

# The ED<sub>50</sub> and ED<sub>95</sub> of Intrathecal Isobaric Bupivacaine with Opioids for Cesarean Delivery

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**Background:** The ideal intrathecal isobaric bupivacaine dose for cesarean delivery anesthesia is uncertain. While small doses (5–9 mg) of bupivacaine may reduce side effects such as hypotension, they potentially increase spinal anesthetic failures. This study determined the ED<sub>50</sub> and ED<sub>95</sub> of intrathecal isobaric bupivacaine (with adjuvant opioids) for cesarean delivery.

**Methods:** After institutional review board approval and written informed consent were obtained, 48 parturients undergoing elective cesarean delivery under combined spinal–epidural anesthesia were enrolled in this double-blind, randomized, dose-ranging study. Patients received a 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12-mg intrathecal isobaric bupivacaine dose with 10 µg fentanyl and 200 µg morphine. Overall anesthetic success was recorded when no intraoperative epidural supplement was required during the cesarean delivery. ED<sub>50</sub> and ED<sub>95</sub> values for overall anesthetic success were determined using a logistic regression model.

**Results:** ED<sub>50</sub> and ED<sub>95</sub> values for overall anesthetic success were 7.25 and 13.0 mg, respectively. No advantages for low doses could be demonstrated with regard to hypotension, nausea, vomiting, pruritus, or maternal satisfaction, although this study was underpowered to detect significant differences in secondary outcome variables.

**Conclusions:** The ED<sub>50</sub> and ED<sub>95</sub> values (7.25 and 13.0 mg, respectively) for intrathecal isobaric bupivacaine in this circumstance are similar to values the authors determined recently for hyperbaric bupivacaine using similar methodology. These ED<sub>50</sub> and ED<sub>95</sub> values are significantly higher than those advocated in previous reports in which success was claimed using lower intrathecal bupivacaine doses. The current study used stricter criteria to define “successful” anesthesia and support the use of larger bupivacaine doses to ensure adequate patient comfort.

THE use of intrathecal isobaric bupivacaine for cesarean delivery has been reported in a number of studies.<sup>1–5</sup> Isobaric solutions may have potential advantages (less hypotension and nausea) over hyperbaric solutions, perhaps because of a more gradual spinal block onset associated with hypobaric solutions.<sup>6,7</sup> Isobaric solutions may also offer additional benefits when blocks are performed in the sitting position and there is potential for delay in assuming the horizontal position (e.g., in a mor-

bidity obese patient or with a combined spinal–epidural technique).

There is uncertainty regarding the ideal dose of intrathecal isobaric bupivacaine for cesarean delivery, with doses ranging from 5 to 20 mg reported in the literature.<sup>1,3,8,9</sup> Limiting the dose of bupivacaine has been advocated for reducing the incidence of maternal hypotension and vasopressor requirements, decreasing nausea, reducing time to discharge from the postanesthesia care unit, and improving maternal satisfaction.<sup>1</sup> However, lower doses of intrathecal local anesthetics are also associated with more reports of intraoperative pain, nausea, and late spinal anesthetic failures, sometimes requiring conversion to general anesthesia.<sup>1,9</sup>

Although studies to determine the optimal dose of hyperbaric bupivacaine for cesarean delivery have been undertaken,<sup>10,11</sup> no previous study has determined the ideal dose of intrathecal isobaric bupivacaine coadministered with an opioid for cesarean delivery.

In this study, we used logistic regression to determine the ED<sub>50</sub> and ED<sub>95</sub> (effective dose in 50% and 95% of patients, respectively) of isobaric intrathecal bupivacaine when coadministered with intrathecal fentanyl (10 µg) and morphine (200 µg) for cesarean delivery. We also compared these results with those previously obtained for hyperbaric bupivacaine when studied by our group under similar study conditions.<sup>10</sup>

## Materials and Methods

### Design

We used a prospective, randomized, double-blind, dose-ranging study to determine the ED<sub>50</sub> and ED<sub>95</sub> of intrathecal isobaric bupivacaine for cesarean delivery.

