A Comparative Evaluation of Ropivacaine-Fentanyl and Bupivacaine-Fentanyl for Labour Analgesia Using Patient Controlled Epidural Analgesia (PCEA) Technique.

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Abstract
Background: The aim of thestudy was to produce acceptable pain relief in the parturient without producing motor block using either ropivacaine or bupivacaine in combination with fentanyl (2μg/ml)using PCEA, and to evaluate the differences between the two local anaesthetics, if any.

Methods:The study model was a prospective, randomized double-blind study;100 (50 in each group) ASA physical status I and II parturient in the age group 18-30 yrs, with term singleton pregnancy received epidural labour analgesia using either of the drugcombinations. Patients in labour received 12ml as a bolusto initiate epidural analgesia. This was followed by a basal infusion of 8ml/hr along with patient controlled bolus of 5ml at 15mins lockout intervals.

Results: Both bupivacaine and ropivacaine provided effective labour analgesia with little or no difference in maternal satisfaction or mode of delivery. Although the use of ropivacaine resulted in an increase in the duration of the first stage of labour (Ropivacaine-435 vs Bupivacaine-232.5, P=0.026). In parturients who delivered vaginally, there were no differences in other outcomes. At high doses ropivacaine is less cardiotoxic than bupivacaine.

Conclusions: From a clinical and safety perspective, both ropivacaine and bupivacaineare equallyeffective for labour analgesia.

Keywords: anaesthesia, obstetric; anaesthetic technique, epidural; anaesthetic local, bupivacaine; anaesthetic local, ropivacaine; analgesic opioid, fentanyl

I. Introduction

Studies have shown that epidural analgesia provides adequate pain relief in labour patients.[1,2] Bupivacaine is a commonly used local anaesthetic in labour analgesia but is said to be associated with fetal heart rate deceleration.[3,4] This drawback and its potential to cause dense motor blockade lead to the search for an alternative agent.

Ropivacaine, introduced in 1996, is less cardiodepressant and arrythmogenic[5-7] and produces selective sensory block at lower concentrations than bupivacaine. Bupivacaine has been found to be more potent than ropivacaine[8] therefore we used weaker solution of bupivacaine compared to ropivacaine. Subsequent studies compared equipotent concentrations of bupivacaine.[9] It has been reported that as labour progresses concentration needs of local anaesthetics increases leading to breakthrough pain and repeated patient demands.[9] Hence, for continuous pain relief throughout labour an appropriate concentration of drug needs to be used.

In the current study we compared 0.2% of ropivacaine and 0.1% of bupivacaine with fentanyl (2μg/ml) as an adjunct for labour analgesia using PCEA technique. Aim of the study was to evaluate and compare effects of both drugs with regard to: quality and duration of labour, degree of motor block, mode of delivery, duration of labour, perinatal outcome and side effects if any. Maternal satisfaction was also assessed subjectively as described by the patient.

II. Material and method

After approval from hospital ethics and scientific committee, one hundred parturient ASA physical status I or II were enrolled in the study. Participants were primigravida with uncomplicated course of singleton pregnancy in the age group of 18 to 30 years, admitted with established labour and with cervical dilatation of 3-5 cm. None had received parenteral opioid prior to epidural placement.

Patients administered parenteral analgesics before epidural injection, those with local infection at the site of injection, bleeding disorders, multiple gestations and who were unable to understand how to use PCEA pump were excluded.

Parturient were placed in a left lateral position and their baseline pulse, blood pressure, oxygen saturation and fetal heart rate were recorded. An epidural catheter was placed at L2-L3 or L3-L4 interspace and

advanced at 3 cm into the epidural space under all aseptic precautions. Test dose of 3ml of 1.5% lidocaine with adrenaline 1:200000 (0.005mg/ml) was given.

