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Clinical Effects and Maternal and Fetal Plasma Concentrations of 0.5% Epidural Levobupivacaine versus Bupivacaine for Cesarean Delivery

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Background: **Bupivacaine exists as a mixture of two enantiomers, levobupivacaine and dexbupivacaine. Data suggest that levobupivacaine has equal local anesthetic potency, with reduced potential for central nervous system and cardiovascular toxicity. The present study compares the efficacy of 0.5% levobupivacaine with 0.5% bupivacaine for epidural anesthesia in parturients undergoing elective cesarean delivery.**

Methods: **Sixty healthy obstetric patients undergoing elective cesarean delivery with epidural anesthesia completed the study. Patients were randomized to receive 30 ml of either 0.5% levobupivacaine or 0.5% bupivacaine in a double-blind fashion. The efficacy endpoint measures included onset, offset, and quality of anesthesia. Neonatal blood gas analyses, Apgar score determinations, and neurobehavioral examinations were performed. Venous samples for pharmacokinetic studies and serial electrocardiograms were obtained in 10 patients in each group.**

Results: **Levels of sensory block, motor block, muscle relaxation, and overall quality of anesthesia did not differ between groups. The frequency of hypotension was 84.4% in the levobupivacaine group and 100% for the bupivacaine group ($P \leq 0.053$). No significant difference in observed maximum concentration of drug after dosing or area under the plasma drug concentration *versus* time curve were seen. The maximum concentrations were 1.017 and 1.053 μg/ml, and the areas were 4.082 and 3.765 h(μg/ml) for the levobupivacaine and bupivacaine groups, respectively. Umbilical vein-to-maternal vein ratios were 0.303 for the levobupivacaine group and 0.254 for the bupivacaine group.**

Conclusions: **The use of epidural 0.5% levobupivacaine for cesarean delivery results in equally efficacious anesthesia compared with 0.5% bupivacaine. Pharmacokinetic parameters were similar in the two groups. (Key words: Local anesthetics; obstetric anesthesia.)**

LEVOBUPIVACAINE is a long-acting amide derived from pipecholyl xylidine. Pipecholyl xylidine contains an asymmetric carbon atom, and the compounds in this series therefore exist as stereoisomers. The racemates of two members of this series, bupivacaine and mepivacaine, are commonly used. Bupivacaine exists as a racemic mixture of levobupivacaine and dexbupivacaine. Ropivacaine was the first of the single-isomer local anesthetics in this series to be introduced. When the individual enantiomers of bupivacaine were separated and investigated in animals, the S-isomer was found to have less cardiotoxicity without loss of local anesthetic potency.[1] Laboratory evidence using isolated heart models showed that QRS widening and occurrence of severe arrhythmias were much less pronounced with levobupivacaine than with both dexbupivacaine and racemic bupivacaine.[2,3] The present study was undertaken to compare the efficacy and safety of 0.5% levobupivacaine with 0.5% bupivacaine for epidural anesthesia in patients undergoing elective cesarean delivery.

Materials and Methods

The protocol used was approved by the hospital's human research committee, and written informed consent was obtained from all participants. Inclusion criteria were uncomplicated singleton pregnancy between 37 and 42 weeks, maternal age 18–40 yr, weight less than 110 kg, scheduled elective cesarean delivery, and planned epidural anesthesia.

Sixty-five patients with American Society of Anesthesiologists physical status I or II undergoing elective cesarean delivery with epidural anesthesia were randomized to receive either levobupivacaine or bupivacaine, and 30

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patients in each group completed the protocol. Before induction of epidural anesthesia, each patient received 10 mg metoclopramide intravenously and 30 ml sodium citrate solution orally. Acute volume expansion was achieved with 1,000 ml of Ringer's lactate solution intravenously. Oxygen saturation, electrocardiographic, and blood pressure monitoring was performed as described below.

The epidural space was identified using a 17-gauge Weiss needle at the L2–L3 or L3–L4 interspace using the loss-of-resistance-to-air technique. A catheter (Braun multiport) was placed 3 cm into the epidural space. After catheter placement, patients were placed in the supine position with left uterine displacement. A test dose of 3 ml 1.5% lidocaine with 1:200,000 epinephrine was given through the epidural catheter. Patients were randomized in a double-blinded fashion to receive a total of 30 ml of either levobupivacaine or racemic bupivacaine in fractionated doses *via* the epidural catheter over a 10-min period. A numerical assignment scheme was randomly generated; the drug was drawn up in the pharmacy and distributed in syringes labeled with the number assigned.

