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A Multicenter, Randomized, Controlled Trial Comparing Bupivacaine with Ropivacaine for Labor Analgesia

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Background: **A meta-analysis of studies comparing high doses of bupivacaine with ropivacaine for labor pain found a higher incidence of forceps deliveries, motor block, and poorer neonatal outcome with bupivacaine. The purpose of this study was to determine if there is a difference in these outcomes when a low concentration of patient-controlled epidural bupivacaine combined with fentanyl is compared with ropivacaine combined with fentanyl.**

Methods: **This was a multicenter, randomized, controlled trial, including term, nulliparous women undergoing induction of labor. For the initiation of analgesia, patients were randomized to receive either 15 ml bupivacaine, 0.1%, or 15 ml ropivacaine, 0.1%, each with 5 μg/ml fentanyl. Analgesia was maintained with patient-controlled analgesia with either local anesthetic, 0.08%, with 2 μg/ml fentanyl. The primary outcome was the incidence of operative delivery. We also examined other obstetric, neonatal, and analgesic outcomes.**

Results: **There was no difference in the incidence of operative delivery between the two groups (148 of 276 bupivacaine recipients *vs.* 135 of 279 ropivacaine recipients; $P = 0.25$) or any obstetric or neonatal outcome. The incidence of motor block was significantly increased in the bupivacaine group compared with the ropivacaine group at 6 h (47 of 93 *vs.* 29 of 93, respectively; $P = 0.006$) and 10 h (29 of 47 *vs.* 16 of 41, respectively; $P = 0.03$) after injection. Satisfaction with mobility was higher with ropivacaine than with bupivacaine (mean ± SD: 76 ± 23 *vs.* 72 ± 23, respectively; $P = 0.013$). Satisfaction for analgesia at delivery was higher for bupivacaine than for ropivacaine (mean ± SD: 71 ± 25 *vs.* 66 ± 26, respectively; $P = 0.037$).**

Conclusions: **There was no difference in the incidence of operative delivery or neonatal outcome among nulliparous patients who received low concentrations of bupivacaine or ropivacaine for labor analgesia.**

BUPIVACAINE has been used for more than 3 decades for labor analgesia. Ropivacaine, a newer local anesthetic, was developed to reduce cardiovascular and central nervous system toxicity. In addition, ropivacaine may have other advantages when compared with bupivacaine, such as reduced lower extremity motor block in the parturient and better neonatal outcomes. A meta-analysis of earlier studies suggested that ropivacaine may reduce the incidence of instrumental vaginal delivery when compared with bupivacaine.[1] However, this report was based on studies that employed high concentrations of both agents.

Numerous studies have compared bupivacaine with ropivacaine for labor analgesia. However, none has had sufficient power to detect important differences in obstetric outcomes. In addition, there is some evidence from ED_{50} studies to suggest that ropivacaine may be less potent than bupivacaine.[2]

Recently, patient-controlled epidural analgesia with low doses of local anesthetic combined with opioids has become an important way of maintaining epidural analgesia.[3] In the current study, we used this method of maintenance to compare bupivacaine with ropivacaine in a clinically relevant way. The primary purpose of this study was to determine whether there is a difference in obstetric outcomes between the two drugs.

Methods

This study was conducted in four university hospitals in Canada. Each institution provided ethical approval, and we obtained written consent from each participant. We included healthy (American Society of Anesthesiologists risk classification I or II) term, nulliparous patients in induced labor between 37 and 42 weeks' gestation. We excluded patients for fetal reasons (major anomalies, intrauterine growth retardation, fetal distress, twins, and nonvertex presentation) and maternal reasons (a contraindication to epidural analgesia, significant bleeding during the pregnancy, significant medical disease, severe pregnancy-induced hypertension, or a body mass index of greater than 35).

When the patient requested epidural analgesia, she was randomized to receive either epidural bupivacaine or ropivacaine. The randomization (in random-sized blocks of between four and eight patients) was performed separately at each site and concealed either by the hospital pharmacy or in opaque, sealed, numbered envelopes. The anesthesiologist, patient, other caregivers, and recruiting personnel were blinded to drug allocation.

