A RANDOMIZED COMPARISON OF 0.125% LEVOBUPIVACAINE, 0.125% ROPIVACAINE AND 0.125%BUPIVACAINE COMBINED WITH 2µG/ML FENTANYL FOR EPIDURAL LABOR ANALGESIA
Gopal Reddy Narra1, S. Manohar2, P. Supriya3, A. Himani4, Mounica5

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ABSTRACT: The labor pain is one of the most severe pains that a woman could ever be suffered. Today, many medical and psychological methods are used in an effort to reduce labor pain. Epidural analgesia is the best current method used for the purposes of obstetric analgesia. OBJECTIVE: To compare analgesic efficacy and intensity of sensory block with continuous infusions of bupivacaine, levobupivacaine and ropivacaine for labor epidural analgesia. Design: Prospective, randomized, double-blind study. PATIENTS: 95 ASA physical status I and II, term, primigravida. Interventions: All patients received epidural labor analgesia. Epidural medication consisted of an initial bolus of 10 mL 0.125% local anesthetic combined with2µg/ml Fentanyl followed by an infusion at 10 ml/h of local anesthetic with2µg/ml Fentanyl. Patients were allocated to three groups, as follows: each group received bolus and infusion of 0.125%local anaesthetic group1 bupivacaine, group 2 levobupivacaine and group 3 ropivacaine respectively. MEASUREMENTS: Maternal vital signs, pain visual analog scale (VAS) score, sensory levels, and motor block (Bromage score) were recorded at intervals. Duration of first and second stage and mode of delivery were also recorded. CONCLUSION: All three regimens were effective during first stage of labor although pain scores were higher in those receiving levobupivacaine and ropivacaine. Motor block was greater with bupivacaine than with levobupivacaine and ropivacaine.

KEYWORDS: Obstetric Analgesia, Epidural Analgesia, Local Anesthetics, Levobupivacaine, Bupivacaine and Ropivacaine, Opioid-Fentanyl.

INTRODUCTION: 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.1, 2 Use of higher concentrations and doses of local anaesthetic which cause dense neural block is undesirable because of unwanted sequelae3 such as:

- Marked motor block – leading to unpleasant numbness, immobility, inability to walk or squat, urinary retention and poor efforts at birth.
- An increased incidence of hypotensive episodes.
- Shivering/shaking.
- A prolonged second stage due to an absent urge to push, leading to an increased risk of instrumental birth.
- Increased risk of local anaesthetic toxicity.

The use of low dose epidurals and fentanyl combination is recommended for initial boluses and for maintenance with patient controlled delivery. Advantages compared with more concentrated solutions are:
Less immediate and delayed onset of increasing leg weakness, such that the majority of women are initially capable of weight bearing.\textsuperscript{4, 6}

The urge to push is retained by most women.\textsuperscript{6}

The incidence of hypotension, shivering and urinary catheterization are reduced,\textsuperscript{3, 7, 8, 9}

Instrumental birth rates are reduced,\textsuperscript{3, 10, 11}

Maternal satisfaction is higher.\textsuperscript{12, 13, 14}

Adverse foetal and neonatal clinical effects are rarely seen in the healthy, mature fetus.\textsuperscript{15, 16}

Although epidural bupivacaine is highly effective in providing pain relief, its use is limited because of side effects including motor blockade and cardiovascular toxicity.\textsuperscript{17} However, bupivacaine is one of the most cardiotoxic local anesthetics in current use and motor block is still a problem.\textsuperscript{18} Levobupivacaine and ropivacaine are relatively new local anaesthetics that have effect similar to bupivacaine. They are believed to be less toxic to central nervous system and cardiovascular system. They have also been reported to cause less motor blockade.\textsuperscript{19, 20, 21} However relative potency of drugs is controversial. While some researchers have found a similar potency for both levobupivacaine and ropivacaine,\textsuperscript{22} while others have observed that levobupivacaine is more potent than ropivacaine.\textsuperscript{23, 24}

The possible differences in potency may be masked by the presence of opiates.\textsuperscript{25} Many local anesthetics such as bupivacaine exist in 2 forms, levorotatory and dextrorotatory.

