

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

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**Background:** Successful cesarean delivery anesthesia has been reported with use of small doses (5–9 mg) of intrathecal bupivacaine coadministered with opioids. This double-blind, randomized, dose-ranging study determined the ED<sub>50</sub> and ED<sub>95</sub> of intrathecal bupivacaine (with adjuvant opioids) for cesarean delivery anesthesia.

**Methods:** Forty-two parturients undergoing elective cesarean delivery with use of combined spinal–epidural anesthesia received intrathecal hyperbaric bupivacaine in doses of 6, 7, 8, 9, 10, 11, or 12 mg in equal volumes with an added 10 µg intrathecal fentanyl and 200 µg intrathecal morphine. Sensory levels (pinprick) were evaluated every 2 min until a T6 level was achieved. The dose was a success<sub>(induction)</sub> if a bilateral T6 block occurred in 10 min; otherwise, it was a failure<sub>(induction)</sub>. In addition to being a success<sub>(induction)</sub>, the dose was a success<sub>(operation)</sub> if no intraoperative epidural supplement was required; otherwise, it was a failure<sub>(operation)</sub>. ED<sub>50</sub> and ED<sub>95</sub> for both success<sub>(induction)</sub> and success<sub>(operation)</sub> were determined with use of a logistic regression model.

**Results:** ED<sub>50</sub> for success<sub>(induction)</sub> and success<sub>(operation)</sub> were 6.7 and 7.6 mg, respectively, whereas the ED<sub>95</sub> for success<sub>(induction)</sub> and success<sub>(operation)</sub> were 11.0 and 11.2 mg. Speed of onset correlated inversely with dose. Although no clear advantage for low doses could be demonstrated (hypotension, nausea, vomiting, pruritus, or maternal satisfaction), this study was underpowered to detect significance in these variables.

**Conclusions:** The ED<sub>95</sub> of intrathecal bupivacaine under the conditions of this study is considerably in excess of the low doses proposed for cesarean delivery in some recent publications. When doses of intrathecal bupivacaine less than the ED<sub>95</sub>, particularly near the ED<sub>50</sub>, are used, the doses should be administered as part of a catheter-based technique.

THE use of intrathecal bupivacaine is routine for both elective and emergency cesarean deliveries. Recent studies have claimed successful anesthesia with very low doses of intrathecal bupivacaine (5–9 mg) when coadministered with opioids.<sup>1–5</sup> Limiting the bupivacaine dose has been advocated, with the goals of decreasing maternal hypotension, vasopressor requirements, nausea, and time to discharge from the PACU and improving

maternal satisfaction.<sup>4</sup> Advocates of low-dose intrathecal bupivacaine acknowledge the lack of “studies to determine the reliable minimum dose (both in terms of the sensory block as well as its duration) of bupivacaine–fentanyl for cesarean delivery.”<sup>4</sup> Until now, the most extensive of these studies have been based on three or fewer drug doses,<sup>1</sup> making a dose–response relation difficult to assess. Furthermore, assessment of the reliable minimum dose of intrathecal bupivacaine should incorporate currently standard adjuvant opioid regimes. Such an assessment is of particular importance when administering spinal anesthesia as a “one-shot” technique (without the security offered by a catheter-based technique), as suggested by some proponents of low-dose spinal anesthesia. For these one-shot spinal anesthetics, an ED<sub>95</sub> represents the dose associated with a 5% anesthetic failure, a failure rate presumably unacceptable to most practitioners.

In this study, we used logistic regression to determine the ED<sub>50</sub> and ED<sub>95</sub> of intrathecal bupivacaine, based on data from a linear range of seven different doses (6–12 mg) of intrathecal bupivacaine, when coadministered with intrathecal fentanyl (10 µg) and intrathecal morphine (200 µg). We also assessed whether lower bupivacaine doses were associated with any clinically significant advantages.