### Subjects and Setting

Forty-eight healthy, term parturients presenting for elective cesarean delivery were enrolled in this study. The study was conducted at Lucile Packard Children’s Hospital, Stanford University Medical Center (Stanford, California). Parturients were enrolled during a 6-month period after institutional review board approval and signed informed consent had been obtained.

Inclusion criteria were American Society of Anesthesiologists physical status class I or II, age between 18 and 40 yr, body weight less than 110 kg, height greater than 150 cm, singleton pregnancy, gestational age of more than 37 completed weeks, and scheduled elective cesarean delivery. Exclusion criteria were active labor, rup-

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tured membranes, three or more previous cesarean deliveries, diabetes or gestational diabetes, pregnancy-induced hypertension or preeclampsia, intrauterine growth retardation, placenta previa, and congenital anomaly.

### Study Protocol

All patients received 1,000 ml lactated Ringer's solution plus 500 ml hetastarch after obtaining peripheral intravenous access. All patients were premedicated with oral sodium citrate (30 ml) and intravenous metoclopramide (10 mg) and ranitidine (50 mg). Fluid infusion and premedication were given approximately 30 min before the spinal anesthesia. After enrollment, patients were randomized using blinded opaque envelopes containing computer-generated random allocations. Patients were allocated to one of eight possible groups to receive 5, 6, 7, 8, 9, 10, 11, or 12 mg intrathecal isobaric 0.5% bupivacaine (Abbott Laboratories, North Chicago, IL). Fentanyl, 10  $\mu$ g (0.2 ml), and 200  $\mu$ g morphine (0.4 ml) were added to each intrathecal bupivacaine injection, with normal saline (0-1.4 ml) to make the total volume 3 ml in all cases. Combined spinal-epidural anesthesia was performed at the L2-L3 or L3-L4 interspace using a loss-of-resistance-to-air technique, with the patient in the sitting position. The spinal component was performed with a needle-through-needle technique using a 26-gauge Gertie Marx needle. After aspiration of cerebrospinal fluid, the intrathecal dose was injected over 5-10 s. A multiple-orifice spring-wound epidural catheter (B. Braun, Bethlehem, PA) was threaded 5 cm into the epidural space. No drug was injected into the epidural catheter at this time. The patient was immediately laid on her right side, and the epidural catheter was taped into place. She was then rapidly transferred to the supine position, with a right pelvic wedge placed to cause left uterine displacement.

The success or failure of the intrathecal block was the primary data endpoint. Success<sub>(induction)</sub> was defined as a bilateral T6 sensory level to pinprick within 10 min of the intrathecal drug administration. A failure<sub>(induction)</sub> was recorded when a T6 sensory level was not obtained within 10 min after intrathecal drug administration. If a failure<sub>(induction)</sub> was recorded, an epidural supplementation was administered to attain a T6 level. A success<sub>(operation)</sub> was defined as a successful initial sensory level, with no additional epidural anesthetic required during surgery. A failure<sub>(operation)</sub> was recorded when, despite an adequate T6 sensory level, supplemental epidural analgesia was required to complete surgery because of either a visual analog pain scale score (VAPS; 0-100; 0 = no pain and 100 = worse pain imaginable) greater than 20 or patient's request for additional analgesia. In cases of failures<sub>(induction)</sub> and failures<sub>(operation)</sub>, supplemental epidural anesthesia consisted of 2% lidocaine (with bicarbonate and 1:200,000 epinephrine) administered as

5-ml bolus injections, repeated as required. Hypotension was defined as systolic blood pressure (SBP) less than 90% baseline SBP. Baseline SBP was taken as the average of three readings at admission. Ephedrine was used to treat hypotension, keeping SBP greater than 90% above baseline.

An incident of nausea was defined as any nausea (visual analog scale [VAS] score > 0).

### Measurements

Demographic variables recorded included age, height, weight, parity, number of previous cesarean deliveries, and gestational age. Neonatal weight and Apgar scores were recorded after delivery. SBP was determined by noninvasive blood pressure measurements made at baseline (averaged over three measurements), at 2-min intervals after drug injection for the first 10 min, at 5-min intervals until the end of surgery, and at 15-min intervals in the postanesthesia care unit. The lowest SBP (absolute and change from baseline) and the total dose of ephedrine administered were recorded. The sensory level was determined bilaterally by pinprick at 2, 4, 6, 8, and 10 min after drug administration.