Parturient were allotted to one of the two groups in a double blind, randomized, prospective study design. The course of randomization and the handling of study vials was duty of one of the participants involved in this study who used to prepare the study solution of either 0.2% ropivacaine with 2μg/ml fentanyl or 0.1% bupivacaine with 2μg/ml fentanyl. The other participant performed the procedure and subsequent assessment and was blinded to the local anaesthetic used. A total of 12 ml of study solution was given in 4 ml increments over 10 mins. Patient was then turned to the supine position; the epidural catheter was connected to the PCEA pump and epidural infusion rate was set at 8ml/hr basal infusion and a patient controlled bolus of 5ml at 15 mins lockout intervals limiting total amount to 20ml/hr. Patients who experienced inadequate analgesia during labour, defined as request for additional analgesia, received an additional 8 ml bolus of study solution in increments of 4 ml each through the PCEA pump at 10 mins interval.

Pain assessment was done on a visual analogue scale (VAS) with 0 being no pain and 10 defined as worst pain as experienced by the patient. The VAS was assessed before administration of drug, at 2mins interval after administration of drug for 10mins, at 5mins interval until 30mins, then every 15mins till 2hrs and every 2hrs till delivery.

Patients pulse rate, blood pressure and oxygen saturation were measured for 30mins after giving bolus dose of the study solution. Fetal heart rate (FHR) was also measured for the same period using cardiotocography. Hypotension was defined as systolic blood pressure < 90 mmHg and a reduction of > 20% from baseline and was treated with left uterine displacement, intravenous bolus fluid and intravenous mephentermine.

The level of sensory block was assessed bilaterally at midclavicular line by pin prick after 30mins of bolus dose of the study solution.

Motor assessment was done by using Modified Bromage Scale (MBS) from 0 to 3 after 30mins of bolus dose of study solution. (0 = can raise extended leg off bed, 1 = able to bend knees, 2 = able to move only ankles, 3 = unable to bend knees or move ankles).

Side effects like nausea, pruritus and respiratory depression were assessed at 5mins, 60mins and then at 2hrly intervals. Foetal outcome was assessed using Apgar score at 0, 5 and 10mins.

Maternal satisfaction was noted at the end of delivery and graded as excellent, good, fair, satisfactory or unsatisfactory as perceived by the patient.

The total volume of the test solution given during the whole duration of labour analgesia including the number of self-administered top up doses was noted. The number of physician or nurse administered top up doses if any were recorded as well.

III. Statistical analysis

Statistical testing was conducted with the statistical package for the social science system version SPSS 17.0. Results are expressed as mean ± SD, median (min-max) or numbers and percentages. The comparison of normally distributed continuous variables between the groups was performed using Student's t test. Nominal categorical data between the groups were compared using Chi-squared test or Fisher's exact test as appropriate. Non-normal distribution continuous variables were compared using Wilcoxon Rank Sum test. $P<0.05$ was considered statistically significant.

IV. Results

One hundred parturient were divided into two groups of fifty patients in each (Group I- ropivacaine with fentanyl and Group II- bupivacaine with fentanyl). Demographic variables were similar between the two groups.

Table 1. Demographic data. Data are mean (standard deviation). No significant difference between the two groups.

	Group I (n=50)	Group II (n=50)
Age (yr)	26.74 (2.59)	26.4 (2.416)
Height (cm)	157.64 (4.91)	159.5 (5.926)
Weight (kg)	69.1 (8.897)	67.4 (9.934)
Gestational age (week)	38.98 (2.025)	39.7 (2.092)