## Materials and Methods

### Design

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

### Subjects and Setting

Forty-two healthy, term parturients presenting for elective cesarean delivery were enrolled in this study, which was conducted between February 2000 and February 2001 in the Labor and Delivery Unit of Lucile Packard Children’s Hospital, Stanford University Medical Center (Stanford, California). Subjects were enrolled after institutional review board approval and signed informed consent had been obtained. Inclusion criteria were age between 18 and 40, American Society of Anesthesiologists physical status class I or II, body weight less than 110 kg, singleton pregnancy, and gestational age of more than 36 completed weeks. Exclusion criteria were active labor, ruptured membranes, three or more previous cesarean deliveries, diabetes or gestational diabetes, pregnancy-

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Received from the Department of Anesthesia, Stanford University, Stanford, California, and the Department of Anesthesiology and Critical Care Medicine, Hadassah Hebrew University Medical School, Jerusalem, Israel. Submitted for publication April 7, 2003. Accepted for publication August 11, 2003. Support was provided solely from institutional and/or departmental sources. Presented at the 33rd Annual Meeting of the Society of Obstetric Anesthesiology and Perinatology, San Diego, California, April 25–28, 2001, and the Annual Meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, October 13–17, 2001.

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induced hypertension or preeclampsia, intrauterine growth retardation, placenta previa, and congenital anomaly.

### *Study Protocol*

All patients had an intravenous catheter inserted in a peripheral arm vein and 1,000 ml lactated Ringer's solution administered together with 500 ml hetastarch. All patients were premedicated with oral sodium citrate (30 ml) and intravenous metoclopramide (10 mg) and ranitidine (50 mg). Premedication and fluid loading was initiated approximately 30 min before anesthesia.

After enrollment, patients were randomized by means of blinded opaque envelopes that had been sorted by computer-generated random allocation. Patients were allocated to one of seven possible groups to receive 6, 7, 8, 9, 10, 11, or 12 mg hyperbaric intrathecal bupivacaine (0.75% in 8.25% dextrose; 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 injection, with 10% dextrose added (0–0.8 ml) to make the total volume 2.2 ml in all cases. Combined spinal-epidural (CSE) anesthesia was administered, with the patient sitting at the L2–L3 or L3–L4 interspace. An 18-gauge epidural needle was inserted into the epidural space with use of loss of resistance to air. A 26-gauge Gertie Marx needle was inserted into the intrathecal space, and cerebrospinal fluid was aspirated. The intrathecal dose was diluted with cerebrospinal fluid to a final volume of 3 ml and injected over 10 s; the ability to aspirate cerebrospinal fluid was reconfirmed at the end of injection.

The spinal needle was withdrawn, and a multiport epidural catheter was threaded 3–5 cm into the epidural space. No drug was injected into the epidural catheter at this time. The patient was immediately laid on her left side, and the epidural catheter was taped into place. She was then rapidly moved 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. A success<sub>(induction)</sub> was recorded if a bilateral T6 sensory level to pinprick was attained within 10 min after the time of intrathecal drug administration; otherwise, a failure<sub>(induction)</sub> was recorded, and epidural supplementation was given at that stage. A success<sub>(operation)</sub> was recorded if, after a successful induction of spinal anesthesia, no supplemental epidural anesthetic was required during surgery. A failure<sub>(operation)</sub> was recorded when, despite attaining a T6 sensory level within 10 min after intrathecal drug administration, supplemental epidural analgesia was required to complete surgery (because of either a patient request for additional analgesia or a visual analog pain scale [VAPS] score > 20 mm on a 100-mm scale). In cases of failure<sub>(induction)</sub> and failure<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. Ephedrine was used to treat mean arterial pressure (MAP) below 60 mmHg.

### *Measurements*

The following demographic variables were recorded on enrollment in the study: age, height, weight, parity, number of previous cesarean deliveries, and gestational age. Neonate weight was recorded after delivery.

Mean arterial pressure 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 PACU. The lowest MAP (absolute and percent change from baseline), the time to lowest MAP, the lowest MAP (absolute and percent change from baseline) that occurred within the first 10 min after intrathecal drug administration, and the total dose of ephedrine administered were all recorded.