The end of injection of the study drug was deemed time 0 for the purposes of assessment. The level of sensory anesthesia to pinprick was assessed bilaterally at the midaxillary line. Sensory block was assessed at 0, 5, 10, 15, 20, 25, 30, 45, and 60 min. Sensory block measurements were continued every 30 min until the block regressed to T10, then every hour until complete recovery from sensory block. Motor block was assessed using a modified Bromage scale at 0, 5, 15, 30, and 60 min, then every 30 min until the return to full motor power.[4] Motor block was assessed on a scale of 0 = no paralysis, 1 = inability to raise extended leg, 2 = inability to flex knee, and 3 = inability to flex ankle. Muscle relaxation during the procedure was assessed by the anesthesiologist and obstetrician on a scale from 0 to 4, representing worst, poor, fair, good, and best (no specific criteria were provided).

Maternal heart rate and systolic and diastolic blood pressures were noninvasively recorded prior to induction of anesthesia and every 5 min from the time injection of local anesthetic was completed until the patient arrived in the recovery room. Monitoring was continued every 30 min in the recovery room. Hypotension was defined as a decrease greater than 30% of baseline systolic pressure. Ephedrine was administered in doses determined at the discretion of the anesthesiologist. A 12-lead electrocardiogram was obtained prior to induction of anesthesia and at the time of adequate block for surgery (sensory block T4–T6).

Patients were asked to rate their perceived pain on a 100-mm visual analog scale with 0 as no pain and 100 as "worst pain ever." Visual analog scale assessments were observed at the following times: (1) at skin incision, (2) at uterine incision, (3) at uterine exteriorization, and (4) on arrival in the recovery room.

Fetal heart rate monitoring was performed continuously during induction of anesthesia. Neonatal assessments were done by measuring umbilical vein and artery blood gas values from a segment of double-clamped umbilical cord obtained at the time of delivery. A simultaneous maternal venous sample was also obtained. Apgar scores at 1 and 5 min were determined by a pediatrician. All infants were examined at 2 and 24 h of life using the neurologic and adaptive capacity score (NACS).[5] Examinations were performed by a trained investigator blinded to the patient's group assignment.

A second separate randomization scheme was used to randomize patients who underwent pharmacokinetic analysis. Pharmacokinetic assessments were performed on 10 patients in each group *via* an in-dwelling large-bore intravenous catheter with a stopcock connected. After a 5-ml discard, venous blood samples of 5 ml were collected for determination of drug concentration at the following times: before epidural drug administration (baseline); 0 (end of local anesthetic injection), 15, 30, 45, and 60 min; and 2, 4, 6, 8, and 10 h after completion of the injection. Umbilical artery and vein blood samples were also analyzed for drug concentration at the time of delivery. Blood samples were centrifuged immediately after collection, and the plasma was immediately frozen and maintained at −20°C. Patients undergoing pharmacokinetic assessments had additional signal-averaging electrocardiograms performed with each pharmacokinetic timepoint. These electrocardiograms specifically measure QT intervals between groups and were analyzed by a cardiologist who was blinded as to which drug patients had received.

The total plasma concentrations of local anesthetics were determined with an analytical method involving the extraction of levobupivacaine, dexbupivacaine, and the internal standard, prilocaine, under basic conditions into methyl tertiary butyl ether. The methyl tertiary butyl ether was evaporated using nitrogen, and the samples were reconstituted in mobile phase and analyzed by liquid chromatography–mass spectrometry using positive ion atmospheric pressure chemical ionization. The data were quantified following peak integration using

Table 1. Patient Characteristics

	Levobupivacaine	Bupivacaine
Maternal age (yr)	34 ± 3	34 ± 3
Maternal height (cm)	161 ± 5	163 ± 7
Maternal weight (kg)	80 ± 12	82 ± 12
Gestation (wk)	38 ± 1	39 ± 1
Previous cesarean (%)	65.6	76.7

Data are mean ± SD. There were no significant differences between groups.

peak area internal standardization with weighted linear-regression analysis for the calibration lines. The analytical range for the assay was in the range of 10 to 500 ng/ml.

For each analytical batch, the acceptance criterion was that the determined concentrations of the calibration and quality control standards were within 15% of the nominal concentration. Plasma concentration data from study samples were reported from batches that met the criterion. The interday accuracy of the quality control samples at concentrations of 30, 200, and 400 ng/ml was 102.8, 105.3, and 98.9%, respectively, for levobupivacaine and 106.3, 103.2, and 100.4%, respectively, for dexbupivacaine. These data indicate that the performance of the method was acceptable to quantify the drugs assayed in the plasma samples generated by this clinical study.

