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Hyperbaric versus isobaric bupivacaine for spinal anaesthesia for caesarean section (Review)

Sng BL, Siddiqui FJ, Leong WL, Assam PN, Chan ESY, Tan KH, Sia AT

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[Intervention Review]

Hyperbaric versus isobaric bupivacaine for spinal anaesthesia for caesarean section

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ABSTRACT

Background

Bupivacaine is an amide local anaesthetic used in hyperbaric and isobaric forms. These are administered intrathecally into the spine to provide regional anaesthesia for caesarean section. Several trials have compared hyperbaric and isobaric bupivacaine but none have conclusively shown the benefit of either. This review was first published in 2013 and updated in 2016.

Objectives

Our objectives were to:

1. Determine the effectiveness of hyperbaric bupivacaine compared to isobaric bupivacaine for spinal anaesthesia in women undergoing caesarean section;
2. Determine the safety of hyperbaric bupivacaine compared to isobaric bupivacaine for spinal anaesthesia in women undergoing caesarean section.

Search methods

We originally searched the following databases to January 2011: CENTRAL, MEDLINE and Embase.

For this update, we reran our search in the above databases from January 2011 to March 2016; two studies are awaiting a response from authors for assessment and will be dealt with when we next update the review.

We imposed no language restriction.

Selection criteria

We included all randomized controlled trials (RCTs) involving parturients undergoing spinal anaesthesia for elective caesarean section that compared the use of hyperbaric with isobaric bupivacaine.

Data collection and analysis

Two authors independently extracted the data. The data that were extracted included the number of events and the sample sizes in both the intervention and control groups. For continuous outcomes, we extracted mean and standard deviation.

Hyperbaric versus isobaric bupivacaine for spinal anaesthesia for caesarean section (Review)

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We reported odds ratios (ORs) and risk ratios (RRs) for binary outcomes, and mean differences (MDs) for continuous outcomes.

Main results

We included three new RCTs in this update, which now comprises 10 studies with a total of 614 participants. We judged most trials as having uncertain risk of bias regarding randomization. Other than this, the overall risk of bias was low. Most included trials had small sample sizes. All of the trials assessed the primary outcome of conversion to general anaesthesia. Ten trials comparing anaesthesia performed with hyperbaric and isobaric bupivacaine failed to show any difference in need for conversion to general anaesthesia (RR 0.33, 95% CI 0.09 to 1.17, 614 participants, *very low quality of evidence*). Nine trials also failed to show a difference in the need for supplemental analgesics (RR 0.61, 95% CI 0.26 to 1.41, 554 participants, *very low quality of evidence*). Four trials comparing requirement for ephedrine did not show any difference (RR 0.89, 95% CI 0.57 to 1.38, 256 participants, *very low quality of evidence*). Seven trials did not provide convincing evidence of difference in nausea and vomiting (RR 0.99, 95% CI 0.57 to 1.72, 433 participants, *low quality of evidence*). Three trials failed to show a difference in headache (OR 1.82, 95% CI 0.47 to 6.99, 234 participants, *low quality of evidence*). Two trials showed that the time until sensory block to the thoracic 4th (T4) spinal level was shorter with hyperbaric bupivacaine (MD -1.06 minutes, 95% CI -1.80 to -0.31, 128 participants, *moderate quality of evidence*). Six trials showed no difference in the amount of ephedrine used (RR 0.23, 95% CI -1.65 to 2.12, 386 participants, *moderate quality of evidence*). Three trials failed to show any difference in high block (RR 0.88, 95% CI 0.16 to 4.90, 205 participants).

Authors' conclusions

Data are limited for some of the outcomes. Reporting of the included trials is less than optimal. For these reasons the overall quality of evidence is low or very low for most of the outcomes, based on the GRADE method of assessment. This review found that intrathecal hyperbaric bupivacaine had a more rapid onset of sensory blockade at the 4th thoracic vertebra (T4) level than isobaric bupivacaine. However, despite incorporating more data in the analysis, we found little evidence that the need for conversion to general anaesthesia and supplemental analgesia differed between the hyperbaric or isobaric bupivacaine groups. This is mainly due to the rarity of these outcomes, variability in the dose, use of adjuvant drugs and differences in the technique used for regional anaesthesia. There were no differences in the adverse effects studied. Any possible advantage of hyperbaric bupivacaine needs to be confirmed in larger randomized trials. In future research, criteria for conversion to general anaesthesia need to be defined objectively and applied uniformly.

PLAIN LANGUAGE SUMMARY

Does denser compared to normal bupivacaine, given as a lower back injection, give more effective and safer anaesthesia during caesarean section

Background: A pain-relieving drug, bupivacaine, is used during caesarean section through lower back injection. However, it is not clear that using hyperbaric bupivacaine (denser than the spinal fluid) is more or less effective in pain relief than isobaric bupivacaine (density equal to the spinal fluid). This Cochrane Review summarizes the best available evidence for the effectiveness and safety of the denser form of bupivacaine compared to the isobaric form when spinal anaesthesia (injection of medications into the lower back) is used for delivery of a baby by caesarean section.

Study characteristics: The evidence is current to March 2016. We found 10 clinical trials evaluating these two types of bupivacaine, involving 614 women. The studies assessed the following effects of the two types of medicine: women needing to switch to general anaesthesia, additional drugs for pain relief or low blood pressure, experiencing nausea and vomiting, headache and excessive numbness. We found that all the studies had been done properly. None of them reported their source of funding. We await responses from the authors of two more studies, and will cover these when we next update the review.

Key results: We found that there is insufficient evidence to establish whether denser or normal bupivacaine is the more effective in reducing the need for: a) switching to general anaesthesia; b) additional pain relief medication. Denser bupivacaine had a more rapid onset of pain relief.

Quality of evidence: Due to the differences among the included studies in doses given, variety of additional drugs used for pain relief, variation in regional anaesthesia techniques and the small numbers of participants, we rated the overall quality of evidence for different outcomes from very low to moderate, as very few women experienced untoward events in all trials.

Conclusion: We conclude that the denser form provides faster pain relief than the normal one. More research is required to be certain about the effectiveness of the denser form for other outcomes.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Hyperbaric bupivacaine compared to Isobaric bupivacaine for spinal anaesthesia for caesarean section

Hyperbaric bupivacaine compared to isobaric bupivacaine for spinal anaesthesia for caesarean section

Patient or population: women with spinal anaesthesia for caesarean section

Settings: Hospitals in various countries

Intervention: Hyperbaric bupivacaine

Comparison: Isobaric bupivacaine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Isobaric bupivacaine	Hyperbaric bupivacaine				
Conversion to GA ⁴	Study population		RR 0.33 (0.09 to 1.17)	614 (10 studies)	⊕⊕⊕⊕ very low ^{1,2}	
	26 per 1000	9 per 1000 (2 to 31)				
	Low					
	15 per 1000	5 per 1000 (1 to 18)				
	High					
	35 per 1000	12 per 1000 (3 to 41)				
Supplemental analgesia ⁵	Study population		RR 0.61 (0.26 to 1.41)	554 (9 studies)	⊕⊕⊕⊕ very low ^{1,3}	
	40 per 1000	24 per 1000 (10 to 56)				
	Low					
	30 per 1000	18 per 1000 (8 to 42)				

	High			
	50 per 1000	31 per 1000 (13 to 70)		
Requirement for ephedrine ⁶	Study population		RR 0.89 (0.57 to 1.38)	256 (4 studies)
	508 per 1000	452 per 1000 (290 to 701)		⊕⊕⊕⊕ very low ^{1,3}
	Low			
	400 per 1000	356 per 1000 (228 to 552)		
	High			
	600 per 1000	534 per 1000 (342 to 828)		
Nausea and vomiting ⁷	Study population		RR 0.99 (0.57 to 1.72)	433 (7 studies)
	248 per 1000	245 per 1000 (141 to 426)		⊕⊕⊕⊕ low ¹
	Low			
	200 per 1000	198 per 1000 (114 to 344)		
	High			
	300 per 1000	297 per 1000 (171 to 516)		
Headache ⁸ Participant-re- ported	Study population		OR 1.82 (0.47 to 6.99)	234 (3 studies)
	34 per 1000	61 per 1000 (17 to 200)		⊕⊕⊕⊕ low ^{1,3}
	Low			
	20 per 1000	36 per 1000		

	(10 to 125)			
	High			
	40 per 1000	70 per 1000 (19 to 226)		
Time to der-matomal block T4 block (mins)⁹	The mean time to der-matomal block t4 block (mins) ranged across control groups from 4.0 to 6.5 minutes	The mean time to dermatomal block t4 block (mins) in the intervention groups was 1.06 lower (1.8 to 0.31 lower)	128 (2 studies)	⊕⊕⊕⊖ moderate ¹
Amount of ephedrine used(mg/per-son)¹⁰	The mean amount of ephedrine used(mg/person) ranged across control groups from 11.8 - 35 mg/person	The mean amount of ephedrine used(mg/person) in the intervention groups was 0.23 higher (1.65 lower to 2.12 higher)	386 (6 studies)	⊕⊕⊕⊖ moderate ¹

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

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Most of the studies did not provide details of randomization methods employed. Hence labelled as having 'Uncertain risk of bias'.

²The results are not precise due to paucity of numbers and conclusion changes at limits of the pooled CI. Results are also sensitive to methods of analysis.

³Conclusion changes at two limits of 95% CI of the pooled estimate

⁴Evidence downgraded for risk of bias by 1 level. Evidence downgraded for imprecision by 2 levels.

⁵Evidence downgraded for risk of bias by 1 level. Evidence downgraded for imprecision by 2 levels.

⁶Evidence downgraded for risk of bias by 1 level. Evidence downgraded for imprecision by 2 levels.

⁷Evidence downgraded for risk of bias by 1 level. Evidence downgraded for imprecision by 2 levels.

⁸Evidence downgraded for risk of bias by 1 level. Evidence downgraded for imprecision by 2 levels.

⁹Evidence downgraded for risk of bias by 1 level.

¹⁰Evidence downgraded for risk of bias by 1 level.

BACKGROUND

The incidence of caesarean section is reported to be 27.3% in an Asian global study (Lumbiganon 2010), and ranges from 15% in Thailand, 36% in Korea, to 48% in Sweden (Chanrachakul 2000; Chung 2014; Odland 2003). For non-emergency caesareans, regional anaesthesia is generally preferred to general anaesthesia. In some tertiary centres the use of regional anaesthesia for caesarean section is as high as 96.4% (Tsen 1998).

