Lowering the dose of the local anesthesia significantly reduces the risks of spinal anesthesia-induced hypotension in an elective cesarean delivery. Determination of the mean effective dose of hyperbaric bupivacaine will aid clinicians in managing maternal hypotension. The systematic search of studies evaluating the mean effective dose of hyperbaric bupivacaine yielded 10 clinical trials reporting the minimum effective dose in 50% (ED_{50}) and 95% (ED_{95}) of patients. The up-down method and the random allocation design were the dose-finding strategies used in all trials included in the review. The calculated ED_{50} and ED_{95} of bupivacaine varied according to different patient subgroups. The estimated ED_{50} of hyperbaric bupivacaine with or without opioid ranged from 4.7 mg to 9.8 mg. The calculated ED_{95} ranged from 8.8 mg to 15 mg. Doses at the level of ED_{50} minimized spinal anesthesia-induced hypotension yet increased intraoperative pain supplementation, whereas doses at the level of ED_{95} provided adequate surgical anesthesia with increased risk of maternal hypotension. Furthermore, the addition of intrathecal administration of opioids reduced local anesthetic doses. In the clinical setting, low-dose spinal anesthesia should be used only in combination with the combined spinal-epidural technique.

Keywords: Cesarean section, ED_{50}, ED_{95}, hyperbaric bupivacaine, low dose.
The aim of this systematic review is to summarize and results of these studies were conflicting. Therefore, the aim of this systematic review is to summarize and identify the minimum effective dose of intrathecal hyperbaric bupivacaine for an elective cesarean delivery.

Methods
This systematic review was conducted following the guidelines described in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.13

• Search Strategy. A systematic search using PubMed/MEDLINE, Cochrane Collaboration Database, Cumulative Index to Nursing & Allied Health Literature (CINAHL), Embase, and Google Scholar was conducted without date restriction. The search strategy included keywords and MeSH terms such as median effective dose, minimum effective dose, ED50, ED95, hyperbaric bupivacaine, and cesarean section, which were used alone and in combination. Cited references from suitable articles were searched and reviewed for relevance. An extensive search using the “similar section” tool in PubMed was conducted to check for potentially relevant articles.

• Inclusion Criteria. Title and abstract of each article were screened for inclusion. The following inclusion criteria were used: (1) clinical controlled studies evaluating the ED50 and ED95 of intrathecal hyperbaric bupivacaine, (2) elective cesarean delivery, and (3) English-language peer-reviewed articles. Excluded from the review were retrospective studies, cohort and descriptive papers, abstract-only articles, editorials, and narrative reviews.

• Data Extraction. Two authors (T.D.T., V.L.R.) separately abstracted the data. Any disagreements were resolved by discussion with the third author (L.F.). With use of a piloted data extraction form, the following information was obtained from each study: number and age range of participants; ASA physical status classification; type of regional anesthesia technique; dose-finding methods; types of LA and opioid used for regional block and top-up supplementation; incidence of spinal anesthesia complications, such as SIH, bradycardia, nausea and vomiting, and of intraoperative analgesia supplementation; and the ED50 and ED95 of the intrathecal LA.

• Quality Assessment. All included studies were assessed for methodologic quality according to the guidelines recommended by the Cochrane Handbook for Systematic Reviews of Interventions.14 The 7 domains evaluated were random sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective reporting; and other sources of bias. Discussion with the third review author (L.F.) resolved any discrepancies or disagreements. Each category was appraised as “high risk,” “low risk,” or “unclear risk.” When there was no sufficient information to assess a criterion, the authors graded the category as “unclear.”

• Statistical Analysis. A meta-analysis was not conducted because of the variability in study methods and outcomes. The incidence of SIH and the efficacy of the anesthesia technique were not pooled because of different outcome measures and an insufficient amount of extracted data. Therefore, only qualitative systematic review was performed.

Results
The initial search yielded 57 studies. A total of 24 full-text articles were identified after the authors appraised and screened the titles and abstracts and eliminated duplicate articles. After thorough investigation, 10 studies15-24 were included for review. The flow diagram and study selection are presented in Figure 1.

• Patient Demographics and Study Characteristics. All 10 trials evaluated parturients scheduled for an elective cesarean delivery, with a total of 604 patients.15-24 All studies used the combined spinal epidural (CSE) technique to allow flexibility and rescue when surgical anesthesia was inadequate before and during surgery. Seven studies15-20,24 examined ASA classification 1 and 2 patients; 3 studies21-23 failed to report patient ASA classification. Table 1 shows the characteristics of included studies.

The planned CSE was performed at the L2-3 and L3-4 interspaces. Induction of spinal anesthesia was performed with the patient sitting15,16,19,22 and in left lateral21,23,24 and right lateral22,23 decubitus positions. All patients were placed in a supine position immediately after induction of spinal anesthesia and placement of the epidural catheter. Sensory blockade was assessed using touch with ethyl alcohol15,20 and pinprick16,19,21-23 to the desired dermatomal level specified in the study methods. One study24 did not report methods of assessing sensory blockade. Assessment for sensory block was performed 10 minutes,16,19,23,24 15 minutes,21,22 and 20 minutes15,17,18,20 after injection of spinal anesthesia.

Effective LA anesthetic dose was defined as successful sensory block at the level of T4,17,21 T5,24 T6,16,19,21,23 T7,18 and the xiphoid process.15,20 Unsuccessful sensory blockade was assessed by using a visual analog score,15,16,19,22-24 by failure to achieve sensory level described in the study design,15-24 and by patients complaining of intraoperative pain.18

• Hyperbaric Bupivacaine. Hyperbaric bupivacaine is the most commonly used LA for spinal anesthesia in cesarean delivery because of its predictable sensory blockade, faster onset, and the decreased risk of conversion to general anesthesia compared with isobaric.
bupivacaine. Various concentrations and doses of hyperbaric bupivacaine were used in all 10 studies (see Table 1). Six studies used a 0.5% concentration, and 4 studies investigated 0.75% hyperbaric bupivacaine. Of the 10 clinical studies in this review, 9 studies reported ED50 and 5 studies recorded ED95 of intrathecal hyperbaric bupivacaine. The calculated minimum effective dose (ED50) of 0.50% intrathecal hyperbaric bupivacaine ranged between 4.7 mg and 7.8 mg. For intrathecal hyperbaric bupivacaine 0.75%, the estimated ED50 dose was between 4.7 mg and 9.8 mg.

