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Combined spinal-epidural versus epidural analgesia in labour (Review)

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[Intervention Review]

Combined spinal-epidural versus epidural analgesia in labour

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ABSTRACT

Background

Traditional epidural techniques have been associated with prolonged labour, use of oxytocin augmentation and increased incidence of instrumental vaginal delivery. The combined spinal-epidural (CSE) technique has been introduced in an attempt to reduce these adverse effects. CSE is believed to improve maternal mobility during labour and provide more rapid onset of analgesia than epidural analgesia, which could contribute to increased maternal satisfaction.

Objectives

To assess the relative effects of CSE versus epidural analgesia during labour.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (28 September 2011) and reference lists of retrieved studies. We updated the search on 30 June 2012 and added the results to the awaiting classification section.

Selection criteria

All published randomised controlled trials (RCTs) involving a comparison of CSE with epidural analgesia initiated for women in the first stage of labour. Cluster-randomised trials were considered for inclusion. Quasi RCTs and cross-over trials were not considered for inclusion in this review.

Data collection and analysis

Three review authors independently assessed the trials identified from the searches for inclusion, assessed trial quality and extracted the data. Data were checked for accuracy.

Main results

Twenty-seven trials involving 3274 women met our inclusion criteria. Twenty-six outcomes in two sets of comparisons involving CSE versus traditional epidurals and CSE versus low-dose epidural techniques were analysed.

Of the CSE versus traditional epidural analyses five outcomes showed a significant difference. CSE was more favourable in relation to speed of onset of analgesia from time of injection (mean difference (MD) -2.87 minutes; 95% confidence interval (CI) -5.07 to -0.67; two trials, 129 women); the need for rescue analgesia (risk ratio (RR) 0.31; 95% CI 0.14 to 0.70; one trial, 42 women); urinary retention (RR 0.86; 95% CI 0.79 to 0.95; one trial, 704 women); and rate of instrumental delivery (RR 0.81; 95% CI 0.67 to 0.97; six trials, 1015 women). Traditional epidural was more favourable in relation to umbilical venous pH (MD -0.03; 95% CI -0.06 to -0.00; one trial, 55 women). There

were no data on maternal satisfaction, blood patch for post dural puncture headache, respiratory depression, umbilical cord pH, rare neurological complications, analgesia for caesarean section after analgesic intervention or any economic/use of resources outcomes for this comparison. No differences between CSE and traditional epidural were identified for mobilisation in labour, the need for labour augmentation, the rate of caesarean birth, incidence of post dural puncture headache, maternal hypotension, neonatal Apgar scores or umbilical arterial pH.

For CSE versus low-dose epidurals, three outcomes were statistically significant. Two of these reflected a faster onset of effective analgesia from time of injection with CSE and the third was of more pruritus with CSE compared to low-dose epidural (average RR 1.80; 95% CI 1.22 to 2.65; 11 trials, 959 women; random-effects, $T^2 = 0.26$, $I^2 = 84\%$). There was no significant difference in maternal satisfaction (average RR 1.01; 95% CI 0.98 to 1.05; seven trials, 520 women; random-effects, $T^2 = 0.00$, $I^2 = 45\%$). There were no data on respiratory depression, maternal sedation or the need for labour augmentation. No differences between CSE and low-dose epidural were identified for need for rescue analgesia, mobilisation in labour, incidence of post dural puncture headache, known dural tap, blood patch for post dural headache, urinary retention, nausea/vomiting, hypotension, headache, the need for labour augmentation, mode of delivery, umbilical pH, Apgar score or admissions to the neonatal unit.

Authors' conclusions

There appears to be little basis for offering CSE over epidurals in labour, with no difference in overall maternal satisfaction despite a slightly faster onset with CSE and conversely less pruritus with low-dose epidurals. There was no difference in ability to mobilise, maternal hypotension, rate of caesarean birth or neonatal outcome. However, the significantly higher incidence of urinary retention, rescue interventions and instrumental deliveries with traditional techniques would favour the use of low-dose epidurals. It is not possible to draw any meaningful conclusions regarding rare complications such as nerve injury and meningitis.

PLAIN LANGUAGE SUMMARY

Combined spinal-epidural versus epidural analgesia in labour

Regional analgesia has been shown to be effective in providing pain relief in labour. Regional analgesia can be an epidural, a spinal or a combination of the two. An epidural is when the pain-relieving drugs are injected into the part of the body which surrounds the spinal column (epidural space). It is most common for these drugs to be infused through a very fine tube (catheter) positioned in the epidural space. Traditionally, high concentrations of local anaesthetic drugs were used. These numbed the woman from the waist downwards giving pain relief for most women. However, it also caused leg weakness, poor mobility and difficulty for the mother giving birth. This led to increased instrumental vaginal births with subsequent increased bruising, pain and incontinence later on for the mother. More recently with epidurals, low-dose local anaesthetic drugs have been used in combination with opioid drugs. Here there is less numbing of the woman's legs but the opioid drugs cross the placenta and may make the baby sleepy.

A spinal is when the analgesic drugs are injected directly into the fluid surrounding the nerves in the spinal column and is quicker to take effect than an epidural. However, because a single spinal injection is only effective for a short period of time, they are not commonly used on their own for pain relief in labour. Also, the use of very fine catheters in the spinal space has been associated with increased injury to nerves. Hence, the combination of a single spinal injection combined with the use of an epidural catheter for ongoing pain relief was developed. This combined spinal-epidural was thought to have the benefits of being quicker to provide pain relief but with no change to the incidence or severity of side effects for the mother or baby.

This review of trials compared CSE with traditional and with low-dose epidurals. There were 27 trials, involving 3274 women. The data showed no difference in the mothers' satisfaction between CSE and epidurals. However, CSEs had a slightly faster onset of effective pain relief, but more women itched than with low-dose epidurals. There was no difference seen for mobility in labour, headaches, caesarean section or adverse effects for the baby. Any differences for rare complications such as nerve injury and meningitis remain unknown. There appears to be little difference overall between these techniques.

BACKGROUND

This review is one in a series of Cochrane reviews examining pain management in labour. These reviews contribute to an overview of systematic reviews of pain management for women in labour (Jones 2011b).

Epidural analgesia has been shown to be the most effective method of providing pain relief in labour (Glosten 1999) when compared with non-epidural methods (Anim-Somuah 2011; Howell 2001). On a national level, an epidural technique is used for pain relief in approximately 25% of labouring women in the UK (Khor 2000; NOAD 2004) and in as many as 58% in the USA (Declercq 2002). Administration of regional analgesia traditionally involves an injection of local anaesthetic through a catheter positioned in the epidural space. Epidural solutions are administered either by bolus or infusion which permits analgesia to be maintained throughout labour. Bolus administration may be at the discretion of the woman in labour in which case it is referred to as patient-controlled epidural analgesia (PCEA). In addition, a functioning epidural catheter usually gives the option of providing regional anaesthesia for obstetric interventions such as forceps delivery or caesarean section, thus avoiding the risks of general anaesthesia (Hibbard 1996).

Traditional epidural techniques, employing high concentrations of local anaesthetic (at least 0.25% bupivacaine), have been associated with prolonged labour, use of oxytocin augmentation and an increased incidence of instrumental vaginal delivery (Anim-Somuah 2011). This is probably secondary to a dense motor block which results in leg weakness, poor mobility, decreased pelvic muscle tone and an impaired bearing-down reflex during the delivery of the baby (Thornton 2001). Newer regional techniques for labour analgesia use a low concentration of local anaesthetic often in combination with an opioid. This low-dose combination appears to provide the excellent analgesia of higher concentrations of epidural local anaesthetics (Akerman 1988) while maintaining motor function. The mother is therefore more likely to have the ability to walk during her labour or deliver without assistance (COMET 2001a; Russell 2000).

The combined spinal-epidural involves an injection of an analgesic or local anaesthetic drug, or both, into the intrathecal space immediately before or after epidural catheter placement. A number of variations in the technique have been described (Cook 2000) but typically an epidural needle is first used to identify the epidural space (Brown 1999) at the level of the third lumbar vertebra. A smaller diameter, longer needle is then passed through the epidural needle lumen piercing the dura and arachnoid to allow administration of analgesic medications (e.g. opioids) into the cerebrospinal fluid. The spinal needle is then removed and an epidural catheter is inserted and secured in the normal way. Further analgesia usually in the form of a low-dose local anaesthetic solution combined with an opioid is then provided through the epidural catheter. Both epidural and spinal drugs are believed to access sites of action within the spinal cord and the peripheral nerve roots (Butterworth 1998), which supply the uterus. Spinal analgesia is not usually used as the sole technique for pain relief in labour because of its relatively short duration. The insertion and use of spinal micro-catheters has previously been associated with a higher risk of permanent neurological damage (Rigler 1991) and this technique is not in widespread use. CSE is claimed to combine the advantages of both epidural and spinal techniques including: faster onset, more reliable analgesia (due to the spinal component), minimal motor and sensory blockade, improved mobilisation (Collis 1993; Rawal 1997a), lower maternal and cord blood local anaesthetic concentrations (Brown 1999), and higher patient satisfaction (Collis 1994). Since its introduction, CSE has become increasingly popular (Macarthur 1999; Riley 1999) and is used routinely at many institutions for obstetric analgesia (Collis 1994; Rawal 2000).

Although all regional techniques can provide effective pain relief, this needs to be balanced with the risk of potential adverse effects (Bromage 1999). Complications common to both CSE and epidural analgesic techniques include failure to provide satisfactory pain relief, maternal hypotension, post dural puncture headache (PDPH) (Macarthur 2009), urinary retention, itching and transient backache over the injection site. Rare serious complications include meningitis, compression of the spinal cord from a blood clot or abscess and damage to nerve roots causing paraesthesia or weakness. In addition, inadvertent administration of an epidural dose of local anaesthetic intravenously or intrathecally can result in convulsions or total spinal anaesthesia respectively, requiring resuscitation and urgent delivery (Rawal 1997a). The use of two needles in CSE, one epidural and one spinal, may increase the potential for disruption of the protective dural barrier with an associated increase in maternal complications (Macarthur 1999). Modern spinal needles are designed to minimise the incidence of PDPH (Choi 2005), which is approximately 1.5% to 2%. Epidural needles are not designed to enter the intrathecal space and if they do so accidentally, which occurs in approximately 1.5% of women, they are associated with an approximately 50% chance of developing a PDPH (Macarthur 2009). This complication can sometimes be disabling (Weir 2000). If the headache fails to resolve spontaneously an epidural blood patch is a common form of treatment which has been shown to be more effective than conservative management (Boonmak 2010), providing complete relief of headache at seven days in over 80% of women (van Kooten 2007). Although a high block may occur with spinal or epidural anaesthesia alone, CSE may increase the risk of this complication (Macarthur 1999; Rawal 1997; Shaw 2001), which can lead to maternal hypotension, respiratory arrest or loss of consciousness. Neonatal effects such as fetal bradycardia (Nielsen 1996) or the need for resuscitation have been associated with the use of both CSE and epidural techniques (COMET 2001a). Differences in the management of labour (Russell 2000) as well as differences in CSE and epidural techniques (COMET 2001a) themselves may affect the need for other interventions during labour or delivery.

OBJECTIVES

To assess the relative efficacy and side effects of combined spinal-epidural versus epidural analgesia during labour.

METHODS

Criteria for considering studies for this review

Types of studies

All published randomised controlled trials comparing combined spinal-epidural with epidural analgesia during labour. Cluster-randomised trials were considered for inclusion. Quasi RCTs and cross-over trials were not considered for inclusion in this review.

Types of participants

Women having combined spinal-epidural or epidural analgesia commenced during the first stage of labour.

Types of interventions

Combined spinal-epidural analgesia compared with traditional and low-dose epidural analgesia.

Types of outcome measures

Primary outcomes

The outcomes of interest for the mother are as follows.

- Mean time and standard deviation from request of analgesia to the time she felt the level of pain relief was satisfactory.
- Mean time and standard deviation from first spinal or epidural injection to the time she felt the level of pain relief was satisfactory.
- Number of women after 10 minutes from the time of first spinal or epidural injection experiencing satisfactory pain relief.
- Number of women requiring an additional intervention for pain relief at any time after combined spinal-epidural (CSE)/epidural insertion, e.g. new technique such as intravenous analgesia (e.g. fentanyl) replacing epidural catheter.
- Number of women satisfied with their labour analgesia.
- Number of women who were mobile. Maternal mobility is defined as the mother demonstrating that she was able to walk during labour on at least one occasion following the CSE or epidural.
- Number of women with post dural puncture headache.
- Number of women with a known dural tap.
- Number of women requiring an epidural blood patch for a post dural puncture headache.
- Number of women with any complication requiring treatment/intervention specifically identified: pruritus, urinary retention, nausea or vomiting, or both, hypotension, respiratory depression/arrest, headache (any), sedation.
- Number of women with any other complication requiring intervention such as fever, persistent paraesthesia, high block.
- Number of women having an instrumental delivery.
- Number of women having a caesarean section.

For the neonate

- Number of neonates with Apgar scores less than seven at five minutes.
- The number of neonates admitted to the neonatal unit and the reason for such admission.

Economic/use of resources

- Costs of hospital stay.

Secondary outcomes

The outcomes of interest for the mother are as follows.

- Number of women requiring augmentation of labour at any time.
- Number of women requiring augmentation after analgesic intervention.
- Number of women having a normal delivery including vacuum extraction.
- Number of women requiring follow-up for any reason or with long-term outcomes, e.g. meningitis, neuropraxia, paralysis, intensive care unit admission, backache, footdrop, unresolved post dural puncture headache.
- Number of women requiring general anaesthesia for caesarean section after analgesic intervention.

For the neonate

- Mean pH and standard deviation for: umbilical artery, umbilical vein, umbilical cord.
- Number of neonates with Apgar scores less than eight at five minutes.

Economic/use of resources

- Length of hospital stay.
- The number of women re-admitted to hospital within one month of being discharged home and reason for admission.
- The number of women requiring ongoing anaesthetic follow-up following discharge from 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 (28 September 2011). We updated this on 30 June 2012 and added the results to Studies awaiting classification.

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. weekly searches of EMBASE;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and EMBASE, 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.

Searching other resources

We searched reference lists of retrieved studies.

We did not apply any language restrictions.

Data collection and analysis

For the methods used when assessing the trials identified in the previous version of this review, *see* Appendix 1.

For this update we used the following methods when assessing the reports identified by the updated search.

Selection of studies

Three review authors independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, by consultation with a fourth person.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted a third person. We entered data into Review Manager software (RevMan 2011) and checked for accuracy.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We described 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 assessed the method as:

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

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

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

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

(3) Blinding of participants, personnel and outcome assessment (checking for possible performance bias or detection bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered studies to be at low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel;
- low, high or unclear risk of bias for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We state whether attrition and exclusions were reported and 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 was supplied by the trial authors, we re-included missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk of bias (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);
- high risk of bias (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 risk of bias.

(6) Other bias (checking for bias due to problems not covered by 1 to 5 above)

We described for each included study any important concerns we have about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(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 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it likely to impact on the findings. We planned to explore the impact of the level of bias through undertaking sensitivity analyses - *see* 'Sensitivity analysis'.

Measures of treatment effect

Dichotomous data

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

Continuous data

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

Unit of analysis issues

Cluster-randomised trials

There were no cluster-randomised trials for inclusion in this review.

We intended to include cluster-randomised trials in the analyses along with individually randomised trials using the methods described in the *Cochrane Handbook* (Higgins 2011). Their sample sizes would be adjusted using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), or from another source. If we used ICCs from other sources, we would report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we had identified both cluster-randomised trials and individually randomised trials, we planned to synthesise the relevant information. We would 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.

Cross-over trials

We did not include cross-over trials.

Dealing with missing data

For included studies, we noted levels of attrition. We planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we 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 analysed 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 was 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 (< 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

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

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2011).

We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary if an average treatment effect across trials was considered clinically meaningful. We treated 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 did not combine trials.

Where we used random-effects analyses, the results are presented as the average treatment effect with 95% confidence intervals, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identified substantial heterogeneity, we investigated it using subgroup analyses and sensitivity analyses. We considered whether an overall summary was meaningful and, if it was, we used random-effects analysis to produce it.

We planned, where possible, to carry out the following subgroup analyses based on type of combined spinal-epidural:

- Combined spinal epidural versus opioid combined spinal epidural versus null combined spinal epidural.

We considered all outcomes in subgroup analysis.

We assessed subgroup differences by interaction tests available within RevMan (RevMan 2011).

Sensitivity analysis

We planned to carry out sensitivity analyses to explore the effect of trial quality assessed by concealment of allocation, high attrition rates, or both, with poor quality studies being excluded from the analyses in order to assess whether this made any difference to the overall result. We also planned to explore the effects of fixed-effect versus random-effects analyses for outcomes with substantial statistical heterogeneity. Where this was the case relevant comments are made in the body of the text.

RESULTS

Description of studies

Twenty-seven trials, involving 3274 labouring women, met our criteria for inclusion.

(a) Cochrane Pregnancy and Childbirth Group's Trials Register (September 2011). From the references identified, 54 trials met the criteria for assessment and 27 were included.
(b) Manual search: three received, all meeting criteria for assessment, one added as additional reference to study already included.
(c) Manual search from reference list in assessed studies: three studies assessed, none included.
(d) Personal communications: ongoing.

Results of the search

Twenty-seven trials, involving 3274 women, were included. We excluded 27 studies. For details of the individual included and excluded studies, *see* the tables of Characteristics of included studies and Characteristics of excluded studies.

Included studies

Methods and techniques

All included studies reported obtaining informed consent from the participants after prior ethics committee approval. In one study, verbal rather than written consent was obtained (Nickells 2000), the explanation being that the techniques being compared were already in routine use. There was no indication as to the form of the consent in five other studies (Cohen 2006; Goodman 2006; Medina 1994; Patel 2003a; Thomas 2005).

Eighteen studies mentioned a fluid preload with crystalloid before the insertion of epidural or combined spinal-epidural (CSE); the volumes were either not stated (Medina 1994; Ngamprasertwong 2007) or highly varied: 500 mL (COMET 2001a; Gomez 2001; Price 1998; Roux 1999; Vernis 2004), 500 to 1000 mL (Breen 1999; Parry 1998), or at least 1000 mL (Skupski 2009; Tsen 1999; Zeidan 2004). Four studies related the fluid bolus to parturient weight, giving 10 mL/kg (Abrao 2009; Bhagwat 2008; Cortes 2007) or 15 mL/kg over 15 minutes (Van de Velde 1999).

Almost all studies described a single space, needle-through-needle technique for CSE; six studies gave no indication (Abrao 2009; Cohen 2006; Cortes 2007; Goodman 2006; Patel 2003a; Skupski 2009). Where stated, patient position was relatively evenly divided between the sitting (Dunn 1998; Gomez 2001; Hepner 2000; Nickells 2000; Parry 1998; Roux 1999; Sezer 2007; Thomas 2005; Vernis 2004) and lateral (Bhagwat 2008; Kartawiadi 1996; Medina 1994; Ngamprasertwong 2007; Price 1998; Tsen 1999; Van de Velde 1999; Zeidan 2004) alternatives. One study allowed either sitting or lateral position for insertion (COMET 2001a) and in the remaining nine studies (Abouleish 1991; Abrao 2009; Breen 1999; Caldwell 1994; Cohen 2006; Cortes 2007; Goodman 2006; Patel 2003a; Skupski 2009) there is no detail of patient position. Only one study (Skupski 2009) specifically commented on maternal position during labour or ongoing intravenous fluid therapy, both of which could conceivably have had an effect on maternal and fetal parameters subsequently measured. Operators in the included studies were not blinded to the technique although in all studies the assessor was reported as being blinded to group allocation for at least some of the outcome assessments. One further study (Gomez 2001) was described as single-blinded but this was not further defined.

In all of the included studies a CSE technique was compared with epidural analgesia in the first stage of labour. In five of the included papers (Breen 1999; Dunn 1998; Nickells 2000; Parry 1998; Patel 2003a) the study period involved only the initial intrathecal or epidural bolus with assessments and data collection stopping at the time of request for "top-up" analgesia. In the remaining studies there was a varied assortment of regimens for epidural maintenance based around timing of commencement relative to initial injection as well as mode of epidural delivery and the types of solutions used. Local anaesthetic boluses of bupivacaine 0.125% or 0.25% for rescue analgesia were specified in a number of studies (Abouleish 1991; Abrao 2009; Cohen 2006; Cortes 2007; Dunn 1998; Gomez 2001; Goodman 2006; Hepner 2000; Ngamprasertwong 2007; Price 1998; Roux 1999; Skupski 2009; Thomas 2005; Tsen 1999; Vernis 2004), while in others this was left up to the discretion of the attending anaesthetist (COMET 2001a; Nickells 2000; Van de Velde 1999). No specific statement was made regarding criteria for intervention in the event of inadequate analgesia in the remaining eight studies (Breen 1999; Caldwell 1994; Kartawiadi 1996; Medina 1994; Parry 1998; Patel 2003a; Sezer 2007; Zeidan 2004).

Participants

All the included trials studied healthy women in labour requesting regional analgesia. Most stipulated a singleton, obstetrically uncomplicated pregnancy at term, as with Ngamprasertwong 2007 and Skupski 2009. Nineteen studies specifically defined the stage of labour by stating the degree of cervical dilatation as an upper limit for inclusion or as an exclusion. In these studies, the acceptable dilatation of the cervix ranged to an upper limit of 4 cm or less (Goodman 2006; Roux 1999; Tsen 1999; Zeidan 2004) or up to 5 cm (Bhagwat 2008; Breen 1999; Cortes 2007; Dunn 1998; Gomez 2001; Hepner 2000; Kartawiadi 1996; Medina 1994; Price 1998; Sezer 2007; Thomas 2005), 6 cm (Abrao 2009; Sezer 2007; Vernis 2004) or 7 cm (Van de Velde 1999). Of the other eight included studies that did not specifically state a degree of cervical dilatation there were less specific or indirect means of determining the stage of labour. Thus 'first stage of labour' was one inclusion (Parry 1998) and 'imminent delivery' was another specific exclusion (COMET 2001a). Exclusion criteria varied greatly with nine included studies not stating any explicit criteria preventing participation (Abouleish 1991; Caldwell 1994; Cohen 2006; Cortes 2007; Medina 1994; Patel 2003a; Nickells 2000; Sezer 2007; Thomas 2005). Only three of the included studies (Gomez 2001; Sezer 2007; Tsen 1999) stipulated spontaneous onset of labour as an entry criterion and no study excluded women on the basis of need for labour augmentation. Eight included studies (Abouleish 1991; Breen 1999; COMET 2001a; Dunn 1998; Kartawiadi 1996; Parry 1998; Vernis 2004; Zeidan 2004)

specified previous opioid administration over a range of one to four hours as a criterion for exclusion and in two further studies (Abrao 2009; Van de Velde 1999) women were excluded if they had received "sedative or analgesic drugs".

Interventions

There was considerable heterogeneity between trials with respect to the drug combinations used, both intrathecally and epidurally, the timing of subsequent dosing after initial analgesia and the method of epidural drug delivery. In the context of categorising the epidural drug dose/concentration used, the term traditional was used for trials where the epidural local anaesthetic (LA) concentration was the equivalent of bupivacaine 0.25% or more; lower concentrations were defined as low-dose. In the CSE groups, there were three types of interventions; LA plus opioid, opioid alone or null CSE where there was a dural puncture with no intrathecal injection of drugs. Using these definitions the comparisons fell into six categories as detailed below:

1. LA plus opioid CSE versus traditional epidural - three studies, 846 women (COMET 2001a; Gomez 2001; Tsen 1999);
2. LA plus opioid CSE versus low-dose epidural - 18 studies, 2086 women (Abrao 2009; Bhagwat 2008; Cohen 2006; COMET 2001a; Goodman 2006; Hepner 2000; Kartawiadi 1996; Medina 1994; Nickells 2000; Parry 1998; Patel 2003a; Price 1998; Skupski 2009; Van de Velde 1999; Vernis 2004; Zeidan 2004);
3. opioid only CSE versus traditional epidural - four studies, 229 women (Caldwell 1994; Cortes 2007; Ngamprasertwong 2007; Roux 1999);
4. opioid only CSE versus low-dose epidural - two studies, 102 women (Abouleish 1991; Sezer 2007);
5. opioid only CSE versus test LA/opioid epidural - two studies, 111 women (Breen 1999; Dunn 1998);
6. null CSE versus traditional epidural - one study, 251 women (Thomas 2005).

There were eight trials that included a traditional epidural group (Caldwell 1994; COMET 2001a; Cortes 2007; Gomez 2001; Ngamprasertwong 2007; Roux 1999; Thomas 2005; Tsen 1999). One of these studies (COMET 2001a) involved comparisons of a CSE group with both traditional and a low-dose epidural group (*see* below) and so contributed an additional 704 women to category (1) above and 701 women to category (2). With the exception of one study (Thomas 2005), all studies fulfilling this criterion used 0.25% bupivacaine boluses at some time, with volumes ranging from 6 to 12 mL; Thomas 2005 used 2% lignocaine to a total volume of 10 mL. In the three trials with a LA plus opioid group, the CSE technique involved an intrathecal injection of bupivacaine 2.5 mg in combination with either fentanyl (COMET 2001a; Gomez 2001) or sufentanil (Tsen 1999). Of the four trials with an opioid only CSE group, Caldwell 1994 used a combination of fentanyl 25 µg plus morphine 0.25 mg intrathecally, while Roux 1999 used sufentanil 10 µg; the other two trials (Cortes 2007; Ngamprasertwong 2007) used 25 µg of fentanyl only. Whilst the techniques of drug dosing varied between studies, it was noted in these trials that there were essentially two approaches to subsequent epidural management in the CSE groups, either using effectively the same total epidural drug administration as in the epidural group (Caldwell 1994; Cortes 2007; Ngamprasertwong 2007; Roux 1999; Thomas 2005) or using less (COMET 2001a; Gomez 2001; Tsen 1999). Four studies (Caldwell 1994; Gomez 2001; Ngamprasertwong 2007; Tsen 1999) involved the use of a low-dose infusion down the epidural catheter for maintenance. In these studies the infusions were started immediately after the initial bolus in the epidural groups. In three other studies (COMET 2001a; Cortes 2007; Roux 1999) maintenance was with intermittent epidural boluses at patient request. COMET 2001a used 0.25% bupivacaine in the epidural group but bupivacaine 0.15% plus fentanyl 2 µg/mL in the CSE group; both Cortes 2007 and Roux 1999 used 0.25% bupivacaine in both. In the remaining trial (Thomas 2005) in which no intrathecal drugs were injected as part of the CSE technique, all women received the same epidural management. This was also the only trial in this category which employed a patient-controlled epidural analgesia (PCEA) technique for maintenance of analgesia. This involved bupivacaine 0.11% plus fentanyl 2 µg/mL at 10 mL/hour with 5 mL bolus and lockout of 10 minutes.

There were 16 included studies that employed a low-dose LA epidural group compared with CSE. In these trials there was a range of techniques used to establish the epidural block in the epidural groups. All employed bupivacaine as the local anaesthetic in concentrations from 0.0625% to 0.125% and in combination with fentanyl (20 to 75 µg) or sufentanil (5 to 10 µg) to a total volume of between 10 and 20 mL. Seven trials (Abouleish 1991; Abrao 2009; Goodman 2006; Kartawiadi 1996; Medina 1994; Van de Velde 1999; Vernis 2004) used bupivacaine 0.125% with added fentanyl or sufentanil. Eight further studies used even lower concentrations with bupivacaine 0.1% (Nickells 2000; Parry 1998; Price 1998) and 0.0625% (Bhagwat 2008; Hepner 2000; Skupski 2009; Zeidan 2004) and in Cohen 2006 0.04% ropivacaine plus sufentanil was used. In relation to the CSE groups, in all except one trial (Abouleish 1991), the initial intrathecal injection consisted of LA plus opioid using bupivacaine and either sufentanil or fentanyl. In the Abouleish 1991 trial the CSE group consisted of intrathecal morphine 0.2 mg alone and in Cohen 2006, 5 µg of sufentanil and 2 mg of ropivacaine was used. For the other studies the doses employed ranged from 1.25 to 3.75 mg bupivacaine, 5 to 25 µg fentanyl and 1.5 to 5 µg sufentanil. A common technique used in six studies was that of bupivacaine 2.5 mg plus fentanyl 25 µg. In three studies (Nickells 2000; Parry 1998; Patel 2003a) there was no maintenance analgesia stated. In two of the remaining studies intermittent boluses of either 0.1% (Nickells 2000) or 0.125% (Kartawiadi 1996) bupivacaine were delivered down the indwelling epidural catheter for maintenance after return of pain. Six studies (Goodman 2006; Hepner 2000; Medina 1994; Ngamprasertwong 2007; Skupski 2009; Zeidan 2004) used low-dose LA plus opioid bolus then infusion for maintenance after return of pain in both groups. In Hepner 2000 the first additional analgesia was provided by a bolus of 0.0625% bupivacaine with added fentanyl, bicarbonate and epinephrine. Zeidan 2004 used 0.0625% bupivacaine plus fentanyl 1.5 µg/mL and Medina 1994 used 0.125% bupivacaine plus sufentanil 0.5 µg/mL. In Goodman 2006, Ngamprasertwong 2007 and Skupski 2009 both groups had infusion of bupivacaine 0.0625% plus fentanyl 2 µg/mL at 12 mL/hr.The low-dose epidural infusion group in COMET 2001a had analgesia established with a bolus of 0.1% bupivacaine with fentanyl and an immediate infusion of the same solution for maintenance. Data from this group were independently compared with the traditional epidural group. Five studies used a PCEA technique for maintenance of analgesia. One (Van de Velde 1999) used boluses of 4 mL 0.125% bupivacaine with sufentanil 0.75 µg/mL and epinephrine 1.25 µg/mL and a lockout time of 15 minutes. The second (Price 1998) used 10 mL 0.1% bupivacaine with added fentanyl 2 µg/mL delivered with a lockout time of 30 minutes. Vernis

2004 used bupivacaine 0.125% plus sufentanil 0.25 µg/mL with a 4 mL bolus and 10 minute lockout. Sezer 2007 used PCEA with 5 mL bolus of bupivacaine 0.1% plus fentanyl 2 µg/mL with a 10 minutes lockout. Bhagwat 2008 used bupivacaine 0.0625% plus fentanyl 2 µg/mL at a rate of 8 to 12 mL/hr to maintain T10 block via PCEA pump. In Abrao 2009 different concentrations of bupivacaine were given based on cervical dilation upon patient request.

In two studies the main epidural bolus consisted of opioid alone, either fentanyl 100 µg (Breen 1999) or sufentanil 4 µg (Dunn 1998). In each case the opioid bolus was only administered after a test dose of 3 mL lignocaine 1.5%. The intrathecal component of the CSE in both trials was sufentanil 10 µg; there was no stated analgesia maintenance in either study.

Maternal outcomes

No study reported time taken from request of maternal analgesia to the time the mother felt the level of pain relief was satisfactory. However, one study (Hepner 2000) commented on the need to take into account the additional time required to prepare certain solutions and the impact this may have on the time from patient request to establishing analgesia. We also evaluated onset of pain relief from time of initial injection, acknowledging that this result comes more from the practical realities of conducting a research trial rather than what may be of interest to consumers. The stated primary outcome of 18 of the included studies was related to the quality of analgesia and data on analgesic efficacy were presented as a secondary outcome in a further eight trials (Bhagwat 2008; Breen 1999; COMET 2001a; Gomez 2001; Hepner 2000; Skupski 2009; Tsen 1999; Zeidan 2004). These data took the form of visual analogue scores in most cases (Abouleish 1991; Breen 1999; Dunn 1998; Gomez 2001; Hepner 2000; Kartawiadi 1996; Medina 1994; Price 1998; Roux 1999; Tsen 1999; Van de Velde 1999; Vernis 2004; Zeidan 2004) and in one study was retrospectively assessed by a postnatal interview (COMET 2001a). Eleven studies (Abouleish 1991; COMET 2001a; Dunn 1998; Gomez 2001; Hepner 2000; Medina 1994; Nickells 2000; Price 1998; Thomas 2005; Vernis 2004; Zeidan 2004) detailed the requirement for additional analgesic intervention. Only two studies (Parry 1998; Patel 2003a) did not quote any data regarding the effectiveness of pain relief but had primary outcomes related to effects on the baby and epidural/CSE effects on dorsal column function respectively.

All but 10 studies (Abouleish 1991; Abrao 2009; Bhagwat 2008; Caldwell 1994; Goodman 2006; Medina 1994; Patel 2003a; Roux 1999; Skupski 2009; Thomas 2005) quoted figures for degree of motor blockade, but only data from papers quoting numbers of women who actually walked during labour were used in the analysis of ability to mobilise (Breen 1999; Cohen 2006; COMET 2001a; Dunn 1998; Parry 1998; Price 1998; Zeidan 2004). In one trial (Collis 1995) only women receiving the CSE technique were assessed for motor block and if able to straight-leg-raise satisfactorily, they were encouraged to mobilise. However, the women receiving the traditional epidural analgesia were not assessed and not encouraged to walk. One other study (Nageotte 1997) involved two CSE groups, identical in all other respects except that the women in one group were actively encouraged to walk while those in the second CSE group were discouraged from mobilising. No data on mobility were presented for the women in the epidural group. As there was an actively promoted difference in treatment between epidural and CSE groups in both studies, this cast doubt on the maintenance of blinding, suggesting the possibility of performance bias and a loss of the benefit of randomisation. Sensitivity analysis was performed and both studies (Collis 1995; Nageotte 1997) were excluded. Similarly in COMET 2001a only women in the low-dose infusion and CSE groups were allowed to mobilise, with no data from the traditional epidural group for comparison. In Cohen 2006 and Cortes 2007 all women in both groups were able to mobilise.

The incidence of short-term side effects and complications, along with maternal and neonatal effects was also presented in most studies. Maternal satisfaction with analgesia was the primary outcome for one excluded study (Collis 1995) but measurement of satisfaction postdelivery featured as a secondary outcome in seven of the included trials (Gomez 2001; Hepner 2000; Kartawiadi 1996; Price 1998; Van de Velde 1999; Vernis 2004; Zeidan 2004). Typically, the assessment of satisfaction was very simple. For example, Vernis 2004 used a four-point Likert scale response to the written question, 'Were you satisfied with your labour?'. Gomez 2001 presented satisfaction data as visual analogue scale scores at time of delivery but these could not be included in the data tables. Incidence of headache in the days following delivery was quoted widely, and the use of blood patch for post dural puncture headache was analysed from eight studies (Abouleish 1991; Dunn 1998; Hepner 2000; Kartawiadi 1996; Price 1998; Roux 1999; Vernis 2004; Zeidan 2004). One study quoted dural tap rate but not rate of headache or blood patch requirement (COMET 2001a). One excluded study (Finegold 2003) investigated uterine contraction rates and endogenous oxytocin levels as primary outcomes but these were not included in our measures.

The effect on the progress of labour was the main outcome in four studies, two assessing the rate of cervical dilatation (Bhagwat 2008; Tsen 1999) and two focusing on mode of delivery (COMET 2001a; Zeidan 2004). Other side effects analysed included the occurrence of hypotension, respiratory depression, pruritus, nausea and vomiting, urinary retention and sedation. Data concerning longer-term outcomes were presented in only one (Medina 1994) of the trials although another (COMET 2001a) explicitly referred to the collection of such data not yet completed. Of note, no study looked at the economics and use of resources involved in the provision of both analgesic regimens, such as comparative cost of consumables, duration and cost of stay in hospital, or need for readmission or follow-up after discharge. The effect on the progress of labour was the main outcome in four studies, three assessing the rate of cervical dilatation (Bhagwat 2008; Sezer 2007; Tsen 1999) and one focusing on mode of delivery (COMET 2001a).

