Small dose spinal bupivacaine for Cesarean delivery does not reduce hypotension but accelerates motor recovery

[Une faible dose de bupivacaine intrathécale lors de l'accouchement par césarienne ne réduit pas l'hypotension, mais accélère la récupération motrice]

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Background: Maternal hypotension occurs in 60–94% of Cesarean deliveries with 10–15 mg spinal bupivacaine. Reduced doses of bupivacaine may decrease the incidence of hypotension, nausea, and vasopressor use. The primary objective of this study was to compare 4.5 mg and 12 mg doses of intrathecal bupivacaine on maternal hemodynamics. The secondary objective was to determine if anticipated reductions in side effects were reflected in increased patient satisfaction.

Methods: Following Research Ethics Board approval and informed consent 52 term parturients undergoing elective Cesarean delivery were randomly assigned to isobaric bupivacaine 4.5 mg or hyperbaric bupivacaine 12 mg for spinal anesthesia. All patients received fentanyl 50 µg and morphine 200 µg intrathecally. Intravenous fluid and vasopressor administration were standardized. Maternal hemodynamics, and sensorimotor levels were recorded at regular intervals. Side effects and patient satisfaction were documented.

Results: Median cephalad sensory block was C8 in both groups (NS) but the intensity of motor block was significantly less ($P < 0.001$) and of shorter duration ($P < 0.001$) with bupivacaine 4.5 mg. The proportion of patients requiring ephedrine ($> 70\%$) and the quantities of ephedrine used were similar in both groups (NS). Use of supplemental analgesia, side effects, and measures of patient satisfaction were comparable in both groups.

Discussion: Intrathecal bupivacaine 4.5 and 12 mg yielded similar sensory block and side effects during Cesarean delivery. Patients receiving 4.5 mg did, however, experience significantly less motor blockade of shorter duration.

Contexte : L'hypotension maternelle se rencontre dans 60-94 % des accouchements par césarienne avec 10-15 mg de bupivacaine intrathécale. Des doses réduites de bupivacaine pourraient réduire l'incidence d'hypotension et de nausées, ainsi que l'utilisation de vasopresseurs. L'objectif premier de cette étude était de comparer l'effet de doses intrathécales de bupivacaine de 4,5 mg et 12 mg respectivement sur l'hémodynamie maternelle. Le deuxième objectif était de déterminer si les réductions anticipées d'effets secondaires se reflétaient par une satisfaction accrue des patientes.

Méthode : Le Comité d'éthique de la recherche ayant donné son accord, cinquante-deux parturientes à terme devant subir un accouchement non urgent par césarienne ont été randomisées en deux groupes pour la rachianesthésie : bupivacaine isobare 4,5 mg ou bupivacaine hyperbare 12 mg. Toutes les patientes ont reçu du fentanyl 50 µg et de la morphine 200 µg en intrathécal. L'administration de liquide intraveineux et de vasopresseurs a été standardisée. L'hémodynamie maternelle ainsi que les niveaux sensori-moteurs ont été enregistrés à intervalles réguliers. Les effets secondaires et la satisfaction des patientes ont été documentés.

Résultats : Le bloc sensitif moyen en direction de la tête était situé à C8 dans les deux groupes (NS), mais l'intensité du bloc moteur était significativement plus faible ($P < 0,001$) et d'une durée moindre ($P < 0,001$) avec la bupivacaine 4,5 mg. La proportion de patientes nécessitant de l'éphédrine ($> 70\%$) et les quantités d'éphédrine administrées étaient similaires dans les deux groupes (NS). L'utilisation d'analgesie supplémentaire, les effets secondaires et la satisfaction des patientes étaient comparables dans les deux groupes.

Discussion : Dans le cas d'accouchements par césarienne, les doses de 4,5 mg et 12 mg de bupivacaine intrathécale produisent un bloc sensitif et des effets secondaires similaires. Toutefois, les patientes ayant reçu 4,5 mg ont ressenti un bloc moteur plus faible et plus court, et cette différence était significative.

