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Determination of the Full Dose–Response Relation of Intrathecal Bupivacaine, Levobupivacaine, and Ropivacaine, Combined with Sufentanil, for Labor Analgesia

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Background: **Ropivacaine and levobupivacaine are local anesthetics that produce less motor block and greater sensory–motor separation when compared with equal milligram doses of bupivacaine. Although minimum local analgesic concentration studies suggested that they are less potent than bupivacaine, full dose–response studies have not been performed. The current trial describes the dose–response relation of levobupivacaine, ropivacaine, and bupivacaine, combined with sufentanil, when used for intrathecal labor analgesia.**

Methods: **Four hundred fifty term parturients in active labor were included in this double-blind, randomized trial. Combined spinal–epidural anesthesia was performed, and ropivacaine, levobupivacaine, or bupivacaine was intrathecally administered in a dose of 1.0, 1.5, 2.0, 2.5, 3.0, or 3.5 mg, always combined with 1.5 μg sufentanil. Patients were considered responders to spinal analgesia if the visual analog scale score for pain was less than 25 mm within 15 min and the visual analog scale score remained less than 25 mm for 45 min. Patient demographics, obstetric data, maternal side effects, and fetal and neonatal well-being were noted. Group-specific dose–response curves were constructed using a probit regression model.**

Results: **The ED_{95} of bupivacaine was 3.3 mg (95% confidence interval, 2.9–4.1). The ED_{95}s of ropivacaine and levobupivacaine were 4.8 mg (95% confidence interval, 4.0–6.7) and 5.0 mg (95% confidence interval, 4.1–7.0), respectively. Racemic bupivacaine was significantly more potent than ropivacaine ($P = 0.0027$) and levobupivacaine ($P = 0.0006$). Ropivacaine and levobupivacaine were of similar potency ($P = 0.91$).**

Conclusions: **This full dose–response study suggests that ropivacaine and levobupivacaine are of similar potency, whereas bupivacaine is more potent than both other drugs.**

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ROPIVACAINE and levobupivacaine are the two most recently introduced amide local anesthetics which at equal milligram doses possess a lower risk for cardiotoxicity when compared with racemic bupivacaine.[1] Some clinical evidence also suggests that at equal milligram doses, ropivacaine and levobupivacaine have less motor blocking properties than racemic bupivacaine.[2–4] However, the perceived benefits of ropivacaine and levobupivacaine in relation to toxicity, motor block sparing, and differential sensory blockade must be reevaluated in view of their relative potency. Up-and-down sequential allocation is a simple technique to determine the median effective dose (ED_{50}) or concentration (EC_{50}) for different local anesthetics. Based on epidural minimum local analgesic concentration (MLAC) studies, it seems that ropivacaine is less potent than bupivacaine,[5,6] whereas levobupivacaine is of similar potency to bupivacaine or is slightly less potent.[7] Two further MLAC studies recently demonstrated that levobupivacaine and ropivacaine are almost indistinguishable when used epidurally to produce labor analgesia.[8,9] Based on these trials, a potency hierarchy can be described indicating that racemic bupivacaine is the most potent drug, ropivacaine is the least potent, and levobupivacaine is of intermediary potency.

Combined spinal–epidural (CSE) analgesia is a popular technique to produce rapid onset analgesia during labor.[10] Initial intrathecal analgesia can be obtained using lipid-soluble opioids or local anesthetics, either alone or in combination.[11] Racemic bupivacaine is the most widely used local anesthetic for spinal labor analgesia, usually combined with opioids.[11–13] Also ropivacaine and levobupivacaine, combined with opioids, have been used to initiate intrathecal labor analgesia.[14,15] Dosages of intrathecal local anesthetics have been arbitrarily chosen without knowledge of the dose–response relation of these drugs for labor analgesia.

Two studies evaluated the minimum local analgesic dose (MLAD) of various intrathecal local anesthetics used for labor analgesia.[16,17] Sia *et al.*[16] demonstrated that, when corrected for the number of molecules per milligram, levobupivacaine was 20% more potent than ropivacaine. Camorcia *et al.*[17] were the first to determine the MLAD of ropivacaine, levobupivacaine, and bupivacaine and established the intrathecal potency ra-

tios for these three drugs. The previously established epidural potency hierarchy was confirmed. The latter authors suggested a potency hierarchy of spinal bupivacaine > levobupivacaine > ropivacaine.

Unfortunately, MLAC and MLAD studies only describe one point of the dose–response curve, the effective dose in 50% of the population. These studies do not provide information about the shape and slope of the curve, and in fact, at the ED_{95} point, dose–response curves may be overlapping.