Neonatal outcomes

Neonatal assessment was carried out in all but six studies (Breen 1999; Gomez 2001; Goodman 2006; Nickells 2000; Price 1998; Tsen 1999). In all other studies, Apgar scores were used as an outcome measure. In Dunn 1998 and Ngamprasertwong 2007 neonatal Apgar scores were stated as not differing between groups but no actual numbers were quoted. In the remaining eight included studies, four quoted numbers of neonates with Apgar scores of less than seven at five minutes, while four others gave data on those scoring less than eight (Abouleish 1991; COMET 2001a; Kartawiadi 1996; Parry 1998). In addition, five studies included cord blood gas analysis (Abouleish 1991; Abrao 2009; Caldwell 1994; Hepner 2000; Van de Velde 1999). These data were presented as mean pH +/- SD, rather than the number of neonates demonstrating a predefined degree of acidosis. Only one study (COMET 2001a) included data on the

number of neonates requiring admission to a special care neonatal unit. Two studies looked at fetal bradycardia as primary outcome (Abrao 2009; Skupski 2009). In the study by Bhagwat 2008, there was one stillbirth with cord around the neck in the CSE group noted. Four other studies included mean Apgar score and found no difference between groups (Abrao 2009; Bhagwat 2008; Cohen 2006; Sezer 2007).

Excluded studies

Twenty seven studies were excluded. Reasons for exclusion fell into three broad categories. Nine studies (Camann 1992; Camann 1998; Collis 1994; Collis 1999a; Collis 1999b; D'Angelo 1994; Harsten 1997; Pham 1996; Rosenfeld 1998; Van de Velde 2004) consisted of study designs in which all women received a spinal injection or dural puncture plus epidural and as such were not specifically comparing a combined spinal epidural with epidural alone. Six other studies (Cascio 1996; Cooper 2010; Groves 1995; Kassapidis 1997; Patel 2003b; Stocche 2001), although comparing CSE with epidurals for labour analgesia, reported outcomes that were not part of our analysis. A further 12 studies (Backus 1996; Collis 1995; Dresner 1999; Finegold 2003; Fogel 1999; Leighton 1996; Nageotte 1997; Nielson 1996; Norris 1994; Norris 2001; Pan 1996; Pinto 2000) exhibited a variety of methodological and study design issues. For example, Leighton 1996, Nielson 1996, Norris 1994 and Norris 2001 were not randomised studies. Also, Backus 1996 and Fogel 1999 had significant treatment differences within groups, while in Collis 1995 and Nageotte 1997 there were significant differences in the management of patients between groups which are likely to have directly influenced outcomes, notably mobilisation.

Risk of bias in included studies

There was a wide range of methodological quality. Details are shown in the table of Characteristics of included studies. Of the 27 included studies, only four (Breen 1999; Goodman 2006; Hepner 2000; Kartawiadi 1996) were fully consistent with the methodological principles defined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

See Figure 1 and Figure 2 for summary of 'Risk of bias' assessments for all studies.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

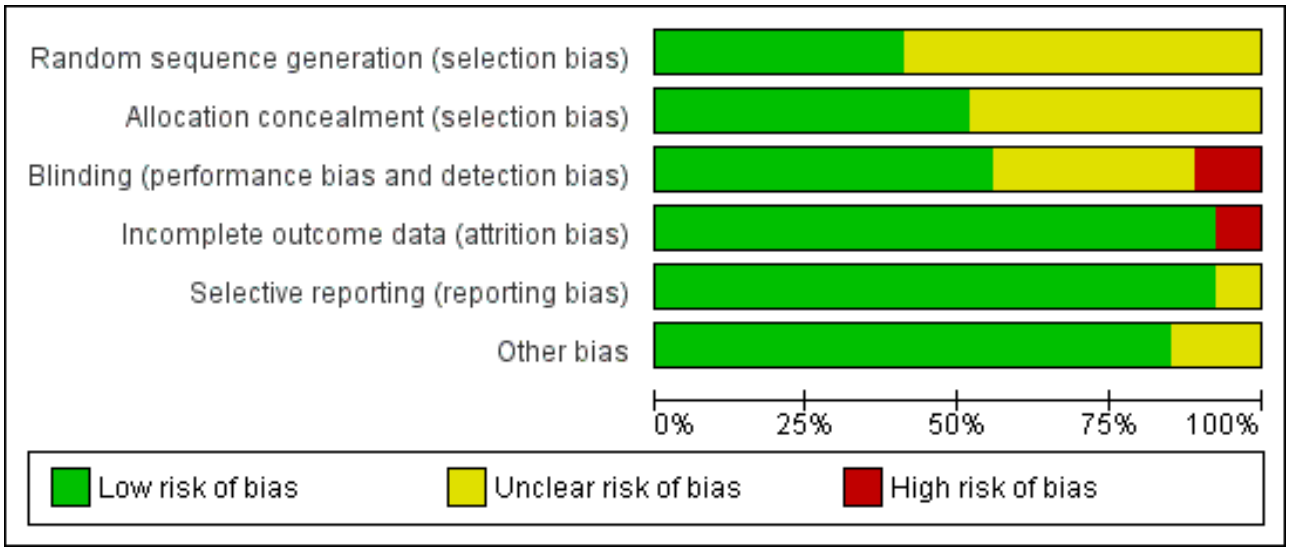


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

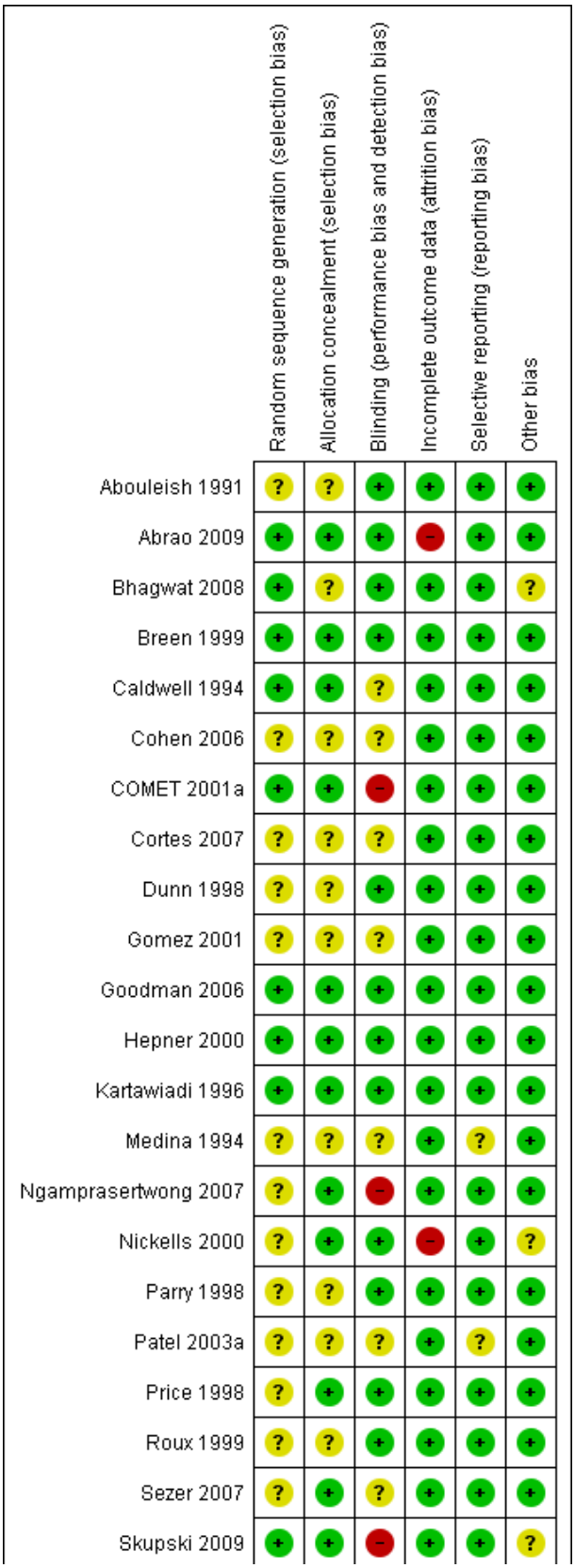


Figure 2. (Continued)

Allocation

All included studies stated that women were randomly allocated to treatment groups. Whilst a range of methods for randomisation and concealment of allocation were stated, we assessed 11 studies as being at low risk of bias for randomisation (Abrao 2009; Bhagwat 2008; Breen 1999; Caldwell 1994; COMET 2001a; Goodman 2006; Hepner 2000; Kartawiadi 1996; Skupski 2009; Thomas 2005; Zeidan 2004) and 14 studies as being at low risk of bias for allocation concealment (Abrao 2009; Breen 1999; Caldwell 1994; COMET 2001a; Goodman 2006; Hepner 2000; Kartawiadi 1996; Ngamprasertwong 2007; Nickells 2000; Price 1998; Sezer 2007; Skupski 2009; Tsen 1999; Vernis 2004). Methods employed included computer randomisation and numbered, sealed, opaque envelopes (Caldwell 1994), random-number tables with sealed envelopes (Hepner 2000) and computerised allocation provided by external sources (COMET 2001a). In the remaining studies, the methods of randomisation and allocation concealment used were not clearly described.

Blinding

We assessed 15 studies as being at low risk of bias for performance and detection bias (Abouleish 1991; Abrao 2009; Bhagwat 2008; Breen 1999; Dunn 1998; Goodman 2006; Hepner 2000; Kartawiadi 1996; Nickells 2000; Parry 1998; Price 1998; Roux 1999; Thomas 2005; Tsen 1999; Van de Velde 1999); in nine studies risk of bias was unclear (Caldwell 1994; Cohen 2006; Cortes 2007; Gomez 2001; Medina 1994; Patel 2003a; Sezer 2007; Vernis 2004; Zeidan 2004); and we assessed three studies as being at high risk of bias (COMET 2001a; Ngamprasertwong 2007; Skupski 2009).

Incomplete outcome data

This was an issue for two studies (Abrao 2009; Nickells 2000). In Abrao 2009, of those originally randomised, 15% were not analysed; for neonatal pH this was 29%. In Nickells 2000, unclear data tables prevented us from using some of their reported data for analysis and it was not clear whether 18 analgesic failures (nine in each group) were included in the analysis of their results. In all the remaining studies, complete outcome data were available.

Selective reporting

We assessed 25 studies as being at low risk of bias for selective reporting (Abouleish 1991; Abrao 2009; Bhagwat 2008; Breen 1999; Caldwell 1994; Cohen 2006; COMET 2001a; Cortes 2007; Dunn 1998; Gomez 2001; Goodman 2006; Hepner 2000; Kartawiadi 1996; Ngamprasertwong 2007; Nickells 2000; Parry 1998; Price 1998; Roux 1999; Sezer 2007; Skupski 2009; Thomas 2005; Tsen 1999; Van de Velde 1999; Vernis 2004; Zeidan 2004) as all expected outcomes were reported. We assessed the remaining two studies as being at unclear risk of bias: in one study primary and secondary outcomes were not stated (Medina 1994); and in the other study reporting of detail of outcomes was unclear (Patel 2003a).

Other potential sources of bias

No other sources of bias were identified in 23 of the included studies (Abouleish 1991; Abrao 2009; Bhagwat 2008; Breen 1999; Caldwell 1994; Cohen 2006; COMET 2001a; Cortes 2007; Dunn 1998; Gomez 2001; Goodman 2006; Hepner 2000; Kartawiadi 1996; Medina 1994; Ngamprasertwong 2007; Nickells 2000; Parry 1998; Patel 2003a; Price 1998; Roux 1999; Sezer 2007; Skupski 2009; Thomas 2005; Tsen 1999; Van de Velde 1999; Vernis 2004; Zeidan 2004). In the other four studies, we assessed other risk of bias as being unclear (Bhagwat 2008; Nickells 2000; Skupski 2009; Vernis 2004): one study (Bhagwat 2008) had not dealt with one still birth in the CSE group (cord around neck); one study (Nickells 2000) was stopped after three months and so there were slightly uneven group sizes; one study (Skupski 2009) was underpowered to detect the difference in fetal heart rate changes; and one study (Vernis 2004) was stopped early.

Effects of interventions

Twenty-seven trials, involving 3274 labouring women, met our criteria for inclusion.

We performed analyses on all included studies against 26 outcomes. This was performed as two separate sets of comparisons. The first set involved all combined spinal-epidural (CSE) variants versus traditional epidurals and the second set was all CSE forms versus low-dose epidurals and variants. For a summary of analyses *see* Data and analyses.

CSE versus traditional epidural

Of the CSE versus traditional epidural analyses four outcomes showed a significant difference. The time from first injection to effective analgesia was less with CSE (mean difference (MD) -2.87 minutes; 95% confidence interval (CI) -5.07 to -0.67; 129 women (Analysis 1.1)) based on two studies (Ngamprasertwong 2007; Roux 1999). There was a reduced need for rescue analgesia for CSE based on one study (Gomez 2001) with a risk ratio (RR) of 0.31 (95% CI 0.14 to 0.70; 42 women (Analysis 1.3)). CSE was also more favourable with respect to the need for instrumental delivery with RR 0.81 (95% CI 0.67 to 0.97; 1015 women (Analysis 1.19)) based on six studies

(COMET 2001a; Cortes 2007; Gomez 2001; Ngamprasertwong 2007; Roux 1999; Tsen 1999). CSE was also associated with less urinary retention based on the COMET 2001a study (RR 0.86; 95% CI 0.79 to 0.95; one study, 704 women (Analysis 1.10)). CSE was associated with a slightly lower umbilical venous pH in comparison to the epidural group, although this result was based on only one study involving morphine and fentanyl for the initial intrathecal injection (Caldwell 1994), and statistical significance was borderline (MD -0.03; 95% CI -0.06 to -0.00; one study, 55 women (Analysis 1.22)).

No differences between CSE and epidural were seen for the number of women who mobilised, post dural puncture headache, pruritis, nausea and vomiting, hypotension or the rate of caesarean birth. Also, there were no significant differences for the following neonatal outcomes: umbilical arterial pH, Apgar score less than seven or less than eight at five minutes and the number of admissions to the neonatal unit.

Due to results not being statistically significant or outcomes reported with zero data, it was not possible to draw any conclusions with respect to the following outcomes: number of women with effective analgesia in the first 10 minutes after injection, number of women satisfied with analgesia, number of women requiring a blood patch, maternal respiratory depression and umbilical cord pH.

Subgroup analyses

No subgroup differences between opioid CSE and CSE were observed: known dural tap (Analysis 1.7); pruritus (Analysis 1.9); nausea/vomiting (Analysis 1.11); hypotension (Analysis 1.12); labour augmentation required (Analysis 1.16); normal delivery (Analysis 1.18); instrumental delivery (Analysis 1.19) or caesarean section (Analysis 1.20).

CSE versus low-dose epidural

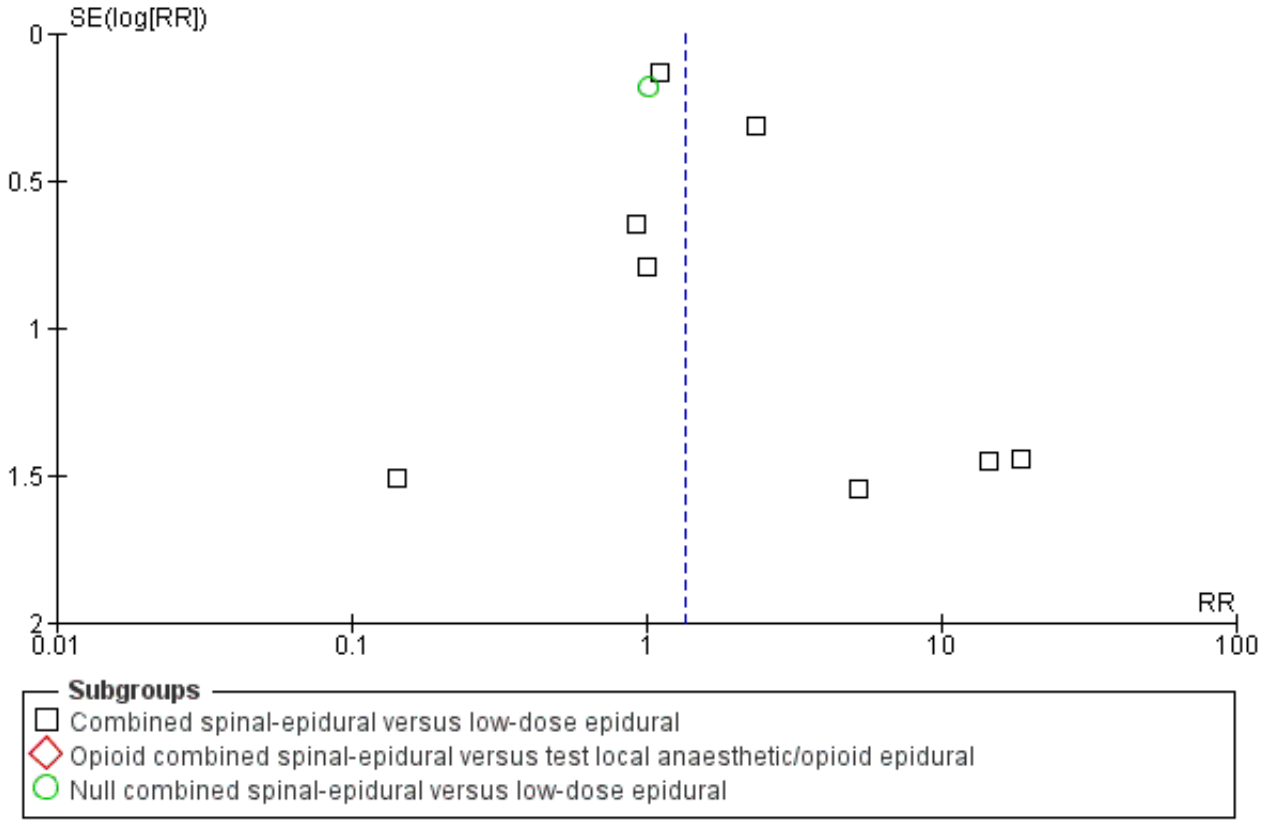
For the analyses of CSE versus low-dose epidurals and variants there were three outcomes which were statistically significant. Both measures of speed of onset of analgesia from the time of injection indicated a faster onset for CSE versus low-dose epidural. The mean time of onset of effective analgesia was -5.42 minutes (95% CI -7.26 to -3.59; five studies, 461 women; random-effects,T^2 = 3.27, I^2 = 77% (Analysis 2.1)), while the risk ratio of effective analgesia at 10 minutes was 1.94 in favour of CSE (95% CI 1.49 to 2.54) based on a single study with 101 women (Analysis 2.2). Time of onset of effective analgesia showed substantial heterogeneity, but this would be expected given the variation in techniques between studies. However, as has been remarked upon in previous versions of this review, no study reported our primary outcome of interest with regards to time of onset of pain relief in labour from the time of patient request.

For the analyses of CSE versus low-dose epidurals, CSE was associated with more pruritus (average RR 1.80; 95% CI 1.22 to 2.65; 11 studies, 959 women; random-effects, T^2 = 0.26, I^2 = 84% (Analysis 2.9)). There was substantial heterogeneity between studies reflecting once again the marked variability in definitions used.

There were no significant differences between CSE and low-dose epidural with regard to modes of delivery and the need for labour augmentation. There was also no significant difference between CSE and low-dose epidurals with respect to the maternal side effects of urinary retention, nausea and vomiting, post dural puncture headache, known dural tap and need for a blood patch, or for the need of rescue analgesia. Maternal satisfaction with analgesia was also not significantly different based on seven studies (520 women) (see Analysis 2.4). However, there was substantial heterogeneity in this result and this probably reflects the wide variation in and perhaps simplistic methods generally used for assessing this important outcome.

In relation to all of the neonatal outcomes there was also no difference with umbilical venous pH, umbilical cord pH, Apgar scores at five minutes and the number of neonates requiring neonatal unit admission. It was not possible to draw any conclusions with respect to the following outcomes: maternal respiratory depression and maternal sedation. No women experienced maternal respiratory depression in the studies that reported on this outcome and maternal sedation was not a reported outcome in the included studies. Two other outcomes are worth highlighting specifically. Firstly, mobilisation in labour was reported by seven studies (involving 1200 participants) and there was no difference between the techniques. Secondly, the occurrence of hypotension exhibited substantial heterogeneity, again as a result of the diverse range of definitions used. We have reported this outcome as not significant. However we conducted both subgroup and sensitivity analyses as a result of the wide variation of results seen between different studies and a funnel plot looking for any effects of small studies (Figure 3). The small number of subjects in the different subgroups resulted in there being no discernible effect. However, within the local anaesthetic plus opioid CSE versus low-dose epidural comparison there appears to be a trend to there being a more favourable outcome for epidural over CSE; a fixed-effect analysis would produce a significant result.

Figure 3. Funnel plot of comparison: 2 Combined spinal-epidural versus low-dose epidural, outcome: 2.12 Hypotension.



Adverse events

We included the incidence of longer-term sequelae (e.g. neurological) as an outcome measure as this has been raised as a source of concern in the past regarding the routine use of CSE analgesia for labour. In Medina 1994, in the CSE group there was one case of reflex sympathetic pain of the foot which required two paravertebral blocks to resolve. In another study (Vernis 2004) there was one woman in the CSE group who developed meningitis which responded effectively to intravenous antibiotics. COMET 2001a made reference to the ongoing collection of data not yet completed.

Subgroup analyses

No subgroup differences between opioid CSE, null CSE and CSE were observed for the following outcomes: time from first injection to effective analgesia (Analysis 2.1); need for rescue analgesia (Analysis 2.3); number of women satisfied with analgesia (Analysis 2.4); number of women who mobilise (Analysis 2.5); post dural puncture headache (Analysis 2.6); known dural tap (Analysis 2.7); number of women requiring blood patch (Analysis 2.8); urinary retention (Analysis 2.10); nausea/vomiting (Analysis 2.11); hypotension (Analysis 2.12); labour augmentation required (Analysis 2.16); normal delivery (Analysis 2.18); instrumental delivery (Analysis 2.19); caesarean section (Analysis 2.20); umbilical arterial pH (Analysis 2.21); umbilical venous pH (Analysis 2.22) or Apgar score less than seven at five minutes (Analysis 2.24).

However, subgroup differences were observed for the following two outcomes: number of women who mobilise (P = 0.04, I^2 = 76.5%; Analysis 2.5) and pruritus (P = 0.03, I^2 = 79.4%; Analysis 2.9).

DISCUSSION

There is no standard combined spinal-epidural (CSE) or epidural technique and this necessitated categorising individual interventions into groups for analysis, and the use of multiple comparisons for individual outcomes. *See* additional tables, Table 1 and Table 2, for details. Nonetheless, in an attempt to maintain relevance with evolving clinical practice, we performed comparisons separately for CSE versus traditional epidurals and for low-dose epidurals. This appears to have some clinical relevance supported by this review with there being several outcomes significantly favouring CSE over the traditional forms which was not apparent when CSE was compared with the lower-dose variants, notably higher urinary retention, higher instrumental delivery rate and the need for rescue analgesia with traditional epidurals.

Proposed benefits of CSE analgesia in labour over epidural pain relief are increased mobility and a postulated beneficial effect on mode of delivery. In this update there are now data from eight studies involving 1240 women including one study involving traditional epidurals (Cortes 2007; 40 women) and seven studies (1200 women) involving low-dose epidurals (Breen 1999; Cohen 2006; COMET 2001a; Dunn 1998; Parry 1998; Price 1998; Zeidan 2004). There was no difference seen in the number of women who

actually mobilised. In relation to mode of delivery there is also no apparent benefit attributable to CSE other than for a lower instrumental rate when compared with traditional epidurals. The rate of caesarean section would appear to be influenced by factors that to date have not emerged against these modes of regional analgesia. This is of interest not only in regard to progress of labour but also in relation to concerns for unfavourable fetal heart rate changes that have been attributed to the use of CSE techniques. This review does not include any outcomes specifically linked to fetal heart rate. However, if these effects are real there appears to be no support from this review of a significant translation of concern for the fetus to an increased rate of caesarean delivery. In relation to neonatal outcome there was no difference between CSE and epidural as identified by Apgar scores less than eight or seven at five minutes or the need for neonatal unit admission. Any possible differences between the two techniques in relation to the occurrence of unfavourable fetal heart rate changes during labour were not apparent from these results.

CSE was associated with a higher incidence of pruritus compared with low-dose epidural techniques. This is almost certainly a result of direct injection of opioids into the subarachnoid space.

From studies included in this review there was no difference in the number of women who expressed satisfaction with CSE analgesia compared with epidural. This was based on seven studies (involving 520 women), all of which involved low-dose epidurals (Bhagwat 2008; Hepner 2000; Kartawiadi 1996; Sezer 2007; Van de Velde 1999; Vernis 2004; Zeidan 2004). It would appear that the marginally faster onset from the time of injection, potentially favouring CSE, and the higher incidence of pruritus, presumably favouring epidurals, do not significantly impact on the overall sense of satisfaction. It was noted, however, that the measurement of satisfaction was typically very simplistic, using four-point scales of a seemingly global experience.

Randomised controlled trials are not the best means of assessing differences in the risk of rare complications, such as meningitis, as they invariably fail to recruit the number of participants necessary to show such differences. In this review a total of over 3200 women participated in all 27 included studies combined. This is insufficient to assess the occurrence of very rare events. However, the inclusion of data on long-term outcomes should still form part of large trials, such as COMET 2001a, so that perhaps in the future some benefit may be gained by collating the evidence from large numbers of studies. In the meantime, clinicians will have to rely on other forms of evidence, such as case reports and large cohort studies, for information on such rare events as meningitis and other neurological complications.

AUTHORS' CONCLUSIONS

Implications for practice

Both combined spinal-epidural and epidural techniques are shown to provide effective pain relief in labour. There appears to be little basis for offering one technique over the other, with no difference in overall maternal satisfaction despite a slightly faster onset with combined spinal-epidural (CSE) and less pruritus with low-dose epidurals. There is no difference in ability to mobilise, obstetric outcome or neonatal outcome. The significantly higher incidence with traditional epidural techniques of urinary retention based on one study involving 703 women and of rescue interventions, also with one other study involving 42 women, would favour the use of low-dose epidurals, although this should be tempered by the knowledge that only single studies have been involved in both instances.

Implications for research

Future trials should include as an endpoint the time taken from maternal request for pain relief until effective pain relief is established. This may be important as the additional tasks involved in the preparation for, and performance of, a combined spinal-epidural block may potentially offset some of the advantage of quicker onset of analgesia. The difference in time of onset from the time of injection from this review is of the order of one contraction. In a busy obstetric service there are many factors that contribute to the total time between a woman requesting pain relief and when it is actually delivered and these may be far more relevant to the consumer.

While most papers gave data on numbers of women requiring delivery by caesarean section, none mentioned the type of anaesthesia for the surgery or the need for conversion to general anaesthesia for operative delivery. Avoidance of general anaesthesia still remains an important goal for obstetric anaesthetists. In this setting there are pros and cons for both the CSE and epidural techniques. The untested epidural catheter of a combined regimen may fail when topped up for theatre or result in intravascular injection. On the other hand, there are potential benefits of the intrathecal drugs used in terms of providing good surgical conditions and intra-operative comfort for the woman. The rate of conversion from regional to general anaesthesia is sufficiently common that a very large study may have sufficient power to provide some answers. This could be the basis of a future review if sufficient studies included these data.

The collection of data on longer-term sequelae following both CSE and epidural pain relief in labour is important. Rare and long-term adverse effects of spinal and epidural techniques are difficult to quantify through small randomised trials such as in this review. There are other side effects, however, that can be more specifically addressed. Most papers have focused on obstetric outcomes. In this review we have also attempted to identify other factors through outcome measures such as respiratory depression and maternal sedation but very few papers investigated these issues. Future research work should more specifically address the possible impact of intrathecal and epidural opioids on both mother and baby. One specific area of interest in this regard is a possible link to breastfeeding success which could be different between CSE and epidural variants with differing amounts of opioids.

No reviewed study addressed the economic aspects of both types of regional pain relief. Future research could include data on such aspects as cost of consumables, cost and length of hospital stay, consequences of hospital readmission and resources needed for patient follow-up after discharge.

Suggested systematic reviews

A number of studies, both included (Breen 1999; Dunn 1998; Parry 1998) and excluded from this review (e.g. Camann 1992) compared an intrathecal injection with an epidural bolus, and ended the study period with the first request for additional analgesia. While the exclusion of some such papers was made on other methodological grounds, the comparison of epidural and intrathecal (as opposed

to combined spinal-epidural) analgesia for labour could form the basis of a future review.

Within this review there were a wide range of interventions included. Not only did the drugs used differ but also the techniques, with studies using repeat boluses or infusions, or both, at different time intervals for the maintenance of analgesia. For the purposes of this review, all have been included together but with an attempt to categorise them into broad groups to assist with interpretation of results. The use of this or a similar structure may facilitate the review of further studies in the future.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Abouleish 1991

Methods	Randomisation: method not stated "62 women randomly divided into 3 groups".

Abouleish 1991 *(Continued)*

	Blinding: investigators were not blinded to the group allocation. Participant, midwife, obstetrician and neonatologist were blinded. Criteria for rescue analgesia: if analgesia inadequate after 40 min 10 mL boluses 0.125% bupivacaine administered until pain relief achieved. Data from all participants used for all outcomes except caesarean section women who were excluded from analysis re duration and urinary catheterisation.
Participants	Inclusions: 62 women ASA 1 or 2 at term, with singleton cephalic fetus. Exclusions: none mentioned. No. lost to follow-up: 0. NB: 13 women required caesarean section and these women were excluded from the comparison of urinary retention as they all had an indwelling catheter.
Interventions	Epidural (n = 22): bolus 10 mL bupivacaine 0.125%. Then as requested further 10 mL boluses given to maintain analgesia. CSE (n = 20): single space, needle-through-needle (18 G/26 G). IT injection morphine 0.2 mg, then epidural bolus 10 mL bupivacaine 0.125%. Then boluses of 10 mL bupivacaine 0.125% as requested. IT morphine group (n = 20): CSE technique as above, but only the IT morphine 0.2 mg given. The epidural catheter only used for additional analgesia on request, when 10 mL bupivacaine 0.125% was given as needed. (This arm was not used in the systematic review analysis.)
Outcomes	VAS pain (0 to 10) every 10 min for 1 hr, then every 20 min. Vital signs monitored at same time intervals as VAS. SpO2 monitored for 24 hr in all women. Mode of birth and duration of labour noted. Occurrence of respiratory depression, nausea/vomiting, pruritus and urinary retention noted. Number with post dural puncture headaches and treatment required recorded. Neonatal assessment by Apgar scores and cord blood gas analysis.
Notes	USA.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated, "...patients randomly divided".
Allocation concealment (selection bias)	Unclear risk	Investigators were aware of group allocation.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participant, midwife, obstetrician and neonatologist were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data from all participants used for all outcomes except caesarean section women who were excluded from analysis re duration and urinary catheterisation.
Selective reporting (reporting bias)	Low risk	Only with respect to duration and urinary catheterisation for caesarean section women who were excluded from analysis.
Other bias	Low risk	No other bias evident.

Abrao 2009

Methods	Randomisation: a computer-generated random number series. Allocation concealment: sealed opaque envelopes were generated by a person not related to the protocol and the anaesthetist received the next in a numbered series. Blinding: participant blinded; outcome assessor and obstetrician blinded to allocation. Criteria for rescue analgesia: not stated. Statistics were not performed on an intention-to-treat basis; of the 91 participants originally randomised, 14 were excluded from analysis, 8 in the control group and 6 in the treatment group (11 failure to maintain adequate CTG recording, 2 proceeding to vaginal birth in less than 30 minutes, 1 failed spinal); a further 12 did not have umbilical artery pH data.
Participants	Inclusions: 77 singleton, cephalic, full term, in active labour with cervical dilatation < 7 cm at time of epidural request. Exclusions: regional contraindicated, previous systemic opioids, prostaglandins for cervical ripening, amniotic infection, maternal or fetal medical conditions.
Interventions	All women received 10 mL/kg crystalloid prior to epidural insertion. Epidural (n = 36): initial bolus 10 mL bupivacaine 0.125% + sufentanil 10 µg. After at least 20 minutes, with request for additional analgesia, boluses of bupivacaine of varying concentration were administered; 0.125% until 7 cm cervical dilatation, then 0.25% at 8 to 9 cm and 0.5% in second stage. CSE (n = 41): single space, needle-through-needle. IT injection bupivacaine 2.5 mg + sufentanil 2.5 µg. Subsequent epidural boluses as above.
Outcomes	Primary outcomes: prolonged fetal heart rate decelerations (decrease of 15 bpm for 2 to 10 minutes or baseline < 100) and increase uterine tone (10 mmHg) in the first 15 minutes after injection. Secondary outcome maternal hypotension (systolic < 100 mmHg or 20% fall). VAS (0 to 10) pain scores assessed; mean scores at 5, 10,15 and 20 minutes post-injection. Intervention failures reported and percentage of caesarean births. Neonatal assessment by Apgar scores at 1 and 5 min and pH.
Notes	Brazil.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers is appropriate.
Allocation concealment (selection bias)	Low risk	Sealed, opaque envelopes allocated by independent person via a sequentially numbered series.
Blinding (performance bias and detection bias) All outcomes	Low risk	Management and outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Of those originally randomised, 15% were not analysed; for neonatal pH this was 29%.
Selective reporting (reporting bias)	Low risk	The primary and secondary outcomes were reported.
Other bias	Low risk	No other bias evident.

Bhagwat 2008

Methods	Randomisation: using a computer-generated randomisation list. Blinding: progress of labour was assessed by an obstetrician who was blinded, observations were made by another anaesthetist who was not present at the time of procedure.
Participants	Inclusions: 60 nulliparous women in labour, cephalic, singleton with cervical dilatation 4 to 5 cm. Exclusions: cervical dilatation more than 5 cm, non vertex presentation, contraindication to neuraxial analgesia. No. lost to follow-up: 1 (CSE group) went for emergency caesarean section.
Interventions	All women received 10 mL/kg crystalloid prior to epidural insertion. Epidural (n = 30): test dose 3 mL 1.5% lidocaine plus 15 µg of epinephrine, followed by 10 mL bupivacaine 0.062% plus 0.0002% fentanyl. After 10 minutes an epidural infusion of 0.0625% bupivacaine plus 0.0002% fentanyl was started using a patient controlled analgesia pump at a rate of 8 to 12 mL/hr and titrated to maintain sensory level of T10. CSE (n = 30): single space, needle-through-needle, sitting or lateral position. IT injection of 1.25 mg bupivacaine + fentanyl 25 µg. Then after 10 minutes an epidural infusion of 0.0625% bupivacaine plus 0.0002% fentanyl was started using PCEA pump at the rate of 8 to 12 mL/hr to maintain T10 sensory block.
Outcomes	Maternal: VAS pain < 3 at 30 minutes post block and the number of women requiring additional analgesia and those who were satisfied on a 4-point scale. Number requiring caesarean birth and the occurrence of hypotension, nausea/vomiting and pruritus noted. Neonatal assessment by Apgar scores, cord blood gas analysis and need for admission to the neonatal unit.
Notes	One still birth in the CSE group was excluded (cord around the neck).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used a computer-generated randomisation list.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Low risk	Progress of labour was assessed by an obstetrician who was blinded, observations were made by another anaesthetist who was not present at the procedure and presumably blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All of the parturients were followed up.
Selective reporting (reporting bias)	Low risk	The primary and secondary outcomes were reported.
Other bias	Unclear risk	The study has not dealt with one still birth in the CSE group (cord around neck), excluded from study.

