ED$_{50}$ and ED$_{95}$ of Intrathecal Bupivacaine in Morbidly Obese Patients Undergoing Cesarean Delivery

Brendan Carvalho, M.B.B.Ch., F.R.C.A.,* Jeremy Collins, M.B.Ch.B., F.R.C.A.,†
David R. Drover, M.D.,‡ Lindsey Atkinson Ralls, M.D.,§ Edward T. Riley, M.D.‖

ABSTRACT

Background: It has been suggested that morbidly obese parturients may require less local anesthetic for spinal anesthesia. The aim of this study was to determine the effective dose (ED$_{50}$/ED$_{95}$) of intrathecal bupivacaine for cesarean delivery in morbidly obese patients.

Methods: Morbidly obese parturients (body mass index equal to or more than 40) undergoing elective cesarean delivery were enrolled in this double-blinded study. Forty-two patients were randomly assigned to receive intrathecal hyperbaric bupivacaine in doses of 5, 6, 7, 8, 9, 10, or 11 mg (n = 6 per group) coadministered with 200 μg morphine and 10 μg fentanyl. Success (induction) was defined as block height to pinprick equal to or more than T6 and success (operation) as success (induction) plus no requirement for epidural supplementation throughout surgery. The ED$_{50}$/ED$_{95}$ values were determined using a logistic regression model.

Results: ED$_{50}$ and ED$_{95}$ (with 95% confidence intervals) for success (operation) were 9.8 (8.6–11.0) and 15.0 (10.0–20.0), respectively, and were similar to corresponding values of a nonobese population determined previously using similar methodology. We were unable to measure ED$_{50}$/ED$_{95}$ values for success (induction) because so few blocks failed initially, even at the low-dose range. There were no differences with regard to secondary outcomes (*i.e.*, hypotension, vasopressor use, nausea, and vomiting).

Conclusions: Obese and nonobese patients undergoing cesarean delivery do not appear to respond differently to mod-

What We Already Know about This Topic

- Whether obese parturients require less spinal local anesthetic for anesthesia for cesarean delivery is unknown

What This Article Tells Us That Is New

- Using a randomized dose response of spinal bupivacaine with fentanyl and morphine, the median dose of bupivacaine for successful anesthesia in morbidly obese parturients was 9.8 mg, similar to a previous study in nonobese parturients

est doses of intrathecal bupivacaine. This dose-response study suggests that doses of intrathecal bupivacaine less than 10 mg may not adequately ensure successful intraoperative anesthesia. Even when the initial block obtained with a low dose is satisfactory, it will not guarantee adequate anesthesia throughout surgery.

CESAREAN delivery is most commonly performed under spinal anesthesia using hyperbaric bupivacaine.[1] Bupivacaine provides an appropriate duration of anesthesia to perform cesarean delivery. Hyperbaric and hypobaric bupivacaine both provide effective spinal anesthesia for cesarean delivery,[2–4] although with smaller intrathecal doses, hyperbaric solutions may ensure a more predictable block.[5] Many investigators recommend a reduced intrathecal dose in morbid obesity due to an observed lower neuraxial local anesthetic requirement.[6–8] This is supported by Hogan *et al.*,[9] who reported lower cerebrospinal fluid volumes in patients with a high body mass index (BMI). Cerebrospinal fluid volumes can be reduced by several mechanisms that exert external pressure on the dural sac: increased intraabdominal pressure from abdominal fat; epidural venous plexus engorgement secondary to compression of the inferior vena cava and diversion of venous return; and the inward movement of soft tissue (especially fat) in the intervertebral foramen displacing cerebrospinal fluid.[9,10]

Although successful spinal anesthesia has been reported with a low dose of 5 mg hyperbaric bupivacaine in a morbidly

◇ This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 9A.

◆ This article is accompanied by an Editorial View. Please see: Palmer CM: Let's just call it "evidence-based practice." ANESTHESIOLOGY 2011; 114:481–2.

obese patient,[11] the limited studies that have investigated the relationship between weight and the spread of intrathecal local anesthetics have demonstrated conflicting results.[12–19] In women undergoing cesarean delivery, Norris *et al.*[15,16] showed no correlation between the height of the sensory block and the patient's BMI. However, morbidly obese patients were not specifically studied, and fixed doses of hyperbaric bupivacaine were used.