The sensory level was determined bilaterally by pinprick (22-gauge needle in the anterior axillary line), and motor power was assessed with use of the Bromage scale. At the outset of the study, sensory and motor assessments were made at 5 and 10 min after intrathecal drug administration, although because of a subsequent refinement in the protocol, most patients had sensory and motor assessments at 2, 4, 6, 8, and 10 min after drug administration.

Subjective pain scores were determined with use of the VAPS at the following intervals: skin incision, delivery, uterine exteriorization, peritoneal closure, and skin closure. In addition, subjective pain (VAPS), nausea (visual analog scale [VAS]), and pruritus (VAS) were assessed at 15-min intervals, from intrathecal drug administration until the end of surgery.

In the PACU, the following variables were measured at 15-min intervals until discharge: MAP, motor power (Bromage scale), subjective pain (VAPS), nausea (VAS), and pruritus (VAS). The time until the patient met discharge criteria (hemodynamic stability, sensory and motor block receding, ability to move legs) was recorded.

### *Statistical Analysis*

Demographic data are presented as mean  $\pm$  SD or median (interquartile range) where appropriate. Analysis was performed with use of the SPSS 10.0 for Windows statistical package (Chicago, IL). Data were assessed for normal distribution of variance. Means were assessed by one-way analysis of variance if normally distributed, medians and nonnormally distributed means were assessed by Mann-Whitney U test, and 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 Data**

	6 mg (n = 6)	7 mg (n = 6)	8 mg (n = 6)	9 mg (n = 6)	10 mg (n = 6)	11 mg (n = 6)	12 mg (n = 6)
Age, yr	34 ± 7	34 ± 7	28 ± 6	33 ± 4	36 ± 4	31 ± 7	36 ± 5
Height, cm	168 ± 9	165 ± 4	161 ± 6	165 ± 11	164 ± 7	159 ± 8	164 ± 4
Weight, kg	82 ± 10	76 ± 14	72 ± 10	72 ± 10	83 ± 24	77 ± 9	75 ± 10
Parity (median)	2	1	1	1	1	1	2
Previous cesarean deliveries (median)	1	1	1	1	1	1	1
Gestational age, wk	39 ± 2	39 ± 1	38 ± 1	39 ± 1	39 ± 0	39 ± 1	39 ± 1
Weight of neonate, g	3,709 ± 201	3,474 ± 364	3,608 ± 582	3,343 ± 326	3,659 ± 447	3,420 ± 496	3,385 ± 381

Values are presented as mean ± SD or median. Means were assessed by one-way analysis of variance if normally distributed, medians and abnormally distributed means were assessed by Mann-Whitney *U* test, and incidence data were analyzed by Fisher exact test. There were no significant differences among groups.

### Logistic Regression Analysis of ED<sub>50</sub> and ED<sub>95</sub>

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

$$\text{probability of successful block} = \text{dose}^\gamma / (\text{dose}_{50}^\gamma + \text{dose}^\gamma)$$

where dose is the spinal bupivacaine dose in milligrams, dose<sub>50</sub> 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. Logistic regression requires a binary endpoint; accordingly for an assessment of success<sub>(operation)</sub>, success was compared with failure, regardless of whether the failure was early or late. For an assessment of success<sub>(induction)</sub>, a similar assessment was made to compare the binary options of success or failure<sub>(operation)</sub> against failure<sub>(induction)</sub>. A naive pooled analysis was performed, with each subject providing one data point for the fit. A Laplacian estimation method was used with NONMEM statistical package version V (NONMEM Project Group, University of California, San Francisco, CA). 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.