The purpose of the current trial is to describe the full dose–response relation of intrathecal bupivacaine, levobupivacaine, and ropivacaine, combined with sufentanil, when used for analgesia during active labor.

Materials and Methods

After institutional ethical committee approval (Ethical Committee Clinical Trials Universitaire Ziekenhuizen Leuven, Catholic University of Leuven, Leuven, Belgium) and written, patient informed consent, 450 term (≥ 37 weeks), American Society of Anesthesiologists physical status I or II parturients in labor were recruited to participate in this double-blind, randomized trial. All women had uncomplicated, vertex-presenting, singleton pregnancies and requested regional analgesia. Patients were aged between 18 and 45 yr. Exclusion criteria included American Society of Anesthesiologists physical status III or IV, maternal height less than 150 cm, body mass index greater than 40, fetus with known or suspected congenital abnormalities, gestational age less than 37 weeks, cervical dilation greater than 7 cm, visual analog scale (VAS) score for pain less than 50 mm, and administration of parenteral or oral analgesics before initiation of neuraxial analgesia.

Before initiation of analgesia, the following parameters were recorded: maternal age, height, weight, cervical dilation, gestational age, type of labor, status of the membranes, use of prostaglandins, use of oxytocin, and medical history. The fetal heart rate was recorded for 15 min before analgesia using external cardiotocography. Maternal blood pressure and heart rate during the last antenatal visit and just before analgesia were noted. Pain was assessed using a VAS (100 mm; 0 = no pain and 100 = worst pain imaginable) and recorded 10 min before the CSE.

A fluid load consisting of lactated Ringer's solution in a dose of 10 ml/kg was intravenously administered 10 min before initiation of the regional block. The epidural space was identified at the L3–L4 or L4–L5 interspace with an 18-gauge Tuohy needle using the loss of resistance to saline technique with the patient sitting. A 27-gauge pencil-point spinal needle perforated the dura *via* the Tuohy needle. When free-flowing, cerebrospinal fluid was obtained, the spinal study solution (2 ml) was injected intrathecally (T0). A 20-gauge epidural catheter was positioned 4 cm in the epidural space. No epidural test dose was given.

If pain relief was inadequate 15 min after initial spinal analgesia, an additional 10-ml bolus of 0.175% ropivacaine with 0.75 μg/ml sufentanil was epidurally administered. Adequate pain relief was defined as a VAS score of less than 25 mm. Analgesia was maintained with patient-controlled epidural analgesia using 4 ml ropivacaine, 0.175%, with 0.75 μg/ml sufentanil and a lockout of 15 min with a continuous background infusion of 2 ml/h. The patient-controlled epidural analgesia device was started immediately after the first request for additional pain relief.

The spinal study solution contained 1.5 μg sufentanil combined with either racemic bupivacaine, levobupivacaine, or ropivacaine in a dose of 1.0, 1.5, 2.0, 2.5, 3.0, or 3.5 mg, dissolved in 2 ml saline. Thus, 18 study groups were defined (B1, 3.5; L1, 3.5; R1, 3.5). In each group, 25 patients were included. Study solutions were prepared by the hospital pharmacist and numbered from 1 to 450. Each number corresponded to a certain dose and drug. Study solutions were delivered in batches of fifty 2-ml vials. Each batch could contain vials from any of the groups. Patients were randomly assigned to one of the 18 study groups by taking a numbered vial from the batch.

Pain was assessed at 5, 10, 15, 20, 30, 40, 50, and 60 min after the end of the spinal injection and every 60 min until delivery. In addition, pain was assessed at the moment the patient requested additional analgesia. The duration of initial analgesia was defined as the time between the end of the spinal injection and the moment additional analgesia was requested. VAS scores were also assessed for every contraction during the first 15 min. The moment the VAS score decreased below 25 mm was recorded. The difference between this moment and T0 was defined as the onset time of analgesia.

Sensory block, motor block, maternal heart rate and blood pressure, fetal heart rate, and the presence of pruritus and nausea and/or vomiting were recorded at the same predetermined time points as we assessed pain. Motor block was measured using a six-point scale where 1 = no motor impairment; 2 = weak hip flexion; 3 = weak knee extension; 4 = weak knee flexion; 5 = weak foot dorsiflexion; and 6 = weak foot plantar flexion. Maternal hypotension (a decrease of mean blood pressure of > 20% from prelabor baseline) was recorded. If maternal hypotension occurred, additional lactated Ringer's solution was administered and intravenous ephedrine in 5- or 10-mg increments was given until blood pressure returned within 20% of prelabor values. Prelabor blood pressures were measured during the last antenatal visit.

