

Spinal Ropivacaine for Cesarean Section

A Dose-finding Study

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Background: The dose-response relation for spinal ropivacaine is undetermined, and there are few data available for obstetric patients.

Methods: In a prospective, randomized, double-blind investigation, the authors studied 72 patients undergoing elective cesarean delivery. An epidural catheter was placed at the L2-L3 vertebral interspace. Lumbar puncture was then performed at the L3-L4 vertebral interspace, and patients were randomized to receive a dose of spinal ropivacaine diluted to 3 ml with normal saline: 10 mg (n = 12), 15 mg (n = 20), 20 mg (n = 20), or 25 mg (n = 20). Sensory changes assessed by ice and pin prick and motor changes assessed by modified Bromage score were recorded at timed intervals. A dose was considered effective if an upper sensory level to pin prick of T7 or above was achieved and epidural supplementation was not required intraoperatively.

Results: Anesthesia was successful in 8.3, 45, 70, and 90% of the 10-, 15-, 20-, and 25-mg groups, respectively. A sigmoid dose-response curve and a probit log dose-response plot were obtained, and the authors determined the ED₅₀ (95% confidence interval) to be 16.7 (14.1-18.8) mg and the ED₉₅ (95% confidence interval) to be 26.8 (23.6-34.1) mg. Duration of sensory and motor block and degree of motor block, but not onset of anesthesia, were positively related to dose.

Conclusions: The ED₅₀ and estimated ED₉₅ for spinal ropivacaine were 16.7 and 26.8 mg, respectively. Ropivacaine is a suitable agent for spinal anesthesia for cesarean delivery.

ROPIVACAINE is a recently introduced amino amide class of local anesthetic with structural and pharmacodynamic similarity to bupivacaine.¹ Several recent reports have described the use of ropivacaine for spinal anesthesia.²⁻⁶ Doses used in clinical studies have ranged from 8 to 22.5 mg, and it has been suggested that ropivacaine is less potent than bupivacaine.^{2,3,6} However, the optimum dosage regimen for spinal ropivacaine has not been determined. Furthermore, few data are available on dose requirements of spinal ropivacaine in obstetric patients; data from nonobstetric patients cannot be directly extrapolated to obstetrics because of lower dose requirements.⁷ Because the optimal dose of spinal ropivacaine in obstetric patients is unknown, we have designed this randomized double-blind study to

determine the dose-response of spinal ropivacaine for elective cesarean delivery.

Methods

This study received approval from the Clinical Research Ethics Committee of the Chinese University of Hong Kong (Hong Kong, China), and all patients gave informed written consent. We planned to enroll 80 patients with American Society of Anesthesiologists physical status I or II who were scheduled to undergo cesarean delivery at term during regional anesthesia. Patients with multiple pregnancies, suspected fetal abnormality, or complicated pregnancies were excluded. All patients received premedication of 150 mg ranitidine orally the night before and on the morning of surgery. Sodium citrate, 30 ml orally, was administered at the time of arrival to the operating room. Patients had standard monitoring, including continuous electrocardiography, pulse oximetry, and noninvasive measurement of arterial blood pressure, cycled at 1-min intervals. Intravenous access was secured in the nondominant forearm during local anesthesia, and intravenous preload of 20 ml/kg lactated Ringer's solution was administered over approximately 15 min.

Before the commencement of anesthesia, patients were instructed on the method of sensory and motor assessments, and baseline measurements were performed. Sensory changes were recorded bilaterally along the midclavicular line by assessing changes in pin-prick sensation using a safety pin protruding 2 mm through a guard, and changes in temperature sensation were assessed using frozen plastic ampules of water. Motor block in the lower limbs was graded according to the modified Bromage scale⁸ (0 = able to lift extended leg at the hip; 1 = able to flex the knee but not lift extended leg; 2 = able to move the foot only; 3 = unable to move even the foot).