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CONTEMPORARY anesthesia texts advocate the use of 12 mg doses of hyperbaric bupivacaine for subarachnoid block for Cesarean delivery.^{1,2} Regrettably maternal hypotension occurs in 60–94% of such anesthetics.^{3–5} Fluid preloading⁶ and the prophylactic use of ephedrine⁴ do not consistently prevent maternal hypotension. Maternal hypotension frequently results in nausea and vomiting, which is distressing to the parturient lying supine on the operating table. The extensive motor block may result in severe claustrophobia and panic in susceptible parturients, sometimes requiring induction of general anesthesia.⁷ Dense motor blockade may last two to three hours and delay discharge from the postanesthesia care unit (PACU).

Factors traditionally assumed to be of greatest importance in determining the spread of local anesthetics in subarachnoid block include the baricity of local anesthetic solution, the dose of anesthetic chosen, the volume of injectate, and patient position following injection.⁸ Previous research has explored the influence of baricity and dose in the context of combined spinal-epidural anesthesia for Cesarean delivery. Sarvela *et al.*⁹ demonstrated that 9 mg doses of hyperbaric and isobaric bupivacaine provided similar anesthesia and hemodynamics during Cesarean delivery but > 50% of patients in both groups required vasopressor support. In contrast, Vercauteren *et al.*¹⁰ demonstrated that a 6.6-mg dose of hyperbaric bupivacaine provided superior anesthesia and less hypotension than a similar dose of isobaric bupivacaine. To further complicate the issue, Ben-David *et al.*³ found that when using isobaric bupivacaine reducing the dose from 10 to 5 mg decreased the incidence of hypotension, nausea, and the quantity of vasopressor used however, the interpretation of these findings is obscured by the selective use of intrathecal opioids in the low dose group.

The goal of this study was to maximize differences between traditional and low dose techniques by comparing of hyperbaric bupivacaine 12 mg to isobaric bupivacaine 4.5 mg in the context of a consistent regimen of intrathecal opioids. The doses and solutions were chosen to reflect those readily available to Canadian anesthesiologists. The primary objective of this study was to compare maternal vasopressor use during Cesarean delivery in patients receiving spinal bupivacaine 12 mg and 4.5 mg. The secondary objective was to determine if anticipated reductions in hypotension, nausea, and motor blockade were reflected in increased patient satisfaction.

Methods

Following approval of the Ottawa Hospital Research Ethics Board parturients undergoing elective Cesarean delivery of singleton pregnancy at greater than 36 weeks gestation via a lower segment transverse incision were approached for informed written consent. Eligible patients were between 20 and 40 yr of age and of ASA physical status I–II. Patients with the following characteristics were excluded: known hypersensitivity to any of the study medications; active labour; urgent or emergent deliveries; pre-eclampsia; pregnancy-induced hypertension; cardiac, renal, neurologic or other organ-system disease; < 152 cm or > 174 cm in height; body weight > 100 kg.

A randomization schedule allocating patients to the two study groups in random-permuted blocks of four was created using a computer-generated random numbers table. Allocation to 4.5 and 12 mg groups was concealed using sequentially numbered, opaque envelopes. The randomization sequence remained concealed on a secure, password protected computer until all recruitment was complete. Patients were randomized on the day of delivery. Following randomization an investigator not involved with intra-operative care or measurement opened the envelope and prepared the study syringes. Patients in the small dose group received isobaric bupivacaine 4.5 mg (0.9 mL of 0.5% bupivacaine) while those in the large dose group received hyperbaric bupivacaine 12 mg (1.6 mL of 0.75% bupivacaine in dextrose). Patients in both groups received fentanyl 50 µg (1 mL) and morphine 200 µg (0.4 mL). All drugs for intrathecal injection were diluted with saline 0.9% to a final volume of 3 mL. The syringes were placed on a sterile spinal anesthesia tray in the operating room before the arrival of the patient, anesthesiologist, other study personnel, or operating room staff. The tray was covered with a sterile drape to prevent contamination.

