Efficacy of low-dose bupivacaine in spinal anaesthesia for Caesarean delivery: systematic review and meta-analysis

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Summary. Spinal anaesthesia is the preferred anaesthetic technique for elective Caesarean deliveries. Hypotension is the most common side-effect and has both maternal and neonatal consequences. Different strategies have been attempted to prevent spinal-induced hypotension, including the use of low-dose bupivacaine. We conducted a systematic search for randomized controlled trials comparing the efficacy of spinal bupivacaine in low dose (LD \( \leq 8 \) mg) with conventional dose (CD \( > 8 \) mg) for elective Caesarean delivery. Thirty-five trials were identified for eligibility assessment, 15 were selected for data extraction, and 12 were finally included in the meta-analysis. We investigated sources of heterogeneity, subgroup analysis, and meta-regression for confounding variables (baricity, intrathecal opioids, lateral vs sitting position, uterine exteriorization, and study population). Sensitivity analysis was performed to test the robustness of the results. In the LD group, the need for analgesic supplementation during surgery was significantly higher [risk ratio (RR) = 3.76, 95% confidence interval (95% CI) = 2.38–5.92] and the number needed to treat for an additional harmful outcome (NNTH) was 4 (95% CI = 2–7). Furthermore, the LD group exhibited a lower risk of hypotension (RR = 0.78, 95% CI = 0.65–0.93) and nausea/vomiting (RR = 0.71, 95% CI = 0.55–0.93). Conversion to general anaesthesia occurred only in the LD group (two events). Neonatal outcomes (Apgar score, acid–base status) and clinical quality variables (patient satisfaction, surgical conditions) showed non-significant differences between LD and CD. This meta-analysis demonstrates that low-dose bupivacaine in spinal anaesthesia compromises anaesthetic efficacy (risk of analgesic supplementation: high grade of evidence), despite the benefit of lower maternal side-effects (hypotension, nausea/vomiting: moderate grade of evidence).

Keywords: anaesthesia, obstetric; anaesthetic techniques, subarachnoid; anaesthetics local, bupivacaine; complications, hypotension; safety, techniques

Regional anaesthesia is a major factor in patient safety during Caesarean delivery.1 Resurgence of spinal anaesthesia as a popular technique was possible due to the development of small-bore needles with pencil-point tips and has become the preferred method of anaesthesia for elective and for many emergency Caesarean deliveries if an epidural catheter is not already in situ.2 While effective surgical anaesthesia is the primary objective of the spinal technique, it must be accomplished while minimizing maternal and neonatal side-effects.

Although various factors influence the appropriate sensory nerve block for surgical anaesthesia, the local anaesthetic dose is the main determinant of its success.3 Anaesthesia textbooks recommend bupivacaine in a dose of between 12 and 15 mg.4 5 However, the use of this dose range has been associated with an incidence of maternal arterial hypotension of 69% to >80%, resulting in maternal and neonatal morbidity.6 A number of studies have sought an optimal dose of bupivacaine, but produced dissimilar findings with doses ranging from 5 to 20 mg.7 8 The use of a lower dose aims to decrease maternal side-effects (hypotension, intraoperative nausea/vomiting), reduce the time to discharge from the post-anaesthesia care unit, and improve maternal satisfaction.7 However, such a strategy could compromise the adequacy of anaesthesia, and require supplementary analgesia, with possible neonatal consequences and may require conversion to general anaesthesia, a situation known as a risk factor for anaesthesia-related maternal morbidity and mortality.1 9

Recent narrative reviews have addressed the controversy of spinal bupivacaine in low dose (LD).10 11 Although useful, they are essentially descriptive and conclude with opinion-based recommendations. Systematic reviewing allows the
efficient integration of the evidence due to explicit methods used to summarize the data, limiting bias and improving the accuracy of the conclusions, and thus providing a reliable source and basis that can be used for rational decision-making.\textsuperscript{12} We therefore conducted a systematic review of the literature and meta-analysis on the efficacy and adverse effects of spinal bupivacaine in LD compared with conventional dose (CD) for elective Caesarean delivery.

