fractures. Fluoride (Haguenauer 2000) has an ability to increase BMD at lumbar spine but no reduction of vertebral fractures. None of these reviews are studied with vitamin K for the prevention and treatment of osteoporosis in postmenopausal women.

Description of the intervention

Vitamin K denotes a group of lipophilic, hydrophobic vitamins that are needed for the posttranslation modification of certain proteins, mostly required for blood coagulation. There are two types of natural vitamin K (K1; Phylloquinone and K2; Menatetrenone, Menaquinone). The major dietary sources of vitamin K are green leafy vegetables (such as kale, spinach, salad greens, cabbage, broccoli and Brussels sprouts) and plant oils (such as soybean and canola oils). Vitamin K2 synthesized by bacteria (Schurgers 1999). Several decades ago, study demonstrated that vitamin K promotes fracture healing and vitamin K has an important role in regulating bone turnover, including bone formation (Hara 1995; Koshihara 1997).

How the intervention might work

Vitamin K is a coenzyme for glutamate carboxylase which mediates the gamma-carboxylation of glutamyl residues on several bone proteins, notably osteocalcin. High serum concentrations of undercarboxylated osteocalcin and low serum concentrations of vitamin K are associated with lower bone mineral density and increased risk of hip fracture (Minisola 1996; Szulc 1993; Vergnaud 1997; Sugiyama 2001). Besides, there is increasing evidence that vitamin K can effect the synthesis and excretion of nephrocalcin and interleukin-1,6 which can regulate calcium balance and bone metabolism (Luo 2003).

Why it is important to do this review

Today there are a number of effective treatment options available that have been shown to act quickly (within one year), to maintain bone density and to reduce the risk of having fractures. Some medications are high cost and some have more complications or side effects. It is important that the choice of treatment be tailored to patient's specific medical needs and lifestyle. However, there is lack of evidence on the potential benefits of using menatetrenone (vitamin K2) therapy in postmenopausal women for preventing and treatment of osteoporosis.

OBJECTIVES

To assess efficacy and safety of vitamin K1 or vitamin K2 for prevention and treatment of postmenopausal osteoporosis.

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METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomized controlled trials (RCTs) of vitamin K in postmenopausal women for preventing and treating postmenopausal osteoporosis. We will exclude quasi-randomized trials.

Types of participants

Postmenopausal women, including those with natural or surgical menopause will be included. Osteoporosis should be diagnosed on a bone mineral density (BMD) test, which can be detected by one of the examinations but not limited to: single photon absorptiometry, dual photon absorptiometry, quantitative computed tomography (QCT), dual energy X-ray absorptiometry (DXA), peripheral dual energy X-ray absorptiometry (pDXA). A T score of < -2.0 SD is a reference criteria for osteoporosis. Women with secondary osteoporosis including corticosteroid-induced due to diseases affecting metabolism of bone, disability of the heart and cerebral vessels, liver, kidney, and hematopoietic system, will be excluded.

Types of interventions

(1) Vitamin K (in all forms) alone or in combination with calcium and/or vitamin D versus placebo, alone or in combination with calcium and/or vitamin D;
(2) Vitamin K (in all forms) alone or in combination with calcium and/or vitamin D versus other osteoporosis treatment, alone or in combination with calcium and/or vitamin D;
(3) Vitamin K (in all forms) administrated in different doses, comparing dose effects.

Types of outcome measures

Primary outcomes

(1) incidence of fractures (vertebral, non-vertebral, hip and wrist)
(2) Vertebral deformities
(3) Adverse effects, including:
a) change of prothrombin time
b) thromboembolism
c) abdominal discomfort
d) skin rash
e) abnormal liver enzymes
(4) Serious adverse event (SAE, which means any adverse experience that results in any of the following outcomes: death, a life-threatening experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or requiring intervention to prevent permanent impairment or damage).

Secondary outcomes

(1) Bone mineral density (BMD) (as defined by authors e.g. DXA, QUS, CT)
(2) Bone biochemical markers (e.g. Collagen Type-1 C-Telopeptide (CTX), N-telopeptide of type I collagen (NTX), total osteocalcin, bone specific alkaline phosphatase and undercarboxylated osteocalcin level).
(3) Quallity of life, patient satisfaction.

Search methods for identification of studies

See: Cochrane Musculoskeletal Group methods used in reviews.
We will search the following electronic bibliographic databases: Cochrane Musculoskeletal trials register, Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 3, 2009), MEDLINE (1950 to present), Embase (1980 to present), CINAHL (1982 to present).
Hand searching will be searched. The list of handsearched journals can be found in the Cochrane Musculoskeletal Group.
We will develop the search strategies set out in Appendix 1 for MEDLINE. We will adapt similar search strategies to search the other databases.
We will not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors, Thananit Sangkomkamhang (TS) and Ussanee S Sangkomkamhang (US) will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through consultation a third person.

Data extraction and management

We will design a form to extract data. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third person. Data will be entered into Review Manager software (RevMan 2008) and checked for accuracy.
When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

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Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). Any disagreement will be resolved by discussion or by involving a third assessor.

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias.