Subjective pain scores were determined with use of a VAPS (0-100; 0 = no pain and 100 = worse pain imaginable) at the following intervals: skin incision, delivery, uterine exteriorization, peritoneal closure, and skin closure. In addition, subjective pain (VAPS), nausea (VAS, 0-100), and pruritus (VAS, 0-100) were assessed at 15-min intervals, from intrathecal drug administration until the end of surgery. SBP, motor power (modified Bromage scale: 0 = able to move both knees and toes; 1 = able to move knees only; 2 = able to flex toes only; 3 = unable to move hip, knees, or toes), subjective pain (VAPS), nausea (VAS), and pruritus (VAS) were measured at 15-min intervals in the postanesthesia care unit until the time the patient met discharge criteria (hemodynamic stability, sensory and motor block receding, ability to move legs). Criteria for discharge from the postanesthesia care unit included a block to pinprick lower than T4 and two-segment regression of block compared with the level at admission.

### Statistical Analysis

Demographic data are presented as mean  $\pm$  SD or median (interquartile range) where appropriate. Analysis was performed with use of the SPSS 11.0 for Windows statistical package (Chicago, IL). Data were assessed for normal distribution of variance. Normally distributed data were assessed by one-way analysis of variance, and nonnormally distributed data were assessed by Mann-Whitney U test. Incidence data were analyzed by Fisher exact test. Statistical significance was defined as  $P < 0.05$ . Correlations were assessed with use of linear regression unless otherwise indicated.

**Table 1. Demographic and Obstetric Data**

	5 mg (n = 6)	6 mg (n = 6)	7 mg (n = 6)	8 mg (n = 7)	9 mg (n = 6)	10 mg (n = 6)	11 mg (n = 6)	12 mg (n = 5)
Age, yr	33 ± 3	34 ± 5	32 ± 5	31 ± 5	36 ± 2	34 ± 8	37 ± 2	34 ± 4
Height, cm	161 ± 8	162 ± 9	163 ± 5	164 ± 9	166 ± 8	162 ± 9	167 ± 7	161 ± 1
Weight, kg	79 ± 17	70 ± 12	82 ± 10	75 ± 7	77 ± 9	79 ± 11	78 ± 8	74 ± 3
Parity	2	3	2	2	3	2	3	2
Gestational age, wk	39 ± 1	38 ± 1	39 ± 0	39 ± 1	38 ± 0	39 ± 1	39 ± 1	39 ± 1
Neonatal weight, kg	3.5 ± 0.4	3.2 ± 0.5	3.8 ± 0.6	3.3 ± 0.3	3.4 ± 0.5	3.5 ± 0.4	3.4 ± 0.2	3.6 ± 0.3

Values are presented as mean ± SD, except parity, which is presented as median.

P = not significant among groups.

### Logistic Regression Analysis of $E_{50}$ and $E_{95}$

The success or failure (binary option) and corresponding spinal bupivacaine dose were fitted to the following version of the Hill equation:

$$\text{Probability of successful block} = \frac{\text{dose}^\gamma}{\text{dose}^\gamma_{50} + \text{dose}^\gamma},$$

where dose is the spinal bupivacaine dose in milligrams,  $\text{dose}_{50}$  is the dose of bupivacaine at which there is a 50% probability of success of the spinal block, and  $\gamma$  is the slope of the response curve and describes the shape of the data distribution. The binary endpoints used for the logistic regression included  $\text{success}_{(\text{operation})}$  compared with  $\text{failure}_{(\text{operation})}$  and  $\text{success}_{(\text{induction})}$  compared with  $\text{failure}_{(\text{induction})}$ . A naive pooled analysis was performed, with each subject providing one data point for the fit.  $\text{ED}_{50}$  and  $\text{ED}_{95}$  were estimated using NONMEM<sup>®</sup> version V (GloboMax, Hanover, MD). The quality of the fit was considered based on improvement in the log likelihood value of NONMEM (an improvement of 4 of the log likelihood value consistent with  $P < 0.05$  was considered significant) and visual assessment of the fit.