The optimal dose of intrathecal bupivacaine in the morbidly obese population undergoing cesarean delivery with spinal anesthesia is unknown. Previous studies have determined the optimal dose of hyperbaric bupivacaine for cesarean delivery in patients of normal body habitus.[20,21] The aim of this study was to use logistic regression to determine the ED_{50} and ED_{95} values of intrathecal hyperbaric bupivacaine when coadministered with intrathecal fentanyl (10 μg) and morphine (200 μg) in morbidly obese patients (BMI $\geq$40). We hypothesized that the dose requirements would be lower than obtained for hyperbaric bupivacaine in nonobese patients when using the same logistic regression methodology under similar study conditions.[20]

Materials and Methods

Design, Study Population, and Setting

We used a prospective, randomized, double-blinded, dose-ranging study to determine the ED_{50} and ED_{95} values of intrathecal hyperbaric bupivacaine for cesarean delivery. Forty-two healthy term parturients presenting for elective cesarean delivery were enrolled after written informed consent into this Stanford University Institutional Review Board–approved study. The study was conducted at Lucile Packard Children's Hospital, Stanford University Medical Center (Stanford, CA). Parturients were enrolled over a 24-month period.

Inclusion criteria included the following: American Society of Anesthesiologists physical status class II patients, aged between 18 and 40 yr, current (at time of enrollment) BMI greater than or equal to 40, height more than 150 cm, singleton pregnancy, and gestational age of more than 37 completed weeks undergoing elective cesarean delivery. Exclusion criteria included labor, ruptured membranes, more than three previous cesarean deliveries, significant medical or obstetric morbidity, intrauterine growth retardation, placenta previa, and congenital anomaly.

Study Protocol

All patients received 1,000 ml lactated Ringer's solution plus 500 ml hetastarch *via* peripheral intravenous access. Fluid infusion and a premedication (intravenous metoclopramide 10 mg and ranitidine 50 mg) were administered approximately 30 min before spinal anesthesia. After enrollment, patients were randomly assigned using batched computer-generated random allocations, and blinding was maintained using opaque envelopes containing dose assignments. Pa-

tients were allocated to one of seven possible groups to receive 0.75% hyperbaric bupivacaine (0.75% in 8.25% dextrose; Abbott Laboratories, North Chicago, IL) in doses of 5, 6, 7, 8, 9, 10, or 11 mg. Fentanyl 10 μg (0.2 ml) and morphine 200 μg (0.4 ml) were added to each bupivacaine injection, with 10% dextrose added (0–0.8 ml) to make the total volume 2.1 ml in all cases. A combined spinal epidural (CSE) was performed at the L2/L3 or L3/L4 interspace using a loss of resistance technique with the patient in the sitting position. The spinal component was performed with a needle-through-needle technique using a 26-gauge pencil-point needle. After aspiration of cerebrospinal fluid, the intrathecal dose was injected over 5–10 s. A multiple orifice epidural catheter 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. The patient was then rapidly transferred to the supine position, with a right pelvic wedge placed to facilitate left uterine displacement.

The success or failure of the intrathecal block was the primary data endpoint. Success (induction) was defined as a bilateral T6 sensory level to pinprick within 10 min of intrathecal drug administration. A failure (induction) was recorded when a T6 sensory level was not obtained within 10 min after drug administration. If a failure (induction) was recorded, an epidural supplementation of 2% lidocaine (with sodium bicarbonate 1 mEq per 10 ml and epinephrine 1:200,000) in 5-ml increments was administered to attain a T6 level. A success (operation) was defined as a successful initial sensory level, with no additional epidural anesthetic required during surgery. A failure (operation) 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 (0–100 mm; 0 = no pain and 100 = worst pain imaginable) more than 20 mm, or patient's request for additional analgesia. In cases of failure (operation), 2% lidocaine (with bicarbonate and 1:200,000 epinephrine) was administered in 5-ml bolus injections and repeated as required. Hypotension was defined as mean arterial pressure (MAP) less than 90% baseline MAP. Baseline MAP was taken as the average of three readings at admission. Phenylephrine (50–100 μg) boluses were used to treat hypotension, keeping MAP more than 90% of baseline. Intraoperative nausea and vomiting were treated with intravenous ondansetron (4 mg).