A combined spinal and epidural technique was used with the patient in the right lateral position. After skin disinfection and infiltration with 1% ropivacaine, the epidural space was located at the L2-L3 lumbar vertebral interspace using a 16-gauge Tuohy needle, and an epidural catheter was inserted 2-3 cm and secured aseptically. The catheter was gently aspirated and checked for the presence of blood or cerebrospinal fluid, but no test dose was administered. Midline lumbar puncture was then performed at the L3-L4 interspace, using a 25-gauge Whitacre needle oriented with the orifice facing

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Received from the Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong, China. Submitted for publication February 22, 2001. Accepted for publication July 19, 2001. Supported by the Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong. Presented in part at the 11th Association of South East Asian Nations Congress of Anaesthesiologists, Kuala Lumpur, Malaysia, July 7-11, 1999.

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cephalad. Insertion was aided with an 18-gauge introducer needle. Patients were randomly allocated by drawing coded shuffled opaque envelopes to receive one of four doses of spinal ropivacaine: 10, 15, 20, or 25 mg. To facilitate blinding, all doses were diluted to 3.0 ml with normal saline and were prepared by an investigator not involved with subsequent patient assessments. After confirming free flow of cerebrospinal fluid, spinal solutions were injected over approximately 60 s.

Immediately after spinal injection, patients were turned supine with left lateral tilt. Sensory and motor assessments were performed at 1 min, 2.5 min, and subsequently at 2.5-min intervals for the first 30 min. Thereafter, the blocks were assessed at 15-min intervals until complete recovery of motor function and sensation at the S2 dermatome.

After 30 min, surgery was allowed to commence if the upper dermatomal level of loss of discrimination to pin prick was at or above T7. Otherwise, the epidural catheter was topped up using 2% alkalized lidocaine with 1:200,000 epinephrine and 75–100 μ g fentanyl administered in incremental doses until satisfactory dermatomal anesthesia was obtained. Patients who reported intraoperative pain with moderate to severe discomfort were treated with an intravenous bolus dose of 10 mg ketamine, which was repeated if pain was unrelieved after 5 min. If pain remained intolerable, with a score of 7 or greater on a 10-point numerical score (0 = no pain and 10 = most severe pain) after the second dose of ketamine, the epidural was topped up. For patients requiring epidural top-up, the spinal anesthesia was classified as a failure, but data for the onset of spinal anesthesia before epidural top-up were included for analysis.

Hypotension, defined by a decrease in systolic arterial pressure to less than 100 mmHg or less than 80% from baseline,⁹ was treated with intravenous boluses of 9 mg ephedrine as required. Nausea and vomiting were treated with 10 mg intravenous metoclopramide, after hypotension had been excluded.

Times of skin incision, uterine incision, delivery, and completion of surgery were recorded. After delivery, Apgar scores were assessed at 1 and 5 min by the attending pediatrician, and arterial and venous blood samples were taken from a double-clamped segment of umbilical cord for immediate blood gas analysis using a Ciba-Coring 278 Blood Gas System (Ciba-Corning, Medfield, MA) blood gas analyzer.

Postoperative analgesia was provided *via* patient-controlled analgesia (PCA) using a Graseby 9300 (Graseby Medical Ltd., Watford, Herts, United Kingdom). The PCA device was set to deliver a morphine bolus of 1.5 mg with a lockout time of 5 min and a maximum 4-h limit of 30 mg. The time of first PCA demand was subsequently recorded from the electronic memory of the PCA device. All patients had routine follow-up by an anesthesiologist on the day after surgery and an assessment by a research

nurse 24 h postoperatively, with instructions to report the occurrence of complications, such as residual neurologic symptoms or back pain.

For assessment of the onset of anesthesia, the time for sensory block to develop to T10, T7, and maximum block height and the time to achieve each increment of Bromage score were compared. To assess the duration of the sensory block, the two-segment regression time from the maximum block height and time for regression to L1 and S1 were compared. Duration of motor block was assessed by comparison of time to each decrement of Bromage score.

