

Ropivacaine versus Bupivacaine 0.125% with Fentanyl 1µg/ml for Epidural Labour Analgesia : Is Daily Practice More Important Than Pharmaceutical Choice ?

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Summary : Ropivacaine might be superior to bupivacaine for epidural labour analgesia because it appears to induce less lower extremity motor blockade. The clinical relevance of this difference is not yet clear. **Methods :** In a double-blind randomised trial bupivacaine and ropivacaine each at 0.125% with 1 µg/ml fentanyl were compared for epidural labour analgesia. This study was performed in two university hospitals. **Results :** Sixty-three nulliparous women with singleton pregnancies at term were included. There were no differences between bupivacaine and ropivacaine as far as motor blockade, analgesic outcome, mode of delivery and neonatal outcome are concerned. However, the clinical management of epidural analgesia differed significantly between the two institutions involved. Parturients of one institution had their epidural catheter placed earlier, needed less top-up medication, and had more successful mobilisations, when compared to the other institution. **Conclusions :** Institutional clinical practice can be significantly different. Pharmacological differences between bupivacaine and ropivacaine at 0.125% with 1µg/ml fentanyl seem to be less important than differences between institutions in terms of clinical practice.

Key words : Analgesia ; Epidural ; Bupivacaine ; Ropivacaine ; Parturition.

Bupivacaine provides excellent analgesia for labour and delivery and remains the most widely used epidural local anaesthetic in obstetric anaesthesia (14). Ropivacaine, an amino-amide local anaesthetic that is structurally similar to bupivacaine, has a lower potential for cardiovascular and central nervous system toxicity. In addition, ropivacaine might be superior to bupivacaine because it appears to induce less lower extremity motor blockade, although the clinical value of this difference is unclear (9). A meta-analysis of studies comparing higher concentrations of ropivacaine and bupivacaine (0.25%-0.5%) suggested that the use of ropivacaine was associated with less instrumental deliveries and less motor blockade than bupivacaine (16). A more recent meta-analysis in 2074

patients (10) and a multi-centre study of the same group (9) were not able to confirm a difference in obstetric outcome. We performed a double-blind, randomised, multicentre comparison of bupivacaine and ropivacaine each at our routine clinical concentration of 0.125% with 1µg ml⁻¹ fentanyl. The primary outcome measure of this study was the incidence of motor blockade.

METHODS

Local Research Ethics Committees approved this prospective, randomized and double blind study. Inclusion criteria were : written informed consent, ASA status I or II, nulliparity, singleton pregnancy, vertex presentation and cervical dilatation of ≤ 6 cm. Exclusion criteria were : absence of informed consent, contraindications for epidural anaesthesia, allergy to amide local anaesthetics, multi-parity, multi-foetal gestations, pre-term pregnancy (< 38th week of gestation) and cervical dilatation of > 6 cm at the time of epidural catheter placement.

Randomisation was performed by the pharmacy of the Basel University Hospital where identical solutions of either ropivacaine or bupivacaine were prepared at a 0.125% concentration and identified by incremental numbers. A 20 ml syringe of the same drug at a concentration of 0.25% was labelled

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with the same number and available in case of insufficient analgesia (see below). The randomisation code was not revealed until completion of the study and digital data acquisition. Fentanyl was added to the epidural infusion to reach a final concentration of $1\mu\text{g ml}^{-1}$ (0.0001%) immediately before placement of the epidural catheter.

After written informed consent, the parturient was positioned in a left lateral position. The epidural space was identified at L3/4 or L2/3 with an 18-gauge Tuohy needle using the loss of resistance technique to 0.9% saline. A 20-gauge single orifice epidural catheter (Perifix, B. Braun, Melsungen, Germany) was inserted 2-3 cm into the epidural space. After a negative test dose of 60 mg plain lidocaine 2%, the study solution was injected in increments of 5 ml every 3-10 min up to a maximum of 20 ml with adequate analgesia (visual analogue scale [VAS] of ≤ 3) as an endpoint.