Outcome of labor was recorded. Neonatal outcome was assessed using Apgar scores at 1 and 5 min after

birth and umbilical artery blood gases at birth, and admittance to the neonatal intensive care unit was noted. Admittance to the neonatal intensive care unit was at the discretion of the attending neonatologist who evaluated each neonate after birth. Neonatal weight was recorded. The occurrence of post–dural puncture headache was registered. Post–dural puncture headache was defined as any new-onset headache that had a postural character and that persisted for at least 12 h.

Patients were not considered for analysis if cervical dilation progressed beyond 9 cm within 1 h after T0 or if patients delivered within 60 min after T0. Patients were also excluded from data analysis if cerebrospinal fluid could not be obtained or if technical problems (broken vials, drug spillage, or failure to record all necessary data) occurred.

Statistical Analysis

The power was calculated for different scenarios, according to varying ED values and sample sizes at different dose levels. For each scenario, 500 data sets were simulated. Data were generated using a probit regression model with group-specific parameters implied by prespecified ED_{50} and ED_{95} values in each group. It was concluded that to achieve a power of 80% with an α level set at 0.05, a sample size of 20 per group was required, assuming a difference at the ED_{95} of 1 mg between bupivacaine and ropivacaine or levobupivacaine. It was decided to randomize 25 patients per group to allow for dropouts.

For the primary analysis, group-specific dose–response curves were constructed for patients treated with racemic bupivacaine, levobupivacaine, and ropivacaine, using a probit regression model. The block was deemed successful if the VAS score was less than 25 mm 15 min after T0 and remained less than 25 mm for 45 min. Analgesia was deemed unsuccessful if the VAS score was greater than 25 mm 15 min after T0 or if the VAS score returned to greater than 25 mm within 45 min. The ED_{50} and ED_{95} were calculated for each group. A likelihood ratio test was used to compare the dose–response curves of the three groups. A Bonferroni correction was applied for the pairwise tests. Confidence intervals (CIs; using the profile likelihood method) were constructed for the pairwise differences in ED_{50} and ED_{95}.

In a secondary analysis, group-specific dose–response curves were constructed using a similar statistical model, but with a different definition of successful analgesia. For this secondary analysis, analgesia was deemed successful if the VAS score was less than 25 mm at 15 min after T0. The block was deemed unsuccessful if the VAS score was greater than 25 mm at 15 min after T0.

Durations of analgesia, according to dose and drug used, in those subjects who achieved effective analgesia were compared. Kaplan-Meier estimators were used to construct survival curves, and log-rank tests were used to compare survival curves.

Chi-square tests were used to compare dichotomous responses among the three groups. Continuous measurements (*e.g.*, blood pressure) were compared among the three groups using analysis of variance techniques. If multiple values (taken over time) were available per subject, a repeated analysis framework (using a multivariate normal model or a linear mixed model) was used to make the between-group and within-group comparisons. A Kruskal-Wallis test was used to compare block heights among the three groups. The analgesic response was related to a set of predictors (maternal age, weight, height, body mass index, neonatal weight, preblock VAS score, parity, use of oxytocin, and cervical dilation) using probit regression analysis and logistic regression analysis for each predictor separately, after correction for group and dose level and their interaction.

Because the current study is significantly underpowered to detect any differences in side effects related to dose, data related to side effects were aggregated and analyzed according to the drug used.

Analysis was performed using the statistical package SAS, version 9.1 (SAS Institute Inc., Cary, NC). $P < 0.05$ was considered to be statistically significant. Data are presented as mean ± SD, percentage of group total, or median and interquartile range.

Results

A total of 450 patients were recruited and randomized, but 17 patients were excluded from data analysis. Eight patients delivered or progressed to 9 cm or more cervical dilation within 60 min after intrathecal injection; in 6 patients, the spinal component of the CSE failed; and in 3 patients, part of the 2 ml study solution was spilled. Excluded patients were distributed over the different groups, and no differences among the groups existed.

No demographic differences among bupivacaine-, levobupivacaine-, and ropivacaine-treated patients were observed (table 1). Labor characteristics and outcome of labor were similar among the three treatment groups (table 2) and among the different subgroups. The incidences of side effects related to neuraxial block were comparable among the three groups (table 3). No differences related to fetal heart rate or neonatal outcome could be identified among patients treated with bupivacaine, levobupivacaine, and ropivacaine (table 4).