The aim of this study was to evaluate the analgesic efficacy of continuous epidural infusion of levobupivacaine, ropivacaine and to compare them with bupivacaine infusions in the first and second stage of labor. Epidural bupivacaine has been used for many years for labor analgesia. Although this drug provided excellent sensory analgesia, large doses of bupivacaine were associated with cardiac and central nervous system toxicity when accidentally injected intravenously.\textsuperscript{26} Levobupivacaine was developed to reduce these side effects. Levobupivacaine is a pure S (-) enantiomer of racemic bupivacaine, whereas bupivacaine consists of both an S (-) and R (+) enantiomer.\textsuperscript{27, 28} Ropivacaine is less lipophilic than bupivacaine and is less likely to penetrate large myelinated motor fibers; therefore, it has selective action on the pain-transmitting A\textsubscript{β} and C nerves rather than A\textsubscript{β} fibres, which are involved in motor function.

**MECHANISM OF ACTION:** Ropivacaine causes reversible inhibition of sodium ion influx, and thereby blocks impulse conduction in nerve fibres.\textsuperscript{31} This action is potentiated by dose-dependent inhibition of potassium channels.\textsuperscript{32} Ropivacaine is less lipophilic than bupivacaine and is less likely to penetrate large myelinated motor fibers; therefore, it has selective action on the pain-transmitting A\textsubscript{β} and C nerves rather than A\textsubScript{β} fibres, which are involved in motor function.

**METHODS:** After obtaining Institutional Ethics Committee approval and written informed consent from recruits, 95 Primigravida were selected to this double-blind, randomized trial. The study was carried out for about 2 years in the Kamineni Institute of Medical Sciences. Parturients at greater than 37 weeks of gestation in active labor with full-term pregnancy with a single fetus in cephalic position and of ASA physical status I or II were included in the study. Those who had received parenteral analgesics, weight >90 kg, height <150 cm, expected duration of labor <1 h, a past history of alcoholism or a history of allergy to local anesthetics were excluded. Before performing the epidural, baseline maternal pulse and non-invasive blood pressure were measured and visual analogue pain
score (0 mm = no pain, 100mm = worst pain imaginable) noted. The procedure and importance explained to all the recruits. 500-ml intravenous preload of Ringer’s lactate solution was administered before the epidural was sited. Using an aseptic technique, the procedure was performed by the principal investigator, with the patient in the left lateral position. The skin was infiltrated with a 3-ml maximum of 1% lidocaine and the epidural space identified at L3-4 using a midline approach and loss of resistance to air with a 18-gauge Tuohy needle. A multiorifice catheter was advanced 3-4 cm into the epidural space. For the purpose of this study no test dose was given. Patients were randomly allocated to receive 0.125% levobupivacaine combined with 2µg/ml Fentanyl (group -L), 0.125% ropivacaine combined with 2µg/ml Fentanyl (group -R) or 0.125% bupivacaine combined with 2µg/ml Fentanyl (group- B). An anesthetist who took no further part in the study prepared all epidural solutions. Distilled water was used to dilute the drugs to obtain the desired concentrations. Neither the principal investigator nor the parturients were aware of the type of local anesthetic. The patients were given an initial 10-ml dose of study solution administered over 2 min. The time to achieve a reduction of pain score to <40mm was considered to represent the onset of analgesia. If analgesia was not achieved by 20 min, an additional 8-ml bolus of the study solution was administered. A maximum of two additional boluses given at 20-minute intervals were administered. If at this point the VAS was still P40mm, the patient was excluded from the study and was not replaced. When analgesia was achieved a continuous epidural infusion of the study solution was started at 10 ml/h. If pain relief was inadequate during the first stage of labor (VAS score >40mm) a supplementary 8-ml bolus dose of the study solution was given. No other local anesthetic was administered over the course of the study. Data were collected until the woman reached full cervical dilatation or if cesarean section was performed. The start of the epidural infusion was regarded as time= 0. Women were assessed at 10, 20, 40 and 60 min and at half hourly till 4 hours and on reaching full cervical dilatation. At these times, pain scores, motor block, block height, cervical dilatation, blood pressure, and heart rate and spo2 were recorded. At the same times information on adverse events such as nausea and pruritus was sought.