Visual Analogue Scale (VAS) was similar between the two groups at all-time intervals, 8.5 and 8 before epidural analgesia for ropivacaine and bupivacaine respectively and 0-2 after epidural analgesia for both the drugs.
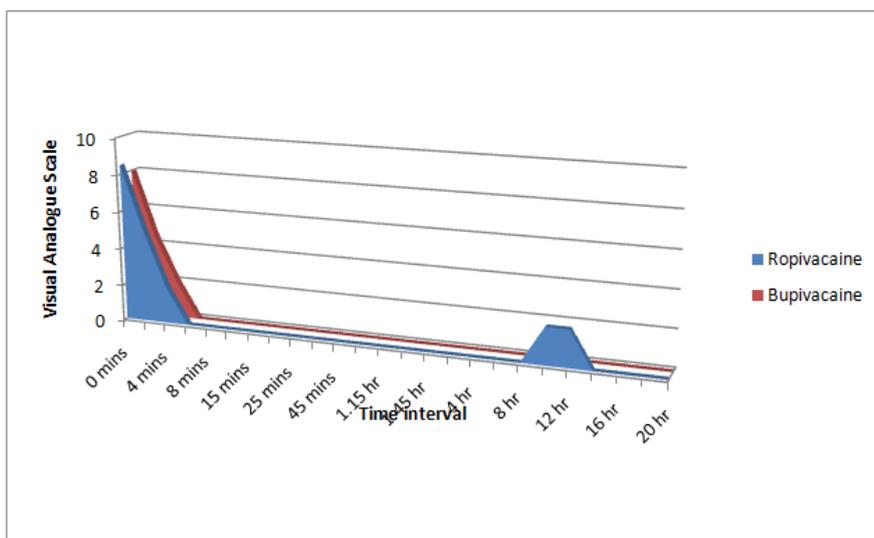
Fig 1. Median visual analogue scale as a function of time during labour for the two groups.

Patients who were administered ropivacaine-fentanyl developed lesser degree of motor block than those who received bupivacaine-fentanyl with statistically insignificant *P* of 0.242. There was profound motor block (MBS-3) in 3 cases among bupivacaine group. The differences in motor block between the two groups became apparent within 60 minutes of epidural catheter placement and persisted throughout labour.
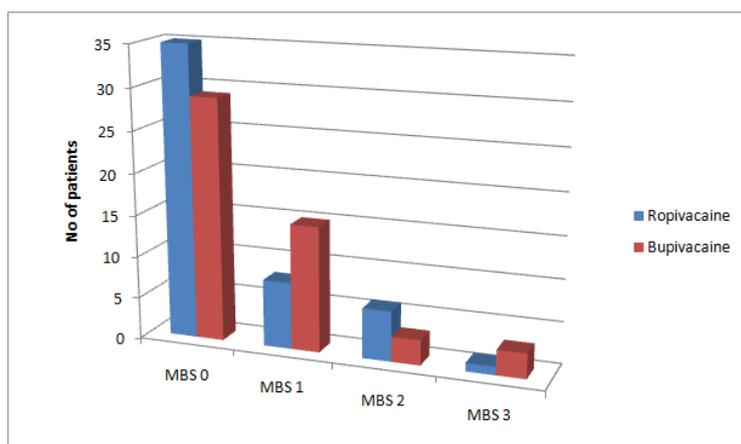

Fig 2. Modified Bromage Scale (MBS) for motor blockade among the two groups

A similar distribution of the highest level of cutaneous sensory loss was observed in both the groups. But in 2 cases in the ropivacaine group pin pricks could be felt even in thighs.

Hemodynamic variation didn't show much difference in both the groups. Hypotension was seen in 2 cases in ropivacaine group that required mephentermine administration. Maternal bradycardia and heavy headedness was experienced by 2 patients in bupivacaine group. Nausea, pruritus and vomiting were observed in 3 patients in ropivacaine group.

Labour characteristics and incidence of caesarean deliveries did not differ between the two groups. The occurrence of instrumental deliveries and caesarean section was more in bupivacaine group compared to ropivacaine group, however, it was statistically insignificant (*P*= 0.481). The indication for caesarean section in our study was either fetal distress or non-progression of labour.

Of the patients who delivered vaginally, duration of labour was significantly shorter in bupivacaine group (median-232.5) than ropivacaine group (median-435) (*P*=0.026).