The dose–response relation of the three investigated local anesthetics during CSE labor analgesia is described in figures 1 and 2. In figure 1, the dose–response relation derived from our primary analysis is presented. The ED_{50} and ED_{95} of racemic bupivacaine were 1.7 mg (95% CI,

Table 1. Demographic Data in Patients Treated with Intrathecal Bupivacaine, Levobupivacaine, or Ropivacaine

	Bupivacaine (n = 145)	Ropivacaine (n = 142)	Levobupivacaine (n = 146)
Age, yr	29.0 ± 5.1	30.2 ± 4.5	29.9 ± 4.3
Weight, kg	80 ± 13	82 ± 15	81 ± 12
Height, cm	167 ± 7	166 ± 6	167 ± 6
Gestational age, weeks	39.3 ± 1.3	39.4 ± 1.4	39.5 ± 1.5

Data are expressed as mean ± SD. No statistically significant differences were observed.

1.4–1.9) and 3.3 mg (95% CI, 2.9–4.1), respectively. The ED_{50} and ED_{95} of ropivacaine were 2.2 mg (95% CI, 1.8–2.6) and 4.8 mg (95% CI, 4.0–6.7), respectively. The ED_{50} and ED_{95} of levobupivacaine were 2.3 mg (95% CI, 2.0–2.7) and 5.0 mg (95% CI, 4.1–7.0), respectively. Racemic bupivacaine was significantly more potent than ropivacaine ($P = 0.0027$) and levobupivacaine ($P = 0.0006$). Racemic bupivacaine was found to be 1.5 (95% CI, 1.1–1.9) and 1.4 (95% CI, 1.0–1.7) times more potent than levobupivacaine and ropivacaine, respectively, at the ED_{95} point of the dose–response curve. Ropivacaine and levobupivacaine were of similar potency ($P = 0.91$), with a potency ratio at the ED_{95} between levobupivacaine and ropivacaine of 1.0 (95% CI, 0.7–1.4).

In figure 2, the dose–response relation derived from our secondary analysis is presented. Basically, the results of our primary analysis are confirmed in terms of relative analgesic potency among the three drugs. The ED_{50} and ED_{95} of racemic bupivacaine were 1.3 mg (95% CI, 0.9–1.6) and 3.2 mg (95% CI, 2.7–4.0), respectively. The ED_{50} and ED_{95} of ropivacaine were 1.5 mg (95% CI, 0.6–1.9) and 4.6 mg (95% CI, 3.7–7.0), respectively. The ED_{50} and ED_{95} of levobupivacaine were 1.1 mg (95% CI, 0.0–2.2) and 6.2 mg (95% CI, 2.9–9.7), respectively. Racemic bupivacaine was significantly more potent than ropivacaine ($P = 0.002$) and levobupivacaine ($P = 0.0036$). Ropivacaine and levobupivacaine were of similar potency ($P = 0.52$).

Duration of effective analgesia for those subjects achieving adequate analgesia, according to drug and dose used, is presented in table 5. Duration of effective analgesia is determined by the dose used ($P = 0.0028$) and not by the drug used ($P = 0.12$).

Age, height, weight, body mass index, parity, cervical dilation, type of labor, use of oxytocin, and birth weight did not independently predict the response to analgesia. The presence or absence of ruptured membranes independently predicted the response to analgesia ($P = 0.006$; odds ratio, 0.574; 95% CI, 0.385–0.856). More local anesthetic was required when ruptured membranes were present. After correction for the influence of ruptured membranes, racemic bupivacaine was found to be 1.5 (95% CI, 1.1–1.9) and 1.5 (95% CI, 1.1–1.9) times more potent than levobupivacaine and ropivacaine, respectively, at the ED_{95} point of the dose–response curve. Ropivacaine and levobupivacaine remained of similar potency, with a potency ratio at the ED_{95} between levobupivacaine and ropivacaine of 1.0 (95% CI, 0.7–1.4).

The onset of analgesia was significantly faster with racemic bupivacaine as compared with ropivacaine and levobupivacaine ($P < 0.001$; fig. 3).