## Results

All 48 patients who were enrolled and randomly assigned to a group completed the study according to the protocol and were included in the analysis. There were six parturients allocated to each of the 5-, 6-, 7-, 9-, 10-, and 11-mg bupivacaine groups, seven patients allocated to the 8-mg bupivacaine group, and five patients allocated to the 12-mg group because of the randomized group allocation. The unequal numbers in the groups were due to a randomization error. Demographic and baseline obstetric characteristics were similar among treatment groups (table 1). There was no correlation between any of these demographic variables and the success or failure of anesthesia.

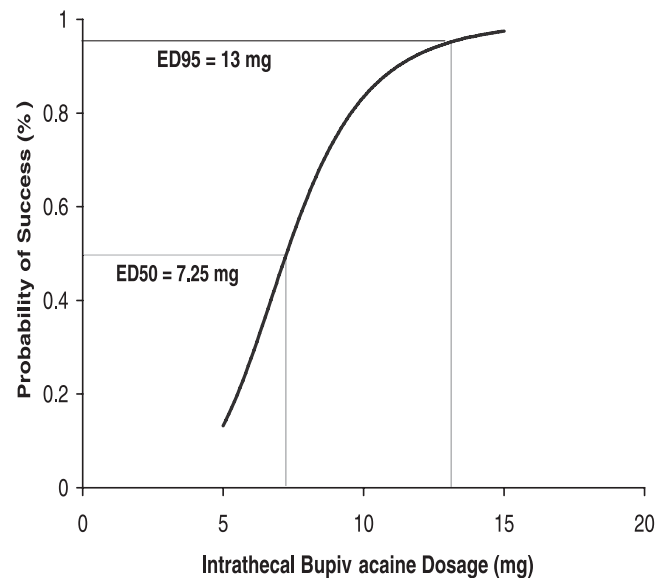
The mean duration of surgery was  $62 \pm 14$  min (range, 33–105 min), with no differences among the groups. The mean time to failure in cases of  $\text{failure}_{(\text{operation})}$  was  $35 \pm 19$  min (range, 12–71 min). Uterine exteriorization was performed in the majority of cases (38 cases). Those who did not have uterine exteriorization included 3, 1,

2, 2, 1, and 1 patients in the 5-, 6-, 8-, 9-, 10-, and 11-mg groups, respectively.

### Anesthetic Effect

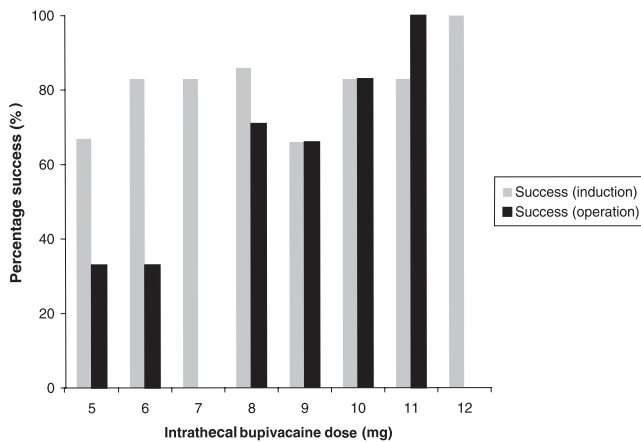
A logistic plot was drawn for overall anesthetic success ( $\text{success}_{(\text{operation})}$ ) (fig. 1). The 0.5 and 0.95 y-intercepts show the  $\text{ED}_{50}$  and  $\text{ED}_{95}$ , respectively (fig. 1). The slope of the curves ( $\gamma$ ) for  $\text{success}_{(\text{operation})}$  was 5.0 (SE, 1.6). Overall anesthetic success ( $\text{success}_{(\text{operation})}$ )  $\text{ED}_{50}$  and  $\text{ED}_{95}$  were 7.25 mg (SE, 0.6) and 13 mg (SE, 2.0), respectively (fig. 1).