Breen 1999

Methods	Randomisation: computer-generated randomisation in blocks of 4 with allocation concealed in sealed envelopes. Blinding: procedure performed by an anaesthesiologist not involved in subsequent assessments. Both assessor and participant blinded to allocation. Criteria for rescue analgesia: not specifically stated. Statistics were not performed on an intention-to-treat basis. One woman in the epidural group was excluded due to loss of blinding, and data from this participant were not used in analysis.
Participants	Inclusions: 41 participants were initially enrolled into the study, all ASA class 1 or 2, at least 18 years old, with a singleton fetus with cervical dilatation < 6 cm. Exclusions: inability to give informed consent, allergy to study drugs and contraindication to regional blockade. No. lost to follow-up: 1 woman in epidural group dropped from analysis due to loss of blinding.
Interventions	Epidural (n = 20): all women received 750 to 1000 mL crystalloid prior to epidural insertion. The initial epidural bolus was a 3 mL test dose of 1.5% lidocaine with 1:200,000 epinephrine. This was followed 3 min later with a bolus 100 µg fentanyl diluted to a volume of 10 mL with saline down the epidural catheter. The study period ended with the first request for additional analgesia. CSE (n = 21): single space, needle-through-needle. An intrathecal injection of sufentanil 10 µg diluted to 2 mL with saline. The epidural catheter was placed in the same manner as for the epidural group, but no drugs were given down it until additional analgesia was requested, at which point the study period ended.
Outcomes	Primary outcome was time from injection of narcotic until request for additional analgesia (duration of analgesia). VAS pain scores were assessed at 0, 5, 10, 15 and 30 min, and thereafter every 30 min. Motor block on Bromage scale was assessed at 30 min. Ability to walk and void urine was only assessed in those with full motor power. The incidence of itch was assessed by VAS scores.
Notes	Canada.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation in blocks of 4.
Allocation concealment (selection bias)	Low risk	Used opaque, sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded, both women and the anaesthesiologist collecting the data were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One woman in epidural group dropped from analysis due to loss of blinding.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were reported except for one epidural group patient.
Other bias	Low risk	No other bias evident.

Caldwell 1994

Methods	Randomisation: not stated. "Patients were randomly assigned...". Blinding: not mentioned at all anywhere in the paper. Follow-up request: "Randomisation was by computer-generated random numbers. Sequentially numbered, sealed envelopes prepared by a non-investigator. Participant and anesthesiologist-investigator were blinded to treatment group; upon opening the sealed envelope, a non-investigator anesthesiologist confidentially prepared the study drug for administration." Criteria for rescue analgesia: no specific mention of rescue analgesia per se. On request for additional analgesia, participants in the CSE group were given 10 mL bupivacaine 0.25% and then an infusion of bupivacaine 0.125% with fentanyl 10 µg/mL was started. Women in the epidural group received an infusion immediately after the initial bolus of bupivacaine 0.125% with sufentanil 100 µg/mL. No mention made of additional rescue analgesia. No participants were lost to follow-up and data from all were included in the statistical analysis.
Participants	Inclusions: all women were ASA class 1 in labour with a singleton fetus. Exclusions: none stated. No. lost to follow-up = 0.
Interventions	Epidural: 33 women received epidural analgesia, initiated with 10 mL bupivacaine 0.25% and sufentanil 10 µg. This was followed immediately by an infusion of bupivacaine 0.125% with sufentanil 0.2 µg/mL. CSE: 26 women had CSE analgesia initiated in a single space, needle-through-needle technique (18 G, 24 G Sprotte). An initial intrathecal injection of morphine sulphate 0.25 mg and fentanyl 25 µg. Nothing was given down the epidural catheter until a request for additional analgesia, at which time a bolus of 10 mL bupivacaine 0.25% was given and followed immediately by an infusion of bupivacaine 0.125% with fentanyl 1 µg/mL.
Outcomes	Maternal: blood pressure and heart rate recorded every 15 min until delivery. The occurrence of nausea/vomiting, pruritus, PDPH and respiratory depression was noted. Mode of delivery was noted as either "normal" or "operative", i.e. either caesarean or instrumental. Neonatal: Apgar scores and umbilical arterial and venous pH.
Notes	USA.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was by computer-generated random numbers.
Allocation concealment (selection bias)	Low risk	Upon opening the sealed envelope, a non-investigator anaesthesiologist confidentially prepared the study drug for administration.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.

Caldwell 1994 *(Continued)*

Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes reported.
Other bias	Low risk	No other bias evident.

Cohen 2006

Methods	Parturients who requested epidural analgesia were randomised.
Participants	Inclusions: 136 parturients who requested epidural analgesia for labour pain. Exclusions: none stated. No. lost to follow-up: 5 CSE women were removed from the study following failure to pierce the dura - and presumably were replaced to leave 68 in both groups. The data from the successful women were included.
Interventions	Epidural: 68 women received 20 mL ropivacaine 0.04% (8 mg) with adrenaline and sufentanil 1 µg/mL (20 µg) followed by PCEA using same solution with 4 mL bolus and 10 minute lockout plus background infusion of 4 mL/hr. CSE: 68 women received ropivacaine 2 mg with sufentanil 5 µg intrathecally followed by PCEA as above. Both groups received rescue of 0.25% ropivacaine from 20 minutes if VAS > 3.
Outcomes	Maternal: time from first injection to maximal analgesia; the number who mobilised; the occurrence of hypotension and pruritus and the need for bladder catheterisation. Fetal bradycardia during the fist 30 minutes after block was also noted (this is not an outcome for this review). Neonatal: Apgar scores (actual scores not available).
Notes	USA. Abstracts only: 2004, 2004 and 2006.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Parturients "were randomized".
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for the women who completed the study were available.
Selective reporting (reporting bias)	Low risk	The primary and secondary outcomes were reported.
Other bias	Low risk	No other bias evident.

COMET 2001a

Methods	Randomisation: using a customised randomisation programme provided by clinical trials experts. Blinding: participant not blinded. Assessor only blinded with respect to obstetric management. Criteria for rescue: in the traditional 0.25% bupivacaine (higher-dose) group rescue given as fentanyl 50 µg or more concentrated bupivacaine. For CSE and low-dose infusion (0.1% bupivacaine = fentanyl 2 µg/mL) a further 10 mL of this solution was used or 0.25% bupivacaine if necessary. Statistical analysis was performed on an intention-to-treat basis. Separate comparisons between mobile techniques and traditional group.
Participants	Inclusions: 1054 nulliparous women in labour. Exclusions: contraindication to epidural analgesia, previous epidural or spinal procedure, imminent delivery, injection of pethidine within the previous 4 hours. No. lost to follow-up (post partum interview): 13.
Interventions	Epidural (n = 353): test dose 3 mL 2% lidocaine (60 mg) followed after 5 min with 10 mL bupivacaine 0.25%. Subsequent boluses of 10 mL bupivacaine 0.25% on request. Low-dose infusion (n = 350): bolus of 15 mL bupivacaine 0.1% with fentanyl 2 µg/mL, followed by an infusion of the same at 10 mL/hr. CSE (n = 351): single space, needle-through-needle, sitting or lateral position. IT injection of 2.5 mg bupivacaine + fentanyl 25 µg. Then epidural boluses of 15 mL bupivacaine 0.1% + fentanyl 2 µg/mL on request.
Outcomes	Primary outcome measure mode of delivery. Secondary outcomes progress of labour (duration of first and second stages), oxytocin augmentation, regular pain assessments (VAS), women's perceptions of their ability to push and urinary retention. Neonatal assessments of Apgar scores at 1 and 5 min, resuscitation requirements and admission to the special care unit. Birthweight was recorded after delivery.
Notes	UK. Funded by grants from the NHS Research and Development Mother and Child Health Programme.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used a customised randomisation programme.
Allocation concealment (selection bias)	Low risk	The study group code was not revealed before completion of recruitment.
Blinding (performance bias and detection bias) All outcomes	High risk	The participants and those in attendance were not blinded. Trial midwives assessing VAS 24 hours after delivery were blinded to obstetric management.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Total number lost 13 (of 1054 randomised).

COMET 2001a *(Continued)*

Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were reported.
Other bias	Low risk	No other bias evident.

Cortes 2007

Methods	Randomisation: method not stated, "randomly divided into two groups". Blinding: not stated.
Participants	Inclusions: 40 women, singleton, term in labour at 4 to 5 cm dilatation. Exclusions: none stated. No. lost to follow-up: 0
Interventions	Epidural: 20 women received 8 mL bupivacaine 0.25% (20 mg) with adrenaline and fentanyl 100 µg followed by intermittent bolus of 4 mL bupivacaine 0.25% with adrenaline as required. CSE: 20 women received fentanyl 25 µg intrathecally followed by intermittent epidural boluses as above. Supplementation of 6 mL was available for both groups for delivery.
Outcomes	Maternal: VAS scores at 0, 5, 10, 15 and 20 minutes post initial injection; the number who mobilised; the occurrence of hypotension, pruritus, respiratory depression and nausea/vomiting. The mode of delivery was also noted. Neonatal: Apgar scores.
Notes	Brazil - translated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated only, "randomly divided into two groups".
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All the data are available.
Selective reporting (reporting bias)	Low risk	Outcomes are all reported.
Other bias	Low risk	No other bias evident.

Dunn 1998

Methods	Randomisation: method not stated. "Patients were randomised into 2 groups." Blinding: outcome assessor blinded. Criteria for rescue analgesia: if inadequate analgesia after 20 min, 15 mL bupivacaine 0.125% given down epidural, followed by 10 mL lidocaine 2% if needed. If this was ineffective then catheter replaced and data excluded from analysis. Statistical analysis not performed on an intention-to-treat basis.
Participants	Inclusions: 70 healthy ASA 1 or 2 women in early labour (cervical dilatation < 5 cm). Exclusions: history of previous caesarean section or IV opioids before requesting epidural analgesia. No. lost to follow-up: 1.
Interventions	Epidural (n = 35): test dose 3 mL lidocaine 1.5% + 1:200,000 epinephrine. Then bolus sufentanil 40 µg in 10 mL saline down epidural catheter. Study ended at request for additional analgesia. CSE (n = 34): single space, needle-through-needle, sitting. IT injection sufentanil 10 µg diluted to 1 mL. Epidural catheter sited but nothing administered down it until requested, at which point study ended.
Outcomes	VAS pain scores and severity of side effects assessed at 5, 10, 15, 20 and 30 min, and thereafter every 30 min. Maternal blood pressure, pulse and respiratory rate, and motor block were assessed at the same times. Time of request for additional analgesia noted and study ended. Mode of delivery noted and incidence of PDPH recorded. Neonate assessed by Apgar scores.
Notes	USA.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated, "randomised into 2 groups".
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Low risk	Stated, "observations were made by an individual blinded to the analgesic technique".
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient lost to follow-up.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes reported.
Other bias	Low risk	No other bias evident.

Gomez 2001

Methods	Randomisation: method not stated. Blinding: stated as "single blinded" study but unclear as to specifically whether the outcome assessor was blinded to allocation. Criteria for rescue analgesia: when VAS pain score 3 or greater, 4 mL bolus bupivacaine 0.25% administered. Minimum 30 min between injections. Nil lost to follow-up.
Participants	Inclusions: 42 ASA 1 or 2 women in spontaneous labour with a singleton, vertex presentation fetus. Cervical dilatation 2 to 5 cm. Exclusions: obstetric pathology, meconium stained liquor, ruptured membranes, previous caesarean section. No. lost to follow-up = 0.
Interventions	Epidural (n = 21): test dose 3 mL bupivacaine 0.25% + adrenaline 1:200,000 followed by 5 mL of the same solution. Immediate infusion of bupivacaine 0.125% with fentanyl 1 µg/mL at 8 mL/hr. CSE (n = 21): sitting, otherwise technique not stated. IT injection of bupivacaine 2.5 mg + 25 µg fentanyl + adrenaline 1:200,000. Once VAS of 3 to 4, 8 mL bupivacaine 0.125% + adrenaline 1:200,000 and an infusion of the same solution and rate as the epidural group.
Outcomes	Maternal: VAS pain scores at 5, 10, 15 and 30 min and then hourly. At the same time intervals sensory block to pinprick and motor block (Bromage scale) were assessed. Number of additional rescue analgesia boluses was noted. VAS maternal satisfaction recorded at delivery. Presence of arterial hypotension (decrease from baseline of greater than 20%) was documented. Maternal bradycardia (rate less than 60 bpm) was noted. Adverse effects noted: nausea and vomiting, pruritus. Mode of delivery recorded as normal, instrumental or caesarean. Neonatal: occurrence of fetal bradycardia less than 100 bpm noted. No recorded neonatal assessments.
Notes	Spanish (translated).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were divided randomly into two groups".
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated, except "prospective, randomised, blinded study".
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes are stated.
Other bias	Low risk	No other bias evident.

Goodman 2006

Methods	Randomisation: computer-generated randomisation table, placed in opaque envelope. Blinding: the women and the nurses caring for the patient and the outcome investigator were blinded. Criteria for rescue analgesia: if after 15 minutes post epidural or spinal dose still had inadequate pain relief, 5 mL bolus of bupivacaine 0.25% was administered via the epidural catheter.
Participants	Inclusions: 100, ASA 1 to 2, parous (1 or more prior vaginal delivery) women at term in early labour (< 5 cm cervical dilatation). Exclusions: women with severe scoliosis, BMI > 45, any contraindication to neuraxial analgesia, or were taking other pain medication. No. excluded: 16 (9 protocol violations which included 5 in CSE group and 4 in epidural group. 2 women had missing data (1 in each group), 2 spinal anaesthetics resulted in only partial drug administration (CSE group) and 3 epidural catheters failed.
Interventions	Epidural (n = 41) 3 mL test dose of 0.25% bupivacaine followed 5 min later by 10 mL of bupivacaine 0.125% with fentanyl 50 µg. CSE (n = 43): single space, needle-through-needle, 17 gauge Touhy needle and 27 gauge Whitacre needle, intrathecally bupivacaine 2.5 mg and fentanyl 25 µg. Both groups were commenced on a continuous infusion of bupivacaine 0.0625% with fentanyl 2 µg/mL at 12 mL/hr within 15 min of administration of the spinal or epidural dose.
Outcomes	Maternal: VAS (0 to 10) pain scores at 10 and 30 minutes post procedure and the number with VAS > 3 at 10 minutes; hypotension, pruritus, number requiring caesarean section. Maternal satisfaction with analgesia recorded. Total failures of primary technique were also documented. No neonatal outcomes.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stated, "using computer generated randomisation table".
Allocation concealment (selection bias)	Low risk	Opaque envelopes were used for allocation.
Blinding (performance bias and detection bias) All outcomes	Low risk	The subject and the investigator were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar numbers were not analysed from both groups - a total of 16 of 100.
Selective reporting (reporting bias)	Low risk	The primary and secondary outcomes are available.
Other bias	Low risk	No other bias evident.

Hepner 2000

Methods	Randomisation: method not stated "randomised to either technique". Follow-up request: "1. randomisation: random-number table, 2. allocation concealment: sequentially-numbered, sealed, opaque envelopes, 3. blinding: the resident performing the technique was aware of the group assignment but the staff evaluating the outcome was not". Blinding: mother and outcome assessor blinded. Criteria for rescue analgesia: inadequate analgesia at 20 min treated with 13 mL bupivacaine 0.0625% + fentanyl 2 µg/mL + 0.05 mL sodium bicarbonate 8.4% + epinephrine 1:200,000. Data from all participants analysed as no loss from study.
Participants	Inclusions: "healthy term parturients". Exclusions: pregnancy-induced hypertension, diabetes, preterm labour, bleeding problems, scoliosis, cervical dilatation > 5 cm, previous IV opioid. No. lost to follow-up: 0.
Interventions	Epidural (n = 24): 16 mL bupivacaine 0.0625% + fentanyl 2 µg/mL + 0.05 mL NaHCO3 8.4% + epinephrine 1:200,000 (BFSE). At request for additional analgesia further bolus 13 mL and infusion started of bupivacaine 0.0625% + fentanyl 2 µg/mL + epinephrine 1:400,000 at 10 mL/hr. CSE (n = 26): single space, needle-through-needle, sitting. IT LA bupivacaine 2.5 mg + fentanyl 25 µg. On request for additional analgesia 13 mL BFSE (see above) and infusion commenced at 10 mL/hr as above.
Outcomes	Maternal blood pressure, heart rate and haemoglobin saturation, and fetal heart rate and uterine activity monitored throughout labour. VAS pain scores. Parturient satisfaction at delivery and day 1 postpartum. Motor block at 15 and 30 min. Times: infiltration - catheter taping - initial analgesia - request for additional analgesia. Need for supplemental analgesia, treatment of hypotension, pruritus, nausea/vomiting. Hypotension defined as reduction in systolic blood pressure to < 100 mmHg or reduction of > 30% from baseline. Fetal heart rate changes. Neonatal Apgar scores, umbilical arterial and venous pH.
Notes	USA.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random number table was used.
Allocation concealment (selection bias)	Low risk	Used sequentially numbered, sealed, opaque envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	"Another anaesthesiologist, blinded to the technique, was in charge of collecting the data".
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 in each group delivered before initial block wore off and not included in duration analysis.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes are reported.
Other bias	Low risk	No other bias evident.

Kartawiadi 1996

Methods	Randomisation: method not stated "63 ASA class 1-3 parturients...randomly assigned...". Blinding: outcome assessor blinded to allocation. Follow-up request 2006: "randomisation was done with randomisation tables and the sequence of allocation was put in separate numbered envelopes. After the procedure these were resealed and kept by the third author until the end of the study". Criteria for rescue analgesia: not stated. No loss of participants from the study so all included in statistical analysis. NB 13 delivered before requesting additional analgesia and so were not included in statistics for duration of analgesia.
Participants	Inclusions: 63 ASA 1-3, singleton, vertex at 36-41 weeks' gestation. In active labour with cervical dilatation < 5 cm at time of epidural request. Exclusions: history of hypertension or pre-eclampsia. No. lost to follow-up: 13 for duration data, 0 for all other parameters.
Interventions	Epidural (n = 31): initial bolus 10 mL bupivacaine 0.125% + sufentanil 10 µg + epinephrine 12.5 µg. On request for additional analgesia 10 mL boluses of same were delivered down the catheter. CSE (n = 32): single space, needle-through-needle, lateral. IT injection bupivacaine 1.0 mg + sufentanil 5 µg + epinephrine 25 µg. Immediate epidural bolus 10 mL saline given. On request for additional analgesia, same 10 mL bolus given as for the epidural group (see above).
Outcomes	Maternal blood pressure and ECG monitoring. VAS (0 to 10) pain scores assessed. Time to VAS < 2.5 or < 50% baseline taken as onset. Total dose of local anaesthetic required and adverse effects. Sensory and motor block assessed post injection. Maternal satisfaction with analgesia recorded. Neonatal assessment by Apgar scores at 1 and 5 min.
Notes	Belgium.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used randomisation tables.
Allocation concealment (selection bias)	Low risk	Used separate sealed numbered envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	The investigating anaesthesiologist was different to the one performing the block.
Incomplete outcome data (attrition bias) All outcomes	Low risk	13 (of 63 randomised; 7 in one and 6 in the other group) delivered before requesting additional analgesia and were not included in duration analysis; all others included.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes are reported.
Other bias	Low risk	No other bias evident.

Medina 1994

Methods	Randomisation, allocation concealment, blinding and assessment bias are all unclear.
Participants	Inclusions: 28 women 3 to 5 cm dilatation, primigravid. Exclusions: none stated. No. lost to follow-up: 2, 1 complete failure in each group.
Interventions	Epidural (n = 12): initial bolus 10 mL 0.125% bupivacaine, plus 10 µg sufentanil. CSE: 3.75 mg bupivacaine plus 3 µg sufentanil. Both groups given ED infusion after reappearance of pain: 7 to 10 mL/hour of 0.125% bupivacaine plus 0.5 µg/mL sufentanil.
Outcomes	Maternal: VAS pain scores at 5, 10, 30, 60, 75, 90, 120, 150, 180, 210, 240 minutes. Adverse effects; itch, vomiting, hypotension, high block, bradycardia, reflex sympathetic pain.
Notes	Italy. Poster from ASRA meeting.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients randomly allocated".
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One in each group lost to follow-up (one in each group was excluded for complete failure).
Selective reporting (reporting bias)	Unclear risk	Primary and secondary outcomes were not stated.
Other bias	Low risk	No other bias evident.

Ngamprasertwong 2007

Methods	Randomisation: "a sealed-envelope technique". Blinding: single-blinded: obstetric residents and labour nurses managed the labours according to standardised protocols and were unaware of the anaesthetic administration. Rescue analgesia 10 mL of 0.25% bupivacaine if inadequate analgesia after 20 min of initial analgesia. No losses to follow-up and all were included in statistical analysis.
Participants	Inclusions: 50 women, nulliparous and multiparous, healthy, full term, in labour. Exclusion: twins, pregnancy induced hypertension, placenta praevia, regional contraindication. No. lost to follow-up: 0.

Ngamprasertwong 2007 *(Continued)*

Interventions	Epidural (n = 25): crystalloid preload (quantity not stated). Test dose 3 mL of 0.25% bupivacaine plus bolus of 7 mL of 0.25% bupivacaine. Then infusion of 0.0625% bupivacaine with fentanyl at 12 mL/hr started immediately. CSE (n = 25): crystalloid preload. Single space, needle-through-needle, using Quicke 27 G needle. 25 µg of fentanyl injected intrathecally. Epidural catheter was inserted and 3 mL of 0.25% bupivacaine given as test dose, 0.0625% bupivacaine with fentanyl 2 µg/mL was infused at 12 mL/hr.
Outcomes	Primary: onset of effective analgesia. Secondary: motor blockade, mode of delivery and side effects.
Notes	Quinke needles used (27G). Thailand.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No mention of the actual randomisation method.
Allocation concealment (selection bias)	Low risk	Sealed envelopes were used.
Blinding (performance bias and detection bias) All outcomes	High risk	Labour attendants were unaware but assessors were not.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were reported.
Other bias	Low risk	No other bias evident.

Nickells 2000

Methods	Randomisation: sealed envelopes. Blinding: participant and midwife blinded to allocation. Assessment of motor block and proprioception made by an unblinded anaesthetist. Criteria for rescue analgesia: any participants with persistently painful contractions at 30 min were treated at the discretion of the anaesthetist to ensure adequate analgesia. Unclear if statistical analysis was performed on an intention-to-treat basis.
Participants	Inclusions: 142 women in established labour, gestation at least 36 weeks, singleton, cephalic fetus. Exclusions: pethidine within 4 hours of requesting epidural analgesia. No. lost to follow-up: there were 18 analgesic failures (9 in each group) but were included in analysis for outcomes other than time to effective analgesia.
Interventions	Epidural (n = 73): initial bolus 10 mL bupivacaine 0.125% + fentanyl 50 µg. Further boluses 10 mL bupivacaine 0.1% + fentanyl 2 µg/mL given on request for additional analgesia. CSE (n = 69): single space, needle-through-needle, sitting.

Nickells 2000 *(Continued)*

	IT injection bupivacaine 2.5 mg + fentanyl 25 µg. Additional analgesia provided on request as for the epidural group.
Outcomes	Analgesia onset measured as time to first "comfortable" contraction. Maternal blood pressure every 5 min for 20 min (hypotension defined as decrease in SBP < 100 mgHg). Continuous fetal heart monitoring with fetal bradycardia < 100 bpm noted. At 30 min assessment of motor block and proprioception.
Notes	UK.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Low risk	Used sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	Midwife who assessed the speed of onset and pain was blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	There were 18 analgesic failures (9 in each group); all other data outcomes complete.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were reported.
Other bias	Unclear risk	Study stopped after 3 months so slightly uneven group sizes.

Parry 1998

Methods	Randomisation: method not stated. "patients....were randomly allocated...". Blinding: assessments made by an anaesthetist blinded to group allocation and treatment. Criteria for rescue analgesia: not mentioned. No participants were lost to follow-up and data from all participants were included in analysis.
Participants	Inclusions: ASA 1 or 2 women at term requesting analgesia in the first stage of labour or elective LSCS under regional. Exclusions: pre-existing neurological impairment or diabetes mellitus. No. lost to follow-up: 0.
Interventions	Epidural (n = 30): all women were preloaded with 500 to 1000 mL crystalloid prior to epidural insertion while sitting. Initial bolus 15 mL bupivacaine 0.1% with fentanyl 2 µg/mL. CSE (n = 30): fluid preloading as for the epidural group. Single space, needle-through-needle, sitting. Intrathecal injection of bupivacaine 2.5 mg + fentanyl 25 µg in a total volume 2.5 mL. Epidural catheter placed for subsequent analgesia (after study period).

Parry 1998 *(Continued)*

Outcomes	'Routine' measurement of maternal and fetal heart rates and maternal blood pressure were performed in all groups. (Hypotension was defined as a decrease in systolic blood pressure to < 100 mmHg or of > 20% from baseline.) Assessment of sensory and motor block and dorsal column modalities was performed 20 to 30 min after initial injection. Normal delivery rate was recorded in each group. Assessment was made for spinal headache and neurological complications. LSCS group was analysed as a separate subgroup, enabling comparison of CSE and ED subgroups. Neonatal assessment was by Apgar scores at 5 min.
Notes	UK.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated: "patients were randomly allocated".
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Low risk	Outcome assessor blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes reported.
Other bias	Low risk	No other bias evident.

Patel 2003a

Methods	Randomisation: method not stated, "...prospective, double-blind study and randomised...". Blinding: stated to be "double-blind". Criteria for rescue: not stated.
Participants	Inclusions: 115 healthy women, 2 to 6 cm dilatation requesting regional. Exclusions: not stated. 2 lost to CTG analysis.
Interventions	Epidural (n = 53): all women received initial bolus 20 mL bupivacaine 0.1% + fentanyl 40 µg. CSE: all women received intrathecal bupivacaine 2.5 mg + fentanyl 5 µg. Subsequent management: not stated.
Outcomes	Maternal: mode of delivery (no results stated). Fetal: umbilical artery pH and base excess; Apgars at 1 and 5 min; CTG abnormalities.
Notes	UK. Abstract only.

Risk of bias

Patel 2003a *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated, "double blind study and randomised", no other information.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated to be double-blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 lost to CTG analysis.
Selective reporting (reporting bias)	Unclear risk	Reporting of detail of outcomes is unclear.
Other bias	Low risk	No other bias evident.

Price 1998

Methods	Randomisation: sealed and numbered envelopes. Blinding: mother and outcome assessments. Criteria for rescue: additional analgesia delivered as 10 mL bupivacaine 0.25%. Statistics not performed on intention-to-treat basis.
Participants	Inclusions: 100 women in labour cervix < 6 cm dilated. Exclusions: pethidine < 3 hr before epidural request, pregnancy-induced hypertension. No. lost to follow-up = 7.
Interventions	Epidural (n = 48): 15 mL bupivacaine 0.1% + fentanyl 75 µg bolus then PCEA 10 mL bupivacaine 0.1% + fentanyl 2 µg/mL with 30 min lockout. CSE (n = 45): single space, needle-through-needle, lateral position, IT LA: 2.5 mg bupivacaine + 25 µg fentanyl then PCEA 15 mL 0.1% bupivacaine + fentanyl 2 µg/mL, 30 min.
Outcomes	Pain scores and motor block at 0, 30, 60, 180 min. Maternal confidence in walking. Time to first epidural top-up and need for additional analgesia. Adverse effects: hypotension (no definition given), pruritus, need for urinary catheterisation. Maternal satisfaction postpartum #1.
Notes	UK.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated.

Price 1998 *(Continued)*

Allocation concealment (selection bias)	Low risk	Used "sealed, numbered envelopes".
Blinding (performance bias and detection bias) All outcomes	Low risk	The patient and the investigator were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was no loss to follow-up and drop out was similar in both groups (7 in total).
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes are reported.
Other bias	Low risk	No other bias evident.

Roux 1999

Methods	Randomisation: by drawing lots. Blinding: states "double blinded for all assessments not involving problems at performance of block". Criteria for rescue: not mentioned. Data not analysed on an intention-to-treat basis. (NB all participants' data included for complications on insertion.)
Participants	Inclusions: 80 women between 37 and 42 weeks' gestation, in active labour with cervical dilatation not more than 3 cm. All with singleton, cephalic fetus. Exclusions: any contraindication to CSE or epidural. No. lost to follow-up: 1 participant not included as failure to site CSE successfully. Data used only in analysis regarding complications at insertion.
Interventions	Epidural (n = 40): all given 500 mL crystalloid prior to insertion of epidural in the sitting position. Initial bolus given down the catheter of 6 to 8 mL bupivacaine 0.25% with sufentanil 20 µg. Top-up boluses were delivered on request of 6 to 8 mL bupivacaine 0.25%. CSE (n = 39): sitting, single space, needle-through-needle (18 G, 29 G). Initial bolus IT sufentanil 10 µg in total volume 3 mL with isotonic saline. Top-up bolus given down epidural catheter when requested, as 6 to 8 mL bupivacaine 0.25% in increments of 2 to 3 mL.
Outcomes	Pain scores assessed on VAS 0 to 10 at injection, then 5, 10, 15, 20, 30 min and thereafter every 30 min. Complete analgesia was defined as a VAS score = 0. Time from initial bolus to first top-up request was noted as bolus duration. The incidence of complications at time of insertion was recorded. Maternal systolic blood pressure and oxygen saturation were recorded. (Hypotension was defined as SBP of 90 mmHg or lower and was corrected with IV fluid bolus.) Continuous cardiotocograph recording was taken throughout the labour. The duration of first and second stages of labour were noted and the mode of delivery. The occurrence of itch, nausea, vomiting and sedation was noted at the same times as VAS pain. Incidence of headache was assessed on the third postpartum day. Neonatal assessment by Apgar scores at 1 and 5 min.
Notes	France (translated).
Risk of bias	

Roux 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Allocation by drawing lots.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded or single-blinded if problem in performing the block.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant not included as failure to site CSE successfully. Data used only in analysis regarding complications at insertion.
Selective reporting (reporting bias)	Low risk	The primary and secondary outcomes were reported.
Other bias	Low risk	No other bias evident.

Sezer 2007

Methods	Randomisation: "prospectively randomized" using closed envelope allocation into 2 groups. Blinding: not stated.
Participants	Inclusions: 40 nulliparous women ASA 1 at term with singleton, cephalic fetus, in spontaneous labour with cervical dilatation less than 6 cm. Exclusions: none stated. No. lost to follow-up: 0.
Interventions	Epidural (n = 20): test dose of 3 mL of lignocaine 1.5% plus adrenaline, then 7 mL bolus of 0.1% bupivacaine plus fentanyl 50 µg. CSE (n = 20): intrathecal dose of fentanyl 20 µg in 1.5 mL of saline plus epidural test dose of 3 mL of 1.5% lignocaine plus adrenaline after 45 minutes. Both groups were maintained with PCEA of 5 mL bolus of bupivacaine 0.1% plus fentanyl 2 µg/mL on demand with lockout of 10 minutes and maximum of 15 mL in 1 hour.
Outcomes	Maternal: time from injection to VAS (0 to 10) pain score of less than or equal to 3. Maternal satisfaction with analgesia and number with pruritus and nausea and vomiting; mode of delivery. Neonatal outcomes: mean Apgar score at 5 minutes.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Prospectively randomized".

Sezer 2007 *(Continued)*

Allocation concealment (selection bias)	Low risk	"Closed envelope allocation".
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No mention of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There is no loss to follow-up.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes are reported.
Other bias	Low risk	No other bias evident.

Skupski 2009

Methods	Randomisation: used web-based randomisation software for 200 women divided into 2 blocks of 100 without stratification. Allocation concealment using opaque, sequentially numbered, sealed envelopes kept off-site. Blinding: no blinding of subjects or investigators. Statistical analysis was performed on an intention-to-treat basis.
Participants	Inclusions: 127 women, 18 to 50 years old, term, cephalic, singleton, BMI < 40, with or without induction. Exclusions: morbid obesity, non reassuring fetal heart rate pattern, planned caesarean, hypertension for any reason, significant obstetric medical condition. No. lost to follow-up: 0.
Interventions	All women received 1 litre of intravenous fluid 30 to 40 min before block. Epidural (n = 63): 15 mL of bupivacaine 0.0625% plus fentanyl 2 µg/mL. CSE (n = 64): 1 mL of 0.25% bupivacaine plus fentanyl 20 µg intrathecally. Both groups received immediate infusion of bupivacaine 0.0625% plus fentanyl 2 µg/mL at 12 mL/hr.
Outcomes	Primary outcome was prolonged deceleration of fetal heart rate and secondary outcomes of fetal heart rate changes (which are not outcomes for this review). Other maternal: VAS pain scores (1 to 10) every 2 minutes for 10 minutes after block placement, then every 5 minutes for 20 minutes, then every 10 minutes for 30 minutes; hypotension, pruritus, nausea and vomiting, back pain and urinary retention; number requiring caesarean section. No neonatal outcomes.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Skupski 2009 *(Continued)*

Random sequence generation (selection bias)	Low risk	Used website random number generator.
Allocation concealment (selection bias)	Low risk	Used sequentially numbered, sealed, opaque envelopes unavailable to those doing recruitment.
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding of the type of neuraxial block was not performed for either subjects or investigators.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were reported.
Other bias	Unclear risk	Study is underpowered to detect the difference in fetal heart rate changes.

Thomas 2005

Methods	Randomisation: computerised random-number generator. Blinding: outcome assessments blinded. Criteria for rescue: top-ups of 5 mL 0.25% bupivacaine to 15 mL, then ED catheter withdrawn 1 to 2 cm increments and then replaced.
Participants	Inclusions: 251 healthy, in labour, < 6 cm dilatation, uncomplicated pregnancies, requesting analgesia. Exclusions: not stated. Number lost to follow-up: 21, 20 from CSE group, 1 from ED group. A subgroup was generated for analysis from 18 CSE participants where no CSF obtained.
Interventions	Epidural (n = 124): all given initial 10 mL divided dose 2% plain lignocaine via ED catheter, then immediately commenced on PCEA. CSE (n = 127): dural puncture with 27 G Whitacre with nil intrathecal drugs; 10 mL lignocaine as per ED group, followed immediately by PCEA as per ED group. PCEA: bupivacaine 0.11% + fentanyl 2 µg/mL at 10 mL per hour with 5 mL bolus and 10 minute lock-out.
Outcomes	Maternal: additional interventions, known dural tap, hypotension, labour augmentation, mode of delivery.
Notes	USA. Institutional funding.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stated, "computerized random number generator".
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Low risk	Outcome assessor and patient were blinded; unblinded operator performing the procedure recorded the initial parameters.

Thomas 2005 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	20 women were excluded (2 because of inadvertent dural puncture and 18 because no CSF return from spinal needle). These 18 women were analysed in another subgroup for separate data analysis and the data are available.
Selective reporting (reporting bias)	Low risk	The primary and secondary outcomes were reported.
Other bias	Low risk	No other bias evident.

Tsen 1999

Methods	Randomisation: sealed and numbered envelopes. Blinding: both participant and outcome assessor blinded. Rescue analgesia as either 6 mL bupivacaine 0.25% or fentanyl 50 µg in 10 mL saline. No losses to follow-up and all were included in statistical analysis.
Participants	Inclusions: 100 women, nulliparous, ASA 1 or 2, at term, in spontaneous labour with singleton, cephalic fetus. Cervical dilatation < 5 cm. Exclusion: cervical dilatation > 5 cm. No. lost to follow-up: 0.
Interventions	Epidural (n = 50): 1000 mL crystalloid preload. "Dummy" spinal (no dural puncture) before placement of catheter. Bolus 12 mL bupivacaine 0.25% then infusion bupivacaine 0.125% + fentanyl 2 µg/mL at 10 mL/hr. CSE (n = 50): 1000 mL crystalloid preload. Single space, needle-through-needle, lateral position. IT injection bupivacaine 2.5 mg + sufentanil 10 µg. When requested, epidural bolus given as 6 mL bupivacaine 0.25% then infusion of bupivacaine 0.125% + fentanyl 2 µg/mL at 10 mL/hr.
Outcomes	VAS pain scores, sensory level (pin prick) and motor block assessed at onset of analgesia, 60 min and then at 90 min intervals. Incidence of hypotension (no definition), nausea and pruritus noted. Data on labour progress including cervical dilatation, use and maximum dose of oxytocin and mode of delivery. Neonatal assessment of weight, gender and Apgar scores.
Notes	USA. Funded solely from institutional and departmental sources.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated, "sequentially numbered, opaque, shuffled envelopes", but randomisation method not stated.
Allocation concealment (selection bias)	Low risk	Stated, "sequentially numbered, opaque, shuffled envelopes".
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded, in epidural group the spinal needle placed without puncturing the dura and "dosed" with an empty syringe to blind any observers to the technique being used.

