Comparison of 0.5% Ropivacaine and 0.5% Bupivacaine for Epidural Anesthesia in Patients Undergoing Lower-Extremity Surgery

David L. Brown, M.D.,* Randall L. Carpenter, M.D.,† Gale E. Thompson, M.D.†

Ropivacaine is an amide local anesthetic structurally related to, but appearing less cardiotoxic, than bupivacaine. The authors' investigation was designed in a randomized, double-blind fashion to compare the clinical effectiveness of ropivacaine and bupivacaine in patients undergoing lower-extremity surgery. Forty-five patients were randomized to receive 20 ml of 0.5% ropivacaine or bupivacaine. Intermittent sensory (pinprick) and motor (Bromage score) measurements were made while the block was in effect, and changes in heart rate, blood pressure and amounts of additional analgesics, sedatives and other medications were also recorded. Presence of tourniquet pain and the quality of anesthesia were also assessed. One patient was excluded from analysis; thus, 22 patients each received ropivacaine or bupivacaine. No differences were found in patient or perioperative characteristics between the groups. The quality and extent of sensory and motor blockade between groups were comparable, although bupivacaine was slightly longer acting. Cardiovascular changes, incidence of tourniquet pain, and the amounts of supplemental medications necessary were also similar between groups. The authors found 0.5% ropivacaine and bupivacaine to be clinically similar in both sensory- and motor-blocking characteristics, with the exception that bupivacaine produced a blockade of slightly longer duration. Because ropivacaine is reported to be less cardiotoxic than bupivacaine in animal studies, the similarity of clinical epidural anesthesia may make ropivacaine the preferred agent. (Key words: Anesthetics, local: bupivacaine; ropivacaine. Anesthetic techniques, epidural. Surgery, orthopedic.)

ROPIVACAINE is an amide local anesthetic structurally related to bupivacaine that is being investigated because it is reported to be less cardiotoxic than bupivacaine in animal studies.[1] It is unique among local anesthetics because it is prepared as a single enantiomer (the S form), rather than a racemic mixture. Although studied in animals, the relative potency and duration of sensory and motor block of ropivacaine compared with bupivacaine in humans is unknown. For example, some animal investigations have shown ropivacaine to be shorter acting and less potent than bupivacaine,[2,3] while human investigation has shown a more profound motor block with ropivacaine and sensory anesthesia comparable in length to bupivacaine.[4] It has been suggested that a higher concentration

of ropivacaine will be required to produce anesthesia equieffective with that produced by bupivacaine.[2]

In order to make a logical decision about drug choice based on the potential for clinical cardiotoxicity, the relative potency and doses required for effective clinical anesthesia need to be determined for ropivacaine and compared with bupivacaine. Our investigation was designed in a randomized, double-blind fashion to compare the clinical effectiveness of ropivacaine and bupivacaine in patients undergoing lower-extremity surgery.

Materials and Methods

After obtaining approval from the Institutional Review Board, 45 ASA Physical Status 1 or 2 patients scheduled for lower-extremity orthopedic surgery gave informed consent and were included in a double-blind randomized comparison of epidural ropivacaine (0.5%) and bupivacaine (0.5%). Inclusion criteria identified both men and women 18–70 yr, 50–100 kg, and 150–200 cm. Patients were excluded from entering this study if they had a prior history of neurologic, cardiopulmonary or psychiatric disease, or active liver or renal impairment. Also excluded were pregnant women or those of childbearing potential, and individuals with ongoing alcohol, drug, or medication abuse, or those taking antidysrhythmic drugs, including β-adrenergic blocking drugs.

Thirty to ninety minutes prior to epidural blockade patients received 5–10 mg of diazepam orally. Immediately prior to blockade additional sedation included from 1–3 mg of midazolam and/or 50 μg of fentanyl, and 500–1000 ml of balanced electrolyte solution. Skin and subcutaneous infiltration were provided with 2 ml of 1.5% lidocaine and all epidural blocks were performed by one of the three investigators (DLB, RLC, or GET) in the midline, at L2-3 or L3-4 interspaces, with 18- or 19-G Quincke or Touhy needles. The needle bevels were directed cephalad and the patients were in a lateral decubitus position. Following identification of the epidural space with a loss of resistance technique and a negative test dose of 3 ml of 1.5% lidocaine with epinephrine 1:200,000 (5 μg/ml), 20 ml of the blinded study drug was injected incrementally over 2 min. The patients were immediately turned supine and block measurements initiated.

Two nurse observers, blinded to the drug, performed all repetitive blockade assessments. These measurements included bilateral upper and lower extent of anesthesia to pinprick with a blunt 27-G needle at 5, 10, 15, 20, 25, and 30 min, and thereafter every 15 min for 5 h, and then every 30 min until sensory block resolved. Motor blockade was estimated at these same intervals using the Bromage Scale (0 = no motor paralysis; 1 = inability to raise extended leg; 2 = inability to flex knee; and 3 = inability to flex ankle joint). Quality of anesthesia was judged by the blinded nurse observer at the end of surgery as satisfactory or unsatisfactory, based on whether surgery could be performed without general anesthesia for up to 4 h after the study drug was injected into the epidural space. Tourniquet pain was judged as present or absent when applicable. Heart rate and systolic and diastolic blood pressures were recorded prior to premedication and immediately prior to administration of the epidural, and at 5, 10, 15, 20, 25, 30, 45, and 60 min, and every 30 min thereafter for 3 h following completion of local anesthetic injection. Additional sedatives and analgesics required during the surgical procedure were tabulated, as were doses of ephedrine and atropine.

Differences in characteristics of patients and epidural blockade, i.e., time of sensory and motor blockade onset and regression, maximum motor block and peak block height were assessed by Mann-Whitney U test. The frequency of motor block reaching Bromage level 2 was compared using chi-square. The blood pressure and heart rate changes accompanying blockade, as well as extent of sensory block over time, were assessed by ANOVA for repeated measures models. Post hoc testing of individual time points to identify these differences was carried out with ANOVA. Blockade success, requirement for general anesthesia, and presence of tourniquet pain were analyzed by the Fisher exact test.

Results

Forty-five patients were included in the study, 22 patients in both the ropivacaine and bupivacaine groups,

TABLE 1. Patient Characteristics in the Ropivacaine and Bupivacaine Groups

Variable	Ropivacaine	Bupivacaine
Age (yr)	43.4 ± 16.9	41.7 ± 16.1 (NS)
Height (cm)	175.8 ± 11.4	176.5 ± 8.0 (NS)
Weight (kg)	79.5 ± 12.6	82.8 ± 10.4 (NS)
Gender		
Males	15	18 (NS)
Females	7	4 (NS)
ASA Physical Status		
1	11	10 (NS)
2	11	12 (NS)

NS = not significant.

TABLE 2. Distribution of Operative Procedures Between the Ropivacaine and Bupivacaine Groups

Operation	Ropivacaine	Bupivacaine
Knee ligament/cartilage	9	11
Total knee replacement	6	2
Hip surgery	2	1
Ankle or foot surgery	1	4
Lower leg surgery	3	4
Upper leg surgery	1	0
Total	22	22

and one patient who was excluded from data analysis. The patient was excluded because during local anesthetic injection it was clear that the needle was not in the epidural space, and the patient subsequently did not develop epidural anesthesia. No differences were found in patient or perioperative characteristics between the two groups (tables 1, 2, and 3). The onset of sensory analgesia and peak sensory height did not differ between the groups (table 4). In both groups sensory blockade of the sacral dermatomes was virtually complete at 20 min (table 4). The regression of the upper sensory level was more rapid with ropivacaine ($P = 0.0001$, fig. 1), and the duration of sensory block significantly longer with bupivacaine in the T12 to S5 dermatomes ($P < 0.05$). The investigators' assessment of adequacy of anesthesia (21/22 ropivacaine and 22/22 bupivacaine) and muscle relaxation for the surgery (21/22 ropivacaine and 16/20 bupivacaine) was not different between groups. Among those having motor blockade, the duration of Bromage level 1 was significantly longer with bupivacaine. The onset of motor blockade, peak motor block Bromage score, and absence of tourniquet pain (15/20 ropivacaine and 17/20 bupivacaine) were also not different between groups.

The cardiovascular changes, i.e., heart rate and blood

TABLE 3. Periblock Management Characteristics of the Ropivacaine and Bupivacaine Groups

Variable	Ropivacaine	Bupivacaine
Amount of preblock diazepam sedation (mg)	8.9 ± 4.6	8.0 ± 5.0 (NS)
Amount of preblock fentanyl sedation (μg)	53 ± 19	59 ± 25 (NS)
Amount of preblock midazolam sedation (mg)	2.1 ± 1	2.0 ± 0.9 (NS)
Volume of preblock balanced electrolyte solution (ml)	495 ± 157	468 ± 159 (NS)
Number of patients per site of blockade		
L2-3	14	13 (NS)
L3-4	8	9 (NS)
Time between injection and operation (min)	44.6 ± 13.5	50.4 ± 24.1 (NS)
Length of surgery (min)	165 ± 97	189 ± 70 (NS)

NS = not significant.

TABLE 4. Sensory and Motor Anesthesia Characteristics Between Ropivacaine and Bupivacaine Groups

Variable	Ropivacaine	Bupivacaine
Block onset and peaks		
T10** (min)	10.7 ± 5.6	13.0 ± 10.7 (NS)
S5 (min)	20.5 ± 7.9	19.5 ± 10.2 (NS)
Peak block height*	T5 ± 2	T5 ± 3 (NS)
Time to peak block height (min)	45 ± 20	55 ± 25 (NS)
Peak Bromage motor block score	1 ± 1	1 ± 1 (NS)
Block regression		
2 dermatome (min)	177 ± 49	181 ± 68 (NS)
T10* (min)	237 ± 65	257 ± 51 (NS)
No sensory block (min)	333 ± 54	394 ± 53 (0.001)***
Duration of motor block** (min)	220 ± 52 (n = 9)	276 ± 52 (P = 0.02) (n = 11)

* T = thoracic dermatome.
** P = Mann-Whitney U test. (Only those patients in whom the surgical procedure allowed continuous assessment of motor blockade were included in this analysis.)
*** P = Mann-Whitney U test.

pressure changes, were similar between the groups. The measurement of heart rate preblock and 30 and 60 min postblock showed ropivacaine and bupivacaine group values of 71 ± 11 and 70 ± 11 beats per min preblock, 72 ± 13 and 72 ± 12 beats per min at 30 min, and 65 ± 10 and 62 ± 12 beats per min at 60 min, respectively. The measurement of systolic blood pressure preblock and 30 and 60 min postblock showed ropivacaine and bupivacaine group values of 126 ± 21 and 124 ± 16 mmHg preblock, 116 ± 19 and 113 ± 16 mmHg at 30 min, and 116 ± 19 and 112 ± 14 mmHg at 60 min, respectively.

During the anesthetic ropivacaine (R) and bupivacaine (B) patients received similar amounts of midazolam (2.8 ± 2.3 mg [R] vs. 3.6 ± 2.8 mg [B]), fentanyl (119 ± 114 μg [R] vs. 153 ± 136 μg [B]) and sodium thiopental (42 ± 98 mg [R] vs. 48 ± 157 mg [B]), as well as similar amounts of ephedrine and atropine. Likewise, the duration of the surgical procedures did not vary between the two groups (table 3).

Discussion

The development of long-acting amide local anesthetics has traditionally focused on ever increasing duration of local anesthetic action. Ropivacaine's development diverges from this tradition because its duration of sensory anesthesia is similar to that of currently available local anesthetics. Additionally, it is different from other local anesthetics because it is prepared as a single enantiomer (the S form), rather than a racemic mixture. The clinical importance of this difference may be related to a separation of local anesthetic potency and the potential for cardiotoxicity, although until further investigations are

performed this concept must remain speculative.[5] Nevertheless, ropivacaine is being evaluated after animal studies indicate it is less cardiotoxic than equivalent doses of bupivacaine.[1] However, the question that needs to be answered is "How much safer will ropivacaine be in humans?" The answer will depend on two factors: 1) the relative human cardiotoxicity of ropivacaine; and 2) the relative local anesthetic potency of ropivacaine in humans. The first factor is unlikely to be studied because a randomized blinded investigation of cardiotoxicity in humans would be impossible for ethical reasons. Thus, we need to rely on animal data. Nevertheless, the second factor, relative potency, can be answered and our study addresses this important issue.

What are comparable doses of ropivacaine and bupivacaine for epidural anesthesia in humans? Most animal studies indicate ropivacaine is less potent than bupivacaine.[2,3] If these studies are correct, and ropivacaine needs to be administered in greater doses than bupivacaine to produce effective anesthesia, the lessening of cardiotoxicity will be partially offset by the larger dose of ropivacaine needed. Potentially affecting this postulate are pharmacokinetic data obtained during an open-label evaluation of epidural ropivacaine at our institution, suggesting that after comparable doses blood concentrations following 0.5% ropivacaine may be less than those following 0.5% bupivacaine. (C_{max}: ropivacaine 0.5 ± 0.2 mg/l; bupivacaine 1.2 mg/l [range 0.7–1.7])[6,7] Differences in methodology between the studies make accurate comparison difficult, and will necessarily require additional investigation.