Patients received no premedication other than ranitidine 150 mg *po* with a sip of water two hours before surgery. Demographic data (height, weight, parity, indication for surgery) were recorded. Patients received 500 mL of lactated Ringers' solution before intrathecal injection. Lumbar puncture was performed at the L 2–3 interspace in the sitting position using a 25-G pencil-point spinal needle. Investigators were instructed to inject study medications over three seconds with the orifice of the needle in the cephalad direction. Following spinal injection the parturient was immediately placed in the supine position with left uterine displacement.

Automated, non-invasive blood pressure measurements were taken before injection of study medication,

every minute for 15 min after injection, then every three minutes until the end of surgery. Ephedrine, in 5–10 mg *iv* boluses, was given when systolic blood pressure was < 95 mmHg or when a < 25% decrease was measured compared with baseline (pre-spinal) value. These systolic blood pressure limits define the term hypotension for the purpose of this study. The total amount of ephedrine (mg) used intraoperatively and total volume of lactated Ringer's solution infused were recorded.

The sensory and motor block progression was assessed with a blunt pin-prick and Bromage score respectively. Sensory motor block was assessed 5, 10, 30, 60, 90 min after intrathecal injection, then every 30 min until resolution of the block. Motor block was assessed using the Bromage scale (0–3) and assessments were withheld during surgery. The definitions of this scale are: 0, able to straight leg raise (SLR) and flex both feet and knees; 1, unable to SLR, able to flex knees and feet; 2, unable to SLR or flex knees, able to flex feet; and 3, unable to move legs or feet.

Apgar scores, neonatal weight, and acid-base data from umbilical artery and vein were recorded. All patients received ondansetron 4 mg, dexamethasone 8 mg, and oxytocin at a rate of 3 U·hr⁻¹ after delivery. Patients complaining of discomfort during delivery received fentanyl 1.5 µg·kg⁻¹ (repeated once) then ketamine 0.2 mg·kg⁻¹ *iv*. The incidence and timing of nausea, vomiting or discomfort were recorded.

Satisfaction with intraoperative anesthesia for Cesarean delivery was recorded on arrival in the PACU using a visual analogue scale (VASS) with “very dissatisfied” at 0 cm and “very satisfied” at 10 cm. Those patients having had a previous Cesarean delivery were asked if they preferred their present or their previous anesthetic technique. Surgeons were asked to grade operating conditions as “very good,” “good,” or “poor.”

On postoperative day one, two, and three patients were asked to assess the quality of their recovery using the quality of recovery (QoR) score.¹¹ The QoR poses nine questions about quality of recovery and scores each response 0, 1, or 2. Possible results of the QoR range from 0 to 18 with higher scores representing better recovery. At the same intervals patients completed the visual analogue scale (VASR) with “poor recovery” at 0 cm and “excellent recovery” at 10 cm.

Frequency of hypotension, nausea, vomiting, intraoperative discomfort, and preference for present technique among those undergoing repeat Cesarean delivery were assessed using the Chi-square statistic. Peak sensory dermatomal levels and Bromage scores were compared with the Wilcoxon rank sum test. The

TABLE I Demographic data

	4.5 mg Bupivacaine	12 mg Bupivacaine	<i>P</i> value
Number	27	25	
Age (yr)	32.3 ± 4.1	31.9 ± 6.0	NS
Weight (kg)	78.2 ± 8.3	83.0 ± 10.8	NS
Parity			
Nullipara (<i>n</i>)	3	9	
Primipara (<i>n</i>)	18	9	NS
Multipara (<i>n</i>)	6	7	
Previous Cesarean delivery (<i>n</i>)	22	14	0.047
Baseline systolic blood pressure (mmHg)	127 ± 12	133 ± 14	NS
Fluid preload (mL)	585 ± 190	524 ± 72	NS
Uterus exteriorized (<i>n</i>)	5	2	NS
Duration of surgery (min)	40 ± 9	38 ± 15	NS
Duration of anesthesia (min)	54 ± 10	53 ± 16	NS

Results expressed as mean ± SD when applicable. NS = not statistically significant.

VASS, VASR and QoR scores were compared at individual time points with unpaired *t* tests. Hemodynamic variables were compared using repeated measures analysis of variance (ANOVA). Statistically significant differences were assumed if *P* < 0.05.