Analysis of comparisons were done using a two-sided test with an alpha level of 0.05. A survival analysis using the product limit (Kaplan–Meier) approach with study drug as a treatment factor was used to analyze mean time to onset and offset of sensory and motor block. Overall assessment scales were analyzed by a *t* test. The electrocardiogram ratings for 12-lead electrocardiograms were compared across treatment groups at each time point by a Fisher exact test. The following electrocardiogram ratings were used: normal, abnormal–not clinically significant, and abnormal–clinically significant. Clinically significant cardiograms were defined as requiring medical intervention. These determinations were made by the investigator administering the anesthetic. Differences in intervals on signal-averaging electrocardiograms were analyzed using analysis of variance. Infant Apgar scores were dichotomized to < 8 and ≥ 8 and analyzed by a Fisher exact test. Infant NACSs were dichotomized into < 35 and ≥ 35 and analyzed at 2 and 24 h by a Fisher exact test. Following logarithmic transformation, values for the area under the plasma drug concentration *versus* time curve (AUC[0−t]) and the observed maximum concentration of drug after dosing (C_{max}[obs]) were analyzed using analysis of variance techniques.

Results

Patient Characteristics

Maternal demographics and baseline characteristics are described in table 1. Consent was obtained from 65 patients. Two patients had to be withdrawn before the study began: One patient scheduled for an elective cesarean delivery went into labor prior to the scheduled operation; the second was found to be 41-yr-old after consent was obtained. A total of 32 patients remained in the levobupivacaine group and 31 patients in the bupivacaine group. One patient assigned to the bupivacaine group was eliminated from the study when it was determined that the catheter had been placed intravascularly. Two patients were eliminated from the levobupivacaine group because no demonstrable block was obtained after epidural injection of 30 ml of study drug, presumably because of improper catheter placement. If a patient was eliminated after randomization, the pharmacy was contacted so that an appropriate replacement could be selected and the investigators could remain blinded. This resulted in 30 patients completing the protocol in each group.

Sensory and Motor Blockade

There were no statistically significant differences between treatment groups in mean time to onset of sensory block, time to T10 regression, and time to complete offset of sensory block (table 2). No significant differences were found in times to onset and offset of motor block (table 3). By 30 min after the completion of the epidural injection, all patients assessed in both groups had Bromage scores of 2 or 3. No significant differences were found between treatment groups with respect to muscle-relaxation scores rated by the obstetrician. As described previously, two patients were withdrawn

Table 2. Evaluation of Sensory Blockade

Time (min)	Levobupivacaine	Bupivacaine
Time to onset (T4–T6 block)	8.2 ± 4.7	6.4 ± 4.0
Time to T10 regression	329.2 ± 78.7	317.1 ± 80.7
Time to complete offset	451.0 ± 68.9	428.1 ± 69.0

Data are mean ± SD. There were no significant differences between groups.

Table 3. Evaluation of Motor Blockade

Time (min)	Levobupivacaine	Bupivacaine
Time to onset*	17.2 ± 12.16	12.5 ± 8.26
Time to complete offset	241.2 ± 89.59	265.2 ± 81.70

Data are mean ± SD. There were no significant differences between groups.
* Time at which patient had a motor block rating of 2 or 3.

from the study because no block was demonstrated after administration of the total dose of study drug. No other patient had anesthesia rated as a failure or unsatisfactory by the obstetrician or anesthesiologist. In terms of overall muscle-relaxation assessment, 75% of patients in the levobupivacaine group and 76.7% of patients in the bupivacaine group were rated as "best" by the obstetrician.

Cardiovascular Parameters

The incidence of hypotension was 84.4% in the levobupivacaine group and 100% in the bupivacaine group ($P = 0.053$). Cardiovascular data are presented in table 4. Mean ephedrine doses were 15 ± 15 mg in the levobupivacaine group and 23 ± 16 mg in the bupivacaine group ($P = 0.051$). Electrocardiograms recorded at baseline and presurgery in all patients and at the times of pharmacokinetic sampling in patients undergoing pharmacokinetic analysis did not show any clinically significant abnormalities. When signal-averaged electrocardiograms were analyzed in patients undergoing pharmacokinetic analysis, no differences in intervals were seen between the two groups at any point measured in the study.