Of the 5 trials that evaluated the ED50 of intrathecal hyperbaric bupivacaine, only one study used 0.5% hyperbaric bupivacaine. Danelli and associates estimated that the effective spinal anesthesia dose (ED95) was 0.06 mg/cm in height. At this dose, the authors reported adequate sensory block 20 minutes after intrathecal injection of the LA. The other 4 studies recorded adequate spinal anesthesia at the calculated dose ranging between 8.82 mg and 15 mg.

The dose evaluated in all 10 studies differed because of the methods used in calculating effective dose, varying LA concentration, coadministration of lipophilic and hydrophilic opioids, assessment techniques for evaluating adequate surgical anesthesia endpoints, and the different patient subgroups.

• Complications of ED50 and ED95 Doses. Although low-dose hyperbaric bupivacaine minimized the hemodynamic side effects of spinal anesthesia, patients treated with the ED50 dose experienced a longer time to reach sensory blockade. One study suggested the time to reach adequate sensory block inversely correlated with the LA dose. In addition, patients treated with a low dose complained of more pain and discomfort requiring...
supplemental anesthesia and analgesia. The included studies reported pain during uterine externalization and peritoneal and skin closure.

Local anesthetic used for top-up doses were 2% lidocaine \(16,19,21,23,24\) and 0.5% bupivacaine \(15,20,22\) with different incremental doses. Only one study used intravenous (IV) ketamine (10 mg) when top-up dose was unsuccessful. \(21\) Two studies described the use of IV fentanyl for unsuccessful top-up dose of LA. \(18,21\) When the patient required additional pain control after a top-up dose, additional IV fentanyl, 0.1 mg \(16\) and 50 μg, with ketamine \(21\) was administered.

Patients treated with a conventional dose of hyperbaric bupivacaine (ED\(_{50}\)) were at high risk of nausea and vomiting and maternal hypotension. In one study, the mean arterial pressure significantly decreased 10 minutes after spinal anesthesia. \(19\) In another study, Xiao and associates \(23\) reported that 55% of patients with a dose greater than 8 mg experienced hypotension compared with 13% of those treated with ED\(_{50}\).

- **Spinal Anesthesia-Induced Hypotension.** The definition of maternal hypotension varied across all 10 studies (Table 2). Maternal hypotension was defined as greater than 20% decrease of systolic arterial pressure (SAP) from baseline \(15,21-23\) or a measurement above 30% of SAP from baseline. \(17,18\) Two studies treated hypotension when SAP was less than 90 mm Hg. \(18,24\) one when SAP was under 100 mm Hg, \(15\) and one when SAP was below 110 mm Hg. \(23\) Mean arterial pressure was used to define hypotension in 2 studies. \(16,19\) Prophylaxis strategy included the administration of crystalloid \(15,17-24\) and colloid solution. \(16\) Only one study used the coloading technique when fluids were administered before induction of spinal anesthesia. \(21\) Hypotension was treated with ephedrine \(15,17-22\), phenylephrine \(16,20,21,23,24\) and IV fluid bolus. \(18\)

- **Coadministration of Opioids.** Three studies used fentanyl \(15,20,22\) 2 used sufentanil, \(23,24\) and 3 used a combination of fentanyl and morphine \(16,19,21\) as adjunctive intrathecal opioids with varying dosages. Two studies did not use opioids as adjuvants for spinal anesthesia. \(17,18\) None of the studies compared sufentanil and fentanyl or opioid with nonopioid anesthesia. In studies using sufentanil, the ED\(_{50}\) was lower compared with studies using fentanyl. \(23,24\) Only one study reported the incidence of pruritus with the use of fentanyl in patients with pre-eclampsia. \(22\) None of the studies reported the time that the first postoperative analgesia was administered.

- **Patient Subgroups.** There were various patient subgroups in this systematic review. Two studies \(16,21\) included patients with a body mass index (BMI) of 40 kg/m\(^2\) or greater, and 2 trials examined patients with a history of pre-eclampsia. \(22,23\) One study each investigated the effects of ephedrine, \(20\) phenylephrine, \(20\) magnesium sulfate, \(24\) and epidural volume extension (EVE) \(15\) on the effective dose of hyperbaric bupivacaine.

- **Obesity.** Two studies \(16,21\) reported ED\(_{95}\) and 1 study \(16\) analyzed ED\(_{50}\) of intrathecal hyperbaric bupivacaine in patients with a BMI of 40 kg/m\(^2\) or higher. In one study, Lee and associates \(27\) compared patients with a BMI of 40 kg/m\(^2\) or higher and “normal” weight patients. The study included the use of 0.75% hyperbaric bupivacaine combined with fentanyl, 10 μg, and morphine, 100 μg, in 40 patients (24 normal weight, 16 obese). The dose of hyperbaric bupivacaine was decreased by 0.75 mg if a sensory level of T6 was achieved and no supplemental analgesia was required within 15 minutes after spinal injection. Otherwise, the dose of hyperbaric bupivacaine was increased by 0.75 mg. Seventeen percent of the patients had unsatisfactory block, and all required epidural supplementation. Only 5% experienced hypotension and required phenylephrine.