We were unable to measure the  $\text{success}_{(\text{induction})}$   $\text{ED}_{50}$  and  $\text{ED}_{95}$  because of much data overlap between initial successful and failed doses and to few initial failures (spinal block < T6) even in the low dose range. The data resulted in an indeterminate transition point, and we were unable to construct a logistic regression curve for  $\text{success}_{(\text{induction})}$ .  $\text{Success}_{(\text{induction})}$  did not reliably predict overall intraoperative success ( $\text{success}_{(\text{operation})}$ ).



**Fig. 1.** Overall anesthetic success ( $\text{success}_{(\text{operation})}$ )  $\text{ED}_{50}$  and  $\text{ED}_{95}$  for isobaric intrathecal bupivacaine for cesarean delivery calculated from the logistic regression plot of probability of successful anesthesia versus dose of intrathecal bupivacaine. Probabilities of 0.05 and 0.95 were used to derive the  $\text{ED}_{50}$  and  $\text{ED}_{95}$ , respectively.  $\text{Success}_{(\text{operation})}$  was defined as a successful initial sensory level (bilateral T6 sensory level to pinprick within 10 min of spinal) with no additional epidural anesthetic required during surgery.





**Fig. 2.** Initial (success<sub>(induction)</sub>) and overall (success<sub>(operation)</sub>) successful anesthesia at different doses of isobaric intrathecal bupivacaine. This bar chart differentiates success<sub>(induction)</sub> in the gray bar (defined as a bilateral T6 sensory level to pinprick within 10 min of intrathecal drug administration) from success<sub>(operation)</sub> in the solid black bar (defined as a successful initial sensory level with no additional epidural anesthetic required during surgery).

The success<sub>(induction)</sub> and success<sub>(operation)</sub> at each of intrathecal bupivacaine doses are shown in figure 2. The majority of the failures occurred in the lower dose range. There were no failures<sub>(operation)</sub> in doses above 10 mg intrathecal plain bupivacaine (fig. 2).

We found no correlation between bupivacaine dose and the speed of T6 block onset, time to anesthetic supplementation, or block duration. The mean time to T6 sensory block onset to pinprick was  $8 \pm 4$  min. There was an inverse correlation between the dose of intrathecal bupivacaine and pain on uterine exteriorization ( $R^2 = -0.49$ ,  $P = 0.002$ ). We were unable to detect a difference in VAPS score among the groups at any one of the other surgical stimulus landmarks (skin incision, delivery, peritoneal closure, and skin closure). The mean postanesthesia care unit stay was  $63 \pm 11$  min (range, 30–95 min), with no differences detected among the different bupivacaine dose groups. Overall maternal satisfaction (VAS, 0–100) was high,  $96 \pm 6$ , with no differences among the doses studied.

### Adverse Effects

The changes in SBP after spinal anesthesia, the dose of ephedrine required to maintain the SBP, the occurrence of nausea/vomiting, and the degree of motor block at the end of surgery are all summarized in table 2. There were no correlations between bupivacaine dose and incidence of hypotension or vasopressor requirements. We found no significant differences in the incidence of pruritus, nausea, or vomiting among the doses studied. Ten of the 48 patients studied (21%) experienced either nausea or vomiting intraoperatively. No dose-dependent differences were found with the incidence of nausea or vomiting (table 2).

### Discussion

This study quantifies the ED<sub>50</sub> and ED<sub>95</sub> for intrathecal isobaric bupivacaine coadministered with intrathecal fentanyl and morphine for cesarean delivery. The ED<sub>50</sub> for success<sub>(operation)</sub> was similar (7.25 vs. 7.6 mg) to that previously reported by our group using similar methodology for hyperbaric bupivacaine.<sup>10</sup> The ED<sub>95</sub> for success<sub>(operation)</sub> was slightly higher than we previously reported for hyperbaric bupivacaine (13.0 vs. 11.2 mg);<sup>10</sup> however, this difference is not statistically or clinically significant. The success<sub>(operation)</sub> ED<sub>95</sub> of 13 mg is higher than the upper limit study dose (12 mg) because of mathematical extrapolation of the logistic regression dose curve to the ED<sub>95</sub> point (fig. 1).

