

Minimum Local Analgesic Doses of Ropivacaine, Levobupivacaine, and Bupivacaine for Intrathecal Labor Analgesia

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Background: Doses for intrathecal opioid–local anesthetic mixtures have been arbitrarily chosen. The aim of this study was to compare the analgesic efficacies of intrathecal ropivacaine, levobupivacaine, and bupivacaine for labor analgesia and to determine the analgesic potency ratios for these three drugs. For this purpose, the authors used the up–down sequential allocation model, which estimates the minimum local analgesic dose for intrathecal local anesthetic.

Methods: Ninety-seven nulliparous term parturients in spontaneous labor, requesting combined spinal–epidural analgesia, were randomly allocated to one of three groups to receive 0.25% spinal ropivacaine, levobupivacaine, or bupivacaine. The initial dose of the local anesthetic drug was chosen to be 2.5 mg, and the testing interval was set at 0.25 mg. The subsequent doses were determined by the response of the previous parturient. Efficacy was accepted if the visual analog pain score decreased to 10 mm or less on a 100-mm scale within 30 min. The minimum local analgesic dose was calculated using the method of Dixon and Massey.

Results: The intrathecal minimum local analgesic dose was 3.64 mg (95% confidence interval, 3.33–3.96 mg) for ropivacaine, 2.94 (2.73–3.16) mg for levobupivacaine, and 2.37 (2.17–2.58) mg for bupivacaine. The relative analgesic potency ratios were 0.65 (0.56–0.76) for ropivacaine:bupivacaine, 0.80 (0.70–0.92) for ropivacaine:levobupivacaine, and 0.81 (0.69–0.94) for levobupivacaine:bupivacaine. There were significant trends ($P \leq 0.021$) for greater motor block with bupivacaine and levobupivacaine.

Conclusions: This study suggests a potency hierarchy of spinal bupivacaine > levobupivacaine > ropivacaine.

COMBINED spinal–epidural (CSE) analgesia for labor is a popular technique allowing rapid onset of analgesia with minimal motor block, and various local anesthetics and opioids have been used for this purpose, either alone or in combination. The local anesthetic that has been used most extensively is bupivacaine, in doses ranging from 1 to 2.5 mg, usually combined with opioids.^{1–3} More re-

cently, the chiral drugs have been used for CSE labor analgesia.

Intrathecal ropivacaine in the range of 2–4 mg has been shown to be adequate as an induction drug for labor analgesia when 10 μ g sufentanil was added to the anesthetic solution.^{4,5} A dose of 2.5 mg levobupivacaine in combination with 0.75 μ g/ml sufentanil and 1:800,000 epinephrine has been reported to produce intrathecal labor analgesia comparable with that produced by the same mixture containing the same dose of bupivacaine.⁶

Dosages of intrathecal opioid–local anesthetic mixtures have been arbitrarily chosen, with little knowledge of the contribution of each component to the overall effectiveness of analgesia. The minimum local analgesic dose (MLAD) of intrathecal bupivacaine in the first stage of labor has been reported,⁷ but there are no studies reporting the potency ratios, and thus the analgesic efficacy, of the other local anesthetics.

The aim of this study was to compare the analgesic efficacies of intrathecal ropivacaine, levobupivacaine, and bupivacaine when used alone for the first stage of labor analgesia. For this purpose, we used the up–down sequential allocation model,⁸ which allows the MLADs for intrathecal local anesthetics to be estimated. By estimating the MLAD, it is possible to compare intrathecal ropivacaine, levobupivacaine, and bupivacaine in equi-potent analgesic doses.

Materials and Methods

After institutional ethical approval (Città di Roma Hospital, Rome, Italy) and written informed consent, we enrolled 97 primiparous women requesting first-stage labor analgesia in this prospective, randomized, double-blind, parallel-group, up–down sequential allocation study. All parturients were at full term gestation (> 36 and < 41 weeks) in singleton pregnancies with cephalic fetal presentation and had an American Society of Anesthesiologists physical status I or II. All parturients were in spontaneous active labor, with a cervical dilatation of 2–4 cm and with an initial pain score greater than 50 mm on a 100-mm visual analog pain scale (VAPS), where 0 represented no pain and 100 represented the worst possible pain. Cervical examinations were performed immediately before the institution of the block. We excluded parturients with presenting part below the ischial spines, parturients receiving oxytocin augmentation before or during the duration of the study, and those who