In one study, 42 patients were randomly allocated to 1 of 7 fixed bupivacaine doses of 5, 6, 7, 8, 9, 10, or 11 mg combined with intrathecal fentanyl, 10 μg, and intrathecal morphine, 200 μg. \(16\) Five patients were given 5 mg, 6 patients were treated with 5, 6, 7, 9, or 10 mg, and 7 patients received 11 mg of intrathecal bupivacaine. Similar to a previous study by Ginosar and associates, \(19\) Carvalho and colleagues \(16\) used the same assessment time points and sensory levels for success and failure of the LA. Their study reported ED\(_{50}\) and ED\(_{95}\) of 9.8 and 15 mg, respectively. The ED\(_{95}\) result was extrapolated from the plateau located at the top of the dose-response curve. It must be emphasized that this dose was not evaluated because the highest dose examined in the study was 11 mg. Therefore, the authors of this study do not recommend the use of 15 mg as ED\(_{50}\) for intrathecal bupivacaine; however, they caution against the use of an intrathecal bupivacaine dose less than 10 mg in a single-shot spinal. \(16\)

- **Preeclampsia.** Two studies \(22,23\) addressed the minimum effective dose for patients with preeclampsia. In one clinical study, 36 patients (18 normotensive group, 18 preeclampsia group) were enrolled and treated using 0.5% hyperbaric bupivacaine combined with fentanyl, 20 μg. \(22\) The incidence of SIH and intraoperative pain supplementation did not differ between groups. The ED\(_{50}\) was estimated at 4.7 mg in both normotensive and preeclamptic patients.

Xiao and associates \(23\) randomly assigned 200 patients to 4, 6, 8, or 10 mg of hyperbaric bupivacaine coadministered with fentanyl 25 μg. Assessment of success or failure of the spinal anesthesia was similar to the method of Carvalho and associates. \(16\) Intraoperative top-up supplementation of lidocaine 2% was higher in patients who received 4 mg of bupivacaine (76% vs 21%), and phenylephrine doses were higher in patients treated with 8 to 10 mg of bupivacaine (55% vs 8%).

- **Effects of Other Adjuvant Medications.** The influ-
<table>
<thead>
<tr>
<th>Source/Country</th>
<th>N/ASA class/study groups</th>
<th>Dose-finding method</th>
<th>Dosing interval</th>
<th>Intrathecal solution</th>
<th>Lumbar level/position/assessment method for sensory level</th>
<th>Minimum effective dose</th>
<th>Other outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beale et al, 2005 United Kingdom</td>
<td>52 ASA 1 and 2 EVE compared with no EVE</td>
<td>Up-and-down with probit analysis</td>
<td>Started with 10 mg of hyperbaric bupivacaine with 25 μg of fentanyl. Dosing interval: 1 mg of hyperbaric bupivacaine</td>
<td>Hyperbaric 0.5% bupivacaine with fentanyl, 25 μg</td>
<td>L2-L3, L3-L4 Sitting Touch with ethyl alcohol</td>
<td>ED₅₀: 5.1 mg for EVE; 6.1 mg for no EVE</td>
<td>Use of EVE did not affect dose of LA; No difference in incidence of SIH in both EVE and no EVE groups; mean ephedrine use: 20.8 mg for EVE group vs 23.3 mg for no EVE group</td>
</tr>
<tr>
<td>Carvalho et al, 2011 United States</td>
<td>42 ASA 2 BMI ≥ 40 kg/m², &gt; 150 cm in height Allocated to 7 groups (5, 6, 7, 8, 9, 10, or 11 mg of hyperbaric bupivacaine)</td>
<td>Random-dose allocation with 7 possible doses of hyperbaric bupivacaine (5-11 mg)</td>
<td>No dosing interval protocol</td>
<td>Hyperbaric 0.75% bupivacaine with morphine, 100 μg, and fentanyl, 10 μg</td>
<td>L2-L3, L3-L4 Sitting Pinprick</td>
<td>ED₉₀: 9.8 mg ED₉₅: 15 mg</td>
<td>Study examined effective dose before and during surgery; obese and nonobese patients did not respond differently to modest doses of IT bupivacaine; IT bupivacaine dose requirements similar between obese and nonobese patients</td>
</tr>
<tr>
<td>Danelli et al, 2001 Italy</td>
<td>24 ASA 1 and 2 Sequential allocation</td>
<td>Up-and-down with probit analysis</td>
<td>Initial dose was 0.075 mg/cm of height. Successful block in 20 min; dose for the next patient was decreased by 0.01 mg/cm of height</td>
<td>Hyperbaric 0.5% bupivacaine</td>
<td>L2-L3, L3-L4 Left lateral decubitus Pinprick</td>
<td>Recorded height of patients in study: 160-175 cm ED₅₀: 0.036 mg/cm of height based on height of 5.76-6.3 mg ED₉₅: 0.06 mg/cm of height based on height of 9.10.5 mg</td>
<td>Minimum effective dose of 0.06 mg/cm provided superior analgesia; used height as LA dose indicator</td>
</tr>
<tr>
<td>Geng et al, 2011 China</td>
<td>40 ASA 1 and 2 Bupivacaine vs ropivacaine</td>
<td>Up-and-down</td>
<td>Initial dose was 10 mg and was increased in increments of 1 mg</td>
<td>Hyperbaric 0.75% bupivacaine</td>
<td>L2-L3 Right lateral decubitus Pinprick</td>
<td>ED₉₀: Ropivacaine 9.45 mg; Bupivacaine 7.53 mg</td>
<td>Bupivacaine was 80% more potent than ropivacaine</td>
</tr>
<tr>
<td>Ginosar et al, 2004 United States</td>
<td>40 ASA 1 and 2 Allocated to 7 groups (6, 7, 8, 9, 10, 11, or 12 mg of hyperbaric bupivacaine)</td>
<td>Random-dose allocation with 7 possible doses of hyperbaric bupivacaine (6-12 mg)</td>
<td>No dosing interval protocol</td>
<td>Hyperbaric 0.75% bupivacaine with fentanyl, 10 μg, and morphine, 200 μg</td>
<td>L2-L3, L3-L4 Sitting Pinprick</td>
<td>ED₉₀: Induction: 6.7 mg; operation: 7.6 mg ED₉₅: Induction: 11.0 mg; operation: 11.2 mg</td>
<td>Hypotension common in the first 10 min after spinal injection; the higher the IT bupivacaine, the higher the risk of MAP &lt; 60 mm Hg; higher ED₉₀ compared with other studies</td>
</tr>
<tr>
<td>Study Authors</td>
<td>Year</td>
<td>Country</td>
<td>Study Design</td>
<td>Initial Dose</td>
<td>Anesthetic Agent</td>
<td>Dosing Interval</td>
<td>ED&lt;sub&gt;50&lt;/sub&gt;</td>
</tr>
<tr>
<td>---------------</td>
<td>-------</td>
<td>---------</td>
<td>--------------</td>
<td>--------------</td>
<td>-----------------</td>
<td>----------------</td>
<td>------------</td>
</tr>
<tr>
<td>Hennebry et al&lt;sup&gt;20&lt;/sup&gt;</td>
<td>2009</td>
<td>United Kingdom</td>
<td>Up-and-down</td>
<td>Initial dose of bupivacaine, 6.1 mg</td>
<td>Hyperbaric 0.5% bupivacaine with fentanyl, 25 μg</td>
<td>L3-L4</td>
<td>Sitting</td>
</tr>
<tr>
<td>Lee et al&lt;sup&gt;21&lt;/sup&gt;</td>
<td>2009</td>
<td>United States</td>
<td>Up-and-down with modified Narayana rule&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Started with 9 mg and adjusted by 0.75-mg increment</td>
<td>Hyperbaric 0.75% bupivacaine with fentanyl, 10 μg, and morphine, 100 μg</td>
<td>L3-L4</td>
<td>paramedian</td>
</tr>
<tr>
<td>Tyagi et al&lt;sup&gt;22&lt;/sup&gt;</td>
<td>2012</td>
<td>India</td>
<td>Up-and-down</td>
<td>Started with 9 mg of 0.5% bupivacaine</td>
<td>Hyperbaric 0.5% bupivacaine with fentanyl, 20 μg</td>
<td>L3-L4</td>
<td>Sitting</td>
</tr>
<tr>
<td>Xiao et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>2015</td>
<td>China</td>
<td>Random-dose allocation</td>
<td>No dosing interval protocol</td>
<td>Hyperbaric bupivacaine with sufentanil, 2.5 μg</td>
<td>L3-L4</td>
<td>Lateral decubitus</td>
</tr>
<tr>
<td>Xiao et al&lt;sup&gt;24&lt;/sup&gt;</td>
<td>2017</td>
<td>China</td>
<td>Up-and-down</td>
<td>Initiated with 8 mg of 0.5% bupivacaine with sufentanil, 5 μg</td>
<td>Hyperbaric 0.5% bupivacaine with sufentanil, 5 μg</td>
<td>L2-L3</td>
<td>Left lateral</td>
</tr>
</tbody>
</table>