We will use the Cochrane 'Risk of bias' tool in RevMan 5, which involves describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry. This involves answering a pre-specified question whereby a judgement of 'Yes' indicates low risk of bias, 'No' indicates high risk of bias, and 'Unclear' indicates unclear or unknown risk of bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we will use the weighted mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We will not include cluster randomized trials as they are not suitable for our intervention.

Crossover trials

If we identify any crossover trials on this topic, and such trials are deemed eligible for inclusion, they will be included in the analyses with parallel group trials, using methods described by (Elbourne 2002).

Dealing with missing data

For included studies, levels of attrition will be noted. The impact of including studies with high levels of missing data in the overall assessment of treatment effect will be explored by using sensitivity analysis.

For all outcomes analyses will be carried out, as far as possible, on an intention-to-treat basis i.e. we will attempt to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity (I^2 greater than 50%), we will explore it by pre-specified subgroup analysis.

Assessment of reporting biases

Where we suspect reporting bias (*see* selective reporting bias above), we will attempt to contact study authors asking them to provide missing outcome data. Where this is not possible, and the missing data are thought to introduce serious bias, the impact of including such studies in the overall assessment of results will be explored by a sensitivity analysis.

Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2008). We will use fixed-effect inverse variance meta-analysis for combining data where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. Where we suspect clinical or methodological heterogeneity between studies sufficient to suggest that treatment effects may differ between trials we will use random-effects meta-analysis.

If substantial heterogeneity is identified in a fixed effect model of meta-analysis this will be noted and the analysis repeated using a random-effects method.

Subgroup analysis and investigation of heterogeneity

If we can include a number of trials, we plan to carry out subgroup analyses for the primary outcome of incidence of fractures in postmenopausal women as following:

1. primary versus secondary fracture prevention;
2. age group 45 to 60 years versus older than 60 years;
3. severity of osteoporosis (osteoporosis versus severe osteoporosis);
4. duration of drugs used (less than one year versus more than one year);

The following outcomes will be used in subgroup analysis:

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5. vertebral fracture versus non-vertebral fracture (fracture around hip and wrist)

For fixed effect model of meta-analyses we will conduct planned subgroup analyses classifying whole trials by interaction tests as described by (Deeks 2001). For random effects model of meta-analyses we will assess differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis

We will perform sensitivity analysis based on trial quality, separating high-quality trials from trials of lower quality. 'High quality' will, for the purposes of this sensitivity analysis, be defined as a trial having adequate allocation concealment and an 'unreasonably expected loss to follow-up' classified as less than 20%, given the stated importance of attrition as a quality measure (Tierney 2005).

Levels of quality of a body of evidence in the GRADE approach

We will use the GRADE approach for grading the quality of evidence, according to the criteria given in the Handbook (Higgins 2008).

Underlying methodology Quality rating

Randomized trials; or double-upgraded observational studies. High

Downgraded randomized trials; or upgraded observational studies. Moderate

Double-downgraded randomized trials; or observational studies. Low

Triple-downgraded randomized trials; or downgraded observational studies or case series/case reports. Very low

ACKNOWLEDGEMENTS

Many thanks to Maria Benkhalti, Research Assistant.

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* *Indicates the major publication for the study*

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APPENDICES

Appendix 1. MEDLINE search strategy

1. exp bone diseases, metabolic/
2. osteoporosis#s.tw.
3. bone density/
4. bone densit$.tw.
5. bone mineral densit$.tw.
6. exp bone/ and bones.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7. bone loss$.tw.
8. osteomalacia.tw.
9. osteodystrophy.tw.
10. exp bone demineralization, pathologic/
11. (bone adj demineralization).tw.
12. osteopenia.tw.
13. bone mass.tw.
14. exp densitometry/
15. densitometry.tw.
16. dexa.tw.
17. exp fractures/
18. fracture$.tw.
19. or/1-18
20. exp Vitamin K/
21. vitamin k1.sh,rn,tw.
22. vitamin k2.sh,rn,tw.
23. vitamin k3.sh,rn,tw.
24. aquamephyton.tw.
25. konakion.tw.
26. menadione.tw.
27. menaquinone$.tw.
28. phyllohydroquinone.tw.
29. phylloquinone.tw.
30. phytomenadione.tw.
31. phytonadione.tw.
32. vi?asol.tw.
33. or/21-32
34. 19 and 33

WHAT'S NEW

5 November 2008	Amended	CMSG ID: C161-P

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HISTORY

Protocol first published: Issue 1, 2010

CONTRIBUTIONS OF AUTHORS

Thananit Sangkomkamhang (TS) and Ussanee S Sangkomkamhang (US) selected the review topic.

TS drafted the protocol. US and Chetta Ngamjarus (CN) revised and approved the protocol.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Khon Kaen Hospital, Khon Kaen, Ministry of Public Health, Thailand.
- Khon Kaen University, Faculty of Public Health, Thailand.