Since 1982, bupivacaine is the most commonly used local anaesthetic in regional anaesthesia for caesarean section (Russell 1982). It is available in two forms: an isobaric form with equal density to the spinal fluid, and a denser hyperbaric form. Both forms have been widely used intrathecally (injecting a drug beneath the spine's arachnoid membrane and directly into the spinal fluid) to provide anaesthesia for caesarean section (Vercauteren 1998). This is known as spinal anaesthesia and is distinct from the other type of regional anaesthesia, epidural anaesthesia.

Several trials have compared hyperbaric bupivacaine and isobaric bupivacaine, but none have conclusively shown one to be better than the other (Sarvela 1999; Vercauteren 1998). This updated systematic review summarizes the best available evidence regarding the effectiveness and safety of hyperbaric bupivacaine compared to isobaric bupivacaine when used to provide spinal anaesthesia for caesarean section.

Description of the condition

Spinal anaesthesia is a common anaesthetic technique used for caesarean delivery. Local anaesthetics or opioids, or both, are administered in the spinal space to cause numbness and weakness in the lower part of the body, to enable the surgeon to perform the caesarean delivery without pain or discomfort to the woman. Bupivacaine, a long-acting local anaesthetic, is the most commonly used. Opioids such as fentanyl, sufentanil and morphine are sometimes co-administered to supplement the effect of the local anaesthetic. There are two forms of commercially-available bupivacaine, isobaric and hyperbaric bupivacaine. The side effects associated with regional anaesthesia for caesarean section include total spinal anaesthesia and hypotension.

Description of the intervention

The denser (hyperbaric) bupivacaine is produced by the addition of glucose (80 mg/mL) to isobaric or plain bupivacaine. The difference in density between the two forms is believed to affect their diffusion patterns and distribution after injection into the intrathecal space.

How the intervention might work

Several trials have shown that hyperbaric bupivacaine appears to cause more predictable sensory blockade than isobaric bupivacaine. The two forms of bupivacaine also appear to differ in their motor blockade pattern (inability to move the lower limbs) and duration of action.

Why it is important to do this review

This review was undertaken to establish the effectiveness and safety of hyperbaric versus isobaric bupivacaine, used in spinal anaesthesia for caesarean section. If one intervention were shown to be more efficacious or safer, the practice of spinal anaesthesia

may be more standardized for caesarean section. The review was first published in 2013 and updated in 2016 (Sia 2013).

OBJECTIVES

Our objectives were to:

1. Determine the effectiveness of hyperbaric bupivacaine compared to isobaric bupivacaine for spinal anaesthesia in women undergoing caesarean section;
2. Determine the safety of hyperbaric bupivacaine compared to isobaric bupivacaine for spinal anaesthesia in women undergoing caesarean section.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs).

Types of participants

We included women undergoing spinal anaesthesia for elective caesarean section requiring the use of hyperbaric bupivacaine or isobaric bupivacaine. We excluded participants with underlying morbidities, undergoing emergency caesarian section, or those women who were in preterm labour.

Types of interventions

We included studies that compared hyperbaric bupivacaine to isobaric bupivacaine in spinal anaesthesia for caesarean section.

We also included studies that used anaesthetic combinations containing spinal opioids (for example, fentanyl, morphine) and those using the combined spinal-epidural technique. The combined spinal-epidural technique involves the use of local anaesthetics in the intrathecal space via a spinal needle that passes through an epidural needle. This is followed by the placement of an epidural catheter without local anaesthetic in the epidural space. This procedure qualifies as a spinal anaesthetic technique, as the local anaesthetic is only introduced into the intrathecal space and not into the epidural space.

We excluded studies using the sequential combined spinal-epidural technique (use of local anaesthetic in both the intrathecal space and epidural space at initiation of anaesthesia), other local anaesthetics concomitantly, regional anaesthesia, or any other form of anaesthesia for caesarean section.

Types of outcome measures

Primary outcomes

1. Inadequate pain control requiring conversion to general anaesthesia (dichotomous)
2. Inadequate pain control requiring use of supplemental analgesics (dichotomous)

Secondary outcomes

1. Requirement for ephedrine (dichotomous)
2. Occurrence of nausea and vomiting (dichotomous)

3. Occurrence of headache within seven days from spinal anaesthesia (dichotomous)
4. Time to dermatomal block at the 4th thoracic vertebra (T4) level (continuous)
5. Amount of ephedrine used (mg/person) (continuous)
6. Occurrence of high dermatomal sensory block (above the cervical vertebra 8 (C8 level)) (dichotomous)

Search methods for identification of studies

Electronic searches

For the original review we searched the databases to January 2011 (Sia 2013).

In this updated version we reran the searches in the following databases from January 2011 to March 2016.

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, 2015 Issue 3); MEDLINE (January 1966 to May 2015); and Embase (January 1980 to May 2015).

Our search strategies are provided in Appendices (CENTRAL, [Appendix 1](#); MEDLINE, [Appendix 2](#); Embase, [Appendix 3](#)).

We also searched the Cochrane Pregnancy and Childbirth Group Trials Register with the Highly Sensitive Search Strategy (HSSS) found in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), with the help of their Information Specialist.

The Cochrane Pregnancy and Childbirth Group Trials Register is maintained by their Information Specialist and contains trials identified from:

1. Quarterly searches of CENTRAL;
2. Monthly searches of MEDLINE;
3. Handsearches of 30 journals (including the *International Journal of Obstetric Anesthesia*) and the proceedings of major conferences;
4. A weekly current awareness search of a further 37 journals.

Trials identified through the searching activities described above are given a topic code (or codes) linked to review topics. The Cochrane Pregnancy and Childbirth Group Information Specialist searches the register for each review using these codes rather than keywords.

We placed no language restrictions on our searches.

Searching other resources

We searched the three major anaesthesia conference abstracts, namely the Australian and New Zealand College of Anaesthetists meeting, the American Society of Anesthesiologists meeting and the European Society of Anaesthesia meeting from 1990 to 2015. We identified no additional abstracts.

We handsearched journals for the original review (2013), but did not handsearch journals for the updated search (see [Differences between protocol and review](#)).

Data collection and analysis

Three authors (WL, BS, FJS) independently collected data from the included studies on a standardized data collection form and a fourth author (AS) resolved disagreements.

Selection of studies

Three authors (WL, BS, FJS) independently reviewed the titles and abstracts from the searches. We retrieved full-text copies of the relevant articles and assessed these according to the '[Criteria for considering studies for this review](#)'.

Data extraction and management

Two authors (WL, FJS) independently extracted the data from the study using a standardized form. We extracted information pertaining to the study design, method of randomization, use of allocation concealment, reporting of the study setting and participants, inclusion and exclusion criteria, sample size, interventions and outcomes. The outcome data included conversion to general anaesthesia, use of supplemental analgesics, complications and rescue interventions during the caesarean section. WL and FJS entered the data independently and BS and AS checked them.

Assessment of risk of bias in included studies

Two authors (FJS, WL) independently assessed trial quality, and a third author (BS) resolved any disagreements.

Based on the Cochrane 'Risk of bias' tool in Review Manager 5 (RevMan 2014), we considered the following:

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective reporting.
7. Other potential bias.

We graded each of the above dimensions of trial quality as low risk, high risk, or unclear risk of bias.

Measures of treatment effect

For data synthesis of dichotomous outcomes we used the Mantel-Haenszel method; for continuous outcomes we used the inverse variance method. Risk ratios were reported by the studies for binary outcomes, so we reported summary results using the same effect measure. We used the MD to pool the results of the continuous outcomes, as all included studies measured outcomes on the same scale.

Unit of analysis issues

We excluded non-randomized studies. We did not include any study that used cross-over or cluster-randomization designs. Hence the participant was the unit of analysis in all of the included studies.

Dealing with missing data

We attempted to contact the authors if key information was unavailable in the publications.

Assessment of heterogeneity

We evaluated clinical heterogeneity by qualitatively appraising the differences in study characteristics such as participants, interventions, outcomes assessed and study methodology. We justified quantitative pooling of the data by a consensual clinical judgement of sufficient clinical homogeneity. We informally evaluated and investigated the degree of statistical heterogeneity by visual inspection of forest plots, and more formally by the I^2 statistic (Higgins 2002). We refrained from quantitative synthesis if a high degree of statistical heterogeneity existed, that is, I^2 above 75%.

Assessment of reporting biases

We checked the methodology sections and study protocols of the primary studies where available. We did not present a funnel plot or any other method as there were too few studies to enable us to obtain reliable information from a funnel plot.

Data synthesis

We used the random-effects model where clinical heterogeneity could not be explained but statistical heterogeneity remained below the cut-off used for 'high' heterogeneity. Otherwise we preferred fixed-effect estimates, as it was deemed appropriate on both clinical and statistical grounds.

Subgroup analysis and investigation of heterogeneity

We did not anticipate any subgroup analysis as there were only 10 included studies and not all of the included studies provided information for all the outcomes. The participant characteristics were also homogeneous, being restricted to pregnant women requiring elective caesarean section. There were some other methodological differences which we took into account by using the random-effects model.

Sensitivity analysis

We planned to conduct sensitivity analysis to evaluate the effect of the method of analysis on the results where events are infrequent. As no single method could be satisfactorily employed, we have used

the Peto, Mantel-Haenszel and inverse variance methods to assess the stability of the results.

Summary of findings

For assessments of the overall quality of evidence for each outcome that included pooled data from RCTs only, we downgraded the evidence from 'high quality' by one level for serious (or by two for very serious) study limitations (risk of bias), indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias. We did not include any non-randomized study in our analysis. We used the GRADE approach to interpret findings (Langendam 2013) and the GRADE profiler (GRADEPRO) allowed us to import data from Review Manager 5 to create a 'Summary of findings' tables. This provides outcome-specific information concerning the overall quality of evidence from studies included in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on the outcomes we considered.

We included the following outcomes in the 'Summary of findings' table:

1. Inadequate pain control requiring conversion to general anaesthesia (dichotomous)
2. Inadequate pain control requiring use of supplemental analgesics (dichotomous)
3. Requirement for ephedrine (dichotomous)
4. Occurrence of nausea and vomiting (dichotomous)
5. Occurrence of headache within seven days from spinal anaesthesia (dichotomous)
6. Time to dermatomal block at the thoracic T4 level (continuous)
7. Amount of ephedrine used (mg/person) (continuous)

RESULTS

Description of studies

Results of the search

See [Figure 1](#)

Figure 1. Article search flow diagram (March 2016).

