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A Randomized Sequential Allocation Study to Determine the Minimum Effective Analgesic Concentration of Levobupivacaine and Ropivacaine in Patients Receiving Epidural Analgesia for Labor

Dan Benhamou, M.D., Caroline Ghosh, M.D.,† Frédéric J. Mercier, M.D., Ph.D.‡*

Background: **This study was designed to determine and compare the minimum local analgesic concentrations of levobupivacaine and ropivacaine when used in epidural obstetric analgesia.**

Methods: **In a double-blind study, healthy women requiring epidural analgesia for labor pain were randomized to receive either ropivacaine or levobupivacaine. Drugs were administered as a 20-ml epidural bolus. The concentration of each started at 0.11% and increased or decreased at intervals of 0.01%, depending on the response of the previous patient, using the technique of up–down sequential allocation. Minimum local analgesic concentrations were calculated using the formula of Dixon and Massey. Efficacy was assessed using visual analog pain scores and motor and sensory block assessments, and safety was assessed by recording maternal and fetal/neonate vital signs and adverse events.**

Results: **Forty-seven patients received levobupivacaine, and 47 received ropivacaine. Minimum local analgesic concentrations for levobupivacaine (0.077%; 95% CI, 0.058–0.096%) were lower than those for ropivacaine (0.092%; 95% CI, 0.082–0.102%). The 0.015% difference was not statistically significant. There was no notable difference between treatment groups in the proportion of patients reporting drug-related adverse events.**

Conclusions: **Levobupivacaine was 19% more potent than ropivacaine and provided similar safety results.**

BUPIVACAINE is a local anesthetic agent that has advantages over other local anesthetic agents because of its sustained duration of action and beneficial ratio of sensory to motor blockade, making it useful in obstetric epidural analgesia.[1] Bupivacaine has a chiral center and is commercially available as a racemate or 50:50 mixture of levobupivacaine and dextrobupivacaine.[2] There is preclinical evidence that S-enantiomers (levobupivacaine and ropivacaine) of amide local anesthetics are less cardiotoxic than racemic bupivacaine.[3] Clinical evidence shows that levobupivacaine retains local anesthetic properties and potency similar to racemate bupivacaine[4–7] and that ropivacaine is less potent than racemic bupivacaine when considering their minimum local anesthetic concentrations (MLACs).[8,9] The aim of the current study was to investigate the efficacy and safety of levobupivacaine in pregnant women in labor, as directly compared with ropivacaine.

Materials and Methods

After we obtained ethics committee approval (Consultative Committee Protecting Persons in Biomedical Research, Paris-Cochin, France) and written informed consent, women requiring epidural analgesia for spontaneous labor pain were recruited in this randomized, double-blind, two-arm parallel study to determine the MLACs of levobupivacaine and ropivacaine. Obstetric patients requiring or electing to receive epidural analgesia were recruited for the study if they fulfilled the following criteria: (1) age between 18 and 40 yr; (2) American Association of Anesthesiologists class I or II; (3) term pregnancy (*i.e.*, $\geq$ 36 weeks); (4) cephalic presentation; (5) cervical dilatation of $\leq$ 5 cm 30 min before dosing; and (6) predose visual analog pain score (VAPS) of $\geq$ 30 mm. Any of the following excluded the patient from the study: known hypersensitivity to amide local anesthetics; neurologic, neuromuscular, or psychiatric disorders; blood clotting disorders or blood dyscrasia; weight greater than 110 kg; height less than 150 cm; known fetal abnormalities; preeclampsia; or multiple pregnancy.

Patients were allocated randomly to receive one of the two study drugs using a randomization code. One epidural injection was prepared per patient. The concentration of levobupivacaine and ropivacaine started at 0.11% and was increased or decreased at intervals of 0.01% in subsequent patients, depending on the response of the previous patient to her epidural injection of the same drug. The study continued until 40 patients had completed the study in each group. The several possible outcomes for each administration were determined by the researcher (C. G.), who was blinded to both the drug and concentration being studied:

- The concentration was deemed to be effective (VAPS decreased to $<$ 10 mm 30 min after injection). The next patient had the concentration decreased by 0.01%.
- The concentration was deemed to be ineffective (VAPS $>$ 10 mm 30 min after injection, but rescue analgesia [12-ml bolus bupivacaine, 0.25%] was effective). The next patient received a higher concentration.

* Professor of Anesthesia and Intensive Care and Chairman, ‡ Assistant Professor of Anesthesiology, † Resident in Anesthesiology.

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Address reprint requests to Dr. Benhamou: Département d' Anesthésie-Réanimation, Hôpital de Bicetre, 78 rue du General Leclerc, Le Kremlin Bicetre, Cedex 94275, France. Address electronic mail to: dan.benhamou@bct.ap-hop-paris.fr.

- The concentration was deemed to be a reject (VAPS > 10 mm 30 min after injection, but rescue analgesia was ineffective). The next patient received a repeat of this concentration.
- Additional patients were entered into the study to replace those who were rejected. The replacement patient was allocated with the same randomization number but prefixed with the letter A.