**Methods**

We conducted a systematic search of the electronic bibliographic databases: Cochrane Central Register of Controlled Trial (CENTRAL), MEDLINE, EMBASE, and LILACS. Both free-text and medical subject headings (MeSH) terms were used according to type of study, participants, interventions, and outcomes. Reference lists from identified studies and journals which appeared to be associated with the most retrieved citations were then hand-searched. The search was restricted to full reports of randomized controlled trials published in peer-reviewed journals without excluding trials published in languages other than English. No date restriction was applied up to October 2008. An update was performed on December 2010, using the literature search strategy constructed for MEDLINE.

Trials studying ASA I–II term parturients for elective or semi-urgent Caesarean delivery under neuraxial spinal anaesthesia [single injection spinal or combined spinal–epidural (CSE)], which compared bupivacaine in a dose $>8$ mg with a dose $\leq 8$ mg (hyperbaric or isobaric, with or without adjuvants). We selectively chose trials reporting the frequency of intraoperative analgesic supplementation by any route and also conversion to general anaesthesia. Such variables were considered primary outcomes in our review, as surrogate outcomes of efficacy of spinal anaesthesia. Secondary outcomes measured were: maternal adverse effects (hypotension, nausea/vomiting) and neonatal outcomes (Apgar score, acid–base status). Patient satisfaction during the intraoperative period and surgical conditions as assessed by the surgeon were also considered as secondary quality outcomes.

Eligibility assessment was performed independently in an unblinded, standardized manner by the two review authors using a customized form, while discrepancies were resolved by consensus. With respect to included studies, a formal measure of agreement between the two reviewers was calculated through Kappa statistic.\textsuperscript{13} We prepared a flow diagram to summarize the study selection process according to PRISMA.\textsuperscript{14}

The reviewers extracted data independently using a standardized data collection form managed electronically through the database software Filemaker Pro\textsuperscript{9}. Any discrepancy was resolved by discussion and re-inspection of the original trial.

The likelihood of the risk of bias was assessed by the review authors independently using two different tools: the Jadad scale\textsuperscript{15} and a domain-based evaluation recommended by the Cochrane Handbook for Systematic Reviews of Interventions.\textsuperscript{16}

**Data analysis**

The main primary outcome was anaesthetic efficacy based on requirement for analgesic supplementation by any route (i.v.; i.m.; inhalation, INH; epidural, EPiD) during the Caesarean delivery. Outcomes were treated as dichotomous variables based mainly on the specific definition that was used in each individual trial and no further attempt was made at standardization, unless stated otherwise in the Results section.

We had expected that information extracted from the individual trials might need some transformation (processing) before it was suitable for analysis, situations such as randomization in more than two intervention groups as a multi-arm study receiving similar but non-identical doses of bupivacaine. Therefore, before seeing the data, we decided to follow the approach recommended by the Cochrane Handbook\textsuperscript{17} to avoid introducing bias into the analysis. The planned method was to combine within each trial all relevant experimental intervention groups into a single group and to combine all relevant control groups into a single control group. Thus, the number of outcome events and total number per group would reflect such a combined approach.

The operational cut-off point was established at $\leq 8$ mg for the LD (intervention group) and $>8$ mg for the CD (control group). Even though, evidence from prospective studies assessing maternal haemodynamic stability shows that lowering the spinal dose renders improvement, there are few dose–response relationship studies to elucidate and define the LD range in terms of anaesthetic efficacy. Therefore, we have considered what has been summarized by authors in published narrative reviews exploring the literature,\textsuperscript{2,\textsuperscript{10}\textsuperscript{11}} and we have established such an arbitrarily operational/instrumental cut-off point in the review process as recommended by the Cochrane Handbook for Systematic Reviews.