We searched the databases in March 2016, and identified 1048 titles. This included those we had identified for the original review (Sia 2013). We removed 1025 of the 1048 titles, as being either duplicates or irrelevant at the title- or abstract-screening stage. After screening by title and abstract, we obtained full texts for 23 citations that we judged to be potentially eligible for inclusion in the review. Of these 23 citations, 12 did not fulfil our inclusion criteria and were excluded for the following reasons:

See [Characteristics of excluded studies](#).

Included studies

We included nine articles covering 10 studies (Das Neves 2003; Javed 2014; Punshi 2012; Richardson 1998; Russell 1987; Saracoglu 2011a; Saracoglu 2011b; Sarvela 1999; Vercauteren 1998; Vichitvejpaisal 1992) reporting results from 614 participants. One study randomized the participants into four groups (Saracoglu 2011a). Two of those four groups received morphine, with one receiving isobaric and the other hyperbaric bupivacaine. The remaining two groups received fentanyl, with one receiving isobaric and the other hyperbaric bupivacaine. We treated these two sets as separate independent trials, since there was no issue of double counting or adjusting for correlation. These two trials are identified as Saracoglu 2011a and Saracoglu 2011b.

All 10 studies enrolled women at term and excluded women with complicated pregnancies. See [Characteristics of included studies](#). Four studies used the combined spinal-epidural technique with intrathecal injection (Saracoglu 2011a; Saracoglu 2011b; Sarvela 1999; Vercauteren 1998), whilst the remaining six studies used the spinal anaesthesia technique (Das Neves 2003; Javed 2014; Punshi 2012; Richardson 1998; Russell 1987; Vichitvejpaisal 1992).

The trials reported our two primary outcome measures, namely: the number of women requiring conversion to general anaesthesia (10 studies), and the number of women requiring supplemental analgesia (nine studies).

Excluded studies

We excluded 12 studies. Three of the 12 excluded studies used hypobaric bupivacaine group (Connolly 1998; Connolly 1999; Connolly 2001), one used mepivacaine (Echevarría 1996); two studies used tetracaine instead of bupivacaine (King 1997; King 1999); three studies used combined spinal epidural technique (Lew 2004; Loubert 2011; Sodhi 2002); one study used differing concentration of isobaric and hyperbaric bupivacaine (Narejo 2012); two studied employed sequential administration of isobaric and hyperbaric bupivacaine (Sudarshan 1994; Yurtlu 2012). Detailed reasons provided in [Characteristics of excluded studies](#) and the [Results of the search](#).

Awaiting assessment

There are two studies awaiting classification. One is awaiting assessment as the full text is not yet available (Huang 2012). We are seeking more information from the authors of the second study (Jabalameli 2012). See [Characteristics of studies awaiting classification](#)

Ongoing studies

We are not aware of any ongoing studies.

Risk of bias in included studies

See [Figure 2](#); [Figure 3](#)

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Das Neves 2003	?	?	+	+	+	+	+
Javed 2014	+	?	+	+	+	+	+
Punshi 2012	+	+	+	+	+	-	+
Richardson 1998	?	?	+	+	+	+	+
Russell 1987	?	?	+	+	+	+	+
Saracoglu 2011a	?	?	+	+	+	+	+
Saracoglu 2011b	?	?	+	+	+	+	+
Sarvela 1999	+	?	+	+	+	+	+
Vercauteren 1998	?	?	+	+	+	+	+
Vichitvejpaisal 1992	?	?	+	+	+	+	+

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

Allocation

Only three studies described the method of randomization ([Javed 2014](#); [Punshi 2012](#); [Sarvela 1999](#)) and one described the method of allocation concealment ([Punshi 2012](#)). Five studies reported that randomization resulted in intervention groups that were balanced at baseline ([Das Neves 2003](#); [Punshi 2012](#); [Russell 1987](#); [Vercauteren 1998](#); [Vichitvejpaissal 1992](#)).

Blinding

All 10 studies were described as double-blinded, but exactly which parties were blinded was not explicitly stated. We deduced that the participants were all blinded, due to the nature of the study. The spinal injections were done in the participant's back. The attending anaesthetists, who were also outcome assessors, were blinded to the group assignment in six of the studies ([Das Neves 2003](#); [Punshi 2012](#); [Russell 1987](#); [Sarvela 1999](#); [Vercauteren 1998](#); [Vichitvejpaissal 1992](#)). A blinded assessor was involved in [Richardson 1998](#), since the attending anaesthetists prepared the injections and followed the study protocol. The adequacy of blinding was not described in [Javed 2014](#). The amount of ephedrine administered was at the discretion of the attending anaesthetist. We judged 10 studies as having low risks of performance bias and detection bias ([Das Neves 2003](#); [Javed 2014](#); [Punshi 2012](#); [Richardson 1998](#); [Russell 1987](#); [Saracoglu 2011a](#); [Saracoglu 2011b](#); [Sarvela 1999](#); [Vercauteren 1998](#); [Vichitvejpaissal 1992](#)). Participants, who were blinded, were the outcome assessors for nausea and headache.

Incomplete outcome data

All 10 studies had a low risk of attrition bias, as all outcome data (recruitment and attrition data) had been reported with no missing data.

Selective reporting

Nine studies ([Das Neves 2003](#); [Javed 2014](#); [Richardson 1998](#); [Russell 1987](#); [Saracoglu 2011a](#); [Saracoglu 2011b](#); [Sarvela 1999](#); [Vercauteren 1998](#); [Vichitvejpaissal 1992](#)) reported all prespecified outcomes.

Other potential sources of bias

All the included studies appeared to be free of other bias.

Effects of interventions

See: [Summary of findings for the main comparison](#) Hyperbaric bupivacaine compared to Isobaric bupivacaine for spinal anaesthesia for caesarean section

Primary outcomes

Requiring conversion to general anaesthesia

Ten studies (614 participants) reported the need for conversion to general anaesthesia ([Das Neves 2003](#); [Javed 2014](#); [Punshi 2012](#); [Richardson 1998](#); [Russell 1987](#); [Saracoglu 2011a](#); [Saracoglu 2011b](#); [Sarvela 1999](#); [Vercauteren 1998](#); [Vichitvejpaissal 1992](#)) (Figure 4). The pooled results were based on three studies ([Das Neves 2003](#); [Javed 2014](#); [Vichitvejpaissal 1992](#)) with 218 participants in which outcomes were observed and showed that the chance of conversion to general anaesthesia with hyperbaric and isobaric bupivacaine were similar (Mantel-Haenszel risk ratio (RR) 0.33, 95% confidence interval (CI) 0.09 to 1.17; $I^2 = 22\%$) ([Analysis 1.1](#)). Seven of the 10 studies reported no conversions in either treatment group ([Punshi 2012](#); [Richardson 1998](#); [Russell 1987](#); [Saracoglu 2011a](#); [Saracoglu 2011b](#); [Sarvela 1999](#); [Vercauteren 1998](#)). We downgraded the quality of the evidence from 'high' to 'very low' due to uncertainty about the adequacy of the randomization methods used and the imprecision of the results incorporating no events.

Figure 4. Forest plot of comparison: 1 Hyperbaric bupivacaine versus isobaric bupivacaine, outcome: 1.1 Conversion to general anaesthetic. **Requiring supplemental analgesia**

Nine studies (554 participants) reported the need for supplemental analgesics (Das Neves 2003; Punshi 2012; Richardson 1998; Russell 1987; Saracoglu 2011a; Saracoglu 2011b; Sarvela 1999; Vercauteren 1998; Vichitvejpaissal 1992) (Figure 5). Four studies (Punshi 2012; Saracoglu 2011a; Saracoglu 2011b; Vichitvejpaissal 1992) had no need for supplemental anaesthesia in either arm and the rest had a very low number of events. In most studies no more than one event

was observed, with clearly less need occurring in the hyperbaric bupivacaine group. The small number of events resulted in wide CIs, with the overall pooled result (Mantel-Haenszel RR 0.61, 95% CI 0.26 to 1.41; $I^2 = 0\%$), showing that participants were unlikely to require supplemental analgesia (Analysis 1.2). We downgraded the quality of the evidence from 'high' to 'very low' due to uncertainty about the adequacy of the randomization methods used and the imprecision of the results incorporating no events.

Figure 5. Forest plot of comparison: 1 Hyperbaric bupivacaine versus isobaric bupivacaine, outcome: 1.2 Supplemental analgesia. **Secondary outcomes****Requirement for ephedrine**

Four studies (256 participants) reported the need for ephedrine (Javed 2014; Richardson 1998; Sarvela 1999; Vercauteren 1998). One study with 97 participants was statistically significantly in favour of hyperbaric bupivacaine for reducing the need for ephedrine (Vercauteren 1998). There was moderate heterogeneity ($I^2 = 68\%$) so we used a random-effects model to account for unexplained variation among the studies. Overall the requirement for ephedrine was similar (Mantel-Haenszel RR 0.89, 95% CI 0.57 to 1.38) (Analysis 1.3).

Different criteria were used in judging the need for ephedrine.

Javed 2014 administered ephedrine when the systolic blood pressure fell more than 20% from the baseline value; Richardson 1998 left the need for ephedrine to the discretion of the attending anaesthetist; Sarvela 1999 administered ephedrine when the systolic blood pressure dropped below 95 mm Hg or decreased more than 20% from the baseline value; Vercauteren 1998 administered ephedrine when systolic blood pressure dropped below 100 mm Hg or decreased more than 25% from the baseline value.

Vercauteren 1998 used small-dose bupivacaine with the combined spinal-epidural technique, possibly leading to less use of ephedrine in both the hyperbaric and isobaric bupivacaine groups. We

downgraded the quality of evidence from 'high' to 'very low' due to uncertainty about the adequacy of the randomization methods used and the imprecision of the results incorporating no events.