Tsen 1999 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	There is no loss to follow-up.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were reported.
Other bias	Low risk	No other bias evident.

Van de Velde 1999

Methods	Randomisation: method not stated "110 healthy women....participated in this prospective and randomised clinical trial". Blinding: both mother and outcome assessor were blinded. Criteria for rescue analgesia: if pain relief inadequate (VAS > 25 mm) PCEA lockout time reduced from 15 min to 10 min and additional epidural boluses given manually as needed. No losses to follow-up and data from all participants were used in statistical analysis.
Participants	Inclusions: 110 women ASA 1 or 2, > 36 weeks with singleton, vertex fetus. Cervical dilatation 2 to 7 cm. No other sedative or analgesic drugs given. Exclusions: VAS < 60 mm at analgesia request. Substance-abusing parturients were excluded. No. lost to follow-up: 0.
Interventions	Epidural (n = 55): 15 mL/kg crystalloid preload over 15 min. Bolus 10 mL bupivacaine 0.125% + sufentanil 0.75 µg/mL + epinephrine 1.25 µg/mL. Then PCEA connected at first request for additional analgesia. PCEA bolus 4 mL of same solution with lockout time 15 min. CSE (n = 55): 15 mL/kg crystalloid preload given over 15 min. Single space, needle-through-needle, lateral position. IT injection bupivacaine 2.5 mg + sufentanil 1.5 µg + epinephrine 2.5 µg. Then immediately 10 mL saline administered down epidural catheter. On request for additional analgesia, PCEA connected as for the epidural group.
Outcomes	Maternal heart rate, blood pressure and VAS for pain recorded. Onset time (VAS < 25 mm or reduced by > 50% from baseline). Incidence of side effects noted. Hypotension defined as reduction of mean arterial pressure of > 20%. Sensory and motor block assessed. Mode of delivery and fetal heart rate changes recorded. Maternal satisfaction noted. Neonatal assessment by Apgar scores at 1 and 5 min and umbilical artery pH.
Notes	Belgium.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.

Van de Velde 1999 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Both women and outcome assessor were blinded (second anaesthetist entered the room after the completion of the puncture and was unaware of group assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were reported.
Other bias	Low risk	No other bias evident.

Vernis 2004

Methods	Randomisation: method not stated, "a prospective double-blind randomised study" and "parturients were randomly included into 1 of 2 study groups, in a blind fashion." Blinding: midwife performing analgesia assessments and women both blinded.
Participants	Inclusions: 113 healthy women 18 to 40 years, 3 to 6 cm dilatation in active labour, > 37 weeks' gestation, singleton, vertex. Exclusions: contraindications to regional, pre-eclampsia, psychological, IV opioid administration, labour 'unduly complicated', after-hours. No. lost to follow-up: 1 from ED group.
Interventions	Epidural (n = 60): 0.125% bupivacaine plus sufentanil 7.5 µg, with adrenaline, volume based on height, 4 mL initially as test dose. 5 mL 0.125% bupivacaine given if analgesia inadequate at 15 min. PCEA commenced immediately. CSE (n = 54): needle-through-needle with 2.5 mg bupivacaine plus 5 µg sufentanil. Test dose and initial ED followed by PCEA after return of pain. PCEA: bupivacaine 0.125% plus sufentanil 0.25 µg/mL; 4 mL bolus with 10 minute lock-out.
Outcomes	Maternal: median time from injection to VAS (0 to 100) less than or equal to 30, satisfaction, dural tap, PDPH and blood patch requirement, major complications, mode of delivery.
Notes	France.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Low risk	Stated, "parturients were randomly included into one of the two study groups in a blind fashion."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated, "prospective double blind study," no other information.

Vernis 2004 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 patient excluded from epidural group, no loss to follow-up.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were reported.
Other bias	Unclear risk	The study was stopped early (after 113 women rather than 128 that were originally intended because of presumed incidence of adverse effects from CSE).

Zeidan 2004

Methods	Randomisation: random number table; "randomised in a double blinded manner". Blinding: not stated.
Participants	Inclusions: 104 women, ASA 1 to 2, requesting epidural, singleton, nulliparous, 36 to 41 weeks' gestation, < 4 cm dilatation. Exclusions: multiple pregnancies, estimated fetal weight < 2500 gm, ED contraindicated, suspected fetal abnormalities, IV analgesics within the previous hour. No. lost to follow-up: 3 in CSE group due to protocol violation; 1 in ED group withdrew.
Interventions	Epidural (n = 51): 1000 mL Ringer's preload, left lateral; 10 to 20 mL 0.0625% (6.25 to 12.5 mg) bupivacaine plus fentanyl 15 to 30 µg. CSE (n = 50): preload as above: 1.25 mg bupivacaine plus fentanyl 25 µg. Subsequent management same in both groups: ED infusion commenced subsequently at patient request of bupivacaine 0.0625% plus fentanyl 1.5 µg/mL, initial 3 mL bolus followed by 6 to 10 mL/hr.
Outcomes	Maternal: VAS pain score at 0, 5, 10, 15 and 30 minutes; additional analgesic interventions required, satisfaction, mobilisation, known dural tap, PDPH and blood patching; adverse events needing treatment - hypotension, respiratory depression, nausea and vomiting, pruritus; major complications, mode of delivery. Fetal/neonatal: number admitted to the neonatal unit.
Notes	Saudi Arabia. Table 4 not in published paper.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stated, "using random number table".
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated, "double blinded", no other information.

Zeidan 2004 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	2 women from CSE group were excluded because of protocol deviation, 1 patient from the epidural group chose to discontinue her participation. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	The primary and secondary outcomes were reported.
Other bias	Low risk	No other bias evident.

ASA: American Society of Anesthesiologists
BFSE: mixture of bupivacaine, fentanyl, sodium bicarbonate and epinephrine
BMI: body mass index
bpm: beats per minute
cm: centimetre
CSE: combined spinal-epidural
CSF: cerebrospinal fluid
CTG: cardiotography
ED: epidural
hr: hour
IJOA: International Journal of Anesthesiology
IT: intrathecal
IV: intravenous
LA: local anaesthetic
LSCS: lower segment caesarean section
µg: microgram
mg: milligram
min: minute
mL: millilitre
NaHCO3: sodium bicarbonate
no.: number
PCEA: patient-controlled epidural analgesia
PDPH: post dural puncture headache
SBP: systolic blood pressure
SpO2: saturation of oxygen
VAS: visual analogue score

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

Study	Reason for exclusion
Backus 1996	There were treatment differences within the groups depending on the degree of cervical dilatation more or less than 5 cm.
Camann 1992	All 24 women in this study had an intrathecal, an epidural and an intravenous injection. Only 1 of the 3 injections contained the active drug, namely sufentanil 10 µg, with the other 2 injections containing saline. The route of sufentanil delivery depended on the group allocation. As all women received a CSE technique, it was felt this did not constitute a direct comparison of CSE with epidural and, therefore, this study was excluded from the review.
Camann 1998	All 100 women entered into the study received an intrathecal injection. In 6 of the 9 groups the intrathecal injection contained sufentanil 2, 5 or 10 µg. The remaining 3 groups received an injection of saline 2 mL. All 100 women also received an epidural bolus containing either bupivacaine or saline. Although the inclusion of groups receiving only saline in the intrathecal injection allowed for complete double-blinding, it led to all women technically receiving a CSE. As a result it was decided that this was not therefore a comparison of CSE with epidural analgesia and the study was excluded.

Study	Reason for exclusion
Cascio 1996	This study looked only at maternal catecholamine levels and did not address any of our outcomes.
Collis 1995	Although this study was described as randomised and blinded, the women receiving CSE analgesia were assessed for motor weakness and in the absence of motor block were allowed to walk if they wished. Women in the epidural group were not assessed in this way and were not encouraged to mobilise.
Collis 1999a	All women received CSE analgesia.
Collis 1999b	All women received CSE analgesia.
Cooper 2010	Although this is one of the COMET cluster of reports, this study specifically deals with comparisons involving low-dose epidurals with traditional epidurals and hence is not relevant to this review.
D'Angelo 1994	All women in the 'epidural' group received an intrathecal injection of saline 2 mL enabling both mother and operator to be blinded to treatment group allocation. However, this means that all women in the trial technically received a CSE and so this study was excluded from analysis.
Dresner 1999	All data relating to motor block and analgesic efficacy were collected retrospectively and took the form of subjective maternal assessments on the first day postpartum. Intrapartum assessments were made by midwives not blinded to treatment allocation. Assessments by the women were potentially biased as subjects were not blinded either. In addition, 50 women withdrawn from the study for a variety of reasons were excluded from all statistical analysis.
Finegold 2003	Abstract only. Methodological quality unclear in relation to randomisation, allocation concealment, blinding and attrition. No data presented against stated review outcomes.
Fogel 1999	Excluded as treatment not the same for all participants within each group. Boluses of drugs given differed according cervical dilatation.
Groves 1995	Only addressed the rate of progress of labour which was not one of outcomes. No other information presented is able to be analysed against our outcomes.
Harsten 1997	All women received a CSE.
Kassapidis 1997	Study looked only at umbilical cord blood flow which was not one of outcomes.
Leighton 1996	Women were not randomised for group allocation. CSE or epidural analgesia was provided on the basis of patient request.
Nageotte 1997	Like the Collis paper, here women who received CSE analgesia were treated differently with regard to mobilisation. There were 2 CSE groups in this study, 1 where mobilisation was encouraged and 1 where walking was actively discouraged.
Nielson 1996	Women were not randomised with regard to group allocation. "The type of anaesthetic technique used was based on patient request, anesthesiologist's preference and obstetrician's choice".
Norris 1994	The women in this study were not randomised with regard to the type of analgesia they received. Allocation was based on patient request.
Norris 2001	This is stated to be "quasi-randomised", with randomisation actually being in relation to day of week and no allocation concealment. Treatments varied within groups at undefined operator discretion.
Pan 1996	A very small study with insufficient detail regarding randomisation, allocation concealment, blinding and outcome measurement for inclusion.

Study	Reason for exclusion
Patel 2003b	This is a dose-ranging study investigating minimum local analgesic requirements for epidural bupivacaine after CSE or epidural, which was not in our stated outcomes for inclusion.
Pham 1996	The 40 women entered into the study were randomly allocated to 1 of 2 groups. Those in the sufentanil group received intrathecal sufentanil 10 µg followed by an epidural bolus of saline. The women in the bupivacaine group received an intrathecal injection of saline 2 mL followed by an epidural bolus 12 mL bupivacaine 0.25%. As all women in the study had a CSE technique performed, albeit with saline delivered as one of the injections in each case, this study was excluded from data analysis.
Pinto 2000	Randomisation, allocation concealment, blinding and attrition are all unclear. The study is a comparison of 2 CSE techniques with an epidural control that is not valid for inclusion.
Rosenfeld 1998	All women received a CSE.
Stocche 2001	Primary outcomes were not stated outcomes for this review.
Van de Velde 2004	All women received a dural puncture; the epidural control included 2 mL intrathecal saline.

CSE: combined spinal-epidural

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

Arya 2007

Methods	
Participants	
Interventions	
Outcomes	
Notes	Abstract only. Information regarding the following is inadequate to determine classification: randomisation method, allocation concealment, the reason for the large number excluded; missing data for Apgar scores, satisfaction and the number that actually mobilised.

Celik 2005

Methods	
Participants	
Interventions	
Outcomes	
Notes	Poster only. Information regarding the following is inadequate to determine classification: randomisation method, allocation concealment, the number originally allocated, the number lost to follow-up, the reason for the large number excluded, missing data for Apgar scores, satisfaction and the actual numbers in each group for mode of delivery.

de Souza 2009

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting clarification of numerous methodological matters.

Gupta 2002

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting clarification of numerous methodological matters.

Kayacan 2006

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting clarification of numerous methodological matters.

Lee 2007

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting clarification of numerous methodological matters.

Lee 2007a

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting clarification of numerous methodological matters.

Lian 2008

Methods	
Participants	
Interventions	
Outcomes	
Notes	Abstract only. There is no mention of Ethics approval or consent. The randomisation and allocation processes are not defined. There appears to have been a control group in which no analgesia was offered. There are no usable data presented. Further information may enable inclusion.

Mantha 2007

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting clarification of numerous methodological matters.

Nakamura 2009

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Olmez 2003

Methods	
Participants	
Interventions	
Outcomes	
Notes	Turkish; requires translation. Abstract is deficient in ethics approval and informed consent; there is no detail regarding the processes of randomisation or allocation concealment, the inclusion and exclusion criteria and the data pertinent to this review.

Pascual 2011

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Pascual-Ramirez 2010

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Pascual-Ramirez 2011

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Patel 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Salem 2007

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting clarification of numerous methodological matters.

Sweed 2011

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Wilson 2011

Methods	
Participants	
Interventions	
Outcomes	
Notes	

DATA AND ANALYSES

Comparison 1. Combined spinal-epidural versus traditional epidural

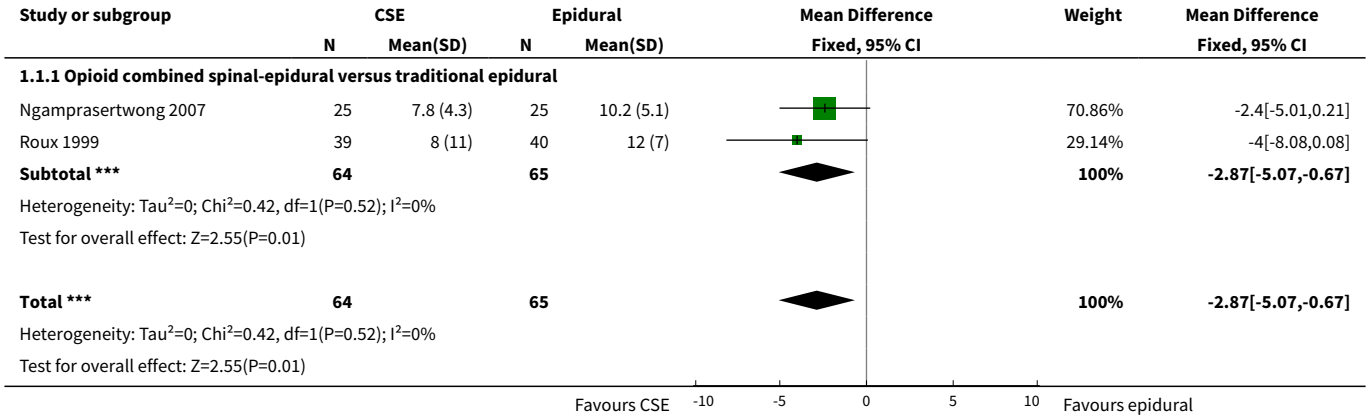
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time from first injection to effective analgesia (minutes)	2	129	Mean Difference (IV, Fixed, 95% CI)	-2.87 [-5.07, -0.67]
1.1 Opioid combined spinal-epidural versus traditional epidural	2	129	Mean Difference (IV, Fixed, 95% CI)	-2.87 [-5.07, -0.67]
2 Number of women with effective analgesia 10 minutes after first injection	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Need for rescue analgesia	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.14, 0.70]
3.1 Combined spinal-epidural versus traditional epidural	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.14, 0.70]
4 Number of women satisfied with analgesia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Number of women who mobilise	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.91, 1.10]
6 Post dural puncture headache	3	188	Risk Ratio (M-H, Fixed, 95% CI)	3.78 [0.16, 89.09]
6.1 Opioid combined spinal-epidural versus traditional epidural	3	188	Risk Ratio (M-H, Fixed, 95% CI)	3.78 [0.16, 89.09]
7 Known dural tap	3	842	Risk Ratio (M-H, Random, 95% CI)	2.47 [0.36, 17.12]
7.1 Combined spinal-epidural versus traditional epidural	1	704	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.20]
7.2 Opioid combined spinal-epidural versus traditional epidural	2	138	Risk Ratio (M-H, Random, 95% CI)	6.14 [0.73, 51.83]
8 Number of women requiring blood patch for post dural puncture headache	1	79	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.1 Opioid combined spinal-epidural versus traditional epidural	1	79	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Pruritus	6	370	Risk Ratio (M-H, Random, 95% CI)	7.34 [0.14, 375.82]
9.1 Combined spinal-epidural versus traditional epidural	2	142	Risk Ratio (M-H, Random, 95% CI)	5.5 [1.38, 21.86]
9.2 Opioid combined spinal-epidural versus traditional epidural	4	228	Risk Ratio (M-H, Random, 95% CI)	8.35 [0.02, 3322.35]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Urinary retention	1	704	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.79, 0.95]
10.1 Combined spinal-epidural versus traditional epidural	1	704	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.79, 0.95]
11 Nausea/vomiting	6	370	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.55, 3.95]
11.1 Combined spinal-epidural versus traditional epidural	2	142	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.03, 2.05]
11.2 Opioid combined spinal-epidural versus traditional epidural	4	228	Risk Ratio (M-H, Random, 95% CI)	1.97 [0.77, 5.05]
12 Hypotension	6	1002	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.64, 1.01]
12.1 Combined spinal-epidural versus traditional epidural	3	833	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.65, 1.03]
12.2 Opioid combined spinal-epidural versus traditional epidural	3	169	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.12, 2.53]
13 Respiratory depression	3	178	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.1 Opioid combined spinal-epidural versus traditional epidural	3	178	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Headache (any)	1	79	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.07, 15.83]
14.1 Opioid combined spinal-epidural versus traditional epidural	1	79	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.07, 15.83]
15 Sedation	1	79	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.46, 2.31]
15.1 Opioid combined spinal-epidural versus traditional epidural	1	79	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.46, 2.31]
16 Labour augmentation required	3	883	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.84, 1.09]
16.1 Combined spinal-epidural versus traditional epidural	2	804	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.80, 1.11]
16.2 Opioid combined spinal-epidural versus traditional epidural	1	79	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.95, 1.05]
17 Augmentation after analgesia	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.24, 1.06]

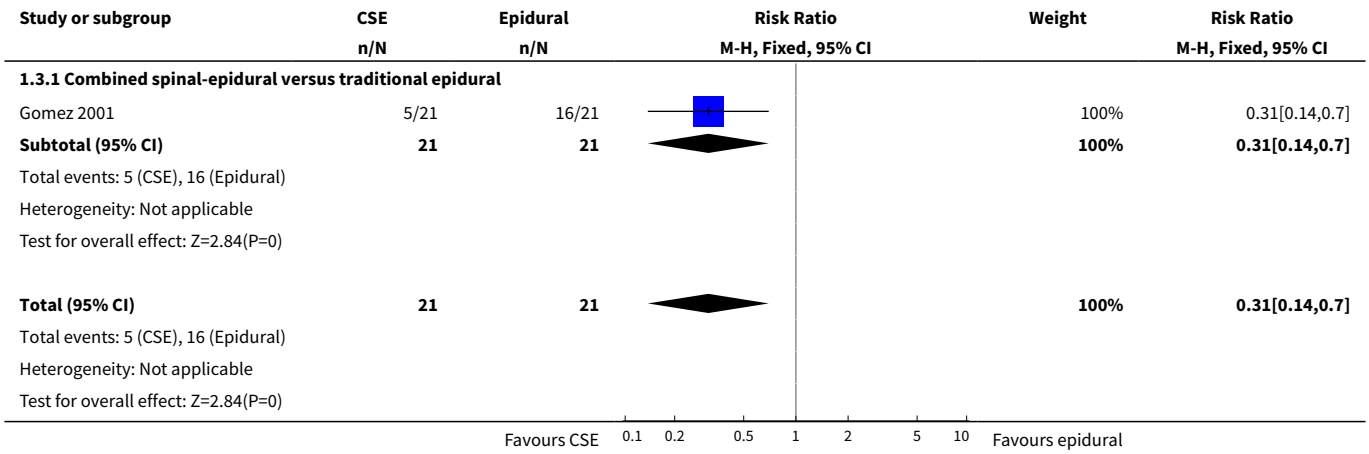
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 Combined spinal-epidural versus traditional epidural	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.24, 1.06]
18 Normal delivery	7	1074	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.90, 1.18]
18.1 Combined spinal-epidural versus traditional epidural	3	846	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.98, 1.32]
18.2 Opioid combined spinal-epidural versus traditional epidural	4	228	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.76, 1.10]
19 Instrumental delivery	6	1015	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.67, 0.97]
19.1 Combined spinal-epidural versus traditional epidural	3	846	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.65, 0.98]
19.2 Opioid combined spinal-epidural versus traditional epidural	3	169	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.52, 1.37]
20 Caesarean section	6	1015	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.85, 1.32]
20.1 Combined spinal-epidural versus traditional epidural	3	846	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.82, 1.28]
20.2 Opioid combined spinal-epidural versus traditional epidural	3	169	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.65, 3.87]
21 Umbilical arterial pH	1	55	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.06, 0.02]
21.1 Opioid combined spinal-epidural versus traditional epidural	1	55	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.06, 0.02]
22 Umbilical venous pH	1	55	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.06, -0.00]
22.1 Opioid combined spinal-epidural versus traditional epidural	1	55	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.06, -0.00]
23 Umbilical cord pH	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
24 Apgar score < 7 at 5 minutes	3	842	Risk Ratio (M-H, Fixed, 95% CI)	2.10 [0.63, 6.97]
24.1 Opioid combined spinal-epidural versus traditional epidural	3	842	Risk Ratio (M-H, Fixed, 95% CI)	2.10 [0.63, 6.97]
25 Apgar score < 8 at 5 minutes	1	704	Risk Ratio (M-H, Fixed, 95% CI)	2.35 [0.61, 9.00]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25.1 Combined spinal-epidural versus traditional epidural	1	704	Risk Ratio (M-H, Fixed, 95% CI)	2.35 [0.61, 9.00]
26 Number admitted to neonatal unit	1	704	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.29, 1.37]
26.1 Combined spinal-epidural versus traditional epidural	1	704	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.29, 1.37]

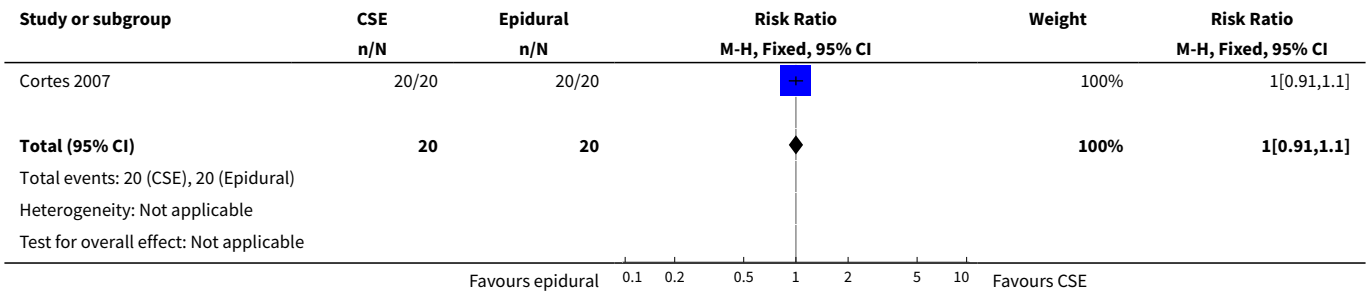
Analysis 1.1. Comparison 1 Combined spinal-epidural versus traditional epidural, Outcome 1 Time from first injection to effective analgesia (minutes).



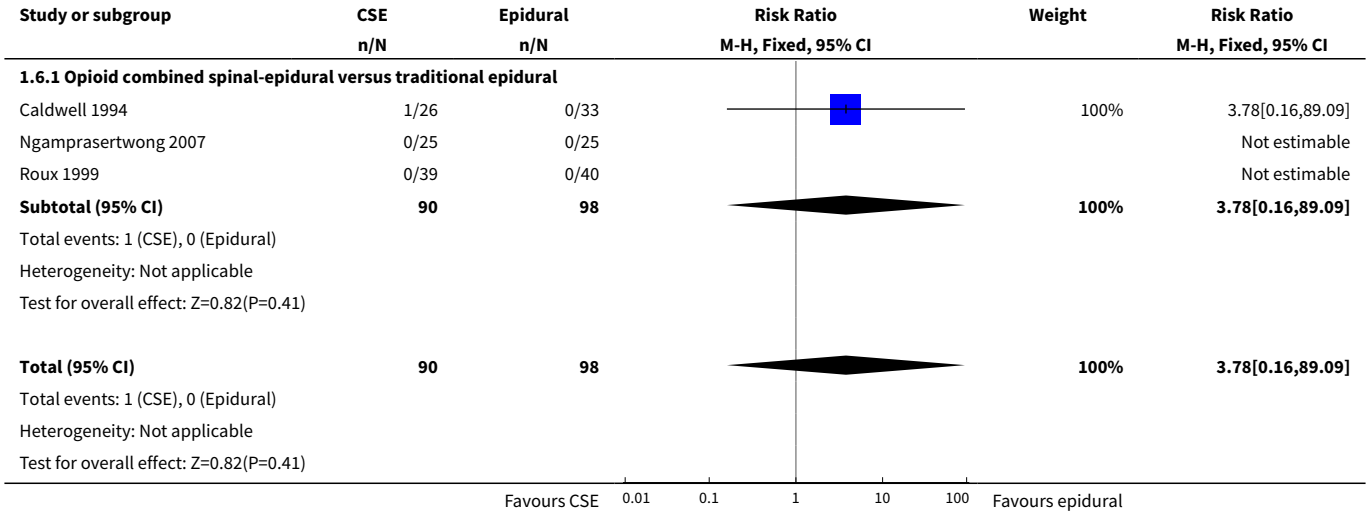
Analysis 1.3. Comparison 1 Combined spinal-epidural versus traditional epidural, Outcome 3 Need for rescue analgesia.



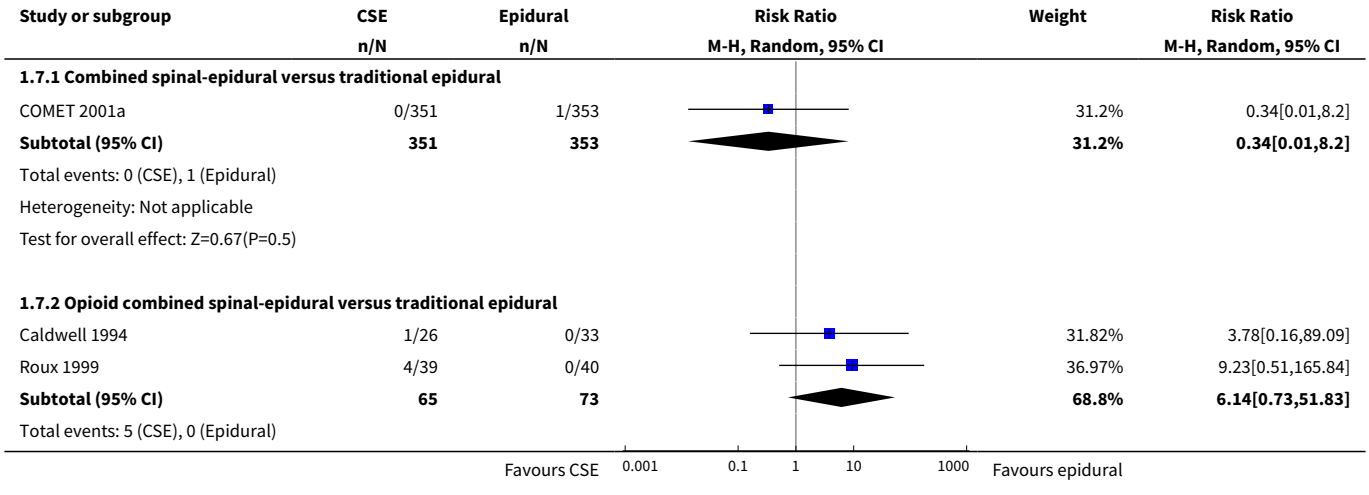
Analysis 1.5. Comparison 1 Combined spinal-epidural versus traditional epidural, Outcome 5 Number of women who mobilise.

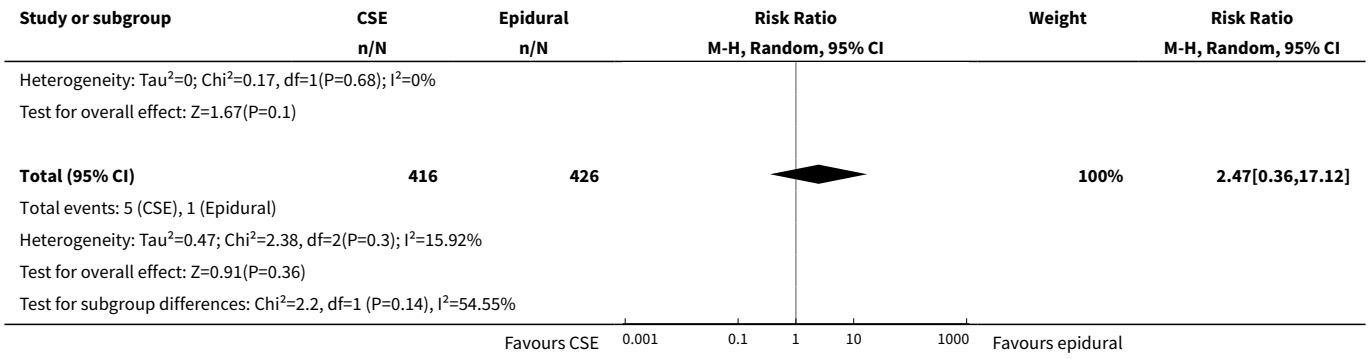


Analysis 1.6. Comparison 1 Combined spinal-epidural versus traditional epidural, Outcome 6 Post dural puncture headache.

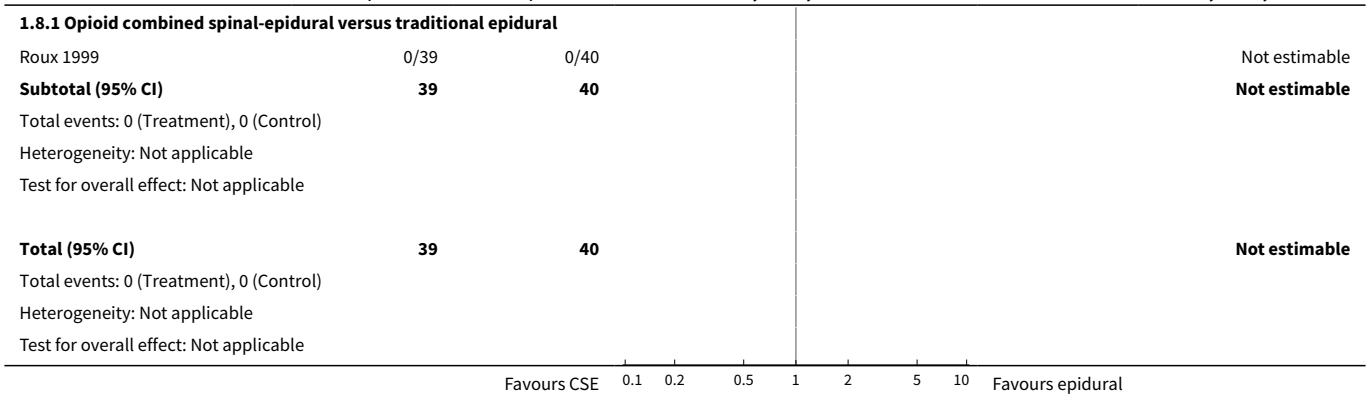


Analysis 1.7. Comparison 1 Combined spinal-epidural versus traditional epidural, Outcome 7 Known dural tap.

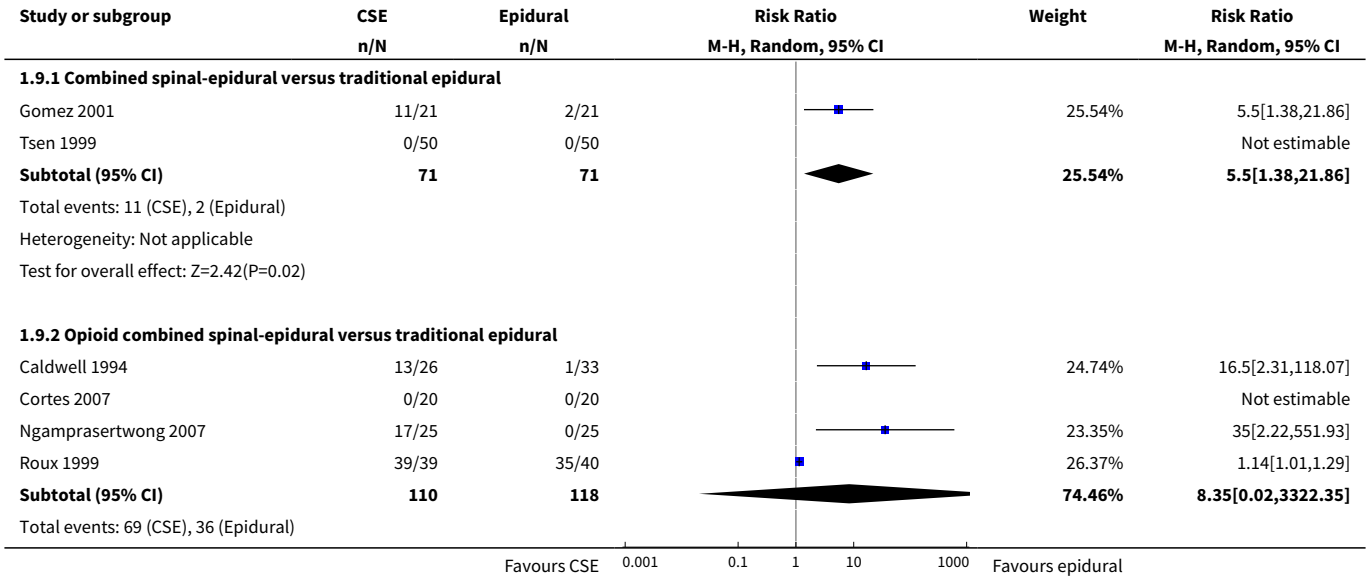


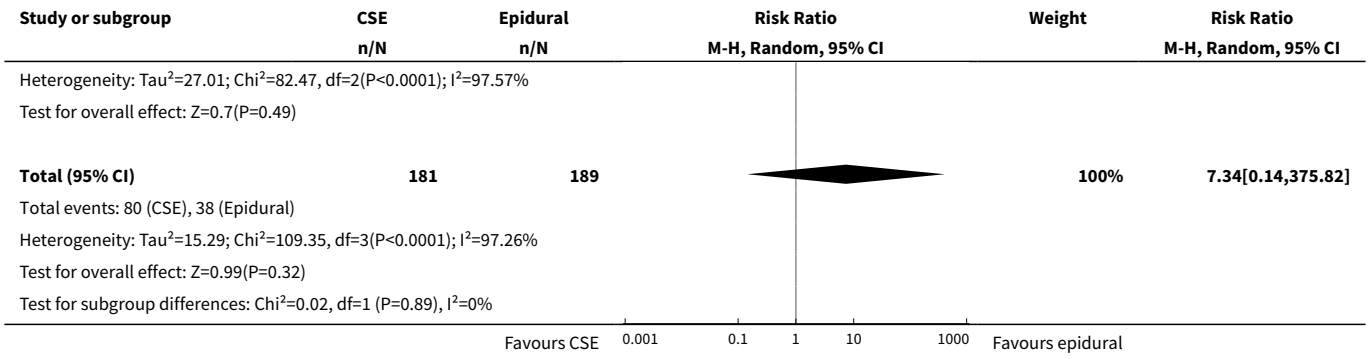


Analysis 1.8. Comparison 1 Combined spinal-epidural versus traditional epidural, Outcome 8 Number of women requiring blood patch for post dural puncture headache.

