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Relative Analgesic Potencies of Ropivacaine and Bupivacaine for Epidural Analgesia in Labor

Implications for Therapeutic Indexes

Linda S. Polley, M.D.,* Malachy O. Columb, F.R.C.A.,† Norah N. Naughton, M.D.,‡
Deborah S. Wagner, Pharm.D.,§ Cosmas J. M. van de Ven, M.D.||

Background: The minimum local analgesic concentration (MLAC) has been defined as the median effective local analgesic concentration in a 20-ml volume for epidural analgesia in the first stage of labor. The aim of this study was to assess the relative analgesic potencies of epidural bupivacaine and ropivacaine by determining their respective minimum local analgesic concentrations.

Methods: Seventy-three parturients at ≤ 7 cm cervical dilation who requested epidural analgesia were allocated to one of two groups in this double-blinded, randomized, prospective study. After a lumbar epidural catheter was placed, 20 ml of the test solution was given, either ropivacaine ($n = 34$) or bupivacaine ($n = 39$). The concentration of local anesthetic was determined by the response of the previous patient in that group to a higher or lower concentration using up-down sequential allocation. Analgesic efficacy was assessed using 100-mm visual analog pain scores with ≤ 10 mm within 30 min defined as effective. An effective result directed a 0.01% wt/vol decrement for the next patient. An ineffective result directed a 0.01% wt/vol increment.

Results: The minimum local analgesic concentration of ropivacaine was 0.111% wt/vol (95% confidence interval, 0.100–0.122), and the minimum local analgesic concentration of bupivacaine was 0.067% wt/vol (95% confidence interval, 0.052–0.082). Ropivacaine was significantly less potent than bupivacaine, with a potency ratio of 0.6 (95% confidence interval, 0.49–0.74). No difference in motor effects was observed.

Conclusion: Ropivacaine was significantly less potent than bupivacaine for epidural analgesia in the first stage of labor. (Key words: Dixon and Massey; obstetric; pregnancy.)

EPIDURAL bupivacaine provides excellent analgesia for labor and delivery and remains the most widely used local anesthetic in obstetric anesthesia. However, disadvantages include the potential for motor blockade and cardiovascular toxicity. These concerns have prompted the search for alternative agents. Ropivacaine is a recently introduced amino amide local anesthetic that is structurally similar to bupivacaine. Many animal and human studies have been published that compared ropivacaine with racemic bupivacaine, and findings suggest that ropivacaine is associated with less central nervous system and cardiac toxicity¹⁻³ and produces less motor block of shorter duration when compared with bupivacaine.⁴⁻⁶

However, it is difficult to draw conclusions regarding analgesic efficacy and side-effect profiles in the absence of information regarding the relative analgesic potencies of the two agents. To evaluate the pharmacodynamic contributions of various epidural analgesics, a clinical model was devised to determine the relative potencies of local anesthetics in the first stage of labor^{7,8} and to estimate the local anesthetic sparing potential of epidural opioids.⁹⁻¹¹ The minimum local analgesic concentration (MLAC) has been defined as the median effective local analgesic concentration in the first stage of labor. The aim of this study was to determine the relative analgesic potencies of bupivacaine and ropivacaine by determining their respective MLAC values.

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* Assistant Professor, Division of Obstetric Anesthesiology.

† Consultant in Anaesthesia and Intensive Medicine, South Manchester University Hospital, Withington, United Kingdom.

‡ Assistant Professor, Division of Obstetric Anesthesiology.

§ Clinical Instructor.

|| Assistant Professor, Division of Maternal-Fetal Medicine.

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Address reprint requests to Dr. Polley: Department of Anesthesiology, 1500 E. Medical Center Drive, Room F3900 Mott Hospital, Ann Arbor, Michigan 48109-0211. Address electronic mail to: lpolley@umich.edu

Materials and Methods

This research was conducted at the University of Michigan Health System at Ann Arbor. After ethical approval from the institutional review board and written informed consent, 73 parturients classified as American Society of Anesthesiologists physical status I and II who requested epidural analgesia were enrolled. Participants had singleton pregnancies of greater than 36 weeks' gestation with vertex fetal presentation. All women were in active labor with cervical dilation of 3–7 cm when catheters were placed. Those who had received opioid or sedative medication were excluded.

After intravenous prehydration with 1,000 ml lactated Ringer's solution, patients were placed in the flexed sitting position. After raising a midline skin wheal with 1% wt/vol lidocaine, the epidural space was identified using loss of resistance to saline (2 ml) at the L2–L3 or L3–L4 level, and a multiport epidural catheter was advanced 3 cm into the epidural space. No test dose was used.

Participants were allocated to one of two groups in a double-blinded, randomized, prospective study design. The first group ($n = 34$) received 20 ml ropivacaine (Naropin; Astra USA, Westborough, MA), and the second group ($n = 39$) received 20 ml bupivacaine (Marcaine; Abbott Laboratories, North Chicago, IL). The concentration of local anesthetic received by a particular patient was determined by the response of the previous patient in that group to a higher or lower concentration, using an up-down sequential allocation technique. The testing interval was 0.01% wt/vol. The first patient in each group received 0.10% wt/vol ropivacaine or bupivacaine based on an estimate of MLAC from a previous study.¹¹ Each study solution was freshly prepared by the operating room pharmacist using preservative-free saline as the diluent to achieve the desired concentration at room temperature (20°C). After catheters were inserted, patients were placed in the supine position with left uterine displacement and 30° elevation of the head of the bed. The injectate was given within 5 min. Patients were monitored using a Dinamap (Critikon, Tampa, FL) blood pressure monitor, pulse oximetry, and tococardiography.

The anesthesiologist performing the procedure and subsequent assessment was blinded to the concentration used and the group allocation. Efficacy of the study drug was assessed using 100-mm visual analog pain scores (VAPS), where 0 represented "no pain" and 100 was "worst possible pain" at 5-min intervals for the first 30

min after bolus injection. A VAPS of 10 mm or less was defined as effective. Three outcomes were considered:

1. Effective: A VAPS of 10 mm or less during contractions within 30 min of injection. A result defined as effective directed a 0.01% wt/vol decrement for the next patient randomized to that group.
2. Ineffective: A VAPS greater than 10 mm because of pain that responded to rescue with a 12-ml bolus of 0.25% wt/vol of the same local anesthetic. A result defined as ineffective directed a 0.01% wt/vol increment for the next patient randomized to that group.
3. Reject: A VAPS greater than 10 mm because of pain that was not responsive to rescue. A result defined as a reject directed that the same concentration be repeated for the next patient randomized to that group.

At 30 min, participants not defined as having effective analgesia were given the rescue bolus. Those who did not respond to rescue doses were designated as rejects. Further management then included repeated epidural catheterization, intrathecal opioid with or without bupivacaine, or parenteral opioid as appropriate.

In addition to VAPS assessment, other data collected at 5-min intervals included maternal blood pressure and heart rate, fetal heart rate, and sensory level as determined by a perceived temperature difference to alcohol swab. Motor block was assessed bilaterally at 15-min intervals using the modified Bromage scale of 0 = no motor block; 1 = inability to raise the extended leg, able to move knees and feet; 2 = inability to raise the extended leg and to move knees, able to move feet; and 3 = complete motor block of the lower limbs. To further assess motor block, patients with effective ropivacaine or bupivacaine analgesia at 30 min were asked to do a partial knee bend from a standing position at the bedside.

To determine the duration of effective analgesia, women reporting a VAPS ≤ 10 mm were assessed at 15-min intervals until the first request for additional medication. At that time, the study was complete, and patients were started on an infusion of 0.0625% bupivacaine with 3 μ g/ml fentanyl.

Fetal Assessment

Fetal heart rate was monitored continuously by tococardiography, and any adverse events were recorded. A perinatologist blinded to the study group allocation reviewed fetal heart rate tracings obtained during the first hour of the study using the National Institutes of Health research guidelines for interpretation of electronic fetal heart rate monitoring.¹²

Table 1. Demographic and Obstetric Data

	Ropivacaine	Bupivacaine
Age (yr)	27.4 (4.92)	27.8 (5.17)
Height (cm)	165.1 (7.33)	163.2 (8.03)
Weight (kg)*	87.9 (25.56)	73.1 (10.72)
Gestation (wk)	39.9 (1.22)	40.2 (1.5)
Cervical dilatation (cm)	4.6 (1.12)	4.4 (0.95)
Nulliparous	18	15
Oxytocin	6	13
Initial VAPS (mm)	76 [50–100]	69 [45–100]

Results are expressed as mean (SD), median [range], and count as appropriate.

VAPS = visual analog pain score.

* $P = 0.012$ (Welch's unpaired t test).

Statistical Analysis

Demographic and obstetric data were collected and are presented as the mean (SD), median [range], and count as appropriate. Means (SD) were analyzed using unpaired Student t or Welch t tests for differing variances; medians [ranges] were evaluated using the Mann-Whitney U test, and counts or proportions were analyzed using Fisher exact test. Median effective concentrations were estimated from the up-down sequences using the method of Dixon and Massey,¹³ which allowed us to determine MLAC values with 95% confidence intervals (95% CI). The sequences were also subjected to Wilcoxon and Litchfield probit regression analyses as back-up or sensitivity tests. Analyses were performed using the following software: Microsoft Excel 97 (Redmond, WA), Statistical Package for the Social Sciences 7.51 (SPSS, Inc., Chicago, IL), GraphPad InStat 3.0 (San Diego, CA), and Pharmacological Calculation System 4.2 for DOS. Statistical significance was defined for an overall α error at the 0.05 level. All P values were two-sided.

Sample size estimations were based on the standard deviation (SD 0.028% wt/vol) from previous MLAC bupivacaine studies.^{10,11} Power was given at 0.8, with a minimum difference of 25% in potency considered significant. We estimated that a minimum of 24 women would be necessary per group.

Results

There were no significant obstetric differences in the two groups (table 1). The only significant demographic difference was the greater weight ($P = 0.012$) of the ropivacaine

Table 2. Hemodynamic Data

	Ropivacaine	Bupivacaine
Baseline MAP (mmHg)	94.0 (11.01)	93.6 (9.05)
Lowest MAP (mmHg)	78.4 (8.17)	79.9 (10.25)
Baseline maternal HR (bpm)	85.8 (14.77)	83.8 (14.36)
Maternal HR change (bpm)	4.7 (23.17)	0.5 (19.00)
Baseline FHR (bpm)	134.9 (12.15)	131.3 (10.39)
Lowest FHR (bpm)	125.3 (5.98)	123.9 (11.79)

Results are expressed as mean (SD).

MAP = mean arterial pressure; HR = heart rate; FHR = fetal heart rate.

group (mean, 87.9 kg) compared with the bupivacaine group (mean, 73.1 kg). There were no significant hemodynamic differences between the two groups (table 2). Maternal hypotension, defined as a systolic blood pressure less than 100 mmHg, which also represented a decrease from baseline mean arterial pressure of more than 15%, was observed in two women in the ropivacaine group and two in the bupivacaine group.

Of the 34 women enrolled in the ropivacaine group, 9 were rejected (table 3), leaving 25 for analysis. Figure 1 shows the sequences of effective and ineffective analgesia. The MLAC of ropivacaine in the first stage of labor was 0.111% wt/vol (95% CI, 0.100–0.122) using the formula of Dixon and Massey and was 0.109% wt/vol (95% CI, 0.098–0.121) using probit regression analysis as a back-up test of sensitivity.

Of the 39 women enrolled in the bupivacaine group, 14 were rejected (table 3), leaving 25 for analysis. Figure 2 shows the sequences of effective and ineffective analgesia. The MLAC of bupivacaine in the first stage of labor was 0.067% wt/vol (95% CI, 0.052–0.082) using the formula of Dixon and Massey and was 0.063% wt/vol (95% CI, 0.053–0.074) using probit regression analysis as a back-up test of sensitivity.

Table 3. Distribution of Rejects

% wt/vol	Ropivacaine	Bupivacaine
0.13	1(A) 1(B)	
0.12	1(A) 1(B)	
0.11	2(C)	
0.10	2(A) 1(B)	
0.09		
0.08		3(A) 2(B) 1(C)
0.07		1(B) 2(C)
0.06		
0.05		1(A) 2(B) 2(C)
0.04		

A = VAPS > 10 mm due to pain that fails to respond to rescue; B = protocol violation; concentration repeated; C = 2nd stage of labor prior to study completion; concentration repeated.

Tallarida RJ, Murray RB: Manual of Pharmacologic Calculations with Computer Programs, 2nd Edition. New York, Springer-Verlag New York Inc., 1987.

MLAC Ropivacaine in Labor

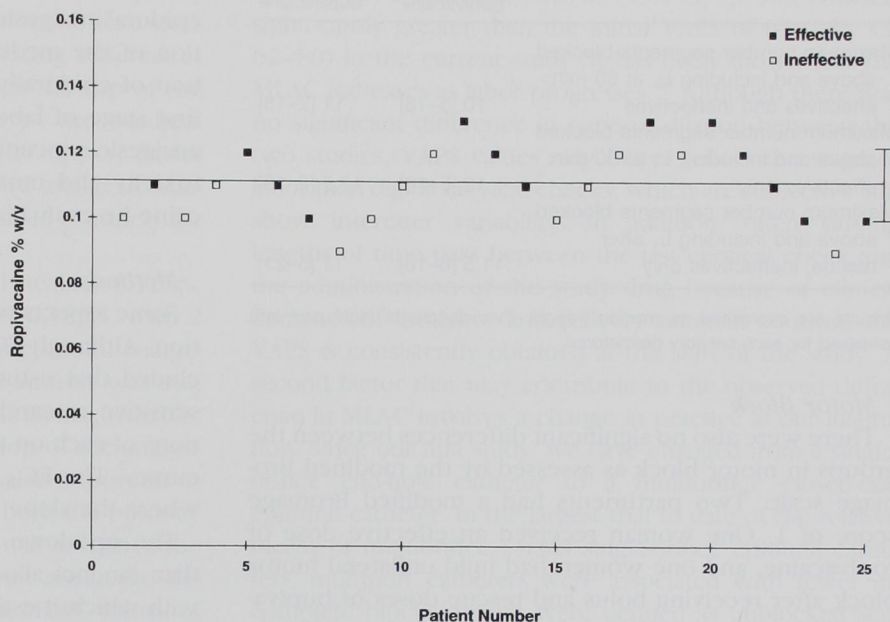


Fig. 1. The median effective local anesthetic concentration of ropivacaine as determined by the technique of up-down sequential allocation. The minimum local anesthetic concentration is 0.111% wt/vol. Error bars represent 95% confidence intervals. The testing interval was 0.01% wt/vol.

Ropivacaine is significantly less potent ($P < 0.0001$; 95% CI difference % wt/vol, 0.027-0.061) than bupivacaine, with a potency ratio of 0.6 (95% CI, 0.49-0.74).

Sensory Block

There were no significant differences between the groups in the number of segments blocked (table 4).

MLAC Bupivacaine in Labor

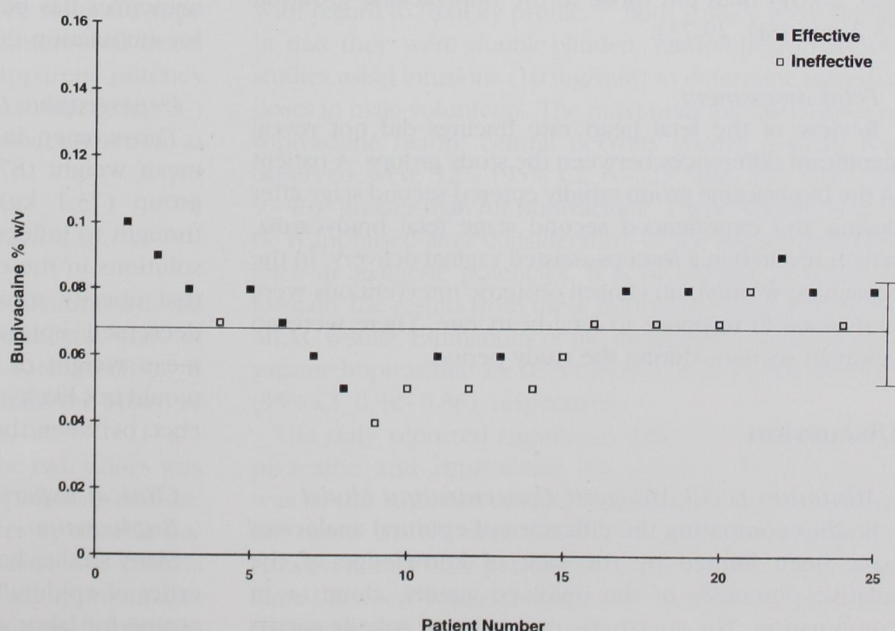


Fig. 2. The median effective local anesthetic concentration of bupivacaine as determined by the technique of up-down sequential allocation. The minimum local anesthetic concentration is 0.067% wt/vol. Error bars represent 95% confidence intervals. The testing interval was 0.01% wt/vol.

Table 4. Maximum Number of Segments Blocked

	Ropivacaine	Bupivacaine
Maximum number segments blocked above and including L ₁ at 30 min; effectives and ineffectives	10 [5-18]	11 [2-18]
Maximum number segments blocked above and including L ₁ at 30 min; effectives only	12 [5-18]	12.5 [2-18]
Maximum number segments blocked above and including L ₁ after rescue; ineffectives only	11.5 [6-16]	11 [5-21]

Results are expressed as median [range]. Two segments (right and left) assessed for each sensory dermatome.

Motor Block

There were also no significant differences between the groups in motor block as assessed by the modified Bromage scale. Two parturients had a modified Bromage score of 1. One woman received an effective dose of ropivacaine, and one woman had mild unilateral motor block after receiving bolus and rescue doses of bupivacaine. Eleven patients who received effective analgesia performed the bedside partial knee bend without difficulty. Many patients declined because of advanced labor or sleep deprivation. Of the 11 patients, 7 were in the ropivacaine group, and 4 were in the bupivacaine group.

Block Duration

The women in the ropivacaine group experienced a longer mean duration of effective analgesia at 93.7 min (SD, 28.61) than did those in the bupivacaine group at 73.2 min (SD, 29.73).

Fetal Assessment

Review of the fetal heart rate tracings did not reveal significant differences between the study groups. A patient in the bupivacaine group rapidly entered second stage after dosing and experienced second stage fetal bradycardia, which resulted in a forceps-assisted vaginal delivery. In the remaining women, no clinical obstetric interventions were performed in response to fetal heart rate. There were no cesarean sections during the study period.

Discussion

Minimum Local Anesthetic Concentration Model

Studies comparing the efficacies of epidural analgesics have been limited by the lack of knowledge of the relative potencies of the involved agents, alone or in combination. The anesthetic potencies of volatile agents

have been quantified in terms of minimum alveolar concentration, and the same concept can be applied to epidural analgesics. The MLAC model allows the estimation of the median effective local anesthetic concentration of epidurally administered local anesthetics in the first stage of labor.^{7,8} Only with the use of equipotent analgesic concentrations can the relative local anesthetic toxicity and motor effects of ropivacaine and bupivacaine be evaluated properly.

Methods

Some aspects of our methods require further explanation. Although EC₉₅ is more clinically relevant, we concluded that estimation of EC₅₀ would provide a more sensitive research tool because of the respective positions of each on the cumulative concentration-response curve.⁷ The EC₅₀ corresponds with the inflection point where the slope is greatest.

The up-down sequential allocation technique, rather than random allocation, was chosen because of the ease with which it estimates EC₅₀ of a sample. This technique has been used to determine dose-response pharmacodynamics for inhalational and intravenous anesthetics.¹⁴⁻¹⁶

A modified Bromage scale was used to evaluate lower extremity strength. This measure of motor blockade is easily obtained in the laboring patient but may not be sufficiently sensitive to detect subtle diminutions in muscle strength. To improve sensitivity, we also asked the study participants who received an effective concentration to perform a partial knee bend at the bedside. This maneuver has been described previously as a criterion for ambulation during labor.¹⁷

Demographic Difference

The women in the ropivacaine group had a greater mean weight (87.9 kg) than those in the bupivacaine group (73.1 kg). Although weight generally is not thought to influence the distribution of local anesthetic solutions in the epidural space, there is some evidence that obesity results in greater cephalad spread and a decreased epidural dose requirement.¹⁸ The greater mean weight of the women in the ropivacaine group would not likely exaggerate the observed potency difference between the two local anesthetics.

Clinical Experience with Ropivacaine versus Bupivacaine

Many studies have compared the local anesthetic properties of epidurally administered ropivacaine and bupivacaine for labor analgesia. Most investigators have com-

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pared ropivacaine, 0.25%, and bupivacaine, 0.25%,¹⁹⁻²¹ and they did not find significant differences in the quality of analgesia, sensory block, or motor block. These studies highlight the difficulty of demonstrating differences in potency when high concentrations at the top of the analgesic concentration-response curve⁷ are studied. These concentrations correspond to the upper, flatter part of the dose-response curve, where analgesic success is predictable. They are no longer used routinely for labor analgesia.

A more recent study compared ropivacaine, 0.125%, with 2 µg/ml fentanyl and bupivacaine, 0.125%, with 2 µg/ml fentanyl using patient-controlled epidural analgesia.²² The preliminary conclusion of the authors was that the local anesthetics were clinically indistinguishable. Again, these concentrations are at the top of the analgesic concentration-response curve. It is also important to realize that with an infusion technique both the potency and duration of the administered drugs will influence the number of patient-controlled epidural analgesia demands made over time. Conversely, the MLAC values of ropivacaine and bupivacaine reflect analgesic potency alone and in a "snapshot" manner.

Block Duration

Effective ropivacaine analgesia lasted longer than that observed with bupivacaine. This may reflect the greater concentration of local anesthetic administered or may be a pharmacokinetic effect. Although most studies report faster clearance for ropivacaine than bupivacaine, one human study reported a lesser clearance value for ropivacaine than for bupivacaine after an intercostal nerve block.²³ Vasoactivity can also affect apparent potency and local anesthetic duration. It has been noted that S(-) enantiomers in particular produce vasoconstriction at lower concentrations.²⁴⁻²⁷

Minimum Local Analgesic Concentration of Bupivacaine

Several groups of investigators have determined the MLAC of bupivacaine. A British study reported the MLAC of bupivacaine as 0.065% wt/vol (95% CI, 0.045-0.085).⁷ A previous study at our institution determined the MLAC of bupivacaine to be 0.104% wt/vol (95% CI, 0.090-0.117).¹¹ At that time, the discrepancy between the two values was attributed to differences in the study populations and the tendency to place epidural catheters later in labor at our institution. In this study, MLAC bupivacaine was 0.067% wt/vol (95% CI, 0.052-0.082), which closely approximates the British measurement. Several explanations for the dif-

ference in MLAC may exist. Of note, the initial median VAPS in the earlier study was 83 (95% CI, 73-90), which is significantly greater than the initial VAPS of 69 (95% CI, 62-80) in the current study. It has been shown that the MLAC increases as labor progresses.²⁸ Although there was no significant difference in cervical dilation between the two studies, VAPS values may better reflect the stage of labor than digital cervical checks, which are subjective and show interrater variability. In addition, often varying lengths of time pass between the last cervical check and the administration of the study drug because of clinical demands of the labor and delivery suite. In contrast, the VAPS is consistently obtained at the start of the study. A second factor that may contribute to the observed difference in MLAC involves a change in practice at our institution. Since our first study, we have changed from a single-orifice end-hole catheter to a multiorifice closed-end epidural catheter. In the largest trial to date of the relative merits of multiorifice *versus* single-orifice epidural catheters, multiport catheters were associated with fewer incomplete blocks, which were defined as unblocked segments or unilateral blocks.²⁹ With the MLAC method, patients experiencing pain from unblocked segments would report higher pain scores, which effectively increases the occurrence of ineffective analgesia and results in higher subsequent concentrations and MLAC values.

Therapeutic Index

Two human toxicology studies comparing ropivacaine and bupivacaine have reported advantages for ropivacaine with regard to toxicity profile.^{2,3} Both studies were similar in that they were double-blinded, randomized crossover studies using infusions (10 mg/min) to determine tolerated doses in male volunteers. The maximum tolerated doses of ropivacaine before central nervous system toxicity was observed were 12% (95% CI, 6-32)² and 25% (95% CI, 9-46)³ greater than for bupivacaine. These studies need to be reappraised after consideration of the significant difference in analgesic potencies. It is of interest to compare formally the results from these toxicology studies with our MLAC results. Estimations of the therapeutic ratios for ropivacaine:bupivacaine are 0.75 (95% CI, 0.58-0.96) and 0.67 (95% CI, 0.52-0.88), respectively.

The only reported significant difference between bupivacaine and ropivacaine for cardiovascular toxicity was in the Knudsen study,³ where QRS durations were increased by 6% and 2.4% ($P < 0.05$), respectively. However, this only amounted to an overall 1-ms difference between the drugs and must be considered among the many end points analyzed.

Although 12–25% more ropivacaine than bupivacaine may be tolerated for central nervous system toxicity,^{2,3} the 40% reduction in the analgesic potency of ropivacaine ensures that the therapeutic ratio significantly favors bupivacaine.

Conclusions

Epidural ropivacaine has been advocated as superior to bupivacaine as an agent for labor analgesia based on claims of decreased motor blockade and a reduced potential for cardiotoxicity. At the low concentrations now used for labor analgesia, motor block is not significant with either agent. Considering the relative potencies of the two local anesthetic agents, therapeutic indexes will need to be reevaluated. We have shown that ropivacaine was significantly less potent than bupivacaine for epidural analgesia in the first stage of labor for the parturients in this study.

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