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Table 1. Evaluation Scales for Motor Block

Scale	Score
Bromage scale	
Fully able to flex knees and feet	0
Just able to move knees	1
Unable to move knees, able to move feet only	2
Unable to move knees and feet	3
Straight leg raise test	
Complete ability to raise straight legs (> 30°)	0
Partial ability to raise straight legs (< 30°)	1
Inability to raise straight legs	2
Perineal squeezing	
Preserved	0
Decreased	1
Impossible	2

Table 2. Demographics

	Ropivacaine (n = 32)	Levobupivacaine (n = 33)	Bupivacaine (n = 32)
Age, yr	31.3 (3.6)	32.1 (3.5)	30.2 (4.4)
Weight, kg	67.2 (6)	71.2 (9.3)	72.8 (8.2)
Height, cm	164.7 (5.5)	163.4 (6.2)	165.5 (5.7)
Gestational age, weeks	40 (1.7)	39.2 (1.9)	39.4 (1.2)
VAPS, cm	85 (50–100)	86 (55–100)	95 (50–100)
Station of fetal head	–1 (0 to –3)	–1 (0 to –2)	–1 (0 to –2)
Cervical dilatation, cm	3.8 (1.2)	3.6 (1.4)	4 (1.1)

Data are presented as mean (SD) or median (range). Visual analog pain scale (VAPS), station of fetal head, and cervical dilatation before the spinal block.

had received opioid or analgesic medications. An intravenous infusion of 500 ml lactated Ringer's solution was started before institution of the block.

All parturients received a CSE technique while in the left lateral decubitus position. The epidural space was located using a 16-gauge Tuohy needle and loss of resistance to saline technique at the L3–L4 interspace. When a free flow of clear cerebrospinal fluid was obtained in the hub of a 26-gauge Whitacre spinal needle passed through the Tuohy needle, the study drug was injected into the intrathecal space. The spinal needle was then withdrawn, and a 16-gauge closed-end, triple-port epidural catheter was threaded through the epidural needle. After the placement of the epidural catheter, parturients were positioned supine with left uterine displacement.

Parturients were randomly allocated to one of three equal groups, with use of a computer-generated list, to receive 0.25% spinal ropivacaine, levobupivacaine, or bupivacaine. The initial dose of the local anesthetic solution chosen was 2.5 mg, and the testing interval was set at 0.25 mg for all the three groups. The dose of the drug in each group was determined by the outcome in the previous parturient, according to the up-down sequential allocation technique.

We used the commercially available 0.25% levobupivacaine and 0.25% bupivacaine. The 0.25% ropivacaine solution was prepared by combining 1% weight/volume ropivacaine with 0.9% sterile saline solution as the diluent to achieve the required 0.25% concentration. All solutions were made by one investigator, who did not have subsequent involvement in the data collection. All of the assessments were made by an anesthetist who was blinded to the group assignment as well as to the drug injected and was not involved in the patient's care.

Efficacy of the study drug was assessed using a 100-mm VAPS, where 0 represented no pain and 100 represented the worst pain ever, at 5-min intervals for 30 min after intrathecal injection. VAPS score was assessed at the peak of contraction, using a slide rule with the patient's side unmarked and the observer's side marked from 0 to 100 mm.

We evaluated three possible outcomes:

Effective: This outcome required a VAPS score of 10 mm or less within 30 min from the intrathecal injection and directed a decrement of 0.25 mg of the local anesthetic dose for the next parturient assigned to that group.

Ineffective: This outcome required a VAPS score of more than 10 mm within 30 min from the intrathecal injection. In this case, a rescue bolus of 15 ml epidural levobupivacaine, 0.125% (Chirocaine; Abbott, Abbott Park, IL), was given after 30 min, and an increment of 0.25 mg of the local anesthetic dose was directed for the next parturient assigned to that group.

Rejected: A further cervical examination was performed at 30 min, and parturients with progression of labor beyond 4 cm cervical dilatation or descent of the fetal head below the ischial spines were withdrawn from the study, and the outcome was rejected. In such case, the dose was repeated for the next woman assigned to the same group.