Discussion

The current trial is, to the best of our knowledge, the first to describe and compare the full dose–response relation of intrathecal bupivacaine, levobupivacaine, and ropivacaine, combined with sufentanil, used for labor analgesia. Both *S*-enantiomer local anesthetic drugs were found to be significantly less potent than racemic bupivacaine at the ED_{50} and ED_{95} points of the dose–response curve. Bupivacaine is 40–50% more potent than ropivacaine and levobupivacaine. Ropivacaine and levobupivacaine were found to be of similar potency. The current study also revealed that the duration of effective analgesia is af-

Table 2. Obstetric Data and Data on Outcome of Labor in Patients Treated with Intrathecal Bupivacaine, Levobupivacaine, or Ropivacaine

	Bupivacaine (n = 145)	Ropivacaine (n = 142)	Levobupivacaine (n = 146)
Inductions, %	65	68	61
Ruptured membranes, %	61	65	60
Nulliparous patients, %	57	59	60
Cervical dilation, cm	4.1 ± 1.5	4.0 ± 1.5	3.9 ± 1.3
Duration of labor, min	224 ± 164	227 ± 142	231 ± 188
Spontaneous delivery, %	79	80	71
Cesarean delivery, %	9	7	8
Instrumental delivery, %	12	13	21

Data are expressed as mean ± SD or as percentage of group total. No statistically significant differences were observed.

Table 3. Side Effects Related to Labor Analgesia in Patients Treated with Intrathecal Bupivacaine, Levobupivacaine, or Ropivacaine

	Bupivacaine (n = 145)	Ropivacaine (n = 142)	Levobupivacaine (n = 146)
Hypotension, %	10	8	12
Ephedrine, %	10	9	9
Ephedrine, mg	0.8 ± 2.4	0.8 ± 2.7	0.6 ± 2.1
Pruritus, %	33	43	38
Nausea, %	2	1	2
Motor block Bromage > 0, %	8	10	10

Data are expressed as mean ± SD or as percentage of group total. No statistically significant differences were observed.

fected by the intrathecal dose administered and not by the drug used.

At equivalent doses, ropivacaine and levobupivacaine possess a lower risk for cardiotoxicity when compared with racemic bupivacaine.[1] Some clinical evidence also suggests that at equivalent doses, ropivacaine and levobupivacaine have less motor blocking properties than racemic bupivacaine.[2–4] Reduced toxicity, motor block sparing, and differential sensory blockade are especially advantageous in obstetric patients. However, these advantages should be evaluated in view of the relative potency of these drugs.

Previously, two studies evaluated the MLAD of various intrathecal local anesthetics used for labor analgesia.[16,17] Sia *et al.*[16] demonstrated that, when corrected for the number of molecules per milligram, levobupivacaine was 20% more potent than ropivacaine. Camorcia *et al.*[17] were the first to determine the MLAD of ropivacaine, levobupivacaine, and bupivacaine and established the intrathecal potency ratios for these three drugs. The latter authors suggested a potency hierarchy of spinal bupivacaine > levobupivacaine > ropivacaine.

Relative analgesic potency of these three local anesthetics, when epidurally administered, has been previously described using a similar methodology. However, no direct MLAC comparisons of all three local anesthetics in one study have been published. All conclusions about relative analgesic potency have been derived from comparisons between two products, levobupivacaine/bupivacaine, ropivacaine/bupivacaine, and levobupivacaine/ropivacaine. Lyons *et al.*[7] demonstrated that levobupivacaine was 11% less potent than bupivacaine. Capogna *et al.*[5] and Polley *et al.*[6] provided MLAC evidence that ropivacaine was 40% less potent than bupivacaine. More recently, Benhamou *et al.*[9] and Polley *et al.*[8] described ropivacaine to be between 2% and 16% less potent than levobupivacaine. These results have been confirmed by several studies that evaluated the motor blocking potencies of these local anesthetics using a similar methodology.[18,19]

The current full dose–response study, comparing all three local anesthetics, only partially corroborates the previously reported potency hierarchy. This study showed that bupivacaine is significantly more potent than both *S*-enantiomer drugs. However, spinal levobupivacaine and ropivacaine are of indistinguishable potency in the current trial. In fact, when corrected for the number of molecules per milligram, levobupivacaine is slightly less potent than ropivacaine. These results are more in line with those of Polley *et al.*,[8] who found epidural levobupivacaine and ropivacaine to be of similar potency. Of course, differences in study design and methodology may account for the observed variants in relative analgesic potency between the current trial and the two previous trials investigating spinal local anesthetics. The current trial is the first to directly compare the full dose–response curves of all three different local anesthetics. In MLAC- and MLAD-type studies, the technique of up-and-down sequential allocation is used to estimate the ED_{50}. The shape and slope of the dose–response curve is unknown. Because only a limited number of parturients are enrolled in up–down studies, it is difficult to control for confounding variables. In fact, many different absolute MLAC values for each local anesthetic have been reported despite nearly identical study designs.[20]