The principal investigator was responsible for data collection. Infusions were continued throughout the second stage of labor but data were not recorded. Motor block was evaluated according to the modified Bromage scale (0 = no motor block; 1 = inability flex hip; 2 = inability to flex hip and knee; 3 = complete block of lower limb). Sensory level was determined by perceived temperature difference to alcohol swab or sometimes with needle prick in case of doubt. Hypotension was defined as a decrease of 20% below baseline. When hypotension occurred the woman was positioned on her left side and the rate of fluid administration increased 5-10ml/minute. If these measures were not effective, a 5-mg bolus of i.v. ephedrine was administered and repeated after 5 min if necessary. Fetal heart rate and uterine activity were monitored continuously throughout labor. The total dose of local anesthetic administered during the continuous epidural infusion was calculated by adding the amount given during the infusion to that of the additional bolus doses. We also recorded the dose necessary to achieve effective analgesia, the time to onset, duration of the second stage, Levobupivacaine, Ropivacaine and bupivacaine in labor 3 mode of delivery, Apgar scores of the neonate. After delivery the woman was asked to score her satisfaction with epidural analgesia on a numerical scale (0 = totally unsatisfied, 100 = totally satisfied).
STATISTICAL ANALYSIS: To have 95% power to detect a difference in mean VAS scores of 10 mm, assuming a standard deviation of 10 mm and using a two-group test with a 0.05 two-sided significance level, a sample size of 30 in each group was required. More than thirty subjects were chosen at random per group as a precaution against possible losses for analysis. Qualitative variables are described as frequencies and percentages, normally distributed variables as mean and standard deviation (SD); other continuous and ordinal variables as median and interquantile range (IQR). Means and 95% confidence intervals (95% CI) for pain VAS scores were adjusted by means of an ANCOVA model using the basal VAS value as co-variants.

RESULTS: 95 women were recruited to the study. Five were excluded when required criteria not achieved.

Demographic data and pre block characteristics were similar (Table 1).

| Particulars                  | Group L (n = 30) | Group-R (n = 30) | Group B (n = 30) | P   |
|------------------------------|------------------|------------------|------------------|-----|
| Age (years)                 | 23.30 (4.0)      | 23.32 (3.2)      | 23.28 (2.9)      | 0.949 |
| Weight (kg)                 | 61 (9)           | 62 (9)           | 0.110            |
| Gestational age (weeks)     | 38.44 (1)        | 60 (10)          | 38.28 (1)        | 0.991 |
| Cervical dilatation at epidural placement (cm) | 2.7 (0.7) | 38.34 (1) | 2.4 (1.0) | 0.346 |
| Baseline pain score, (VAS 0–100 mm) mean | 86.3 | 2.5 | [82–90] 81.5 | 0.320 |

Table 1: Patient demographics and labor characteristics

| Particulars                  | Group L          | Group-R          | Group-B          | P   |
|------------------------------|------------------|------------------|------------------|-----|
| Dose bolus                   | 12.5 mg [8–16] mg| 12.5 mg [8–16] mg| 12.5 mg [8–16] mg| (P <0.001) |
| Additional dose              | [8–16] mg        | [8–16] mg        | [8–16] mg        |      |
| Onset of analgesia           | 20 min [15-30]   | 20 min [15-30]   | 20 min [15-20]   | (P > 0.05) |

Table 2: The initial dose required, including the additional bolus if required, expressed as a median

Group L = levobupivacaine 0.125%; Group R = ropivacaine 0.125%; Group B = bupivacaine 0.125%.