Our comparison of 0.5% plain ropivacaine and bupivacaine in patients undergoing lower extremity orthopedic surgery suggests that the intensity of sensory
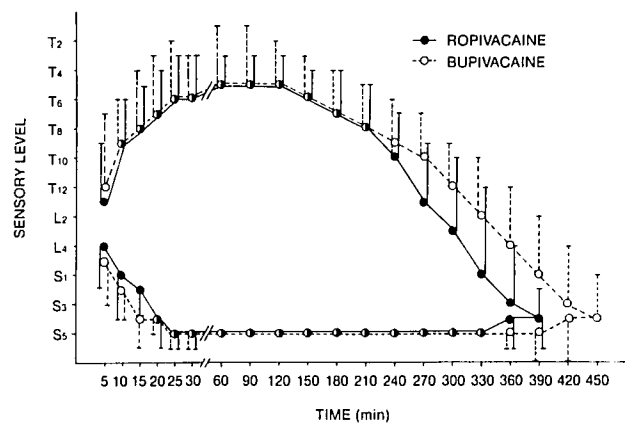

FIG. 1: Graphic representation of onset and regression of sensory block with ropivacaine and bupivacaine. The regression of the upper level of sensory blockade was significantly different. ($P = 0.0001$, ANOVA with repeated measures; and all time points after 240 min were significantly different, $P < 0.03$ by ANOVA.)

anesthesia is indistinguishable at the 0.5% concentration (table 4). Bupivacaine produced slightly longer-lasting sensory anesthesia than ropivacaine, although both were in the long-acting range (fig. 1). This slight difference in length of sensory anesthesia following centroneuraxis block is consistent with results from animal investigation.[3] It has been theorized that the shorter duration is a result of the lesser lipid solubility of ropivacaine.[3] The duration of sensory anesthesia with ropivacaine has also been determined in open-label studies of ropivacaine, and the total duration found in this study is similar to prior reports.[7,8]

The motor block characteristics of the two drugs also appear to be clinically indistinguishable, with mean Bromage scores of approximately 1 (table 4). In the patients in whom the surgical procedure allowed almost continuous motor block assessment, the bupivacaine patients had slightly longer-lasting motor block (table 4). In spite of similar motor blocking characteristics and successful use of the 0.5% concentrations, we postulate that higher concentrations will be necessary when abdominal muscle relaxation is required during ropivacaine epidural anesthesia or for complete motor blockade during lower-extremity surgery.

In summary, we found 0.5% ropivacaine and bupivacaine to be clinically similar in both sensory and motor blocking characteristics, with the exception that bupivacaine produced a slightly longer duration of blockade. If ropivacaine is less cardiotoxic than bupivacaine in humans, the similarity of clinical effectiveness indicates that ropivacaine may have a better margin of safety for epidural anesthesia. The margin of safety for other techniques can not be addressed until additional investigations are performed to determine equipotency of ropivacaine and bupivacaine throughout their useful clinical concentrations.

References

1. Reiz S, Haggmark S, Johansson G, Nath S: Cardiotoxicity of ropivacaine—A new amide local anesthetic. Acta Anaesethiol Scand 33:93–98, 1989
2. Feldman HS, Covino BG: Comparative motor-blocking effects of ropivacaine and bupivacaine, a new amino amide local anesthetic, in the rat and dog. Anesth Analg 67:1047–52, 1988
3. Akerman B, Hellberg IB, Trossvik C: Primary evaluation of the local anaesthetic properties of the amino amide agent ropivacaine (LEA-103). Acta Anaesthesiol Scand 32:571–578, 1988
4. Ramamurthy S, Blanchard J, Hickey R, Hoffman J: Efficacy of a new local anesthetic—0.5% Ropivacaine—for brachial plexus block (abstract). Anesth Analg 68:S230, 1989
5. Yeh JZ: Blockage of sodium channels by sterioisomers of local anesthetics. Progr Anaesthiol 2:35–44, 1980
6. Moore DC, Mather LE, Bridenbaugh PO, Bridenbaugh LD, Balfour RI, Lysons DF, Horton WG: Arterial and venous plasma levels of bupivacaine following epidural and bilateral intercostal nerve blocks. ANESTHESIOLOGY 45:39–45, 1976
7. Thompson GE, Brown DL, Carpenter RL: An initial study of ropivacaine for epidural anesthesia (abstract). Anesth Analg 68: S290, 1989
8. Concepcion M, Steele S, Bader A, Arthur GA, Covino BG: A new local anesthetic—ropivacaine—its epidural effects in man (abstract). Anesth Analg 68:S58, 1989