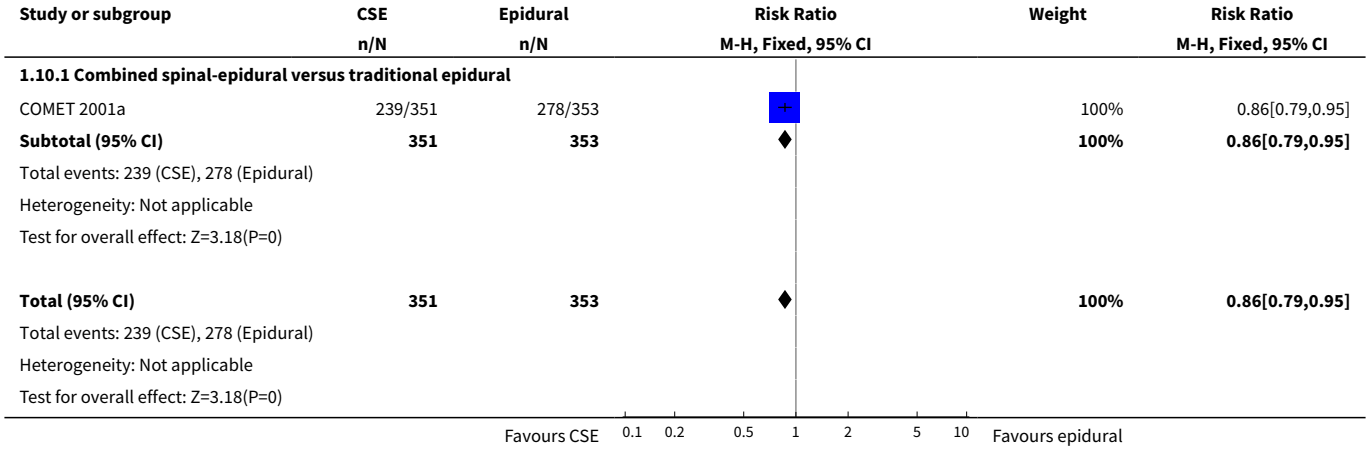


Analysis 1.9. Comparison 1 Combined spinal-epidural versus traditional epidural, Outcome 9 Pruritus.

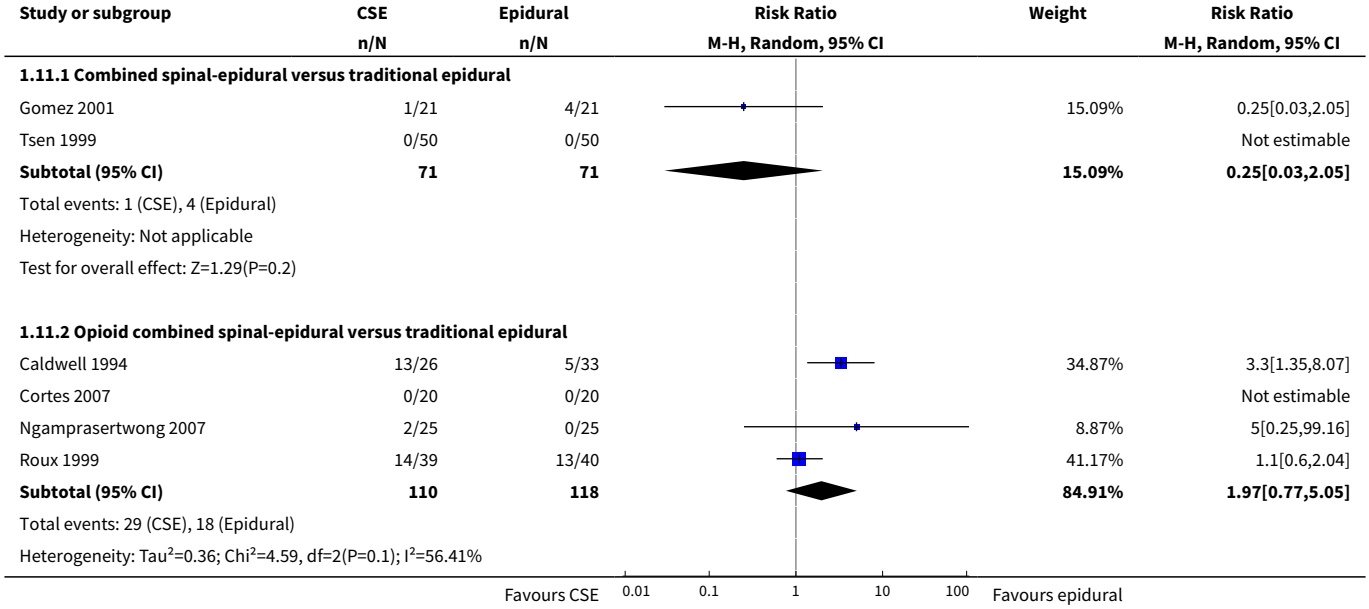


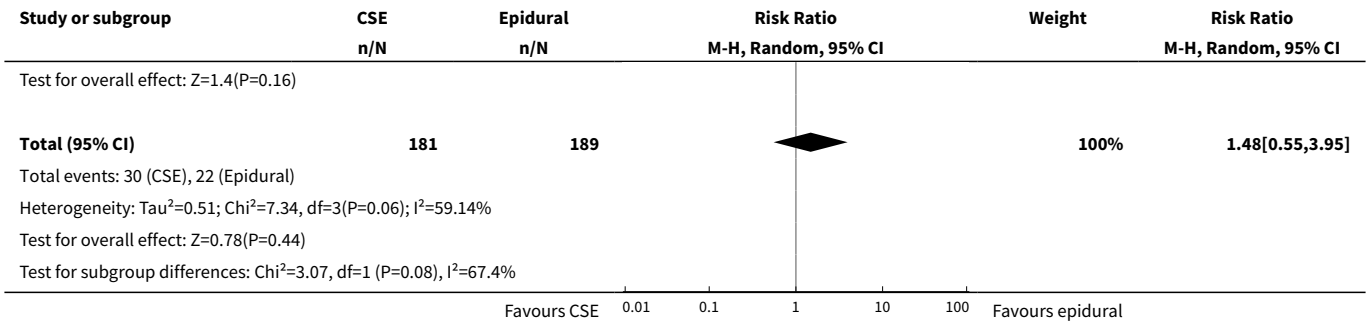


Analysis 1.10. Comparison 1 Combined spinal-epidural versus traditional epidural, Outcome 10 Urinary retention.

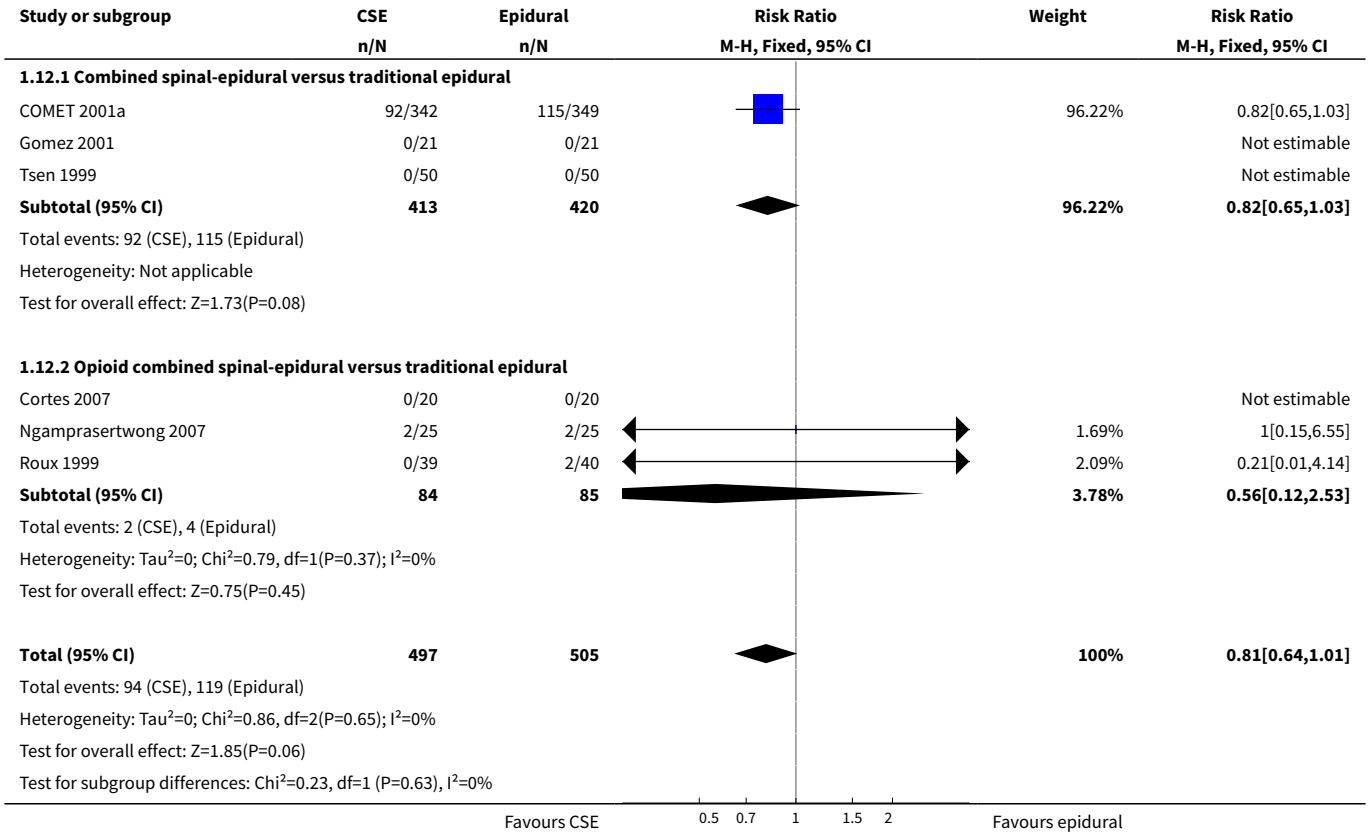


Analysis 1.11. Comparison 1 Combined spinal-epidural versus traditional epidural, Outcome 11 Nausea/vomiting.

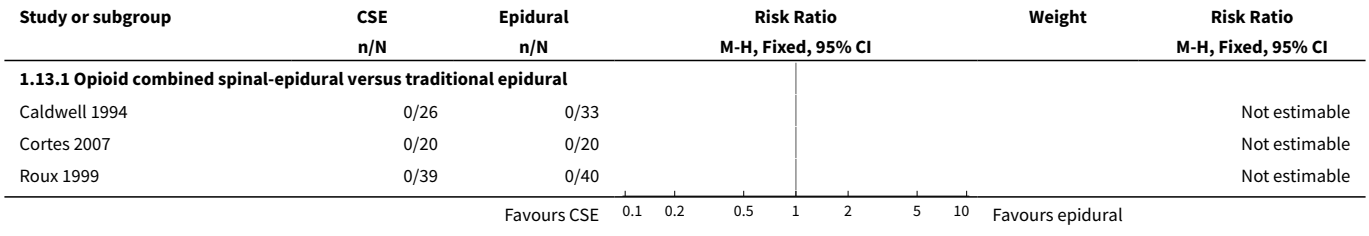


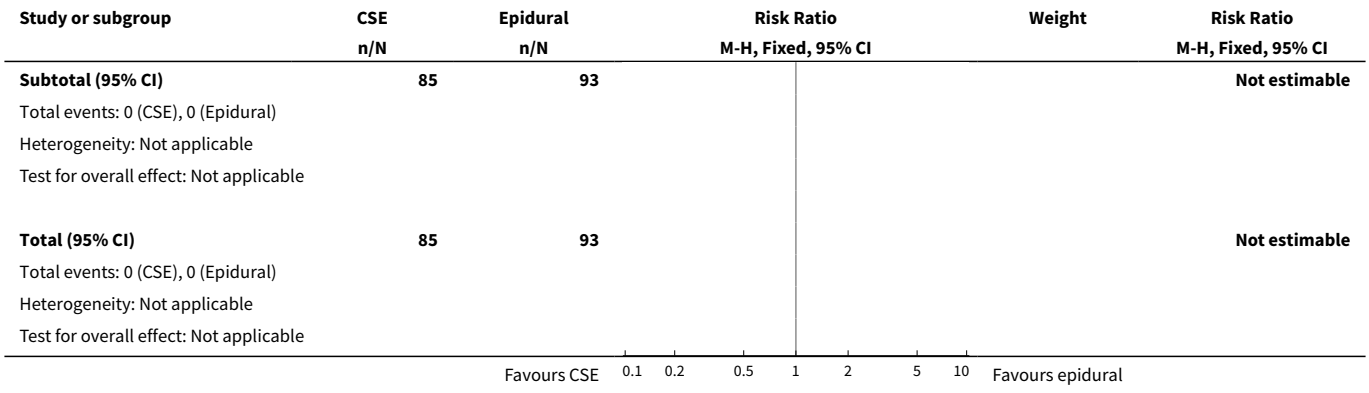


Analysis 1.12. Comparison 1 Combined spinal-epidural versus traditional epidural, Outcome 12 Hypotension.

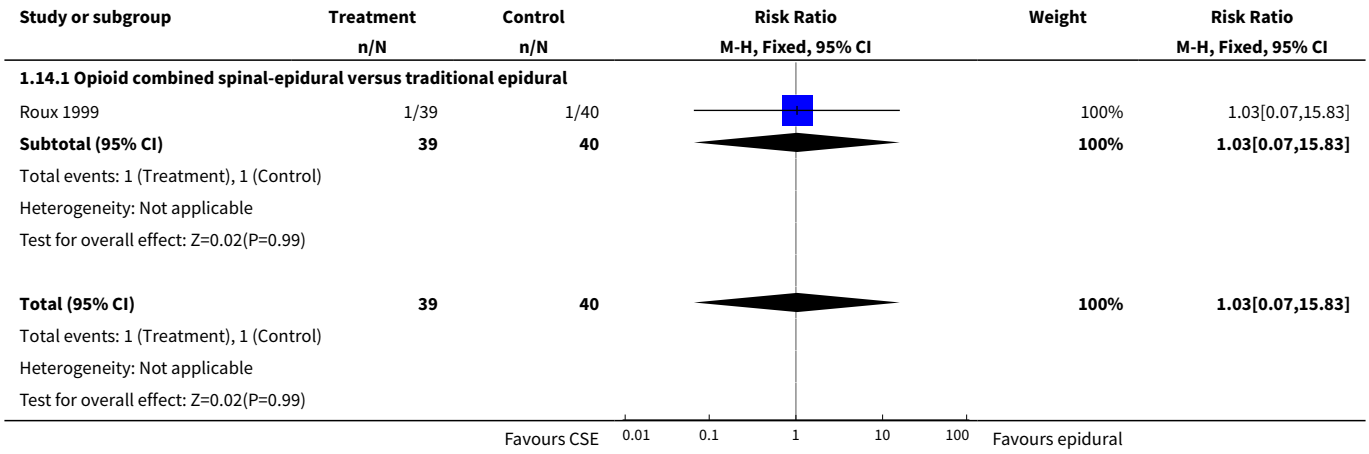


Analysis 1.13. Comparison 1 Combined spinal-epidural versus traditional epidural, Outcome 13 Respiratory depression.

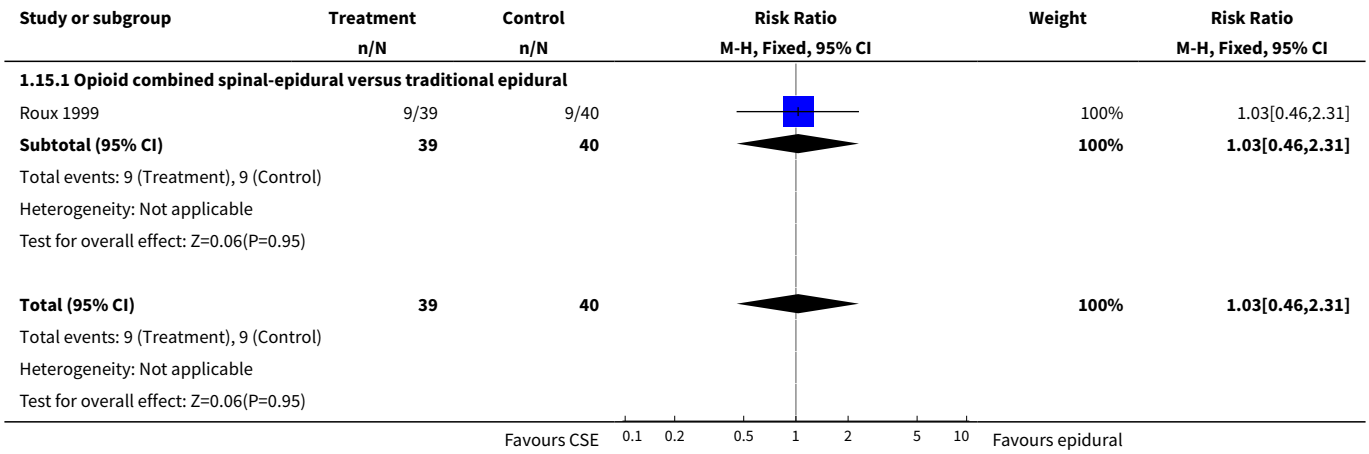




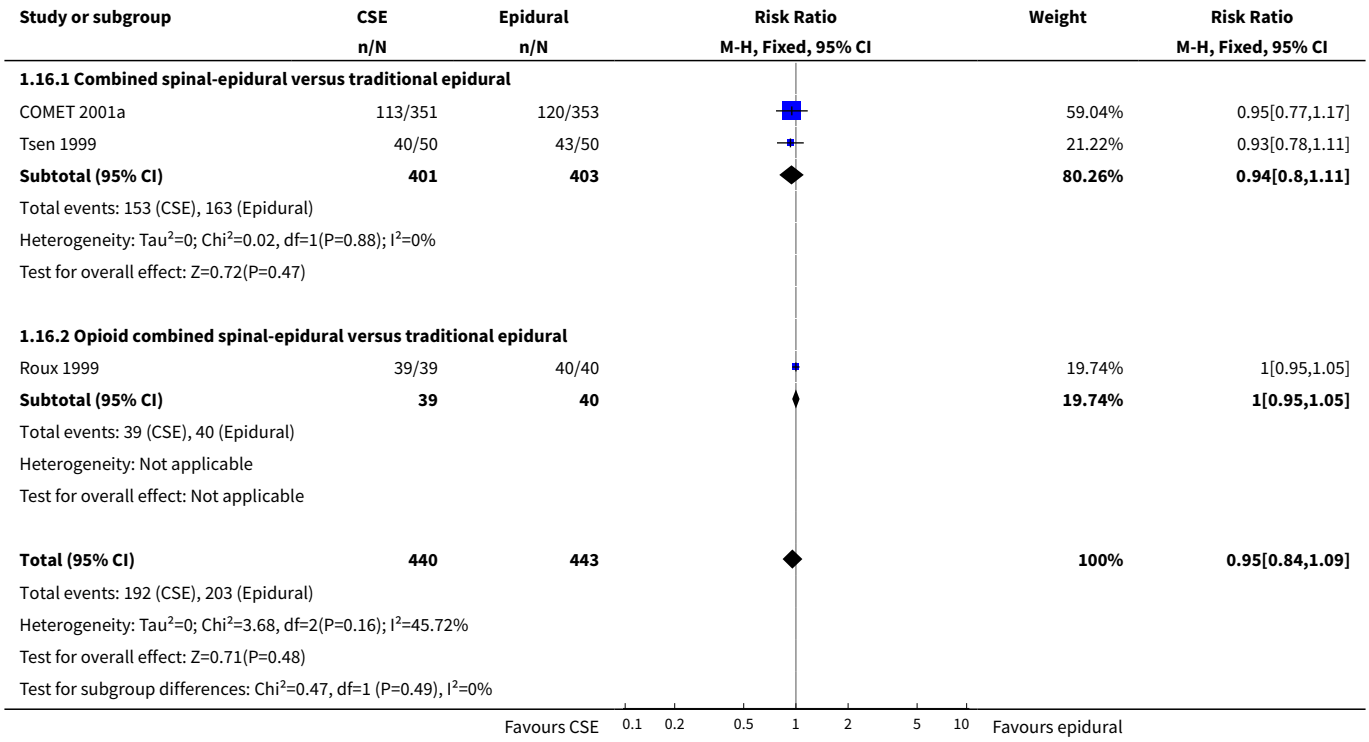
Analysis 1.14. Comparison 1 Combined spinal-epidural versus traditional epidural, Outcome 14 Headache (any).



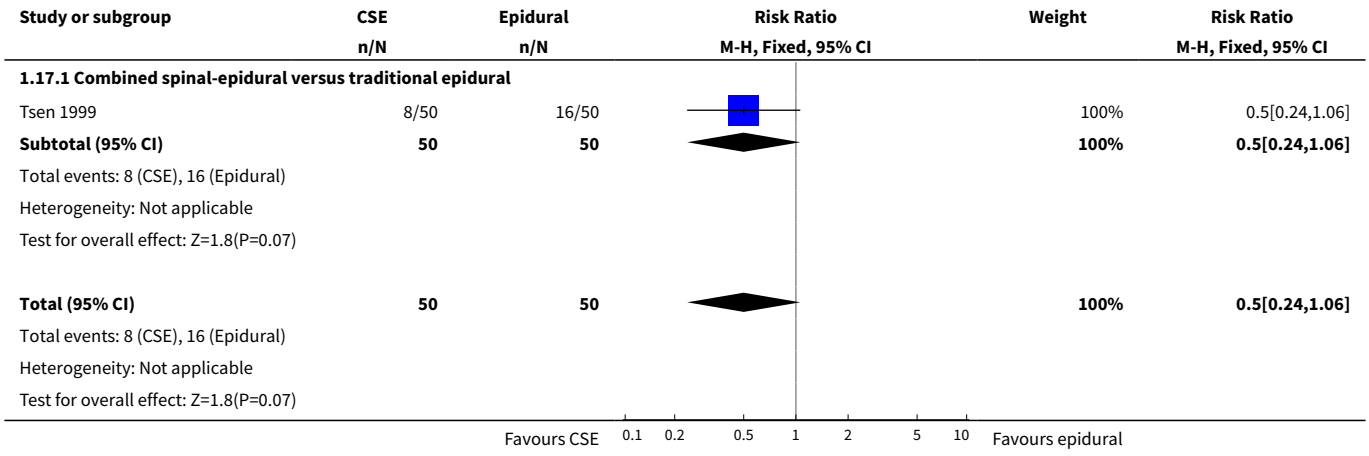
Analysis 1.15. Comparison 1 Combined spinal-epidural versus traditional epidural, Outcome 15 Sedation.



Analysis 1.16. Comparison 1 Combined spinal-epidural versus traditional epidural, Outcome 16 Labour augmentation required.

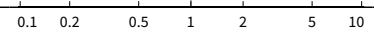


Analysis 1.17. Comparison 1 Combined spinal-epidural versus traditional epidural, Outcome 17 Augmentation after analgesia.



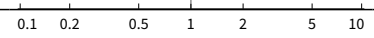
Analysis 1.18. Comparison 1 Combined spinal-epidural versus traditional epidural, Outcome 18 Normal delivery.

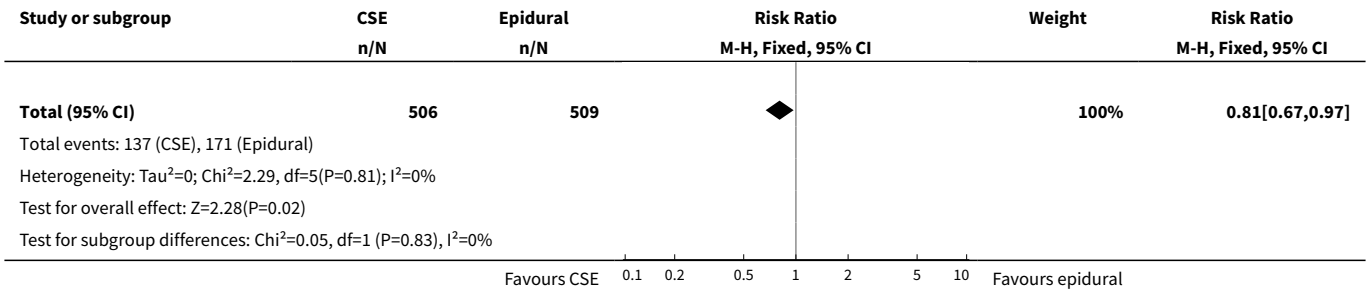
Study or subgroup	CSE n/N	Epidural n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.18.1 Combined spinal-epidural versus traditional epidural					
COMET 2001a	150/351	124/353		32.82%	1.22[1.01,1.47]
Gomez 2001	11/21	12/21		5.56%	0.92[0.53,1.59]
Tsen 1999	34/50	33/50		18.77%	1.03[0.78,1.36]
Subtotal (95% CI)	**422**	**424**		**57.15%**	**1.14[0.98,1.32]**
Total events: 195 (CSE), 169 (Epidural)					
Heterogeneity: Tau^2=0; Chi^2=1.66, df=2(P=0.44); I^2=0%					
Test for overall effect: Z=1.67(P=0.09)					
1.18.2 Opioid combined spinal-epidural versus traditional epidural					
Caldwell 1994	14/26	23/33		9.11%	0.77[0.51,1.18]
Cortes 2007	12/20	11/20		5.89%	1.09[0.64,1.86]
Ngamprasertwong 2007	11/25	9/25		3.68%	1.22[0.62,2.42]
Roux 1999	29/39	33/40		24.18%	0.9[0.71,1.14]
Subtotal (95% CI)	**110**	**118**		**42.85%**	**0.92[0.76,1.1]**
Total events: 66 (CSE), 76 (Epidural)					
Heterogeneity: Tau^2=0; Chi^2=1.79, df=3(P=0.62); I^2=0%					
Test for overall effect: Z=0.95(P=0.34)					
Total (95% CI)	**532**	**542**		**100%**	**1.03[0.9,1.18]**
Total events: 261 (CSE), 245 (Epidural)					
Heterogeneity: Tau^2=0.01; Chi^2=7.12, df=6(P=0.31); I^2=15.79%					
Test for overall effect: Z=0.42(P=0.67)					
Test for subgroup differences: Chi^2=3.2, df=1 (P=0.07), I^2=68.79%					



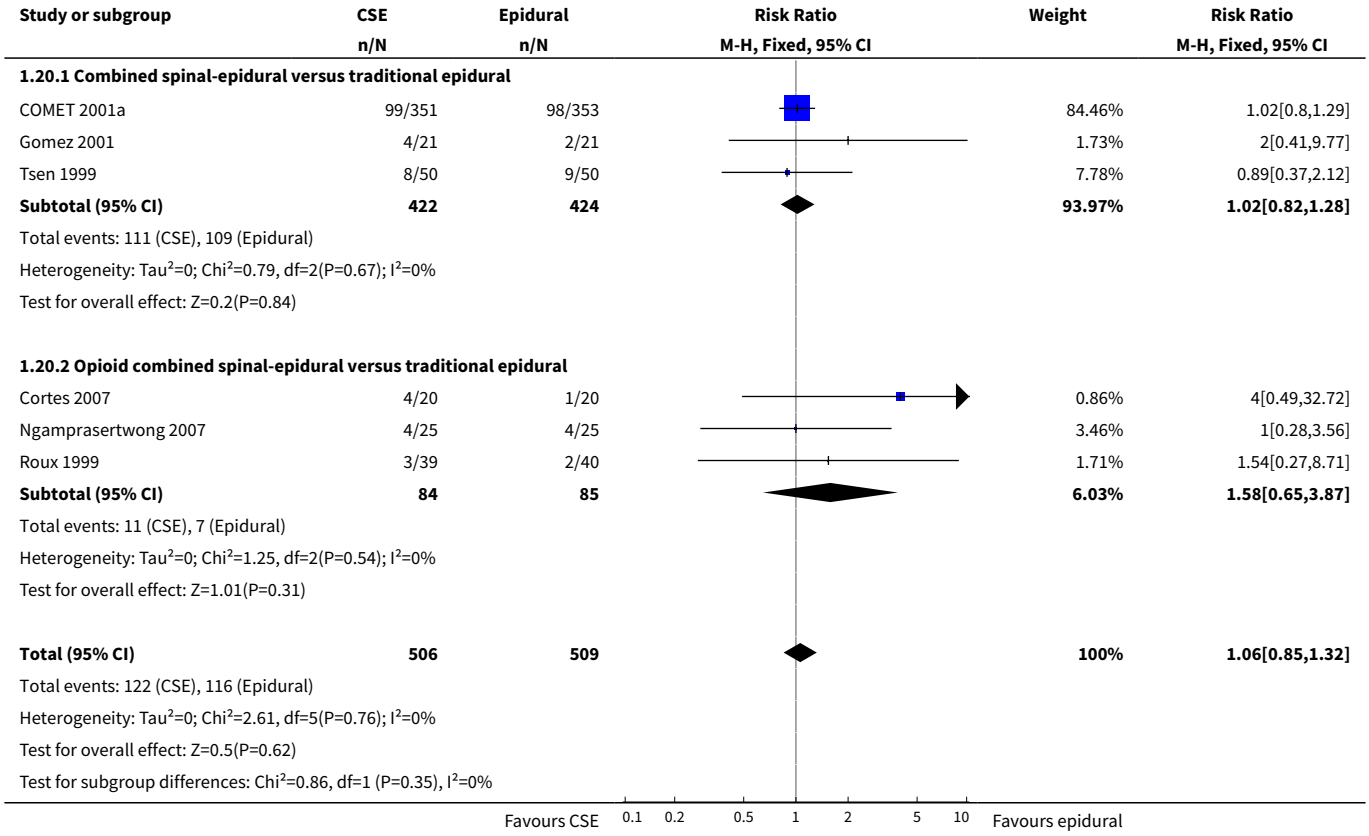
Analysis 1.19. Comparison 1 Combined spinal-epidural versus traditional epidural, Outcome 19 Instrumental delivery.

Study or subgroup	CSE n/N	Epidural n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.19.1 Combined spinal-epidural versus traditional epidural					
COMET 2001a	102/351	131/353		76.59%	0.78[0.63,0.97]
Gomez 2001	6/21	7/21		4.1%	0.86[0.35,2.12]
Tsen 1999	8/50	8/50		4.69%	1[0.41,2.46]
Subtotal (95% CI)	**422**	**424**		**85.38%**	**0.8[0.65,0.98]**
Total events: 116 (CSE), 146 (Epidural)					
Heterogeneity: Tau^2=0; Chi^2=0.3, df=2(P=0.86); I^2=0%					
Test for overall effect: Z=2.19(P=0.03)					
1.19.2 Opioid combined spinal-epidural versus traditional epidural					
Cortes 2007	4/20	8/20		4.69%	0.5[0.18,1.4]
Ngamprasertwong 2007	10/25	12/25		7.04%	0.83[0.44,1.56]
Roux 1999	7/39	5/40		2.89%	1.44[0.5,4.14]
Subtotal (95% CI)	**84**	**85**		**14.62%**	**0.85[0.52,1.37]**
Total events: 21 (CSE), 25 (Epidural)					
Heterogeneity: Tau^2=0; Chi^2=1.97, df=2(P=0.37); I^2=0%					
Test for overall effect: Z=0.69(P=0.49)					

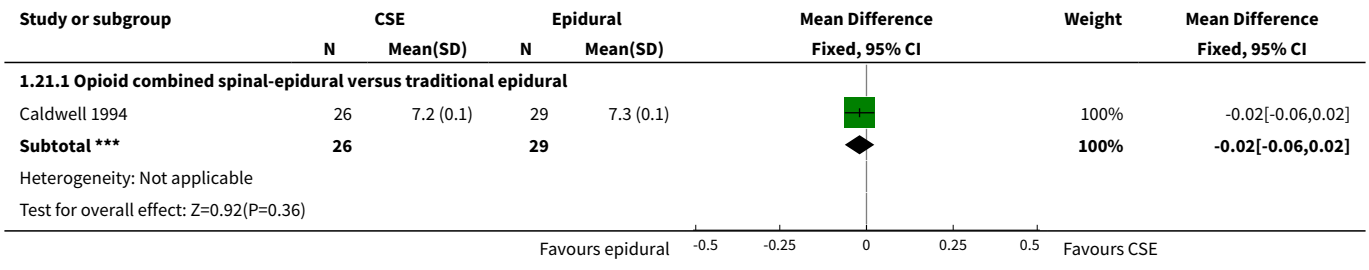


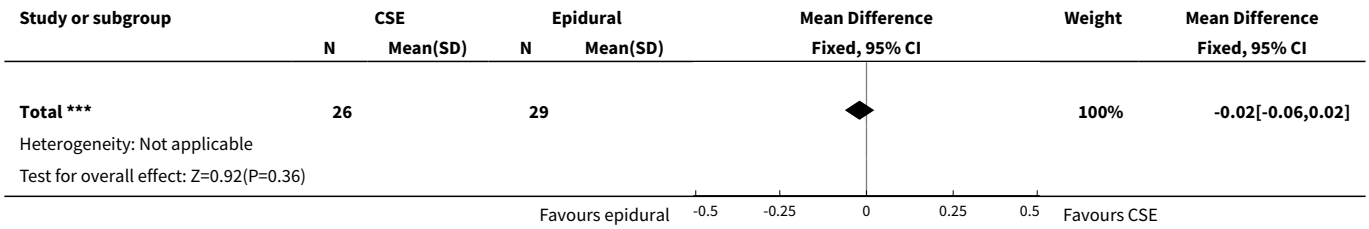


Analysis 1.20. Comparison 1 Combined spinal-epidural versus traditional epidural, Outcome 20 Caesarean section.

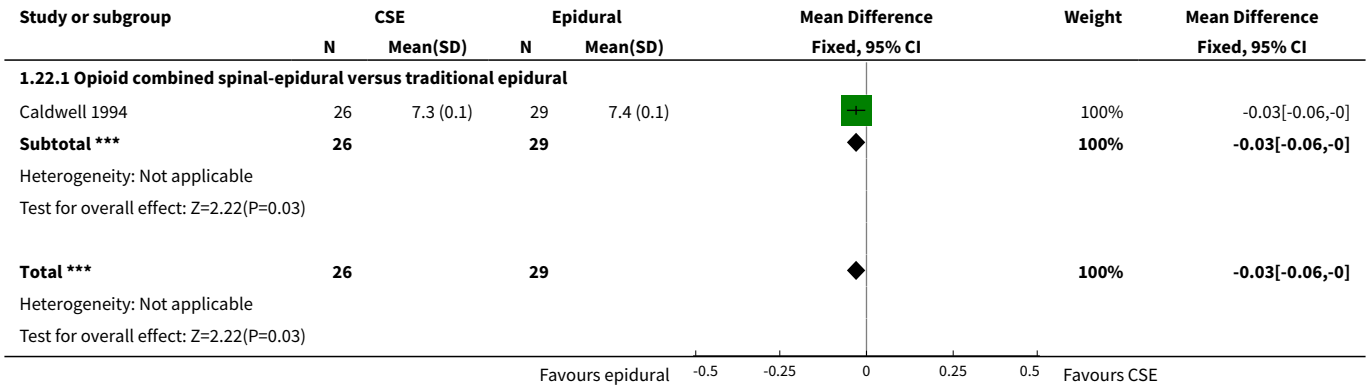


Analysis 1.21. Comparison 1 Combined spinal-epidural versus traditional epidural, Outcome 21 Umbilical arterial pH.