Statistical combination of data from two or more separate trials in a meta-analysis was decided based on the evaluation of the clinical and methodological heterogeneity. The inconsistency throughout trials was quantified with the $I^2$ statistic proposed by Higgins and colleagues,\textsuperscript{18} assuming a value more than 50% as a substantial heterogeneity. The summary effect measure chosen was risk ratio (RR) and number needed to treat for an additional harmful outcome (NNTH), along with their corresponding 95% confidence intervals (CI). The meta-analysis was planned to be performed through a random-effects model and Mantel–Haenszel (M–H) statistical method, anticipating that trials would present multiple dose-schemes and assuming that the actual true effects have a normal distribution. In order to explore publication bias, we performed logarithmic transformation of the RR effect estimates and its standard errors, construction of Begg’s funnel plots, and assessment of the degree of symmetry with Egger’s test (weighted
regression). Sensitivity analyses were performed to test the robustness of the results. Subgroup analyses and meta-regression were performed on prespecified confounding variables: bupivacaine baricity, position during injection, uterine exteriorization, and original groups vs re-grouping. Short-acting intrathecal opioid use (other than intrathecal morphine) was incorporated as a new confounding variable after data extraction, and also study population. Analyses were conducted using Review Manager (RevMan5, Cochrane Collaboration) and STATA 9.2 (College Station, TX, USA) for Macintosh.

This systematic review was carried out using the methods established by the Cochrane Handbook for Systematic Reviews of Interventions and we followed the recommendations and checklist items from the PRISMA Statement for Reporting Systematic Reviews and Meta-analysis.

Results

The search strategies identified 186 (CENTRAL), 139 (MEDLINE), 366 (EMBASE), and 94 (LILACS) studies and another four from some other sources. After a process of successive screening for eligibility, 35 studies were selected for a more detailed evaluation (Fig. 1). The subsequent eligibility assessment excluded 20 studies; therefore, 15 studies were included for the data extraction process and eventual description of study characteristics involving 1004 participants. Reasons for study exclusion included: (i) mixed interventions without isolation of the efficacy of the intrathecal component (CSE with epidural supplementation, epidural volume extension); (ii) comparison groups not complying with the operational definition of LD and CD; and (iii) lack of reporting primary outcomes data for further analysis. The level of agreement between reviewers in this final assessment yielded a kappa statistic of 0.7, considered to reflect substantial agreement. One of the trials reported two different studies in the same publication, meaning two independent samples of subjects under similar protocol, but independent randomization process and data analysis. Whereas only one of those studies uniformly includes the addition of fentanyl as an adjuvant in groups under comparison, they are presented and counted separately as two studies but one publication reference (Choi and colleagues-a and -b). During the meta-analysis stage, three studies were excluded for presenting clinical co-intervention. Consequently, 12 studies were deemed for the final meta-analysis involving 693 participants (Fig. 1).

The 15 studies analysed were published between 2000 and 2010 and were performed in North America, South America, Europe, Asia, and Africa. We contacted one author for clarification on the primary outcome data. The studies were published in English, Spanish, and Japanese.

The mean age of the patients included ranged from 24 to 37 yr. While mean weight reported was between 58 and 62 kg in three studies, between 65 and 70 kg in four

![Fig 1 PRISMA flow chart.](image)
Table 1  Description of the included studies. CSE, combined spinal–epidural anaesthesia; UtD, uterine displacement; IB, isobaric bupivacaine; HB, hyperbaric bupivacaine; Fen, fentanyl; Morph, morphine; Ket, ketamine; Lid, lidocaine; Epip, epinephrine; Mepiv, mepivacaine; Epid, epidural; GA, induction of general anaesthesia; LLD, left lateral decubitus; RLD, right lateral decubitus; n/a, information not available; Sx, characteristics of the surgical technique; Ext, Uterine exteriorisation; SuffSx, sufficiency for the surgery; SenB, sensory block; Trend, Trendelenburg position; R-Trend, reverse Trendelenburg; Pain assess, pain assessment; Intraop, intraoperative