Sample size calculation was based on the results of a previous trial comparing high and low dose spinal anesthesia in Cesarean delivery.³ All calculations assumed a two-tailed alpha error of 5% and 80% power. A trial of only eight patients per group was required to confirm the reduction in the risk of hypotension reported by Ben-David (94% in 10 mg group *vs* 31% in the 5 mg group).³ The risk of hypotension reported in the high dose group far exceeded our clinical experience and the baseline risk of hypotension reported in a systematic review of Cesarean anesthesia.⁴ Using the control rate of hypotension reported in the systematic review (69%) a trial of 26 patients per group was required to confirm the rate of hypotension reported in Ben-David's low dose group (31%).

Results

A total of 55 women were recruited. Two women were withdrawn after randomization when their surgery was postponed and a third was excluded for hypertension. The remaining 52 women completed the study protocol. The demographic characteristics of those completing the study are shown in Table I.

Cord pH at the time of delivery was 7.23 ± 0.08 and 7.26 ± 0.08 in the 4.5 and 12 mg groups, respectively (NS). No infant had a cord pH of less than 7.00 at delivery. Apgar scores at one minute were 8.5 ± 1.2

FIGURE Systolic blood pressure versus time following spinal anesthesia. Data presented are means and SD. Systolic blood pressure decreased significantly with time ($P < 0.001$) using repeated measures analysis of variance, but there was no significant difference between groups ($P = 0.390$).

and 8.3 ± 1.6 in the 4.5 and 12 mg groups, respectively (NS). Similarly, Apgar scores at five minutes were 9.1 ± 0.3 and 9.0 ± 0.0 in the 4.5 and 12 mg groups (NS). Two neonates, one in each group, with a one minute Apgar less than 6 scored 9 at five minutes. No child had an Apgar of less than 9 at five minutes and none required resuscitation.

There was no difference in any of hemodynamic variables between dose groups (ANOVA: NS). Systolic arterial pressure is depicted graphically in the Figure. Hypotension requiring treatment was present in 20 of 27 patients in the bupivacaine 4.5 mg group and 19 of 25 patients in the bupivacaine 12 mg group (NS). Quantities of ephedrine (12.8 ± 12.5 mg *vs* 11.8 ± 12.1 mg, NS) and total intravenous fluids (1573 ± 285 mL *vs* 1678 ± 521 mL, NS) administered were similar in the 4.5 and 12 mg dose groups, respectively.

Characteristics of the motor and sensory blocks observed are summarized in Table II. All patients in both groups had sensory blocks above the sixth thoracic dermatome within five minutes of induction. Use of supplemental analgesia in both groups was not significantly different (five of 27 in the 4.5 mg group *vs* one of 25 in the 12 mg group dose, NS). One patient in the low dose group required a single dose of ketamine 10 mg following fentanyl 150 µg *iv* in two divided doses to resolve intraoperative discomfort. All other complaints of inadequate analgesia were resolved with fentanyl < 100 µg *iv*. No patient

TABLE II Characteristics of motor and sensory blocks

	4.5 mg Bupivacaine	12 mg Bupivacaine	P value
Maximum cephalad sensory level	C8 (C6, T2)	C8 (C6, T1)	NS
Time to maximum cephalad sensory level (min)	12.6 ± 9.4	19.2 ± 17.4	NS
Time for two segment regression of sensory level (min)	46.3 ± 23.9	58.4 ± 26.7	NS
Maximum Bromage score (0-3)	0 (0,1)	3 (3,3)	< 0.001
Time to maximum Bromage score (min)	5.4 ± 1.3	17.4 ± 21.8	0.006
Time to recovery to Bromage score = 1 (min)	32.0 ± 33.2	158.6 ± 44.9	< 0.001

Ordinal data expressed as median (interquartile range).

Continuous data expressed as mean $\pm$ SD. NS = not statistically significant.