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. MAP 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 and at 5-min intervals until the end of surgery. The lowest MAP (absolute and change from baseline) and the total dose of phenylephrine administered were all recorded. The sensory level was determined bilater-

Table 1. Demographic and Obstetric Data

	5 mg (n = 6)	6 mg (n = 6)	7 mg (n = 6)	8 mg (n = 5)	9 mg (n = 6)	10 mg (n = 6)	11 mg (n = 7)
Age, yr	31 ± 7	31 ± 5	27 ± 5	30 ± 5	33 ± 7	27 ± 9	32 ± 5
Height, cm	167 ± 12	160 ± 8	163 ± 7	163 ± 9	162 ± 8	167 ± 9	163 ± 10
Weight, kg	133 ± 26	124 ± 26	140 ± 17	127 ± 7	124 ± 21	122 ± 13	127 ± 23
BMI	47 ± 5	48 ± 5	53 ± 4	48 ± 7	47 ± 4	44 ± 3	48 ± 5
Parity	1 (1–2)	2 (2–3)	2 (1–2)	1 (1–1)	1 (1–2)	1 (1–1)	1 (1–2)
Gestational age, wk	39 (38–39)	38 (37–38)	39 (38–40)	39 (39–39)	38 (38–39)	39 (38–40)	38 (38–39)
Neonatal weight, kg	3.8 ± 0.4	3.9 ± 0.4	3.7 ± 0.7	3.7 ± 0.3	3.9 ± 0.4	3.8 ± 0.6	3.9 ± 0.7

Values are presented as mean ± SD, with the exception of parity and gestational age, which are presented as median (interquartile range). *P* = not significant among groups.

BMI = body mass index.

ally by pinprick at 2, 4, 6, 8, and 10 min after drug administration. Subjective pain scores were determined with the use of a visual analog pain scale (0–100 mm; 0 = no pain and 100 = worst pain imaginable) at the following intervals: skin incision, delivery, uterine exteriorization, and skin closure. The incidence (*i.e.*, presence or absence) of nausea and vomiting was assessed at 15-min intervals from intrathecal drug administration until the end of surgery. Maternal satisfaction with anesthesia (0–100%) was assessed at end of surgery. The times at which patients met recovery discharge criteria (*e.g.*, hemodynamic stability, sensory, and motor block receding) were also recorded.

Statistical Analysis

Demographic data are presented as mean (± SD) or median (interquartile range), where appropriate. Analysis was performed with use of the SPSS 17.0 for Windows statistical package (SPSS, Inc., Chicago, IL). Data were assessed for normal distribution of variance. Normally distributed data were assessed by one-way ANOVA, and nonnormally distributed data were assessed by the Kruskal-Wallis test. Incidence data were analyzed by the Fisher exact test. Statistical significance was defined as $P < 0.05$. Correlations were assessed with the use of linear regression, unless otherwise indicated.

Logistic Regression Analysis of ED50 and ED95

The success or failure (binary option) and corresponding spinal bupivacaine dose were fitted to the following version of the Hill equation: Probability of successful block = dose$^{\gamma}$/(dose$^{\gamma}_{50}$ + dose$^{\gamma}$), where dose is the spinal bupivacaine dose in milligrams, dose$_{50}$ is the dose of bupivacaine at which there is a 50% probability of success of the spinal block, and γ is the slope of the response curve and describes the shape of the data distribution. The binary endpoints used for the logistic regression included success (operation) compared with failure (operation), and success (induction) compared with failure (induction). A naïve pooled analysis was performed,

with each subject providing one data point for the fit. ED_{50} and ED_{95} values were estimated using NONMEM® 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. This same methodology was used to determine whether the parameter estimates were different from previously published results. Comparisons between the populations were made of the equations as a whole. The equation was structured on the ED_{50} value and thus better predicts the ED_{50} value. The ED_{95} value was an extrapolation of the curve, and the equation was also parameterized for the ED_{95} value to allow ED_{95} value estimates.

Results

All 42 patients enrolled and randomly assigned completed the study according to the protocol and were included in the analysis. There were 6 parturients randomly allocated to each of the 5-, 6-, 7-, 9-, 10-, and 11-mg bupivacaine groups, 5 patients to the 8-mg bupivacaine group, and 7 patients to the 11-mg group. The unequal numbers in the groups were due to a randomization allocation error. Demographic and baseline obstetric characteristics were similar among treatment groups (table 1). The mean duration of surgery was 61 (56–75) min, with no differences among the groups.