Nausea and vomiting

Seven studies (433 participants) reported the occurrence of nausea and vomiting (Richardson 1998; Russell 1987; Saracoglu 2011a; Saracoglu 2011b; Sarvela 1999; Vercauteren 1998; Vichitvejpaisal 1992). Of these, one study was statistically significantly in favour of hyperbaric bupivacaine (Vercauteren 1998) and one study was statistically significantly in favour of isobaric bupivacaine in decreasing the incidence of nausea and vomiting (Vichitvejpaisal 1992). We used the random-effects model to pool the data from these five studies. The pooled result was not significant (RR 0.99, 95% CI 0.57 to 1.72) (Analysis 1.4). There was moderate heterogeneity, with $I^2 = 51\%$. We performed a sensitivity analysis to explore the underlying cause of the heterogeneity, but could find no apparent reason to account for it, although differing definitions of nausea and vomiting could not be discounted. Sensitivity analysis did not change the conclusion. We downgraded the quality of the evidence from 'high' to 'low' due to uncertainty about the adequacy of the randomization methods used.

Headache

Three studies (234 participants) reported the occurrence of headaches (Russell 1987; Vercauteren 1998; Vichitvejpaisal 1992). The pooled results were based on two studies (Russell 1987; Vichitvejpaisal 1992) with 137 participants. There was no increased risk of headache between the two groups (OR 1.82, 95% CI 0.47 to 6.99; $I^2 = 0\%$) (Analysis 1.5). We downgraded the quality of the evidence from 'high' to 'low' due to uncertainty about the adequacy of the randomization methods used and the imprecision of the results incorporating no events.

Time to dermatomal block thoracic T4

Two studies (128 participants) reported the time taken for the sensory block to reach the thoracic T4 level (Richardson 1998; Vichitvejpaisal 1992). The time taken was considerably shorter for hyperbaric bupivacaine (mean difference (MD) -1.06, 95% CI -1.80 to -0.31) (Analysis 1.6). There was no heterogeneity in the analysis. We downgraded the quality of the evidence from 'high' to 'moderate' due to uncertainty about the adequacy of the randomization methods used.

Amount of ephedrine used (mg/person)

Six studies (386 participants) reported the amount of ephedrine used (Das Neves 2003; Punshi 2012; Saracoglu 2011a; Saracoglu 2011b; Sarvela 1999; Vercauteren 1998). One study with 97 participants was statistically significantly in favour of hyperbaric bupivacaine decreasing the amount of ephedrine used (Vercauteren 1998). Punshi 2012 showed results favouring isobaric bupivacaine decreasing the amount of ephedrine used. The six studies had a pooled MD of 0.23 (95% CI -1.65 to 2.12), showing no difference in the amount of ephedrine used (Analysis 1.7). There was moderate heterogeneity with $I^2 = 64\%$. We found no obvious methodological heterogeneity and hence we used the random-effects model to account for unexplained variation between studies. We downgraded the quality of evidence from 'high' to 'moderate' due to uncertainty about adequacy of the randomization methods used.

High dermatomal sensory block (C8)

Three studies (205 participants) reported the occurrence of undesirably high sensory block (higher than the C8 level) (Russell 1987; Sarvela 1999; Vercauteren 1998). There was moderate statistical heterogeneity in the results ($I^2 = 59\%$), but Vercauteren 1998, which used low-dose bupivacaine with the combined spinal-epidural technique, differed directionally from the other two. Due to this clinical heterogeneity, we used the random-effects model to account for the additional variation. The pooled RR was 0.88 (95% CI 0.16 to 4.90) (Analysis 1.8).

Sensitivity analysis

Data and results of the outcomes conversion to general anaesthesia, supplemental analgesia, and headache only partially satisfied the criteria to use Mantel-Haenszel or Peto methods (Table 1). We repeated the analyses using the Mantel-Haenszel and inverse variance methods so that we could assess the impact of the analysis method. This sensitivity analysis revealed that except for conversion to general anaesthesia, where the pooled result changed from significantly in favour of hyperbaric bupivacaine (Peto method) to no significant difference (Mantel-Haenszel and inverse variance methods), all other conclusions remained unchanged (no significant differences).

DISCUSSION

Summary of main results

Evidence from the 10 studies (614 participants) contributing data to the primary outcomes of this review showed that inadequate pain relief requiring conversion to general anaesthesia and supplemental analgesia showed no difference between hyperbaric and isobaric bupivacaine. Only three studies (Das Neves 2003; Javed 2014; Vichitvejpaisal 1992) contributed to the result of similar conversion to general anaesthesia and five studies (Das Neves 2003; Richardson 1998; Russell 1987; Sarvela 1999; Vichitvejpaisal 1992) contributed to the result of similar requirement for supplemental analgesia.

Two studies (Richardson 1998; Vichitvejpaisal 1992) contributed to the result of more rapid onset of sensory block at the T4 level with hyperbaric bupivacaine. All other analyses showed no differences. In addition, the sample sizes of the included studies dictate that all of our results should be treated with caution, as future larger studies may modify these findings.

Overall completeness and applicability of evidence

Conversion to general anaesthesia was a rare event in the 10 studies. Most studies did not report any conversions to general anaesthesia (Punshi 2012; Richardson 1998; Russell 1987; Saracoglu 2011a; Saracoglu 2011b; Sarvela 1999; Vercauteren 1998); Das Neves 2003 and Javed 2014 did not show any significant differences and the evidence for the superiority of hyperbaric bupivacaine comes primarily (78% weight) from one study (Vichitvejpaisal 1992). The criterion used in Vichitvejpaisal 1992 for conversion to general anaesthesia was when the analgesic level was deemed inadequate, but no further details were given. Caution should be exercised in interpreting the clinical significance of the finding.

The pooled estimate for use of supplemental analgesia was also dominated by a single study (Vercauteren 1998) (61% weight), as this study reports more events and was significantly larger than the other studies. The larger number of events might be attributable to the use of the combined spinal-epidural technique with small-dose hyperbaric and isobaric bupivacaine leading to a higher event rate for supplemental analgesia.

The use of ephedrine was lowest in Vercauteren 1998, as the dose of bupivacaine was only 6.6 mg using the combined spinal-epidural technique, compared to a higher ephedrine consumption by Das Neves 2003 (12.5 mg bupivacaine) and Sarvela 1999 (9 mg bupivacaine) using spinal anaesthesia.

For caesarean delivery, an anaesthesia level of T4 has been widely deemed to be the standard to allow pain-free delivery of the infant. We therefore reviewed the mean time to onset of T4 blockade, which was only reported in two studies (Richardson 1998; Vichitvejpaisal 1992). Both studies used the loss of sensation to pin-prick as the test for sensory level. We could not investigate the maximum sensory level achieved during intrathecal block or recession of sensory blockade, due to the different methods used to test sensory level. Vercauteren 1998 used ether swabs to test the height of block, while others used loss of sensation to pin-prick or cold.

We reran the searches in CENTRAL, MEDLINE and Embase between January 2011 and March 2016, and identified five new studies, of which two are awaiting assessment (Studies awaiting classification).

Quality of the evidence

There was unclear risk of bias for allocation concealment selection bias, as the methods were not reported in nine studies (Das Neves 2003; Javed 2014; Richardson 1998; Russell 1987; Saracoglu 2011a; Saracoglu 2011b; Sarvela 1999; Vercauteren 1998; Vichitvejpaisal 1992). In Richardson 1998, the two groups were not balanced for prognostically important factors, e.g. previous caesarean sections. Other than Punshi 2012, which had a high risk of reporting bias, there were low risks of performance bias, detection bias, attrition bias, reporting bias or other potential biases.

All the studies were described as double-blind studies, but details were not explicit. Nevertheless, the participants were likely to be blinded, as the spinal injection was performed at the back, away from the woman's vision. The attending anaesthetists did not prepare the medications in five of the studies (Das Neves 2003; Russell 1987; Sarvela 1999; Vercauteren 1998; Vichitvejpaisal 1992), so they would not know the group assignment. In Richardson 1998 and Punshi 2012, the attending anaesthetist prepared the medications. Javed 2014 did not describe the preparation of medication. Although a blinded observer was involved as the outcome assessor, the dose of ephedrine used was at the discretion of the attending anaesthetist. There were different hypotension thresholds and a range of ephedrine doses that could be administered each time, so there was considerable variation in the ephedrine-related outcomes. However, the attending anaesthetist was blinded, so we rated this at low risk of bias. For most of the dichotomous outcomes events were rare. This resulted in imprecision in the results, precluding firm conclusions. Therefore, considering both risk of bias and imprecision, we downgraded the

evidence to either very low or low for five of the seven outcomes assessed using GRADE methods.

Potential biases in the review process

The dose of bupivacaine used in the studies varied from 6.6 mg to 15 mg. Some studies included intrathecal opioids such as morphine (Richardson 1998; Saracoglu 2011a), sufentanil (Vercauteren 1998) and fentanyl (Punshi 2012; Sarvela 1999; Saracoglu 2011b), while others did not use adjuvant intrathecal drugs (Das Neves 2003; Javed 2014; Russell 1987; Vichitvejpaisal 1992). There was also variability in the technique of regional block, with four studies performing the combined spinal-epidural technique (delivering the drug directly into the spinal fluid with a small catheter placed in the space surrounding the spinal column) to administer the intrathecal drugs (Saracoglu 2011a; Saracoglu 2011b; Sarvela 1999; Vercauteren 1998).

Other potentially relevant outcomes not reported in most studies were pain on injection and recovery, duration of anaesthesia following delivery, pain with delivery of spinal anaesthesia, pain after delivery, and ability to walk around.

Three factors (intrathecal drug dose, adjuvant drugs, and technique of administration) have been shown to affect the spread of local anaesthetic in the intrathecal space. However, since the methodology has not been standardized, it is difficult to draw a definitive conclusion from the studies in this review. It may be necessary to conduct a large randomized trial to confirm these findings, as well as to examine the economic impact so that more reliable conclusions can be made with higher quality evidence.

Agreements and disagreements with other studies or reviews

We did not find any other review comparing hyperbaric and isobaric bupivacaine.

AUTHORS' CONCLUSIONS

Implications for practice

There is no compelling evidence in favour of the use of intrathecal isobaric or hyperbaric bupivacaine for spinal anaesthesia for caesarean section. Due to the suggestive evidence of faster onset to T4 sensory block, intrathecal hyperbaric bupivacaine may have some advantages.

Implications for research

There is a lack of clear evidence on this topic. An adequately-powered randomized controlled trial is required, in which the criteria for conversion to general anaesthesia and the need for supplemental analgesia should be defined objectively, applied uniformly and reported explicitly. Other clinically important outcomes, such as pain scores in the peri-operative period and time to walking, need to be evaluated in a standardized manner. All clinically-relevant side effects should be evaluated. Reporting standards should adhere to the CONSORT guidelines (CONSORT 2012) with more details of randomization, blinding and complete outcome data assessment.