TABLE III Patient satisfaction and quality of recovery

	4.5 mg Bupivacaine	12 mg Bupivacaine	P value
Intraoperative satisfaction VAS (0-10)	9.0 ± 1.2	9.0 ± 1.3	NS
Postoperative recovery VASR (0-10)			
Postoperative day 1	8.2 ± 1.5	7.8 ± 1.3	NS
Postoperative day 2	8.3 ± 1.5	7.9 ± 1.7	NS
Postoperative day 3	8.6 ± 1.9	7.9 ± 1.5	NS
Quality of recovery score (0-18)			
Postoperative day 1	15.1 ± 2.0	14.8 ± 2.6	NS
Postoperative day 2	16.0 ± 1.4	16.0 ± 2.7	NS
Postoperative day 3	16.5 ± 2.6	16.1 ± 2.5	NS
Previous Cesarean delivery (n)	22	14	
Preferred current technique	13 (59 %)	11 (79 %)	NS
No preference	7 (32 %)	3 (21 %)	
Preferred previous technique	2 (9 %)	0 (0 %)	

Results expressed as mean $\pm$ SD and number (%). VASR = visual analogue scale recovery, 10 cm scale; Maximum score on the quality of recovery score is 18. NS = not statistically significant.

required conversion to general anesthesia. The depth of motor block and the time required for resolution of the motor block were significantly less in the 4.5 mg group (Table II). The less intense and shorter motor block observed in the 4.5 mg group permitted 26 of 27 patients to transfer themselves to the stretcher at the end of surgery; in contrast, only one of 25 patients in the 12 mg group could transfer unassisted ($P < 0.001$). Surgeons described operating conditions

as very good in 24 of 27 cases in the 4.5 mg group and 24 of 25 in the 12 mg group (NS). No surgeon graded operating conditions as poor.

Side effects were common in both groups. Despite antiemetic prophylaxis, nausea and/or vomiting occurred in nine of 27 patients in the 4.5 mg group compared with ten of 25 patients receiving 12 mg (NS). Similarly, pruritus was noted in 24 of 27 and 20 of 25 patients in the 4.5 mg and 12 mg groups, respectively (NS).

Patient satisfaction and QoR scores are summarized in Table III. Satisfaction with intraoperative anesthesia was high in both groups. Patient assessment of recovery by VASR and QoR scores was similarly high in both 4.5 and 12 mg dose groups on postoperative days one, two and three. Correlations between VASR and QoR scores at similar times were statistically significant ($P < 0.001$ at each assessment) suggesting convergent validity between these measures of recovery. Among women who had previously had a Cesarean delivery only two preferred their previous anesthetic to that received in the present study.

Discussion

The primary results of this study suggest that decreasing the bupivacaine dose from 12 mg to 4.5 mg does not lead to reductions in hypotension and vasopressor use during Cesarean section. The 4.5 mg dose, in combination with fentanyl and morphine, provided intraoperative analgesia, operating conditions, and side effect profile comparable to a 12 mg dose. Low dose spinal anesthesia resulted in a motor block that was significantly less dense and of shorter duration, but did not influence patient satisfaction or quality of recovery.

Contrary to the results of the present study, Ben-David *et al.*³ demonstrated a threefold decrease in the incidence of hypotension and a nearly tenfold reduction in the amounts of ephedrine required in those patients receiving lower dose spinal anesthetics. Both studies employed similar fluid preloading strategies, definitions of hypotension and indications for vasopressor use. The only significant difference in the trials was noted in the median height of spinal block noted in the low dose groups. Patients in the 4.5 mg group in the present study were noted to have blocks several dermatomes higher than those in either group of the Ben-David study. The broader spread of sensory anesthesia and sympathetic blockade might account for the minimal influence of dose on hemodynamic outcomes noted presently.

Factors influencing distribution of sensory and block during spinal anesthesia include baricity, rate

of injection and volume of injection of the solutions employed. The baricity of the low dose solutions used in the present study¹² was less than that of the cerebrospinal fluid of term parturients¹³ and would be comparable to those used in previous research.³ Horlocker *et al.*¹⁴ noted that an injection rate of 0.5 mL·sec⁻¹ (equivalent to six seconds for the present study) yielded blocks approximately four dermatomes higher than when a similar dose was injected at 0.02 mL·sec⁻¹ (equivalent to 150 sec). Similarly, the findings from an *in vitro* model of hypobaric spinal anesthesia demonstrate that injection rates ranging from 0.1 to 0.6 mL·sec⁻¹ resulted in a wider distribution of drug ten minutes following the more rapid injection. These findings have not been replicated in other studies^{15,16} but suggest that the relatively fast injection (1 mL·sec⁻¹) employed in our study, compared with the 0.2 mL·sec⁻¹ rate of injection used by Ben-David *et al.*³ may have contributed to the rapid onset of block. Finally the influence of volume of injectate has been evaluated in a clinical trial comparing 2, 5, and 10 mL injections of a similar milligram dose of bupivacaine. Cephalad spread was greater in those receiving 10 mL but subjects given 2 mL and 5 mL behaved similarly.¹⁷ In this context, the volume of the solution used in the present study (3 mL) was not significantly different from the previous trial (2 mL).³ The extensive cephalad spread of anesthesia in both high and low dose groups described in our study may have obscured correlation between lower doses of bupivacaine and decreased maternal hypotension noted in previous research. These findings may be attributable to the faster rate of injection and slightly larger volume of injectate employed.

Patient and surgeon satisfaction with 4.5 mg bupivacaine anesthesia was comparable to that noted with 12 mg doses. Supplementation with parenteral opioid occurred in fewer than 20% of subjects and no patient required general anesthesia. These results conflict to some degree with Carvalho *et al.*'s¹⁸ finding that 7.25 mg is the dose required to provide effective operative analgesia in 50% of subjects while 13 mg is required to for effective analgesia in 95% of subjects. Onset times, cephalad extension of block, and hemodynamic endpoints were not clinically different in the present study and in Carvalho *et al.*'s patients, but anesthesia was successful at much lower doses in the present study. The divergence of outcomes may be explained by the present use of much a larger dose of intrathecal fentanyl.

Intrathecal fentanyl doses ranging from 2.5–60 µg were reported in a systematic review of intrathecal opioids for Cesarean delivery.¹⁹ The findings of this

review suggest that intrathecal fentanyl in doses less than 35 µg was associated with a 50% relative reduction in pruritus (34 vs 68%) with comparable rates of nausea and vomiting when compared to doses 40–60 µg. It is important to note that requests for supplemental analgesia were significantly reduced only in those patients receiving 40 µg doses or greater. As our study explored doses of bupivacaine well below those reported in the literature we chose a dose of fentanyl (50 µg) most likely to provide adequate analgesia.

Lower doses of fentanyl might have reduced the relatively high incidence of pruritus (85%) and nausea (37%) reported here. The concomitant use of intrathecal morphine for postoperative analgesia may, however, be responsible for some of the side effects noted. Systematic review¹⁹ identified pruritus resulted in over 50% of subjects receiving intrathecal morphine 100 µg or more and nausea in 35% of those receiving the dose described in the present study. The QoR scores reported six hours postoperatively were similar to those noted following minor surgery¹¹ suggesting opioid-related side effects did not significantly impair recovery.

Readers may question whether a low dose bupivacaine would work in their practice. We placed no limitations on our surgeon's practice in this study and made no attempt to alter the pace of their work. The uterus was exteriorized in approximately one fifth of subjects and "skin-to-skin" times of up to one hour in duration were recorded in those patients allocated to the 4.5 mg group. A trend toward increased use of supplemental analgesia was noted in the low dose group. Post-hoc power analysis suggest that our study had only 38% power to confirm this trend and that a threefold increase in sample size would be required to document this finding with 80% power. It is important to note that among patients who had previously undergone Cesarean delivery a majority preferred the technique employed in this study.

In summary, the results of this study suggest that 4.5 and 12 mg doses of bupivacaine administered with of fentanyl 50 µg and morphine 200 µg intrathecally provide similar anesthesia for Cesarean delivery. The lower dose was associated with neither a reduced incidence of hypotension nor a decrease in vasopressor use, most likely because of the rapid extension of the sensory block to the lower cervical dermatomes in both dose groups. Marked reduction in depth and duration of motor block were apparent in the lower dose group but did not influence patient satisfaction or quality of recovery. Future research is required to determine the dose of intrathecal fentanyl required to provide an adequate compromise between intraoperative analgesia and side effects.

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