Statistical Analysis

Results are presented as mean and SD or median and range where appropriate. Measurements from the right and left sides were averaged, and statistical comparisons were performed using analysis of variance with *post hoc* analysis using the Tamhane T2 test.¹⁰ We used the two-tailed two proportions test to compare patients with complete motor block in the two asymmetric groups, and we used linear regression and chi-square test for trend to determine the dose-response relation of motor block. Analyses were performed using SPSS version 10.0 (Chicago, IL) and PASS version 6.0 (Kaysville, UT). $P < 0.05$ was considered significant.

The dose-response relation for spinal ropivacaine was determined using probit analysis. An *effective dose* (success) was defined as a dose that provided adequate sensory dermatomal anesthesia to pin prick to T7 or higher and required no epidural top-up for surgery to be completed. Data for successful responses for each dosage category were used to plot a sigmoid dose-response curve and a probit log dose-response relation. Probit regression was performed, the coefficients were estimated using the maximum likelihood estimation, and interpolation was used to obtain the ED₅₀, ED₉₀, and ED₉₅. For positive findings, we used linear regression to determine the dose-response relation, and we used non-linear regression iterative methodology to simulate a dose-response sigmoid curve.

Results

Seventy-two patients completed the study. Recruitment to the 10-mg group was stopped after 12 patients when interim analysis of the first 40 cases showed an unacceptably high failure rate of 11 of 12 cases (92%). The investigator was unable to locate the subarachnoid space in one patient, and epidural anesthesia was used instead. This patient was excluded, and the randomization repeated for recruitment of another patient as a replacement.

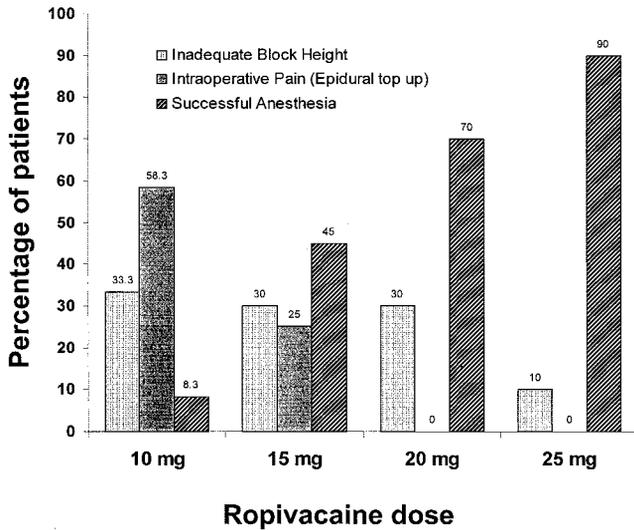


Fig. 1. Anesthetic outcome for all patients.

Demographic data were similar between the respective 10-, 15-, 20-, and 25-mg groups for age, weight, and height. Surgical durations were similar, ranging from 29 to 80 min, and there were no differences in the 1- and 5-min Apgar scores and parameters of umbilical cord gases.

The outcomes of anesthesia are summarized in figure 1. In 18 patients (25%), the upper dermatomal level of sensory anesthesia to pin prick was below T7, and the epidural was topped up before starting surgery. Twelve patients (17%) experienced intraoperative pain that was not relieved by intravenous boluses of ketamine, and these patients required epidural supplementation. In these 12 patients, median (range) upper dermatomal segment before the commencement of surgery was T3 (T2-T7) to pin prick and T2 (C7-T4) to ice, and pain was felt 24 (± 9) min after the commencement of surgery. Of note, only four of these patient patients (33%) had complete motor block (Bromage score of 3), compared with

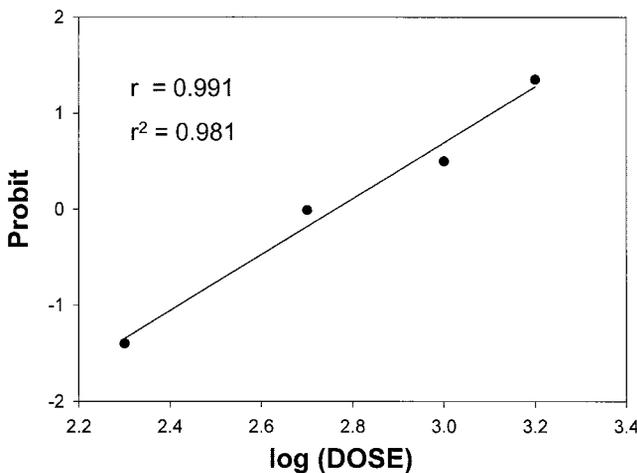


Fig. 2. Linear regression plot of the probit value against the log (dose).