**Table 1. Study Characteristics of Studies Examining ED<sub>50</sub> and ED<sub>95</sub> of Intrathecal Hyperbaric Bupivacaine for Cesarean Delivery**

Abbreviations: BMI, body mass index; ED<sub>50</sub>, minimum effective dose in 50% of the patients; ED<sub>95</sub>, minimum effective dose in 95% of the patients; EVE, epidural volume expansion; IT, intrathecal; LA, local anesthetic; MAP, mean arterial pressure; NR, not reported; SIH, spinal anesthesia-induced hypotension.

<sup>a</sup>The up-and-down sequential allocation method in dose-finding studies. An initial dose was determined before commencement of the clinical study. The subsequent dose was determined based on the success or failure of the previous dose. If previous bupivacaine dose was ineffective, the dose was increased. However, if previous dose was effective, the subsequent dose was decreased as described in the study method.

<sup>b</sup>The random-dose allocation method for dose-finding studies. The ED<sub>50</sub> and ED<sub>95</sub> values were extrapolated from the dose-response curve. A predetermined dose was allocated to subgroups of patients.

<sup>c</sup>Extrapolated from the plateau located in the top portion of the dose-response curve using logistic regression. This dose was higher than the dose tested in the study (11 mg). This bupivacaine dose (915 mg) was not evaluated in the study.

<sup>d</sup>In the up-and-down design, this method was used to estimate the higher quartiles for the anesthetic dose such as ED<sub>95</sub>.

<sup>e</sup>Severe preeclampsia was defined as systolic blood pressure ≥ 160 mm Hg, diastolic pressure ≥ 110 mm Hg, and proteinuria ≥ 300 mg/dL.
### Table 2. Incidence and Management of Spinal Anesthesia-Induced Hypotension (SIH) in Studies Examining ED<sub>50</sub> and ED<sub>95</sub> of Intrathecal Hyperbaric Bupivacaine for Cesarean Delivery