On the basis of initial dose requirements the hourly epidural infusion rate was set between 8 and 12 ml h^{-1} . Initial dose and time required to reach a VAS ≤ 3 were noted. Vital parameters, VAS score, motor block (modified Bromage scale (3), i.e. 0 : normal movement in hip, knee and foot ; 1 : weakness in hip muscle ; 2 : weakness of the knee muscles ; 3 : motor block of hip, knee and foot and sensory level of anaesthesia were recorded after 15, 30 and 60 min and then every 60 min.

Inadequate analgesia was defined as VAS >3 and treated with incremental interventions : a 5 ml bolus of the study solution, epidural application of $1\mu\text{g kg}^{-1}$ fentanyl (maximal 100 μg) and a 5 ml bolus of a 0.25% study solution. If insufficient analgesia persisted, the patient was excluded from the study and the catheter had to be resited.

Statistical analysis

With an estimated incidence of motor block (Bromage >1) of 30-40% in the bupivacaine group,

Table 1

Characteristics of parturients receiving either bupivacaine or ropivacaine for epidural labour analgesia. Values are number (proportion) or mean (SD).

	Bupivacaine	Ropivacaine
Studied in Basel	11 (52%)	10 (48%)
Studied in Geneva	22 (56%)	17 (44%)
Age ; years	29.3 (5.2)	28.7 (5.5)
BMI ; kg/m^2	27.9 (3.5)	28.4 (4.3)
Gestation age ; weeks	39.5 (1.1)	39.6 (1.5)
Duration of epidural analgesia ; min	374.5 (159.8)	392.8 (150.5)
Application of oxytocin	12 (36%)	8 (30%)
Cervical dilation < 4 cm	26 (79%)	18 (66%)

BMI = Body mass index

we expected a reduction in motor block of about 50% in the ropivacaine group. To achieve a power of 0.8 we needed 34 parturients in each group. Values presented are mean and standard deviation. Nominal data were compared using the Chi-square test and Fisher's exact test where appropriate. Continuous parameters were compared with student's t-test for unpaired samples, pain scores and motor block were compared using Mann-Whitney U-tests. Significance levels were set to 5%.

RESULTS

Sixty-three parturients were included in the study, 30 in the ropivacaine and 33 in the bupivacaine group. Three parturients of the ropivacaine group were excluded from further analyses, one due to technical problems with the epidural analgesia, and two because they did not meet the inclusion criteria : one parturient had a twin pregnancy, the other one was multipara. There were no significant differences in demographic data (Table 1).

Table 2 shows that 15 parturients (45%) in the bupivacaine group and 17 (63%) in the ropivacaine group did not show any motor block (Bromage = 0) throughout labour ; there were no differences in motor block between the two drugs (Chi-Square = 1.84, $p = 0.4$). As parturients with epidural analgesia were not commonly mobilized at the time the study was performed, mobilisation was not attempted in 32 parturients (53%). In 5 patients mobilisation was not possible (3 in the bupivacaine, 2 in the ropivacaine group), motor block being the reason in 4 of the 5.

Table 2
Maximal motor block

	Bupivacaine n = 33	Ropivacaine n = 27
Bromage 0	15 (45%)	17 (63%)
Bromage 1	13 (39%)	7 (26%)
Bromage 2	5 (15%)	3 (11%)
Bromage 3	0	0

Table 3

Obstetrical outcomes for parturients receiving either bupivacaine or ropivacaine for epidural labour analgesia. Values are number (proportion).

	Bupivacaine n = 33	Ropivacaine n = 27
Spontaneous vaginal delivery	11 (33%)	13 (48%)
Instrumental vaginal delivery	15 (45%)	11 (41%)
Caesarean section	7 (21%)	3 (11%)