ED50 and ED95

A logistic regression plot was drawn for success (operation) (fig. 1). The 0.5 and 0.95 *y*-intercepts show the ED_{50} and ED_{95} values, respectively. The slope of the curve (γ) for success (operation) was 7.6 (SE, 1.6). Overall anesthetic success (success [operation]) ED_{50} and ED_{95} values (with 95% confidence interval; CI) in this morbidly obese study population were 9.8 (8.6–11.0) and 15 mg (10.0–20.0), respectively (fig. 1). These values compare with calculated ED_{50} and ED_{95} values in nonobese (mean BMI, 29) patients of 7.6 (6.7–8.5) and 11.0 (9.1–12.9), respectively, previ-
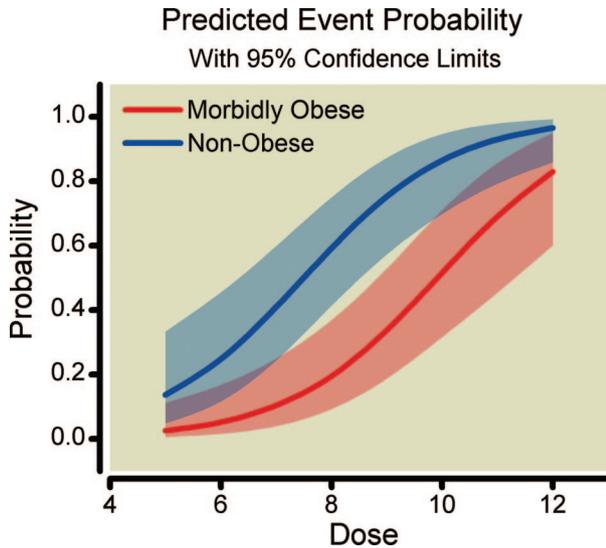
Fig. 1. The success (operation) ED_{50} and ED_{95} values (both with 95% confidence intervals) for hyperbaric intrathecal bupivacaine for cesarean delivery of this study's morbidly obese population and of nonobese patients (from a previous study using similar methodology and study conditions[20]). Values were calculated from a logistic regression plot of probability of successful anesthesia *versus* dose of intrathecal bupivacaine. Probabilities of 0.5 and 0.95 were used to derive the ED_{50} and ED_{95} values, respectively. Success (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.

ously reported by our group using similar methodology and study conditions (fig. 1).[20]

We were unable to measure the success (induction) ED_{50} and ED_{95} values due to too many initial successes and too few 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 success (induction). Success (induction) did not reliably predict overall intraoperative success (success [operation]). The success (induction) and success (operation) at each of intrathecal bupivacaine doses are shown in figure 2. The majority of the failures occurred in the lower dose range (fig. 2). The mean time to failure in cases of failure (operation) was 47 (20–62) min ($P = 0.07$ among groups).

The mean time to T6 sensory block onset to pinprick among the success (induction) group was 8 ± 2 min. We found no correlation between bupivacaine dose and the speed of T6 block onset to pinprick (R = −0.03, $P = 0.856$). There were no differences in pain scores among the groups at skin incision, uterine externalization, delivery, and skin closure. There was an inverse correlation between the dose of bupivacaine and pain on uterine exteriorization (R = −0.44, $P = 0.016$). Overall median (interquartile range) maternal satisfaction with anesthesia was 100 (96–100), with no differences among the doses studied ($P = 0.913$). The mean postanesthetic care unit stay was 74 ± 20 min,
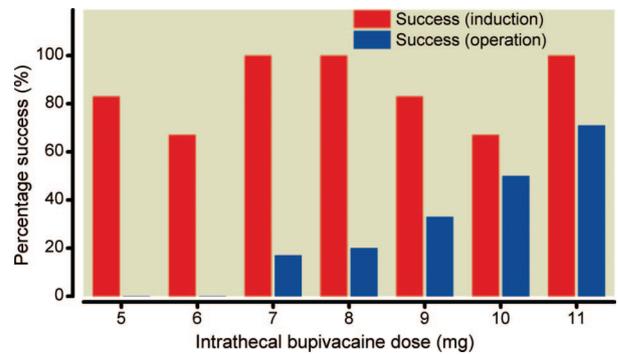
Fig. 2. Initial and overall successful anesthesia at different doses of hyperbaric intrathecal bupivacaine. This bar chart differentiates success (induction) in the red bars (defined as a bilateral T6 sensory level to pinprick within 10 min of intrathecal drug administration) from success (operation) in the blue bars (defined as a successful initial sensory level with no additional epidural anesthetic required during surgery).

with no differences detected among the different bupivacaine dose groups ($P = 0.329$).