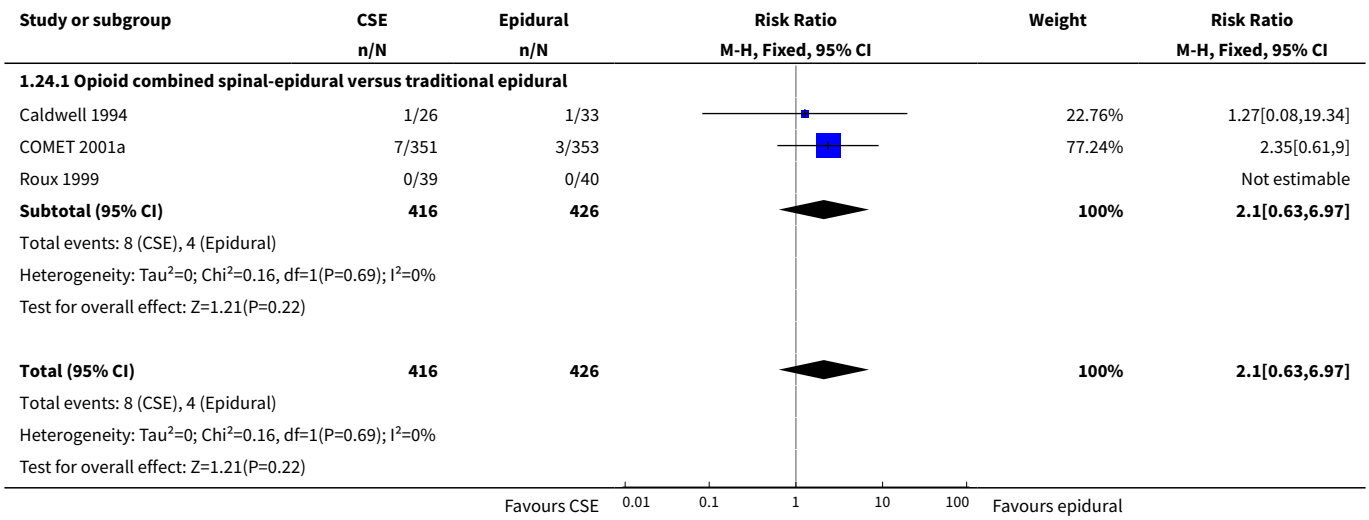




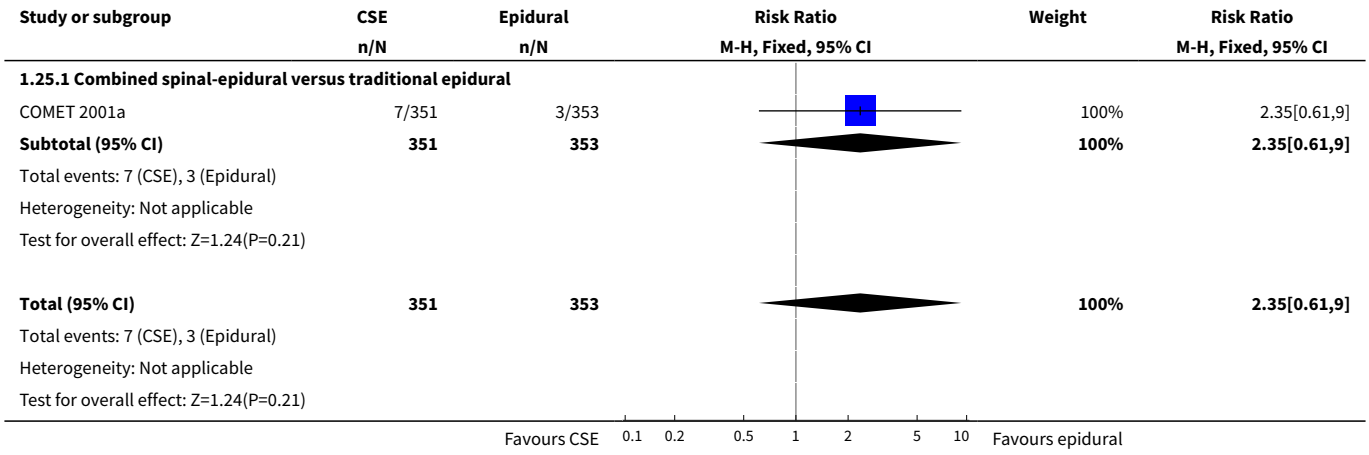
Analysis 1.22. Comparison 1 Combined spinal-epidural versus traditional epidural, Outcome 22 Umbilical venous pH.



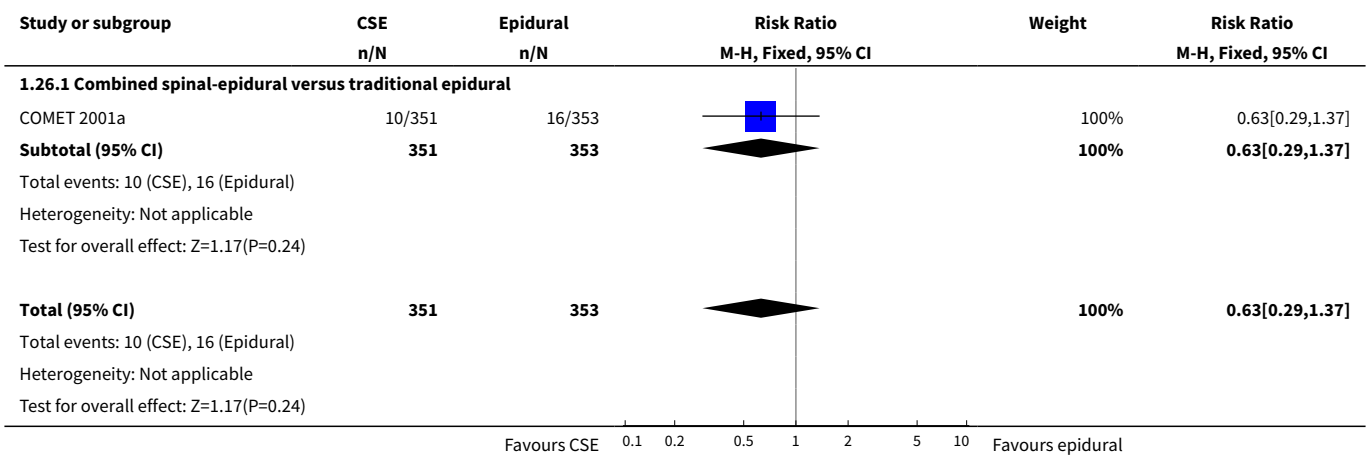
Analysis 1.24. Comparison 1 Combined spinal-epidural versus traditional epidural, Outcome 24 Apgar score < 7 at 5 minutes.



Analysis 1.25. Comparison 1 Combined spinal-epidural versus traditional epidural, Outcome 25 Apgar score < 8 at 5 minutes.



Analysis 1.26. Comparison 1 Combined spinal-epidural versus traditional epidural, Outcome 26 Number admitted to neonatal unit.



Comparison 2. Combined spinal-epidural versus low-dose epidural

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time from first injection to effective analgesia (minutes)	5	461	Mean Difference (IV, Random, 95% CI)	-5.42 [-7.26, -3.59]
1.1 Combined spinal-epidural versus low-dose epidural	4	421	Mean Difference (IV, Random, 95% CI)	-5.73 [-7.99, -3.48]
1.2 Opioid combined spinal-epidural versus low-dose epidural	1	40	Mean Difference (IV, Random, 95% CI)	-4.24 [-6.17, -2.31]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Number of women with effective analgesia 10 minutes after first injection	1	101	Risk Ratio (M-H, Fixed, 95% CI)	1.94 [1.49, 2.54]
2.1 Combined spinal-epidural versus low-dose epidural	1	101	Risk Ratio (M-H, Fixed, 95% CI)	1.94 [1.49, 2.54]
3 Need for rescue analgesia	9	1645	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.80, 1.23]
3.1 Combined spinal-epidural versus low-dose epidural	7	1328	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.77, 1.21]
3.2 Opioid combined spinal-epidural versus test local anaesthetic/opioid epidural	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.69]
3.3 Null combined spinal-epidural versus low-dose epidural	1	248	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.64, 2.98]
4 Number of women satisfied with analgesia	7	520	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.98, 1.05]
4.1 Combined spinal-epidural versus low-dose epidural	6	480	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.97, 1.06]
4.2 Opioid combined spinal-epidural versus low-dose epidural	1	40	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.91, 1.10]
5 Number of women who mobilise	7	1200	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.90, 1.15]
5.1 Combined spinal-epidural versus low-dose epidural	5	1091	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.09]
5.2 Opioid combined spinal-epidural versus test local anaesthetic/opioid epidural	2	109	Risk Ratio (M-H, Random, 95% CI)	1.33 [1.01, 1.75]
6 Post dural puncture headache	9	701	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.42, 6.81]
6.1 Combined spinal-epidural versus low-dose epidural	7	590	Risk Ratio (M-H, Fixed, 95% CI)	3.06 [0.50, 18.69]
6.2 Opioid combined spinal-epidural versus test local anaesthetic/opioid epidural	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.69]
6.3 Opioid combined spinal-epidural versus low-dose epidural	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Known dural tap	6	1326	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.16, 6.37]
7.1 Combined spinal-epidural versus low-dose epidural	4	1006	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.03, 14.14]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2 Opioid combined spinal-epidural versus test local anaesthetic/opioid epidural	1	69	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.3 Null combined spinal-epidural versus low-dose epidural	1	251	Risk Ratio (M-H, Random, 95% CI)	1.95 [0.18, 21.26]
8 Number of women requiring blood patch for post dural puncture headache	7	531	Risk Ratio (M-H, Fixed, 95% CI)	2.22 [0.51, 9.64]
8.1 Combined spinal-epidural versus low-dose epidural	3	257	Risk Ratio (M-H, Fixed, 95% CI)	4.85 [0.24, 97.11]
8.2 Opioid combined spinal-epidural versus test local anaesthetic/opioid epidural	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.69]
8.3 Opioid combined spinal-epidural versus low-dose epidural	3	205	Risk Ratio (M-H, Fixed, 95% CI)	5.45 [0.27, 111.13]
9 Pruritus	11	959	Risk Ratio (M-H, Random, 95% CI)	1.80 [1.22, 2.65]
9.1 Combined spinal-epidural versus low-dose epidural	9	877	Risk Ratio (M-H, Random, 95% CI)	1.60 [1.13, 2.28]
9.2 Opioid combined spinal-epidural versus low-dose epidural	2	82	Risk Ratio (M-H, Random, 95% CI)	10.53 [2.05, 53.99]
10 Urinary retention	4	964	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.69, 1.35]
10.1 Combined spinal-epidural versus low-dose epidural	3	930	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.55, 1.34]
10.2 Opioid combined spinal-epidural versus low-dose epidural	1	34	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.70, 2.98]
11 Nausea/vomiting	7	539	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.65, 1.45]
11.1 Combined spinal-epidural versus low-dose epidural	4	388	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.56, 1.47]
11.2 Opioid combined spinal-epidural versus test local anaesthetic/opioid epidural	1	69	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.38, 2.48]
11.3 Opioid combined spinal-epidural versus low-dose epidural	2	82	Risk Ratio (M-H, Random, 95% CI)	2.25 [0.23, 22.01]
12 Hypotension	14	2040	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.89, 2.04]
12.1 Combined spinal-epidural versus low-dose epidural	12	1741	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.85, 2.96]

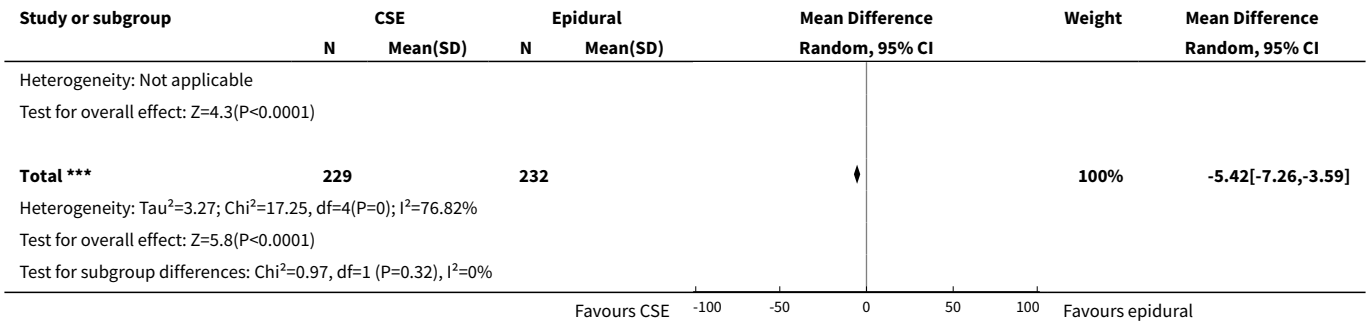
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.2 Opioid combined spinal-epidural versus test local anaesthetic/opioid epidural	1	69	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.3 Null combined spinal-epidural versus low-dose epidural	1	230	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.71, 1.45]
13 Respiratory depression	5	375	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.1 Combined spinal-epidural versus low-dose epidural	3	264	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Opioid combined spinal-epidural versus test local anaesthetic/opioid epidural	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.3 Opioid combined spinal-epidural versus low-dose epidural	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Headache (any)	1	110	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.70]
14.1 Combined spinal-epidural versus low-dose epidural	1	110	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.70]
15 Sedation	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Labour augmentation required	6	1285	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.88, 1.13]
16.1 Combined spinal-epidural versus low-dose epidural	3	944	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.80, 1.13]
16.2 Opioid combined spinal-epidural versus test local anaesthetic/opioid epidural	1	69	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.56, 4.28]
16.3 Opioid combined spinal-epidural versus low-dose epidural	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.05, 5.61]
16.4 Null combined spinal-epidural versus low-dose epidural	1	230	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.92, 1.24]
17 Augmentation after analgesia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Normal delivery	12	1672	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.92, 1.06]
18.1 Combined spinal-epidural versus low-dose epidural	8	1291	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.91, 1.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.2 Opioid combined spinal-epidural versus test local anaesthetic/opioid epidural	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.77, 1.22]
18.3 Opioid combined spinal-epidural versus low-dose epidural	2	82	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.80, 1.22]
18.4 Null combined spinal-epidural versus low-dose epidural	1	230	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.83, 1.08]
19 Instrumental delivery	11	1612	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.88, 1.30]
19.1 Combined spinal-epidural versus low-dose epidural	7	1231	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.87, 1.30]
19.2 Opioid combined spinal-epidural versus test local anaesthetic/opioid epidural	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.14, 6.51]
19.3 Opioid combined spinal-epidural versus low-dose epidural	2	82	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.4 Null combined spinal-epidural versus low-dose epidural	1	230	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.54, 3.03]
20 Caesarean section	15	1960	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.82, 1.16]
20.1 Combined spinal-epidural versus low-dose epidural	11	1579	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.79, 1.14]
20.2 Opioid combined spinal-epidural versus test local anaesthetic/opioid epidural	1	69	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.36, 4.14]
20.3 Opioid combined spinal-epidural versus low-dose epidural	2	82	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.44, 2.53]
20.4 Null combined spinal-epidural versus low-dose epidural	1	230	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.61, 2.52]
21 Umbilical arterial pH	4	306	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.03, 0.03]
21.1 Combined spinal-epidural versus low-dose epidural	3	264	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.04, 0.02]
21.2 Opioid combined spinal-epidural versus low-dose epidural	1	42	Mean Difference (IV, Random, 95% CI)	0.04 [-0.03, 0.11]
22 Umbilical venous pH	2	85	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.00, 0.07]

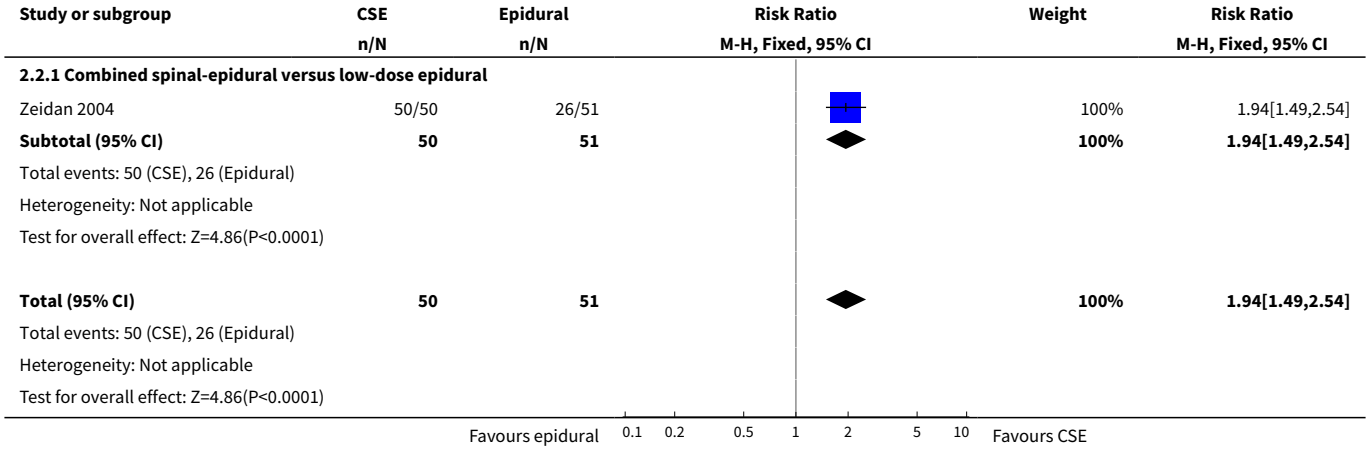
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.1 Combined spinal-epidural versus low-dose epidural	1	43	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.04, 0.08]
22.2 Opioid combined spinal-epidural versus low-dose epidural	1	42	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.00, 0.08]
23 Umbilical cord pH	1	110	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.05, 0.01]
23.1 Combined spinal-epidural versus low-dose epidural	1	110	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.05, 0.01]
24 Apgar score < 7 at 5 minutes	6	1092	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.31, 1.59]
24.1 Combined spinal-epidural versus low-dose epidural	6	1092	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.31, 1.59]
25 Apgar score < 8 at 5 minutes	5	979	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.39, 2.12]
25.1 Combined spinal-epidural versus low-dose epidural	4	937	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.33, 1.97]
25.2 Opioid combined spinal-epidural versus low-dose epidural	1	42	Risk Ratio (M-H, Fixed, 95% CI)	3.29 [0.14, 76.33]
26 Number admitted to neonatal unit	3	852	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.34, 1.73]
26.1 Combined spinal-epidural versus low-dose epidural	3	852	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.34, 1.73]

Analysis 2.1. Comparison 2 Combined spinal-epidural versus low-dose epidural, Outcome 1 Time from first injection to effective analgesia (minutes).

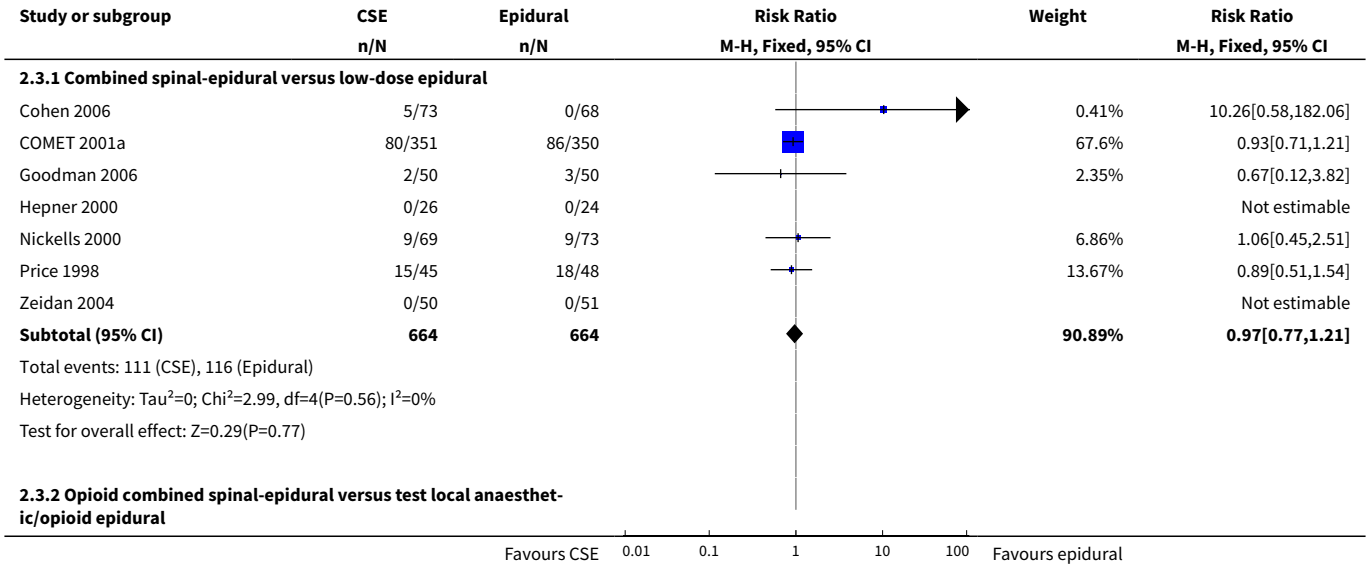
Study or subgroup	CSE N	CSE Mean(SD)	Epidural N	Epidural Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.1.1 Combined spinal-epidural versus low-dose epidural							
Cohen 2006	68	8.4 (6.8)	68	15.6 (6.7)		18.97%	-7.2[-9.47,-4.93]
Kartawiadi 1996	25	4 (2)	25	10.4 (2.5)		23.77%	-6.4[-7.65,-5.15]
Nickells 2000	61	10 (5.7)	64	12.1 (6.5)		19.6%	-2.1[-4.24,0.04]
Van de Velde 1999	55	5.4 (2.7)	55	12.8 (9.8)		17.04%	-7.34[-10.02,-4.66]
Subtotal ***	**209**		**212**			**79.39%**	**-5.73[-7.99,-3.48]**
Heterogeneity: Tau²=4.14; Chi²=15.08, df=3(P=0); I²=80.1%							
Test for overall effect: Z=4.99(P<0.0001)							
2.1.2 Opioid combined spinal-epidural versus low-dose epidural							
Sezer 2007	20	5.3 (1.2)	20	9.5 (4.3)		20.61%	-4.24[-6.17,-2.31]
Subtotal ***	**20**		**20**			**20.61%**	**-4.24[-6.17,-2.31]**

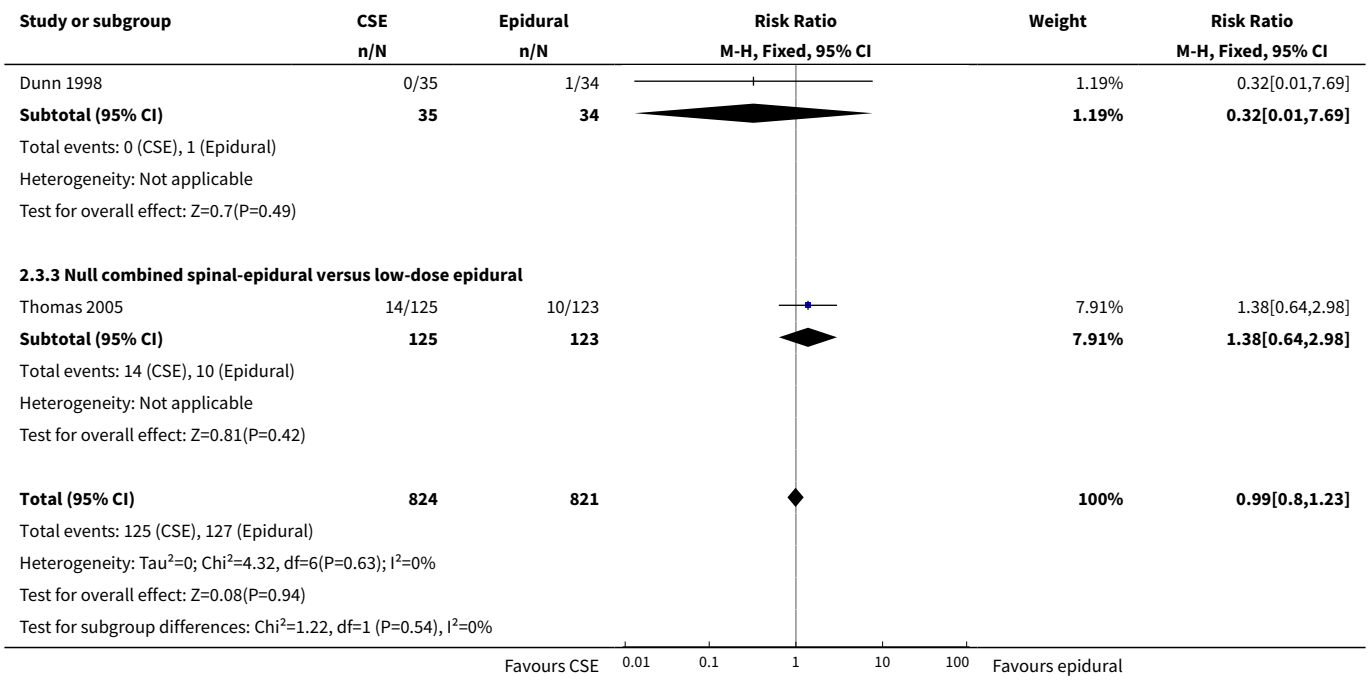


Analysis 2.2. Comparison 2 Combined spinal-epidural versus low-dose epidural, Outcome 2 Number of women with effective analgesia 10 minutes after first injection.

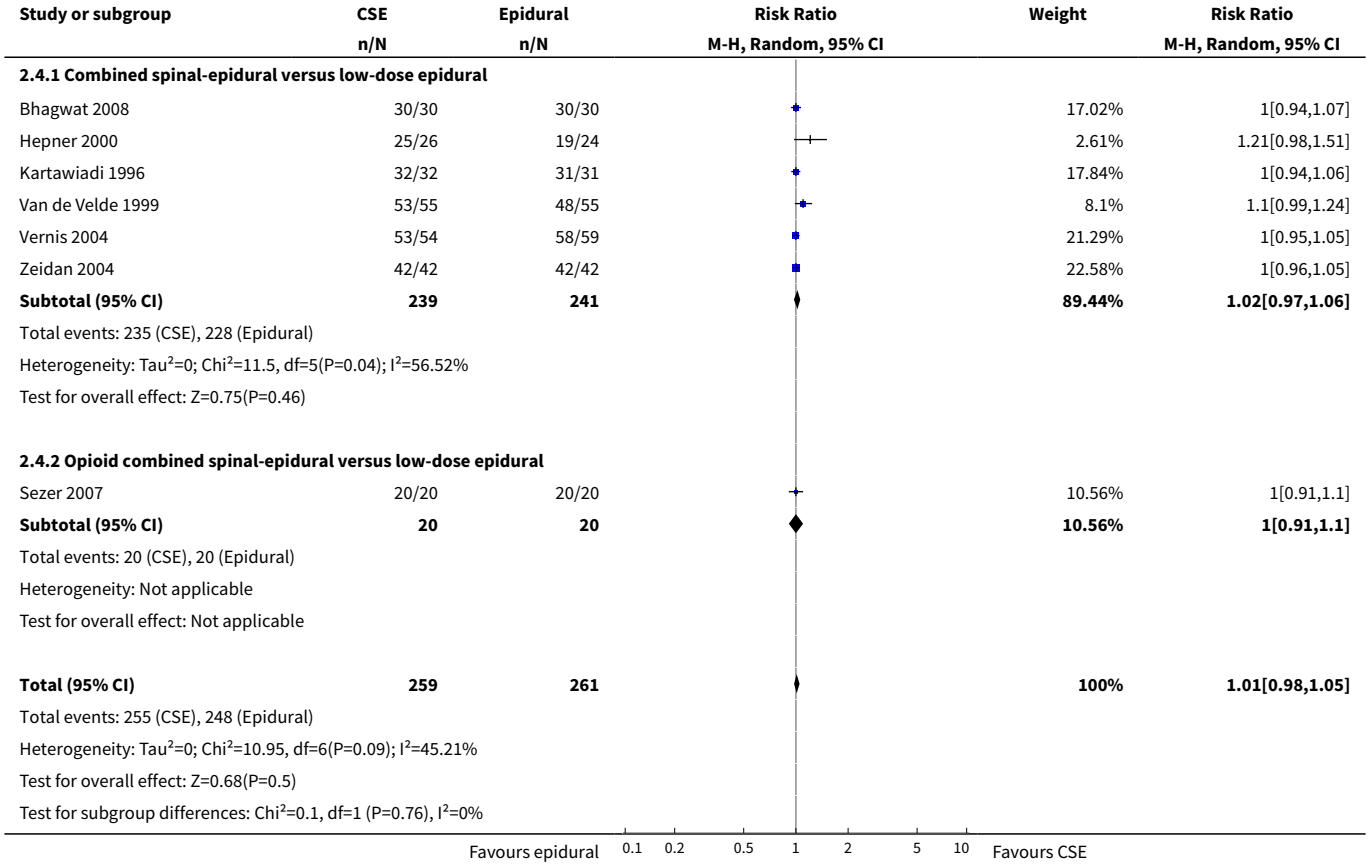


Analysis 2.3. Comparison 2 Combined spinal-epidural versus low-dose epidural, Outcome 3 Need for rescue analgesia.



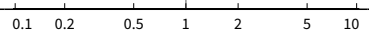


Analysis 2.4. Comparison 2 Combined spinal-epidural versus low-dose epidural, Outcome 4 Number of women satisfied with analgesia.



Analysis 2.5. Comparison 2 Combined spinal-epidural versus low-dose epidural, Outcome 5 Number of women who mobilise.

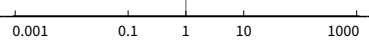
Study or subgroup	CSE n/N	Epidural n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 Combined spinal-epidural versus low-dose epidural					
Cohen 2006	32/68	41/68		11.9%	0.78[0.57,1.07]
COMET 2001a	133/351	128/350		23.17%	1.04[0.85,1.26]
Parry 1998	27/30	27/30		26.52%	1[0.84,1.18]
Price 1998	21/45	28/48		8.43%	0.8[0.54,1.19]
Zeidan 2004	33/50	31/51		13.16%	1.09[0.81,1.46]
Subtotal (95% CI)	**544**	**547**		**83.19%**	**0.98[0.88,1.09]**
Total events: 246 (CSE), 255 (Epidural)					
Heterogeneity: Tau²=0; Chi²=3.85, df=4(P=0.43); I²=0%					
Test for overall effect: Z=0.42(P=0.68)					
2.5.2 Opioid combined spinal-epidural versus test local anaesthetic/opioid epidural					
Breen 1999	20/21	13/19		11.75%	1.39[1.01,1.92]
Dunn 1998	17/35	14/34		5.07%	1.18[0.7,2]
Subtotal (95% CI)	**56**	**53**		**16.81%**	**1.33[1.01,1.75]**
Total events: 37 (CSE), 27 (Epidural)					
Heterogeneity: Tau²=0; Chi²=0.34, df=1(P=0.56); I²=0%					
Test for overall effect: Z=2.05(P=0.04)					
Total (95% CI)	**600**	**600**		**100%**	**1.02[0.9,1.15]**
Total events: 283 (CSE), 282 (Epidural)					
Heterogeneity: Tau²=0.01; Chi²=8.45, df=6(P=0.21); I²=28.98%					
Test for overall effect: Z=0.28(P=0.78)					
Test for subgroup differences: Chi²=4.25, df=1 (P=0.04), I²=76.48%					



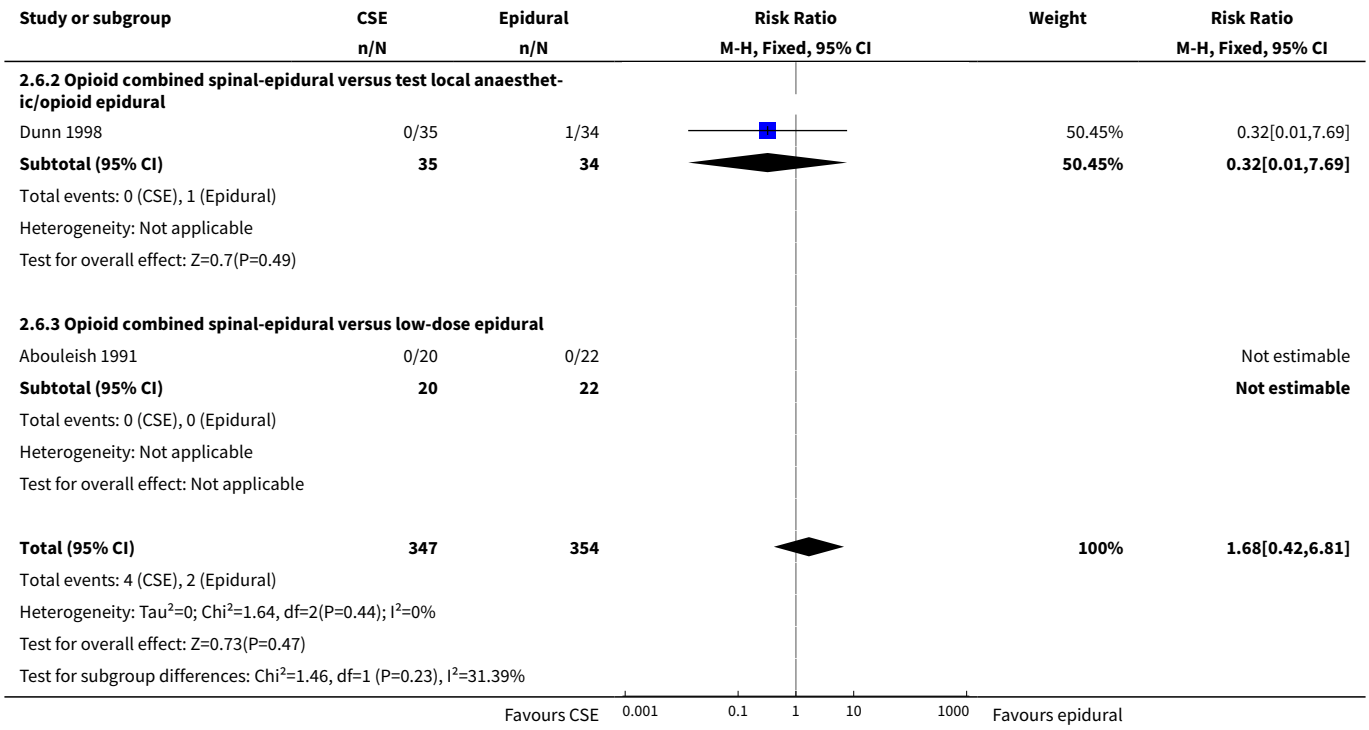
Favours epidural — Favours CSE

Analysis 2.6. Comparison 2 Combined spinal-epidural versus low-dose epidural, Outcome 6 Post dural puncture headache.