Patient-perceived Quality of Anesthesia

Comparison of visual analogue pain scores with a scale ranging from 0 to 100 mm did not show statistically significant differences between treatment groups at the times measured. All patients in both groups reported a pain score of 0 at the time of incision. Pain scores at the time of uterine manipulation were 1.2 ± 4.5 in the levobupivacaine group and 5.6 ± 17.9 in the bupivacaine group out of a total possible score of 100. The difference between the groups was not significant.

Neonatal Outcomes

No significant differences were seen in infant Apgar scores or NACS). Greater than 90% of the neonates had an Apgar score of 8 or 9 at the 1-min time point and a score of 9 at the 5-min time point. All NACSs in both groups were within normal limits (> 35). Blood gas values did not differ between groups. Mean umbilical artery pH values were 7.29 ± 0.07 in the bupivacaine group and 7.28 ± 0.06 in the levobupivacaine group. Mean umbilical venous pH values were 7.35 ± 0.05 in the bupivacaine group and 7.35 ± 0.04 in the levobupivacaine group.

Adverse Events

Reports of nausea and postoperative pain were comparable between treatment groups. The incidence of nausea was 40.6% in the levobupivacaine group and 38.7% in the bupivacaine group. Three patients in each group vomited. Hypotension was reported in 84.4% of patients in the levobupivacaine group and 100% of patients in the bupivacaine group ($P = 0.053$). One patient, randomized to 0.5% bupivacaine, was discontinued from the study because intravascular injection of local anesthetic. This was determined by the investigator dosing the drug, and the patient did not suffer adverse consequences. No neonatal adverse events were determined to be related to the study drug.

Pharmacokinetic Analysis

Plasma concentration *versus* time profiles for levobupivacaine and bupivacaine are shown in figure 1. No significant difference in C_{max} or AUC(0−t) were seen. C_{max} was 1.017 and 1.053 μg/ml and AUC(0−t) was 4.082 and 3.765 h(μg/ml) for the levobupivacaine and bupivacaine groups, respectively. Umbilical vein/maternal vein drug ratio values were 0.303 for the levobupivacaine group and 0.254 for the bupivacaine group. At the time of delivery, umbilical venous concentrations of drug were 0.266 and 0.191 μg/ml for levobupivacaine and bupivacaine, respectively. Maternal drug concentrations at delivery were 0.900 μg/ml for levobupivacaine and 0.767 μg/ml for bupivacaine. The time at which C_{max}(obs) was apparent was 0.49 h in the levobupivacaine group and 0.53 h in the bupivacaine group.

Discussion

Levobupivacaine was developed because of concern regarding bupivacaine cardiotoxicity and preclinical evidence suggesting that there is stereospecificity with regard to blockade of impulse conduction in the cardiovascular system.[2,6–9]

Clinical studies have shown that levobupivacaine is equipotent to bupivacaine in terms of anesthesia efficacy. No significant differences in onset time, maximum spread of sensory block, or intensity of motor block

Table 4. Maternal Heart Rate and Blood Pressure

Time (min)	Heart Rate		Systolic Blood Pressure	
	Levobupivacaine	Bupivacaine	Levobupivacaine	Bupivacaine
Preinjection	88 ± 13	90 ± 13	119 ± 12	120 ± 12
0	96 ± 16	97 ± 14	113 ± 16	112 ± 12
5	96 ± 16	89 ± 13	111 ± 14	106 ± 14
10	92 ± 16	91 ± 12	114 ± 13	109 ± 20
15	90 ± 13	85 ± 14	110 ± 17	108 ± 15
20	93 ± 20	87 ± 13	110 ± 13	112 ± 10
30	91 ± 15	92 ± 16	113 ± 12	112 ± 16
40	95 ± 19	93 ± 13	113 ± 15	110 ± 15

Data are mean ± SD. There were no significant differences between groups.

were seen when 0.5% levobupivacaine, 0.75% levobupivacaine, and 0.5% racemic bupivacaine were compared for lower extremity surgery using epidural anesthesia.[10] When equal volumes of 0.25% levobupivacaine, 0.5% levobupivacaine, and 0.5% racemic bupivacaine were compared for supraclavicular brachial plexus block, no significant differences in onset time, dermatomal spread, or duration of both sensory and motor block were demonstrated among the three groups.[11] There were also no differences in the overall success rate of the technique. No significant differences in the *in vitro* and *in vivo* efficacy of the two bupivacaine enantiomers were demonstrated.[1] When serial dilutions of the bupivacaine enantiomers were given to volunteers as intradermal injections, levobupivacaine, unlike dexbupivacaine, was found to produce vasoconstriction at low concentration.[12] In this study levobupivacaine also appeared to be more potent and longer-acting, although the vasoconstrictor effect may have contributed to these observations.[12]