Before performing the epidural block, an intravenous infusion of lactated Ringer's solution was established. A mid-line approach was used with the patient in the left lateral or sitting position. The skin was anesthetized using a maximum of 1.8 ml lidocaine, 3%. The epidural space at L2–L3 or L3–L4 was identified by loss of resistance to saline solution (≤ 2 ml) using an 18-gauge Tuohy needle. A three side-hole epidural catheter was advanced cephalad 4 to 5 cm into the epidural space and aspirated. If there was any evidence of entry into an epidural vein or cerebrospinal fluid, the patient was excluded from the study. After negative aspiration, a 20-ml bolus of the particular concentration of study drug being evaluated was given over 5 min. A test dose was omitted for the purpose of the study. All drugs administered before delivery and until 2 h after the index dose were recorded. Any medications taken after this point that were related to adverse events were also recorded.

Immediately before epidural analgesia, patients recorded their pain during contractions using a 0- to 100-mm visual analog scale, in which 0 mm = "no pain" and 100 mm = "worst pain imaginable." Once two consecutive scores of ≥ 30 mm were recorded, patients were eligible to enter the trial and a randomization number was allocated. Pain was then assessed at 5-min intervals until 30 min after the dose.

The extent of block was measured using a blunted 23-gauge needle 30 min after the dose (± 10 min) in all patients. If a patient required rescue medication, sensory block was also measured at 15 min and, if appropriate, at 30 min after rescue (± 10 min). The extent of the block was recorded for both the left and right sides with assessments in the direction of cephalad to caudal. Motor block was assessed using the modified Bromage scale as follows: 0 = no paralysis, full flexion of hips, knees, and ankles; 1 = inability to raise extended leg, able to move knees; 2 = inability to flex knee, able to flex ankle; and 3 = inability to move lower limb. Motor block was assessed 30 min after the dose only in those patients who had an effective outcome (VAPS ≤ 10 mm). In those who required rescue medication, motor block was assessed at 15 min and, if appropriate, at 30 min after rescue (± 10 min). Motor block was recorded for both left and right sides. Patients were scored "yes" or "no" based on their ability to stand, perform a deep knee bend, and return to a standing position. Heart rate and arterial blood pressure were recorded before the epidural dose and 15, 30, 45, and 60 min after the dose. Fetal heart rate was monitored continuously on a cardiotocograph either externally or with a fetal scalp electrode; it was recorded at the same intervals as maternal cardiovascular variables.

Adverse events were recorded throughout the study. A serious adverse event was defined as any event that was fatal, life threatening, permanently or temporarily disabling, or incapacitating; resulted in hospitalization or a prolonged hospital stay; or was associated with congenital abnormality, carcinoma, or overdose (either accidental or intentional). In addition, any event that the investigator regarded as serious or that would suggest any significant hazard, contraindication, side effect, or precaution that may have been associated with the use of the drug was reported as a serious adverse event. A telephone call was made to the patient 3–7 days after discharge to determine if there was any additional unwanted effect of epidural analgesia. A letter was sent if the patient could not be contacted by telephone.

Categorical data are presented using counts and percentages, whereas continuous variables are presented using the mean ± SD, median (range), and number of patients (n). All statistical analyses were performed at the 5% significance level. The potency ratio of the MLACs was calculated as levobupivacaine relative to ropivacaine. The ratio is presented together with a 95% CI. The primary efficacy endpoint was defined to be the MLACs obtained from sequential allocation for the two treatment groups. From a previous study in a similar group of patients, the SD of the MLAC for bupivacaine was estimated as 0.02%.[8] For the purposes of this calculation, it was assumed that the SDs of the MLACs for bupivacaine, levobupivacaine, and ropivacaine are similar. Using this estimate ($\alpha = 0.05$, $\beta = 0.2$), the proposed sample size of 40 patients per group was expected to be adequate to detect a difference of 0.015% between the MLACs for levobupivacaine and ropivacaine.

Results

A total of 102 obstetric patients receiving epidural analgesia for labor entered the study. Eight patients were withdrawn before receiving study medication, five in the ropivacaine group and three in the levobupivacaine group. All 94 patients who received the study medication were included in the safety data set, 47 in the ropivacaine group and 47 in the levobupivacaine group. Seven patients were withdrawn (ropivacaine [n = 6], levobupivacaine [n = 1]) after dosing but none because of an adverse event. Seven patients were classed as "rejects," after failing to respond to rescue medication. One had been given ropivacaine, and six had been given levobupivacaine, leaving 40 patients in each group for analysis of MLAC. Demographic details are summarized

Table 1. Demographic Characteristics of the Two Groups

	Ropivacaine (n = 47)	Levobupivacaine (n = 47)
Age (yr)	31 ± 5	32 ± 5
Height (cm)	166 ± 5	164 ± 5
Weight (kg)	76 ± 11	75 ± 12
Gestational age (wk)	40 ± 1	40 ± 1
Primiparous (%)	42	34
Cervical dilatation (cm)	3 (1–5)	4 (2–5)

None of the differences was significant.

in table 1. The up–down oscillation curves are illustrated graphically in figure 1. The MLAC for levobupivacaine (0.077%; 95% CI, 0.058–0.096%) was lower than the MLAC for ropivacaine (0.092%; 95% CI, 0.082–0.102%). The difference of −0.015% (−0.037–0.008) was not statistically significant. Levobupivacaine was thus 1.193 (CI, 0.911–1.476) times more potent than ropivacaine (not significant).