<table>
<thead>
<tr>
<th>Source</th>
<th>Definition of SIH</th>
<th>Incidence of SIH</th>
<th>Prophylaxis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beale et al, &lt;sup&gt;15&lt;/sup&gt; 2005</td>
<td>&lt; 100 mm Hg SAP, &gt; 20% decreased from SBP baseline; onset of nausea treated with ephedrine, 6 mg</td>
<td>NR</td>
<td>Similar ephedrine use in both EVE and no-EVE groups</td>
<td>Hartmann’s solution, 500 mL; IV ephedrine, 6-mg bolus preload&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Carvalho et al, &lt;sup&gt;16&lt;/sup&gt; 2011</td>
<td>MAP &lt; 90% baseline MAP; baseline MAP was taken as the average of 3 readings at admission</td>
<td>NR</td>
<td>No significant difference in MAP between low-dose and high-dose LA</td>
<td>LR, 1 L, plus hetastarch, 500 mL; preload&lt;sup&gt;a&lt;/sup&gt; IV phenylephrine boluses of 50-100 μg to maintain MAP &gt; 90% of baseline. Phenylephrine requirements were similar in all 7 groups</td>
</tr>
<tr>
<td>Danelli et al, &lt;sup&gt;17&lt;/sup&gt; 2001</td>
<td>SPB &lt; 30% from baseline</td>
<td>4 patients required ephedrine to treat hypotension</td>
<td>LR, 15 mL/kg; preload&lt;sup&gt;a&lt;/sup&gt;</td>
<td>IV ephedrine, 5 mg</td>
</tr>
<tr>
<td>Geng et al, &lt;sup&gt;18&lt;/sup&gt; 2011</td>
<td>SBP &lt; 90 mm Hg &gt;30% from baseline</td>
<td>20% of patients in ropivacaine group and 30% of patients in bupivacaine group required ephedrine</td>
<td>LR, 10 mL/kg; preload&lt;sup&gt;a&lt;/sup&gt;</td>
<td>IV ephedrine, 6 mg, and additional LR</td>
</tr>
<tr>
<td>Ginosar et al, &lt;sup&gt;19&lt;/sup&gt; 2004</td>
<td>MAP &lt; 60 mm Hg</td>
<td>MAP &lt; 60 mm Hg</td>
<td>LR, 1 L, plus hetastarch, 500 mL; preload&lt;sup&gt;a&lt;/sup&gt;</td>
<td>IV ephedrine</td>
</tr>
<tr>
<td>Hennebry et al, &lt;sup&gt;20&lt;/sup&gt; 2009</td>
<td>&lt; SAP to 80% of baseline for 2 consecutive readings despite the infusion running</td>
<td>53% experienced hypotension in phenylephrine and 31% in ephedrine group</td>
<td>Hartmann’s solution, 500 mL; preload&lt;sup&gt;a&lt;/sup&gt;</td>
<td>IV ephedrine, 6 mg, or phenylephrine, 75 μg</td>
</tr>
<tr>
<td>Lee et al, &lt;sup&gt;21&lt;/sup&gt; 2009</td>
<td>20% below baseline despite prophylactic vasopressors</td>
<td>5% SIH</td>
<td>LR, 10 mL/kg; coload&lt;sup&gt;b&lt;/sup&gt;</td>
<td>IV phenylephrine, 100 μg, or ephedrine, 5 mg, if HR &lt; 55/min</td>
</tr>
<tr>
<td>Tyagi et al, &lt;sup&gt;22&lt;/sup&gt; 2012</td>
<td>20% below baseline</td>
<td>27% SIH in normotensive patients compared with 36% SIH in severely preeclamptic</td>
<td>LR, 10 mL/kg; preload&lt;sup&gt;a&lt;/sup&gt;</td>
<td>IV ephedrine, 3 mg</td>
</tr>
<tr>
<td>Xiao et al, &lt;sup&gt;23&lt;/sup&gt; 2015</td>
<td>SBP &lt; 119 mm Hg or 25% reduction from baseline</td>
<td>Higher incidence of SIH with doses at level of ED&lt;sub&gt;95&lt;/sub&gt; or higher</td>
<td>LR, 10 mL/kg; preload&lt;sup&gt;a&lt;/sup&gt;</td>
<td>IV phenylephrine, 40 μg</td>
</tr>
<tr>
<td>Xiao et al, &lt;sup&gt;24&lt;/sup&gt; 2017</td>
<td>SBP &lt; 90 mm Hg or &gt; 20% reduction from baseline</td>
<td>20% of SIH with patients treated with magnesium group; 27% of SIH in placebo</td>
<td>LR, 10 mL/kg preload&lt;sup&gt;a&lt;/sup&gt;</td>
<td>IV phenylephrine, 40 μg</td>
</tr>
</tbody>
</table>

Abbreviations: ED<sub>50</sub>, minimum effective dose in 50% of the patients; ED<sub>95</sub>, minimum effective dose in 95% of the patients; HR, heart rate; IV, intravenous; LA, local anesthetic; LR, lactated Ringer’s solution; MAP, mean arterial pressure; NR, not reported; SAP, systolic arterial pressure.

<sup>a</sup>Crystalloid and colloid adminstration before the induction of spinal anesthesia.

<sup>b</sup>Crystalloid and colloid administration immediately and during induction of spinal anesthesia.
### Table 3. Quality of Anesthesia in Studies Examining ED\textsubscript{50} and ED\textsubscript{95} of Intrathecal Hyperbaric Bupivacaine for Cesarean Delivery