<table>
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<tr>
<th>Study</th>
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<th>Neuraxial technique</th>
<th>Sx Analg/anaesth supplementation Efficacy criteria</th>
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<td>Ben-David7</td>
<td>32</td>
<td>IB 0.5%: 5 mg + Fen 25 µg; 10 mg</td>
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<td>Ext Fen 1 µg kg⁻¹ (i.v.); GA Pain assess; SuffSx</td>
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<td>Choi and colleaguesa21</td>
<td>60</td>
<td>HB 0.5%: 8 mg; 10 mg; 12 mg</td>
<td>Spinal; LLD; UTD</td>
<td>n/a Fen 30 µg (i.v.) Pain assess; SenB T6</td>
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<tr>
<td>Choi and colleaguesb21</td>
<td>60</td>
<td>HB 0.5% + Fen 10 µg: 8 mg; 10 mg; 12 mg</td>
<td>Spinal; LLD; UTD</td>
<td>n/a Fen 30 µg (i.v.) Pain assess; SenB T6</td>
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<tr>
<td>Kiran and Singal28</td>
<td>60</td>
<td>HB 0.5%: 7.5 mg; 8.75 mg; 10 mg</td>
<td>Spinal; LLD; Trend</td>
<td>n/a Ket 20 mg, 10 mg (i.v.) Pain assess; SenB T8 at 4 min</td>
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<td>Ginosar and colleagues23</td>
<td>42</td>
<td>HB 0.75% + Fen 10 µg + Morph 200 µg: 6 mg; 7 mg; 8 mg; 9 mg; 10 mg; 11 mg; 12 mg</td>
<td>CSE; sitting; UTD</td>
<td>Ext Lid 2% + Epin 5 µg ml⁻¹ (5 ml bolus-Epid) Pain assess; SenB T6 at 10 min</td>
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<td>Nagata and colleagues31</td>
<td>33</td>
<td>HB 0.5%: 8 mg; 10 mg</td>
<td>Spinal; RLD; R-Trend; UtD</td>
<td>n/a Analgesic supplementation not needed Pain assess; SenB T6 at 10 min</td>
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<tr>
<td>Rivero and colleagues26</td>
<td>109</td>
<td>HB 0.5% + Fen 15 µg: 7.5 mg; 12.5 mg</td>
<td>Spinal; LLD; UTD</td>
<td>n/a Fen (i.v.) Pain Assess; SenB T4 at incision</td>
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<tr>
<td>Carvalho and colleagues22</td>
<td>48</td>
<td>HB 0.5% + Fen 10 µg + Morph 200 µg: 5 mg; 6 mg; 7 mg; 8 mg; 9 mg; 10 mg; 11 mg; 12 mg</td>
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<td>Ext Lid 2% + Epin 5 µg ml⁻¹ (5 ml bolus-Epid) Pain assess; SenB T6 at 10 min</td>
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<td>HB 0.5% + Fen 20 µg: 6.5 mg; 11 mg</td>
<td>Spinal; sitting; UTD</td>
<td>n/a Fen 100 µg (i.v.); GA Pain assess</td>
</tr>
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<td>Kimoto and colleagues32</td>
<td>47</td>
<td>IB 0.5% + Fen 20 µg: 5 mg; 7.5 mg; 10 mg; 12.5 mg</td>
<td>CSE; LLD</td>
<td>n/a Mepiv 2% (10–15 ml bolus-Epid) Pain assess; SenB T6 at 10 min</td>
</tr>
<tr>
<td>Meléndez and colleagues25</td>
<td>239</td>
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<td>Ext Fen 50 µg (i.v.) Pain assess</td>
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<tr>
<td>Bryson and colleagues24</td>
<td>52</td>
<td>Fen 50 µg + Morph 200 µg: IB 0.5% (4.5 mg); HB 0.75% (12 mg)</td>
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<td>Ext Fen 1.5 µg kg⁻¹ (i.v.); Ket 0.2 mg kg⁻¹ (i.v.) Pain assess</td>
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<td>Leo and colleagues29</td>
<td>60</td>
<td>HB 0.5% + Morph 100 µg: 7 mg; 8 mg; 9 mg</td>
<td>CSE; RLD; UTD</td>
<td>n/a Lid 1.5% (alkalinized) + Epin 5 µg ml⁻¹ (5 ml bolus Epid) up to 20 ml; Entonox; Fen (i.v) Pain assess; SenB T4 at 15 min; SenB below T6 intraop SenB T6 at 15 min</td>
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<td>Turhanoglu and colleagues30</td>
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<td>IB 0.5%: 4 mg + Fen 25 µg; 10 mg</td>
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<td>Mebazaa and colleagues31</td>
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<td>IB 0.5% + Fen 25 µg + Morph 100 µg: 7.5 mg; 10 mg</td>
<td>Spinal; sitting; UTD</td>
<td>No ext Fen (i.v.) Pain assess</td>
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</table>