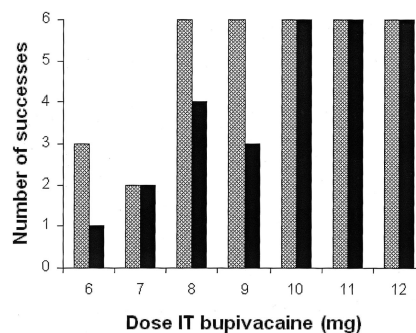
## Results

All 42 patients enrolled completed the study according to the protocol and were included in the analysis. The demographic data are summarized in table 1. There was no correlation between any of these demographic variables and the success or failure of anesthesia. Based on early and late anesthetic failures at each dose of intrathecal bupivacaine, a simple bar chart of success<sub>(induction)</sub> and success<sub>(operation)</sub> for each dose is shown (fig. 1). There were no early or late anesthetic failures in doses above 10 mg intrathecal bupivacaine. The mean duration of surgery was  $64 \pm 16$  min (range, 44–120 min), and the mean time to late failure in cases of failure<sub>(operation)</sub> was  $62 \pm 16$  min (range, 45–93 min). Uterine exteriorization was performed in all cases, with one exception.

### Anesthetic Effect

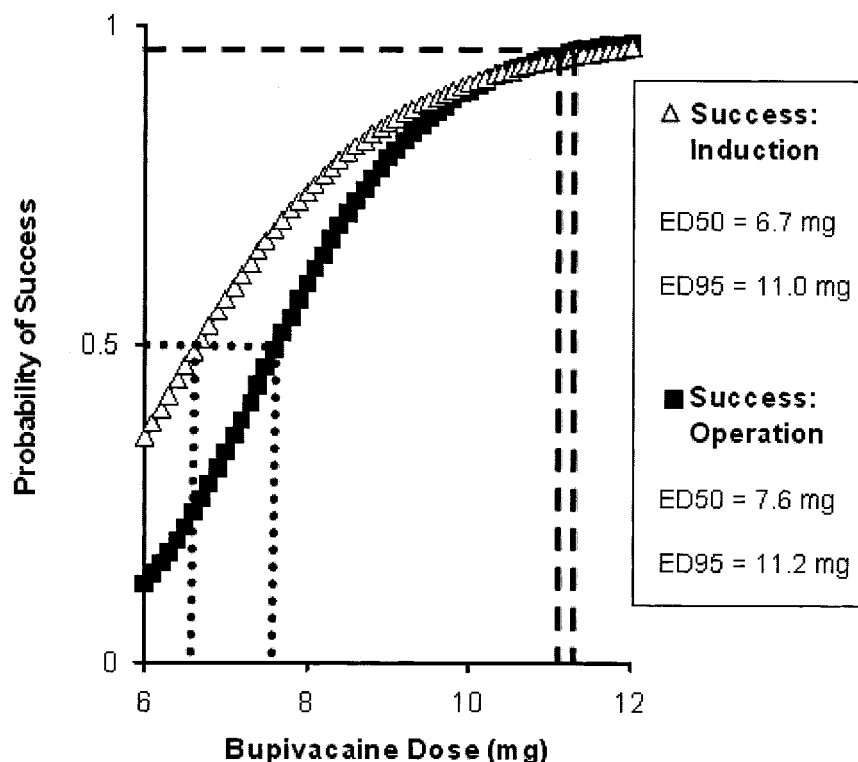
Logistic regression plots were drawn for success<sub>(induction)</sub> and success<sub>(operation)</sub> (fig. 2). The 0.5 and 0.95 y-intercepts were used to calculate the ED<sub>50</sub> and ED<sub>95</sub>, respectively, for both plots. The ED<sub>50</sub> for success<sub>(induction)</sub> was 6.7 mg (SE = 0.6), and the ED<sub>50</sub> for success<sub>(operation)</sub> was 7.6 mg (SE = 0.4). The slopes of the curves ( $\gamma$ ) for success<sub>(induction)</sub> and success<sub>(operation)</sub> were 5.7 (SE = 1.8) and 8.2 (SE = 2.1), respectively. The ED<sub>95</sub> for success<sub>(induction)</sub> was 11.0 mg, and the ED<sub>95</sub> for success<sub>(operation)</sub> was 11.2 mg. There was an inverse correlation between the dose of intrathecal bupivacaine and the number of supplemental epidural bolus doses of lidocaine that were required ( $R^2 = 0.23$ ,  $P = 0.001$ ). The time to achieve a bilateral T6 sensory level correlated inversely with dose ( $R^2 = 0.25$ ,  $P = 0.001$ ).

Of the 42 patients in this study, only 7 reported a VAPS score greater than 10 mm at any one of the surgical stimulus landmarks (skin incision, delivery, uterine exteriorization, peritoneal closure, and skin closure). These 7 patients were as follows: 6 mg (failure<sub>(operation)</sub>), 7 mg (failure<sub>(induction)</sub>), 8 mg (failure<sub>(operation)</sub>), 8 mg (fail-



**Fig. 1. Successful anesthesia at different doses of intrathecal (IT) bupivacaine.** This bar chart differentiates between successful induction only (where the sensory level to nerve stimulation was at least T6 bilaterally within 10 min after spinal injection) and overall success (where not only was induction successful, but also no supplemental analgesia was required throughout surgery). The early (EFs) and late failures (LFs) were as follows: 6 mg: 3 EF, 2 LF; 7 mg: 4 EF, 0 LF; 8 mg: 0 EF, 2 LF; 9 mg: 0 EF, 3 LF. There were no early or late failures above 10 mg intrathecal bupivacaine. All patients received adjuvant opioids (0.01 mg fentanyl and 0.2 mg morphine). *Hatched bars* = successful induction; *solid bars* = successful operation.

Fig. 2. Logistic regression plot of anesthesia success: calculation of ED<sub>50</sub> and ED<sub>95</sub>. The logistic regression plot of anesthesia success versus dose of intrathecal bupivacaine is shown. Probabilities of 0.5 and 0.95 were used to derive ED<sub>50</sub> and ED<sub>95</sub>, respectively, for both the success of induction of regional anesthesia and the success throughout surgery.



ure<sub>(operation)</sub>), 10 mg (success), 12 mg (success), and 12 mg (success). In the PACU, only 5 of 42 patients reported VAPS scores greater than 10 mm at any of the 15-min assessments. These 5 patients were as follows: 6 mg (failure<sub>(induction)</sub>), 8 mg (success), 8 mg (success), 10 mg (success), and 10 mg (success).

#### Adverse Effects

The changes in MAP after spinal anesthesia, the dose of ephedrine required to control MAP, the occurrence of nausea/vomiting, and the degree of residual motor block

on arrival in the PACU are all summarized in table 2. In the first 10 min after spinal anesthesia, there was a statistically significant correlation between bupivacaine dose and the percentage decrease in blood pressure ( $R^2 = 0.14$ ,  $P < 0.05$ ). However, the bupivacaine dose was not significantly correlated with the overall incidence and severity of hypotension, ephedrine requirements, or the lowest blood pressure before delivery.

Only four patients described either nausea or vomiting at any stage either intraoperatively or postoperatively (until discharge from the PACU). No patients in the

Table 2. Adverse Effects Associated with Different Doses of Intrathecal Bupivacaine

	6 mg (n = 6)	7 mg (n = 6)	8 mg (n = 6)	9 mg (n = 6)	10 mg (n = 6)	11 mg (n = 6)	12 mg (n = 6)
Lowest MAP, mmHg	63 ± 7	55 ± 19	55 ± 10	59 ± 7	55 ± 10	53 ± 6	55 ± 14
Maximal reduction in MAP, %	24 ± 4	39 ± 22	35 ± 14	30 ± 10	37 ± 13	37 ± 6	37 ± 9
Lowest MAP in first 10 min, mmHg	69 ± 9	67 ± 10	56 ± 11	63 ± 11	57 ± 10	57 ± 10	57 ± 17
Maximal reduction in MAP in first 10 min, %	17 ± 6	28 ± 14	34 ± 15	26 ± 11	35 ± 11	31 ± 11	35 ± 13
Ephedrine dose, mg	4 ± 9	14 ± 18	11 ± 14	13 ± 16	14 ± 15	18 ± 13	18 ± 21
Nausea/vomiting*	0/6	0/6	0/6	1/6	1/6	1/6	1/6
Motor block at end of surgery†	1 (0–2)	0 (0–2)	1 (0–3)	1 (0–3)	1 (0–3)	0 (0–2)	0 (0–1)

Values are presented as mean ± SD, median (range), or incidence/n. Means were assessed by one-way analysis of variance if normally distributed, medians and abnormally distributed means were assessed by Mann-Whitney *U* test, and incidence data were analyzed by Fisher exact test. There were no significant differences among groups.

\* Nausea/vomiting: 9 mg: nausea (75 on visual analog scale) intraoperatively at 45 min from spinal injection. 10 mg: nausea (100 on visual analog scale) at 30 min postoperatively. 11 mg: nausea (30 on visual analog scale) intraoperatively at 60 min from spinal injection. 12 mg: vomiting at 30–45 min postoperatively.

† Motor block was assessed with use of the Bromage scale.

MAP = mean arterial pressure.



low-dose groups (6–8 mg) experienced nausea or vomiting; for each of the higher-dose groups (9–12 mg), one out of six patients experienced either nausea or vomiting (table 2); these patients were neither more hypotensive nor in more pain than the nonnauseated patients.

## Discussion

### *Anesthetic Effect*

This study reports the ED<sub>50</sub> and ED<sub>95</sub> for intrathecal bupivacaine based on a wide range of different doses linearly distributed and coadministered with currently popular doses of intrathecal opioids. The values that we report for ED<sub>50</sub> and ED<sub>95</sub> are much higher than might have been expected from reading the published reports of “minidose” intrathecal bupivacaine for cesarean delivery,<sup>1–5</sup> which report reliably successful anesthesia with doses below the ED<sub>50</sub> found in our study. This may be due to several factors.

First, the requirement to achieve a bilateral T6 sensory level within 10 min after intrathecal drug administration inevitably dictated that some patients received epidural supplementation and were recorded as anesthesia failures, despite the possibility that adequate surgical anesthesia may have developed in at least some of them if more time had been allowed. We believed that 10 min to achieve a T6 sensory level is a period of time consistent with the realities of a busy operating suite and the occasional demands for urgent cesarean delivery. Furthermore, waiting longer for the commencement of surgery would inevitably postpone the end of surgery and would possibly provoke additional late failures.

Second, the presence of an epidural catheter might have encouraged the blinded anesthesiologist to administer rescue supplementation epidural anesthesia at a lower degree of discomfort than would have been the case had a single-shot technique been used, where the only alternatives would be sedating medication or general anesthesia. If this is the case, rather than limiting the validity of our data, this raises questions about the adequacy of the anesthesia in the reports of low-dose, single-shot spinal anesthesia. Ben-David *et al.*<sup>4</sup> reported no anesthesia failures when anesthesia failure was defined as patient pain requiring conversion to general anesthesia. However, Ben-David *et al.*<sup>4</sup> and Choi *et al.*<sup>1</sup> reported 50% and 35% incidences, respectively, of some visceral pain and discomfort in their low-dose patients, numbers that seem to indicate that the doses used were less than the ED<sub>95</sub> for those populations. In the current study, in the groups receiving intrathecal bupivacaine in doses of 10 mg or greater (in whom no supplemental anesthesia was needed), only 7% (intraoperative) and 4.7% (postoperative) of patients reported any VAPS assessment greater than 10 mm. In our practice, it is extremely rare for patients to report any pain during a cesarean delivery

of customary duration, a situation we consider to be optimal.

Third, prolonging the sitting position in the presence of hyperbaric local anesthetic may lead to excessive sacral distribution of anesthesia, causing the upper level of block to be inadequate for surgery. A potential drawback of the CSE technique that we used in this study is that the time taken for insertion of the epidural catheter inevitably dictates that the patient remains sitting for longer after the spinal drug injection. Nevertheless, in nonpregnant patients receiving intrathecal hyperbaric bupivacaine, Povey *et al.*<sup>6</sup> demonstrated that sitting for as long as 25 min did not affect the sensory level as compared with sitting for 2 min. A study is in progress at our institution to determine the ED<sub>50</sub> and ED<sub>95</sub> for isobaric bupivacaine under the same conditions that were described in the current study. This next study may help determine the degree to which baricity is a factor in determining the sensory level after CSE in the sitting position.

Fourth, in this study, the surgical technique involved exteriorization of the uterus, a profound surgical stimulus that may be expected to increase anesthetic requirement. However, this standard surgical technique was identical to that described in the minidose study reported by Ben-David *et al.*<sup>4</sup> Furthermore, in our study, only one patient (6 mg bupivacaine) experienced late anesthetic failure at this stage of surgery.

Fifth, the duration of surgery was more than 60 min in this study, which may be significantly longer than the experience in some other medical centers. Of the studies reporting minidose intrathecal bupivacaine for cesarean delivery, only Choi *et al.*<sup>1</sup> reported a mean duration of surgery, which was 45 min. However, Ben-David *et al.*<sup>4</sup> reported that all but one operation were completed by 75 min.

Sixth, the practice of minidose spinal local anesthetics is based on the local anesthetic-sparing effect of intrathecal opioids.<sup>1</sup> The drugs and doses chosen as the adjuvant opioids differ between studies and may be expected to affect the intrathecal local anesthetic requirement. In this study, we determined the ED<sub>50</sub> and ED<sub>95</sub> of intrathecal bupivacaine in the presence of 10  $\mu$ g intrathecal fentanyl and 200  $\mu$ g intrathecal morphine. By comparison, the studies reporting low-dose intrathecal bupivacaine for cesarean delivery (5–9 mg) used 3.3  $\mu$ g sufentanil,<sup>3</sup> 10  $\mu$ g fentanyl,<sup>1</sup> 25  $\mu$ g fentanyl,<sup>2,4</sup> and 15  $\mu$ g fentanyl combined with either 100 or 200  $\mu$ g morphine.<sup>5</sup>

Finally, the doses of intrathecal bupivacaine in this study were not tailored to patient size (height, weight, or vertebral column length). Schnider *et al.*<sup>7</sup> reported that the onset time to achieve an arbitrary sensory level increased linearly with patient height and decreased with increasing weight. Similarly, variability in block duration was partly associated with variability in patient height, such that the duration between the extremes of

a 150-cm-tall person and a 200-cm-tall person would differ by 65 min.<sup>7</sup> McCulloch also showed an increased level of block in obese patients undergoing urologic procedures.<sup>8</sup> In contrast, Hartwell *et al.*<sup>9</sup> showed no correlation of anesthetic spread with patient height, weight, or body mass index in parturients undergoing cesarean delivery but did show some correlation with the length of the vertebral column. Norris *et al.*<sup>10</sup> demonstrated no effects of age, height, weight, body mass index, or vertebral column length on the spread of sensory blockade and concluded that adjusting the intrathecal dose for any of these variables was unnecessary. Notwithstanding, Danelli *et al.*<sup>11</sup> determined the ED<sub>50</sub> and ED<sub>95</sub> of intrathecal bupivacaine based on a dose adjusted to patient height and obtained results similar to (albeit slightly lower than) ours. The ED<sub>50</sub> for their study 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 in our population).<sup>11</sup>

Although review articles and textbooks have suggested various intrathecal doses of bupivacaine for cesarean delivery, this has only once been previously determined from a prospective clinical trial. Danelli *et al.*<sup>11</sup> used the up-down sequential analysis method of Dixon and Massey<sup>12</sup> to determine an ED<sub>95</sub> for intrathecal bupivacaine for cesarean delivery; however, minimum local anesthetic concentration studies do not provide reliable data for an ED<sub>95</sub> assessment because 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>13</sup> In the current study, we used logistic regression to describe the dose-response curve from a linear distribution of seven doses of intrathecal bupivacaine. This technique uses the binary endpoint of this study (success *vs.* failure), is economic in design, and has been validated elsewhere in the anesthetic literature.<sup>14,15</sup>

To place our data in the proper perspective, it is important to understand the strengths and limitations of the determinations of the ED<sub>50</sub> and ED<sub>95</sub>. The ED<sub>50</sub> is determined from the rapidly increasing portion of the dose-response curve and is accordingly an assessment that generally is associated with greater confidence than the ED<sub>95</sub>, which is determined from the plateau portion of the curve and is an extrapolation based on the ED<sub>50</sub>. Although this technique does not allow for the estimation of variability of the ED<sub>95</sub> (unlike the ED<sub>50</sub>), it is a realistic way to present data from a curve that was calculated from actual clinical material.

### Adverse Effects

The ideal dose of intrathecal local anesthetic for cesarean delivery strikes the perfect balance between the conflicting demands of avoiding patient discomfort and avoiding adverse maternal effects (particularly hypotension and nausea). Pedersen *et al.*<sup>16</sup> and Choi *et al.*<sup>1</sup> demonstrated that increasing the dose of intrathecal lo-

cal anesthetic reduced the incidence and severity of visceral pain without increasing maternal hypotension. However, other investigators found that increasing the dose of local anesthetic increased maternal hypotension<sup>2,4,17</sup> and nausea,<sup>4,17</sup> with resultant reduction in maternal satisfaction.<sup>4</sup> In the current study, there was a slightly greater percentage change in MAP within the first 10 min with higher doses of intrathecal bupivacaine. We could not demonstrate an increase in the overall incidence or severity of hypotension or statistically significant differences in the incidence of nausea or vomiting with different doses of intrathecal bupivacaine. There may have been an impact of the fluid preloading. We used colloid preloading, which is more effective at preventing hypotension<sup>18,19</sup> than preloading with crystalloid, which is the normal practice at most institutions. However, more importantly, this study was not sufficiently powered to detect small changes in these variables. This reflects a drawback with the logistic regression design; a linear distribution of multiple different doses represents an efficient approach to determine the dose-response effect based on a binary endpoint (in this case, anesthetic success or failure); however, spreading the patient sample between large numbers of different study groups markedly reduces the power for detecting differences in nonbinary (discrete or continuous) data.

Much of the debate on the optimal dose of intrathecal anesthetics is clouded by the way investigators define and grade maternal discomfort, anesthetic failure, hypotension, and nausea. What emerges is an appreciation of the wide range of anesthetic responses among patients. Anesthetic techniques should be adopted that allow for such a range of responses. Using low-dose bupivacaine, close to the ED<sub>50</sub>, as part of a CSE technique is an example of a regimen that aims to limit the intrathecal local anesthetic dose to accommodate the faster responders but that is flexible enough to supplement anesthesia for the slower responders. A good example is the study by Fan *et al.*,<sup>17</sup> who studied four doses of intrathecal bupivacaine (2.5, 5, 7.5, and 10 mg) as part of a CSE technique for cesarean delivery. They 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, nausea, and dyspnea than the 7.5- and 10-mg groups, which did not need supplemental lidocaine.

The current study did not show a significant clinical advantage with the use of low-dose intrathecal bupivacaine for cesarean delivery anesthesia. There was a correlation between the speed of onset of anesthesia and the dose of drug that would suggest avoiding these lower doses for emergency cesarean delivery. Furthermore, these lower doses were associated with a high failure rate (including late failures presenting intraoperatively). If administered under the same conditions as in our study (hyperbaric bupivacaine, sitting position,

10  $\mu\text{g}$  intrathecal fentanyl, 200  $\mu\text{g}$  intrathecal morphine), this failure rate would make these doses ill suited for a single-shot technique. When doses less than the  $\text{ED}_{95}$  (5% failure rate; 11.2 mg in this study), especially close to or below the  $\text{ED}_{50}$  (50% failure rate; 7.6 mg in this study), are used, they should be used as part of a CSE or other catheter-based technique.

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