Adverse Effects
The changes in MAP after spinal anesthesia, the dose of phenylephrine required to maintain the MAP during surgery, and the occurrence of nausea or vomiting during surgery are summarized in table 2. Eleven of the 42 patients studied (26%) experienced either nausea or vomiting intraoperatively, but no statistically significant dose-dependent differences with incidence of nausea or vomiting were found (table 2; $P > 0.05$).

Discussion

This dose-ranging study suggests that obese and nonobese patients do not respond differently to modest doses of intrathecal bupivacaine. The study quantified the ED_{50} and ED_{95} values for intrathecal hyperbaric bupivacaine (coadministered with intrathecal fentanyl and morphine) in morbidly obese patients undergoing spinal anesthesia for cesarean delivery. A secondary analysis, comparing the ED_{50} and ED_{95} values of this study of morbidly obese patients to a nonobese population previously reported by our group using similar methodology,[20] suggests that intrathecal bupivacaine dose requirements for obese and nonobese women undergoing cesarean delivery are not significantly different. However, the use of a historical control for comparison (*i.e.*, the previous methodologically similar study by our group in nonobese patients) is associated with many known problems and biases. In addition, this secondary analysis only assessed the ED_{50} and ED_{95} values and not the entire dose response, and the power of the study would probably only have detected large differences between the populations. Although these results need to be confirmed in a prospective, controlled study, findings suggests that morbidly obese patients undergoing cesarean delivery with spinal anesthesia with modest

532

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 = 5)	9 mg (n = 6)	10 mg (n = 6)	11 mg (n = 7)
Lowest MAP, mmHg	56 ± 3	56 ± 8	61 ± 11	61 ± 13	61 ± 10	59 ± 12	55 ± 5
Maximal MAP reduction, %	26 ± 9	38 ± 12	28 ± 19	26 ± 17	22 ± 7	30 ± 9	30 ± 6
Phenylephrine requirement, mg	1.0 (0.4–1.6)	1.5 (1.0–1.6)	1 .0 (0.2–2.5)	1.3 (0.6–1.6)	1.2 (0.3–1.4)	0.5 (0.1–2.4)	1.6 (1.5–3.0)
Nausea/ vomiting	2/0	0/0	4/0	0/0	2/0	1/0	2/0

Values are presented as mean ± SD and median (range). Nausea and vomiting presented as incidence (number of patients reporting nausea or vomiting) and was assessed every 15 min throughout surgery. P = not significant among groups.
MAP = mean arterial pressure measured intraoperatively.

doses of bupivacaine have similar, rather than smaller, dose requirements, compared with nonobese patients.

This large local anesthetic dose requirement in a morbidly obese population was an unexpected finding. Possible reasons for this larger than expected dose requirement include more stimulation from the forces necessary to retract adipose tissue and pannus from the surgical field, slower transfer to a supine position after block placement in the sitting position (due to body habitus), which may have affected the cephalad spread of the hyperbaric solutions, longer surgical preparation time, and greater surgical duration.

In contrast to our findings, many reviews suggest a local anesthetic dose reduction for spinal anesthesia in morbidly obese patients due to a potential lower neuraxial local anesthetic requirement.[6–8] Studies that have investigated the relationship between weight and the spread of intrathecal local anesthetics have demonstrated conflicting results.[12–19] Our study does not support an intrathecal dose reduction in morbidly obese patients. Norris *et al.* and Hartwell *et al.* found no effect of weight or BMI on the spread of sensory blockade in women undergoing cesarean delivery.[15,16,22] However, morbidly obese patients were not specifically studied, and fixed doses of hyperbaric bupivacaine were used. A recently published study by Lee *et al.*[23] using a modified up-down sequential allocation method, estimated similar dosing requirements (ED_{95}) for obese (BMI more than 30) and normal-weight patients undergoing cesarean delivery (11.9 mg [95% CI: 11.3–15.6] *vs.* 12.8 mg [95% CI: 10.8 to + infinity], respectively).

Minimizing the dose of intrathecal bupivacaine may reduce the incidence of maternal hypotension, decrease vasopressor requirements, decrease nausea, reduce time to discharge from the postanesthesia care unit, and improve maternal satisfaction.[5,24–26] However, lower intrathecal doses of local anesthetics are also associated with more reports of intraoperative pain, nausea, and late spinal anesthetic failures that sometimes require conversion to general anesthesia.[5,24–26] In the same studies that report these potential advantages outlined above, the incidence of visceral pain

and discomfort using intrathecal bupivacaine doses of 5 and 8 mg was 50[24] and 35%,[25] respectively.