External sources

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

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Admission tests other than cardiotocography for fetal assessment during labour (Protocol)

Khunpradit S, Lumbiganon P, Laopaiboon M

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This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 3

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Admission tests other than cardiotocography for fetal assessment during labour (Protocol)
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TABLE OF CONTENTS

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[Intervention Protocol]

Admission tests other than cardiotocography for fetal assessment during labour

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Editorial group: Cochrane Pregnancy and Childbirth Group.
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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effectiveness of admission tests other than cardiotocography in preventing adverse perinatal outcomes.

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BACKGROUND

Description of the condition

According to WHO estimates, around 3% of approximately 120 million infants born every year in developing countries develop birth asphyxia requiring resuscitation. It is estimated that some 900,000 of these newborns die each year (Costello 1994; WHO 1997).

The goal of intrapartum fetal surveillance is to detect potential fetal decompensation and to allow timely and effective intervention to prevent perinatal morbidity or mortality such as perinatal asphyxia, neonatal hypoxic ischaemic encephalopathy, stillbirth and neonatal death (Liston 2007). The fetal brain is the primary organ of interest, but at present it is not clinically feasible to assess its function during labour. However, fetal heart (FH) rate characteristics can be assessed, and changes in FH rate that precede brain injury constitutes the rationale for FH monitoring; that is, timely response to abnormal FH patterns might be effective in preventing brain injury (Liston 2007).

Description of the intervention

The fetal admission test is a means to identify women who may require caesarean delivery for a non-reassuring FH rate tracing during labour, and be delivered of a depressed newborn infant (Ingemarsson 1986). Cardiotocography for 20 minutes (Ingemarsson 1986), response to vibroacoustic stimulation (Sarno 1990), biophysical profile (Kim 2003), modified biophysical profile (MBPP) (Lalor 2008), rapid biophysical profile (rBPP, the combination of amniotic fluid index and sound-provoked fetal movement detected by ultrasound in predicting intrapartum fetal distress) (Tongprasert 2006; Tongsong 1999), Doppler scans of the umbilical artery (Malcus 1991; Mires 2001), and sonographic assessment of amniotic fluid (Moses 2004; Sarno 1989) are diagnostic modalities that have been used for the assessment of fetal well-being on admission.

Vibroacoustic stimulation

Fetal vibroacoustic stimulation is a simple, non-invasive technique where a device is placed on the maternal abdomen over the region of the fetal head and sound is emitted at a predetermined level for several seconds (East 2005).

Biophysical profile

The BPP combines the assessment of electronic FH rate monitoring (CTG) with four biophysical features, namely (i) fetal movements, (ii) fetal tone, (iii) fetal breathing and (iv) estimation of amniotic fluid volume. These latter four variables are observed using real-time ultrasonography. The FH rate is recorded, usually over a 20-minute period, and is achieved by using a Doppler ultrasound transducer to monitor the FH through the mother's abdomen. Uterine contractions are monitored simultaneously by a pressure transducer on the mother's abdomen. Both transducers are linked to a monitor and this results in a paper trace known as a CTG.

The BPP is performed in an effort to identify babies that may be at risk of poor pregnancy outcome, so that additional assessments of well-being may be performed, or labour may be induced or a caesarean section performed to expedite birth (Lalor 2008; Manning 1980).

The MBPP

A shortened version of the BPP, known as the MBPP, consists of: (i) recording an antenatal CTG (with or without vibroacoustic stimulation) combined with (ii) ultrasound measurement of the amniotic fluid. The MBPP is employed as a first-line screening test (Archibong 1999) and should be followed by the complete BPP as a back-up test when indicated (Lalor 2008).

The rBPP

The rBPP, the combination of amniotic fluid index and sound-provoked fetal movement detected by ultrasound. The rBPP is an effective predictor of intrapartum fetal distress in high-risk pregnancies (Tongprasert 2006).

Doppler scans of the umbilical artery

Doppler ultrasound study of umbilical artery waveforms helps identify the compromised fetus in 'high-risk' pregnancies. Doppler ultrasound detects changes in the pattern of blood flow through the baby's circulation. It may be that problems for the baby could be identified through these changes. Interventions, like early delivery, might then be able to reduce the mortality and morbidity(Alfirevic 2009).

Sonographic assessment of amniotic fluid

Amniotic fluid volume is an important parameter in the assessment of fetal well-being. Oligohydramnios occurs in many high-risk conditions and is associated with poor perinatal outcomes (Nabhan 2008).

A systematic review was conducted to assess the effectiveness of admission FH tracings in preventing adverse outcomes, compared with auscultation only, and to assess the test's prognostic value in predicting adverse outcomes. Three randomised controlled trials including 11,259 women and 11 observational studies including 5831 women were reviewed. Meta-analyses of the controlled trials found that women randomised to the labour admission test were more likely to have minor obstetric interventions like epidural analgesia (risk ratio (RR) 1.2; 95% confidence interval (CI) 1.1 to 1.4), continuous electronic fetal monitoring (RR 1.3; 95% CI 1.2 to 1.5) and fetal blood sampling (RR 1.3; 95% CI 1.1 to 1.5)

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compared with women randomised to auscultation on admission. There were no significant differences in any of the other outcomes. From the observational studies, prognostic value for various outcomes was found to be generally poor. There is no evidence to support the hypothesis that the labour admission test is beneficial in women with no risk factors for adverse perinatal outcome (Blix 2005).