Table 2. Labour and delivery data. Data are median for duration of labour and total amount of study solution used, number of cases for mode of delivery and standard deviation for fetal heart rate

	Group I (n=50)	Group II (n=50)
Duration of labour (min)	435	232.5

Mode of delivery	10	13
-Instrumental delivery	9	12
-Caesarean	31	25
-spontaneous		
Total amount of study solution used (ml)	68.425	41
Fetal heart rate		
-0 mins	6.574	13.351
-5 mins	9.163	13.955
-15 mins	10.746	32.82
-30 mins	12.96	32.033

In one of the cases in bupivacaine group we experienced an episode of fetal bradycardia in early stage of labour that did not require obstetric intervention. Fetal distress was observed in second half of first stage of labour in some of the cases in both the groups which became an indication for caesarean section. Fetal heart rate (FHR) decrement at 30 mins in our study showed a statistically significant (group I 138.78 ± 12.96 vs group II 128.86 ± 32.033) P of 0.045. FHR showed decelerating trend in bupivacaine group although it was within normal range and clinically insignificant.

Apgar score were similar between both the groups with 1 min Apgar score <5 in 2 cases in ropivacaine group and 1 case in bupivacaine group, but by 5 mins Apgar score were >7 in all infants. The mean total volume of ropivacaine-fentanyl administered was 68.425 ml versus 41 ml for bupivacaine-fentanyl. Although being higher for ropivacaine group it was statistically insignificant with P of 0.085. Demand doses in the form of patient top up doses or clinician top up doses indicate inadequate analgesia. The demands for such doses were almost equally distributed among the two groups implying equal analgesic potency of the two drugs used in the study.

Maternal satisfaction was assessed on the basis of perception of the patient. It was found to be more in ropivacaine group but the result was statistically insignificant ($P = 0.594$).

V.   Discussion

A number of studies have compared the analgesic efficacy of equal concentrations of bupivacaine and ropivacaine for obstetric epidural analgesia. A study observed that epidural ropivacaine was significantly less potent than bupivacaine by a factor of 0.4 when given to women in labour. [10] This is the reason to use different concentrations of the two drugs for labour analgesia in our study. The results in our study demonstrate that 0.2% ropivacaine with 2µg/ml fentanyl compared to 0.1% bupivacaine with 2µg/ml fentanyl are equally effective. We observed no significant differences in visual analogue scale, number of bolus doses, level of sensory block, degree of motor block, or patient satisfaction. These findings confirm that bupivacaine is more potent than ropivacaine.

We used pin pricks in the midclavicular line as a means to determine the highest level of cutaneous sensory loss and there was a similar distribution in both the groups. These results were comparable to the previous studies were cold (ice) was used instead of pin pricks in the midclavicular line. [11,12]

In our study VAS score was same between the two groups at all time intervals. Campbell et al [11] also observed that the mean score of visual analogue scale for pain, and mean duration of analgesia were not statistically different between the groups. Hourly local anaesthetic consumption was similar between the two groups. A study by M. Dresner et al [13] using the same concentrations of local anaesthetics as in our study observed statistically significant greater analgesia in ropivacaine group during the first stage of labour with P=0.01 but insignificant in second stage of labour.

In a meta–analysis, [11] the incidence of motor block was found to be more frequent in the bupivacaine group in 19 of 23 studies. As our study used lower concentration of bupivacaine than that of ropivacaine, the difference in motor block was not of much significance. A higher percentage of women in the bupivacaine group had minimal motor block compared with the ropivacaine group which was not statistically significant similar to a study done by M. Dresner et al[13] using 0.2% ropivaciane and 0.1% bupivacaine along with 2µg/ml fentanyl. On the other hand significant motor block in bupivacaine group was observed by Greg C. Meister et al[14] after using 0.125% of both the local anaesthetics. This may be the result of higher concentration of bupivacaine used in this study than that of our study.

The occurrence of instrumental delivery and caesarean section was higher in bupivacaine group, but was statistically insignificant, in our study. Some clinical studies have shown that ropivacaine provided analgesia with less motor block compared with similar concentrations of bupivacaine. [15,16] Writer et al[15] reported a prospective meta-analysis of 6 randomized, double-blind studies with a total of 403 patients in which ropivacaine 0.25% was compared to bupivacaine 0.25%. They also found that instrumental vaginal delivery was less frequent in women who received ropivacaine compared with those who received bupivacaine.