<table>
<thead>
<tr>
<th>Source</th>
<th>Achievement of sensory block based on study method</th>
<th>Failure to achieve sensory block based on study method</th>
<th>Interventions for failed local anesthetic dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beale et al\textsuperscript{15}, 2005</td>
<td>Sensory block to xiphoid process within 20 min of IT injection, with no requirement for an extradural top-up within 45 min</td>
<td>Sensory block not achieved</td>
<td>Bupivacaine 0.5% in small incremental dose</td>
</tr>
<tr>
<td>Carvalho et al\textsuperscript{16}, 2011</td>
<td>Bilateral T6 sensory level to pinprick within 10 min of IT drug administration</td>
<td>T6 sensory level was not obtained within 10 min after drug administration; required epidural top-up, VAS &gt; 20 mm or patient request for additional analgesia</td>
<td>Lidocaine 2% (with sodium bicarbonate, 1 mEq per 10 mL, and epinephrine (1:200,000), 5-mL increments</td>
</tr>
<tr>
<td>Danelli et al\textsuperscript{17}, 2001</td>
<td>Presence of sensory level ≥ T4 with complete motor blockade using a modified Bromage score\textsuperscript{a} of 3 within 20 min after spinal injection</td>
<td>Presence of sensory block not achieved within 20 min after injection</td>
<td>5-8 mL epidural bolus of 2% lidocaine was given to achieve adequate surgical anesthesia; block was considered unsuccessful in patients who had an adequate sensory block but verbalized pain and discomfort</td>
</tr>
<tr>
<td>Beale et al\textsuperscript{15}, 2005</td>
<td>Sensory block to xiphoid process within 20 min of IT injection, with no requirement for an extradural top-up within 45 min</td>
<td>Sensory block not achieved</td>
<td>Bupivacaine 0.5% in small incremental dose</td>
</tr>
<tr>
<td>Carvalho et al\textsuperscript{16}, 2011</td>
<td>Bilateral T6 sensory level to pinprick within 10 min of IT drug administration</td>
<td>T6 sensory level was not obtained within 10 min after drug administration; required epidural top-up, VAS &gt; 20 mm or patient request for additional analgesia</td>
<td>Lidocaine 2% (with sodium bicarbonate, 1 mEq per 10 mL, and epinephrine (1:200,000), 5-mL increments</td>
</tr>
<tr>
<td>Danelli et al\textsuperscript{17}, 2001</td>
<td>Presence of sensory level ≥ T4 with complete motor blockade using a modified Bromage score\textsuperscript{a} of 3 within 20 min after spinal injection</td>
<td>Presence of sensory block not achieved within 20 min after injection</td>
<td>5-8 mL epidural bolus of 2% lidocaine was given to achieve adequate surgical anesthesia; block was considered unsuccessful in patients who had an adequate sensory block but verbalized pain and discomfort</td>
</tr>
<tr>
<td>Geng et al\textsuperscript{18}, 2011</td>
<td>Sensory dermatomal anesthesia to pinprick to T7 or higher was attained within 20 min. Required no supplementary epidural injection for procedure until at least 50 min after the IT injection</td>
<td>Sensory level was not achieved (at level of T6) within 15 min after spinal injection</td>
<td>2% lidocaine; fentanyl, 0.1 mg</td>
</tr>
<tr>
<td>Ginosar et al\textsuperscript{19}, 2004</td>
<td>Sensory block bilateral T6 pinprick 10 min after IT injection and no additional epidural top-up necessary to start surgery and during surgery</td>
<td>T6 was not achieved at 10 min after IT and required epidural top-up with 2% lidocaine, VAS &gt; 20 mm, or patient request for additional analgesia</td>
<td>2% lidocaine (with sodium bicarbonate and 1:200,000 epinephrine) administered as 5-mL bolus injections, repeated as required</td>
</tr>
<tr>
<td>Hennebery et al\textsuperscript{20}, 2009</td>
<td>Sensory block to xiphoid process 20 min after IT injection</td>
<td>Intrathecal dose that was ineffective by 20 min</td>
<td>0.5% bupivacaine</td>
</tr>
<tr>
<td>Lee et al\textsuperscript{21}, 2009</td>
<td>Sensory block at least T6 within 15 min of IT injection, and patient did not require supplemental anesthesia</td>
<td>Sensory level was not achieved (at level of T6) within 15 min after spinal injection</td>
<td>Lidocaine 2%, 5 mL; IV fentanyl, 50 μg, and IV ketamine, 10 mg, given if epidural top-up unsuccessful</td>
</tr>
<tr>
<td>Tyagi et al\textsuperscript{22}, 2012</td>
<td>Sensory block to T4 with modified Bromage score\textsuperscript{b} of 1 or 2 within 15 min of IT injection</td>
<td>T4 sensory level not met; intraoperative pain with VAS &gt; 3</td>
<td>Bupivacaine 0.5%, 2-3 mL at incremental doses</td>
</tr>
<tr>
<td>Xiao et al\textsuperscript{23}, 2015</td>
<td>T6 sensory level to pinprick achieved within 10 min after IT drug administration and/or no epidural supplement required during cesarean delivery</td>
<td>T6 sensory level was not obtained within 10 min after drug administration; required epidural top-up, VAS &gt; 20 mm, or patient request for additional analgesia</td>
<td>Lidocaine 2%, 5 mL repeated every 5 min if necessary</td>
</tr>
<tr>
<td>Xiao et al\textsuperscript{24}, 2017</td>
<td>Bilateral T5 or above reached within 10 min of IT injection, with no additional epidural anesthetic needed</td>
<td>T5 not achieved within 10 min after injection; pain score of VAS ≥ 3; ineffective dose: 2%</td>
<td>Lidocaine 2%, 5 mL repeated every 10 min</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Modified Bromage score: 0 = no motor block; 1 = hip blocked; 2 = hip and knee blocked; 3 = hip, knee, and ankle blocked.

\textsuperscript{b}Modified Bromage score: 1 = complete block; unable to move feet or knees; 2 = almost complete block, able to move feet only; 3 = partial block, just able to move knees; 4 = detectable weakness of hip flexion while in supine position, full flexion of knees; 5 = no detectable weakness of hip flexion while in supine position; 6 = able to perform partial knee bend.
ence of phenylephrine and ephedrine on ED₅₀ was examined when 70 patients were allocated to receive 0.5% hyperbaric bupivacaine with fentanyl, 25 μg.²⁰ The effectiveness of the outcome was assessed using light touch at the level of xiphisternum 20 minutes after LA injection. If effective, the subsequent LA dose was reduced by 1 mg and the fentanyl dose remained the same. If sensory block was not assessed at the level of xiphisternum, an incremental dose of 0.5% bupivacaine using the epidural catheter for top-up dose before surgery was implemented. The ED₅₀ of intrathecal bupivacaine for patients with phenylephrine infusion was calculated at 7.8 mg, and the intrathecal dose for bupivacaine was 7.6 mg for patients treated with ephedrine.