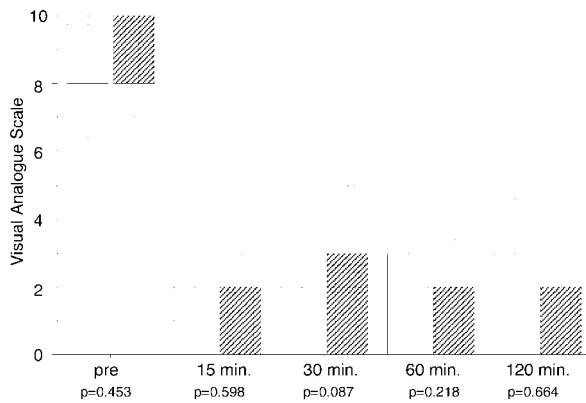


Fig. 1. — Pain scores measured as visual analogue scale in parturients receiving epidural analgesia with bupivacaine (hatched boxes) or ropivacaine (open boxes) 0.125% with 1µg ml⁻¹ fentanyl. Scores before initiation of epidural analgesia (pre) were significantly higher, than those after insertion of the epidural catheter (15 min.) and 30, 60 or 120 minutes later. The data is shown as boxplots indicating median, 10th, 25th, 75th and 90th percentiles. There were no significant differences between the two drugs at any time point, p-values are Mann-Whitney U-tests without correction for multiple comparisons.

Table 4

Neonatal outcomes for parturients receiving either bupivacaine or ropivacaine for epidural labour analgesia. Values are number, median [range] or mean (SD).

	Bupivacaine	Ropivacaine
Apgar at 1 min	9 [7-10]	9 [6-10]
Apgar at 5 min	10 [8-10]	10 [7-10]
Umbilical arterial pH	7.21 (0.065)	7.20 (0.065)

Obstetrical outcomes were comparable, as shown in Table 3, and there were no differences in neonatal outcome as far as Apgar scores at 1 and 5 minutes and umbilical arterial pH were concerned (Table 4). Analgesia was comparable between the ropivacaine and bupivacaine groups, as indicated by comparable frequencies in top-up requirements (Table 5) and lack of significant differences in VAS scores (Fig. 1).

Surprisingly, our post-hoc analysis suggested significant difference between the two institutions

Table 5

Initial local anaesthetic volume and frequency of topup medication with 0.125% and 0.25% local anaesthetics and fentanyl. Values are median (range) or number (proportion).

	Bupivacaine (n = 33)	Ropivacaine (n = 27)
Initial volume of local anaesthetic ; ml	10 (5-20)	10 (3-20)
0.125% top up	22 (66%)	20 (74%)
0.25% top up	5 (15%)	6 (22%)
Fentanyl top up	9 (27%)	8 (30%)

Table 6

Differences in clinical management of epidural labour analgesia between the Basel and Geneva centres. Values are numbers (proportions).

	Basel n = 21	Geneva n = 39	p-value
Cervical dilation < 4 cm	48% (26-70)	87% (71-95)	0.0009
Successful mobilisation	1 (5%)	22 (56%)	0.00003
Fentanyl top up	11 (52%)	6 (15%)	0.006
0.125% top up	14 (67%)	28 (72%)	0.68
0.25% top up	8 (38%)	3 (8%)	0.004

involved in this study. While the distribution of ropivacaine and bupivacaine was homogenous between Basel and Geneva (p = 0.79, Table 1), parturients in Geneva had their epidural catheter placed earlier, needed less top-up medication and had more successful mobilisations (Table 6).

DISCUSSION

We did not find any difference in the incidence of motor block between parturients receiving either ropivacaine or bupivacaine each at 0.125% with 1µg ml⁻¹ fentanyl for epidural labour analgesia. Moreover, there were no differences in analgesic, obstetrical or neonatal outcomes. This study was designed to detect a 50% reduction in motor block incidence during labour epidural analgesia, because such a reduction was thought to be clinically relevant. Indeed, there were more parturients without motor block in the ropivacaine group than in the bupivacaine group (45 vs. 63%). However, this difference was neither statistically significant nor clinically relevant. We note that our study did not have enough power to exclude such a difference. In a larger multicentre, randomised, controlled study comparing dilute concentrations of ropivacaine and bupivacaine (initiation of analgesia with a 15 ml bolus of 0.1% local anaesthetic with fentanyl 5 µg ml⁻¹, followed by patient controlled epidural analgesia with either local anaesthetic at a concentration of 0.08%, with fentanyl, 2 µg ml⁻¹), there was a statistically lower incidence of motor block in the ropivacaine group at 6 h and 10 h after drug injection(9).