Table 4. Neonatal Outcome in Patients Treated with Intrathecal Bupivacaine, Levobupivacaine, or Ropivacaine

	Bupivacaine (n = 145)	Ropivacaine (n = 142)	Levobupivacaine (n = 146)
FHR changes, %	9	8	6
Neonatal weight, g	3,401 ± 508	3,422 ± 521	3,496 ± 495
UA pH	7.255 ± 0.069	7.250 ± 0.068	7.252 ± 0.074
UA pH < 7.2, %	16	17	15
UA BE	−2.71 ± 2.80	−2.49 ± 2.70	−2.84 ± 2.76
Apgar < 7, %	6	7	7
ICU, %	4	1	4

Data are expressed as mean ± SD or as percentage of group total. No statistically significant differences were observed.

BE = base excess; FHR = fetal heart rate; ICU = neonatal intensive care unit admittance; UA = umbilical artery.

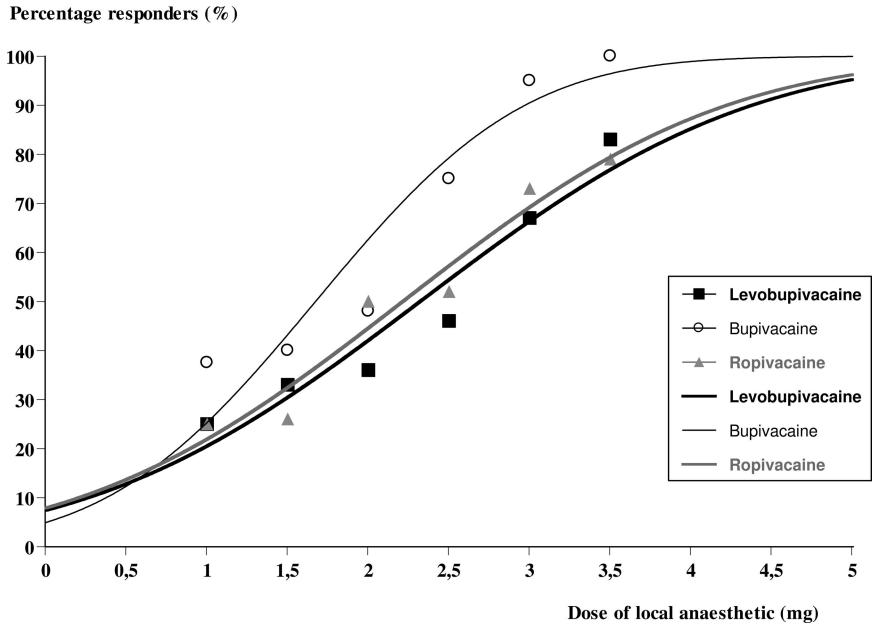

Fig. 1. Predicted (*lines*) and observed (*symbols*) dose–response relation of bupivacaine, levobupivacaine, and ropivacaine in 450 laboring parturients. Dose–response curves have been constructed using a probit regression model. Likelihood ratio tests have been used to compare the dose–response curves among the three groups. No significant difference (P = 0.91) in the dose–response curves of levobupivacaine and ropivacaine were observed. Significant differences in the dose–response curves of bupivacaine and ropivacaine (P = 0.0027) and the dose–response curves of bupivacaine and levobupivacaine (P = 0.0006) were noted. Definition of effective analgesia: The block was deemed successful if the visual analog scale score was less than 25 mm 15 min after initiation of analgesia and remained less than 25 mm for 45 min. Analgesia was deemed unsuccessful if the visual analog scale score was greater than 25 mm 15 min after initiation of analgesia or if the visual analog scale score returned to greater than 25 mm within 45 min.

Perhaps more importantly, the added opioids to the intrathecal mixture may affect the relative local analgesic potency ratios. It has been demonstrated that the addition of opioids affects the potency of local anesthetics.[21–23]

The new *S*-enantiomer drugs, especially ropivacaine, seem to have a greater sensory–motor separation, which is especially advantageous during labor analgesia.[2–4] However, the favorable effect of these new chiral drugs on sensory–motor separation as compared with the racemate may be explained by differences in potency. The results of the current trial support this idea. However, Camorcia *et al.*[17] suggested that, especially during intrathecal use, ropivacaine, by virtue of its lower lipid solubility, may be advantageous in minimizing motor block, even when equipotent doses are administered. It remains to be determined, in future trials comparing equipotent doses at the upper part of the dose–response curve, whether ropivacaine or levobupivacaine produces less motor block than bupivacaine. However, several trials comparing the epidural administration of equivalent doses of ropivacaine or levobupivacaine with bupivacaine, combined with opioids, reported fewer patients, treated with the new *S*-enantiomers, with motor block.[4,24–27]

