

CME

Ropivacaine Versus Bupivacaine for Epidural Labor Analgesia

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Neuraxial analgesia is frequently administered to women in labor. For many years, bupivacaine has been used because of its long duration of action, lack of excessive motor block, and minimal fetal and neonatal effects. However, bupivacaine is one of the most cardiotoxic local anesthetics in current use and motor block is still a problem. Many local anesthetics such as bupivacaine exist in 2 forms, levorotatory and dextrorotatory. Ropivacaine, an amide local anesthetic produced in the pure levorotatory form addresses some of the concerns related to bupivacaine. In this article, we present the literature comparing ropivacaine and bupivacaine to determine whether there is an advantage to using one of these local anesthetics for labor analgesia. We found that there is no advantage to the routine use of ropivacaine for labor analgesia. (Anesth Analg 2010;111:482-7)

Neuraxial analgesia is frequently administered to women in labor.¹ For many years, bupivacaine has been used because of its long duration of action, limited placental transfer,² and minimal neonatal effects.³ Compared with older local anesthetics such as tetracaine, bupivacaine provided better analgesia without excessive motor block.⁴ In addition, compared with lidocaine, there was less tachyphylaxis with long-term administration.⁵ However, bupivacaine is more cardiotoxic than other local anesthetics⁶ and motor blockade accompanies the analgesia especially at higher concentrations.⁷ Many local anesthetics such as bupivacaine exist in 2 forms, levorotatory and dextrorotatory.⁸ Ropivacaine is an amide local anesthetic produced in the pure levorotatory form. Its use may address some of the concerns related to bupivacaine. The purpose of this review is to assess whether there is an advantage to the use of either of these local anesthetics for labor neuraxial analgesia.

Pharmacology

Most amide local anesthetics are chiral compounds because they have an asymmetric carbon molecule and therefore exist in 2 forms known as enantiomers. An enantiomer is 1 of 2 molecules with the same chemical composition; the molecules are nonsuperimposable mirror images of each other. There are 2 systems for naming the individual enantiomers. The first system is based on the direction in which the enantiomer rotates polarized light; the molecule that rotates light clockwise is named dextrorotatory and the

one that rotates light counterclockwise is named levorotatory. The second system uses the Cahn-Ingold-Prelog priority rules based on atomic number and is unrelated to light rotation. If the priority system from the stereocenter moves in the clockwise direction, it is named *R* or rectus and if in the counterclockwise direction it is named *S* or sinister.

Although the molecules have identical chemical structures, they may have distinct pharmacologic, pharmacokinetic, and toxicology properties. Until the early 1990s, local anesthetics were only commercially available as a racemic (50:50) mixture of the dextrorotatory and levorotatory forms. Ropivacaine, an amide local anesthetic produced as the pure levorotatory enantiomer, became commercially available in 1996. It is a homologue of both bupivacaine and mepivacaine; the 3 local anesthetics only differ in the group attached to the pipercol ring. Mepivacaine has a methyl group, bupivacaine has a butyl group, and ropivacaine has a propyl group attached to the ring (Fig. 1). Since its inception, there have been numerous studies comparing ropivacaine to bupivacaine in terms of efficacy, potency, toxicity, and obstetric outcome.

Potency

To compare the therapeutic and side effects of local anesthetics, a measure of potency must be established. The EC₅₀ (median effective concentration, also known as the minimum local anesthetic concentration) has been used for this purpose. The EC₅₀ is determined by the up-down sequential allocation technique using the method of Dixon and Massey.⁹ Based on pilot studies, the investigator chooses an initial concentration (or dose) of local anesthetic for the first patient (administered in a fixed volume). The subsequent concentration within each group is determined by the outcome of the preceding patient in that group. If the response is positive, e.g., relief of labor pain, then a predetermined constant decrease in the concentration is used for the next patient. If negative, e.g., labor pain was not relieved, then a predetermined constant increase in the concentration is used for the next patient.

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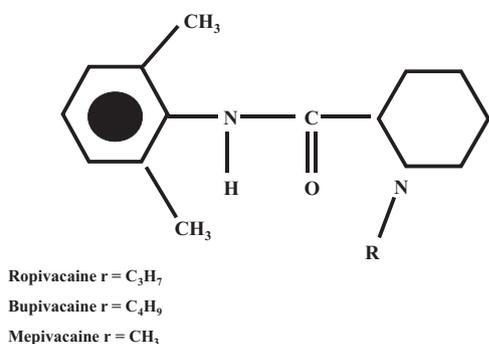


Figure 1. Bupivacaine, mepivacaine, and ropivacaine are similar compounds and only differ by the group (designated as *R*) attached to the piperidine ring. Bupivacaine has a butyl group, mepivacaine has a methyl group, and ropivacaine has a propyl group attached to the ring.

The analgesic potency of epidural ropivacaine and bupivacaine in parturients in early labor was directly compared in 2 studies.^{10,11} In both studies, the investigators gave 20 mL local anesthetic to initiate analgesia. The primary end point was effective analgesia as measured by a visual analog scale (0–100 mm) pain score of <10 mm at 30 minutes. The concentration of local anesthetic was chosen for the first patient in each group, and then decreased by 0.01% if the block was effective, or increased by 0.01% if ineffective. In both studies, the analgesic potency of ropivacaine was approximately 60% that of bupivacaine (Fig. 2). When motor block, as measured by the Bromage score, was the primary outcome, similar results were obtained; ropivacaine was 65% to 76% as potent as bupivacaine.^{12,13} These results are important because most studies that compared the obstetric outcomes of ropivacaine with bupivacaine compared the same concentrations of the drugs and did not consider potency.

Some experts argue, however, that because the complete dose-response curve of both drugs is unknown, it is possible that the EC_{95} of the 2 local anesthetics (the effective concentration for 95% of the population) is similar, even though the EC_{50} of bupivacaine is less than that of ropivacaine.¹⁴ This theory is supported by clinical studies in which similar amounts of ropivacaine and bupivacaine were consumed when women were allowed to titrate to effect bupivacaine or ropivacaine solutions of equal concentration with patient-controlled epidural analgesia.^{15,16} An alternative explanation for these findings is that the EC_{95} values of bupivacaine and ropivacaine are different, but similar doses are consumed during the course of a long labor because other factors such as duration of action (greater with ropivacaine than bupivacaine) have a role in the drugs' clinical profiles.¹¹

There has been at least one attempt to define the EC_{95} . Using a random dose allocation study design and probit analysis, Van de Velde et al.¹⁷ studied laboring parturients given intrathecal ropivacaine or bupivacaine, ranging from 1.0 to 3.5 mg in 0.5-mg increments combined with 1.5 μ g sufentanil. Each dosage group contained at least 20 patients. The ED_{95} for bupivacaine was 3.3 mg (95% confidence interval, 2.9–4.1 mg) and for ropivacaine was 4.8 mg (95% confidence interval, 4.0–6.7 mg). The ED_{95} for ropivacaine was derived by extrapolation because it was larger than the largest

dose tested. Other issues limiting firm conclusions are that patients were of mixed parity in different stages of labor, and some labors were induced and others were not. Furthermore, the potency of the drugs administered into the epidural space may not be the same as when administered intrathecally.

Toxicity

Albright,⁶ in 1979, reported 6 cases of cardiac arrest related to accidental IV injection of bupivacaine or etidocaine. One of the patients was a parturient who received 12 mL of epidural 0.75% bupivacaine (90 mg). This report, in part, led to the United States Food and Drug Administration banning the use of epidural bupivacaine 0.75% for obstetric patients. Because it is more difficult to resuscitate patients from bupivacaine-induced cardiac arrest compared with other local anesthetics such as lidocaine,¹⁸ other changes in anesthesia practice to reduce the risk of IV local anesthetic injection were encouraged. These include the use of a test dose, aspiration of the epidural catheter before administration of local anesthetic, and fractionation of doses. Additionally, a safer local anesthetic drug has been sought.¹⁹

Local anesthetics are toxic to both the central nervous system (CNS) and cardiovascular system. Generally, CNS signs and symptoms, e.g., tinnitus or seizures, occur at lower blood levels than cardiac signs and symptoms, e.g., hypotension or dysrhythmia. In a canine model, Feldman et al.²⁰ infused bupivacaine or ropivacaine at a rate of 2 mg/kg/min and found that the dose required to produce seizures was similar in both groups, 4.31 mg/kg versus 4.88 mg/kg in the bupivacaine and ropivacaine groups, respectively. However, others have found in animal models that the convulsive dose is 1.5 to 2.5 times larger for ropivacaine than bupivacaine on a mg/kg basis,^{21,22} even when controlling for the greater potency of bupivacaine.²² These results were confirmed in a study in nonanesthetized sheep by Ladd et al.,²³ who injected local anesthetic directly into the carotid artery to minimize any cardiac effects; they found that the CNS toxicity was greatest with bupivacaine followed by ropivacaine.

Cardiac toxicity has been studied in vitro in rabbit Purkinje fiber–ventricular muscle preparations. These studies showed that ropivacaine depressed cardiac excitability and conduction to a smaller degree than bupivacaine as measured by action potential amplitude and maximal rate of depolarization (V_{max}).^{24,25} Also, when injected directly into the coronary artery of sheep at doses that minimize CNS effects, ropivacaine produced fewer myocardial depression and conduction changes than bupivacaine.²⁶ Santos et al.²¹ and Nancarrow et al.²⁷ in the sheep model and Feldman et al.²⁰ in the canine model found that the fatal dose was larger in those given ropivacaine versus bupivacaine. Santos et al.²¹ also demonstrated that unlike initial reports,²⁸ local anesthetic toxicity is not enhanced during pregnancy. The study by Feldman et al.²⁰ may have particular clinical relevance because animals in this study received a rapid IV bolus to induce cardiac dysrhythmia and death, whereas in other studies animals received a continuous IV infusion at a slow rate. This is particularly important because most instances of toxicity in clinical practice are from an inadvertent rapid IV bolus rather than increased serum levels that may occur from absorption

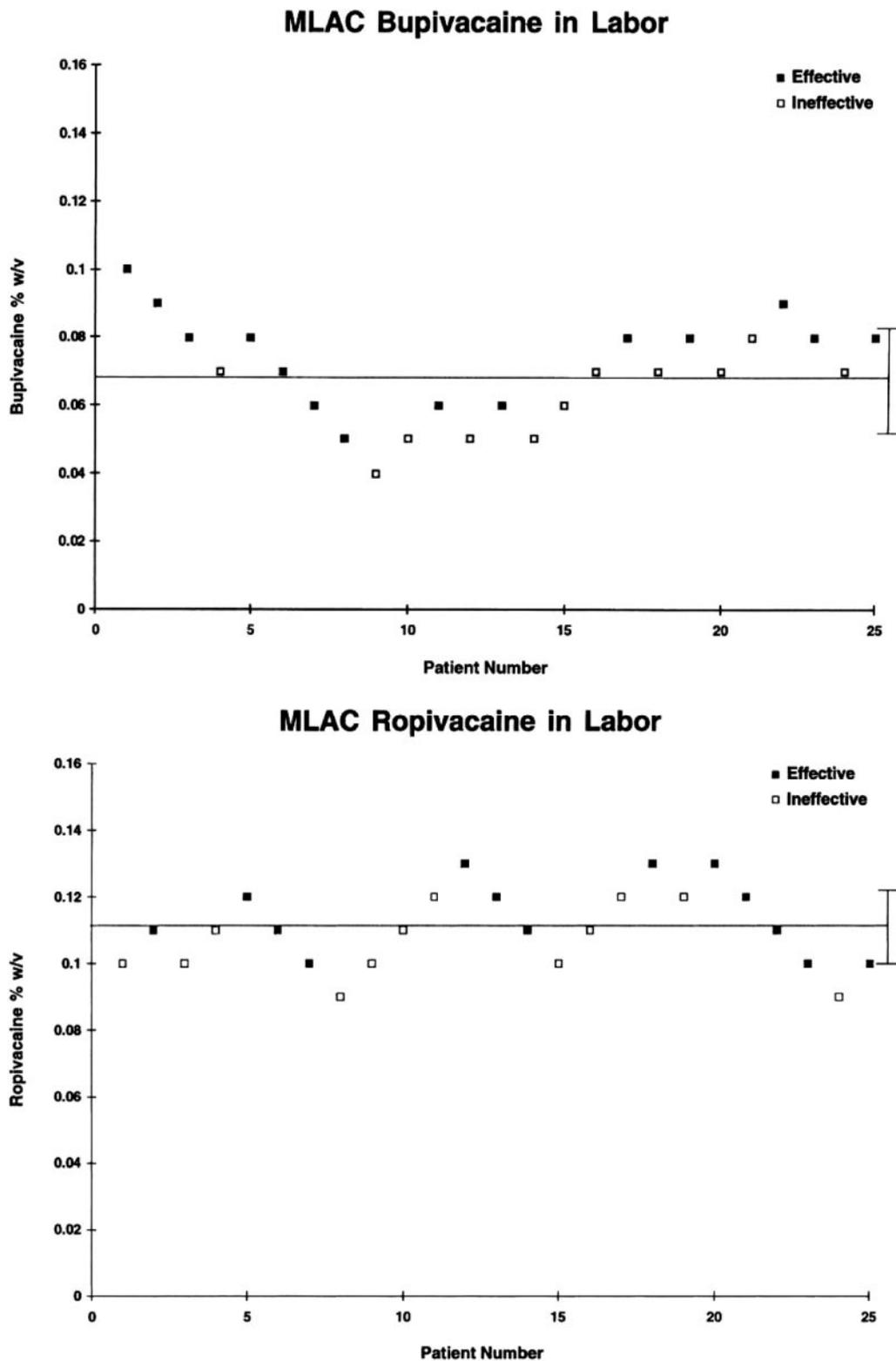
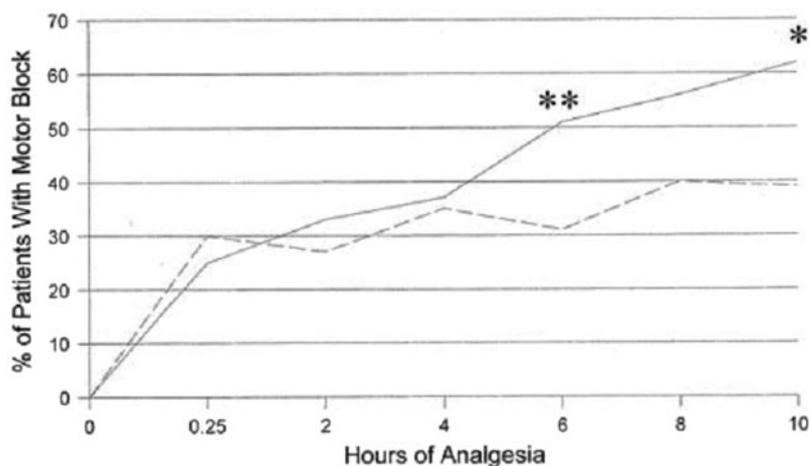


Figure 2. Minimum local anesthetic concentration (MLAC) of bupivacaine and ropivacaine. Note that ropivacaine is approximately 60% as potent as bupivacaine. w/v = weight/volume. (Reproduced from Polley et al.,¹¹ with permission.)

during a properly placed anesthetic block. Feldman et al.²⁰ gave twice the convulsive dose as an IV bolus to the dogs and found more frequent fatality in those given bupivacaine, suggesting that the margin of safety is greater with

ropivacaine. Most studies have found that it is easier to resuscitate an animal from a toxic dose of ropivacaine than from bupivacaine^{29,30} but others found no difference with a high success rate in both groups.³¹

Figure 3. The percentage of patients with motor block (modified Bromage score of 1–5) over time. Solid line represents bupivacaine; dashed line represents ropivacaine. * $P < 0.05$; ** $P < 0.01$. (Reproduced from Halpern et al.,³⁶ with permission.)



Human studies have been limited for obvious reasons. Scott et al.³² studied the toxic effects of ropivacaine in 12 volunteers. The volunteers received both an IV infusion of ropivacaine or bupivacaine in random order separated by at least 7 days and were told to relate the onset of CNS toxicity, e.g., tinnitus, at which time the infusion was stopped. The volunteers were monitored with an interpretive electrocardiograph and echocardiography. The onset of CNS symptoms occurred at a lower dose of bupivacaine and the subjects tolerated approximately 25% more ropivacaine, 124 mg, than bupivacaine, 99 mg. Additionally, 7 of 12 volunteers tolerated the full dose of ropivacaine (150 mg) compared with only 1 of 12 with bupivacaine ($P < 0.01$). Both drugs depressed conductivity and contractility, but these effects were noted at lower plasma concentrations of bupivacaine. A similar study was repeated by Knudsen et al.³³ but the maximum total dose was set at 250 mg. Overall, the findings suggested less toxicity for ropivacaine but the results were not as dramatic as in the study by Scott et al. None of the volunteers tolerated the full dose. Unlike the study by Scott et al., there was no statistically significant difference in average maximum tolerated dose, 115 mg versus 103 mg in the ropivacaine and bupivacaine groups, respectively. CNS symptoms were more pronounced and lasted for a longer duration in the bupivacaine group. Some measures of cardiac toxicity, e.g., increased QRS width and stroke volume, were more pronounced in the bupivacaine group but other findings, e.g., left ventricular ejection fraction, were not.

In conclusion, animal and human studies have found either an advantage with ropivacaine in regard to toxicity or no difference between ropivacaine and bupivacaine. It would seem that if there is a difference, it is minimal. At the very dilute concentrations currently used for labor analgesia, e.g., 0.0625% to 0.1%, it is probably a moot point because cardiac toxicity at these doses is highly unlikely, even when administered inadvertently IV.

Maternal Outcome

Epidural labor analgesia may influence obstetric outcome. In particular, the resultant motor block from the epidural local anesthetic may increase the rate of instrumental

vaginal delivery.⁷ In this section, we describe the investigations that compare ropivacaine with bupivacaine and their effects on maternal outcome such as progress of labor, motor block, analgesic efficacy, and maternal satisfaction.

Early randomized controlled trials compared 0.25% ropivacaine with 0.25% bupivacaine in laboring women of mixed parity. The results of these studies were summarized in a meta-analysis that included almost 400 patients.³⁴ The investigators suggested that ropivacaine was associated with an increased incidence of spontaneous vaginal delivery compared with bupivacaine because of a reduction in the use of forceps. They also demonstrated a reduction in motor block and better late neonatal adaptive capacity scores. The results of these studies should be interpreted with caution because each was a phase III trial designed by the pharmaceutical company to fulfill regulatory requirements for the introduction of ropivacaine into clinical practice.³⁵ Furthermore, the results are not relevant to the current clinical practice of using lower concentrations of local anesthetic drugs with or without adjuvant opioids. Finally, important outcomes such as maternal analgesia and satisfaction were not reported.

There have been 3 randomized controlled trials that compared dilute solutions of bupivacaine and ropivacaine in laboring women.^{36–38} The studies maintained analgesia with equal concentrations of ropivacaine and bupivacaine (0.0625%–0.1%) combined with fentanyl 2 $\mu\text{g}/\text{mL}$. One study reported a statistically significant prolongation in the first stage of labor in the bupivacaine group³⁷ but this was not a consistent finding.^{36,38} None of the studies found any differences between groups in the duration of the second stage of labor, incidence of spontaneous vaginal delivery, instrumental vaginal delivery, or cesarean delivery. There were no differences in maternal analgesia between groups as measured by the number of supplemental boluses of local anesthetic or visual analog scale pain scores, nor were there any differences in the global maternal satisfaction scores.^{36,37} The onset of analgesia for both drugs was similar.³⁸ In all these studies, there was an increased incidence of motor block in the bupivacaine group and it was statistically significant in two.^{36,38} In one of the studies,

Table 1. Maternal Outcomes in Those Who Received Epidural Bupivacaine Versus Ropivacaine for Labor Analgesia

Outcome	No. of patients in bupivacaine group, n/N (%)	No. of patients in ropivacaine group, n/N, (%)	Risk difference (%) and 95% CI	P value
Spontaneous vaginal delivery	499/917 (54%)	538/930 (58%)	1.17 (0.96–1.41)	0.12
Instrumental vaginal delivery	242/889 (27%)	233/898 (26%)	0.89 (0.67–1.18)	0.4
Cesarean delivery	151/910 (17%)	138/921 (15%)	0.88 (0.67–1.14)	0.3
Excellent analgesia	253/331 (76%)	263/341 (77%)	1.07 (0.73–1.59)	0.7
Ambulation	262/391 (67%)	270/393 (69%)	1.17 (0.58–2.38)	0.7
Hypotension	34/308 (11%)	35/307 (11%)	1.04 (0.6–1.8)	0.9

CI = confidence interval.

Adapted from Halpern et al.,³⁹ with permission.

the difference in motor block was noted after 6 hours of analgesia and seemed to increase over time (Fig. 3).³⁶

The results of these studies are in agreement with a recently published meta-analysis of 23 randomized controlled trials comprised of 2074 patients.³⁹ There was no difference in the incidence of adverse maternal obstetric outcomes between groups. The meta-analysis confirmed that there was an increase in the incidence of motor block in the bupivacaine group. However, there was no difference in the ability to ambulate. Maternal satisfaction was very high but there was no difference between groups as measured by a global visual analog scale (Table 1).

We conclude that ropivacaine and bupivacaine are similarly effective as epidural labor analgesics. There may be a small reduction in the incidence of motor block in women who receive ropivacaine especially with longer labors. In view of the lack of effect on progress of labor, ambulation, and maternal satisfaction, this difference may not be clinically important.

Neonatal Outcome

There is no evidence that neonatal outcome is adversely affected when ropivacaine or bupivacaine is used for labor analgesia. The incidence of low Apgar scores at 5 minutes is approximately 2% for both drugs.³⁶ In addition, the umbilical artery and vein pH are well maintained regardless of which local anesthetic is used.³⁷ Finally, the incidence of need for neonatal resuscitation is low and similar with both drugs.³⁸

Cost of the Local Anesthetics

Ropivacaine is more costly than bupivacaine. At The Mount Sinai Hospital in New York City, ropivacaine is approximately 10 times more expensive on a milligram basis than bupivacaine. Currently, ropivacaine is \$4.29 for a 20-mL vial of ropivacaine 0.2% (\$0.10/mg) and \$1 for a 30-mL vial of bupivacaine 0.25% (\$0.01/mg). This is similar to that reported previously in an editorial by D'Angelo in 2000.⁴⁰ D'Angelo estimated that the cost to switch from bupivacaine to ropivacaine for all deliveries in the United States would be \$15,000,000/year. The estimate assumes 3,000,000 vaginal deliveries per year, duration of epidural analgesia of 5.5 hours, and average local anesthetic use of 19 mL/h.

Summary

Overall, both bupivacaine and ropivacaine are effective for providing labor analgesia with little or no difference in

maternal satisfaction, mode of delivery, or other labor characteristics. Ropivacaine seems to cause less motor block, particularly in long labors, but this finding may be attributable to differences in drug potency rather than intrinsic differences between drugs. It is possible that ropivacaine is less cardiotoxic than bupivacaine when high doses are used, but this is clinically unimportant in the usual dose range used for labor analgesia. Therefore, from a clinical and safety perspective, either drug is a reasonable choice for labor analgesia. The last consideration is the cost of the medications, which cannot be ignored in today's environment. Because of cost, it is difficult to justify the routine use of ropivacaine for labor analgesia. ■

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