In addition to VAPS score assessment, other data were collected at 10-min intervals, including sensory level, degree of motor block, and incidence of adverse effects such as hypotension, nausea, and vomiting.

Sensory block was tested in each dermatomal level bilaterally for loss to pinprick sensation, and the density of the block was evaluated on an ordinal scale. Pinprick response was measured using the sharp tip of a sterile 25-gauge pencil-point spinal needle, and the patients were instructed to report when the sharpness of the needle felt the same (= 0), when it was felt as a blunt puncture (= 1), when it was felt as touching (= 2), or when the pricking sensation was completely lost (= 3) as compared with the sensation tested over an unanesthetized area.

Motor block was assessed using a modified Bromage scale⁹ by evaluating the ability to raise a straight leg¹⁰ and assessing whether perineal squeezing was preserved^{11,12} (table 1). Parturients were asked to perform all of the motor block tests before the epidural block to exclude from the study those who were not able to perform them.

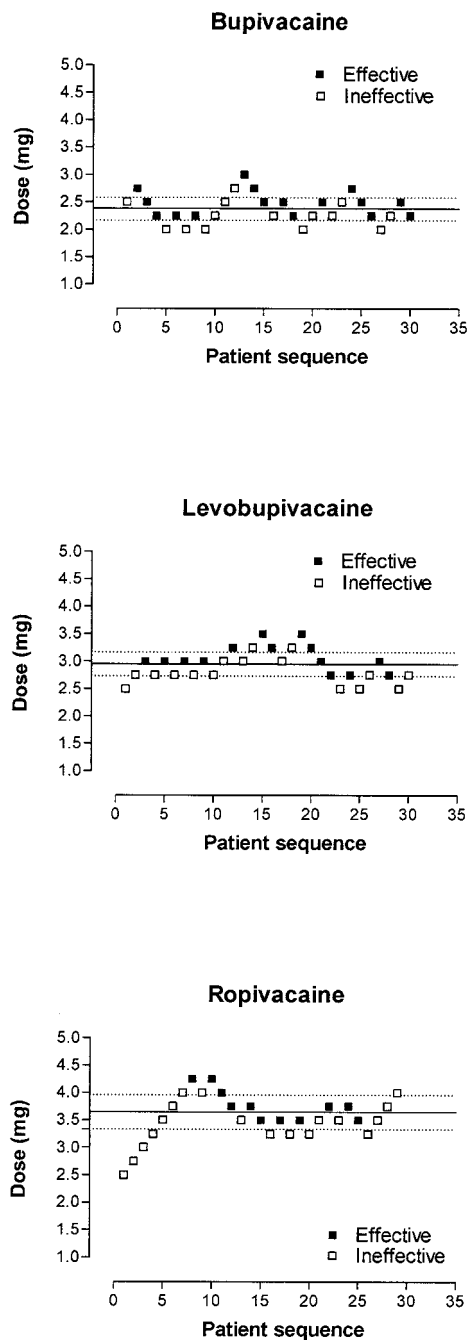


Fig. 1. The minimum local analgesic doses of intrathecal bupivacaine, levobupivacaine, and ropivacaine as determined by the technique of up-down sequential allocation. Sequences of effective and ineffective analgesia. The testing interval was 0.25 mg.

Maternal heart rate, noninvasive blood pressure, pulse oximetry, uterine contractions, and fetal heart rate were monitored from 30 min before the epidural block until the completion of the study. Fetal heart rate recordings were analyzed manually for any changes by an obstetrician who was unaware of the study group.

The occurrence of maternal adverse effects, such as nausea and vomiting, were recorded as a visual analog score using a slide rule marked from 0 to 100 mm (0 =

Table 3. Minimum Local Analgesic Doses with 95% Confidence Intervals

Drug	Dixon and Massey Method	Probit Regression
Bupivacaine, mg (n = 30)	2.37 (2.17–2.58)	2.32 (2.14–2.51)
Levobupivacaine, mg (n = 30)	2.94 (2.73–3.16)	2.95 (2.74–3.20)
Ropivacaine, mg (n = 29)	3.64 (3.33–3.96)	3.75 (3.48–4.12)

no effect; 100 = worst effect). Hypotension was defined as a 20% decrease in the mean arterial blood pressure when compared with the baseline values and treated, if necessary, with 5-mg intravenous boluses of ephedrine.