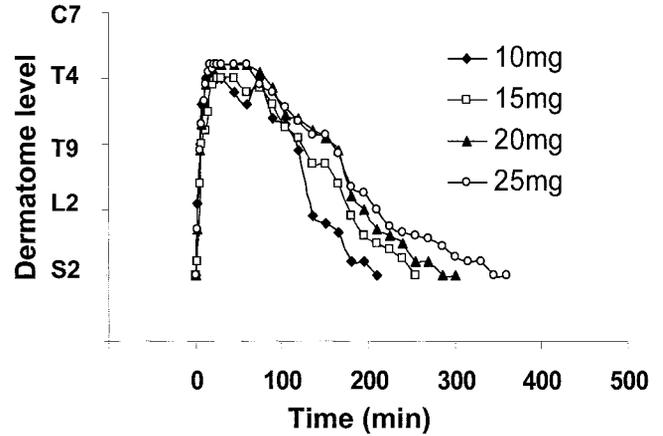


Fig. 3. Time course of dermatomal anesthesia (median) to pin prick.

41 (98%) patients with successful anesthesia ($P = 0.00003$ [< 0.05 critical region]).

Overall, 42 patients (58%) successfully completed their surgery solely during spinal anesthesia. According to our definition, spinal anesthesia was effective in 8.3, 45, 70, and 90% of the 10-, 15-, 20-, and 25-mg groups, respectively. Using probit analysis, the dose-response curve from these data was plotted, and linear regression analysis of the log (dose) response (fig. 2) showed a regression coefficient (r) of 0.991 ($P < 0.01$) and a coefficient of determination (r^2) of 0.981. Based on these results, we determined the ED_{50} (95% confidence interval [CI]) to be 16.7 (14.1-18.7) mg and the ED_{90} (95% CI) to be 24.5 (21.9-30.3) mg. By extrapolation, the ED_{95} (95% CI) for spinal ropivacaine was estimated to be 26.8 (23.6-34.1) mg. Using nonlinear regression iterative method, we were able to simulate a dose-response sigmoid curve with an r^2 of 0.993.

Block characteristics are illustrated in figures 3-5. There were no incidences of unilateral sensory block. The rate of onset of sensory anesthesia and motor block

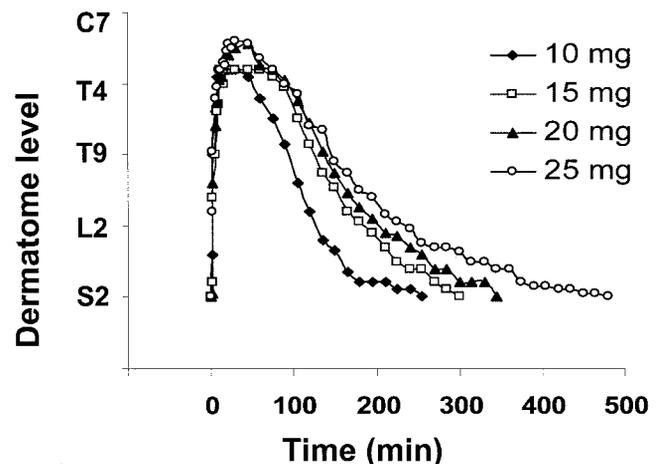


Fig. 4. Time course of dermatomal anesthesia (median) to ice.