Continuous cardiotocography during labour was associated with a reduction in neonatal seizures, but no significant differences in cerebral palsy, infant mortality or other standard measures of neonatal well-being. However, continuous cardiotocography was associated with an increase in caesarean sections and instrumental vaginal births (Alfirevic 2006).

There is a separate Cochrane protocol on the effectiveness of cardiotocography versus intermittent auscultation of FH on admission to labour ward for assessment of fetal well-being (Devane 2005)

These interventions might have different effects in high-risk versus low-risk pregnancy, preterm versus term versus post term.

We plan to conduct subgroup analyses based on these two variables.

How the intervention might work

Ideally, these tests would identify the fetus at risk for decompensation during labour. This could allow timely and effective interventions to prevent perinatal morbidity or mortality.

At present, there is no evidence about the effectiveness of labour admission tests other than cardiotocography.

Why it is important to do this review

Hence, it is important to systematically review the evidence on the effectiveness of labour admission tests other than cardiotocography, such as BPP, Doppler, MBPP, rBPP, sonographic assessment of amniotic fluid, in preventing adverse perinatal outcomes.

OBJECTIVES

To assess the effectiveness of admission tests other than cardiotocography in preventing adverse perinatal outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

Any randomised (individual and cluster) controlled trials, trials comparing other labour admission tests in preventing adverse perinatal outcomes. We will exclude quasi-random study designs and trials using crossover design.

Types of participants

All women at admission to labour room, both primigravidae and multigravidae. We will seek trials of both low and high obstetric risk groups.

Types of interventions

Labour admission tests including vibroacoustic stimulation, biophysical profile (BPP), modified BPP, rapid BPP, Doppler scans of the umbilical artery, and sonographic assessment of amniotic fluid.

Types of outcome measures

Primary outcomes

Mother

1. Incidence of caesarean section
2. Incidence of operative vaginal delivery
3. Incidence of serious maternal complications (e.g. admission to intensive care unit, septicaemia (a form of blood infection, organ failure))

Infant

1. Birth asphyxia
2. Stillbirths
3. Early neonatal death

Secondary outcomes

1. Incidence of continuous electronic fetal monitoring during labour
2. Incidence of artificial rupture of membranes during labour
3. Incidence of artificial oxytocin for augmentation of labour
4. Mobility during labour
5. Perceived control and/or self-confidence during labour6. Incidence of use of pharmacological analgesia during labour and birth (including epidural)
6. Incidence of use of non-pharmacological methods of coping with labour, e.g. transcutaneous electrical nerve stimulation, hydrotherapy
7. Satisfaction with labour experience
8. Incidence of fetal blood sampling

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9. Length of hospital stay (maternal and neonatal)
10. Neonatal neurodevelopment
11. Breastfeeding
12. Maternal and neonatal infection

Search methods for identification of studies

Electronic searches

We will contact the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register.
The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.
Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.
We will not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors (Suthit Khunpradit and Pisake Lumbiganon) will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult a third person.

Data extraction and management

We will design a form to extract data. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third person. We will enter data into Review Manager software (RevMan 2008) and check for accuracy.

When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009). We will resolve any disagreement by discussion or by involving a third assessor.

(1) Sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

- We will assess the method as:
- adequate (any truly random process, e.g. random number table; computer random number generator),
- inadequate (any non-random process, e.g. odd or even date of birth; hospital or clinic record number) or,
- unclear.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal the allocation sequence and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We will assess the methods as:

- adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear.

(3) Blinding (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding could not have affected the results. We will assess blinding separately for different outcomes or classes of outcomes.
We will assess the methods as:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors.

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(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake. We will assess methods as:

- adequate;
- inadequate;
- unclear.

(5) Selective reporting bias

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:

- adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear.

(6) Other sources of bias

We will describe for each included study any important concerns we have about other possible sources of bias.
We will assess whether each study was free of other problems that could put it at risk of bias:

- yes;
- no;
- unclear.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the Handbook (Higgins 2009). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - *see* 'Sensitivity analysis'.

Measures of treatment effect

Dichotomous data

For dichotomous data, such as caesarean section, birth asphyxia, etc, we will present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, such as length of hospital stay, etc., we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Ordinal data

For ordinal data, we will use median and interquartile range.
We will compare:

1. one intervention versus no intervention;
2. one intervention versus another intervention.

Unit of analysis issues

For multiple pregnancies, we will account for dependency of data for the outcomes of the infants who have the same mother in the analysis..

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually randomised trials. We will adjust their sample sizes using the methods described in the Handbook using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.
We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

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For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if T^2 is greater than zero and either I^2 is greater than 30% or there is a low P-value (< 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry. For continuous outcomes we will use the test proposed by Egger 1997, and for dichotomous outcomes we will use the test proposed by Harbord 2006. If asymmetry is detected in any of these tests or is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2008). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with its 95% confidence interval, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We plan to carry out the following subgroup analyses:

1. high-risk versus low-risk pregnancy;
2. preterm versus term versus post term

Subgroup analyses will be restricted to the primary outcomes.