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REFERENCES

References to studies included in this review

Das Neves 2003 {published data only}

Das Neves JF, Monteiro GA, De Almeida JR, Brun A, Cazarin N, Sant'Anna RS, et al. Spinal anesthesia for cesarean section: comparative study between isobaric and hyperbaric bupivacaine with morphine [Raquianestesia para cesariana: estudo comparativo entre bupivacaina isobarica e hiperbarica associadas a morfina]. *Revista Brasileira de Anestesiologia* 2003;**53**(5):573-8. [PUBMED: 19475310]

Javed 2014 {published data only}

Javed K, Ishrat Z, Akhtar N, Ijaz B. Comparative study of intrathecal 0.5% isobaric versus 0.5% hyperbaric bupivacaine in same volume and dose to assess the quality of spinal anaesthesia and haemodynamic changes occurring during cesarean section. *Pakistan Journal of Medical and Health Sciences* 2014;**8**(2):1-9.

Punshi 2012 {published data only}

Punshi GD, Afshan G. Spinal anaesthesia for caesarean section: plain vs hyperbaric bupivacaine. *Journal of Pakistan Medical Association* 2012;**62**(8):807-11.

Richardson 1998 {published data only}

Richardson MG, Collins HV, Wissler RN. Intrathecal hypobaric versus hyperbaric bupivacaine with morphine for cesarean section. *Anesthesia and Analgesia* 1998;**87**(2):336-40. [PUBMED: 9706927]

Russell 1987 {published data only}

Russell IF, Holmqvist EL. Subarachnoid analgesia for caesarean section. A double-blind comparison of plain and hyperbaric 0.5% bupivacaine. *British Journal of Anaesthesia* 1987;**59**(3):347-53. [PUBMED: 3548793]

Saracoglu 2011a {published data only}

Saracoglu A, Saracoglu KT, Eti Z. Comparative study of fentanyl and morphine in addition to hyperbaric or isobaric bupivacaine in combined spinal anaesthesia for caesarean section. *Archives of Medical Science* 2011;**7**:694-9.

Saracoglu 2011b {published data only}

Saracoglu A, Saracoglu KT, Eti Z. Comparative study of fentanyl and morphine in addition to hyperbaric or isobaric bupivacaine in combined spinal anaesthesia for caesarean section. *Archives of Medical Science* 2011;**7**:694-9.

Sarvela 1999 {published data only}

Sarvela PJ, Halonen PM, Korttila KT. Comparison of 9 mg of intrathecal plain and hyperbaric bupivacaine both with fentanyl for cesarean delivery. *Anesthesia and Analgesia* 1999;**89**(5):1257-62. [PUBMED: 10553846]

Vercauteren 1998 {published data only}

Vercauteren MP, Coppejans HC, Hoffmann VL, Saldien V, Adriaensen HA. Small-dose hyperbaric versus plain bupivacaine during spinal anesthesia for cesarean section. *Anesthesia and Analgesia* 1998;**86**(5):989-93. [PUBMED: 9585282]

Vichitvejpaissal 1992 {published data only}

Vichitvejpaissal P, Svastdi-Xuto O, Udompunturux S. A comparative study of isobaric and hyperbaric solution of bupivacaine for spinal anaesthesia in caesarean section. *Journal of the Medical Association of Thailand (Chotmaihet Thangphaet)* 1992;**75**(5):278-82. [PUBMED: 1460407]

References to studies excluded from this review

Connolly 1998 {published data only}

Connolly C, McLeod G, Wildsmith JA. A comparison of glucose 8mg/ml or glucose 80mg/ml with bupivacaine 5mg/ml for spinal anesthesia for Cesarean section. *Regional Anesthesia and Pain Medicine* 1998;**23**(3):51.

Connolly 1999 {published data only}

Connolly C, Wildsmith JA, McLeod G. A comparison of glucose 8 mg/ml or glucose 80 mg/ml with bupivacaine 5 mg/ml for spinal anaesthesia for caesarean section. *International Journal of Obstetric Anesthesia* 1999;**8**:210-1.

Connolly 2001 {published data only}

Connolly C, McLeod GA, Wildsmith JA. Spinal anaesthesia for caesarean section with bupivacaine 5 mg ml⁻¹ in glucose 8 or 80 mg ml⁻¹. *British Journal of Anaesthesia* 2001;**86**(6):805-7. [PUBMED: 11573587]

Echevarría 1996 {published data only}

Echevarría M, Caba F, Bernal L, Pallarés JA, Rodríguez R. Effect of the local anesthetic on visceral pain in cesarean sections done under intradural anesthesia [Influencia del anestésico local en el dolor visceral de cesareas bajo anestesia intradural]. *Revista Española de Anestesiología y Reanimación* 1996;**43**(1):2-6. [PUBMED: 8851828]

King 1997 {published data only}

King HK, Wood L, Khan AK. Spinal anaesthesia for caesarean section: isobaric vs hyperbaric solution. *Regional Anesthesia and Pain Medicine* 1997;**22**(2):14.

King 1999 {published data only}

King HK, Wood L, Steffens Z, Johnson C. Spinal anesthesia for cesarean section: isobaric versus hyperbaric solution. *Acta Anaesthesiologica Sinica* 1999;**37**(2):61-4. [PUBMED: 10410404]

Lew 2004 {published data only}

Lew E, Yeo SW, Thomas E. Combined spinal-epidural anesthesia using epidural volume extension leads to faster motor recovery after elective cesarean delivery: a prospective, randomized, double-blind study. *Anesthesia and Analgesia* 2004;**98**(3):810-4. [PUBMED: 14980942]

Loubert 2011 {published data only}

Loubert C, Hallworth S, Fernando R, Columb M, Patel N, Sarang K, et al. Does the baricity of bupivacaine influence intrathecal spread in the prolonged sitting position before elective cesarean delivery? A prospective randomized controlled study. *Anesthesia and Analgesia* 2011;**113**:811-7.

Narejo 2012 {published data only}

Narejo AS, Memon GN, Wagan F, Wagan MA, Khawaja RA. A study to assess the quality of spinal anesthesia and to observe hemodynamic changes occurring during cesarean section with spinal anesthesia, comparing 0.5% isobaric bupivacaine and 0.75% hyperbaric bupivacaine in same volume and dose. *Medical Channel* 2012;**18**:58-62.

Sodhi 2002 {published data only}

Sodhi R, Fernando R, Hallworth S, Sarang K, Patel N. Does density influence the spread of intrathecal bupivacaine in the prolonged sitting position before elective cesarean section?. *Anesthesiology* 2002;**96** Suppl:69.

Sudarshan 1994 {published data only}

Sudarshan G, Kokri MS, Kumar CM. Evaluation of sequential administration of plain and hyperbaric bupivacaine for spinal anesthesia for lower segment Caesarean section. American Society of Regional Anesthesia & Pain Medicine Annual Meeting Abstracts journals.lww.com/rapm/Citation/1994/19021/Evaluation_of_sequential_administration_of_plain.23.aspx. 1994:P 23.

Yurtlu 2012 {published data only}

Yurtlu BS, Hanci V, Okay RD, Bostankoulu SE, Erdogan Kayhan G, Hakmimoglu S, et al. Effects on hypotension incidence: hyperbaric, isobaric, and combinations of bupivacaine for spinal anesthesia in cesarean section. *Turkish Journal of Medical Sciences* 2012;**42**(2):307-13.

References to studies awaiting assessment

Huang 2012 {published data only}

Huang D-L, Han N-N. Effect of bupivacaine to subarachnoid at different specific gravity on CSEA for caesarean section. *Dalian Medical University* 2012;**34**:390-2.

Jabalameli 2012 {published data only}

Jabalameli M, Mazegh N, Gholami S. The effects of hyperbaric or isobaric bupivacaine on bispectral index in spinal anesthesia for cesarean section. *Journal of Research in Medical Sciences* 2012;**17**:176-81.

Additional references

Chanrachakul 2000

Chanrachakul B, Herabutya Y, Udomsubpayakul U. Epidemic of cesarean section at the general, private and university hospitals in Thailand. *The Journal of Obstetrics and Gynaecology Research* 2000;**26**(5):357-61. [PUBMED: 11147723]

Chung 2014

Chung SH, Seol HJ, Choi YS, Oh SY, Kim A, Bae CW. Changes in the cesarean section rate in Korea (1982-2012) and a review of the associated factors. *Journal of Korean Medical Science* 2014;**29**(10):1341-52.

CONSORT 2012

Altman DG, Moher D, Schultz KF. Improving the reporting of randomised trials: The CONSORT statement and beyond. *Statistics in Medicine* 2012;**31**(25):2985-97.

Higgins 2002

Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics In Medicine* 2002;**21**(11):1539-58.

Higgins 2011

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated September 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Langendam 2013

Langendam MW, Akl EA, Dahm P, Glasziou P, Guyatt G, Schünemann HJ. Assessing and presenting summaries of evidence in Cochrane Reviews. *Systematic Reviews* 2013;**2**(1):1-9.

Lumbiganon 2010

Lumbiganon P, Laopaiboon M, Gülmezoglu AM, Souza JP, Taneepanichskul S, Ruyan P, et al. Method of delivery and pregnancy outcomes in Asia: the WHO global survey on maternal and perinatal health 2007-08. *Lancet* 2010;**375**(9713):490-9.

