ED$_{50}$ of Hyperbaric Bupivacaine With Fentanyl for Cesarean Delivery Under Combined Spinal Epidural in Normotensive and Preeclamptic Patients

Asha Tyagi, MD, DNB, Aanchal Kakkar, MD, Surendra Kumar, MD, Ashok K. Sethi, DA, MD, and Rashmi Salhotra, MD

**Background and Objectives:** The use of reduced intrathecal doses is advised for spinal anesthesia during cesarean delivery. However, there are inadequate data regarding the minimum effective dose of intrathecal bupivacaine for cesarean delivery. Preeclampsia is caused by an endothelial dysfunction leading to generalized vasoconstriction. Whether this can offset the pregnancy-induced decrease in intrathecal dose requirement caused by epidural venous dilation and consequent thecal compression is unknown. There are no data to evaluate the minimum effective dose of intrathecal drug for cesarean delivery in preeclamptic patients. This study aimed to determine the minimum effective dose represented by the ED$_{50}$ of intrathecal hyperbaric bupivacaine for normotensive and severely preeclamptic patients undergoing elective cesarean delivery.

**Methods:** Combined spinal epidural anesthesia was administered using a standardized technique on 18 consecutively preeclamptic and normotensive patients, each carrying an otherwise uncomplicated singleton pregnancy. The dose of intrathecal hyperbaric bupivacaine was decided by using the up-and-down method with an initial dose of 9 mg and dosing change of 1 mg. All patients received 20 µg of fentanyl intrathecally with bupivacaine. A successful block was defined as one that resulted in a sensory block to T4 level with modified Bromage score of 1 or 2 within 15 minutes of intrathecal injection.

**Results:** ED$_{50}$ of intrathecal hyperbaric bupivacaine was identical in severely preeclamptic and normotensive parturients undergoing elective cesarean delivery (4.7 mg; 95% confidence interval, 4.5–4.9 mg).

**Conclusions:** When a combined-spinal epidural is planned in normotensive or severely preeclamptic patients for an elective cesarean delivery, the ED$_{50}$ of intrathecal hyperbaric bupivacaine along with 20 µg of fentanyl is 4.7 mg.

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**MATERIALS AND METHODS**

This prospective sequential allocation study was undertaken after approval from the Institutional Ethical Committee (Guru Teg Bahadur Hospital, Delhi, India) and informed written consent from all subjects. Eighteen consecutive severely preeclamptic (group P) and 18 normotensive pregnant patients (group N), carrying an otherwise uncomplicated singleton pregnancy of gestational age more than 37 weeks and scheduled for elective cesarean delivery were included in the study. The criteria for diagnosing severe preeclampsia was systolic blood pressure exceeding 160 mm Hg or diastolic blood pressure exceeding 110 mm Hg or the presence of preeclampsia with symptoms
of imminent eclampsia, such as severe headache, visual disturbance, epigastric pain, hyperreflexia, dizziness and fainting, or vomiting, and proteinuria >3 or worse. Antepartum management of patients in group P was instituted by obstetricians per institutional practice, based on the American College of Gynecologists’ guidelines for management of preeclampsia.4 Labetalol was administered to control blood pressure when systolic blood pressure was 160 mm Hg or higher or diastolic blood pressure was 105 mm Hg or higher, and magnesium sulfate therapy was initiated for prophylaxis of seizures.

Subjects with extreme height or weight (body mass index <20 kg/m² or >35 kg/m², height <145 cm or >180 cm) were excluded from the study. Patients with any contraindication to central neuraxial block (eg, patients with a history of allergy to local anesthetics, coagulopathy, or infection at the site of injection) or those with eclampsia or medical disease, such as chronic hypertension, heart disease, or diabetes, were not included in the study. Patients with a complicated pregnancy, such as multiple gestation or antepartum hemorrhage, were also excluded.