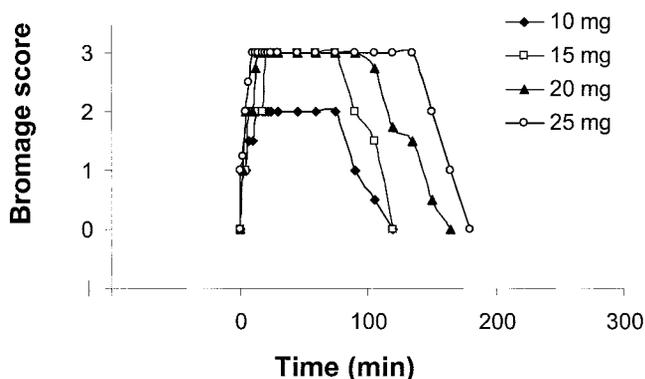


Fig. 5. Plot of Bromage score (median) against time.

were similar among groups as evidenced by similar times to development of sensory changes at T10, T4, and the highest level of sensory block. The median [range] maximum block height was similar among the 10-, 15-, 20-, and 25-mg groups, respectively, for ice (T3 [T9-C7], T2 [T8-C2], T1 [T8-C2], C8 [T3-C2]) and for pin prick (T5 [T12-T2], T3 [T11-C7], T3 [T11-C2] and T3 [T8-C2]).

Onset of sensory anesthesia to ice was faster than to pin prick, and the upper level of sensory anesthesia to ice was also higher than to pin prick ($P < 0.001$). There was no difference among groups in the onset times for each grade of motor block to develop. However, with increasing dose, the proportion of patients with complete motor block increased ($r = 0.894$, linear $\chi^2_3 = 27.28$, $P < 0.001$), and the times for motor blockade to recede at each grade were greater ($P < 0.005$; table 1). Weighted for each milligram dose of ropivacaine, we estimated that the average dose-response increases (95% CI) in the number of subjects for effective (successful) anesthesia and motor block were 5.3 (3.4-7.1)% and 5.4 (3.8-7.1)%, respectively.

The times for two dermatomal regression of upper sensory segments to both ice and pin prick were similar among groups. However, the duration of sensory anesthesia to both ice and pin prick at L1 and S1 was greater with increasing dose ($P < 0.01$). The time to first PCA demand was also greater with increasing dose ($P < 0.05$).

The incidence of hypotension, consumption of ephedrine, and episodes of nausea and vomiting were similar among groups. One patient had post-dural puncture headache on the first day after surgery; her symptoms resolved after conservative treatment with oral analgesics. No patient had residual neurologic changes or back pain when examined 24 h after operation.

Discussion

In this study, we have shown a dose-dependent relation between the duration of sensory analgesia, the extent and duration of motor block, and the success rate of spinal anesthesia for cesarean delivery. The rate of onset of analgesia and motor blockade and the number of segments blocked were not influenced by the dosage.

The primary aim of this study was to determine an effective dose of spinal ropivacaine for cesarean delivery. Using probit analysis, we determined the ED₅₀ (95% CI) to be 16.7 (14.1-18.7) mg and the ED₉₅ (95% CI) to be 26.8 (23.6-34.1) mg. However, it should be noted that our value for ED₉₅ is slightly above the range of doses we tested and was obtained by extrapolation; therefore, some caution should be exercised when interpreting the upper confidence limit because this is well above the range of doses tested.

Previously, ropivacaine has been regarded as equipotent to bupivacaine. However, this assumption has been