In our study total consumption of ropivacaine-fentanyl group was more as compared to bupivacaine-fentanyl group although statistically insignificant. Hofmann-kiefer K et al [17] observed that the mean total

consumption as well as mean hourly drug consumption was significantly increased in the ropivacaine group as compared to bupivacaine group. Same study also observed that there was no difference in analgesic quality between the two groups.

The number of patient directed pump demands and pump doses delivered were similar between the two groups, as was the number of clinician administered top-up doses in our study. This is comparable to study done by Medge D et al.[18]

Duration of labour in our study showed a statistically significant difference between the two groups. Median duration for ropivacaine group was greater than that for bupivacaine group (Group I-435 vs Group II-232.5). It is comparable to the study done by Hofman-kiefer K et al[17] because the analgesic quality was found to be similar in both the groups despite higher consumption of drug in ropivacaine group indicating increased duration of labour in the same group.

There were no toxic effects observed in our study except for few side effects like nausea, vomiting and pruritus in ropivacaine group. Scott et al[19] studied the toxic effects of ropivacaine and bupivacaine. They found that the onset of CNS symptoms occurred at lower dose of bupivacaine and the subjects tolerated approximately 25% more i.e. 124 mg for ropivacaine compared to 99 mg for bupivacaine. Both the drugs depressed conductivity and contractility, but these effects were noted at lower plasma concentrations of bupivacaine. At the very dilute concentrations of bupivacaine currently being used for labour analgesia i.e. 0.0625% to 0.1%, it is safe because cardiac toxicity at these doses is highly unlikely, even when administered inadvertently intravascularly.

The study conducted by us showed no major hemodynamic variations between the two groups except for two cases of hypotension in ropivacaine group which required medical intervention and responded well to mephentermine. Statistically insignificant hypotension of same incidence in ropivacaine group has been observed in some of the previous studies.[14,18,20] Maternal bradycardia was seen in two cases in bupivacaine group. Results obtained were statistically insignificant. Greg C. Meister et al[14] reported similar results in his study.

In a study conducted by Philips et al [21] fetal electrocardiogram waveform analysis was used to assess the effect of epidural bupivacaine on the fetal myocardial conduction. There were no significant changes in either the PR interval or the PR-RR correlation coefficient. There was a significant increase in the fetal heart rate and a significant fall in the T/QRS ratio. Epidural bupivacaine does not alter fetal myocardial conduction as measured by the PR interval and it does not induce ischaemic cardiac changes as assessed by the T/QRS ratio.[21] Although in our study we didn't analyse fetal electrocardiogram but fetal heart rate (FHR) at 30 mins showed a statistically significant difference between the two groups ($P=0.045$). It was the bupivacaine group which showed a decelerating trend but was clinically insignificant as it was not associated with any adverse fetal outcome.An episode of fetal bradycardia in early stage of labour was seen in the bupivacaine group that did not require obstetric intervention. Such an observation of single episode of fetal bradycardia that didn't require obstetric intervention was seen in previous studies as well.[8,11]There occurred fetal distress in later stage of labour in some of the cases in both the groups which became an indication for caesarean section.

No study is in support that neonatal outcome is adversely affected when either ropivacaine or bupivacaine is used for labour analgesia. The incidence for both the drugs is about 2% for low Apgar score at 5 minutes.[22] In addition it has been seen that the umbilical artery and vein pH are well maintained regardless of which local anaesthetic is being used.[23] The incidence of need for neonatal resuscitation is low and similar with both the drugs.[24] Although we obtained Apgar scores, we did not directly assess the effect of ropivacaine on the fetus. However, there were no significant fetal heart rate abnormalities noted throughout the labour.

Few of studies have considered maternal satisfaction as an important outcome. Those that attempted to measure patient satisfaction did not do so with a validated score. Although there is some data published on maternal satisfaction with regards to analgesia, they are related only to pain relief and not specifically to other characteristics of the block. Similar method of assessing maternal satisfaction was adapted in our study keeping in mind the level of analgesia rather than motor block. Results were also comparable to the previous studies.[14,25] The number of patients reporting good or excellent was also similar between the two groups. Few patients reported unsatisfactory analgesia in both the groups which was statistically insignificant ($P=0.594$).

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