For fixed-effect inverse variance meta-analyses we will assess differences between subgroups by interaction tests. For random-effects and fixed-effects meta-analyses using methods other than inverse variance, we will assess differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis

We will carry out sensitivity analysis to explore the effect of study quality. This will involve analyses based on the trial quality ratings for sequence generation, allocation concealment and incomplete outcome data. We will exclude studies of poor quality in the analysis (those categorised as 'no' or 'unclear') in order to assess for any substantive difference to the overall result.

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As part of the pre-publication editorial process, this protocol has been commented on by three peers (an editor and two referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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* *Indicates the major publication for the study*

HISTORY

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CONTRIBUTIONS OF AUTHORS

Suthit Khunpradit devised the idea, applied for the protocol, wrote the draft of the protocol, and approved the final edition. Pisake Lumbiganon and Malinee Laopaiboon edited and approved the final protocol.

DECLARATIONS OF INTEREST

None known.

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Double-bundle versus single-bundle reconstruction for anterior cruciate ligament rupture in adults (Protocol)

Tiamklang T, Sumanont S, Foocharoen T, Laopaiboon M

This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 3

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Double-bundle versus single-bundle reconstruction for anterior cruciate ligament rupture in adults (Protocol)
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TABLE OF CONTENTS

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[Intervention Protocol]

Double-bundle versus single-bundle reconstruction for anterior cruciate ligament rupture in adults

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of anatomic double-bundle versus standard single-bundle for anterior cruciate ligament reconstruction in adults with ACL deficiency.

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BACKGROUND

The anterior cruciate ligament (ACL), which is located within the knee joint, performs a key role in stabilising the knee. It acts to prevent forward movement (anterior translation) of the tibia (shin bone) relative to the femur (thigh bone) as well as to control rotational movements within the knee joint. It is made up of dense connective tissue covered with a synovial membrane (Arnoczky 1983; Dienst 2002). The ACL mainly consists of two distinct portions or 'bundles': an anteromedial (AM) bundle and a posterolateral (PL) bundle, named according to their insertion sites to the tibia (Girgis 1975). Both bundles are critical to knee stability but act differently. The anteromedial band is tight in flexion (knee is bent) whereas the posterolateral band is tight in extension (knee is straightened out). A biomechanical study found that the anteromedial bundle is the primary restraint against anterior tibia translation, while the posterolateral bundle secures the knee when near full extension, particularly against rotational loads (Petersen 2007).

Description of the condition

The exact incidence of anterior cruciate ligament injuries is unknown; however, approximately 200,000 people per year sustain an ACL injury (usually a rupture) in the USA (AAOS 2007). These injuries are most often a result of deceleration, non contact injuries, jumping, or cutting action (Griffin 2000). The person often hears or feels a pop as the knee popped out of joint and then reduced (moved back in). Resumption of activity is usually not possible, and walking with full weight bearing is often difficult. Within two hours, the knee often swells and there is bleeding within the joint. The Lachman test, the most sensitive test for anterior cruciate ligament tears, is usually positive (Benjaminse 2006). Other injuries often occur at the time of the anterior cruciate ligament injury. Approximately 50% to 70% of patients with anterior cruciate ligament injuries also have meniscal injuries. In acute anterior cruciate ligament injuries, the lateral meniscus is more commonly torn (Bellabarba 1997); while in chronic anterior cruciate ligament tears, the medial meniscus is more commonly torn (Naranje 2008). Osteochondral injuries also occur with anterior cruciate ligament tears and are associated with a worse prognosis. In general, people with anterior cruciate ligament-deficient knees who continue sport activities with repeat incidents of instability risk further meniscus tears and osteochondral injuries that ultimately lead to osteoarthritis of the knee (Lohmander 2007).

Description of the intervention

Surgical treatment for ACL rupture usually involves reconstruction of the anterior cruciate ligament by use of a graft (a piece of tendon) that is passed through tunnels drilled into the tibia and femur at the insertion points of the ligament and then fixed. ACL reconstruction is an increasingly common orthopaedic procedure (Lyman 2009). Lyman 2009 estimated there had been over 105,000 reconstructions in the USA in 2006. Reconstruction of the ACL produces better knee stability during daily activities and strenuous activities than non-surgical treatment especially in active individuals (Linko 2005). Over the years, an increased understanding of technical issues of graft selection, placement, tension, and fixation as well as of postoperative rehabilitation has led to improved outcomes from ACL reconstruction. The standard technique for anterior cruciate ligament reconstruction is currently arthroscopic single-bundle (SB) reconstruction with autografts (graft is taken from the patient) such as bone-patellar tendon-bone (BPTB), medial hamstring tendons (semitendinosus and gracilis), or the quadriceps tendon. The single-bundle reconstruction technique has mainly focused on the restoration of the anteromedial bundle while giving limited attention to the posterolateral bundle. Thus single-bundle ACL reconstructions are successful at restoring anterior stability to the knee, but not rotational stability (Woo 2002). Recent advances in arthroscopic knee surgery have allowed separate reconstruction of the two bundles to restore more closely the natural anatomy of the anterior cruciate ligament. The double-bundle anterior cruciate ligament reconstruction technique was first described by Mott 1983. Numerous technical modifications to the procedure have occurred since its introduction. However, double-bundle reconstruction will always be more technically demanding and invasive (four bone tunnels are required instead of two) than single-bundle reconstruction.