In another study, 60 women (30 per group) were randomly allocated into magnesium and saline groups.²⁴ Each participant received intrathecal 0.5% hyperbaric bupivacaine with intrathecal sufentanil, 5 μg. In the intervention group, patients received intrathecal magnesium sulfate, 50 mg. Thirteen patients required a top-up dose with 2% lidocaine in each group. Although the study did not find a significant difference in ED₅₀ for magnesium and saline placebo, patients treated with magnesium had longer onset and duration of sensory and motor blockade (P < .001). Also, 24-hour fentanyl consumption was much lower in the magnesium group compared with the saline placebo group (343 μg vs 550 μg, P < .001).

- **Epidural Volume Extension.** One study reported the use of EVE with normal saline and its influence on the ED₅₀ of hyperbaric bupivacaine.¹⁵ Sixty patients were allocated to the EVE group and placebo using 0.5% hyperbaric bupivacaine combined with fentanyl, 25 μg. More patients with no EVE experienced hypotension and were treated with ephedrine. The ED₅₀ between EVE and non-EVE groups did not differ.

- **Methods of Dose-Finding Studies.** Two dose-finding methods were used in the 10 clinical studies included in this review. The up-and-down sequential design is commonly used to determine experimental patient dosing by determining which level of a drug is appropriate to initiate a positive response or prevent an undesirable effect.²⁷ One of the first anesthesia studies to use this method was the development of the minimum alveolar concentration.²⁷ Use of the up-and-down design in determining the median effective dose of LA in obstetric anesthesia was first described in a study examining the effective concentrations of bupivacaine and lidocaine in the first stage of labor.²⁸ This study reported the minimum local analgesia concentration and the potency ratio of bupivacaine and lidocaine. The up-down allocation was based on the Dixon and Massey formula in which a predetermined dose was used for the first patient and the subsequent patient’s dose was based on the previous patient’s outcomes. In this method, the results are dichotomous data of either effective or ineffective anesthesia. The subsequent dose of the LA is increased incrementally if the previous response is considered ineffective, or the dose is decreased when the previous response is found effective. In up-and-down design studies, the dose-finding method determines and compares the minimum effective dose without consideration of the shape of the dose-response curve.³⁰ The ED₃₀ of the LA, sometimes referred to as the minimum local anesthetic concentration, is calculated using probit and logit analyses. Benefits of using the up-and-down design are the small sample size needed to estimate the ED₅₀, minimizing exposure of subjects to suboptimal treatments, and simplicity of the design.²⁷,³¹ However, this method has one distinct limitation described in the literature. In the classic up-down method, there is difficulty in estimating the doses at higher quantiles of the dose-response curve unless a modified version is used such as the Narayana rule, which clusters the results around the ED₉₅.²² Although the ED₅₀ of a drug is beneficial information, doses that are clinically relevant are often obtained at the higher quantiles (ED₉₅) in the dose-response curve.

In the random-dose allocation method, several subgroups of patients receive a specified dose of the drug. Unlike the up-down design, patients are blindly allocated to predetermined doses. One recognizable advantage of the random-dose allocation design is the ability to estimate doses anywhere in the dose-response curve.³⁰ Conversely, this dose-finding technique requires 2 or 3 times more patients to determine effective doses, which is demanding and time-consuming.²⁷ Also, low and high doses of LA are included in the study, which can cause inadequate anesthesia and deleterious side effects. The two dose-finding methods, the success and failure of sensory block and the interventions for failed LA dose of each study in this review are described in Table 3.

- **Risk of Bias.** The quality of all studies was moderate. Seventy percent of all studies (7 of 10) included in this review reported random sequence generation, and 50% (5 of 10) concealed participant allocation. Seventy percent of the studies blinded either the patients or the outcome assessors. The risks of bias of included studies are presented in Figure 2.

**Discussion**

Results of this review suggest that ED₅₀ for intrathecal hyperbaric bupivacaine ranged from 4.7 mg to 9.8 mg and ED₉₅ ranged from 8.8 mg to 15 mg in patients undergoing elective cesarean delivery. The ED₅₀ did not vary between obese and nonobese patients, or between patients with preeclampsia and normotensive patients. The use of EVE, intrathecal magnesium, IV phenylephrine, or IV ephedrine did not lower the dose requirement of intrathecal bupivacaine. On the other hand, the incidence of SIH was lower in patients receiving an intrathecal bupivacaine dose at or below the ED₃₀ of the LA.

The ED₅₀ and ED₉₅ of hyperbaric bupivacaine for ce-
A study on parturients for cesarean delivery showed no relation between the sensory level block and BMI of the patients.\textsuperscript{35} The amount of the LA required for cesarean delivery in morbidly obese patients was reported to be lower compared with nonmorbidly obese patients. Taivainen and colleagues\textsuperscript{34} indicated that 3 mL of 0.5% bupivacaine increased the cephalad spread of LA in morbidly obese patients, based on a postulated mechanism of thecal compression with body weight.

In patients with preeclampsia, ED\textsubscript{50} of hyperbaric bupivacaine did not differ compared with normotensive patients. At these doses, there was a significant reduction in the incidence of hypotension and use of vasopressors; however, intraoperative supplementation of top-up treatments and muscle movements were significantly increased. Because of sympathetic blockade, intravascular volume depletion, and ventricular dysfunction, patients with preeclampsia are predisposed to experience more hypotension in spinal anesthesia compared with epidural anesthesia.\textsuperscript{33} A lower spinal anesthetic dose would benefit these patients by reducing complications of spinal anesthesia.

The ED\textsubscript{50} of patients treated with EVE was similar to patients treated with conventional CSE. As the modified version of the CSE technique, EVE using either normal saline or LA increases the epidural space. In theory, expanding the epidural space increases cephalad spread of LA and eventually leads to a higher sensory blockade, resulting in reduction of LA dose and incidence of SIH.\textsuperscript{36,37} These desired effects of EVE are believed to be due to thecal compression and leakage of LA into the subarachnoid space. In our review, the resulting low dose of LA increased the need for ephedrine supplementation in patients who received EVE compared with patients who were treated with traditional CSE. This finding is in contrast with those of other studies comparing EVE with the traditional CSE technique that reported decreased SIH in patients with EVE.\textsuperscript{38,39}

The addition of intrathecal magnesium sulfate did not affect the dose of LA; however, it has been effective at prolonging the duration of spinal anesthesia and reducing opioid supplementation and perioperative shivering. The incidence of SIH and intraoperative supplementation of top-up doses were similar in the magnesium group compared with controls. These findings are analogous to those of the previous study in obstetric patients.\textsuperscript{40}

In this review, when preventive phenylephrine and ephedrine infusion were compared, ED\textsubscript{50} was similar between groups. This result is in contrast with previous study findings suggesting that phenylephrine is more effective in decreasing the cephalad spread and the dose of LA compared with ephedrine.\textsuperscript{38,39} In those 2 studies,\textsuperscript{38,39} patients treated with phenylephrine had reduced rostral spread of LA by a median of 2 dermatome levels, supporting the efficacy and potency of phenylephrine over ephedrine in reducing SIH.\textsuperscript{41,42}
Eight trials used intrathecal opioids combined with LA for the spinal injection. Lipophilic opioids such as fentanyl and sufentanil are preferred for their rapid onset of action, moderate duration, and lower tendency for respiratory depression. The addition of opioids intensified the sensory block and, in most cases, reduced the dose of LA. In our review, studies using intrathecal sufentanil reported a much lower ED$_{50}$ LA dose and better intraoperative and postoperative analgesia than trials using fentanyl or morphine. These outcomes may be attributed to sufentanil being a more lipophilic opioid when compared with fentanyl and morphine, demonstrating a higher affinity to opioid receptors and thus a much greater analgesic potency.

There were some limitations in our systematic review. First, the appraisal method used in determining success and failure of sensory blockade varied regarding thoracic level, assessment of sensory blockade, and timing. This was attributed to clinical practice differences and variability in determining adequate surgical anesthesia level for cesarean delivery. Also, assessment of sensory level determination varied between using a pinprick or touch when assessing adequacy of the sensory blocks. Second, the concentration of hyperbaric bupivacaine varied between studies, which also may be attributed to practitioner and clinical setting preferences. In our review, no studies compared the 2 concentrations of LA. Previous studies reported conflicting data that the concentration of the LA might influence the spread of hyperbaric bupivacaine or the duration of the anesthesia. However, earlier evidence indicated that increases in the dose of hyperbaric bupivacaine have increased the spread and duration of anesthesia.

Third, all studies included in this review involved CSE and not a single-shot spinal technique, which is often used in clinical settings. The low-dose spinal anesthetic employed in the CSE technique may not apply to single-shot spinal because of a possible risk of ineffective anesthesia without access to an epidural catheter for supplementation. Finally, because most of the trials used the up-down design for determining the effective dose, estimates of ED$_{50}$ were not calculated, which is more clinically relevant than the ED$_{50}$.

Results of this review affirm areas where future studies are needed. Two of the 10 articles included in this review were more than 10 years old, suggesting new studies must be conducted evaluating minimum effective doses of hyperbaric bupivacaine in cesarean delivery. In addition, we recommend future randomized studies exploring the efficacy and safety of a low-dose intrathecal LA with outcomes such as sensory and motor blockade as well as the onset of the LA. Incidence of hypotension is decreased with a low-dose intrathecal LA, but the speed of onset may be longer, and in many centers, the time between spinal induction and commencement of surgery will be longer; delays may cause institutional concerns.

Although cesarean delivery was successfully performed in many cases, the use of a lower dose of intrathecal hyperbaric bupivacaine at the level of ED$_{50}$ increased the risk of intraoperative pain, often treated with LA or opioid using the epidural catheter or IV infusion. Therefore, we caution the extrapolation of these results to clinical practice because of small sample sizes. If clinicians decide to use the lower intrathecal dose, it should be with CSE as the primary anesthesia technique.

**Conclusion**

The required sensory level for cesarean delivery varies clinically. However, maternal hypotension is common to spinal anesthesia during a cesarean delivery. Decreasing the dose of the LA has been shown to reduce the incidence of SIH and its maternal and fetal consequences. Our review findings suggested that doses at the level of ED$_{50}$ mitigated SIH yet caused more patient discomfort because of inadequate anesthesia. Doses at the level of ED$_{50}$ provided adequate anesthesia yet came with an increased risk of maternal hypotension. It is recommended that clinicians consider their clinical practice and choose the dose that will last the duration of surgery and will increase patient satisfaction. If the chosen dose is at or below the ED$_{50}$, we recommend that a CSE technique be instituted to allow rescue of anesthesia and analgesia intraoperatively.

**REFERENCES**


27. Pace NL, Stylianou MP. Advances in and limitations of up-and-down methodology a précis of clinical use, study design, and dose estimation in anesthesia research. Anesthesiology. 2007;107(1):144-152.


34. Taiwainen T, Tuominen M, Rosenberg PH. Influence of obesity on the spread of spinal analgesia after injection of plain 0.5% bupivacaine at the level L3-4 or L4-5 interspace. Br J Anaesth. 1990;64(5):542-546.


46. Tito D. Tubog, DNAP, CRNA, is a Certified Registered Nurse Anesthetist.
Virginia Londahl Ramsey, DNAP, CRNA, ARNP, is an assistant professor at Florida Gulf Coast University in the Graduate Program of Nurse Anesthesia, Fort Myers, Florida.

Laura Filler, DNAP, CRNA, is a staff CRNA at CHI St. Alexius Health, Bismarck, North Dakota as well as Adjunct Faculty/Clinical Coordinator for Texas Wesleyan University Graduate Programs of Nurse Anesthesia, Fort Worth, Texas.

Richard S. Bramble, RN, BSN, is a perioperative services nurse manager at O'Connor Hospital, San Jose, California.

DISCLOSURES
The authors have declared no financial relationships with any commercial entity related to the content of this article. The authors did not discuss off-label use within the article.