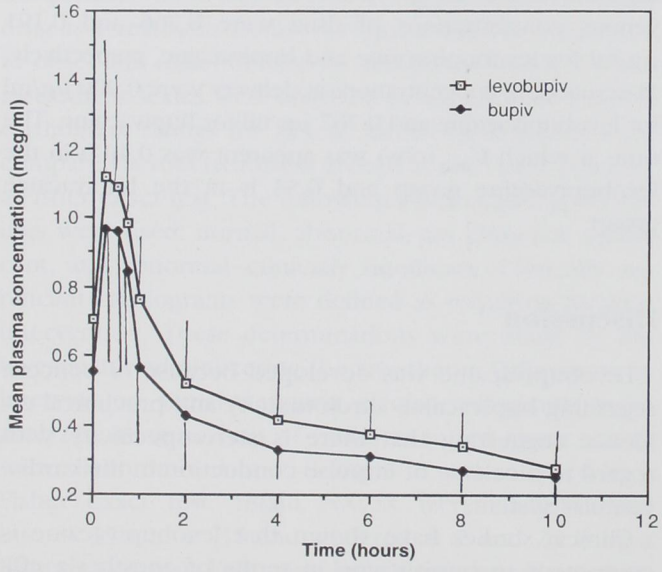

Fig. 1. Mean plasma bupivacaine and levobupivacaine concentrations (μg/ml) *versus* time; error bars eliminated for clarity. No significant differences between groups.

Ropivacaine, unlike levobupivacaine, was a newly developed compound rather than a single enantiomer of an existing racemate. Little comparative information between ropivacaine and levobupivacaine exists, although each has been independently shown to have less cardiotoxic potential than bupivacaine.[2,13] Recent work comparing the effects of levobupivacaine, bupivacaine, and ropivacaine on uterine blood flow in the pregnant ewe showed no deleterious effects on uterine blood flow or intraamniotic pressure at the serum concentrations tested.[14] Fetal serum and tissue levels of the three local anesthetics tested were comparable. Although no direct comparison studies of ropivacaine and levobupivacaine evaluating sensory and motor block exist, levobupivacaine may offer some advantage for major surgical procedures because adequate motor blockade for lower limb procedures has been reported at 0.5% concentrations.[10] In contrast, studies using ropivacaine have reported that the 0.5% concentration may be associated with insufficient motor blockade for major orthopedic procedures.[15]

No previous study has measured the effects of levobupivacaine in the obstetric patient. The present study compared the efficacy of 30 ml of epidural 0.5% levobupivacaine with 0.5% racemic bupivacaine for elective cesarean delivery. The primary efficacy endpoint was time to onset of sensory block adequate to carry out surgery. The groups were clinically comparable in this regard (table 2). No significant differences were found between treatment groups in time to onset of motor block, time to offset of sensory and motor block, and overall quality of anesthesia.

The most frequently occurring adverse event in this study was hypotension. The frequency in the levobupivacaine treatment group was 84.4% compared with 100% for the bupivacaine group. This difference did not attain statistical significance ($P = 0.053$). The mean ephedrine dose given was 15 mg in the levobupivacaine group and 23 in the bupivacaine group, with $P = 0.051$.

Signal-averaging electrocardiograms had been performed to evaluate changes in intervals between the two groups. No differences in effects on the cardiac conducting system were seen between the two groups. If differences in cardiovascular effects between the two groups existed, differences in the signal-averaging electrocardiograms might have been observed. Further studies with larger numbers of patients would be necessary to determine whether actual differences in the incidence of hypotension during cesarean delivery with epidural anesthesia exist. The overall high incidence of hypotension in both groups is likely caused by the relatively rapid administration of the total dose of epidural agent and subsequent rapid onset of sympathetic block and has been reported in other studies by our group using similar methodology.[16] The hypotension was corrected promptly with intravenous fluids and ephedrine, and neonatal outcomes were uniformly good.

In conclusion, the use of epidural 0.5% levobupivacaine for cesarean delivery results in equally efficacious anesthesia compared with 0.5% bupivacaine. Onset and offset of sensory and motor blockade and overall adequacy of anesthesia were clinically comparable. Pharmacokinetic parameters were similar in both groups. No significant maternal or neonatal adverse effects were seen in either group.

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