Several studies have found no or minimal differences when comparing isobaric versus hyperbaric local anesthetic for spinal anesthesia for cesarean delivery.<sup>2,12,13</sup> However, some report that hyperbaric solutions give a more predictable block.<sup>3,7</sup> Although our data for initial success showed marked variation in time to initial T6 sensory onset and block height, overall anesthetic success was reliable and similar to hyperbaric bupivacaine,<sup>10</sup> with no failures<sub>(operation)</sub> in patients receiving doses in excess of 10 mg.

Our effective doses were higher than those used in studies of “minidose” intrathecal bupivacaine for cesar-

**Table 2.** Adverse Effects of the Various Intrathecal Bupivacaine Doses

	5 mg (n = 6)	6 mg (n = 6)	7 mg (n = 6)	8 mg (n = 7)	9 mg (n = 6)	10 mg (n = 6)	11 mg (n = 6)	12 mg (n = 5)
Lowest SBP, mmHg	90 ± 8	94 ± 12	94 ± 9	93 ± 14	96 ± 9	88 ± 8	91 ± 15	83 ± 13
Maximal SBP reduction, %	19 ± 12	25 ± 8	20 ± 7	21 ± 7	26 ± 7	29 ± 9	26 ± 22	29 ± 11
Ephedrine requirement, mg	7 ± 3	5 ± 2	6 ± 3	3 ± 3	9 ± 8	10 ± 5	8 ± 8	9 ± 6
Nausea/vomiting*	0/0	1/0	3/0	1/0	1/0	0/0	1/0	3/1
Motor block†	2 (1–3)	3 (1–3)	2 (1–3)	2 (1–3)	3 (2–3)	3 (1–3)	3 (1–3)	3 (2–3)

Values are presented as mean ± SD, except nausea/vomiting, which is presented as number of patients reporting nausea or vomiting, and motor block, which is reported as median (range).  $P =$  not significant among groups.

\* Nausea and vomiting are presented as incidence. Nausea was assessed using a visual analog scale (0–100 mm) every 15 min throughout surgery. Incidence of nausea was defined as any nausea (score > 0). † Motor block at end of surgery was assessed using a modified Bromage scale (0 = able to move both knees and toes; 1 = able to move knees only; 2 = able to flex toes only; 3 = unable to move hip, knees, or toes).

SBP = systolic blood pressure.

can delivery,<sup>1,3,9,14</sup> in which bupivacaine doses as low as 5 mg (well below the ED<sub>95</sub> and even the ED<sub>50</sub> determined in our studies) were used. The incidence of intraoperative pain in the current study was very low (6%) with doses of 10 mg or greater, which is similar to our previous hyperbaric bupivacaine ED<sub>50</sub>/ED<sub>95</sub> study in which only 7% of patients reported intraoperative pain with doses larger than 10 mg.<sup>10</sup> In previous low-dose intrathecal bupivacaine studies for cesarean delivery, the incidences of visceral pain and discomfort using 5 and 8 mg were 50%<sup>1</sup> and 35%,<sup>9</sup> respectively. In another study, Petersen *et al.*<sup>15</sup> found that increasing the intrathecal dose of bupivacaine from 7.5–10 to 10–12.5 mg decreased the incidence of pain associated with visceral traction from 70.5% to 31.6%, emphasizing the relation between larger doses and greater patient comfort. Differences in reported pain in these compared with the current investigation cannot be explained by the duration of surgery, uterine exteriorization, or use of adjuvant opioids, all of which were similar among the studies. Reducing the dose of local anesthetic in an attempt to decrease maternal hypotension may increase the likelihood of maternal discomfort and result in anesthetic failure in some patients. Such high incidences of intraoperative pain<sup>1,3,9</sup> suggest that anesthesia was suboptimal; such frequent discomfort would be considered unacceptable in our practice.