Odland 2003

Odland V, Haglund B, Pakkanen M, Otterblad Olausson P. Deliveries, mothers and newborn infants in Sweden, 1973-2000. Trends in obstetrics as reported to the Swedish Medical Birth Register. *Acta Obstetrica et Gynecologica Scandinavica* 2003;**82**(6):516-28. [MEDLINE: 12780422]

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Russell 1982

Russell IF. Intrathecal bupivacaine 0.5% for caesarean section. *Anesthesia* 1982;**37**(3):346-7. [MEDLINE: 7091613]

Tsen 1998

Tsen LC, Pitner R, Camann WR. General anesthesia for cesarean section at a tertiary care hospital 1990-1995: indications and implications. *International Journal of Gynaecology and Obstetrics* 1998;**7**:147-52. [MEDLINE: 15321206]

References to other published versions of this review

Sia 2005

Sia AT, Tan KH. Use of hyperbaric versus isobaric bupivacaine for spinal anaesthesia for caesarean section. *Cochrane Database of Systematic Reviews* 2005, Issue 1. [DOI: [10.1002/14651858.CD005143](https://doi.org/10.1002/14651858.CD005143)]

Sia 2013

Sia AT, Tan KH, Sng BL, Lim Y, Chan ESY, Siddiqui FJ. Use of hyperbaric versus isobaric bupivacaine for spinal anaesthesia

for caesarean section. *Cochrane Database of Systematic Reviews* 2013, Issue 5. [DOI: [10.1002/14651858.CD005143.pub2](https://doi.org/10.1002/14651858.CD005143.pub2)]

CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]

Das Neves 2003

Methods	Prospective, randomized and double-blinded study
Participants	n = 60 Trial Centre: Hospital Monte Sinai, Brazil Date of Trial: Not stated Inclusion criteria: term pregnant women undergoing spinal anaesthesia for elective caesarean section 1 isobaric group had referred pain at hysterotomy converted to general anaesthesia. 1 hyperbaric group had partial motor block and pain at incision, converted to epidural anaesthesia. Only the outcomes of supplemental analgesia and ephedrine were obtained
Interventions	30: 0.5% hyperbaric bupivacaine 12.5 mg with 100 mcg morphine 30: 0.5% isobaric bupivacaine 12.5 mg with 100 mcg morphine Left lateral position, paramedian approach, L3 - 4 interspace, 27 G Quincke needle. Preload and co-load with lactated Ringer's solution
Outcomes	Conversion to general anaesthesia Supplemental analgesic Amount of ephedrine used Onset time (absence of sensitivity in L3) Motor and sensory block after 20 minutes
Notes	No funding or declaration of conflict of interest reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"... in this prospective, randomised and double blinded study...". The 2 groups were balanced in the demographic characteristics (Table 1)
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. No further description in the article. Participant likely to be blinded as spinal injection was prepared by the anaesthetist at her back
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"... prospective, randomised and double blind study..."

Das Neves 2003 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Recruitment and attrition data presented. Analyses performed using intention-to-treat principle
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	Appears to be free of other bias. Sample size calculation performed

Javed 2014

Methods	Prospective, randomized and double-blinded study
Participants	n = 60 spinal anaesthesia Trial Centre: Sir Ganga Ram Hospital, Lahore, Pakistan Date of Trial: Not stated Inclusion criteria: ASA I and II Exclusion criteria: Spinal anesthesia, ASA Grade III & IV, hypertension, hypotension, eclamptic
Interventions	30: Hyperbaric bupivacaine 12.5 mg 30: Hypobaric bupivacaine 12.5 mg Sitting position, L3 - 4 interspace, 25 G Quincke needle. Participant turned to supine position immediately with 15 degree left lateral tilt
Outcomes	Conversion to general anaesthesia Achieving level of T6 sensory blockade at 3 mins Achieving level of T8 sensory blockade 3 mins Achieving level of T10 sensory blockade 3 mins Achieving level of T6 sensory blockade at 5 mins Achieving level of T8 sensory blockade at 5 mins Achieving motor blockade at 1 min Achieving motor blockade at 5 min Ephedrine used Change in heart rate Change in systolic blood pressure Change in diastolic blood pressure Mean arterial pressure
Notes	No funding or declaration of conflict of interest reported

Risk of bias

Hyperbaric versus isobaric bupivacaine for spinal anaesthesia for caesarean section (Review)

Javed 2014 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomize into two groups... using a computer generated random number table..." p 3, under Methods
Allocation concealment (selection bias)	Unclear risk	No mention of any method of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"A prospective randomized double blind study in 60 patients..." p 1, under Methods section of Abstract. No further details give in any other section. Outcome 'Conversion to GA' is sensitive to blinding status of the personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"A prospective randomized double blind study in 60 patients..." p 1, under Methods section of Abstract. No further details give in any other section. Outcome 'Ephedrine used' is sensitive to blinding status of the participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	No lost-to-follow-up mentioned but from the number extracted from figure 3, very short follow-up time and established safety of the intervention, we assume it to be zero
Selective reporting (reporting bias)	Low risk	Clinically important outcomes are reported
Other bias	Low risk	No other biases could be identified. Appears to be free of other bias

Punshi 2012

Methods	Prospective, randomized and double-blinded study
Participants	<p>n = 60 spinal anaesthesia</p> <p>Trial Centre: Aga Khan University Hospital, Karachi, Pakistan</p> <p>Date of Trial: 2005 to 2006</p> <p>Inclusion criteria: Elective caesarean section without any comorbidities, gestational age > 37 weeks</p> <p>Exclusion criteria: Pre-eclampsia, placenta previa, multiple pregnancy, weight > 85 kg, height < 150 cm or > 170 cm, any other contraindication for regional anaesthesia</p>
Interventions	<p>30: Hyperbaric bupivacaine 10 mg with 2.5 mcg fentanyl in 0.5 ml normal saline</p> <p>30: Isobaric bupivacaine 10 mg with 2.5 mcg fentanyl in 0.5 ml normal saline</p> <p>Spinal anaesthesia was instituted in sitting position with a 25-G pencil-point. Spinal needle at L2 - 3 or L3 - 4 interspace level</p>
Outcomes	<p>Use of ephedrine (mg)</p> <p>Achieved sensory block at T4 level</p> <p>Time taken to 2 dermatome regression</p> <p>Time taken to maximum extent of motor blockade</p> <p>Complications: Number of episodes of hypotension, number of episodes of bradycardia</p>
Notes	No funding or declaration of conflict of interest reported

Hyperbaric versus isobaric bupivacaine for spinal anaesthesia for caesarean section (Review)

Punshi 2012 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"... the patients were randomly allocated to receive either plain bupivacaine or hyperbaric bupivacaine for spinal anaesthesia induced in sitting position" p 808, para 2, under Patients and Methods But authors do not mention the way the random list was generated
Allocation concealment (selection bias)	Low risk	"Using sealed envelopes, the patients were randomly allocated to receive either plain bupivacaine or hyperbaric bupivacaine for spinal anaesthesia induced in sitting position" p 808, para 2, under Patients and Methods
Blinding of participants and personnel (performance bias) All outcomes	Low risk	For blinding purpose, the primary anaesthetist was responsible for participant randomization and induction of spinal anaesthesia, while the other investigator (unaware of group allocation) was responsible for data collection. p 808, para 2, under Patients and Methods
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"For the purpose of double blinding, the patients were also kept unaware of group allocation." p 808, para 2, under Patients and Methods
Incomplete outcome data (attrition bias) All outcomes	Low risk	No lost-to-follow-up mentioned but from the text in para 1, under Results on p 808, due to very short follow-up time and established safety of the intervention, we assume it to be zero
Selective reporting (reporting bias)	High risk	Adverse outcomes mentioned in the Methods sections were not reported in the Results section (nausea, vomiting, pruritis)
Other bias	Low risk	No other biases could be identified. Appears to be free of other bias

Richardson 1998

Methods	Prospective, randomized and double-blinded study
Participants	n = 30 spinal anaesthesia Trial Centre: Strong Memorial Hospital, Rochester, New York, United States Date of Trial: Not stated Inclusion criteria: ASA I and II, non-labouring parturients scheduled for elective caesarean section with spinal anaesthesia Exclusion criteria: history of chronic opioid use, allergy to any of the study drugs
Interventions	15: hyperbaric bupivacaine 15 mg with 200 mcg morphine 15: hypobaric bupivacaine 15 mg with 200 mcg morphine Sitting position, L3 - 4 interspace, 25 G Quincke needle. Preload with lactated Ringer's solution
Outcomes	Conversion to general anaesthesia outcome measure Supplemental analgesic outcome measure Ephedrine used

Hyperbaric versus isobaric bupivacaine for spinal anaesthesia for caesarean section (Review)

Richardson 1998 (Continued)

Nausea and vomiting

Time to T4

Motor and sensory block

Quality of anaesthesia

Quality of postoperative analgesia

Incidence of side effects

Psychometric scores

Notes No funding or declaration of conflict of interest reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"This prospective, randomised, double-blinded study was approved by the institutional human subjects review board. Subjects were randomized to the hyperbaric or isobaric bupivacaine group"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Participant likely to be blinded as spinal injection was prepared by the anaesthetist at her back. Blinded observer was involved in outcome assessment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"... prospective, randomised and double blind study..."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Recruitment and attrition data presented. Analyses performed using intention-to-treat principle
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	Appears to be free of other bias. Sample size calculation performed

Russell 1987

Methods	Prospective, randomized, double-blinded study
Participants	n = 40 spinal anaesthesia Trial Centre: Hull Royal Infirmary, Anlaby Road, Hull, North Humberside, United Kingdom Date of Trial: Not stated 1 hyperbaric group excluded from analysis: result of deviation from design of the study (had wedge placed under left hip) n = 39
Interventions	19: 0.5% hyperbaric bupivacaine 12.5 mg

Hyperbaric versus isobaric bupivacaine for spinal anaesthesia for caesarean section (Review)

Russell 1987 (Continued)

20: 0.5% plain bupivacaine 12.5 mg

Right lateral position, midline approach, L2 - 3 or L3 - 4 interspace, 25 G needle. Preload with lactated Ringer's solution

Outcomes	Conversion to general anaesthesia Supplemental analgesic Nausea and vomiting Headache Rate of onset of anaesthesia Maximum spread of spinal anaesthesia Rate of high cervical level Duration of anaesthesia Ephedrine consumption Incidence of spinal headache
Notes	No funding or declaration of conflict of interest reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"They were randomly allocated to receive either 0.5% glucose-free bupivacaine 2.5ml (isobaric...)." The 2 groups were balanced in the demographic characteristics (table 1)
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. No further description in the article. Participant likely to be blinded as spinal injection was prepared by the anaesthetist at her back
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"... prospective, randomised and double blind study..."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Recruitment and attrition data presented. Analyses performed using intention-to-treat principle
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	Appears to be free of other bias. Sample size calculation performed