Assessment of sensory and motor block as well as comparison of maternal heart rate and blood pressure after drug administration showed no statistical difference (data not shown).

A total of 86 patients recorded 300 adverse events after dosing. There was no notable difference in the proportion of patients with a drug-related adverse event between the two groups. No drug-related serious adverse events were recorded during the study. Fetal distress was the most often-occurring fetal adverse event in both treatment groups. There was no notable difference in the incidence of fetal adverse events between the treatment groups, with the exception of neonatal hypoglycemia, which was recorded in a higher proportion of patients in the ropivacaine group (11% *vs.* 4%).

Discussion

The main finding of this study is that levobupivacaine is approximately 20% more potent than ropivacaine in a model using epidural analgesia for pain relief in the first stage of labor. Although there have already been studies comparing each of the two study drugs with racemic bupivacaine in similar clinical situations,[7–9] this is the first direct comparison of their analgesic potency. Levobupivacaine was, on average, 19.3% more potent than ropivacaine but could be 8.9% less potent than ropivacaine at the lower end of the 95% CI. Our results partly surprised us, because we did not expect that the difference between the two treatments would be small and insignificant. Moreover, the MLAC values that we found are lower than those previously reported for both drugs.[7–12] We believe that several aspects of our study design might explain our data. One possible factor could be that our patients received no oxytocic drug (neither oxytocin nor prostaglandins), which may explain why pain scores were, on average, lower at inclusion (55–60 mm) than in other trials, leading to lower MLAC values. Although cervical dilatation is a primary factor in the determination of MLAC values,[11] cervical dilatation at inclusion was not significantly less in the ropivacaine group than in the levobupivacaine group (3 cm *vs.* 4 cm).

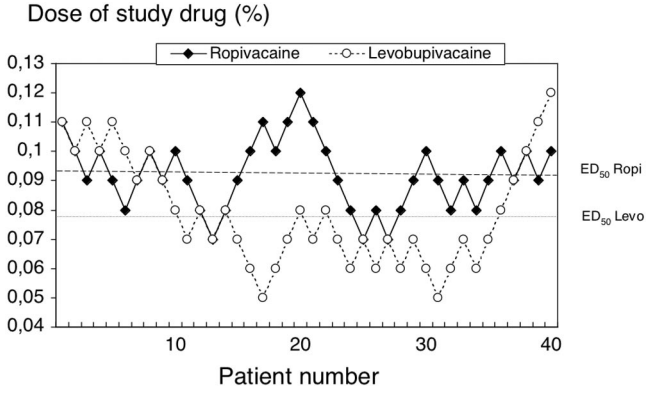

Fig. 1. Up and down oscillation determinations for the two study groups.

Second, variability in our results was greater than expected. When designing the study, levobupivacaine was expected to produce effects similar to those of racemic bupivacaine, because previous obstetric MLAC and surgical trials had suggested that the two drugs were equipotent.[4–6] Hence, study power was calculated using the width of CIs found in previous trials with racemic bupivacaine (*i.e.*, 0.02%).[8,9,12] Unfortunately, our study variability was larger (*i.e.*, 0.04%). *A posteriori* analysis shows that the variability in MLAC results with levobupivacaine found by other researchers is even larger than what we found. Lyons *et al.*[7] found a study variability of 0.05%, whereas Robinson *et al.*[10] observed a 0.08% variability in their MLAC studies. Moreover, variability in the ropivacaine MLAC was similar to that found in previous trials, thus reinforcing the hypothesis that levobupivacaine is associated with a more variable effect.

As mentioned earlier in this article, previous trials have been interpreted as demonstrating that racemic bupivacaine and levobupivacaine are equipotent.[7] It is likely that levobupivacaine is about 10% less potent than racemic bupivacaine, however. Indeed, in the previous MLAC trial, levobupivacaine was 2% less potent for commercial ampoules but 14% less potent if molar concentration is considered.[7] Because the concentration of commercially available levobupivacaine is calculated for the base (molecular weight, 288), whereas that of racemic bupivacaine is calculated for the hydrochloride salts (molecular weight, 325), the former contains 13% more local anesthetic.[13] Burke *et al.*[14] found that although the two drugs were considered clinically similar, levobupivacaine produced a slightly shorter duration of sensory block and was associated with a significantly greater number of patients who did not have adequate pain

relief after the first bolus dose. Finally, using sequential allocation in labor to determine the motor block potency of levobupivacaine and of racemic bupivacaine, Lacassie *et al.*[15] recently observed a 14% difference in motor-blocking properties using commercial preparations.

In conclusion, when using the MLAC methodology in women in labor, levobupivacaine was 19.3% more potent than ropivacaine (although the difference was not statistically significant) and provided similar safety results. Levobupivacaine might be slightly less potent than expected and may provide more variable analgesic results than racemic bupivacaine. Further studies are required to verify this hypothesis.

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