There were few initial failures (spinal block < T6) even in the low dose range, and the initial T6 block to pinprick did not reliably predict overall success. This contrasts with our previous hyperbaric bupivacaine ED<sub>95</sub> study performed under the same conditions as described in this current study.<sup>10</sup> The success<sub>(induction)</sub> of the low doses of isobaric bupivacaine may be due to the drug spreading to a greater extent in the spinal fluid compared with hyperbaric bupivacaine. With the addition of intrathecal opioids coupled with the lower cerebrospinal fluid specific gravity in pregnancy, we would expect isobaric bupivacaine to be hypobaric with respect to the patient's cerebrospinal fluid.<sup>16</sup> Spinal administration with patients in the sitting position would have facilitated cephalad spread. However, with the lower doses, the concentration at the distant effect sites may have been inadequate to provide surgical anesthesia as demonstrated by more failures<sub>(operation)</sub> and a shorter mean time to failure (35 *vs.* 62 min) compared with the hyperbaric bupivacaine. The shorter mean time to intraoperative failure with the hypobaric solution occurred well within the mean surgical time (62 ± 14 min) and may account for the higher failure rate as compared to the hyperbaric solution. We found no correlation between the bupivacaine doses studied and the speed of onset of T6 block, in contrast to our hyperbaric bupivacaine study, in which there was a correlation between speed of onset of block and dose of bupivacaine.<sup>10</sup> The reason for this observed difference is unknown.

In this study, we did not adjust doses of intrathecal bupivacaine to patient height or weight. Although some studies have suggested patient height and weight may affect block characteristics,<sup>17,18</sup> others<sup>19,20</sup> have demonstrated no effects of age, height, weight, or body mass index on the spread of sensory blockade. Norris *et al.*<sup>19</sup> determined that adjusting the intrathecal dose for height and weight variables within the normal range is unnecessary.

To make up the study groups' doses, all patients received a total intrathecal volume of 3 ml composed of 0.6 ml opioid solution (fentanyl and morphine) combined with a variable volume of the isobaric bupivacaine (1–2.2 ml) and normal saline (0.2–1.4 ml). Normal saline with a baricity of 0.99951 g/ml<sup>16</sup> is very similar to 0.5% bupivacaine (baricity of 0.99937 g/ml<sup>16</sup>), so the varying volumes of bupivacaine and normal saline between the groups should not have affected the overall baricity. The upper limit of hypobaricity for intrathecal solutions in cerebrospinal fluid at 37°C is between 1.00016 and 1.00037 g/ml;<sup>16</sup> thus, all groups' solutions were hypobaric. Although we do not believe that the addition of fentanyl (baricity of 0.99333 g/ml<sup>16</sup>) and morphine (baricity of 0.99983 g/ml<sup>16</sup>) would have significantly changed the baricity and/or behavior of these hypobaric solutions in cerebrospinal fluid, it is important to remember that the findings of this study are for isobaric bupivacaine with 10 µg fentanyl and 200 µg morphine. The use of different intrathecal opioids or different fentanyl or morphine doses may result in slightly different ED<sub>50</sub> and ED<sub>95</sub> values.

We are unaware of any previous study that has prospectively determined the ideal dose for isobaric intrathecal bupivacaine with intrathecal fentanyl and morphine for cesarean delivery. In the current study, we used logistic regression to describe the dose–response curve from a linear distribution of eight doses of isobaric bupivacaine. This methodology was previously used by our group to determine ED<sub>50</sub> and ED<sub>95</sub> values for hyperbaric bupivacaine for cesarean delivery.<sup>10</sup> This logistic regression technique uses the binary endpoint of success *versus* failure and has been validated elsewhere in the anesthetic literature.<sup>21,22</sup> It is potentially more accurate than up–down sequential analysis that Danelli *et al.*<sup>11</sup> used to determine the ED<sub>50</sub> and ED<sub>95</sub> for hyperbaric intrathecal bupivacaine for cesarean delivery. Up–down sequential analysis design bias dictates that the data points tend to be distributed about the ED<sub>50</sub> rather than being distributed in a linear fashion.<sup>23</sup> In their study, Danelli *et al.* reported that the ED<sub>50</sub> for bupivacaine was 0.036 mg/cm (equivalent to 5.9 mg in our population), and the ED<sub>95</sub> was 0.06 mg/cm (equivalent to 9.8 mg). However, logistic regression does have potential weaknesses. The ED<sub>50</sub> is generally determined with greater confidence than the ED<sub>95</sub> because it is measured from the rapidly increasing portion of the

dose-response curve. The ED<sub>95</sub> is determined from the plateau portion of the curve and is an extrapolation based on the ED<sub>50</sub>.