Several studies have compared bupivacaine and ropivacaine for labour analgesia. They were recently summarised in a meta-analysis by Halpern et al. (10). In 19 of 23 studies analysed, motor block was more frequent in the bupivacaine group than in the ropivacaine group. However, motor block was not included in their meta-analysis because data

were heterogeneous. Nevertheless, these results are consistent with the trend towards less motor block with ropivacaine, also observed in our study. Many studies have compared equal concentrations of bupivacaine and ropivacaine, although a randomised study design based on sequential up-down allocation of parturients suggested the 50 % effective dose (ED50) of ropivacaine to be 40 % higher than that of bupivacaine (1,4,11,15). However, the ED50 may be a poor predictor for clinically relevant outcomes in labour analgesia (13), as indicated by several studies which did not reveal any difference in the amount of local anaesthetics required by parturient controlled epidural analgesia when identical concentrations of bupivacaine and ropivacaine were used (2,4,6,8,9,15).

In contrast to a meta-analysis performed by Writer *et al.*, which suggested that the use of ropivacaine for labour analgesia was associated with more spontaneous vaginal deliveries than the use of bupivacaine (16), a more recent meta-analysis did not confirm these results (10). The latter included 23 randomised controlled trials composed of 1043 individuals receiving ropivacaine and 1031 receiving bupivacaine for labour analgesia. The incidence of spontaneous vaginal delivery as primary outcome was not different (odds ratio, 1.17, 95% confidence interval 0.98-1.41, $p = 0.12$) between both groups (10). In accordance with these results and other studies, we also did not detect any differences concerning mode of delivery nor neonatal outcome (2,9,12).

Despite the small sample size, we found significantly different outcomes between the two involved institutions. The proportion of parturients receiving epidural analgesia during early labour (cervical dilatation < 4 cm) was almost twice as high in Geneva as in Basel and was associated with a significant reduction in subsequent top-up doses of 0.25% local anaesthetics or supplemental epidural fentanyl. In addition, the proportion of women successfully mobilized was significantly higher in Geneva than in Basel.

These results have to be interpreted with some caution, as differences between the two centres were not defined as outcome variables and are part of the post-hoc analysis. On the other hand rigorous inclusion and exclusion criteria were defined in order to achieve comparable results and reduce the impact of confounding factors. Moreover, all drugs were prepared in one centre (Basel) and this centre also supplied epidural puncture sets with Tuohy needles and epidural catheters.

Geneva is the largest obstetrical unit in Switzerland with about 3800 deliveries per year and an epidural rate exceeding 80%. Basel, on the other hand, has only about 1600 deliveries per year with a markedly lower epidural rate of about 40%. Therefore experience with epidural analgesia might be greater in Geneva than in Basel. We cannot exclude the possibility that differences in patient characteristics and attitudes towards birth experience may have contributed as confounding factors to differences in the management of epidural analgesia found in these two institutions. Obviously, a twofold lower proportion of parturients delivering without epidural analgesia in Basel than in Geneva might lead to a selection bias in Basel in favour of patients presenting with pathological or extremely painful pregnancies. Interestingly, differences in cervical dilation at the time of initiation of epidural analgesia observed in both institutions had no influence on subsequent analgesic requirements. Therefore, despite some observations to the contrary (5), the impact of cervical dilatation as a possible confounding variable was minimal or absent from our trial. It is of interest to note the large difference in the proportion of spontaneous vaginal delivery reported by studies of epidural labour analgesia. Halpern *et al.* found 45-50% spontaneous vaginal delivery, which is in agreement with European and Chinese studies (8,9,12), while investigators from Israel and Turkey report values as high as 80-90% and 100%, respectively (2,7). Many studies have demonstrated comparable analgesia with bupivacaine and ropivacaine for labour analgesia and most would agree with Polley *et al.* that any difference between these drugs is unlikely to have a substantial clinical relevance (14). Differences between institutional policies and experiences, regional and national cultural differences might be far more important, than minor differences in pharmacological properties of ropivacaine versus bupivacaine, at least when dilute concentrations of local anaesthetics combined with lipophilic opioids are used.

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