Morbid obesity confers a higher incidence of difficulty with airway management and oxygenation. If neuraxial anesthesia fails, conversion to general anesthesia may be more problematic, compared with a leaner population. The current study suggests caution when using doses less than 10 mg intrathecal bupivacaine. These results are consistent with those previously reported for hyperbaric and hypobaric bupivacaine in nonobese patients using a similar methodology,[20,27] where doses of bupivacaine greater than 10 mg were required for reliable anesthesia. Similarly, Petersen *et al.*[28] 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 71 to 32%, emphasizing the relationship between larger doses and greater patient comfort.

There were few initial failures (spinal block < T6) in the lower dose range, and an initial T6 block to a pinprick sensation did not reliably predict overall success. This is consistent with our group's previous hyperbaric and hypobaric bupivacaine ED_{95} studies performed under the same conditions as described in this current study.[20,27] These studies highlight that T6 block to pinprick may not be adequate to predict intraoperative anesthetic success, and that the touch modality may be preferable, as suggested by Russell *et al.*, especially when low intrathecal doses are used.[29,30] CSE techniques may cause a higher sensory block of the intrathecal component, possibly as a consequence of opening the epidural catheter to atmospheric pressure.[31] Therefore, the ED_{50} and ED_{95} values may be slightly higher if a single-shot spinal technique is used.

In the current study, we used logistic regression to describe the dose-response curve from a linear distribution of seven doses of hyperbaric bupivacaine. The logistic regression technique uses the binary endpoint of success *versus* failure and has been validated elsewhere in the anesthetic literature.[32,33] This methodology was previously used by our group to determine ED_{50} and ED_{95} values for nonobese

patients for cesarean delivery.[20,27] Logistic regression, as used in this study, does, however, have potential weaknesses. The ED_{50} value is generally determined with greater confidence than the ED_{95} because it is measured from the rapidly increasing portion of the dose-response curve, whereas the ED_{95} value is extrapolated from the plateau portion of the curve. The success (operation) ED_{95} value of 15 mg is higher than the upper limit study dose (11 mg) due to mathematical extrapolation of the logistic regression dose curve to the ED_{95} point (fig. 1). It must be emphasized that we *do not* recommend using this extrapolated ED_{95} value as a guide for clinical dosing in morbidly obese patients. We did not administer or evaluate doses more than 11 mg and therefore cannot comment on the safety of this mathematically derived ED_{95} dose. The likelihood of high spinal or severe cardiovascular side effects at this calculated ED_{95} dose are unknown. Although we do not recommend using doses as large as 15 mg in the morbidly obese patients, we would caution against doses less than 10 mg (*i.e.*, doses less than the ED_{95} 95% CI value), if using a single-shot spinal technique.

The ideal dose of intrathecal local anesthetic for cesarean delivery balances the provision of adequate patient comfort while avoiding adverse maternal effects (particularly hypotension, nausea, and respiratory compromise). Increasing the dose of local anesthetic has been found to increase maternal hypotension[24,26,34] and nausea,[24,34] with a resultant reduction in maternal satisfaction.[24] 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 dose (ED_{50} and ED_{95}), but markedly reduces the power for detecting differences in continuous or discrete data.

This study highlights the difficulty of hyperbaric bupivacaine dose prediction in the morbidly obese population undergoing cesarean delivery. Morbidly obese patients appear to have much more variable response to intrathecal dosing, compared with leaner patients. This is reflected by the narrower confidence intervals around the ED_{95} estimates in our previous study using hyperbaric bupivacaine in a leaner patient population.[20] In addition, there were no failures at doses greater than or equal to 10 mg in the study of leaner patients, whereas in the current study, there were intraoperative failures at every dose studied. Population-based ED_{50} and ED_{95} values may not be helpful in individual dose determination, and determining the optimal dose for every patient is impossible due to the large variations in individual response to intrathecal local anesthetics. A CSE, continuous spinal, or epidural technique for morbidly obese patients undergoing cesarean delivery is therefore advantageous. The CSE neuraxial technique allows the adequate surgical anesthesia obtained initially with the spinal technique to be ex-

tended (with additional boluses of local anesthetic *via* the epidural catheter *in situ*). Butwick *et al.*[35] recently reported that a catheter-based neuraxial technique may be optimal in obese patients undergoing cesarean delivery, based on longer intraoperative times and greater requirements for intraoperative analgesia. This study similarly highlights that morbidly obese patient undergoing cesarean delivery are ill-suited for a single-shot technique, and the intrathecal dose should be used as part of a catheter-based technique.