The ideal dose of intrathecal local anesthetic for cesarean delivery is essentially a balance between the conflicting demands of avoiding patient discomfort and avoiding adverse maternal effects (particularly hypotension and nausea). Increasing the dose of local anesthetic has been found to increase maternal hypotension<sup>1,14,24</sup> and nausea,<sup>1,24</sup> with resultant reduction in maternal satisfaction.<sup>1</sup> We were unable to demonstrate that increasing doses of bupivacaine resulted in a greater incidence or severity of hypotension or significant differences in the incidence of nausea or vomiting. However, this study was not sufficiently powered to detect small changes in these variables. Spreading the patient sample between large numbers of different study groups as we have done in this study is useful for determining a ED<sub>50</sub> and ED<sub>95</sub> but markedly reduces the power for detecting differences in continuous or discrete data.

Although we had a low incidence of perioperative nausea and vomiting (10 of 48), this was higher than in our previous hyperbaric bupivacaine study (4 of 42).<sup>10</sup> This is contrary to findings by Critchley *et al.*<sup>6</sup> that demonstrated less nausea and hypotension with isobaric (plain) 0.5% intrathecal bupivacaine compared with hyperbaric (8% dextrose-containing) bupivacaine. A slower spinal block onset associated with the isobaric solution in the study of Critchley *et al.* may explain the lower incidence of hypotension and resultant nausea.<sup>6,7</sup> However, patient positioning during intrathecal drug administration and the types of intrathecal opioids used are often poorly controlled for in comparative studies. Our higher incidence of perioperative nausea and vomiting compared with our previous hyperbaric study may be explained by the combined spinal-epidural technique performed in the sitting position that would have favored a faster cephalad spread of the isobaric solution over hyperbaric bupivacaine. Our mean T6 block onset time was shorter compared with the previous hyperbaric study (mean, 7.7 vs. 11.2 min;  $P < 0.03$ ).<sup>10</sup>

Although this study determined the ED<sub>50</sub> and ED<sub>95</sub> of isobaric intrathecal bupivacaine for cesarean delivery, determining the optimal dose for every patient is impossible because of the large variations in individual response to intrathecal local anesthetics. Fan *et al.*<sup>24</sup> studied four doses of intrathecal bupivacaine (2.5, 5, 7.5, and 10 mg) as part of a combined spinal-epidural technique for cesarean delivery and found that the 5-mg group needed a mean supplemental dose of 10 ml lidocaine (2%) to attain adequate anesthesia but was associated with less hypotension and nausea than the 7.5- and 10-mg groups, which did not need supplemental lidocaine. Based on the findings from this study, when using low-dose bupivacaine, particularly doses close to the

ED<sub>50</sub>, clinicians should consider using a combined spinal-epidural or continuous spinal technique to allow supplementation of inadequate anesthesia.

If administered under the same conditions as in our study (isobaric bupivacaine, sitting position, 10  $\mu$ g intrathecal fentanyl and 200  $\mu$ g intrathecal morphine), doses less than the ED<sub>95</sub> (13 mg in this study; 5% failure rate) and particularly doses close to or below the ED<sub>50</sub> (7.25 mg in this study; 50% failure rate) would be ill-suited for a single-shot technique and should be used as part of a catheter-based technique.

In this study of isobaric (plain) intrathecal bupivacaine with opioid, we determined that ED<sub>50</sub> and ED<sub>95</sub> values were similar to those reported for hyperbaric bupivacaine with the same opioid combination in our previous study.<sup>10</sup> Isobaric bupivacaine can be used for providing cesarean delivery anesthesia as effectively as hyperbaric bupivacaine, with a similar side effect profile, although initial sensory levels to pinprick were less predictive of successful intraoperative anesthesia.

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