How the intervention might work

Theoretically, double-bundle reconstruction is more likely restore normal knee kinematics compared with a single-bundle technique. Anatomical and biomechanical studies have shown that double-bundle ACL reconstruction restores anterior knee stability and rotational stability in an ACL-deficient knee better than single-bundle ACL reconstruction because of better 'footprint' recreation (restoration of ACL attachments) and restoration of biomechanical functions (Buoncristiani 2006). With the additional restoration of the posterolateral bundle as in double-bundle reconstruction, rotational stability in particular is increased significantly (Yagi 2002). There is also a theoretical advantage to improved graft-bone healing of the double-bundle ACL reconstruction resulting from greater graft-bone contact area than that in single-bundle reconstruction.

Why it is important to do this review

Single-bundle techniques remain the standard approach and are generally but not fully successful. However, the potential for improved knee stability and the proven technical feasibility of double-bundle ACL reconstruction have led to an increased interest

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and application of this relatively 'young' and technically more demanding arthroscopic procedure. But there is concern that double-bundle ACL reconstruction may result in a worse outcome for patients, including in those cases where revision surgery is required. A systematic review of the evidence from randomised clinical trials comparing double-bundle versus single-bundle reconstruction should help to inform decisions in this controversial area of current practice.

OBJECTIVES

To assess the effects of anatomic double-bundle versus standard single-bundle for anterior cruciate ligament reconstruction in adults with ACL deficiency.

METHODS

Criteria for considering studies for this review

Types of studies

Any randomised or quasi-randomised (method of allocating participants to a treatment which is not strictly random: e.g. by date of birth, hospital record number, alternation) controlled clinical trials comparing double-bundle versus single bundle reconstruction for anterior cruciate ligament (ACL) rupture in adults will be considered.

Types of participants

Skeletally mature patients with documented ACL rupture, either isolated or combined with other soft-tissue knee injuries, requiring primary ACL reconstruction.

Types of interventions

Randomised comparisons of double-bundle versus single-bundle reconstruction for treating ACL rupture in adults. Types of tendon graft, which can be either autograft or allograft, include semitendinosus tendon alone, gracilis and semitendinosus tendon, quadriceps tendon, and bone-patellar tendon-bone. Methods of surgical fixation include screw fixation and Endobutton fixation. We will exclude trials that only compare different methods of double-bundle reconstruction or different methods of single-bundle reconstruction.

Types of outcome measures

Primary outcomes

1. Patient or clinician-rated functional knee scores (e.g. IKDC score, Tegner activity score, Lysholm score (Lysholm 1982)) and patient-derived health related quality of life measures (e.g. physical domain of the SF-36)
2. Long-term knee pain (visual analogue scale)
3. Adverse effects and complications (e.g. graft failure; infection; arthrofibrosis)

Secondary outcomes

1. Return to pre-injury level of activity / sport participation
2. Objective measures of knee stability (e.g. KT-1000 arthrometer, KT-2000 arthrometer results; rotational stability (Pivot shift test); anterior stability (e.g. Lachman test, anterior drawer test))
3. Range of motion (flexion-extension deficit)
4. Recurrent injury with and without re-operation

Timing of outcome assessment

We will consider grouping outcomes as follows:

1. Short term (within six months of ACL reconstruction)
2. Intermediate term (within six months up to two years of ACL reconstruction)
3. Long term (greater than two years following ACL reconstruction)

Search methods for identification of studies

Electronic searches

We will search the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (to present), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, current issue), MEDLINE (1966 to present) and EMBASE (1980 to present). We will also search Current Controlled Trials, the WHO International Clinical Trials Registry Platform and the National Research Register (NRR) Archive (to September 2007) for ongoing and recently completed trials. No language restrictions will be applied.

In MEDLINE (OVID WEB), the subject specific strategy will be combined with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (Lefebvre 2009). In EMBASE (OVID WEB), the subject specific strategy will be combined with the RCT search filter developed by the Scottish Intercollegiate Network. Details of search strategies, including *The Cochrane Library* (Wiley InterScience), are shown in Appendix 1.

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Searching other resources

The bibliographies of all relevant papers identified by the search strategies will be handsearched. Specific proceedings of knee surgery, arthroscopic surgery and sports medicine meetings and conferences will be searched from the following organizations: European Society of Sports Traumatology Knee Surgery and Arthroscopy (ESSKA), American Orthopaedic Society for Sports Medicine (AOSSM), International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine (ISAKOS), American Academy of Orthopaedic Surgeons (AAOS), World Congress on Orthopaedic Sports Trauma, and Arthroscopy Association of North America (AANA). To avoid publication bias, the investigators of the trials identified from the proceedings will be contacted to obtain results and data of any unpublished studies. Where appropriate and possible, the corresponding authors of studies identified by the search strategies will be contacted to obtain other relevant studies not previously included for review.