Epidural analgesia was initiated with 10–15 ml allocated local anesthetic, 0.1%, with 5 μg/ml fentanyl (maximum dose, 75 μg). Inadequate analgesia was treated

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with an additional 5- to 10-ml bolus of plain study local anesthetic. If there was inadequate analgesia accompanied by objective evidence of the absence of a bilateral T10 block for more than 20 min, the epidural catheter was replaced, and the procedure was repeated. Analgesia was maintained with study local anesthetic, 0.08%, and 2 μg/ml fentanyl given as patient-controlled epidural analgesia with a background infusion of 5 ml/h, a lockout of 10 min, and a bolus of 5 ml. If analgesia was inadequate, patients received clinician-initiated top-ups with 5–10 ml plain study local anesthetic, 0.1%. Persistent inadequate analgesia was treated with 5–10 ml plain study local anesthetic, 0.2%. The identification of the drug (but not the concentration) of these clinician-initiated top-ups was concealed from the clinician. After each clinician-initiated top-up, the background infusion was increased by 1 ml/h. If analgesia was still unsatisfactory, the clinician was allowed to withdraw the epidural catheter 1 cm and/or administer up to 10 ml lidocaine, 2% (unblinded). If this was inadequate, the treatment of the patient was considered to be a technical failure and the patient was removed from the study.

The management of the first and second stages of labor, including the use of oxytocin augmentation, was by protocol according to the clinical practice guidelines for dystocia of the Society of Obstetrics and Gynaecologists of Canada.[4]

The primary outcome of the study was the difference in the incidence of operative delivery (cesarean section plus operative vaginal delivery) between the two groups. Other important outcomes included the incidence of cesarean section, instrumental vaginal delivery, and episiotomy. Neonatal outcomes included the incidence of an Apgar score of less than 7 at 1 and 5 min, the need for neonatal resuscitation, and an umbilical artery cord pH of less than 7.2. The anesthetic outcomes included the dose of local anesthetic needed to provide initial patient comfort, visual analog scale scores for pain at 15 min after the initiation of the block and every 2 h after (to 10 h), and the need for clinician intervention. Motor block of the lower extremities was measured using the 6-point modified Bromage score[5] (1, no movement of the lower extremities; 2, able to flex ankles; 3, able to flex knees; 4, able to flex hips in the supine position; 5, able to stand; 6, able to stand and do a partial knee bend). In addition, we assessed the ability of the parturient to ambulate and to spontaneously micturate. We measured global maternal satisfaction, maternal satisfaction with analgesia, and maternal analgesia with motor block using visual analog scales within 24 h of delivery.

Analysis

We based our sample size on the following: (1) The rate of operative delivery among induced, nulliparous patients was about 50% at each site. We determined this from inspecting historical data. (2) A clinically important difference between groups was about 12%. On the basis of these assumptions, we needed approximately 285 patients in each group to obtain a power of 80% to detect this difference.

We used descriptive statistics to characterize the demographic data. We used the Fisher exact test for dichotomous variables, including the primary outcome. We used an unpaired Student *t* test for continuous variables such as umbilical artery cord pH and scores. A *P* value of less than 0.05 was considered statistically significant.

Results

We randomized 574 patients from September 1, 1998, until June 30, 2000. Of these patients, 287 were randomized to receive bupivacaine and 287 were randomized to receive ropivacaine. There were 11 patients in the bupivacaine group and seven patients in the ropivacaine group who did not receive the assigned drug or were technical failures and were withdrawn from the study by the attending anesthesiologist. One patient in the ropivacaine group was withdrawn from the study because breech presentation was diagnosed after randomization.

There were minor protocol violations in drug dosages for eight patients. Two patients in the bupivacaine group and six patients in the ropivacaine group received more than 50 ml local anesthetic at the initiation of analgesia. We replaced the epidural catheter in six patients who received bupivacaine and 14 patients who received ropivacaine after initial analgesia was unsatisfactory ($P = 0.07$). These patients were not withdrawn from the study but were analyzed in their respective groups.

The distribution of deliveries among the centers is shown in table 1. The incidence of operative delivery was 49% in hospital 1, 60% in hospital 2, 41% in hospital 3, and 42% in hospital 4. The remaining demographics are shown in table 1.