In conclusion, this study suggests that morbidly obese and nonobese patients do not respond differently to modest doses of intrathecal bupivacaine. Findings from this dose-ranging study show that doses less than 10 mg are not to be recommended when using a single-shot spinal technique in morbidly obese patients undergoing cesarean delivery, and that intrathecal bupivacaine dose reduction is not necessary or prudent. We strongly emphasize that we are not recommending that doses as large as 15 mg are administered in morbidly obese patients undergoing cesarean delivery. This dose was a mathematically extrapolated ED_{95} value and was not administered or evaluated for safety in this study. Obese patients appear to have a more variable response to intrathecal dosing than leaner patients and therefore may be better suited to a CSE, epidural, or continuous spinal anesthetic technique. Even if morbidly obese patients need less intrathecal bupivacaine to achieve an initial dermatomal level, their needs for anesthesia may be greater (perhaps because of greater surgical stimulation from retraction of adipose tissue from the surgical field or due to longer surgical preparation and duration). This study highlights that adequate initial sensory levels to pinprick obtained with low doses do not guarantee adequate intraoperative anesthesia, and future studies should evaluate this important outcome (intraoperative anesthetic adequacy) in parallel to the initial sensory level achieved.

References

1. Aiono-Le Tagaloa L, Butwick A, Carvalho B: A survey of anesthetic practice for cesarean delivery. Anesthesiol Res Pract 2009; 510642

2. das Neves JF, Monteiro GA, de Almeida JR, Brun A, Cazarin N, Sant'Anna RS, Duarte ES: Spinal anesthesia for cesarean section: Comparative study between isobaric and hyperbaric bupivacaine associated to morphine. Rev Bras Anestesiol 2003; 53:573–8

3. Richardson MG, Collins HV, Wissler RN: Intrathecal hypobaric *versus* hyperbaric bupivacaine with morphine for cesarean section. Anesth Analg 1998; 87:336–40

4. Russell IF, Holmqvist EL: Subarachnoid analgesia for caesarean section. A double-blind comparison of plain and hyperbaric 05% bupivacaine. Br J Anaesth 1987; 59:347–53

5. Vercauteren MP, Coppejans HC, Hoffmann VL, Saldien V, Adriaensen HA: Small-dose hyperbaric *versus* plain bupivacaine during spinal anesthesia for cesarean section. Anesth Analg 1998; 86:989–93

6. Roofthooft E: Anesthesia for the morbidly obese parturient. Curr Opin Anaesthesiol 2009; 22:341–6

7. Soens MA, Birnbach DJ, Ranasinghe JS, van Zundert A: Obstetric anesthesia for the obese and morbidly obese patient:

An ounce of prevention is worth more than a pound of treatment. Acta Anaesthesiol Scand 2008; 52:6–19

8. Brodsky JB, Lemmens HJ: Regional anesthesia and obesity. Obes Surg 2007; 17:1146–9

9. Hogan QH, Prost R, Kulier A, Taylor ML, Liu S, Mark L: Magnetic resonance imaging of cerebrospinal fluid volume and the influence of body habitus and abdominal pressure. ANESTHESIOLOGY 1996; 84:1341–9

10. Greene NM: Distribution of local anesthetic solutions within the subarachnoid space. Anesth Analg 1985; 64:715–30

11. Reyes M, Pan PH: Very low-dose spinal anesthesia for cesarean section in a morbidly obese preeclamptic patient and its potential implications. Int J Obstet Anesth 2004; 13:99–102

12. Schnider TW, Minto CF, Bruckert H, Mandema JW: Population pharmacodynamic modeling and covariate detection for central neural blockade. ANESTHESIOLOGY 1996; 85:502–12

13. McCulloch WJ, Littlewood DG: Influence of obesity on spinal analgesia with isobaric 0.5% bupivacaine. Br J Anaesth 1986; 58:610–4

14. Taivainen T, Tuominen M, Rosenberg PH: Influence of obesity on the spread of spinal analgesia after injection of plain 0.5% bupivacaine at the L3–4 or L4–5 interspace. Br J Anaesth 1990; 64:542–6