Saracoglu 2011a

Methods	Prospective, randomized, double-blinded study
Participants	<p>n = 50 combined spinal-epidural anaesthesia</p> <p>Trial Centre: Central Education and Research Hospital, Erzurum, Turkey</p> <p>Date of Trial: Not stated</p> <p>Comined spinal epidural needle through needle technique with 18 G Tuohy needle and 27 G Whitacre needle. Epidural catheter insertion</p> <p>Inclusion criteria: healthy parturients undergoing elective caesarean delivery</p> <p>1 excluded due to accidental dural puncture by Tuohy needle and replaced with another participant</p>
Interventions	<p>25: isobaric 0.5% bupivacaine 9 mg with 200 mcg morphine</p> <p>25: hyperbaric 0.5% bupivacaine 9 mg with 200 mcg morphine</p> <p>Sitting position, midline approach, L4 - 5 interspace, combined spinal epidural technique. Preload with hydroxyethyl starch</p>
Outcomes	<p>Conversion to general anaesthesia outcome measure</p> <p>Supplemental analgesic outcome measure</p> <p>Ephedrine used</p> <p>Nausea and vomiting</p>
Notes	No funding or declaration of conflict of interest reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...included in this randomized, double-blind, prospective study..." The 2 groups were balanced in the demographic characteristics (Table 1)
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind. No further description in the article. Participant likely to be blinded as spinal injection was prepared by the anaesthetist at her back
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"... randomized, double-blind, prospective study..."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Recruitment and attrition data presented. Analyses performed using intention-to-treat principle
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	Appears to be free of other bias

Saracoglu 2011b

Methods	Prospective, randomized, double-blinded study
Participants	<p>n = 50 combined spinal-epidural anaesthesia</p> <p>Trial Centre: Central Education and Research Hospital, Erzurum, Turkey</p> <p>Date of Trial: Not stated</p> <p>Combined spinal epidural needle through needle technique with 18 G Tuohy needle and 27 G Whitacre needle. Epidural catheter insertion</p> <p>Inclusion criteria: healthy parturients undergoing elective caesarean delivery</p> <p>1 excluded due to unsuccessful spinal blockade and replaced with another participant</p>
Interventions	<p>25: isobaric 0.5% bupivacaine 9 mg with 25 mcg fentanyl</p> <p>25: hyperbaric 0.5% bupivacaine 9 mg with 25 mcg fentanyl</p> <p>Sitting position, midline approach, L4 - 5 interspace, combined spinal epidural technique. Preload with hydroxyethyl starch</p>
Outcomes	<p>Conversion to general anaesthesia</p> <p>Supplemental analgesic</p> <p>Ephedrine used</p> <p>Nausea and vomiting</p>
Notes	No funding or declaration of conflict of interest reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...included in this randomized, double-blind, prospective study..." The 2 groups were balanced in the demographic characteristics (Table 1)
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. No further description in the article. Participant likely to be blinded as spinal injection was prepared by the anaesthetist at her back
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"... randomized, double-blind, prospective study..."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Recruitment and attrition data presented. Analyses performed using intention-to-treat principle
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

Saracoglu 2011b (Continued)

Other bias	Low risk	Appears to be free of other bias
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Sarvela 1999

Methods	Prospective, randomized, double-blinded study
Participants	<p>n = 76 combined spinal-epidural anaesthesia</p> <p>Trial Centre: Helsinki University Central Hospital, Helsinki, Finland</p> <p>Date of Trial: Not stated</p> <p>Combined spinal epidural needle through needle technique with 16 G Tuohy needle and 26 G Whitacre needle. Epidural catheter insertion</p> <p>Inclusion criteria: healthy, full-term (gestational age 37 to 42 weeks), singleton parturients undergoing elective caesarean delivery</p> <p>7 excluded. 1 inability of the observer to follow the protocol, 1 premature birth, 4 no backflow of cerebrospinal fluid after spinal anesthesia and conversion of anaesthesia to epidural. 1 patient in the plain bupivacaine group required epidural supplementation although backflow was seen after spinal anaesthesia and therefore was not included in the spinal block data and side effects during caesarean section. n = 70</p>
Interventions	<p>36: hyperbaric bupivacaine 9 mg with 20 mcg fentanyl</p> <p>34: plain bupivacaine 9 mg with 20 mcg fentanyl</p> <p>Right lateral position, midline approach, L2 - 3 interspace, combined spinal epidural technique. Pre-load and colloid with lactated Ringer's solution and ephedrine 15 mg. Uniform surgical technique with exteriorisation of uterus</p>
Outcomes	<p>Conversion to general anaesthesia</p> <p>Supplemental analgesic</p> <p>Ephedrine used</p> <p>Nausea and vomiting</p> <p>High block C8</p> <p>Onset of anaesthesia</p> <p>Duration of anaesthesia</p> <p>Motor and sensory block</p> <p>Rate of high cervical level</p> <p>Supplementary analgesia</p>
Notes	No funding or declaration of conflict of interest reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers

Hyperbaric versus isobaric bupivacaine for spinal anaesthesia for caesarean section (Review)

Sarvela 1999 (Continued)

Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. No further description in the article. Participant likely to be blinded as spinal injection was prepared by the anaesthetist at her back
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"... prospective, randomised and double blind study..."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Recruitment and attrition data presented. Analyses performed using intention-to-treat principle
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	Appears to be free of other bias. Sample size calculation performed

Vercauteren 1998

Methods	Prospective, randomized, double-blinded study
Participants	<p>n = 98 combined spinal-epidural anaesthesia</p> <p>Trial Centre: University Hospital Antwerp, Edegem, Belgium</p> <p>Date of Trial: Not stated</p> <p>Combined spinal epidural BD-Durasafe Adjustable tray</p> <p>Inclusion criteria: scheduled for elective or semi-urgent caesarean section</p> <p>Exclusion criteria: urgent caesarean section, parturients in active labour, those presenting with a pregnancy duration of less than 35 weeks, initial systolic blood pressure exceeding 150 mmHg</p> <p>1 in the plain bupivacaine group was excluded because of an accidental dural tap by the Tuohy needle n = 97</p>
Interventions	<p>49: hyperbaric bupivacaine 6.6 mg with 3.3 mcg sufentanil</p> <p>48: plain bupivacaine 6.6 mg with 3.3 mcg sufentanil</p> <p>Right lateral position, combined spinal epidural technique. Preload with lactated Ringer's solution and HES 6%</p>
Outcomes	<p>Conversion to general anaesthesia</p> <p>Supplemental analgesic (epidural supplementation)</p> <p>Ephedrine used</p> <p>Nausea and vomiting</p> <p>Headache</p> <p>High block C8</p>

Vercauteren 1998 (Continued)

Incidence of hypotension

Amount of ephedrine used (ephedrine consumption)

Height of sensory block

Notes No funding or declaration of conflict of interest reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"in a double-blind, randomised trial,..." (in the abstract). The 2 groups were balanced in the demographic characteristics (Table 1)
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. No further description in the article. Participant likely to be blinded as spinal injection was prepared by the anaesthetist at her back
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"... prospective, randomised and double blind study..."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Recruitment and attrition data presented. Analyses performed using intention-to-treat principle
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	Appears to be free of other bias. Sample size calculation performed

Vichitvejpaisal 1992

Methods	Prospective, randomized study
Participants	<p>n = 98 spinal anaesthesia</p> <p>Trial Centre: Siriraj Hospital, Mahidol University, Bangkok, Thailand</p> <p>Date of Trial: Not stated</p> <p>50 hyperbaric bupivacaine, 48 isobaric bupivacaine</p> <p>Inclusion criteria: caesarean section (cephalopelvic disproportion, elderly primigravidae, previous caesarean section, premature rupture of membrane)</p> <p>Exclusion criteria: deformity of spinal column, skin infection near puncture site, coagulopathy</p>
Interventions	<p>50: hyperbaric bupivacaine 2 ml 0.5%</p> <p>48: isobaric bupivacaine 2 ml 0.5%</p>

Vichitvejpaisal 1992 (Continued)

Lateral position, midline approach, 24 G spinal needle via 18 G introducer needle. Preload with lactated Ringer's solution

Outcomes	Conversion to general anaesthesia Supplemental analgesic Nausea and vomiting Headache Time to T4 (spread of analgesia) Regression of anaesthesia
Notes	No funding or declaration of conflict of interest reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"This led us to perform a randomised double-blind study...". The 2 groups were balanced in the demographic characteristics (Table 1)
Allocation concealment (selection bias)	Unclear risk	Not stated in the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. No further description in the article. Participant likely to be blinded as spinal injection was prepared by the anaesthetist at her back
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"... prospective, randomised and double blind study..."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Recruitment and attrition data presented. Analyses performed using intention-to-treat principle
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	Appears to be free of other bias. Sample size calculation performed

ASA : American Society of Anesthesiologists; BD: BD is the brand of the spinal needle sets; C: cervical level; cm: centimetre; CSE: combined spinal epidural; G: gauge; GA: general anaesthesia; HES: hydroxyethylstarch; Kg: kilogram; L: litre; Mcg: microgram; Mg: milligram; Min: minute

ml: millilitre; N: number of participants; T: thoracic level

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Connolly 1998	Inclusion and exclusion criteria were not clearly defined in the text. Treatment and control groups were not adequately described at entry of study. Comparison of 8 mg/ml glucose versus 80 mg/ml glucose both of which were hyperbaric to cerebrospinal fluid. No isobaric bupivacaine used

Study	Reason for exclusion
Connolly 1999	Inclusion and exclusion criteria were not clearly defined in the text. Treatment and control groups were not adequately described at entry of study. Comparison of 8 mg/ml glucose versus 80 mg/ml glucose both of which were hyperbaric to cerebrospinal fluid. No isobaric bupivacaine used
Connolly 2001	Comparison of 8 mg/ml glucose versus 80 mg/ml glucose both of which were hyperbaric to cerebrospinal fluid. No isobaric bupivacaine used
Echevarría 1996	Comparison of hyperbaric bupivacaine with isobaric mepivacaine and isobaric bupivacaine with adrenaline
King 1997	Comparison of 0.5% tetracaine in 10% dextrose and 0.5% tetracaine
King 1999	Comparison of 0.5% tetracaine in 5% dextrose and 0.5% tetracaine
Lew 2004	Comparison of epidural volume extension with combined spinal-epidural with spinal anaesthesia using hyperbaric bupivacaine The comparisons are not using isobaric solution. The study investigated the effect of epidural volume extension
Loubert 2011	Comparison of hyperbaric, isobaric and hypobaric bupivacaine with fentanyl using combined spinal epidural technique. Study outcome on spread of intrathecal bupivacaine in the prolonged sitting position
Narejo 2012	Different concentrations of bupivacaine were used. Comparison of 0.5% isobaric bupivacaine and 0.75% hyperbaric bupivacaine
Sodhi 2002	Comparison of hyperbaric, isobaric and hypobaric bupivacaine with fentanyl using combined spinal epidural technique. Study outcome on spread of intrathecal bupivacaine in the prolonged sitting position
Sudarshan 1994	Sequential administration and not comparison of hyperbaric versus isobaric bupivacaine
Yurtlu 2012	Sequential administration and not comparison of hyperbaric versus isobaric bupivacaine

mg: milligram; ml: millilitre

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

[Huang 2012](#)