The obstetric outcomes are shown in table 2. There was no statistically significant difference in the number of operative deliveries between the two groups (135 of 279 ropivacaine recipients *vs.* 148 of 276 bupivacaine recipients; $P = 0.25$). Similarly, there was no difference in the incidence of cesarean section or spontaneous vaginal delivery. There was no difference between the groups in the incidence of episiotomy.

The neonatal outcomes are shown in table 3. There was no difference between the groups in the Apgar scores at 1 and 5 min or in the umbilical artery cord pH. Similarly, there was no difference in the need for resuscitation between the groups.

The analgesic outcomes are compared in table 4. There was no difference in the visual analog scale scores for pain at any time during the study (fig. 1). After 6 h,

Table 1. Demographics

Demographics	Bupivacaine	Ropivacaine
No. of patients randomized		
Hospital 1	81	88
Hospital 2	76	72
Hospital 3	78	79
Hospital 4	41	40
Total	276	279
Mean (SD) maternal age, yr	28 (5.4)	28 (4.9)
Mean (SD) maternal body mass index	30 (4)	30 (4)
Mean (SD) gestational age, wk	40 (1.3)	40 (1.4)
Median (range) gravida	1 (1–6)	1 (1–7)
Mean (SD) newborn weight, g	3,563 (586)	3,512 (586)
Mean (SD) length of first stage of labor, min	440 (282)	436 (281)
Mean (SD) length of second stage of labor,* min	147 (93)	147 (116)
Mean (SD) duration of epidural analgesia, min	500 (354)	475 (283)
No. of patients who received oxytocin augmentation	110	100
Median (range) Bishop score before epidural	5 (0–11)	5 (0–12)

* Forty-nine patients in the bupivacaine group and 30 patients in the ropivacaine group were delivered by cesarean section before entering the second stage.

there were fewer patients with any degree of motor block in the ropivacaine group. This finding was statistically significant at 6 and 10 h (fig. 2).

Overall maternal satisfaction with both drugs was very good (table 5). Patient satisfaction with mobility was significantly better in the ropivacaine group ($P = 0.013$). However, patients were less satisfied with analgesia at delivery in this group ($P = 0.037$).

Discussion

We found no difference in the incidence of operative delivery between ropivacaine and bupivacaine when given for labor analgesia, nor was there a statistically significant increase in the incidence of cesarean section or forceps delivery between the groups. Although numerous studies have compared ropivacaine with bupivacaine, none have had sufficient power to detect a difference in obstetric outcomes.[6–25] We chose our population of patients (induced, nulliparous women) in an attempt to study patients at high risk for operative deliveries to maximize the probability of finding a difference.

Table 2. Obstetric Outcomes

Outcome	Bupivacaine No. (%) of Patients	Ropivacaine No. (%) of Patients	*P*
			0.175
Spontaneous vaginal delivery	128 (46)	144 (51)	
Instrumental vaginal delivery	80 (29)	84 (30)	
Cesarean delivery	68 (25)	51 (18)	
Total	276	279	
Operative delivery (instrumental plus cesarean delivery)	148 (54)	135 (48)	0.25
Episiotomy/total no. (%)	70/202 (35)	74/220 (34)	0.84

Table 3. Neonatal Outcomes

Outcome	Bupivacaine	Ropivacaine	*P*
Apgar score at 1 min			
Median (range)	8 (1–10)	8 (0–10)	0.89
<7	46/276	44/279	0.67
Apgar score at 5 min			
Median (range)	9 (4–10)	9 (1–10)	0.79
<7	5/273	11/279	0.14
Mean (SD) umbilical artery pH	7.25 (0.08)	7.24 (0.08)	0.49
Need for resuscitation			
Oxygen	74/276	75/279	1.0
Bag and mask	20/276	32/279	0.08
Naloxone	3/276	2/279	0.69
CPR	0/276	3/279	0.25
Total*	93/276	100/279	0.59

* Some neonates required more than one intervention.

CPR = cardiopulmonary resuscitation.