and between 70 and 85 kg in eight studies.21 25 26 BMI was mentioned in only two.25 29

Sample size ranged from 32 to 239 participants (median = 52) and only two25 26 had larger sample sizes of 109 and 239 (Table 1). Power analysis was mentioned in eight of the 15 studies: the variables considered for calculations were hypotension in five studies,7 24 26 30 33 intraoperative pain,25 maximum sensory block,29 and in one study, interim analysis of their first 10 participants.27

In seven studies, two groups were compared,7 24 26 27 30 31 33 three in five studies,21 25 28 29 and four in one study.32 A dose-ranging protocol was used in two studies,22 23 comparing seven and eight groups in each. Bupivacaine dose in the included studies ranged from 4 to 12.5 mg. We attempted to calculate a representative summary dose for each dose-scheme group, considering the studies sample size, thus resembling a weighted mean value. Hence, we obtained a rounded dose of 7 mg for LD and 11 mg for CD. These are somewhat instrumental and intend to keep the meta-analytic approach of the sample size weights of the studies, but we do not expect to consider them as the final nominal summary dose for LD and CD.

Intrathecal opioids (other than morphine) were used only in the LD and not in the CD (three studies)7 25 30 and therefore, as a result of treating groups unevenly, this situation was considered an element of co-intervention and source of heterogeneity for the analysis.

The anaesthetic technique used in 10 studies was single-injection spinals7 21 24–28 31 33 while five studies22 23 29 30 32 used CSE techniques, in which the intrathecal injection was the main anaesthetic component and the epidural catheter was considered for rescue, analgesic–anaesthetic supplementation, or both. Ringer’s lactate solution was most commonly used for preloading, in the range of 500 ml in two
studies and 1000–1500 ml in the remainder. Four studies also included colloids.

Hypotension was managed with ephedrine as a sole drug in 13 studies. Ephedrine was a second option to phenylephrine when heart rate was <60 beats min in one study and mephenoxamine was used in one study.

**Primary outcomes**

Anaesthetic efficacy: studies administered intraoperative analgesic/anaesthetic supplementation based on four non-excluding criteria: (i) a predetermined threshold of pain on a visual analogue scale (VAS), (ii) pain categories as excellent, good, mild, fair, and poor, (iii) any pain during surgery, and/or (iv) failure to achieve a predetermined dermatomal sensory block before start of surgery.

The analgesic supplementation during single injection spinals was i.v. fentanyl (ketamine in one study). In CSE studies, supplementation was obtained through the epidural catheter.

Conversion to general anaesthesia occurred in only one study in two out of 21 participants in the LD group (0.5% hyperbaric bupivacaine 6.5 mg with fentanyl 20 μg). There were no reported events of conversion to general anaesthesia for CD in any study.