Methods	Comparison of bupivacaine at different specific gravity spinal anaesthesia
Participants	50 women in I group and 50 women in H group
Interventions	I group: 0.75% bupivacaine 2 mls and normal saline 1 ml. H group: 0.75% bupivacaine 2 mls and 10% glucose 1 ml
Outcomes	Onset time, duration of reaching the height level, incomplete block
Notes	Full text not available as yet

Jabalameili 2012

Methods	Double-blind RCT comparing hyperbaric and isobaric bupivacaine in spinal anaesthesia
Participants	42 women in hyperbaric group and 42 women in isobaric group
Interventions	Hyperbaric bupivacaine 2.5 mls Isobaric bupivacaine 2.5 mls
Outcomes	Bispectral index, use of ephedrine
Notes	We have requested more information from the author

ml: millilitre; RCT: randomized controlled trial

DATA AND ANALYSES

Comparison 1. Hyperbaric bupivacaine versus isobaric bupivacaine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Conversion to general anaesthetic	10	614	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.09, 1.17]
2 Supplemental analgesia	9	554	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.26, 1.41]
3 Requirement for ephedrine	4	256	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.57, 1.38]
4 Nausea and Vomiting	7	433	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.57, 1.72]
5 Headache	3	234	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [0.59, 5.00]
6 Time to dermatomal block T4 block (mins)	2	128	Mean Difference (IV, Fixed, 95% CI)	-1.06 [-1.80, -0.31]
7 Amount of ephedrine used (mg/person)	6	386	Mean Difference (IV, Random, 95% CI)	0.23 [-1.65, 2.12]
8 High block C8	3	205	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.39, 1.79]

Analysis 1.1. Comparison 1 Hyperbaric bupivacaine versus isobaric bupivacaine, Outcome 1 Conversion to general anaesthetic.

Study or subgroup	Favours Hyperbaric n/N	Isobaric n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Das Neves 2003	0/30	1/30		16.41%	0.33[0.01,7.87]
Richardson 1998	0/15	0/15			Not estimable
Russell 1987	0/19	0/20			Not estimable
Sarvela 1999	0/36	0/34			Not estimable
Favours Hyperbaric			0.01 0.1 1 10 100 Favours Isobaric

Analysis 1.2. Comparison 1 Hyperbaric bupivacaine versus isobaric bupivacaine, Outcome 2 Supplemental analgesia.

Analysis 1.3. Comparison 1 Hyperbaric bupivacaine versus isobaric bupivacaine, Outcome 3 Requirement for ephedrine.

Analysis 1.4. Comparison 1 Hyperbaric bupivacaine versus isobaric bupivacaine, Outcome 4 Nausea and Vomiting.

Analysis 1.5. Comparison 1 Hyperbaric bupivacaine versus isobaric bupivacaine, Outcome 5 Headache.

Analysis 1.6. Comparison 1 Hyperbaric bupivacaine versus isobaric bupivacaine, Outcome 6 Time to dermatomal block T4 block (mins).

Analysis 1.7. Comparison 1 Hyperbaric bupivacaine versus isobaric bupivacaine, Outcome 7 Amount of ephedrine used (mg/person).

Analysis 1.8. Comparison 1 Hyperbaric bupivacaine versus isobaric bupivacaine, Outcome 8 High block C8.

ADDITIONAL TABLES

Table 1. Sensitivity analysis using odds ratio to evaluate the effect of method of meta-analysis on conclusions of the outcomes with fewer observed events

Method	Outcomes (OR (95% CI))
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Table 1. Sensitivity analysis using odds ratio to evaluate the effect of method of meta-analysis on conclusions of the outcomes with fewer observed events (Continued)

	<i>Conversion to GA</i>	<i>Supplemental analgesia</i>	<i>Headache</i>
Peto	0.27 (0.08 to 0.97)	0.51 (0.19 to 1.39)	2.02 (0.55 to 7.42)
M-H	0.31 (0.08 to 1.16)	0.58 (0.23 to 1.45)	1.94 (0.53 to 7.16)
IV	0.32 (0.07 to 1.53)	0.57 (0.22 to 1.49)	1.82 (0.47 to 6.99)

As the outcomes are rare, the odds ratio is a good approximate of the risk ratio. Although the sensitivity analysis has been done using the odds ratio, it can still be interpreted in line with the main analysis based on risk ratios.

APPENDICES

Appendix 1. Search strategy for CENTRAL, the Cochrane Library

- #1 MeSH descriptor Cesarean Section explode all trees
- #2 (cesarea* or caesarea* or cesaria* or caesaria*)
- #3 (#1 OR #2)
- #4 MeSH descriptor Bupivacaine explode all trees
- #5 bupivacain* and (hyperbaric or heavy or dextrose or glucose or isobaric or plain or hypobaric or isotonic)
- #6 (#4 OR #5)
- #7 (#3 AND #6)

Appendix 2. Search strategy for MEDLINE (OvidSP)

1. exp CESAREAN-SECTION/ or (cesarea* or caesarea* or cesaria* or caesaria*).mp.
2. exp BUPIVACAINE/ or (bupivacain* and (hyperbaric or heavy or dextrose or glucose or isobaric or plain or hypobaric or isotonic)).mp.
3. 1 and 2
4. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.
5. 4 and 3

Appendix 3. Search strategy for Embase (OvidSP)

1. exp CESAREAN-SECTION/ or (cesarea* or caesarea* or cesaria* or caesaria*).mp.
2. exp BUPIVACAINE/ or (bupivacain* and (hyperbaric or heavy or dextrose or glucose or isobaric or plain or hypobaric or isotonic)).mp.
3. 1 and 2
4. (RANDOMIZED-CONTROLLED-TRIAL/ or RANDOMIZATION/ or CONTROLLED-STUDY/ or MULTICENTER-STUDY/ or PHASE-3-CLINICAL-TRIAL/ or PHASE-4-CLINICAL-TRIAL/ or DOUBLE-BLIND-PROCEDURE/ or SINGLE-BLIND-PROCEDURE/ or (RANDOM* or CROSS?OVER* or FACTORIAL* or PLACEBO* or VOLUNTEER* or ((SINGL* or DOUBL* or TREBL* or TRIPL*) adj3 (BLIND* or MASK*))).ti,ab.) not (animals not (humans and animals)).sh.
5. 4 and 3

WHAT'S NEW

Date	Event	Description
8 March 2016	New citation required but conclusions have not changed	3 new studies identified and results incorporated (Javed 2014 ; Punshi 2012 ; Saracoglu 2011a ; Saracoglu 2011b). 2 more studies awaiting classification. No changes in methodology. Primary outcome lost statistical significance. Other results remained unchanged.
8 March 2016	New search has been performed	Review is updated with new literature search done.

HISTORY

Protocol first published: Issue 1, 2005

Review first published: Issue 5, 2013

Date	Event	Description
28 October 2008	Amended	converted to new review format

CONTRIBUTIONS OF AUTHORS

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Conceiving the review: AS, KT, BS,WL

Designing the review: AS, KT, BS, WL

Co-ordinating the review: BS, WL, FJS

Undertaking manual searches: BS, WL

Screening search results: BS, WL

Organizing retrieval of papers: BS, , WL

Screening retrieved papers against inclusion criteria: BS, WL, FJS

Appraising quality of papers: BS, WL, FJS

Abstracting data from papers: BS, WL, FJS

Writing to authors of papers for additional information: BS, WL

Providing additional data about papers: BS, WL

Obtaining and screening data on unpublished studies: BS, WL

Data management for the review: BS, WL, FJS

Entering data into Review Manager 5 ([RevMan 2014](#)): BS, FJS

RevMan statistical data: BS, WL, FJS, EC , PNA

Other statistical analysis not using RevMan: BS, WL, FJS, EC, PNA

Double entry of data: (data entered by person one: FJS; data entered by person two BS)

Interpretation of data: BS, WL, FJS, EC,PNA, AS, KT

Statistical inferences: BS, WL, FJS, EC, PNA

Writing the review: BS, WL, FJS, EC,PNA, AS, KT

Providing guidance on the review: AS, KT

Securing funding for the review: BS

Performing previous work that was the foundation of the present study: AS

Guarantor for the review (one author): BS

Person responsible for reading and checking review before submission: BS

DECLARATIONS OF INTEREST

Ban Leong Sng: none known

Fahad Javaid Siddiqui: none known

Wan Ling Leong: none known

Pryseley N Assam: none known

Edwin SY Chan: none known

Kelvin H Tan: none known

Alex T Sia. none known

SOURCES OF SUPPORT

Internal sources

- KK Women's and Children's Hospital, Singapore.

External sources

- Department of Women's Anaesthesia, KK Women's and Children's Hospital, Singapore.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The following changes were made to the published protocol ([Sia 2005](#)):

1. Ban Leong Sng joined the review team in 2007.
2. Edwin Chan and Fahad Siddiqui joined the review team in 2011.
3. Pryseley Nkouibert and Wan Ling Leong joined the review team in 2014.
4. We handsearched journals for the original review ([Sia 2013](#)), we did not handsearch journals for the updated review's search.
5. September 2016: we simplified the title from 'Use of hyperbaric versus isobaric bupivacaine for spinal anaesthesia for caesarean section' to Hyperbaric versus isobaric bupivacaine for spinal anaesthesia for caesarean section'. This was to bring it into line with Cochrane conventions by dropping 'Use of'.

INDEX TERMS

Medical Subject Headings (MeSH)

*Cesarean Section; Anesthesia, General; Anesthesia, Obstetrical [*methods]; Anesthesia, Spinal [*methods]; Anesthetics, Local [*administration & dosage] [chemistry]; Bupivacaine [*administration & dosage] [chemistry]; Cerebrospinal Fluid; Ephedrine [administration & dosage]; Injections, Spinal; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy