Effect of Epidural Volume Extension on Quality of Combined Spinal-Epidural Anesthesia for Cesarean Delivery: A Systematic Review and Meta-Analysis

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In obstetric procedures, epidural volume extension (EVE) has been suggested to lower intraoperative opioid requirements while improving motor recovery when added to spinal anesthesia. This systematic review with meta-analysis was performed to evaluate the efficacy of EVE in elective cesarean delivery.

We searched PubMed, Embase, and The Cochrane Review Database for randomized controlled trials evaluating EVE compared with single shot spinal and/or combined spinal/epidural anesthesia. The primary outcomes were efficacy of EVE, as defined by the need for intraoperative opioid supplementation, and time to complete motor recovery.

Eighteen randomized controlled trials consisting of 1,670 patients were evaluated. Subgroup analyses of EVE with local anesthetic were statistically significant in decreasing the need for intraoperative analgesic supplementation (risk ratio = 0.30; 95% confidence interval [CI] = 0.13-0.68; P = .004; I² = 50%). Faster motor recovery was also seen (MD −24.14; 95% CI = −47.31 to −0.98; P = .04; I² = 98%). Sequential EVE has been affirmed as a method to decrease intraoperative opioid requirements compared with single shot spinal or combined spinal/epidural anesthesia. Improved motor recovery times were also statistically significant but should be extrapolated with caution because of high heterogeneity of the included studies.

Keywords: Cesarean section, combined spinal-epidural, epidural volume expansion.

The near simultaneous injection of local anesthetic into the subarachnoid and epidural spaces was first described in 1937 in more than 200 cases. This technique, originally called episubdural anesthesia, is known today as combined spinal-epidural anesthesia (CSE) and is widely used in a variety of obstetric and surgical procedures. Even in 1937, Soresi recognized that by combining the 2 techniques, many disadvantages of a single technique were eliminated, while still providing surgical anesthesia, relaxation, and postoperative pain control. Although CSE was first suggested for cesarean delivery in 1979, it was not until 1982 that CSE was performed using a needle-through-needle technique. This innovation allowed both subarachnoid and epidural injections through the same intervertebral space and decreased procedure time.

The dose of local anesthetic is one of the factors that determines the degree and severity of spinal anesthesia–induced hypotension (SIH) during an elective cesarean delivery. Estimates of the incidence of SIH are between 15% and 33% of cases. Lowering the dose of the anesthetic below the median effective dose (ED₃₀) of the local anesthetic, combined with administration of opioid, has been successful in mitigating SIH and other maternal and fetal complications. However, this technique has a few potential disadvantages, including an increased need for intraoperative pain supplementation, conversion to general anesthesia, incomplete motor blockade, and inadequate anesthesia. To enhance the efficacy of low-dose local anesthetic, placement of an epidural catheter as part of the CSE technique has been advocated, which allows for “top-up” dose of local anesthetic or opioid.

A modified version of the CSE technique is the use of epidural volume extension (EVE). This approach incorporates the use of normal saline, opioid, or a small amount of local anesthetic into the epidural space immediately after intrathecal injection of the local anesthetic. When EVE uses local anesthetic, the technique is known as sequential CSE. Theoretically, expanding the epidural space extends sensory blockade from spinal anesthesia. Although there are other proposed mechanisms of EVE, the widely accepted mechanism of action is thecal compression of the subarachnoid space due to volume effect, which promotes cephalad displacement of local anesthetic in the cerebrospinal fluid. The local anesthetic effect, another accepted mechanism of EVE, is due to leakage of the local anesthetic from the spinal needle hole.
and the diffusion of the local anesthetic into the thecal space. Both the volume and local anesthetic effects of EVE during CSE were examined in earlier studies in non-obstetric cases.\textsuperscript{12,13} Stienstra and colleagues\textsuperscript{12} found that EVE with normal saline and local anesthetic increased the sensory block height. Furthermore, Takiguchi and colleagues\textsuperscript{13} reported that injecting 10 mL of saline in the epidural space immediately after subarachnoid block (SAB) increased the sensory blockade.

Published narrative reviews have highlighted a number of benefits of EVE. Aside from increasing the sensory block level, EVE allows the use of lower intrathecal doses of local anesthetic. In a study in nonobstetric patients, the minimum effective dose of plain bupivacaine was reduced.\textsuperscript{14} The lower dose of intrathecal local anesthetic reduces the incidence of hypotension and speeds motor recovery after the procedure.\textsuperscript{15,16}\textsuperscript{15} However, results of published trials examining the efficacy and safety of CSE with EVE in elective cesarean delivery have been inconsistent. Therefore, we performed this systematic review and meta-analysis to investigate the efficacy and safety of CSE with EVE during elective cesarean delivery.

**Methods**

The review and meta-analysis was carried out using the guidelines outlined in Cochrane Handbook for Systematic Reviews of Interventions\textsuperscript{17} and the checklist from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.\textsuperscript{18}

- **Search Strategy.** We searched PubMed, The Cochrane Reviews, MEDLINE, Cumulative Index to Nursing & Allied Health Literature (CINAHL), and Embase for evidence between January and November 2016 for the following text and keywords: *epidural volume extension, EVE, cesarean delivery, and obstetric anesthesia* alone or in combination. Full-text, English-language articles were reviewed with the references of relevant published trials. The ancestry approach and the related articles section in PubMed were also used to retrieve potentially relevant sources.

- **Study Selection.** Two authors (T.K., T.T.) of the current review examined the title and abstract of each relevant article. Only published randomized controlled trials (RCTs) investigating the effect of EVE, regardless of the type of solution used, during an elective cesarean delivery were included in the full article review. Studies comparing EVE to single-shot spinal anesthesia (SSS) and CSE were also included in the review. Retrospective studies, cohort studies, case reports, abstract-only articles, editorials, expert opinions, animal studies, duplications, and poster presentations were excluded for review and analysis. Any disagreements were resolved by discussion and consensus with the third author (J.K.).

Data from all included trials were extracted and summarized using a standardized form, which was reviewed and verified by the 2 authors (T.K., T.T.). Study demographics, methodologic protocols, types of EVE solution, types of local anesthetic drug, concentration and dose, and primary and secondary outcomes of each study were summarized and tabulated for analysis. In studies with more than 2 comparison groups, extracted data were processed before it was suitable for analysis. We then followed the guidelines as recommended by Cochrane Handbook for Systematic Reviews of Interventions to avoid double counting of participants and introducing bias into the analysis.\textsuperscript{17}

- **Risks of Bias.** The methodologic quality of each trial was scored according to the guidelines described by The Cochrane Collaboration. Assessment criteria included random sequence generation, allocation concealment, blinding of outcome data assessment, and selective reporting. Each category was appraised to “high risk,” “low risk,” and “unclear risk.” Assessment data were recorded independently, and any discrepancies were resolved by discussion and consensus.

- **Statistical Analysis.** We used Review Manager (RevMan 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration) for meta-analysis. The primary outcomes of this review were the efficacy of EVE, as it relates to the need for intraoperative opioid supplementation, and the time to complete motor recovery after surgery. There is no universally accepted sensory dermatomal level for adequate surgical anesthesia in cesarean delivery. Therefore, the frequency of intraoperative analgesia supplementation given intravenously or via epidural catheter and conversion to general anesthesia due to failed SAB were used as markers of EVE efficacy. This outcome measure was treated as a dichotomous variable, and no attempt was made at standardization of drug types, dosages, or routes. The secondary outcome for this review is time to first request of postoperative opioid supplementation. Similar to outcomes on intraoperative analgesia requirements, interventions used to treat postoperative pain were not standardized.

For dichotomous outcomes, risk ratio (RR) and 95% confidence interval (CI) were calculated and analyzed using the random effects model. Continuous variables were analyzed using mean difference with inverse variance method. Heterogeneity of the studies was assessed using the $I^2$ statistic. An $I^2$ of more than 50% was considered to have substantial heterogeneity. If heterogeneity was observed, subgroup analyses were performed. Sensitivity analysis was performed to assess robustness of all included trials. The Begg funnel plot and the Egger test were used to test for symmetry and publication bias.

**Results**

We initially reviewed 58 studies for eligibility based on titles and abstracts. Of the 40 examined full-text articles, we identified 18 RCTs\textsuperscript{19-36} for systematic review providing a total of 1,670 patients; all were published between
the years 1992 and 2015 in English-language, peer-reviewed journals. Data from 17 RCTs were subsequently included in the meta-analysis (Figure 1).

- **Demographic Characteristics.** Demographic data were largely homogenous. All patients were ASA class 1 or 2, except in one study that did not report patient classification.19 Lumbar interspaces used for the delivery of the local anesthetic were L1-2,20,21 L2-3,22 L3-4,19 L4-5,25-28 or a combination of these 23,24,29-36 Tuohy introducer sizes 16 g to 18 g were used in each of the studies, although one study did not specify a type/size of introducer.33 Pencil-point needles were used for SAB in all but 2 studies,22,35 which used the Quincke-type needle, and another study that did not differentiate.36 All patients received normal saline or lactated Ringer’s solution as prehydration.

Ten studies compared the use of CSE with EVE vs single-shot spinal (SSS).19-23,25,27,31,32,35 and 11 RCTs examined CSE with EVE compared with CSE alone.24-26,28-34 Of the 18 included studies, 13 trials used normal saline for EVE solution, the rise above “adequate surgical level” was 0 to 4 dermatomes.23,28,30-36 Of the 5 studies comparing SSS to sequential EVE, dermatomal rise above “adequate surgical level” was 0 to 3 dermatomes.19,22,35 Of the 18 studies, 7 RCTs25,26,28-30,34,35 recorded the time when desired sensory block was achieved before incision. Pooled analysis showed no difference in terms of the onset of sensory block considered adequate for surgical anesthesia (mean difference [MD] = −1.41; 95% CI = −5.72 to 2.89; P < .00001; I² = 97%). Sensory regression was similar in patients treated with sequential EVE and those treated with SSS or CSE (MD −2.23; 95% CI −8.09 to 3.63; P = .46; I² = 70%). The sensory block characteristics of included studies are summarized in the Table.

After induction of anesthesia and during the recovery phase, motor blockade was assessed using the modified Bromage scale. The scoring system ranges from 0 to 4, with 4 representing complete immobility of the lower extremities and 0 representing complete mobility. The motor block characteristics of included studies are summarized in the Table.

The type and dose of intrathecal local anesthetic differed between studies, perhaps because of variability of clinical practice. Thirteen studies19,22,24-28,34,36 used 0.5% hyperbaric bupivacaine for spinal anesthesia. Doses of bupivacaine ranged from 6 mg26 to 18 mg,29 with 9 mg as the most common.19,25,28,34,36 Two studies involved injections of 0.5% isobupivacaine in 9- to 10-mg doses,33,34 and 4 studies specified levobupivacaine in 5- to 15-mg doses.20,21,23,35 In addition, 11 studies added narcotic to the spinal anesthetic; fentanyl, 10 to 50 µg, in 8 studies19,24-28,32,35 and sufentanil, 2.5 to 5.0 µg, in 2 studies.20,21 Seven studies used the same subarachnoid dose of local anesthetic in the SAB group as they did in the EVE group.25,30,35 Nine studies used different baricities or doses, or both, between study groups.10-22,31-34,36

- **Primary Outcomes.** The main outcomes, use of intraoperative analgesia supplementation and time to

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**Figure 1.** PRISMA Flow Diagram of Search Strategy and Study Selection

Abbreviations: OB, obstetric; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
<table>
<thead>
<tr>
<th>Source</th>
<th>N</th>
<th>Study groups</th>
<th>Site/patient position</th>
<th>Type/ volume of EVE</th>
<th>Sensory level/ assessment</th>
<th>Assessment method for motor block</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Beale et al, 2005</td>
<td>52</td>
<td>CSE with EVE</td>
<td>L2-L3, L3-L4/ Left lateral</td>
<td>NS/NR/7</td>
<td>T5/Touch</td>
<td>NR</td>
<td>Up/down sequential technique to determine ED&lt;sub&gt;50&lt;/sub&gt; of hyperbaric bupivacaine ED&lt;sub&gt;50&lt;/sub&gt; of hyperbaric bupivacaine for EVE (5.1 mg) and non-EVE (6.1 mg) Sensory regression time to T10 NR</td>
</tr>
<tr>
<td>Blumgart et al, 1992</td>
<td>28</td>
<td>Sequential CSE</td>
<td>L2-L3, L3-L4/ Sitting</td>
<td>Bupivacaine 0.5% and NS/10 min after SAB/10</td>
<td>T4-T5/Pinprick</td>
<td>Bromage scale</td>
<td>All CSE IT dose of 0.5% hyperbaric bupivacaine (&lt; 163 cm, 1.6 mL; &gt; 163 cm, 1.8 mL) Similar effect on sensory extension in CSE with saline and sequential CSE Median sensory dermatomal rise 3-4 segments; sensory regression time NR</td>
</tr>
<tr>
<td>Brizzi et al, 2005</td>
<td>100</td>
<td>Sequential CSE</td>
<td>L1-L2/ Sitting</td>
<td>Levobupivacaine  0.25% /NR/10-12</td>
<td>NR/NR</td>
<td>NR</td>
<td>CSE dose of IT 0.25% levobupivacaine (&lt; 162 cm, 10 mL; &gt; 162 cm, 12 mL) SSS dose of levobupivacaine (&lt; 162 cm, 7.5 mg; &gt; 162 cm, 8 mg) with 5 µg of sufentanil Dermatomal rise and sensory regression time to T10 NR</td>
</tr>
<tr>
<td>Choi et al, 2000</td>
<td>66</td>
<td>Sequential CSE</td>
<td>L2-L3, L3-L4/ Right lateral</td>
<td>Bupivacaine 0.25% and NS/10 min after SAB injection/10</td>
<td>T4/Pinprick</td>
<td>Bromage scale</td>
<td>All CSE IT 0.5% hyperbaric bupivacaine, 8 mg Faster sensory regression to T10 in CSE with saline EVE and CSE alone (93 min vs 98 min) Median block level is higher in CSE with EVE vs CSE alone (T3 vs T4) Sequential EVE better at providing analgesia than CSE with saline EVE</td>
</tr>
<tr>
<td>Choi et al, 2006</td>
<td>100</td>
<td>Sequential CSE</td>
<td>L3-L4/ Right lateral</td>
<td>Bupivacaine 0.25%/5 min after SAB injection/10</td>
<td>T4/Pinprick</td>
<td>Bromage scale</td>
<td>For CSE, IT 0.5% hyperbaric bupivacaine, 6 mg, with fentanyl, 20 µg For SSS, 0.5% hyperbaric bupivacaine, 9 mg, with 20 µg of fentanyl Faster sensory recovery in sequential EVE vs SSS</td>
</tr>
<tr>
<td>Fabris et al, 2013</td>
<td>76</td>
<td>CSE with EVE</td>
<td>L3-L4, L4-L5/ Sitting</td>
<td>NS/Immediately after SAB injection/18-20</td>
<td>NR/Pinprick</td>
<td>Bromage scale</td>
<td>For CSE with saline, IT 0.5% hyperbaric levobupivacaine, at 0.025 mg/cm high For spinal anesthesia, 0.5% hyperbaric levobupivacaine (5 mg/cm high) with fentanyl (&lt; 165 cm, 15 µg; &gt; 175, 25 µg) Time to surgical level and sensory regression to T10 NR</td>
</tr>
<tr>
<td>Gupta et al, 2012</td>
<td>99</td>
<td>CSE with saline EVE</td>
<td>L4-L5/ Left lateral</td>
<td>NS  6% hydroxyethyl starch injection (Hesparin) Immediate after SAB injection/5</td>
<td>T6/Pinprick</td>
<td>Bromage scale</td>
<td>All CSE IT 0.5% hyperbaric bupivacaine, 6 mg, with fentanyl, 25 µg More patients required supplemental ketamine in CSE with no EVE compared with CSE with saline or Hespan EVE</td>
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<tr>
<td>Authors</td>
<td>Year</td>
<td>Study Design</td>
<td>Levels</td>
<td>Technique</td>
<td>Sensory Regression</td>
<td>Time to Surgical Level</td>
<td>Notes</td>
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<tr>
<td>Karaman et al.</td>
<td>2005</td>
<td>Sequential CSE</td>
<td>L2-L3, L3-L4/NR</td>
<td>Bupivacaine 0.25% with 50 µg of fentanyl/10 min after SAB injection/10</td>
<td>T4/Pinprick</td>
<td>CSE IT 0.5% hyperbaric bupivacaine (&lt; 165 cm, 1.5 mL; &gt; 165 cm, 1.8 mL) Epidural anesthesia, 0.5% bupivacaine, 16 mL, with fentanyl, 100 µg; additional 2 mL of bupivacaine per segment unblocked until T4 Postoperative pain treated with epidural morphine</td>
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<tr>
<td>Kaur et al.</td>
<td>2012</td>
<td>CSE with EVE</td>
<td>L3-L4, L4-L5/NR</td>
<td>NS/5 min after SAB injection/10</td>
<td>T5/Pinprick</td>
<td>SS 0.5% hyperbaric bupivacaine, 10 mg, with fentanyl, 25 µg All CSE IT 0.5% hyperbaric bupivacaine, 7 mg, with fentanyl, 25 µg Time to reach surgical level and regression time to T10 NR</td>
<td></td>
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<tr>
<td>Kucukguclu et al.</td>
<td>2008</td>
<td>2 CSE groups (0.5% plain bupivacaine and 0.5% hyperbaric bupivacaine) 2 CSE groups with EVE (0.5% plain bupivacaine and 0.5% hyperbaric bupivacaine)</td>
<td>L3-L4, L4-L5/NR</td>
<td>NS/5 min after SAB injection/10</td>
<td>T4/Pinprick</td>
<td>All CSE IT bupivacaine dose dependent (&lt; 163 cm, 8 mg; &gt; 163, 9 mg) Fentanyl, 20 µg, was added to all anesthetics Dermatomal rise and sensory regression equivalent between CSE groups and CSE with EVE</td>
<td></td>
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<tr>
<td>Lew et al.</td>
<td>2004</td>
<td>SSS CSE with EVE</td>
<td>L4-L5/Sitting</td>
<td>NS/5 min after SAB injection/6</td>
<td>T4/Pinprick</td>
<td>Spinal anesthesia, 0.5% hyperbaric bupivacaine, 9 mg, with fentanyl, 10 µg CSE, IT 0.5% hyperbaric bupivacaine, 5 mg, with fentanyl, 10 µg Time to reach surgical level NR; sensory regression to T10 faster with CSE/EVE</td>
<td></td>
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<tr>
<td>Loubert et al.</td>
<td>2011</td>
<td>SSS CSE</td>
<td>L3-L4, L4-L5/NR</td>
<td>NS/Immediately after SAB injection/5</td>
<td>T4/Pinprick</td>
<td>CSE with EVE, IT hyperbaric bupivacaine, 7.5 mg CSE without EVE, hyperbaric bupivacaine, 10 mg Spinal anesthesia, hyperbaric bupivacaine, 7.5 mg All patients received IT fentanyl, 25 µg Time to surgical level and sensory regression to T10 NR</td>
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<tr>
<td>Malvasi et al.</td>
<td>2010</td>
<td>SSS Sequential CSE</td>
<td>L1-L2/Sitting</td>
<td>Lidocaine 0.5%/Immediately after SAB injection/3-7 depending on height</td>
<td>NR/NR</td>
<td>Spinal anesthesia, 0.15% levobupivacaine, 5 mL, with 5 µg of sufentanil CSE with EVE, IT 0.15% levobupivacaine, 4 mL, with 5 µg of sufentanil Time to surgical level and sensory regression to T10 NR</td>
<td></td>
</tr>
<tr>
<td>Salman et al.</td>
<td>2013</td>
<td>SSS CSE with EVE</td>
<td>L3-L4, L4-L5/NR</td>
<td>NS Levobupivacaine 0.5%/5 min after SAB injection/5</td>
<td>T4-T5/Pinprick</td>
<td>Spinal anesthesia, IT 0.5% levobupivacaine (&gt; 160 cm, 10 mg; 161-164 cm, 12 mg; 165-169, 14 mg; &gt; 170 cm, 15 mg) with fentanyl, 20 µg CSE facilitates early onset of sensory block and faster motor recovery</td>
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<tr>
<td>Thörén et al.</td>
<td>1994</td>
<td>Sequential CSE</td>
<td>L2-L3/Sitting</td>
<td>Bupivacaine 0.5%, fractionated dose</td>
<td>T4/Pinprick</td>
<td>Spinal anesthesia, 0.5% hyperbaric bupivacaine, 12.5 mg CSE with EVE, IT 0.5% hyperbaric bupivacaine, 1.5 mL All CSE without EVE, IT 0.5% isobaric bupivacaine, 2 mL, and 0.5% isobaric bupivacaine, 1.5 mL All CSE with EVE, IT 0.5% isobaric bupivacaine, 2 mL, and 0.5% isobaric bupivacaine, 1.5 mL Time to surgical level and sensory regression to T10 NR</td>
<td></td>
</tr>
<tr>
<td>Tripathi et al.</td>
<td>2015</td>
<td>2 CSE groups, IT 0.5% isobaric bupivacaine, 2 mL 2 CSE with EVE, IT 0.5% isobaric bupivacaine, 2 mL</td>
<td>L3-L4, L4-L5/NR</td>
<td>NS/5 min after SAB injection/15</td>
<td>T5/Pinprick</td>
<td>All CSE without EVE, IT 0.5% isobaric bupivacaine, 2 mL, and 0.5% isobaric bupivacaine, 1.5 mL All CSE with EVE, IT 0.5% isobaric bupivacaine, 2 mL, and 0.5% isobaric bupivacaine, 1.5 mL Time to surgical level and sensory regression to T10 NR</td>
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Table. Included Randomized Controlled Trials Reporting on the Efficacy and Safety of Epidural Volume Extension in Combined Spinal-Epidural Anesthesia During Elective Cesarean Delivery

<table>
<thead>
<tr>
<th>Source</th>
<th>Study groups</th>
<th>N</th>
<th>Type of EVE fluids</th>
<th>Site of epidural volume extension</th>
<th>Timing of epidural volume extension</th>
<th>Assessment method of surgical anesthesia</th>
<th>Sensory level assessment method of surgical anesthesia</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Tyagi et al, 2009 | 2 CSE groups | 56 | NS | Posterior fontanelle, lateral | Immediately after SAB injection | Pinprick | T6 = sensory level for adequate surgical anesthesia | All CSE groups, IT 0.5% hyperbaric bupivacaine, 9 mg, with fentanyl, 10 µg | Time to surgical level faster with SSS and CSE + EVE compared to CSE alone. End point was sensory regression time. |}

Abbreviations: CSE, combined-spinal epidural anesthesia; ED50, median effective dose; EVE, epidural volume extension; IT, intrathecal; NR, not reported; NS, 0.9% normal saline; SAB, subarachnoid block; SSS, single-shot spinal anesthesia.

a Site of epidural space identification and participant’s position during regional technique.
b Type of epidural volume extension fluid (0.9% normal saline vs local anesthesia).
c Sensory dermatomal level for adequate surgical anesthesia.
d Bromage scale is a method to assess motor block of the lower extremities: 0 = full flexion of knees and feet, 1 = able to move knees, 2 = able to move feet only, and 3 = unable to complete motor recovery.

e Use of a local anesthetic for epidural volume extension.

• Intraoperative Analgesia. The use of intraoperative analgesia supplementation was investigated in 13 studies. The overall effect of the RCTs that examined the use of EVE compared with control showed no statistical difference between the 2 groups (RR = 0.71; 95% CI = 0.38-1.34; P = .22; I² = 66%; Figure 2). Similarly, subgroup analysis of 7 studies comparing normal saline EVE against control demonstrated no statistical significance in the use of intraoperative analgesia supplementation (RR = 1.06; 95% CI = 0.71-1.59; P = .78; I² = 27%). However, when 7 studies were evaluated comparing the use of local anesthetic EVE with control, fewer patients treated with sequential CSE required intraoperative analgesia than those patients with SSS or CSE alone (RR = 0.30; 95% CI = 0.13-0.68; P = .004; I² = 50%).

b Time to Complete Motor Recovery. The aggregate effect of 10 RCTs that evaluated the effects of CSE with EVE showed faster motor recovery compared with control (MD = −24.14; 95% CI = −47.31 to −0.98; P = .04; Figure 3). The pooled analysis resulted in a very substantial heterogeneity (I² = 98%). Results of subgroup sensitivity analyses for CSE with EVE vs SSS and CSE without EVE did not change the I² statistics. Two studies reported that motor block between the SSS group and EVE group was statistically significant (P < .001), and their authors opined that the shorter block in the EVE group allowed for more rapid mobilization, but no motor block assessment data were produced. Two studies discussed postoperative evaluation of motor recovery using modified Bromage scores, the authors did not provide data from their evaluation. These last 6 studies could not be included in the analysis of this outcome. One study did not include motor assessments at all.

c Secondary Outcome: Time to First Postoperative Analgesia. Ten studies totaling 626 patients reported the time to first postoperative analgesia request. Pooled analysis of included studies showed no significant differences between CSE/EVE and control for postoperative analgesia (MD = 0.76, 95% CI = −16.16 to 17.67; P < .00001; I² = 92%; Figure 4).
Further subgroup analyses comparing the use of EVE with SSS and CSE alone did not differ in results. Different types of EVE (normal saline vs local anesthetic) were again not statistically significant for this outcome. Only 2 studies reported that time to first postoperative pain control request was shorter in patients treated with EVE.

- **Risks of Bias.** Random sequence generation and allocation concealment were well implemented. One study consecutively assigned participants to study groups, which potentially introduced selection bias. Four
studies\textsuperscript{20-23} introduced bias through a lack of allocation concealment. Some studies were determined to have an unclear risk of bias related to performance and detection. In 6 studies, the authors\textsuperscript{20-23,25,30} did not discuss blinding of participants involved in the placement of the block (performance bias). Blinding of outcome assessment, a type of detection bias, was unclear in 7 studies.\textsuperscript{19-23,25,30} This type of bias may cloud patient reporting of outcomes, encouraging patients to report pain either sooner or later based on clues from the observer. Figure 5 summarizes the risks of bias.

Discussion
To our knowledge, this is the first systematic review and meta-analysis evaluating the effectiveness and safety of EVE for elective cesarean delivery. Epidural injection of normal saline or a small amount of local anesthetic immediately after spinal anesthesia was proposed to extend the sensory block height during cesarean delivery while allowing use of a lower dose of local anesthetic for spinal anesthesia. This adjustment in CSE technique was first characterized by Rawal and colleagues.\textsuperscript{37,38} Until recently, normal saline was more commonly used in the clinical setting than was local anesthetic.

The results of our review demonstrated that the use of EVE is associated with significantly shorter times to complete motor recovery following cesarean delivery. The improved motor block characteristics of EVE are clinically relevant in the implementation of the Enhanced Recovery After Surgery (ERAS) initiative in patients undergoing cesarean delivery. With early regression of motor blockade after spinal anesthesia, 2 key components of ERAS for cesarean delivery, early mobilization and catheter removal, are met.\textsuperscript{39} Until recently, normal saline was more commonly used in the clinical setting than was local anesthetic.

Figure 4. Forest Plot of the Time to First Postoperative Analgesia
Abbreviations: CSE, combined spinal-epidural anesthesia; EVE, epidural volume extension; random, random-effects model

gic supplementation because of pain, discomfort, or failure to achieve sensory blockade adequate for surgical incision. In a previously published meta-analysis, low-dose bupivacaine was related to a higher risk of intraoperative pain.\textsuperscript{10} In our systematic review, analgesic requirement for sequential CSE was lower compared with CSE alone or SSS. This finding may be explained by the local anesthetic effect of EVE. This effect is theorized to occur by the diffusion of the local anesthetic to the subarachnoid space or drug transfer across the dura puncture hole.

On the other hand, EVE showed no significant improvement over control regarding the time of first postoperative opioid request. In theory, groups with EVE would require pain medications earlier than would groups with no EVE because of the lower dose of local anesthetic used in the subarachnoid space. In our review, only 2 studies reported shorter times to first postoperative pain supplementation.

There are limitations to this meta-analysis. First, most of the studies in this review had a relatively small sample size. Individual groups commonly had fewer than 50 participants per group. Second, a large variability in study protocol existed. For example, study design varied on lumbar interspace approach, needle size and type, and SAB drug and dose. Other study design challenges included varying volumes and types of solutions used for EVE. There was no standardization for EVE injection because studies were variable in terms of timing of injection from “immediately” to 10 minutes after CSE placement.

This review suggested areas where future studies are needed. Although our current analysis indicated statistical significance in the areas of decreased intraoperative analgesia needs and improved motor recovery times, we caution the extrapolation of our results to clinical practice because of the small sample size of most of the studies. Larger scale studies with homogenous design, such as similar SAB and similar EVE drug, dosing, and timing, would minimize heterogeneity across studies. Stricter blinding of participants to prevent performance and detection bias would improve methodologic quality. A cost analysis comparing SSS with sequential EVE would be of interest.
Conclusion

Findings of our systematic review with meta-analysis affirm that EVE is an effective approach to decrease intraoperative analgesia requirements while improving motor recovery following elective cesarean delivery. Larger, high-quality randomized trials would strengthen statistical significance.

REFERENCES


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DISCLOSURES

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