Data collection and analysis

The methodology for data collection and analysis is based on the Cochrane Handbook of Systematic Reviews of Interventions (Lefebvre 2009).

Selection of studies

Two authors, Thavatchai Tiamklang (TT) and Sermsak Sumanont (SS), will independently select references identified by the searches for retrieval of full articles. Where there is disagreement or doubt, the full article will be retrieved. Two authors (TT and SS) will independently assess the full study report to see if it meets the review inclusion criteria. Another review author, Thanit Foocharoen (TF), will be consulted in cases of unresolved disagreement. If necessary, the trial authors will be contacted for more information.

Data extraction and management

Two authors (TT and SS) will independently extract trial details and data for the included trials using a data collection form. The third author (TF) will be consulted in cases of unresolved disagreement. When necessary, trial authors will be contacted directly to complete data forms or clarify methodology. Data will be entered into Review Manager software (RevMan 2008) and checked for accuracy.

Assessment of risk of bias in included studies

Two authors (TT and SS) will independently assess the risk of bias for each study using The Cochrane Collaboration's tool (*see* Table 1). Each study will be graded for risk of bias (low, high, unclear) in each of the following domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and two other sources of bias (selection bias from major differences in baseline characteristics; and performance bias from important differences in the provision of care other than the trial interventions). We will assess separately the risk of bias associated with patient-rated outcomes and clinician-rated outcomes for blinding and incomplete outcome data. Any unresolved disagreement will be resolved by discussion with the third author (TF). Titles of journals, names of authors or supporting institutions will not be masked at any stage.

Table 1. Risk of bias tool

Domain	Description	Review authors' judgement
Sequence generation		Was the allocation sequence adequately generated? YES / NO / UNCLEAR
Allocation concealment		Was allocation adequately concealed? YES / NO / UNCLEAR
Blinding of participants, personnel and outcome assessors *Outcome:* Patient-rated outcomes (e.g. functional knee scores, joint position sense, pain, recurrent injury)		Was knowledge of the allocated intervention adequately prevented during the study? YES / NO / UNCLEAR
Blinding of participants, personnel and outcome assessors *Outcome:* Clinician-rated outcomes (e.g. knee stability tests, range of motion, complications)		Was knowledge of the allocated intervention adequately prevented during the study? YES / NO / UNCLEAR

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Table 1. Risk of bias tool (*Continued*)

Incomplete outcome data *Outcome:* Patient-rated outcomes (e.g. functional knee scores, joint position sense, pain, recurrent injury)		Were incomplete outcome data adequately addressed? YES / NO / UNCLEAR
Incomplete outcome data *Outcome:* Clinician-rated outcomes (e.g. knee stability test, range of motion, complications)		Were incomplete outcome data adequately addressed? YES / NO / UNCLEAR
Selective outcome reporting		Are reports of the study free of suggestion of selective outcome reporting? YES / NO / UNCLEAR
Other sources of bias Selection bias: imbalance in confounders at entry. Major differences in baseline characteristics: age, sex, acute versus chronic injuries, isolated ACL rupture versus ACL rupture combined with other soft-tissue knee injuries.		Was the study apparently free of other problems that could put it at a high risk of bias? YES / NO / UNCLEAR
Other sources of bias Performance bias: for instance, provision of other interventions that should be comparable in both groups (e.g. various forms of fixation methods, number of strands of tendon graft, operative techniques, rehabilitation protocols, timing of intervention; or major differences in experience or personal characteristics of treatment providers, especially experience)		Was the study apparently free of other problems that could put it at a high risk of bias? YES / NO / UNCLEAR

Measures of treatment effect

Where appropriate, quantitative data reported in individual trial reports for outcomes listed in the inclusion criteria will be presented in the text and in the analyses. Risk ratios with 95% confidence intervals will be calculated for dichotomous outcomes, and mean differences with 95% confidence intervals for continuous outcomes.

Unit of analysis issues

The unit of randomisation in these trials is usually the individual patient. Exceptionally, as in the case of trials including people with bilateral ACL ruptures, data for trials may be presented for ACL ruptures rather than individual participants. Where such unit of analysis issues arise and appropriate corrections have not been made, we will consider presenting the data for such trials only where the disparity between the units of analysis and randomisation is small. Where data are pooled, we will perform a sensitivity analysis to examine the effects of pooling these incorrectly analysed trials with the other correctly analysed trials.

Dealing with missing data

Where appropriate, we will perform intention-to-treat analyses to include all people randomised to the intervention groups. We will investigate the effect of drop outs and exclusions by conducting

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worst and best scenario analyses. We will be alert to the potential mislabelling or non-identification of standard errors and standard deviations. Unless missing standard deviations can be derived from confidence interval data, we will not assume values in order to present these in the analyses.

Assessment of heterogeneity

Heterogeneity will be assessed by visual inspection of the forest plot (analysis) along with consideration of the test for heterogeneity and the I^2 statistic (Higgins 2003).

Assessment of reporting biases

Where sufficient data are available, we will attempt to assess publication bias by preparing a funnel plot. Our pursuit of trials listed in clinical trial registers should help to avoid publication bias.

Data synthesis

If considered appropriate, results of comparable groups of trials will be pooled. Initially we will use the fixed-effect model and 95% confidence intervals. We will also consider using the random-effects model, especially where there is unexplained heterogeneity.

Subgroup analysis and investigation of heterogeneity

Heterogeneity will be explored by subgroup analyses. Our primary subgroup analyses will be by gender, acute versus chronic injuries, isolated ACL rupture versus ACL rupture combined with other soft-tissue knee injuries and autograft versus allograft. Other subgroup analyses of various types of grafts, forms of fixation methods, numbers of strands of tendon graft, operative techniques and rehabilitation protocols may be considered also. To test whether the subgroups are statistically significantly different from one another, we will test the interaction using the technique outlined in Altman 2003.

Sensitivity analysis

Where possible, we plan sensitivity analyses examining various aspects of trial and review methodology, including the effects of missing data, and inclusion of trials at high risk of bias (such as from lack of allocation concealment) and trials only reported in abstracts.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

The Cochrane Library (Wiley InterScience)

#1 MeSH descriptor Anterior Cruciate Ligament explode all trees
#2 (anterior NEAR/2 cruciate* NEAR/2 ligament*):ti,ab,kw
#3 (#1 OR #2)
#4 MeSH descriptor Joint Instability, this term only
#5 MeSH descriptor Orthopedic Procedures, this term only
#6 MeSH descriptor Tendon Transfer, this term only
#7MeSH descriptor Arthroscopy, this term only
#8 MeSH descriptor Reconstructive Surgical Procedures, this term only
#9 MeSH descriptor Transplants explode all trees
#10 MeSH descriptor Transplantation, Autologous explode all trees
#11 MeSH descriptor Tendons, this term only with qualifier: TR
#12 (graft* or reconstruct* or autograft*):ti,ab,kw
#13 (#4 OR #5 OR #6 OR #7 OR #8 or #9 or #10 or #11 or #12)
#14 (double-bundle* or double bundle* or anatomic*):ti,ab,kw

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#15 (single-bundle* or single bundle* or standard*):ti,ab,kw
#16 (#14 AND #15)
#17 (#3 AND #13 AND #16)

MEDLINE (OVID WEB)

1. Anterior Cruciate Ligament/
2. (anterior adj2 cruciate$ adj2 ligament$).tw.
3. or/1-2
4. Joint Instability/
5. Orthopedic Procedures/
6. Tendon Transfer/
7. Arthroscopy/
8. Reconstructive Surgical Procedures/
9. Transplants/
10. Transplantation, Autologous/
11. Tendons/tr or Tendons, Para-Articular/tr
12. (graft$ or reconstruct$ or autograft$).tw.
13. or/4-12
14. (double-bundle$ or double bundle$ or anatomic$).tw.
15. (single-bundle$ or single bundle$ or standard$).tw.
16. and/14-15
17. and/3,13,16
18. randomized controlled trial.pt.
19. controlled clinical trial.pt.
20. randomized.ab.
21. placebo.ab.
22. drug therapy.fs.
23. randomly.ab.
24. trial.ab.
25. groups.ab.
26. or/18-25
27. exp animals/ not humans/
28. 26 not 27
29. and/17,28

EMBASE (OVID WEB)

1. Anterior Cruciate Ligament Rupture/
2. Anterior Cruciate Ligament/
3. (anterior adj2 cruciate$ adj2 ligament$).tw.
4. or/1-3
5. Tendon Graft/ or Tissue Graft/ or Muscle Graft/
6. Autograft/
7. exp Transplantation/
8. (graft$ or reconstruct$ or autograft$).tw.
9. or/5-8
10. (double-bundle$ or double bundle$ or anatomic$).tw.
11. (single-bundle$ or single bundle$ or standard$).tw.
12. and/10,11
13. and/4,9,12
14. Clinical trial/
15. Randomized controlled trial/

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16. Randomization/
17. Single blind procedure/
18. Double blind procedure/
19. Crossover procedure/
20. Placebo/
21. Randomi?ed controlled trial$.tw.
22. Rct.tw.
23. Random allocation.tw.
24. Randomly allocated.tw.
25. Allocated randomly.tw.
26. (allocated adj2 random).tw.
27. Single blind$.tw.
28. Double blind$.tw.
29. ((treble or triple) adj (blind$).tw.
30. Placebo$.tw.
31. Prospective study/
32. Or/14-31
33. Case study/
34. Case report.tw.
35. Abstract report/ or letter/
36. Or/33-35
37. 32 not 36
38. and/13,37

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Thavatchai Tiamklang drafted the protocol. Sermsak Sumanont, Thanit Foocharoen and Malinee Laopaiboon revised and approved the protocol..

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None known.

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External sources

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

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ภาคผนวกที่ 6

รายชื่อผลงานวิจัยที่ได้รับการอ้างถึงในวารสารต่างประเทศ

มี Citation จำนวน 57 ครั้ง

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