The anesthetic management was similar in both groups. Baseline heart rate and blood pressure of the parturient were recorded in the preoperative room as the average of 3 readings taken 1 minute apart. In the operating room, routine monitoring, including non invasive oscillometric blood pressure measurement, pulse oximetry, and lead(II) electrocardiography was instituted. After initiating an intravenous access, patients were preloaded with Ringer’s lactate 10 mL/kg. A combined spinal epidural block using needle-through-needle set (CSE Cure; Portex, Smiths Medical ASD, Inc, Ashford, UK) was performed on all patients in the sitting position at the L3-4 interspace. The procedure for the block was similar in all patients. After infiltration of the skin with 2% lidocaine in the midline, the epidural space was identified using 18-gauge Tuohy needle with loss of resistance to air technique, limiting the volume of air to less than 2 mL. A 27-gauge Whitacre spinal needle was then passed via the Tuohy needle to obtain free flow of cerebrospinal fluid. Hyperbaric bupivacaine (0.5%) in the designated dose along with 20 µg of fentanyl was injected intrathecally at a speed of approximately 0.5 mL/s with the orifice pointing cephalad.

The dose of intrathecal bupivacaine was decided by using the up-and-down sequential allocation method. While the first patient in each group received 9 mg of bupivacaine, in successive patients, the dose of intrathecal bupivacaine was determined by the outcome of spinal block in the previous patient of that group (ie, in a case where the block was adequate, the dose of bupivacaine was decreased by 1 mg in the next patient, and in a case where the block was inadequate, the dose was increased by 1 mg in the next patient).

An adequate block was defined as one that resulted in a sensory block to T4 level along with modified Bromage score of 1 or 2 within 15 minutes of intrathecal injection. Here, 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 supine, full flexion of knees; 5 = no detectable weakness of hip flexion while supine; and 6 = able to perform partial knee bend. After the intrathecal injection, the spinal needle was removed, and the epidural catheter threaded 4 cm into the epidural space and fixed after confirming absence of CSF or blood in the catheter. All patients were turned supine with a 15-degree tilt to the left side, and oxygen via facemask was started at 4 L/min.

The sensory level of block was assessed by complete loss of sensation to pin prick in the midline, and motor blockade was graded by a modified Bromage score. Both the sensory and motor block characteristics were noted every 3 minutes for the first 15 minutes after intrathecal injection or until 3 identical readings were obtained, followed thereafter by 5-minute intervals until the block receded to T6 level.

If an inadequate block or if intraoperative pain occurred (visual analog scale score >3), epidural injections of bupivacaine (0.5%) were used in increments of 2 to 3 mL.

Intraoperative adverse effects, such as hypotension, nausea or vomiting, pruritus, or shivering, were noted. Hypotension was defined as a decrease of more than 20% in basal systolic blood pressure within 30 minutes of intrathecal injection and was treated with boluses of 3 mg of ephedrine. As per clinical protocol, the management of blood pressure was left to the discretion of the attending anesthesiologist. To assess the neonatal outcome, Apgar score was noted 1 and 5 minutes after birth, and the umbilical arterial pH and base excess were also recorded.

Other observations included the time taken to position the patient supine after completion of the combined spinal and epidural procedure, the time from skin incision to delivery of the baby, the duration of surgery, and the volume of intravenous fluids infused intraoperatively.

All observations, including block characteristics and the associated outcome (ie, adequate or inadequate block), were made by a dedicated anesthesiologist blinded to the intrathecal dose.

Statistical Analysis
The up-and-down sequences of the dose of intrathecal bupivacaine were analyzed for calculation of the ED₅₀ with 95% confidence interval (CI), after rejecting the first 3 identical sequences. Intergroup comparison of parametric data was done using an unpaired t test, whereas for nonparametric data, Mann-Whitney U test was used. χ² test was used for comparison of discrete variables. P <0.05 was considered statistically significant.

Sample Size
When using an up-and-down method for determination of ED₅₀, sample size is considered adequate once 6 pairs of reversal sequence are achieved. In both groups, 6 pairs of reversal were obtained after 18 patients had been studied in each.