Unfortunately, in this trial, the actual ED_{95} dose was higher than the highest administered dose in both the levobupivacaine and ropivacaine groups and could only be derived through extrapolation and not calculation. Surprisingly, 3.5 mg intrathecal ropivacaine and

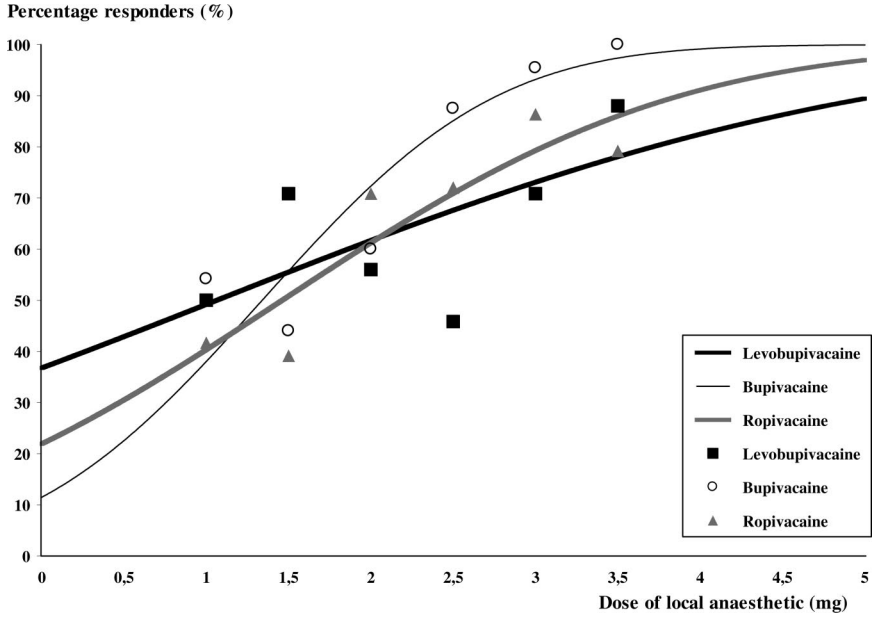

Fig. 2. Predicted (*lines*) and observed (*symbols*) dose–response relation of bupivacaine, levobupivacaine, and ropivacaine in 450 laboring parturients. Dose–response curves have been constructed using a probit regression model. Likelihood ratio tests have been used to compare the dose–response curves among the three groups. No significant difference (P = 0.52) in the dose–response curves of levobupivacaine and ropivacaine were observed. Significant differences in the dose–response curves of bupivacaine and ropivacaine (P = 0.002) and the dose–response curves of bupivacaine and levobupivacaine (P = 0.0036) were noted. Definition of effective analgesia: The block was deemed successful if the visual analog scale score was less than 25 mm at 15 min after initiation of analgesia. The block was deemed unsuccessful if the visual analog scale score was greater than 25 mm at 15 min after initiation of analgesia.

Table 5. Duration of Effective Analgesia in Patients with Effective Analgesia 15 min after the Initial Intrathecal Injection

Drug and Dose (n)	Median (25–75% Interquartile Range)	Delivered, n
Bupivacaine		
1 mg (13)	62 (51–70)	0
1.5 mg (11)	78 (60–116)	0
2 mg (15)	63 (60–85)	0
2.5 mg (21)	65 (60–85)	0
3 mg (21)	93 (70–120)	1
3.5 mg (25)	100 (70–130)	5
Ropivacaine		
1 mg (10)	71 (47–119)	0
1.5 mg (9)	67 (40–75)	0
2 mg (17)	75 (54–127)	0
2.5 mg (18)	81 (45–120)	0
3 mg (19)	66 (62–81)	1
3.5 mg (19)	88 (72–120)	0
Levobupivacaine		
1 mg (12)	61 (42–85)	0
1.5 mg (17)	57 (35–99)	1
2 mg (14)	61 (44–74)	0
2.5 mg (11)	80 (63–91)	0
3 mg (17)	80 (61–105)	0
3.5 mg (22)	75 (65–89)	2

Data are presented as median and interquartile range.