A recent meta-analysis of these studies, including 1,831 patients, showed a result similar to that of the current study, strengthening the conclusion.[26] In particular, although the difference in the incidence of cesarean section between the groups in our study approached statistical significance, this finding was not confirmed by the meta-analysis in which the odds ratio was 0.88 (95% CI, 0.67–1.14), favoring ropivacaine ($P = 0.3$).

In contrast, Writer *et al.*[1] performed a meta-analysis of six selected studies in 1998. They described a significant reduction in the incidence of instrumental vaginal delivery among patients who received ropivacaine compared with bupivacaine. However, their findings were based on only six studies, including about 400 patients, that compared high concentrations of both drugs (0.25–0.5%). Further, because of the multiple comparisons in their analysis, the statistically significant result may have been due to chance. In contrast, although not statistically significant, we found fewer instrumental deliveries in patients who received bupivacaine. Over the last 4 yr, other studies have also reported the incidence of instrumental deliveries to be numerically equal[7,17,19,21] or reduced[9,11,20,22] in the bupivacaine group.

This study showed a statistically significant reduction in motor block after 6 h of use in patients who received ropivacaine (fig. 2). The clinical importance of this finding was confirmed by the fact that patients reported an increase in satisfaction with motor block (table 5) on the postpartum questionnaire ($P = 0.017$). We did not find any other significant differences in other outcomes such as the incidence of ambulation or the need for bladder catheterization that may have been associated with a reduction in motor block. In this study, a reduction in

Table 4. Analgesic Outcomes

Outcome	Bupivacaine	Ropivacaine	*P*
Median (range) volume of local anesthetic (ml) for initiation of analgesia	15 (10–55)	15 (10–55)	0.12
Median (range) total no. clinician top-ups per patient in labor	0 (0–9)	0 (0–9)	0.23
Median (range) no. of clinician top-ups per patient with solution, 0.2%	0 (0–3)	0 (0–5)	0.50
Median (range) no. of clinician top-ups per patient with lidocaine, 2.0%	0 (0–2)	0 (0–6)	0.16
Mean (SD) total volume (ml) of epidural analgesic used	84.8 (61)	87.7 (68)	0.68
Median (range) total dose (μg) of fentanyl	211 (80–925)	215 (78–950)	0.86
Median (range) modified Bromage score,* no. of patients tested			
15 min	6 (1–6), 250	6 (3–6), 254	0.23
2 h	6 (1–6), 198	6 (3–6), 206	0.22
4 h	6 (3–6), 141	6 (2–6), 135	0.72
6 h	5 (3–6), 93	6 (3–6), 93	0.006
8 h	5 (2–6), 47	6 (3–6), 41	0.06
10 h	4 (2–6), 26	5 (2–6), 28	0.03
No. of patients/total no.			
Bladder catheterization	198/276	186/279	0.2
Ambulate to washroom	181/276	191/279	0.4

* Only one patient (bupivacaine) had no lower limb mobility between 15 min and 4 h. Only three patients (bupivacaine) had no lower limb mobility after 6 h.

motor block of the lower extremities did not lead to better obstetric outcomes.

One of the main reasons for using patient-controlled epidural analgesia in this study was to determine whether there was a difference in potency between the two drugs when used in a clinically relevant fashion with opioids added. Although durations of the first and second stages of labor were similar, we could not demonstrate any difference in potency as shown by the mean volume of drug used by each patient (table 4). In addition, there was no difference in the median dose needed to initiate labor analgesia. Of note is the large SD in these volumes, representing wide biologic variability in labor pain, duration of labor, and individual patient requirements. In spite of these sources of variability, a *post hoc* analysis showed that the study had sufficient power to detect a 20% difference in potency with a power of 0.8. Since the analgesic effect was almost identical (fig. 1), we conclude that the difference in motor block was not caused by analgesic potency differences.

Other investigators have noted that bupivacaine may be up to 40% more potent than ropivacaine.[2,27] However, these studies used a different study design and did not consider the addition of an epidural opioid to the local anesthetics. These authors attempted to define the dose–response curve of both drugs by defining a single point on the curve—the ED_{50}. Although a difference in potency may be evident at extremely low concentrations of local anesthetic, this difference was not apparent in the concentrations used in this study.

Of note, one additional study using patient-controlled epidural analgesia also concluded that bupivacaine was more potent than ropivacaine.[28] However, the concentration of both drugs in that study was much higher than in the current study. This may lead to an increase in the total mass of drug administered and a result different from that of the current study.

We found no difference in neonatal outcomes, including 1- and 5-min Apgar scores, umbilical artery pH, and need for neonatal resuscitation. In the meta-analysis cited above, Writer *et al.*[1] found similar results but also reported a higher median neuroadaptive capacity score at 24 h (but not at 2 h) after birth. We chose not to study this endpoint because of the unreliability of the tool.[29]

We found no difference in global maternal satisfaction between the drugs. More than 85% of patients in each group reported that they would be happy to accept the same epidural drug again. Of interest, patients who re-

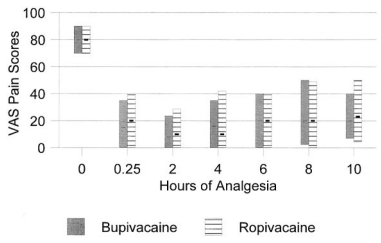

Fig. 1. Visual analog scale (VAS) scores for pain over time. Medians and interquartile ranges are shown.

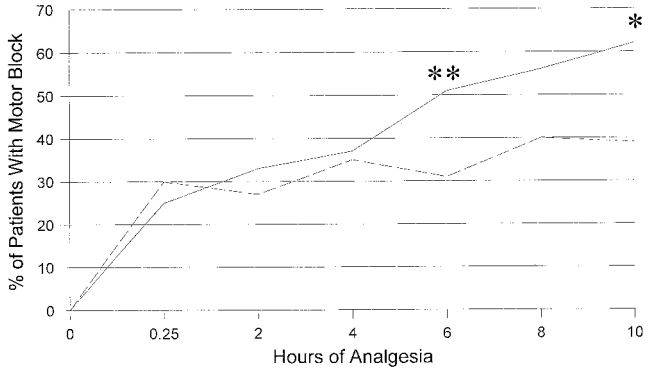

Fig. 2. The percentage of patients with any motor block (modified Bromage score of 1–5) over time. *Solid line* represents bupivacaine; *dashed line* represents ropivacaine. * $P < 0.05$; ** $P < 0.01$.

Table 5. Overall Maternal Pain Relief and Satisfaction

Outcome	Bupivacaine	Ropivacaine	*P*
Overall discomfort: 0 = labor pain much less than expected; 100 = labor pain much more than expected	56 (28)	58 (28)	0.47
Pain relief during first stage of labor: 0 = relieved no pain during labor; 100 = relieved all pain during labor	76 (19)	77 (18)	0.34
Pain relief during delivery: 0 = relieved no pain during delivery; 100 = relieved all pain during delivery	71 (25)	66 (26)	0.037
Overall care met expectations: 0 = met no expectations; 100 = met all expectations	89 (12)	89 (14)	0.85
Overall satisfaction with pain relief: 0 = not at all satisfied; 100 = completely satisfied	81 (19)	81 (19)	0.82
Overall satisfaction with mobility: 0 = not at all satisfied with mobility; 100 = completely satisfied with mobility	72 (23)	76 (23)	0.013
No. of patients who would prefer to have this type of pain relief again/total no.	240/276	236/278	0.49

Data are mean visual analog scale scores (SD) unless stated otherwise.

ceived ropivacaine were less satisfied with second-stage analgesia than were those who received bupivacaine ($P = 0.037$). Whether this finding is clinically significant is unclear. There was no difference in the visual analog scale scores for pain at any time during labor (fig. 1). The difference in satisfaction that we found may reflect reduced effectiveness of ropivacaine during the second stage, or it may have been an artifact created by multiple testing.

In summary, when low concentrations of patient-controlled epidural bupivacaine were compared with ropivacaine for labor analgesia, there was no difference in the incidence of operative delivery or other obstetric outcomes. Similarly, there were no differences in neonatal outcomes. We found no difference in potency between these drugs. We conclude that low concentrations of epidural ropivacaine and bupivacaine when combined with fentanyl provide satisfactory analgesia for labor.

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