Table 2 Local anesthetic used during the continuous epidural infusion Group L (n =30), Group R (n =30) Group B (n = 30) Group L: levobupivacaine 0.125% combined with2µg/ml Fentanyl; group Group R= ropivacaine 0.125 combined with2µg/ml Fentanyl %; B: bupivacaine 0.125% combined with2µg/ml Fentanyl; IQR: interquantile range.

Group L = levobupivacaine 0.125% combined with2µg/ml Fentanyl; Group R= ropivacaine 0.125% combined with2µg/ml Fentanyl; Group B = bupivacaine 0.125% combined with2µg/ml Fentanyl;

IQR = interquantile range.

Post-hoc test of motor block showed significant differences between group L and group B (P < 0.01).

* Significant differences. Levobupivacaine, ropivacaine and bupivacaine in labor =90.
Table 3: Local anesthetic used during the continuous epidural infusion

| Group                          | Group L (n = 30) | Group L (n = 30) | Group B (n = 30) | P     |
|-------------------------------|------------------|------------------|------------------|-------|
| Number of supplemental doses  | 1 [1-1]          | 1 [1-1]          | 1 [1-1]          | 0.849 |
| Total dose of local anesthetic (mg) | 30 [20.2–45.5]   | 32 [20.2–45.5]   | 32.5 [26.7–50]   | 0.158 |
| Duration of epidural infusion (min) | 120 [81.3–192.5] | 125 [86.5–198.5] | 135 [120–210]    | 0.051 |

Time: Mean VAS (mm).

Group L: levobupivacaine 0.125% combined with 2µg/ml Fentanyl; Group R: ropivacaine 0.125% combined with 2µg/ml Fentanyl; Group B: bupivacaine combined with 2µg/ml Fentanyl 0.125%.

Full dil: full dilatation.

*Significant differences between groups L, group R and group B (P < 0.05) at all time periods.

The onset of analgesia was similar between groups: 20 min [15-30] for group L; 20 min [15-20] for group B (P > 0.05). Analgesia was effective during the first stage of labor in all two groups, with VAS scores <40 mm at all measurement periods (Table 2). When VAS between groups was compared, significant differences were found. VAS in group L and R were greater than that in groups B. Post-hoc analysis showed statistically significant differences between group L, R and group B (P <0.05) at all measurement periods. There were no significant differences in the total dose of local anesthetic, the number of rescue boluses and the duration of the infusion (Table 3). Women receiving bupivacaine were more likely to develop motor block (P = 0.04) (Table4). Post-hoc analysis showed that motor block was greater in group B than in group L (P <0.001). The differences were not significant between group L and group R (P = 0.153) or between group B and group R (P = 0.069).

Sensory block was similar in the three groups, as were maternal hemodynamics and the incidence of nausea and pruritus. Maternal satisfaction was similar in the three groups (Table 4). There were no differences in mode of delivery, duration of the second stage, the weight and height of the newborn and Apgar scores (Table 5). At 5 min, all babies had Apgar scores >7 (Table 5). Indications for cesarean section were dystocia (12 women) and fetal distress (twenty four women).

Data are mean and standard deviation unless stated.

Group L: levobupivacaine 0.125% combined with 2µg/ml Fentanyl; Group R: ropivacaine 0.125% combined with 2µg/ml Fentanyl %; Group B: bupivacaine 0.125% combined with 2µg/ml Fentanyl;
**Table 4:** Motor block, sensory block, side effects and maternal satisfaction during continuous infusion of local anaesthetic

| Mode of delivery                              | Group L (n = 30) | Group R (n = 30) | Group B (n = 30) | P value n (%) |
|-----------------------------------------------|------------------|------------------|------------------|---------------|
| Spontaneous vaginal                           | 12(40)           | 14(46.67)        | 13(29)           | 0.938         |
| Instrumental vaginal                          | 8(26.67)         | 7(23.33)         | 10(48.11)        | 0.546         |
| Caesarean delivery                            | 10(33.33)        | 9(30)            | 7(22.6)          |               |
| Second stage(min), Median [IQR]               | 30 [22.5-100.7]  | 30 [31.2-60]     |                  |               |
| Birth weight(g), mean(±SD)                    | 2506(403)        | 2524             | 2529(463)        |               |
| Apgar score <7 at 1 min, n (%)                | 1(3.1)           | 1(3.2)           | 1(3.2)           |               |

**DISCUSSION:** We have demonstrated that levobupivacaine 0.125% combined with 2µg/ml Fentanyl, ropivacaine 0.125% combined with 2µg/ml Fentanyl, bupivacaine 0.125% combined with 2µg/ml Fentanyl.
Fentanyl are effective when given as a continuous epidural infusion during the first stage of labor. With each infusion VAS were less than 4mm throughout the study. The design of our study was based on previous work demonstrating the relative potency of levobupivacaine to bupivacaine was 0.98. This we considered that the two agents would be similar when used for epidural analgesia in labor.

We chose the infusion regimens because they have previously been reported in the literature and they are in common use in our clinical practice. There are limitations to our study design. Firstly, an ampoule of 0.5% of levobupivacaine contains approximately 13% more active local anesthetic than 0.5% racemic bupivacaine. It has implications for comparisons, because in all the studies published (including this) although the quantity in ml of levobupivacaine and bupivacaine administered is the same, the dose of local active anesthetic is not. Secondly, the relative potencies of bupivacaine, levobupivacaine, ropivacaine were estimated with an up-down design in which all data points were concentrated around the 50% effective dose. Therefore, the potency ratio found in these studies is only valid for the median effective analgesic concentrations (EC50) which does not permit conclusions about the potency ratio for the ED95. We concluded that levobupivacaine, ropivacaine might be slightly less potent than expected and may provide more variable analgesic results than racemic bupivacaine.

Throughout the study, pain scores were less than 25 mm in all groups. However, further analysis revealed that women who received levobupivacaine, ropivacaine had higher pain scores than those in the other group; this difference was statistically significant. Other studies have found levobupivacaine, ropivacaine to be of similar potency when used for epidural analgesia, with a relative potency of 0.98. Supandji et al demonstrated that boluses of levobupivacaine, ropivacaine, bupivacaine provided equally effective analgesia. These studies suggest that levobupivacaine, ropivacaine has less potent that racemic bupivacaine. We found that motor block was greater in the women who received bupivacaine compared to levobupivacaine ropivacaine.

This has previously been reported by others and is hardly surprising as sensory block was also greater. When motor block was studied following intrathecal administration of local anesthetic in labor, greater motor block was again found with bupivacaine than with levobupivacaine or ropivacaine. However other studies have found no differences in motor block between levobupivacaine, ropivacaine and bupivacaine. Greater motor-sensory separation would be an advantage when motor block is undesirable, such as during epidural analgesia in labor, but we could not demonstrate this as levobupivacaine and bupivacaine were given in equi-analgesic doses.

We also observed that the length of time from starting the infusion to reaching full cervical dilatation was greater in women who received bupivacaine than in those who received levobupivacaine, ropivacaine though the difference was not significant. Further studies including a greater number of patients would be needed to investigate whether using levobupivacaine could influence labor outcome.

**CONCLUSION:** We found that 0.125% levobupivacaine combined with 2µg/ml Fentanyl, 0.125% ropivacaine 0.125% combined with 2µg/ml Fentanyl and 0.125% bupivacaine combined with 2µg/ml Fentanyl produced adequate epidural analgesia and were well tolerated. Both motor and sensory block were greater with bupivacaine than with levobupivacaine. Further comparative studies between levobupivacaine, ropivacaine, bupivacaine are necessary to determine the optimal dose of levobupivacaine administered in continuous infusion for labor epidural analgesia.
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