Table 1. Recovery Characteristics of Sensory and Motor Block

	10 mg (n = 12)	15 mg (n = 20)	20 mg (n = 20)	25 mg (n = 20)	P Value
Recovery (ice) to L1 dermatome (min)	120	165 (135-233)	183 (105-225)	206 (143-248)	<0.01
Recovery (ice) to S1 dermatome (min)	180	270 (180-345)	293 (185-390)	330 (210-473)	<0.01
Recovery (pinprick) to L1 dermatome (min)	135	173 (120-240)	180 (112-240)	199 (150-278)	<0.01
Recovery (pinprick) to S1 dermatome (min)	172	250 (187-270)	263 (120-330)	293 (195-420)	<0.01
Recovery to Bromage score 2 (min)	NA	90 (45-150)	113 (23-135)	150 (83-210)	<0.001
Recovery to Bromage score 1 (min)	75	90 (90-210)	131 (45-158)	165 (105-240)	<0.001
Recovery to Bromage score 0 (min)	120	120 (90-240)	150 (75-195)	180 (120-270)	<0.005
No. of patients with complete block (%)	0 (0)	15 (75)	15 (75)	20 (100)	<0.001
Time to first analgesic request (min)	77	128 (40)	160 (54)	183 (36)	<0.05

All times are measured from the time of completion of spinal injection. Values are presented as median (range), mean (SD), or number (%).

challenged recently.^{2,3,6,11} For comparison, we are unaware of dose-finding studies of spinal bupivacaine for cesarean delivery that have used methodology similar to ours. However, most commonly, doses in the range of 10–15 mg are recommended.^{12,13} Therefore, our results are in broad agreement with previous suggestions that spinal ropivacaine is significantly less potent than spinal bupivacaine.^{2,3,6} Although our results suggest that this difference in potency may be quite large, accurate quantification would require a separate study using direct comparison.

Interestingly, we found no difference in the maximum height of sensory block, despite a difference in success rates among groups. For cesarean delivery, it has been proposed that to achieve optimum conditions for surgery, one should aim to achieve an upper level of sensory anesthesia of T4.^{14,15} However, in our study, all 12 patients in whom spinal anesthesia failed because of intraoperative pain had an upper sensory level assessed by ice above T4, and 10 patients had an upper sensory level assessed by pin prick above T4. Of these patients, the proportion with complete motor block was significantly smaller compared with patients who had successful anesthesia. This implies that as well as spread, the quality or density of the block is important, and our results suggest that this is related to dosage. Our results would also support the practice of adding an opioid to the local anesthetic, which may reduce intraoperative pain that occurs with small doses of local anesthetic despite apparently adequate spread of sensory anesthesia.¹⁶

We diluted all of our doses to 3 ml with normal saline to facilitate blinding. Previous studies using bupivacaine have shown that volume is not an important determinant of local anesthetic spread.^{17,18} We found no differences in the rate of onset of sensory and motor anesthesia among groups, which is in accordance with previous reports using both plain and hyperbaric spinal ropivacaine that indicate that onset is not dose dependent.^{2–5} However, we found that increasing the dose of spinal ropivacaine prolonged the duration of motor and sensory analgesia as evidenced by greater time for block regression and greater time to first analgesic requirement.

With increasing dosage of ropivacaine, the proportion of patients developing full motor block increased, and this trend is similar to other published findings.^{2–5} Incomplete motor block (low Bromage scores) was associated with failed spinal anesthesia. This suggests that assessment of motor block is an important part of assessing adequacy of spinal anesthesia as well as the height of sensory anesthesia.

We did not record any postoperative neurologic symptoms in any of our patients at 24 h after administration of spinal ropivacaine. Together with other published re-

ports, this suggests that ropivacaine is a suitable alternative spinal anesthetic, provided that a higher dose is used to compensate for its lower potency. It should however be cautioned that the available data regarding neurotoxicity of spinal ropivacaine are still sparse.

In conclusion, we have found that ropivacaine is a suitable agent for spinal anesthesia for cesarean delivery. When used for this purpose, we calculated the ED₅₀ of spinal ropivacaine to be 16.7 mg and the ED₉₅ to be 26.8 mg. Adequacy of spinal anesthesia was related to dose and to the degree of motor block but was poorly correlated with upper level of sensory changes assessed by ice and pin prick.

The authors thank the staff of the Labour Ward (Prince of Wales Hospital, Hong Kong, China) for their cooperation, and Anna Lee, M.P.H., Ph.D. (Assistant Professor, Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong, China), for her statistical advice.