n = number of available subjects; delivered, n = number of patients per group who delivered before requesting additional analgesia.

levobupivacaine, combined with opioids, produced adequate analgesia in only 80% of patients, whereas the ED_{95} of bupivacaine was 3.3 mg. Previously adequate analgesia was reported using 2.5 mg bupivacaine, levobupivacaine, or ropivacaine.[27,28] The measured ED_{50} values for all three agents, administered intrathecally, were also higher than those previously reported in the literature.[16,17] Differences in patient population may account for these differences, as well as differences in study design. In the current trial, a heterogeneous patient population in terms of parity, type, and progress of labor was randomized. Many of our patients were in well-advanced labor, had labor induced, had ruptured membranes, and were multiparous. In these types of patients, therefore, much higher doses of local anesthetic are required to guarantee effective analgesia in most individuals than what is commonly used at most institutions. Especially with the new *S*-enantiomer drugs, significantly more drug should be given intrathecally.

Combined spinal–epidural analgesia is often, although not exclusively, chosen for patients in active, advanced labor. These patients often have rapidly evolving labors with intense pain and request fast-acting effective analgesia. Many factors, such as parity, ruptured membranes, cervical dilation, and others, influence pain intensity.[29,30] Although most of these factors are known when CSE analgesia is initiated, advanced, active labor remains a volatile situation that can change rapidly. Despite the fact that theoretically different doses of local anesthetic solutions can be administered to different patients depending on the presence or absence of certain pain-determining factors, in clinical reality, fixed recipes are often administered to avoid drug errors. Therefore, in clinical reality, anesthetists choose to work with very few different intrathecal doses to initiate CSE analgesia.

Although absolute values of the ED_{50} and ED_{95} may have been influenced by the type of our patient population, it is unlikely that this affected the relative analgesic potency ratio among the different drugs. The only factor that influenced the reaction to analgesia in the current study was the presence of ruptured membranes. However, this factor did not influence the relative analgesic potency of the three drugs.

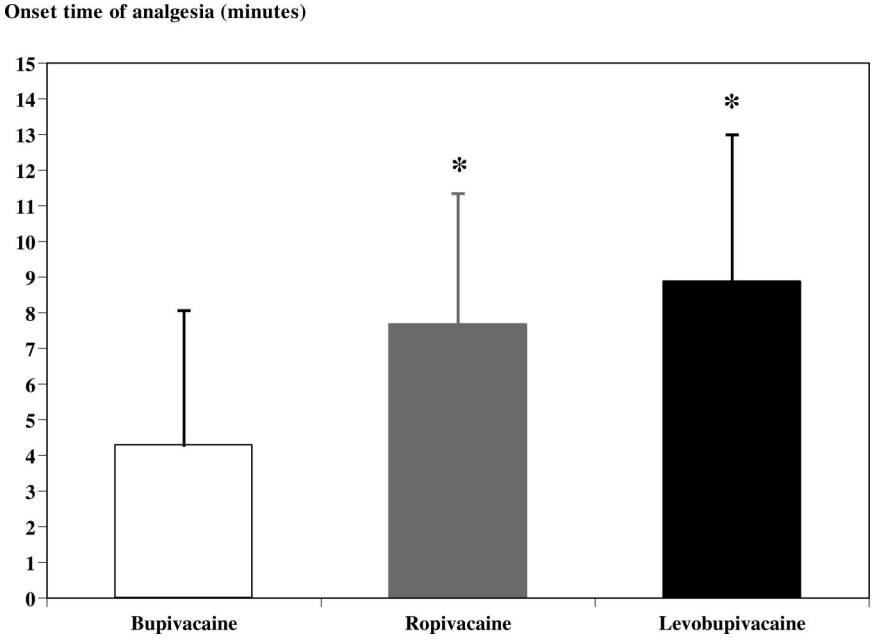

Fig. 3. Onset time of analgesia in responding patients treated with racemic bupivacaine, levobupivacaine, and ropivacaine. Data are presented as mean ± SD. * $P <$ 0.001 *versus* racemic bupivacaine.

The current trial is the first to describe and compare the full dose–response relation of intrathecal bupivacaine, levobupivacaine, and ropivacaine, combined with sufentanil, for labor analgesia. The racemate was found to be significantly more potent than both *S*-enantiomer drugs. This study also showed that, if patients are in well established labor, much higher intrathecal doses are required to guarantee rapid onset analgesia than what is commonly used. Future trials, designed to evaluate the incidence of side effects related to the local anesthetic used, can use the current results to compare equipotent doses.

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