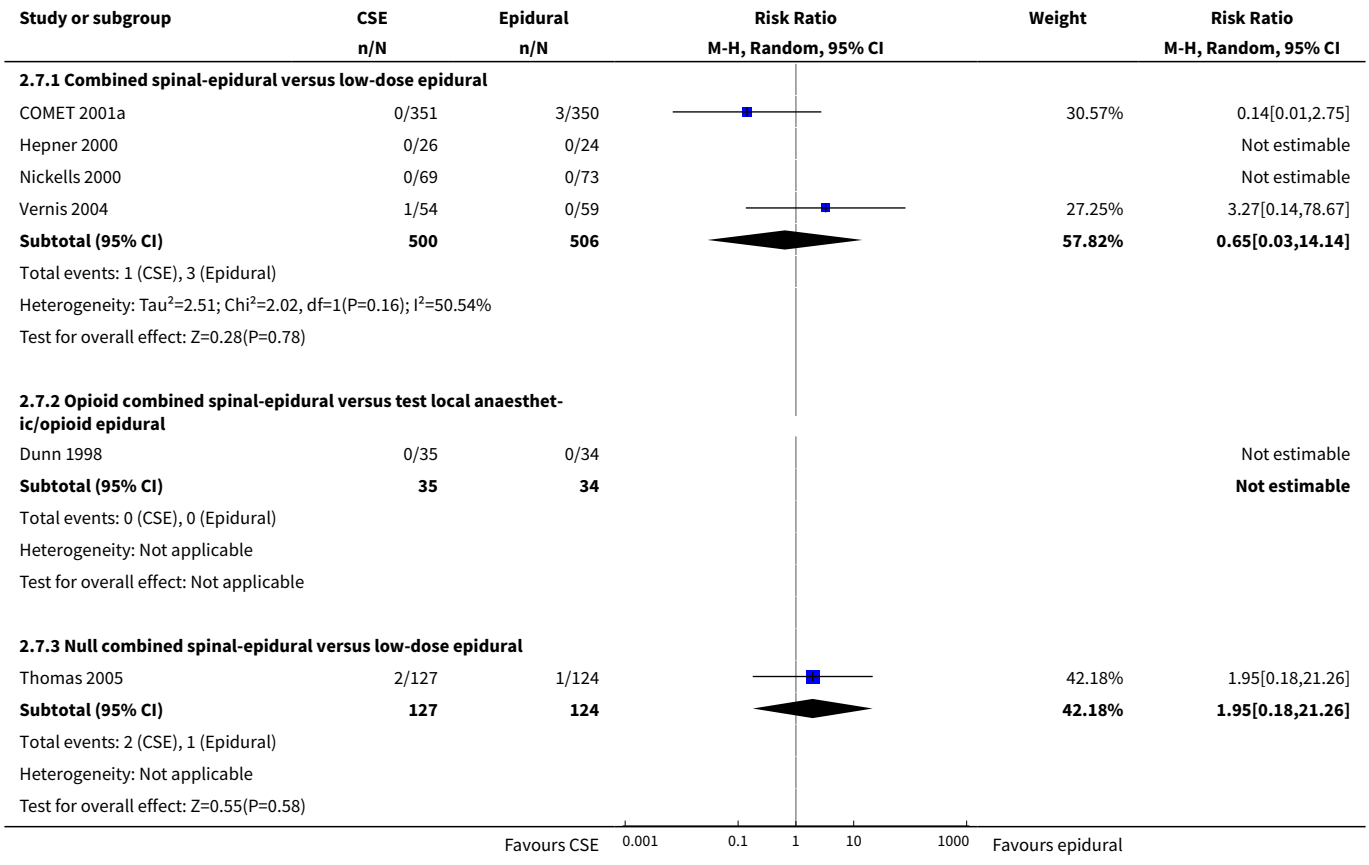
Study or subgroup	CSE n/N	Epidural n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.6.1 Combined spinal-epidural versus low-dose epidural					
Hepner 2000	0/26	0/24			Not estimable
Kartawiadi 1996	2/32	1/31		33.69%	1.94[0.18,20.3]
Parry 1998	0/30	0/30			Not estimable
Price 1998	0/45	0/48			Not estimable
Van de Velde 1999	0/55	0/55			Not estimable
Vernis 2004	2/54	0/59		15.86%	5.45[0.27,111.13]
Zeidan 2004	0/50	0/51			Not estimable
Subtotal (95% CI)	**292**	**298**		**49.55%**	**3.06[0.5,18.69]**
Total events: 4 (CSE), 1 (Epidural)					
Heterogeneity: Tau²=0; Chi²=0.29, df=1(P=0.59); I²=0%					
Test for overall effect: Z=1.21(P=0.23)					

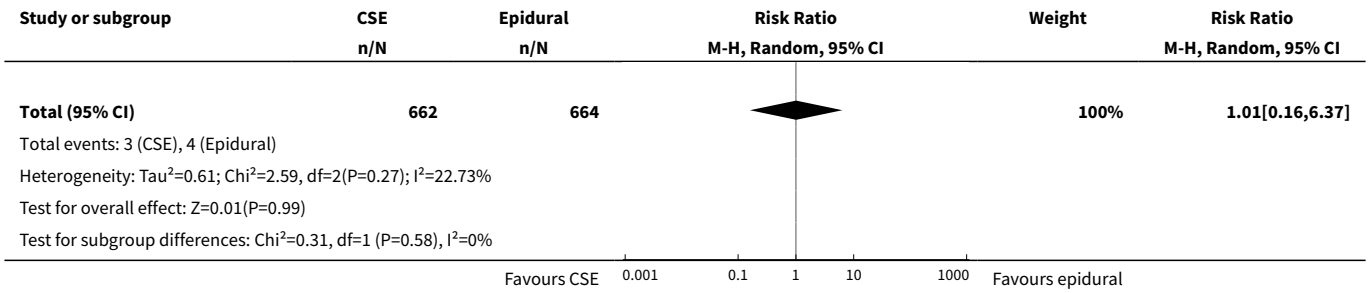


Favours CSE — Favours epidural

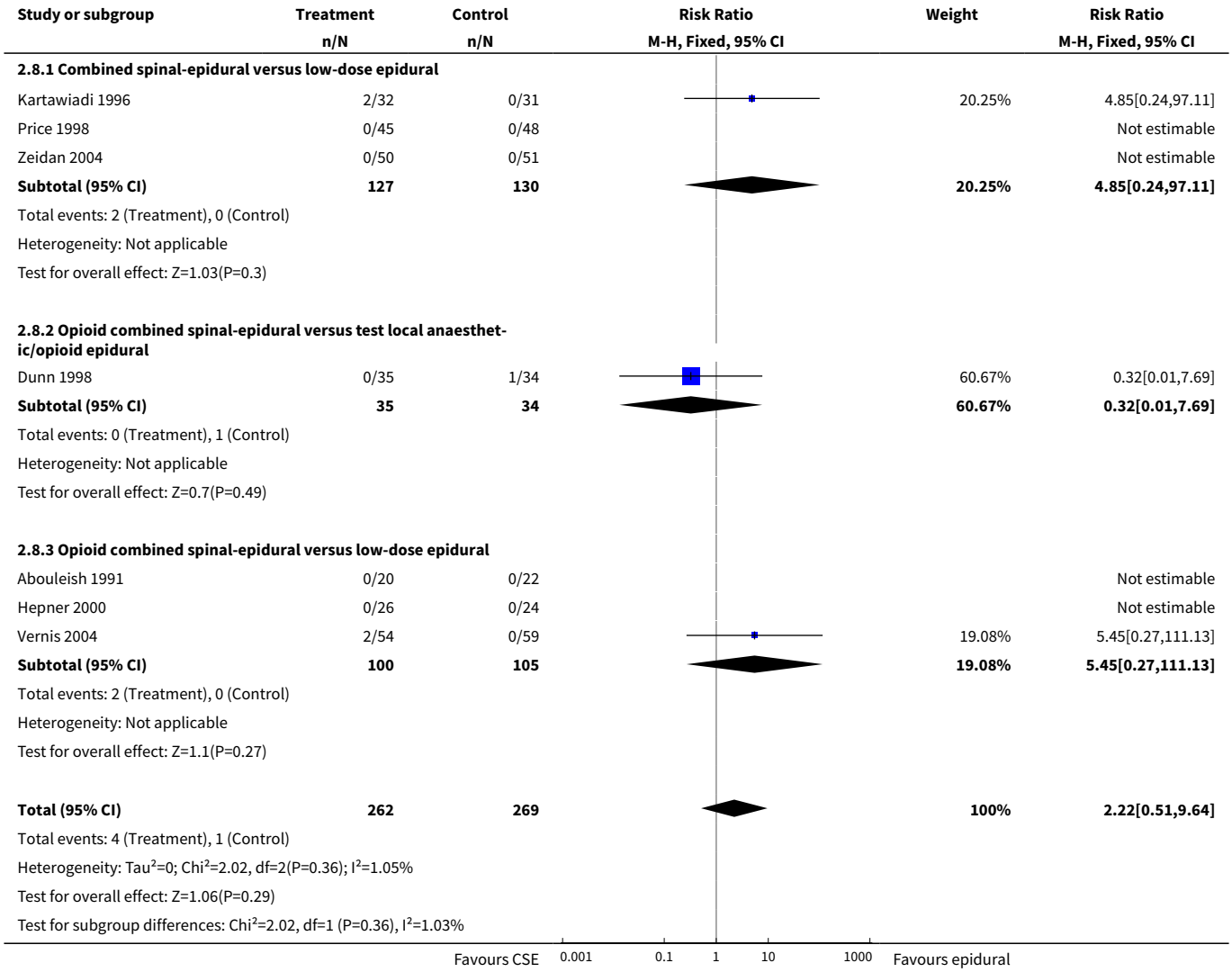


Analysis 2.7. Comparison 2 Combined spinal-epidural versus low-dose epidural, Outcome 7 Known dural tap.



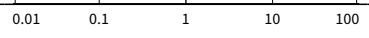


Analysis 2.8. Comparison 2 Combined spinal-epidural versus low-dose epidural, Outcome 8 Number of women requiring blood patch for post dural puncture headache.



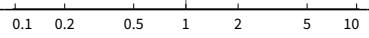
Analysis 2.9. Comparison 2 Combined spinal-epidural versus low-dose epidural, Outcome 9 Pruritus.

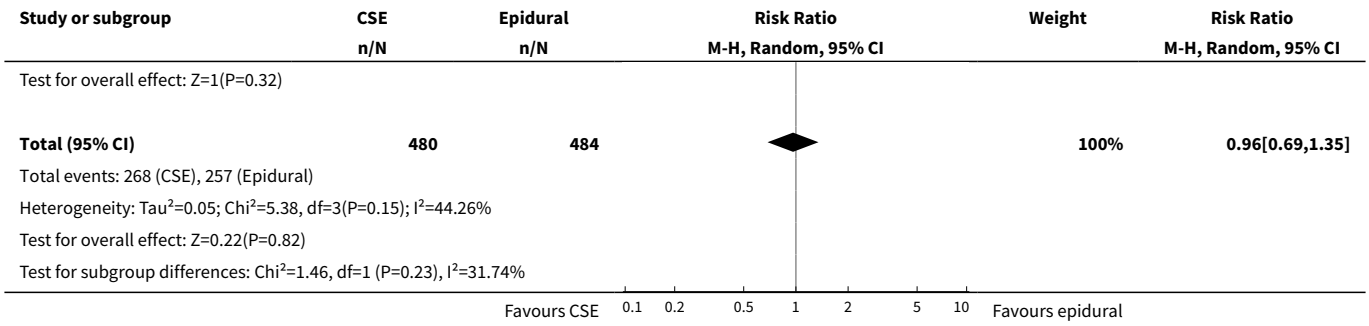
Study or subgroup	CSE n/N	Epidural n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.9.1 Combined spinal-epidural versus low-dose epidural					
Cohen 2006	42/68	38/68		14.24%	1.11[0.83,1.47]
Goodman 2006	15/43	3/41		6.49%	4.77[1.49,15.26]
Hepner 2000	24/26	21/24		14.86%	1.05[0.87,1.27]
Kartawiadi 1996	17/32	8/31		10.48%	2.06[1.04,4.06]
Price 1998	25/45	26/48		13.52%	1.03[0.71,1.48]
Skupski 2009	32/64	19/63		12.78%	1.66[1.06,2.6]
Van de Velde 1999	27/55	20/55		12.85%	1.35[0.87,2.1]
Vernis 2004	34/54	7/59		10.04%	5.31[2.57,10.96]
Zeidan 2004	0/50	0/51			Not estimable
Subtotal (95% CI)	**437**	**440**		**95.26%**	**1.6[1.13,2.28]**
Total events: 216 (CSE), 142 (Epidural)					
Heterogeneity: Tau^2=0.19; Chi^2=40.44, df=7(P<0.0001); I^2=82.69%					
Test for overall effect: Z=2.63(P=0.01)					
2.9.2 Opioid combined spinal-epidural versus low-dose epidural					
Abouleish 1991	6/20	1/22		2.97%	6.6[0.87,50.18]
Sezer 2007	12/20	0/20		1.76%	25[1.58,395.48]
Subtotal (95% CI)	**40**	**42**		**4.74%**	**10.53[2.05,53.99]**
Total events: 18 (CSE), 1 (Epidural)					
Heterogeneity: Tau^2=0; Chi^2=0.64, df=1(P=0.42); I^2=0%					
Test for overall effect: Z=2.82(P=0)					
Total (95% CI)	**477**	**482**		**100%**	**1.8[1.22,2.65]**
Total events: 234 (CSE), 143 (Epidural)					
Heterogeneity: Tau^2=0.26; Chi^2=55, df=9(P<0.0001); I^2=83.64%					
Test for overall effect: Z=2.95(P=0)					
Test for subgroup differences: Chi^2=4.86, df=1 (P=0.03), I^2=79.41%					



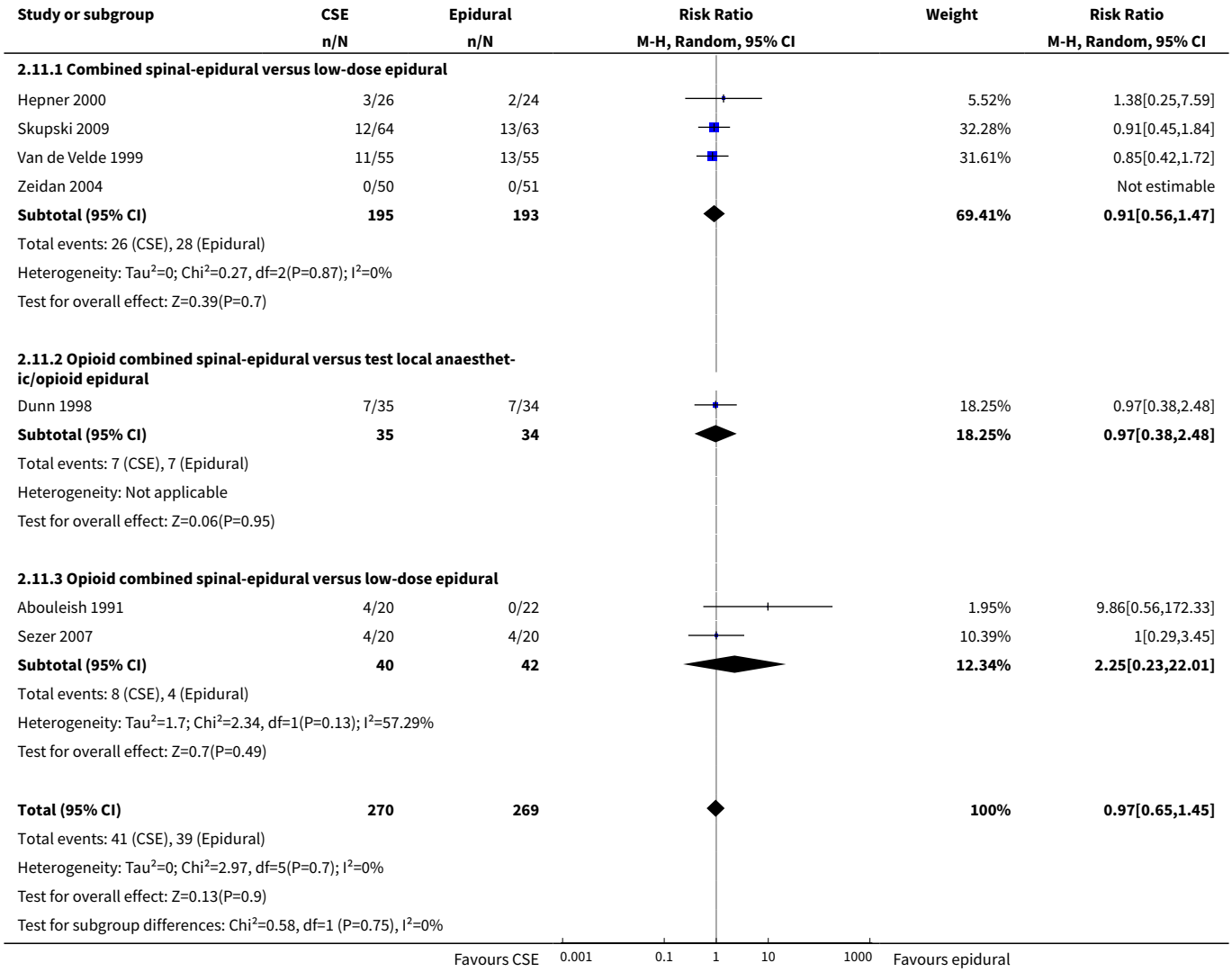
Analysis 2.10. Comparison 2 Combined spinal-epidural versus low-dose epidural, Outcome 10 Urinary retention.

Study or subgroup	CSE n/N	Epidural n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.10.1 Combined spinal-epidural versus low-dose epidural					
Cohen 2006	15/68	23/68		22.2%	0.65[0.37,1.14]
COMET 2001a	239/351	218/350		52.82%	1.09[0.98,1.22]
Price 1998	5/45	9/48		9.26%	0.59[0.21,1.63]
Subtotal (95% CI)	**464**	**466**		**84.28%**	**0.86[0.55,1.34]**
Total events: 259 (CSE), 250 (Epidural)					
Heterogeneity: Tau^2=0.09; Chi^2=4.78, df=2(P=0.09); I^2=58.12%					
Test for overall effect: Z=0.68(P=0.49)					
2.10.2 Opioid combined spinal-epidural versus low-dose epidural					
Abouleish 1991	9/16	7/18		15.72%	1.45[0.7,2.98]
Subtotal (95% CI)	**16**	**18**		**15.72%**	**1.45[0.7,2.98]**
Total events: 9 (CSE), 7 (Epidural)					
Heterogeneity: Not applicable					



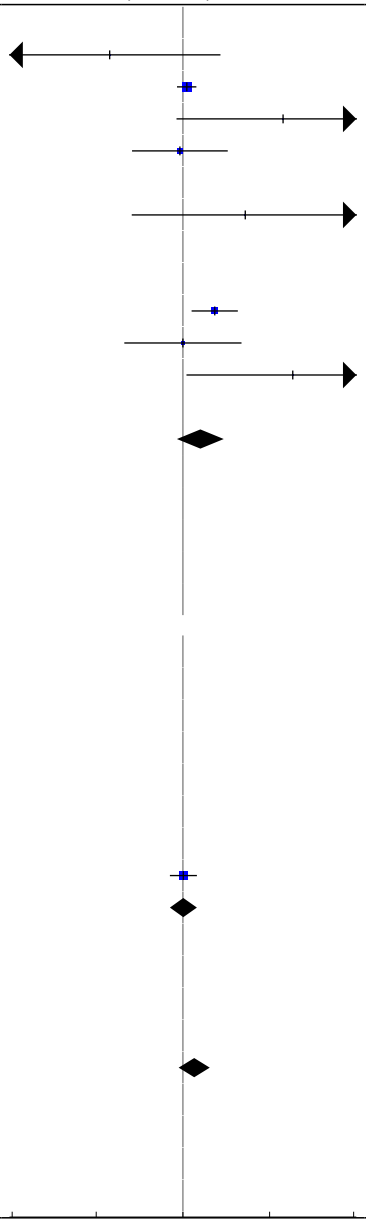


Analysis 2.11. Comparison 2 Combined spinal-epidural versus low-dose epidural, Outcome 11 Nausea/vomiting.



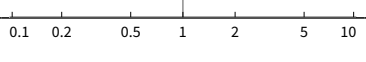
Analysis 2.12. Comparison 2 Combined spinal-epidural versus low-dose epidural, Outcome 12 Hypotension.

Study or subgroup	CSE n/N	Epidural n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.12.1 Combined spinal-epidural versus low-dose epidural					
Cohen 2006	0/68	3/68		1.86%	0.14[0.01,2.71]
COMET 2001a	92/342	82/337		30.84%	1.11[0.86,1.43]
Goodman 2006	7/43	0/41		2.01%	14.32[0.84,242.95]
Hepner 2000	4/26	4/24		8.13%	0.92[0.26,3.29]
Kartawiadi 1996	0/32	0/31			Not estimable
Nickells 2000	2/61	0/64		1.78%	5.24[0.26,107.02]
Parry 1998	0/30	0/30			Not estimable
Price 1998	0/45	0/48			Not estimable
Skupski 2009	26/64	11/63		19.77%	2.33[1.26,4.3]
Van de Velde 1999	3/55	3/55		5.87%	1[0.21,4.74]
Vernis 2004	8/54	0/59		2.01%	18.55[1.1,313.82]
Zeidan 2004	0/50	0/51			Not estimable
Subtotal (95% CI)	**870**	**871**		**72.27%**	**1.59[0.85,2.96]**
Total events: 142 (CSE), 103 (Epidural)					
Heterogeneity: Tau²=0.29; Chi²=14.85, df=7(P=0.04); I²=52.85%					
Test for overall effect: Z=1.46(P=0.14)					
2.12.2 Opioid combined spinal-epidural versus test local anaesthetic/opioid epidural					
Dunn 1998	0/35	0/34			Not estimable
Subtotal (95% CI)	**35**	**34**			**Not estimable**
Total events: 0 (CSE), 0 (Epidural)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.12.3 Null combined spinal-epidural versus low-dose epidural					
Thomas 2005	37/107	42/123		27.73%	1.01[0.71,1.45]
Subtotal (95% CI)	**107**	**123**		**27.73%**	**1.01[0.71,1.45]**
Total events: 37 (CSE), 42 (Epidural)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.07(P=0.94)					
Total (95% CI)	**1012**	**1028**		**100%**	**1.35[0.89,2.04]**
Total events: 179 (CSE), 145 (Epidural)					
Heterogeneity: Tau²=0.13; Chi²=15.86, df=8(P=0.04); I²=49.57%					
Test for overall effect: Z=1.42(P=0.15)					
Test for subgroup differences: Chi²=1.51, df=1 (P=0.22), I²=33.91%					

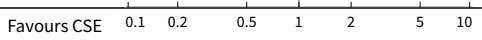


Analysis 2.13. Comparison 2 Combined spinal-epidural versus low-dose epidural, Outcome 13 Respiratory depression.

Study or subgroup	CSE n/N	Epidural n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.13.1 Combined spinal-epidural versus low-dose epidural					
Hepner 2000	0/26	0/24			Not estimable
Vernis 2004	0/54	0/59			Not estimable

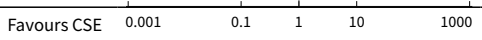


Study or subgroup	CSE n/N	Epidural n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Zeidan 2004	0/50	0/51			Not estimable
Subtotal (95% CI)	**130**	**134**			**Not estimable**
Total events: 0 (CSE), 0 (Epidural)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.13.2 Opioid combined spinal-epidural versus test local anaesthetic/opioid epidural					
Dunn 1998	0/35	0/34			Not estimable
Subtotal (95% CI)	**35**	**34**			**Not estimable**
Total events: 0 (CSE), 0 (Epidural)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.13.3 Opioid combined spinal-epidural versus low-dose epidural					
Abouleish 1991	0/20	0/22			Not estimable
Subtotal (95% CI)	**20**	**22**			**Not estimable**
Total events: 0 (CSE), 0 (Epidural)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**185**	**190**			**Not estimable**
Total events: 0 (CSE), 0 (Epidural)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Not applicable					

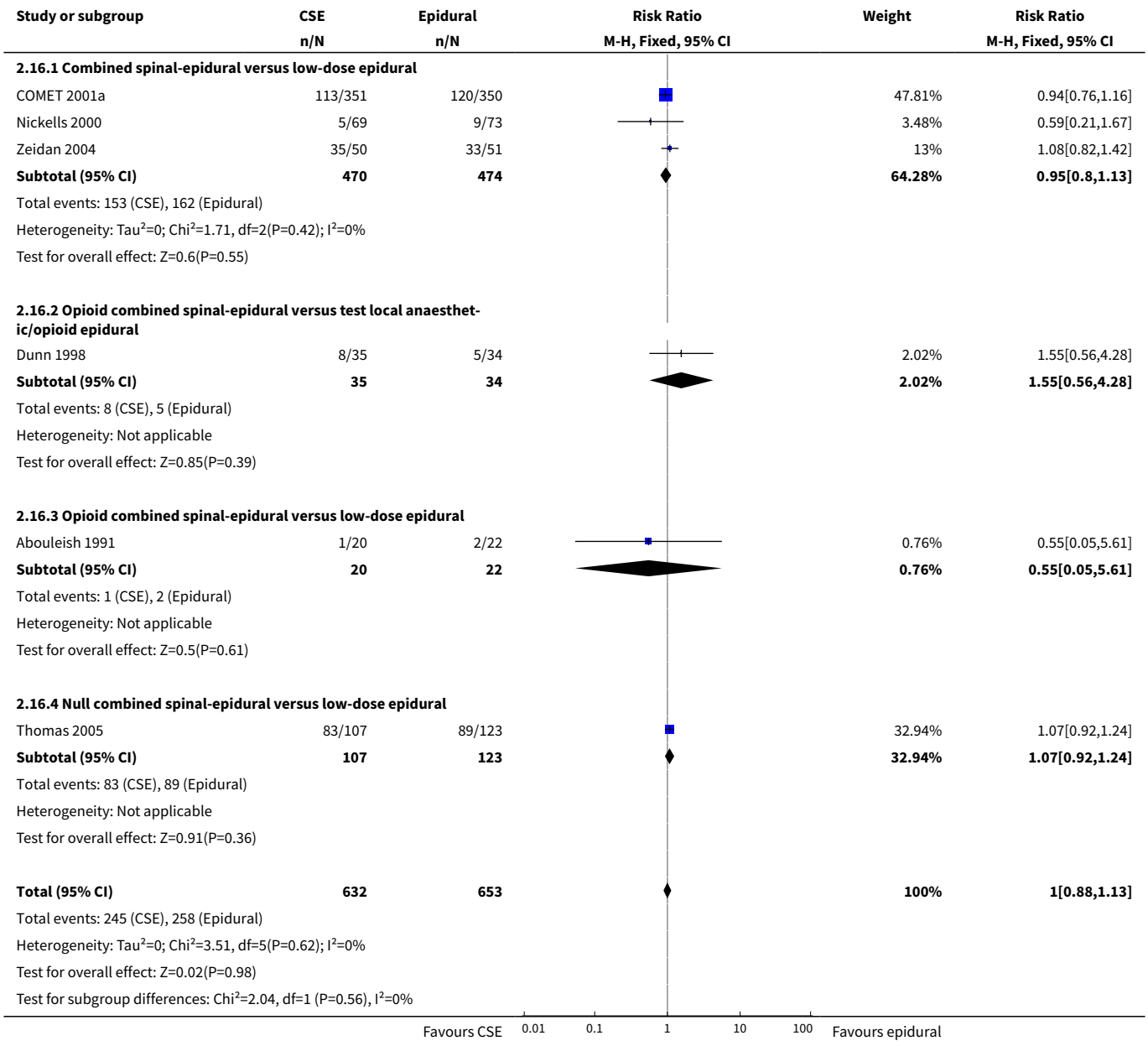


Analysis 2.14. Comparison 2 Combined spinal-epidural versus low-dose epidural, Outcome 14 Headache (any).

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.14.1 Combined spinal-epidural versus low-dose epidural					
Van de Velde 1999	0/55	3/55		100%	0.14[0.01,2.7]
Subtotal (95% CI)	**55**	**55**		**100%**	**0.14[0.01,2.7]**
Total events: 0 (Treatment), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.3(P=0.19)					
Total (95% CI)	**55**	**55**		**100%**	**0.14[0.01,2.7]**
Total events: 0 (Treatment), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.3(P=0.19)					

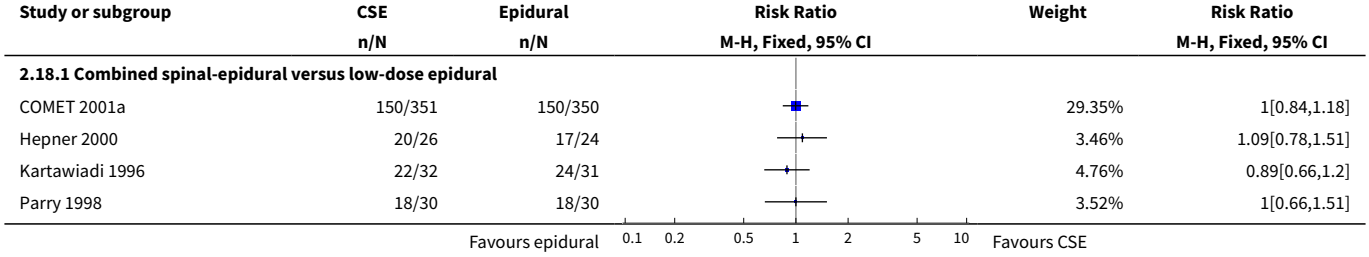


Analysis 2.16. Comparison 2 Combined spinal-epidural versus low-dose epidural, Outcome 16 Labour augmentation required.

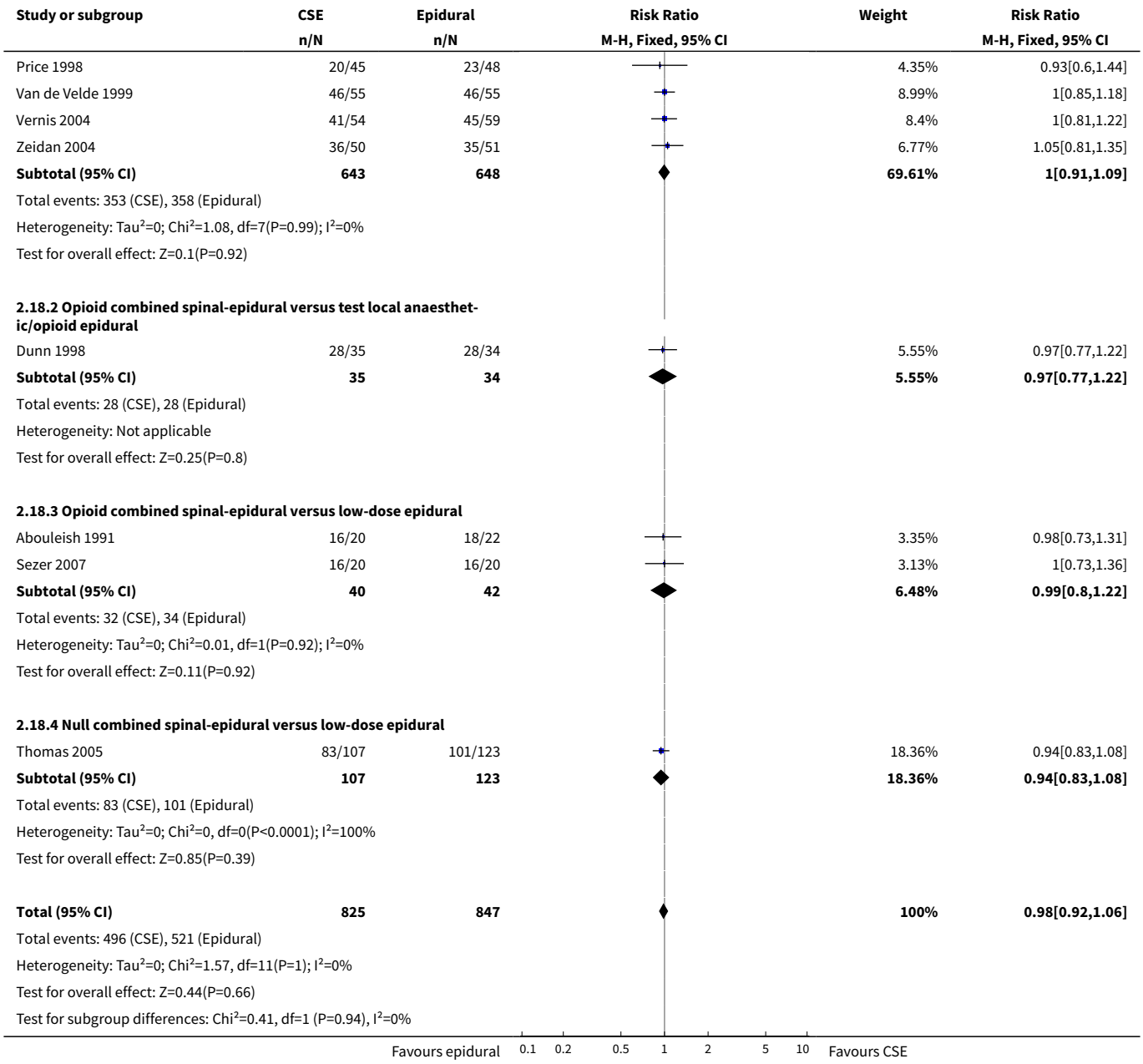


Study or subgroup	CSE n/N	Epidural n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.16.1 Combined spinal-epidural versus low-dose epidural					
COMET 2001a	113/351	120/350		47.81%	0.94[0.76,1.16]
Nickells 2000	5/69	9/73		3.48%	0.59[0.21,1.67]
Zeidan 2004	35/50	33/51		13%	1.08[0.82,1.42]
Subtotal (95% CI)	**470**	**474**		**64.28%**	**0.95[0.8,1.13]**
Total events: 153 (CSE), 162 (Epidural)					
Heterogeneity: Tau^2=0; Chi^2=1.71, df=2(P=0.42); I^2=0%					
Test for overall effect: Z=0.6(P=0.55)					
2.16.2 Opioid combined spinal-epidural versus test local anaesthetic/opioid epidural					
Dunn 1998	8/35	5/34		2.02%	1.55[0.56,4.28]
Subtotal (95% CI)	**35**	**34**		**2.02%**	**1.55[0.56,4.28]**
Total events: 8 (CSE), 5 (Epidural)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.85(P=0.39)					
2.16.3 Opioid combined spinal-epidural versus low-dose epidural					
Abouleish 1991	1/20	2/22		0.76%	0.55[0.05,5.61]
Subtotal (95% CI)	**20**	**22**		**0.76%**	**0.55[0.05,5.61]**
Total events: 1 (CSE), 2 (Epidural)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.5(P=0.61)					
2.16.4 Null combined spinal-epidural versus low-dose epidural					
Thomas 2005	83/107	89/123		32.94%	1.07[0.92,1.24]
Subtotal (95% CI)	**107**	**123**		**32.94%**	**1.07[0.92,1.24]**
Total events: 83 (CSE), 89 (Epidural)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.91(P=0.36)					
Total (95% CI)	**632**	**653**		**100%**	**1[0.88,1.13]**
Total events: 245 (CSE), 258 (Epidural)					
Heterogeneity: Tau^2=0; Chi^2=3.51, df=5(P=0.62); I^2=0%					
Test for overall effect: Z=0.02(P=0.98)					
Test for subgroup differences: Chi^2=2.04, df=1 (P=0.56), I^2=0%					

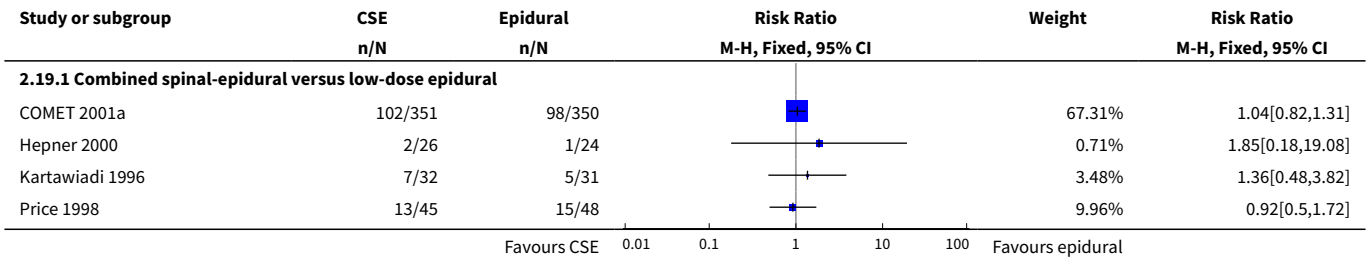
Analysis 2.18. Comparison 2 Combined spinal-epidural versus low-dose epidural, Outcome 18 Normal delivery.