References

1. Akerman B, Hellberg IB, Trossvik C: Primary evaluation of the local anaesthetic properties of the amino amide agent ropivacaine (LEA 103). *Acta Anaesthesiol Scand* 1988; 32:571–8
2. Gautier PE, De Kock M, Van Steenberge A, Poth N, Lahaye-Goffart B, Fanard L, Hody JL: Intrathecal ropivacaine for ambulatory surgery. *ANESTHESIOLOGY* 1999; 91:1239–45
3. McDonald SB, Liu SS, Kopacz DJ, Stephenson CA: Hyperbaric spinal ropivacaine: A comparison to bupivacaine in volunteers. *ANESTHESIOLOGY* 1999; 90:971–7
4. van Kleef JW, Veering BT, Burm AG: Spinal anesthesia with ropivacaine: A double-blind study on the efficacy and safety of 0.5% and 0.75% solutions in patients undergoing minor lower limb surgery. *Anesth Analg* 1994; 78:1125–30
5. Wahedi W, Nolte H, Klein P: Ropivacain zur Spinalanästhesie: Eine Dosisfindungsstudie [Ropivacaine for spinal anesthesia: A dose-finding study]. *Anaesthetist* 1996; 45:737–44
6. Malinovsky JM, Charles F, Kick O, Lepage JY, Malinge M, Cozian A, Bouchot O, Pinaud M: Intrathecal anesthesia: Ropivacaine versus bupivacaine. *Anesth Analg* 2000; 91:1457–60
7. Datta S, Lambert DH, Gregus J, Gissen AJ, Covino BG: Differential sensitivities of mammalian nerve fibers during pregnancy. *Anesth Analg* 1983; 62:1070–2
8. Bromage PR: A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. *Acta Anaesthesiol Scand Suppl* 1965; 16:55–69
9. Rout CC, Akoojee SS, Rocke DA, Gouws E: Rapid administration of crystalloid preload does not decrease the incidence of hypotension after spinal anesthesia for elective caesarean section. *Br J Anaesth* 1992; 68:394–7
10. GLM Univariate Analysis, SPSS Base 9.0 User's Guide. Chicago, SPSS Inc., 1999, pp 269–70
11. Polley LS, Columb MO, Naughton NN, Wagner DS, van de Ven CJ: Relative analgesic potencies of ropivacaine and bupivacaine for epidural analgesia in labor: implications for therapeutic indexes. *ANESTHESIOLOGY* 1999; 90:944–50
12. Russell IF: Spinal anaesthesia for caesarean section: The use of 0.5% bupivacaine. *Br J Anaesth* 1983; 55:309–14
13. Russell IF, Holmqvist EL: Subarachnoid analgesia for caesarean section: A double-blind comparison of plain and hyperbaric 0.5% bupivacaine. *Br J Anaesth* 1987; 59:347–53
14. Reisner LS, Lin D: Anesthesia for cesarean section, *Obstetric Anesthesia: Principles and Practice*, 2nd edition. Edited by Chestnut DH. St. Louis, Mosby, 1999, pp 475
15. Glosten B: Anesthesia for obstetrics, *Anesthesia*, 5th edition. Edited by Miller RD. New York, Churchill Livingstone, 2000, pp 2049
16. Sarvela PJ, Halonen PM, Korttila KT: Comparison of 9 mg of intrathecal plain and hyperbaric bupivacaine both with fentanyl for cesarean delivery. *Anesth Analg* 1999; 89:1257–62
17. Chung CJ, Bae SH, Chae KY, Chin YJ: Spinal anaesthesia with 0.25% hyperbaric bupivacaine for caesarean section: Effects of volume. *Br J Anaesth* 1996; 77:145–9
18. Malinovsky JM, Renaud G, Le Corre P, Charles F, Lepage JY, Malinge M, Cozian A, Bouchot O, Pinaud M: Intrathecal bupivacaine in humans: Influence of volume and baricity of solutions. *ANESTHESIOLOGY* 1999; 91:1260–6