RESULTS
Both groups had statistically similar demographic parameters (P > 0.05; Table 1). The baseline heart rate was statistically

<table>
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<tr>
<th>TABLE 1. Patient’s Characteristics</th>
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<tr>
<td>Group N (n = 18)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
</tr>
<tr>
<td>Height, mean (SD), cm</td>
</tr>
<tr>
<td>Body mass index, mean (SD), kg/m²</td>
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<tr>
<td>Heart rate, mean (SD), bpm</td>
</tr>
<tr>
<td>Baseline systolic blood pressure,</td>
</tr>
<tr>
<td>mean (SD), mm Hg</td>
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<tr>
<td>Duration of surgery, mean (SD), min</td>
</tr>
<tr>
<td>Skin incision delivery time, mean (SD), min</td>
</tr>
<tr>
<td>Intravenous fluid, mean (SD), mL</td>
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*P < 0.001.

bpm indicates beats per minute.
similar between both groups, whereas the systolic blood pressure was significantly higher in group P \( (P < 0.001; \text{ Table 1}) \). Conditions of all patients in group P, when scheduled for the cesarean delivery, had already stabilized using magnesium sulfate and labetalol therapy initiated by the obstetrician. While 10 of the patients in group P were receiving labetalol orally at a dose of 100 mg administered every 8 hours, the other 8 patients were being administered 200 mg at similar intervals. All patients had been administered the loading dose of 4 g of magnesium sulfate intravenously and another 5 g intramuscularly in each buttock before being posted in the surgery theater.

The duration of surgery, skin incision delivery time, and volumes of intravenous fluids infused were statistically similar between both groups (\( P > 0.05; \text{ Table 1} \)).

The sequences of doses for adequate and inadequate blocks in both groups were identical; these are shown in Figures 1 and 2.

The ED\textsubscript{50} of intrathecal hyperbaric bupivacaine was the same in both groups (4.7 mg; 95% CI, 4.5–4.9 mg).

Time taken from completion of the intrathecal injection to positioning the patients supine was statistically similar between group N (101.7 ± 11.9 seconds) and group P (94 ± 14.1 seconds; \( P > 0.05 \)). Intergroup comparison of sensory block characteristics from among those who developed adequate block showed statistically similar maximum sensory level, time required to achieve an adequate block, and for it to recede to T6 level (\( P > 0.05 \); Table 2). The number of patients developing a modified Bromage score of 1 and 2 was also statistically similar between both groups (\( P > 0.05 \)).

None of the patients with adequate block required supplementation through epidural catheter intraoperatively. Epidural supplementation in all patients provided adequate analgesia when administered in the postoperative period.

The lowest systolic blood pressure in the first 30 minutes after the intrathecal injection, the amount of ephedrine used, and the percentage decrease in systolic blood pressure from baseline value were statistically similar in both groups (\( P > 0.05 \); Table 2).

The Apgar score at 1 minute was significantly lower in group P (\( P < 0.05 \)), whereas it was similar between both groups at 5 minutes (\( P > 0.05 \); Table 3). The umbilical artery blood analysis at birth showed significantly lower pH and higher base deficit in group P (\( P < 0.05 \); Table 3).

### TABLE 2. Block Characteristics in Patients With Adequate Blockade

<table>
<thead>
<tr>
<th>Block Characteristics</th>
<th>Group N (n = 11)</th>
<th>Group P (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum sensory block level, median (range)</td>
<td>T4 (3–4)</td>
<td>T4 (3–4)</td>
</tr>
<tr>
<td>Time to develop adequate block, mean (SD), min</td>
<td>12 (2)</td>
<td>11 (4)</td>
</tr>
<tr>
<td>Time for regression to T6 level, mean (SD), min</td>
<td>50 (12)</td>
<td>48 (20)</td>
</tr>
<tr>
<td>No. patients with modified Bromage score of 1</td>
<td>0/11</td>
<td>2/11</td>
</tr>
<tr>
<td>No. patients with modified Bromage score of 2</td>
<td>11/11</td>
<td>9/11</td>
</tr>
<tr>
<td>Lowest SBP, mean (SD), mm Hg</td>
<td>109 (7)</td>
<td>112 (12)</td>
</tr>
<tr>
<td>Ephedrine dose, mean (SD), mg</td>
<td>2 (3)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Fall in SBP, median (range), %</td>
<td>8 (4–21)</td>
<td>17 (6–34)</td>
</tr>
</tbody>
</table>

Results are not statistically different. SBP indicates systolic blood pressure.