15. Norris MC: Height, weight, and the spread of subarachnoid hyperbaric bupivacaine in the term parturient. Anesth Analg 1988; 67:555–8

16. Norris MC: Patient variables and the subarachnoid spread of hyperbaric bupivacaine in the term parturient. ANESTHESIOLOGY 1990; 72:478–82

17. Pitkanen MT: Body mass and spread of spinal anesthesia with bupivacaine. Anesth Analg 1987; 66:127–31

18. Santos A, Pedersen H, Finster M, Edstrom H: Hyperbaric bupivacaine for spinal anesthesia in cesarean section. Anesth Analg 1984; 63:1009–13

19. Hodgkinson R, Husain FJ: Obesity and the cephalad spread of analgesia following epidural administration of bupivacaine for cesarean section. Anesth Analg 1980; 59:89–92

20. Ginosar Y, Mirikatani E, Drover DR, Cohen SE, Riley ET: ED$_{50}$ and ED$_{95}$ of intrathecal hyperbaric bupivacaine coadministered with opioids for cesarean delivery. ANESTHESIOLOGY 2004; 100:676–82

21. Danelli G, Zangrillo A, Nucera D, Giorgi E, Fanelli G, Senatore R, Casati A: The minimum effective dose of 0.5% hyperbaric spinal bupivacaine for cesarean section. Minerva Anestesiol 2001; 67:573–7

22. Hartwell BL, Aglio LS, Hauch MA, Datta S: Vertebral column length and spread of hyperbaric subarachnoid bupivacaine in the term parturient. Reg Anesth 1991; 16:17–9

23. Lee Y, Balki M, Parkes R, Carvalho JC: Dose requirement of intrathecal bupivacaine for cesarean delivery is similar in obese and normal weight women. Rev Bras Anestesiol 2009; 59:674–83

24. Ben-David B, Miller G, Gavriel R, Gurevitch A: Low-dose bupivacaine-fentanyl spinal anesthesia for cesarean delivery. Reg Anesth Pain Med 2000; 25:235–9

25. Choi DH, Ahn HJ, Kim MH: Bupivacaine-sparing effect of fentanyl in spinal anesthesia for cesarean delivery. Reg Anesth Pain Med 2000; 25:240–5

26. Kang FC, Tsai YC, Chang PJ, Chen TY: Subarachnoid fentanyl with diluted small-dose bupivacaine for cesarean section delivery. Acta Anaesthesiol Sin 1998; 36:207–14

27. Carvalho B, Durbin M, Drover DR, Cohen SE, Ginosar Y, Riley ET: The ED$_{50}$ and ED$_{95}$ of intrathecal isobaric bupivacaine with opioids for cesarean delivery. ANESTHESIOLOGY 2005; 103:606–12

28. Pedersen H, Santos AC, Steinberg ES, Schapiro HM, Harmon TW, Finster M: Incidence of visceral pain during cesarean section: The effect of varying doses of spinal bupivacaine. Anesth Analg 1989; 69:46–9

29. Russell IF: A comparison of cold, pinprick, and touch for assessing the level of spinal block at caesarean section. Int J Obstet Anesth 2004; 13:146–52

30. Russell IF: At caesarean section under regional anaesthesia, it is essential to test sensory block with light touch before allowing surgery to start. Int J Obstet Anesth 2006; 15:294–7

31. Ithnin F, Lim Y, Sia AT, Ocampo CE: Combined spinal epidural causes higher level of block than equivalent single-shot spinal anesthesia in elective cesarean patients. Anesth Analg 2006; 102:577–80

32. Van Hemelrijck J, Muller P, Van Aken H, White PF: Relative potency of eltanolone, propofol, and thiopental for induction of anesthesia. ANESTHESIOLOGY 1994; 80:36–41

33. Dershwitz M, Conant JA, Chang Y, Rosow CE, Connors PM: A randomized, double-blind, dose-response study of ondansetron in the prevention of postoperative nausea and vomiting. J Clin Anesth 1998; 10:314–20

34. Fan SZ, Susetio L, Wang YP, Cheng YJ, Liu CC: Low dose of intrathecal hyperbaric bupivacaine combined with epidural lidocaine for cesarean section—a balance block technique. Anesth Analg 1994; 78:474–7

35. Butwick AJ, Carvalho B, Danials C, Riley ET: Retrospective analysis of anesthetic interventions for obese patients undergoing elective cesarean delivery. J Clin Anesth 2010; 22:519–26