The duration of effective spinal analgesia, defined as the time taken for the woman to first feel her contraction becoming uncomfortable,¹³ was also recorded.

Statistical Analysis

Demographic and obstetric data were collected and are presented as mean (SD), median (interquartile range), and count as appropriate. Means (SDs) were analyzed by one-way analysis of variance with Bonferroni correction, medians (interquartile ranges) were analyzed by Kruskal-Wallis one-way analysis with Dunn post test, and counts or proportions were analyzed by chi-square tests. Kaplan-Meier analyses and log rank tests were used for durations of analgesia. The median effective concentrations were estimated from the up-down sequences using the method of Dixon and Massey,⁸ which enabled the MLAC with 95% confidence interval (CI) to be derived. The sequences were also subjected to probit regression analyses as backup or sensitivity tests. Analyses were performed using the following software: Excel 2000 (Microsoft Corp., Redmond, VA), Number Cruncher Statistical Systems 2000 (NCSS Inc., Kaysville, UT), and GraphPad Prism 4.0 (GraphPad Software Inc., San Diego, CA). Statistical significance was defined for an overall α error at the 0.05 level. All P values were two sided.

Based on a previous MLAD study⁷ with a coefficient of variation of 0.27, we estimated that a minimum of 28 subjects in each of the three groups were required to detect a 33% change with 0.8 power at a Bonferroni-corrected threshold of $P = 0.017$ and to maintain overall $P < 0.05$ for an up-down sequential allocation design.

Results

Of the 97 women enrolled, 8 were excluded because the rapid progression of labor. Eighty-nine women remained for further analysis. There were no differences in demographic characteristics, obstetric characteristics, or baseline VAPS scores in the three groups (table 2).

The sequences of effective and ineffective analgesia are shown in figure 1. The intrathecal MLADs for ropi-

Table 4. Analgesic Potency Ratios with 95% Confidence Intervals

Analgesic Potency Ratio	Dixon and Massey Method	Probit Regression	P Value
Bupivacaine: levobupivacaine	0.81 (0.69–0.94)	0.79 (0.70–0.88)	< 0.01
Bupivacaine: ropivacaine	0.65 (0.56–0.76)	0.62 (0.55–0.69)	< 0.001
Levobupivacaine: ropivacaine	0.80 (0.70–0.92)	0.79 (0.70–0.88)	< 0.01

One-way analysis of variance with Bonferroni correction.

vacaine, levobupivacaine, and bupivacaine in the first stage of labor are reported in table 3. Analgesic potency ratios and probit regression analyses are shown in table 4. Among the parturients who had effective analgesia, the duration of analgesia ranged from 40 to 110 min, with no differences between the groups.

None of the parturients had motor impairment or perineal squeezing problems before the CSE procedure was performed. All of the parturients were able to perform the motor block evaluation tests before the anesthetic block. There were significant differences ($P \leq 0.032$) in the frequencies of subjects without any motor block at 30 min after the spinal injection (table 5). In addition, there were significant trends ($P \leq 0.021$) toward greater motor block, suggesting a hierarchy from bupivacaine through levobupivacaine to ropivacaine, which was most pronounced for the perineal squeezing test ($P < 0.0001$). No parturient had any motor block with any of the three motor block tests when given a dose below 3.75, 3.25, or 2.25 mg, respectively, of ropivacaine, levobupivacaine, or bupivacaine. There were no significant differences in the groups regarding the upper level achieved for pinprick sensation, occurrence of maternal hypotension, or nausea or vomiting (table 6).

A review of the fetal heart rate tracings did not reveal significant differences in the study groups. No clinical obstetric interventions were required in response to fetal heart rate during the study period, and the modes of delivery were similar in the groups.