### TABLE 3. Parameters of Neonatal Assessment

<table>
<thead>
<tr>
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<th>Group N (n = 11)</th>
<th>Group P (n = 11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apgar 1, median (range)</td>
<td>10 (9–10)</td>
<td>9 (9–10)</td>
<td>0.034</td>
</tr>
<tr>
<td>Apgar 5, median (range)</td>
<td>10 (10–10)</td>
<td>10 (10–10)</td>
<td>—</td>
</tr>
<tr>
<td>UApH, mean (SD)</td>
<td>7.38 (0.02)</td>
<td>7.26 (0.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UABE, mean (SD)</td>
<td>−7.10 (1.10)</td>
<td>−11.12 (2.82)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

UABE indicates umbilical arterial base excess; UApH, umbilical arterial pH.
The incidence of all intraoperative adverse effects (ie, hypotension, nausea or vomiting, shivering, and pruritus) was statistically similar between both groups (P > 0.05; Table 4).

DISCUSSION

We found the ED50 of intrathecal hyperbaric bupivacaine for cesarean delivery in normotensive and severely preeclamptic patients to be 4.7 mg (95% CI, 4.5-4.9 mg), along with 20 µg of fentanyl. An intrathecal injection of this dose will provide a sensory block level of T4 along with a modified motor Bromage score of 1 or 2 within 15 minutes of intrathecal injection in 50% of patients.

It can be argued that using an ED50 rather than ED90 as the minimum effective dose is more clinically relevant because it will result in an inadequate block in 5% as opposed to 50% of patients. However, published research regarding the requirement of local anesthetics frequently evaluates the minimum effective dose as the ED50.4,17,19,20 Because the findings of this study are related to use of a combined spinal epidural, concern regarding the number of inadequate blocks may not be of great consequence because the epidural catheter allows subsequent topping up.

Pregnancy results in epidural venous engorgement due to increased intra-abdominal pressure and causes consequent thecal compression to decrease the intrathecal dose requirement or increase its intrathecal spread.10 The use of systemic vasoconstrictors, such as phenylephrine, reduces the intrathecal drug spread, suggested to be due to constriction of the epidural veins.1,12 In preeclamptic patients, although not evidenced per se, it seems logical to assume that epidural venoconstriction should be a part of the generalized vasoconstriction pathognomonic of the disease.6 We, therefore, speculated that epidural venous constriction in preeclampsia could offset or increase the pregnancy-induced decrease in intrathecal dose requirement. However, we did not find any difference in the ED50 of intrathecal hyperbaric bupivacaine between normotensive and severely preeclamptic patients. Because we assessed the dose requirement for an elective cesarean delivery, conditions of the preeclamptic patients, although not preeclampsia on admission, had been stabilized with labetalol and magnesium sulfate therapy. The variation in the extent of epidural vasoconstriction or dilation, and hence, intrathecal dose requirement between the 2 groups may thus have been negated.

Previous studies evaluating single shot subarachnoid block in severely preeclamptic patients have used intrathecal hyperbaric bupivacaine in doses ranging from 8 to 12.5 mg, along with opioids, such as sufentanil 3 to 5 µg, morphine 100 µg, or fentanyl 10 to 25 µg.5,7,8,21 Using a combined spinal epidural, Ramanathan et al22 evaluated the feasibility of using 7.5 mg of hyperbaric bupivacaine along with 25 µg of fentanyl in patients with severe preeclampsia, albeit the study was not a randomized controlled trial using various doses. An adequate block level of T4 was noted in 92% of patients. As an agreeable comparison, the use of 4.7 mg per our results would require supplementation in 50% of patients.