**Secondary outcomes**

Maternal adverse effects, hypotension

Various criteria were used to define hypotension throughout the studies, considering different cut-off points in arterial pressure or even a combination of two criteria. Some studies recorded hypotension as (i) systolic arterial pressure <80–90–95–100 mm Hg, or (ii) mean arterial pressure <60 mm Hg, or (iii) predetermined percentage decrease in systolic arterial pressure 10–20–25–30%. Such heterogeneity in variation of clinical definitions for hypotension was anticipated and would have precluded further quantitative analysis. However, pool estimate of combined effect measures was planned to take into consideration such variations across studies.

Intraoperative nausea/vomiting

Incidence was reported either separately or combined. For the quantitative analysis, it was considered to be whichever was the highest occurrence of nausea, vomiting, or combined nausea/vomiting.

Neonatal outcomes (Apgar score, acid–base status)

While seven studies reported Apgar scores at 1 and 5 min, only two mentioned acid–base status. They were all within normal range and showed non-significant differences between LD and CD.

Patient satisfaction during the intraoperative period

Six studies collected data at the post-anaesthesia care unit. Participants were asked to grade their level of overall satisfaction with the anaesthetic (i) on VAS, (ii) in categories as excellent, good, average, or poor, and (iii) participants having had previous Caesarean deliveries were asked if they preferred their present or their previous anaesthetic technique. Scores and categories reported were of high satisfaction without significant differences between LD and CD. Although one study reported a better overall satisfaction in the LD group, a subgroup analysis expressed significant dissatisfaction (average and poor) due to intraoperative pain and to nausea/vomiting when comparing LD with the CD group. Only one study investigated up to 3 days after operation through the quality of recovery (QoR) score and VAS. Follow-up results were similarly high in LD and CD.

**Surgical conditions assessed by surgeon**

Surgical conditions assessed by the surgeon were reported in four studies and all showed favourable conditions without differences between LD and CD.

The internal validity of included trials was assessed according to methods described by the Jadad scale and Cochrane Collaboration (Table 2). With regard to the Jadad scale (maximum score 5; ≥3 satisfactory methodological quality), all studies had acceptable levels of methodological quality with low risk of significant bias in the results. We found a source of performance bias based on co-intervention in three studies. The included studies presented low risk of bias in their methodology.

**Quantitative data synthesis**

We compared LD and CD as the intervention and control groups, respectively, using analgesic supplementation as a surrogate outcome of anaesthetic efficacy. We initially analysed the group of 15 studies included in the data extraction stage, reporting for 1004 patients. In the pooled analysis, LD was associated with a significantly higher risk of analgesic supplementation during Caesarean delivery (RR = 3.30, 95% CI = 1.39–7.85, P = 0.007), but substantial evidence of heterogeneity (I² = 79%, P = 0.00001) was observed. On investigating this heterogeneity, a source of clinical co-intervention was detected in three studies. The groups being compared were not treated uniformly, and the LD group received intrathecal fentanyl as an adjuvant. After excluding these studies, the final meta-analysis considered the pool estimate from 12 studies reporting 693 participants, which remained significant for a higher risk of analgesic supplementation in LD (RR = 3.76, 95% CI = 2.38–5.92, P = 0.00001) once the heterogeneity was resolved (I² = 0%, P = 0.72). We calculated an NNTH of 4 (95% CI = 2–7) based on a published risk of analgesic supplementation of 10.9% and 10.1% from the CD group in our analysis. Publication bias was ruled out by construction of Begg’s funnel plots and assessment of the degree of symmetry by Egger’s test (bias P = 0.274).

Sensitivity analyses demonstrated that our findings were not affected by change in the summary effect measure to odds ratio or by analysis through a fixed-effect model.
Subgroup analyses and meta-regression did not reveal interaction or effect modification by assessing possible confounding variables (bupivacaine baricity, position during injection, uterine exteriorization, intrathecal opioids other than morphine, weight <70 kg, original groups vs re-grouping, Asian vs non-Asian population).