Discussion

This is the first study to determine the MLAD of intrathecal ropivacaine, levobupivacaine, and bupivacaine in

Table 5. Number of Parturients (%) with No Motor Block

	Ropivacaine (n = 32)	Levobupivacaine (n = 33)	Bupivacaine (n = 32)	P Value (Chi-square Test)	P Value (Chi-square Trend)
Bromage scale = 0	31 (97)	25 (76)	24 (75)	0.032	0.021
Straight leg test = 0	30 (94)	22 (67)	22 (69)	0.018	0.019
Perineal squeezing = 0	28 (87)	21 (64)	10 (31)	< 0.0001	< 0.0001

Per protocol of the study, the starting dose was 2.5 mg for all three local anesthetics. The subsequent doses varied according to the response of the previous parturient in each group. According with the up-down sequences, the maximum spinal dose given was 4.25 mg in the ropivacaine group, 3.25 mg in the levobupivacaine group, and 2.75 mg in the bupivacaine group.

Table 6. Maximum Height of Sensory Block and Incidence of Maternal Hypotension and Nausea-Vomiting

	Ropivacaine (n = 32)	Levobupivacaine (n = 33)	Bupivacaine (n = 32)
Sensory block level (pinprick = 1)	T9 (T10 to T8)	T8 (T10 to T7)	T8 (T9 to T7)
Maternal hypotension	1 (3%)	1 (3%)	2 (6%)
Nausea-vomiting	0	0	0

Results are expressed as median (interquartile range) and count (%)

the first stage of labor and establish the intrathecal analgesic potency ratios for these three drugs.

The epidural potency ratios previously reported for bupivacaine:ropivacaine¹⁴⁻¹⁵ are similar to our intrathecal potency ratios. On the contrary, the potency ratios of epidural bupivacaine:levobupivacaine and levobupivacaine:ropivacaine previously reported are different from our findings.¹⁶⁻¹⁸ Our differences in potencies suggest a potency hierarchy of spinal bupivacaine > levobupivacaine > ropivacaine.

Stocks *et al.*⁷ reported the MLAD of intrathecal bupivacaine in the first stage of labor to be 1.99 mg, whereas in our study it was slightly greater at 2.37 mg. However, the parturients in the study of Stock *et al.* had, on average, less pain before analgesia as compared with the parturients in our study. In addition, the study of Stock *et al.* examined a mixed sample of primiparous and multiparous women. Although there is no evidence of a greater analgesic drug requirement in nulliparous as compared with multiparous women, nonetheless, the pattern of pain during labor seems to be somewhat dependent on parity. Consistent findings indicate that during early labor (before 5 cm), nulliparous women on average experience greater sensory pain than multiparous women do.¹⁹ These factors may help to explain the differences in the MLAD values in the studies.

In one study,²⁰ 2.5 mg spinal bupivacaine produced a longer duration of analgesia and the most frequent incidence of lower limb motor block when compared with the same dose of levobupivacaine or ropivacaine. The duration of analgesia produced by bupivacaine in our effective cases was consistent with previous reports,⁷ and we did not observe any differences in duration of analgesia among the three local anesthetic used. Our

study was not designed to assess the duration of analgesia, parturients received different doses of local anesthetic according with the up-down method, and further studies are needed to investigate whether spinal ropivacaine, levobupivacaine, and bupivacaine given at equipotent doses have the same duration of action or degree of motor blockade.

Parturients who received bupivacaine and levobupivacaine had more motor impairment than those receiving ropivacaine. When interpreting these results, one should be take into account that they were produced by different doses and that our study was not designed to investigate motor block.

Previous studies²¹ have suggested the preservation of the potency ratios and the parallel nature of the analgesic and motor responses of epidural pipercolylxylidines. Our study may contribute to the argument that spinal ropivacaine is significantly less potent than bupivacaine and that the potency issues may be used to explain the favorable recovery profile described previously for intrathecal ropivacaine.²² Our data suggest that the lower lipid solubility of ropivacaine may play a more crucial role than chirality in determining the improvement in sensory-motor separation when this drug is injected in the intrathecal space close to the spinal cord compared to epidural administration.

We have previously reported²³ the minimum intrathecal motor blocking dose (ED₅₀ motor block) to be 4.8 mg for levobupivacaine and 5.9 mg for ropivacaine, with a potency ratio of 0.83 for ropivacaine:levobupivacaine. Further studies are needed to determine the intrathecal motor block potency of bupivacaine.

In summary, we presented the MLAD estimates for intrathecal ropivacaine, levobupivacaine, and bupivacaine in the first stage of spontaneous labor in nulliparous women. Our results suggest an analgesic potency hierarchy of spinal bupivacaine > levobupivacaine > ropivacaine.

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