The minimum effective dose of hyperbaric bupivacaine4,5 has been evaluated in normotensive patients undergoing cesarean delivery using a combined spinal epidural. Danelli et al23 reported the ED50 of hyperbaric bupivacaine (0.5%) to be 0.036 mg/cm height, using the up-and-down method similar to our study. For the mean height of approximately 156 cm in our patients, a derived value of 5.6 mg is close to the ED50 reported by us (4.7 mg). Ginosar et al5 noted a larger ED50 of intrathecal hyperbaric bupivacaine despite adding 10 µg of fentanyl and 200 µg of morphine (6.7 versus 4.7 mg). This could be because of a number of differences between the 2 trials. The authors defined an adequate block as one with sensory level of T6 and wherein no intraoperative epidural supplementation was required. In contrast, because a combined spinal epidural block offers the liberty of epidural supplementation whenever required, we did not consider lack of intraoperative supplementation as a criterion for adequacy of intrathecal block. Also, the mean height shows that patients studied by Ginosar et al5 were taller by approximately 10 cm compared with our subjects. Although controversial,10 there is evidence to link intrathecal dose requirement to patient height.23,24 The smaller height of our patients could have contributed to the comparatively lower intrathecal dose requirement in our study. Lastly, Ginosar et al5 used regression analysis to calculate the ED50, whereas we used the up-and-down method. The results for ED50 derived from the regression analysis and the up-and-down method are known to differ.20 The use and efficacy of the up-and-down method for determining ED50 is well accepted in anesthetic research,22 and its primary advantage is its ability to predict the ED50 with accuracy while decreasing the sample size requirement.13 There are reports of usage of bupivacaine in doses as low as 3.7 mg in severely preeclamptic as well as normotensive patients but only when augmented with a mixture of morphine and fentanyl intrathecally as well as a small volume of local anesthetic in epidural space.25,26

Although within the reference range, the umbilical arterial pH was significantly more acidic in babies delivered by preeclamptic patients (7.26 [0.03]) than in babies delivered by normotensive patients (7.38 [0.02]). The percentage decrease in blood pressure was clinically greater in the preeclamptic patients (17% versus 8%) and statistically similar, with the P value denoting a “borderline significance” (0.056). Thus, it may be that the clinically greater drop in blood pressure in preeclamptic patients is responsible for the worse umbilical artery pH. However, no conclusive statement can be drawn because the study was not powered to detect variations in blood pressure.

Although we found no difference in the ED50 of hyperbaric bupivacaine in the 2 groups, a limitation of our study is that we did not record the neonatal weights. Neonatal growth determines the uterine enlargement; hence, it may be hypothesized to affect the epidural venous dilation and intrathecal dose requirement. Aggressive intravenous fluid administration may result in pulmonary edema in preeclamptic patients.27 Without protocol intraoperative fluid therapy, we used approximately 1.5 L of fluid in both groups, including the 500-mL preloading. These volumes are on the liberal side of fluid therapy. However, certain earlier trials in severely preeclamptic patients have used similar volumes.7,8,22 Also, there was no evidence of pulmonary edema in any of our patients.

In conclusion, to conduct elective cesarean delivery using a combined spinal epidural technique in severely preeclamptic or normotensive patients, the minimum effective dose (ie, the ED50 of intrathecal hyperbaric bupivacaine with 20 µg of fentanyl) is 4.7 mg.

Table 4. Adverse Effects in Patients With Adequate Blockade

<table>
<thead>
<tr>
<th></th>
<th>Group N (n = 11)</th>
<th>Group P (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>3 (27)</td>
<td>5 (46)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>1 (9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Shivering</td>
<td>5 (46)</td>
<td>1 (9)</td>
</tr>
</tbody>
</table>

Data are number of patients (%). Results are not statistically different.
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3. Ginosar Y, Mirikatani E, Drover DR, et al. ED\textsubscript{50} and ED\textsubscript{95} of intrathecal hyperbaric bupivacaine coadministered with opioids for caesarean delivery. *Anesthesiology.* 2004;100:676–682.