Conversion to general anaesthesia occurred in only one study reporting two events in the LD group; therefore, a meta-analysis with a pool estimate of combined effect measures was considered inappropriate.

Of the secondary outcomes, the risk of hypotension was lower in the LD group (RR=0.78, 95% CI=0.65–0.93, P=0.005) (Fig. 3). The clinical and methodological heterogeneity of this outcome was confirmed statistically by quantifying a moderate inconsistency across studies (I²=29%, P=0.19). Nausea/vomiting as a combined outcome exhibited a lower risk in the LD group (RR=0.71, 95% CI=0.55–0.93, P=0.01) (heterogeneity; I²=6%, P=0.39) (Fig. 4) under a fixed-effect model.

The other secondary outcomes were not evaluated by meta-analysis due to dissimilarity in the reporting of outcomes.

### Discussion

On the basis of the collected evidence regarding ASA I–II term parturients for elective or semi-urgent Caesarean delivery under neuraxial spinal anaesthesia, the risk of intraoperative analgesic supplementation in the LD bupivacaine-scheme (≤8 mg) is more than three times higher (RR=3.76, 95% CI=2.38–5.92, P<0.00001) than the CD scheme (>8 mg). This suggests that one additional patient will require intraoperative analgesic supplementation due to intraoperative pain for every four patients (95% CI=2–7) receiving an LD spinal rather than a CD spinal. We found no evidence of interaction or effect modification among the possible clinical confounders analysed. The risk of conversion to general anaesthesia could not be estimated based on the included studies (two events in LD). There was a lower risk of maternal side-effects in LD than in CD, with 22% reduction in hypotension and 29% reduction in nausea/vomiting. Neonatal outcomes were similar in both groups, as were patient satisfaction during the intraoperative period and quality of surgical conditions assessed by the surgeon.
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<tr>
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<th>Conventional dose</th>
<th>Risk ratio</th>
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<td></td>
<td>Events</td>
<td>Total</td>
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<td>Mebazaa and colleagues33</td>
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**Fig 2** Forest plot for analgesic supplementation comparing LD vs CD: individual trials and meta-analysis. Events, the total numbers with events (primary outcome = analgesic supplementation) in the intervention (LD) and control (CD) groups; Total, the total numbers of participants in the intervention and control groups; Weight, sample size contribution of the study relative to the pooled sample size of the meta-analysis; M–H, Mantel–Haenszel methods.
Fig 3 Forest plot for hypotension comparing LD vs CD: individual trials and meta-analysis. Events, the total numbers with events (secondary outcome = hypotension) in the intervention (LD) and control (CD) groups; Total, the total numbers of participants in the intervention and control groups; Weight, sample size contribution of the study relative to the pooled sample size of the meta-analysis; M–H, Mantel–Haenszel methods.

Fig 4 Forest plot for nausea/vomiting comparing LD vs CD: individual trials and meta-analysis. Events, the total numbers with events (secondary outcome = nausea/vomiting) in the intervention (LD) and control (CD) groups; Total, the total numbers of participants in the intervention and control groups; Weight, sample size contribution of the study relative to the pooled sample size of the meta-analysis; M–H, Mantel–Haenszel methods.
The quality of the overall body of evidence for each individual outcome was addressed and summarized through the GRADE system (Table 3). The assessment of the analgesic supplementation as a primary outcome was rated as high quality, in view of low risk of bias in trial design and implementation, precise and consistent results in magnitude and direction, and also identified and explained source of heterogeneity. However, the secondary outcomes were rated as moderate quality, considering relatively different criteria for hypotension; results from combined events for nausea/vomiting; and pool estimates not estimable for neonatal outcomes, patient satisfaction, and quality of surgical conditions. Conversion to general anaesthesia and neonatal acid–base status were considered as low quality.

Our systematic review has limitations. The search was restricted to full reports of randomized controlled trials published in peer-reviewed journals, excluding other sources of biomedical literature, which could have possibly collected more studies related to the topic. Although the funnel plots and the corresponding statistical tests did not reflect publication bias, the power is low, considering the small number of studies. The two main limitations of this review are related to the operational cut-off point for the bupivacaine dose and outcome definitions across studies. Potential bias as a systematic error can help explain variation in the results of the studies included in a systematic review. Choosing a different cut-off point for the dose-schemes could have changed not only the final meta-analysis but also the early stage of re-grouping the participants within studies for data extraction, and which studies were eligible, that is with a dose scheme from each side of the cut-off point. Sensory blockade to T2–T6 (most commonly T4) is thought to be adequate for Caesarean delivery, but the method used to assess the block is not always standardized or mentioned explicitly. A block at T4 to pinprick has been shown to be unreliable at predicting a pain-free Caesarean delivery, but, in contrast, others have shown that a block to T5 to touch, or a block to touch that includes T6 at skin incision, is likely to provide a pain-free procedure. The assumption is made that there is a consistent difference in dermatomal block levels between light touch, pinprick, and cold sensations. Although Russell demonstrated a median difference of two segments between these, it was emphasized that there was no constant relationship either within the group or in individual patients. Brown defined analgesia as loss of sharp pinprick sensation and anaesthesia as loss of touch. Increasing the dose of local anaesthetic used can produce a denser sensory block (anaesthesia) without necessarily causing higher levels of block to pinprick, and with less need for analgesic supplementation. Opioids as adjuvants to neuraxial anaesthesia improve the quality of the block without producing a higher level of analgesia to pinprick.

We found that various sensory tests (temperature, pinprick) were used together with various methods of application. Indeed, sometimes the method used to test the block was not explicitly mentioned. The definition of an ‘adequate block’ ranged from T2 to T6. None of the studies reported touch or light touch for dermatome assessment. Whatever the block level or assessment method, ultimately it is the patient’s experience of pain which remains the uppermost outcome of importance. Hence, we used anaesthetic efficacy as assessed by intraoperative analgesic supplementation and conversion to general anaesthesia rather than dermatomal sensory block levels. Studies of prevention and treatment of spinal-induced hypotension show that lowering the dose improves maternal haemodynamic stability, irrespective of what definition is used. Our review shows agreement with this but with moderate quality of evidence. Lastly, ephedrine was used in all studies but one for control of hypotension.

Table 3 Summary of results (GRADE). N, number of studies; n, number of participants; LD, low dose; (1), one study reporting two events for this outcome; (2), categorical data in four studies (Apgar score 8 at 5 min, score 9 and 10 at 5 min) and continuous data in three studies; (3), two studies collecting data for this outcome; (4), categorical data in three studies and continuous data in three studies; (5), categorical data in three studies and one study reporting no difference.
In summary, our review adds to the evidence concerning optimal dosing for spinal anaesthesia. Various prospective studies conclude that an ‘LD’ scheme is a viable option without compromising the anaesthetic efficacy, but sample sizes have usually been calculated based on variables such as hypotension rather than intraoperative pain. Previous reviews related to this subject have had differing conclusions. Consequently, lower anaesthetic doses comparable with our weighted mean values for LD and CD, by logistic regression gave ED50 and ED95 values respectively. By logistic regression giving ED50 and ED95 values comparable with our weighted mean values for LD and CD, by logistic regression gave ED50 and ED95 values respectively. Consequently, lower anaesthetic doses cannot be recommended unless an epidural catheter is in place (CSE) to rescue the block if anaesthesia is inadequate or becomes inadequate during surgery. Low-dose CSE anaesthesia may not be the optimal technique for all patients and institutions. The dilemma of ensuring better anaesthesia while avoiding the higher incidence and severity of hypotension is not yet resolved but we have a better understanding of dose schemes.

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Conflict of interest

None declared.

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