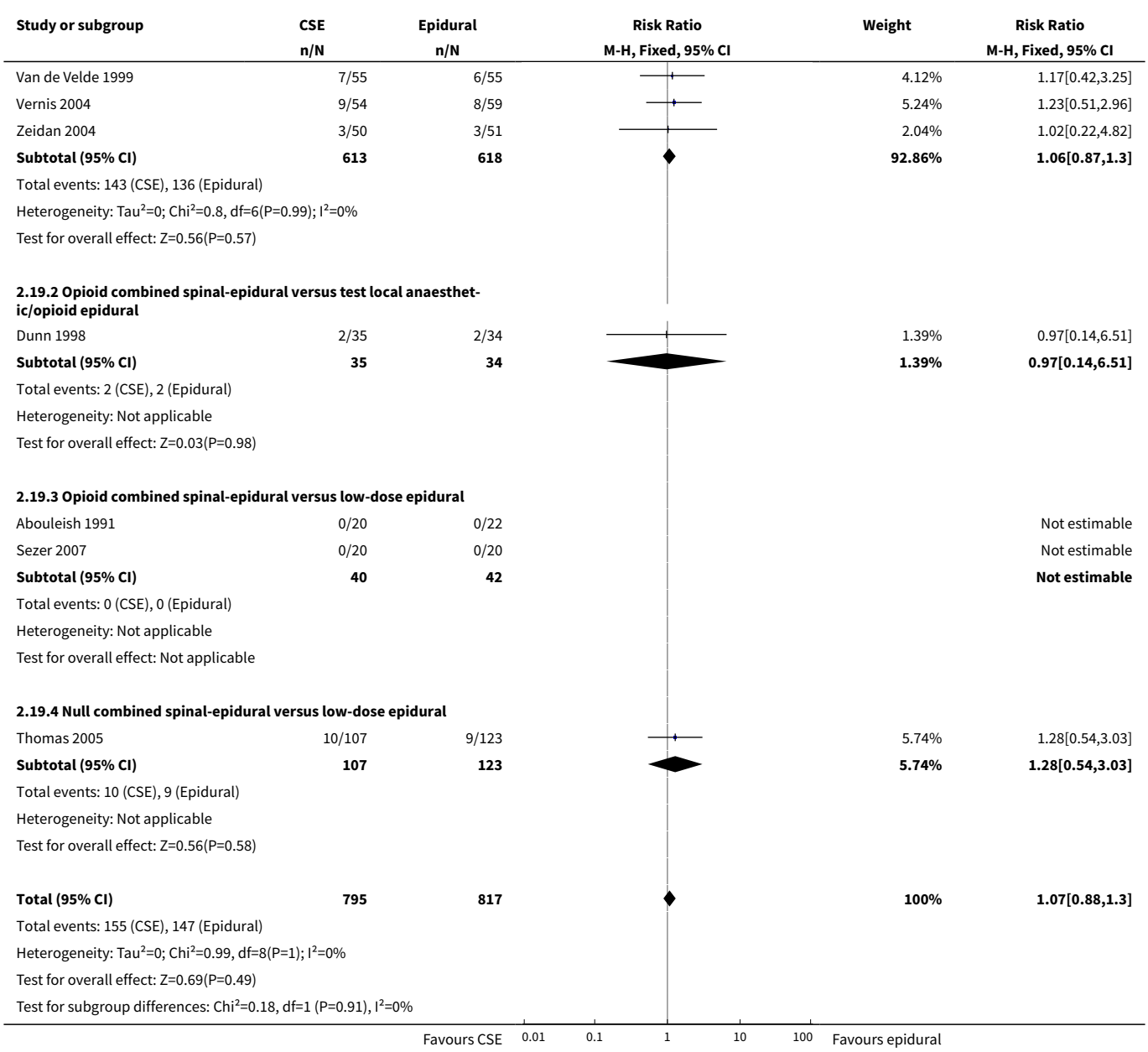


Study or subgroup	CSE n/N	Epidural n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.18.1 Combined spinal-epidural versus low-dose epidural					
COMET 2001a	150/351	150/350		29.35%	1[0.84,1.18]
Hepner 2000	20/26	17/24		3.46%	1.09[0.78,1.51]
Kartawiadi 1996	22/32	24/31		4.76%	0.89[0.66,1.2]
Parry 1998	18/30	18/30		3.52%	1[0.66,1.51]

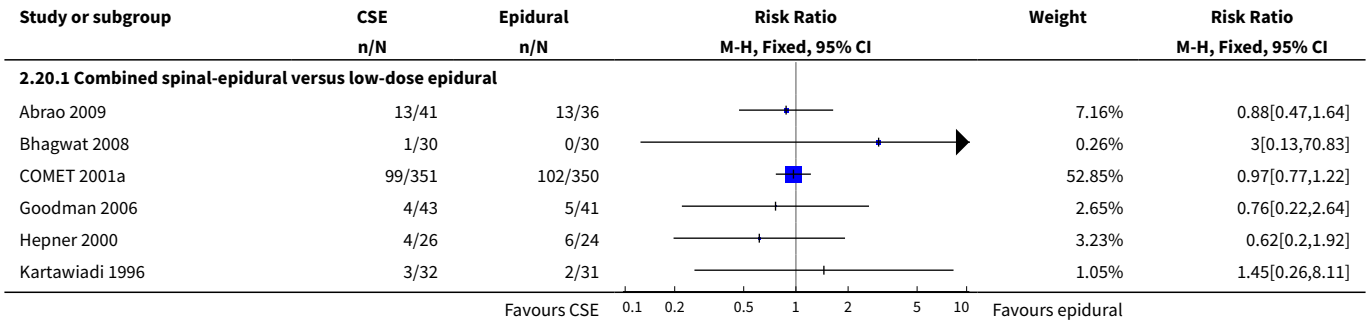


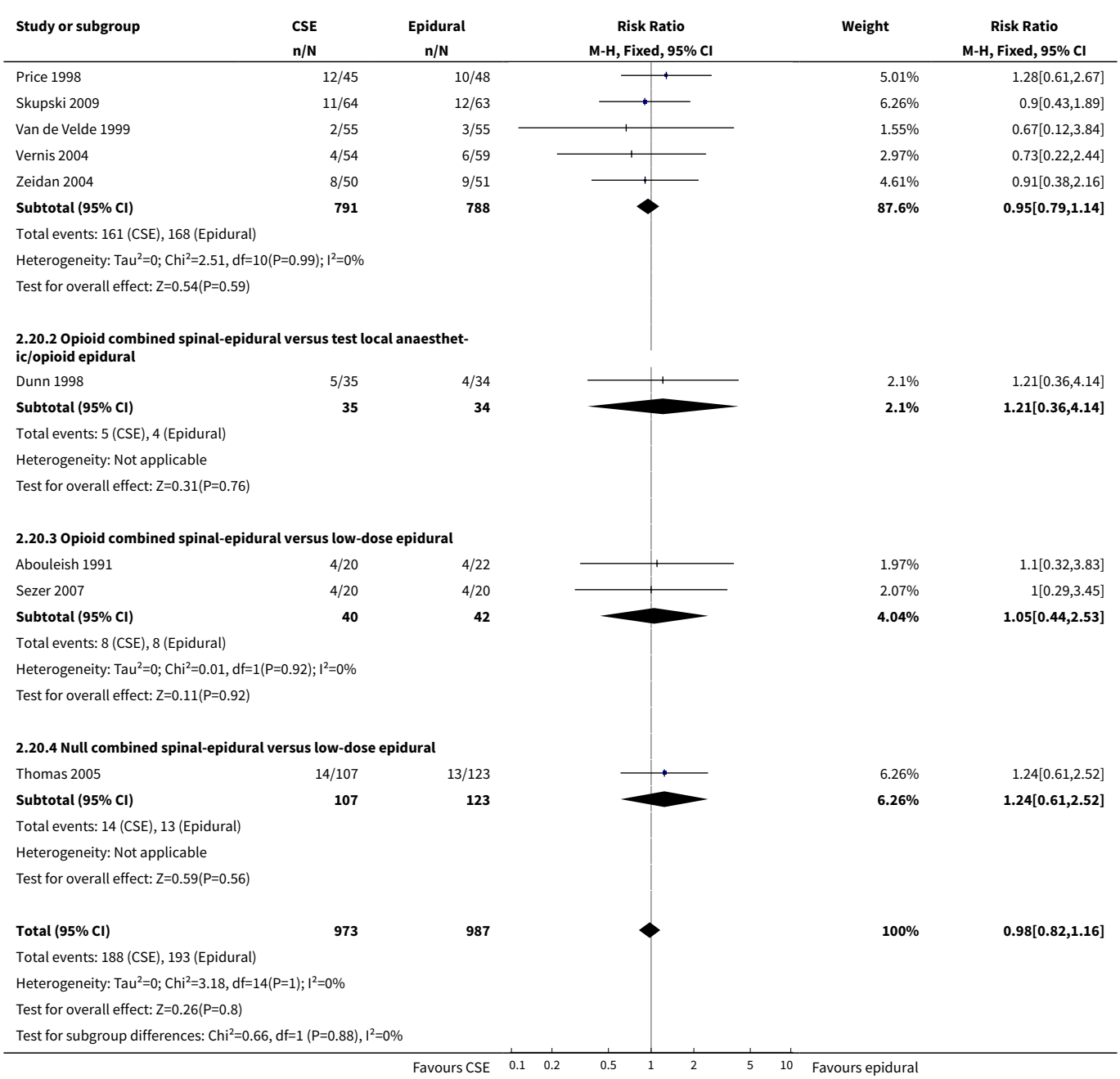
Analysis 2.19. Comparison 2 Combined spinal-epidural versus low-dose epidural, Outcome 19 Instrumental delivery.



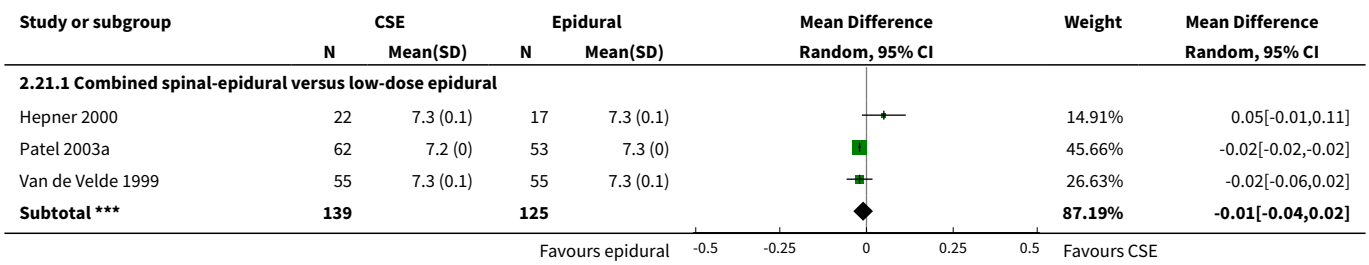


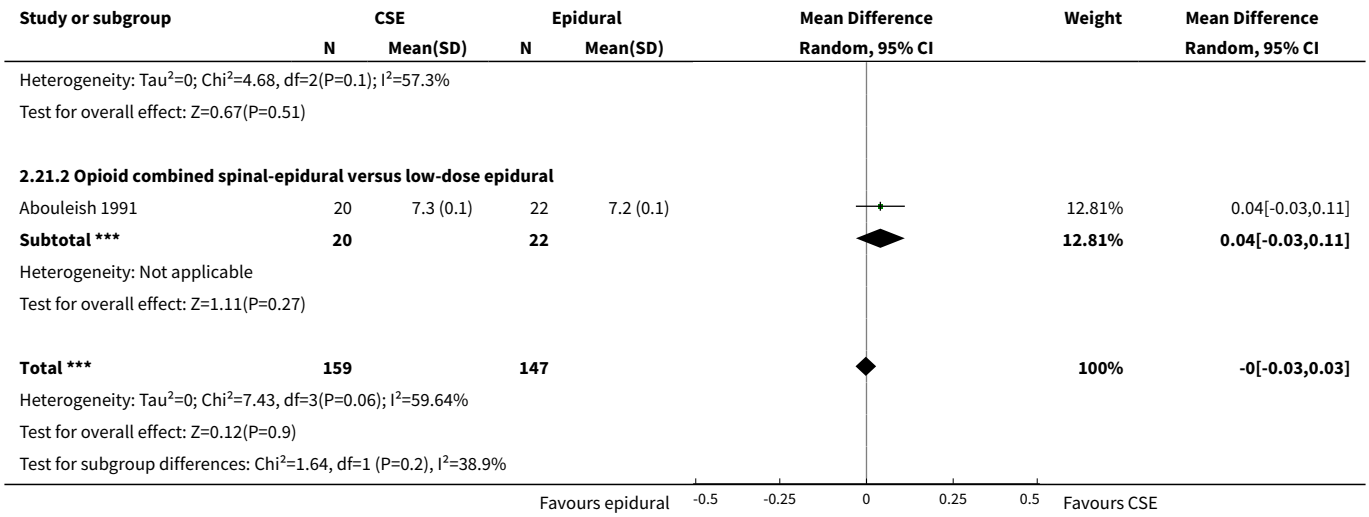
Analysis 2.20. Comparison 2 Combined spinal-epidural versus low-dose epidural, Outcome 20 Caesarean section.



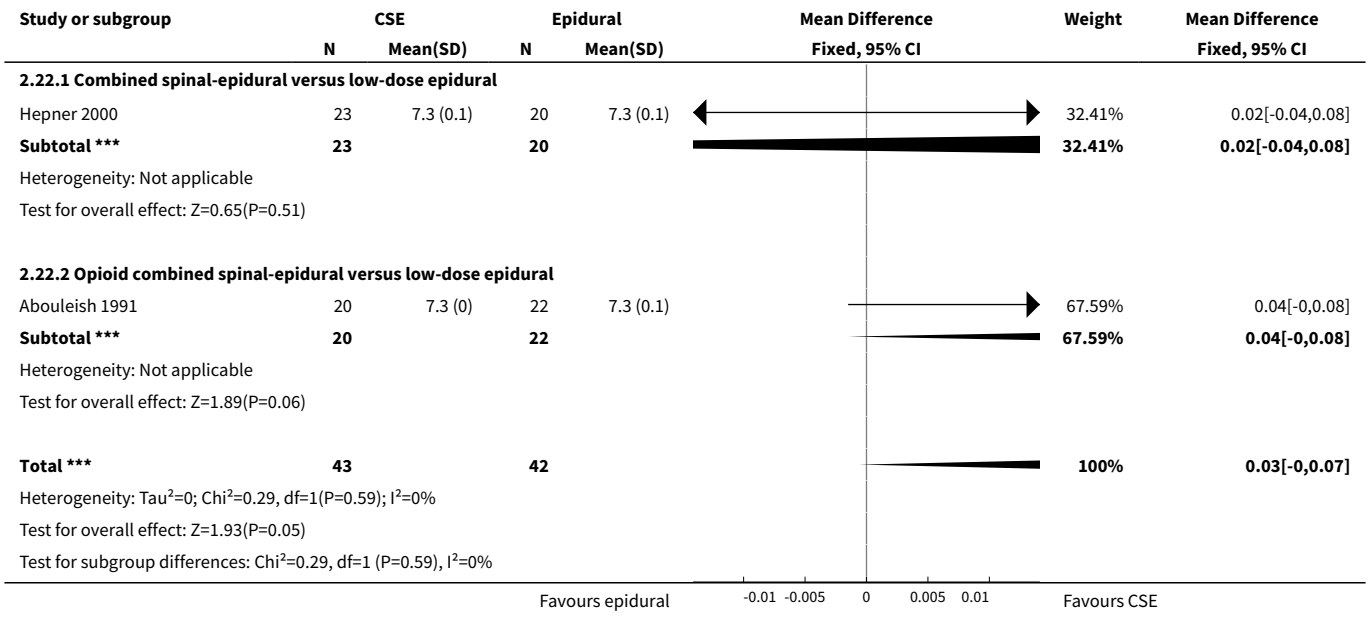


Analysis 2.21. Comparison 2 Combined spinal-epidural versus low-dose epidural, Outcome 21 Umbilical arterial pH.

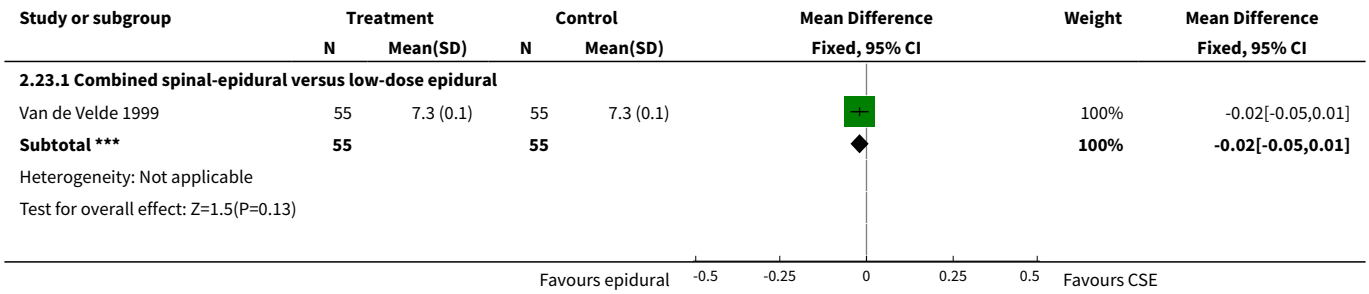


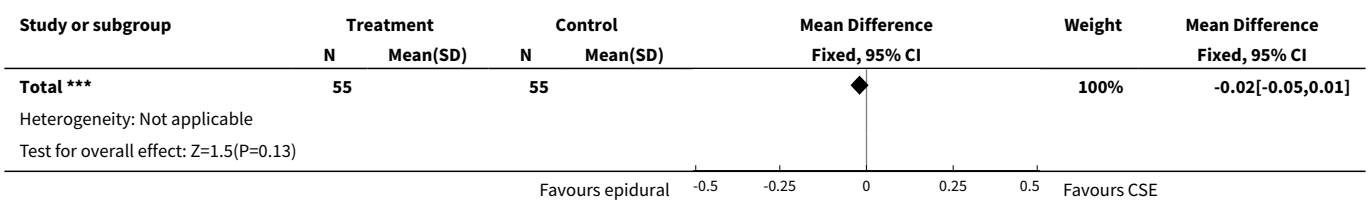


Analysis 2.22. Comparison 2 Combined spinal-epidural versus low-dose epidural, Outcome 22 Umbilical venous pH.

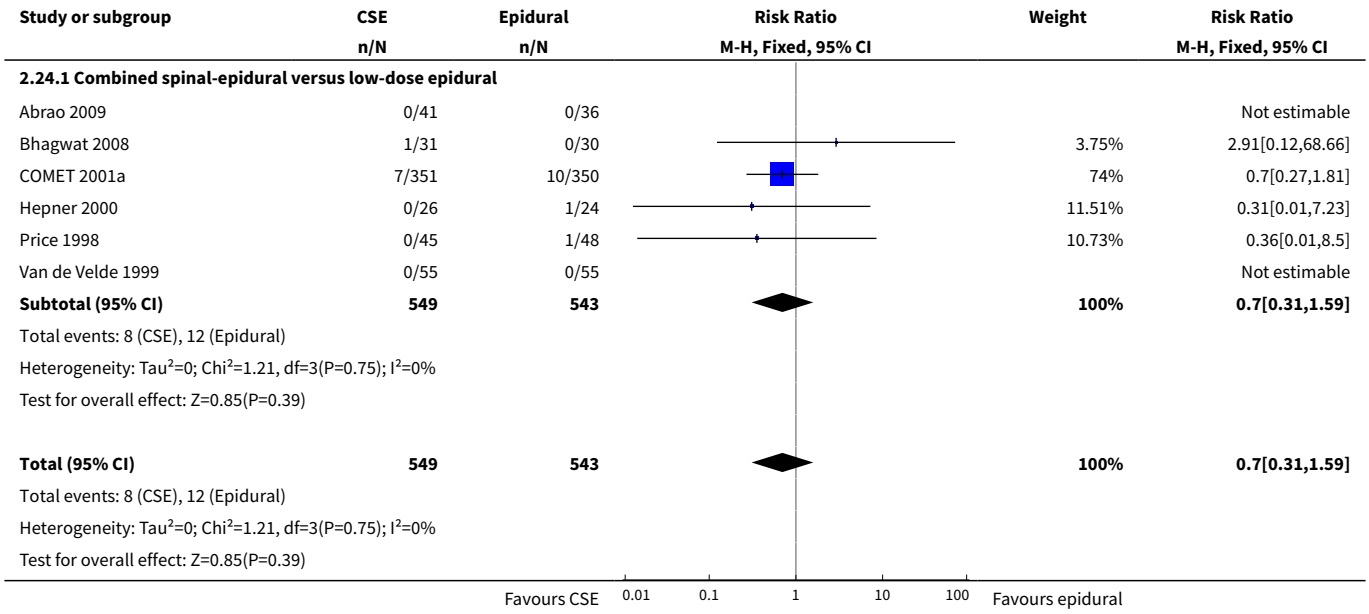


Analysis 2.23. Comparison 2 Combined spinal-epidural versus low-dose epidural, Outcome 23 Umbilical cord pH.

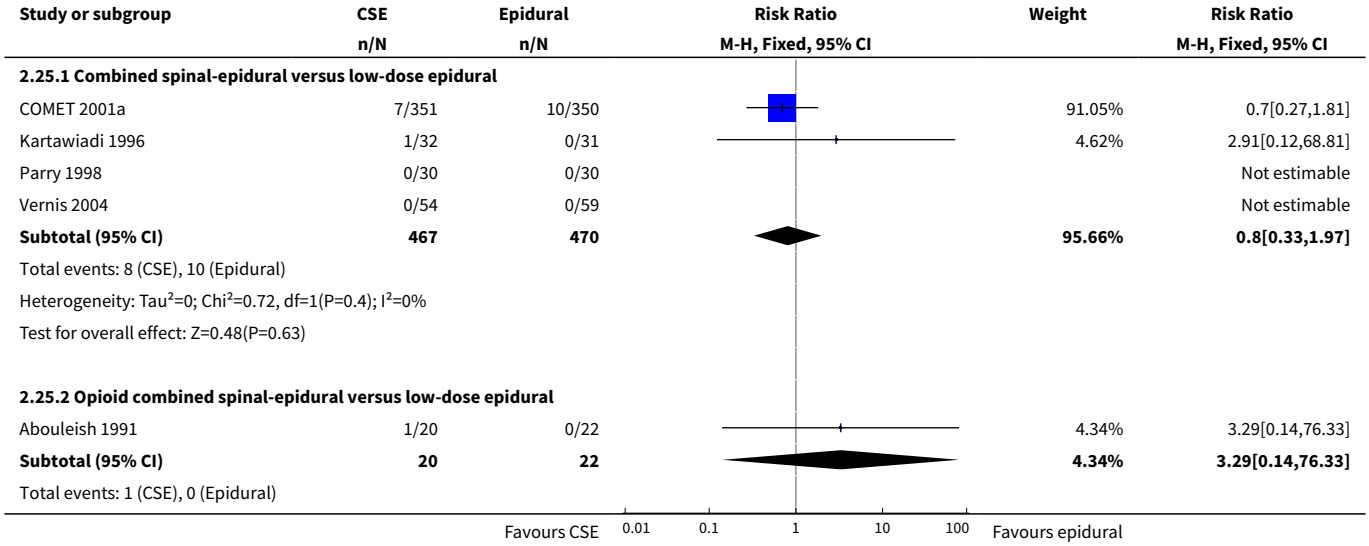


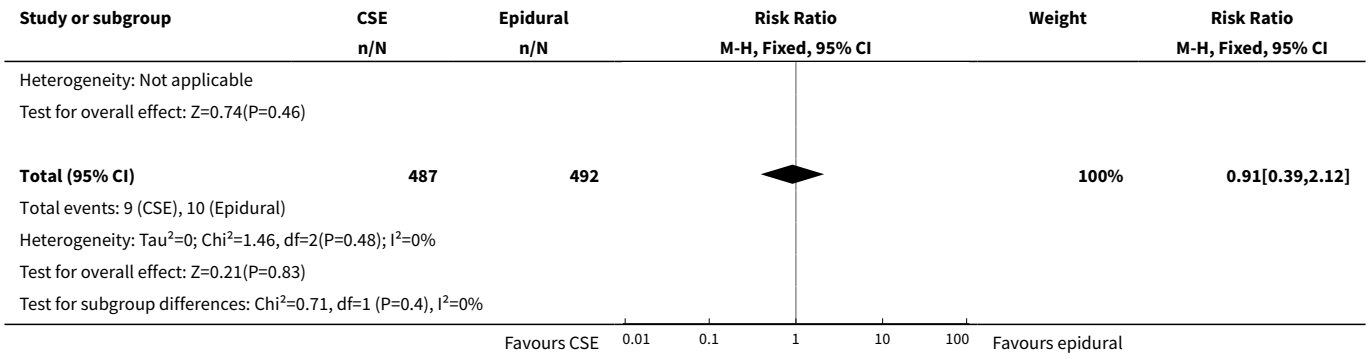


Analysis 2.24. Comparison 2 Combined spinal-epidural versus low-dose epidural, Outcome 24 Apgar score < 7 at 5 minutes.

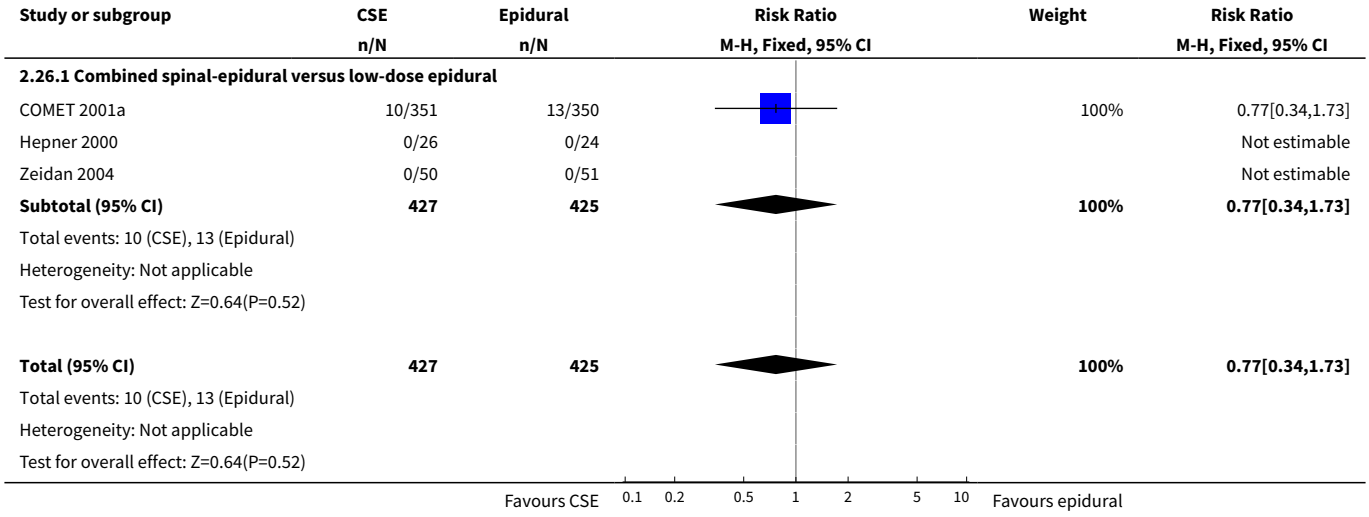


Analysis 2.25. Comparison 2 Combined spinal-epidural versus low-dose epidural, Outcome 25 Apgar score < 8 at 5 minutes.





Analysis 2.26. Comparison 2 Combined spinal-epidural versus low-dose epidural, Outcome 26 Number admitted to neonatal unit.



ADDITIONAL TABLES

Table 1. Epidural techniques used - initial dose and subsequent maintenance

INITIAL DOSE	Nil maintenance	Immediate infusion	Repeat boluses	Repeat boluses	Bolus/infusion	Repeat boluses	PCEA
		LA + opioid	High-dose LA	Low-dose LA	Low-dose LA/ opioid	Low-dose LA/ opioid	
Low-dose bupivacaine < 0.25%				Abouleish 1991			
Traditional dose bupivacaine = 0.25%		Gomez 2001 Ngamprasertwong 2007 Tsen 1999	COMET 2001a Cortes 2007				Thomas 2005
Low-dose bupivacaine < 0.25% + opioid	Parry 1998 Patel 2003a	Bhagwat 2008 COMET 2001a Goodman 2006 Skupski 2009			Hepner 2000 Medina 1994 Zeidan 2004	Abrao 2009 Kartawiadi 1996 Nickells 2000	Cohen 2006 Price 1998 Sezer 2007 Van de Velde 1999 Vernis 2004
Traditional dose bupivacaine + opioid		Caldwell 1994	Roux 1999				
Test lignocaine + opioid	Breen 1999 Dunn 1998						

LA: local anaesthetic
PCEA: patient-controlled epidural analgesia

Table 2. CSE techniques used - initial IT injection and subsequent epidural

CSE technique	Nil epidural	Immediate infusion	Immediate bolus/infusion	Immediate bolus/es	Delay bolus/infusion	Delayed boluses	PCEA
IT INJECTION							

Table 2. CSE techniques used - initial IT injection and subsequent epidural *(Continued)*

IT opioid only	Breen 1999 Dunn 1998	Ngamprasertwong 2007		Caldwell 1994	Abouleish 1991 Cortes 2007 Roux 1999	Sezer 2007
IT LA + opioid	Parry 1998 Patel 2003a	Bhagwat 2008 Goodman 2006 Skupski 2009	Gomez 2001	Hepner 2000 Medina 1994 Tsen 1999 Zeidan 2004	Abrao 2009 COMET 2001a Kartawiadi 1996 Nickells 2000	Cohen 2006 Price 1998 Van de Velde 1999 Vernis 2004
IT nil						Thomas 2005

CSE: combined spinal-epidural
IT: intrathecal
LA: local anaesthetic
PCEA: patient-controlled epidural analgesia

APPENDICES

Appendix 1. Methods used to assess trials included in previous versions of this review

Study identification

Types of studies to be considered for review included all published randomised controlled trials involving a comparison of combined spinal-epidural (CSE) with epidural analgesia initiated for women in the first stage of labour. Trials were identified for inclusion by three review authors independently. Details of reasons for exclusion of any trial considered for review have been clearly stated. If there were any disagreements regarding inclusion of potentially eligible trials these were resolved by discussion and, if necessary, arbitration by a fourth review author.

Quality assessment of included studies

- Three review authors independently assessed the quality of all relevant studies.
- Details of randomisation were recorded as satisfactory, unclear or unsatisfactory. Studies were excluded from the review if randomisation was clearly unsatisfactory, e.g. by day of the week, case note number, date of birth, etc.
- Concealment of allocation was described as adequate, inadequate or unclear.
- Blinding of outcome assessments and the number of women lost to follow-up in included studies was noted.

Data extraction

- Data were extracted using a structured form that captured patient demographics (e.g. primipara/multipara), stage of labour, use of oxytocics prior to regional technique.
- The technique and drug details of the CSE and the epidural groups were noted and classified.
- Three review authors independently extracted the data and differences resolved by referring to the original study.

Data analysis

- Dichotomous data were expressed as risk ratios.
- An intention-to-treat analysis was performed to include all randomised women where possible.

We assessed possible sources of heterogeneity by subgroup analyses and sensitivity analyses. The large diversity of both CSE and epidural techniques used resulted in up to six separate subgroup analyses being conducted. The definition of these groups is covered in detail under the 'Interventions' section below. 'CSE' groups consisted of both local anaesthetic and opioid, 'opioid CSE' groups used only opioids in the CSE, while the 'null CSE' group consisted of studies with a spinal puncture but no intrathecal injection of drugs. 'Low-dose' epidurals used less than 0.25% bupivacaine or equivalent. Some epidural groups used only a test dose of local anaesthetic, i.e. a relatively small dose at the time of initiating the block. Hence, separate analyses were performed for studies comparing:

- CSE with both traditional epidural regimens and also low-dose epidural techniques;
- other types of CSE regimens using an 'opioid only' spinal component with both traditional and low-dose techniques and also where only local anaesthetic as a test dose had been given.

Sensitivity analyses were performed by excluding trials that:

1. do not report comparable groups, e.g. with respect to parity, age, use of oxytocics prior to administration of the regional technique; or
2. where outcomes have not been or may not have been properly blinded.

We tested for publication bias using the funnel plot visually.

We performed statistical analyses with the Review Manager software (RevMan 2008) for calculation of the treatment effect as represented by either the random-effects or the fixed-effect models depending upon the status of heterogeneity.

WHAT'S NEW

Date	Event	Description
31 January 2012	New search has been performed	Search updated in September 2011 and nine new trials identified. Eight new studies have been included (Abrao 2009; Bhagwat 2008; Cohen 2006; Cortes 2007; Goodman 2006; Ngamprasertwong 2007; Sezer 2007; Skupski 2009) and one excluded (Cooper 2010).

Date	Event	Description
		We updated the search on 30 June 2012 and identified seven new reports for considertion at the next update (Nakamura 2009; Pascual 2011; Pascual-Ramirez 2010; Pascual-Ramirez 2011; Patel 2012; Sweed 2011; Wilson 2011) - see Characteristics of studies awaiting classification. The methods have been updated.
31 January 2012	New citation required but conclusions have not changed	Review updated.

HISTORY

Protocol first published: Issue 4, 2001
Review first published: Issue 4, 2003

Date	Event	Description
1 September 2008	Amended	Converted to new review format.
22 May 2007	New citation required and conclusions have changed	Comparisons were restructured to be more clinically relevant around combined spinal-epidural versus either traditional or low-dose epidural techniques. With this approach there appears to be little basis for recommending one technique over the other with there now being no difference in maternal satisfaction or other key outcomes.
31 December 2006	New search has been performed	Search updated. An additional five studies were included (Medina 1994; Patel 2003a; Thomas 2005; Vernis 2004; Zeidan 2004).

CONTRIBUTIONS OF AUTHORS

Planning of review: Allan Cyna.
Writing of draft protocol: Allan Cyna.
Revision of draft protocol: Allan Cyna, Scott Simmons.
Retrieving papers for review: Damien Hughes, Scott Simmons.
Extracting data from reviewed papers: Damien Hughes, Scott Simmons, Alicia Dennis, Neda Taghizadeh
Checking data prior to entry on Review Manager: Damien Hughes, Scott Simmons, Alicia Dennis, Neda Taghizadeh
Checking data entry on Review Manager: Damien Hughes, Scott Simmons, Alicia Dennis.
Writing of draft review: Damien Hughes, Scott Simmons, Allan Cyna.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Department of Health and Ageing, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have updated the methods to reflect the latest *Cochrane Handbook* (Higgins 2011).

INDEX TERMS

Medical Subject Headings (MeSH)

*Labor, Obstetric; Analgesia, Epidural [adverse effects] [*methods]; Analgesia, Obstetrical [adverse effects] [*methods]; Anesthesia, Epidural [adverse effects] [methods]; Anesthesia, Spinal [adverse effects] [*methods]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy