A Randomized Comparison of Levobupivacaine and Bupivacaine for Labor Analgesia

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ABSTRACT

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 IV. Levobupivacaine was developed to reduce these side effects and was released for clinical use in 1996. Since then, numerous studies have been performed to determine whether or not levobupivacaine is suitable for labor analgesia and to determine whether it is superior to bupivacaine.

The aim of this study was to evaluate the analgesic efficacy of continuous epidural infusion of levobupivacaine and to compare this with bupivacaine infusions in the first stage of labor.

Methods: Hundred primigravida in early labor were enrolled in this randomized, double-blind clinical trial. They were randomly assigned to receive one of two continuous epidural infusion regimens after loading dose of 0.125% volume 10 ml : levobupivacaine 0.125% or bupivacaine 0.125% 1.25 mg/ ml at 10ml/h. Supplementary analgesia was provided with an 10ml epidural bolus of the study solution if visual analogue scale (VAS) score for pain was P4(0-10cm). Pain and motor and sensory block were measured at 0, 20, 40 and60 min and every half an hour up to 4hours thereafter up to full cervical dilatation.

Results: Analgesia was satisfactory in all two groups, with VAS score <40mm at all measurements. VAS scores were greater in those receiving levobupivacaine (P <0.005). Motor block was greater with bupivacaine than levobupivacaine (P <0.01).

Conclusion: All two regimens were effective during first stage of labor although pain scores were higher in those receiving levobupivacaine. Motor block was greater with bupivacaine than with levobupivacaine.

Keywords: Obstetric Analgesia, Epidural Analgesia, Local Anesthetics, Levobupivacaine, Bupivacaine.

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 sequelae [4] such as:

- Less immediate and delayed onset of increasing leg weakness, such that the majority of women are initially capable of weight bearing. [3,4,5,6]
- The urge to push is retained by most women. [6]
- The incidence of hypotension, shivering and urinary catheterization are reduced [7,8,9]
- Instrumental birth rates are reduced [10,11]
- Maternal satisfaction is higher [12,13,14]
- Adverse fetal and neonatal clinical effects are rarely seen in the healthy, mature fetus. [14,15]

Although epidural bupivacaine is highly effective in providing pain relief, its use is limited because of side effects including motor blockade and cardiovascular toxicity. [16] However, bupivacaine is one of the most cardiotoxic local anesthetics in current use and motor block is still a problem. [17] Levobupivacaine is relatively new local anaesthetic that has effect similar to bupivacaine. It is believed to be less toxic to central nervous system and cardiovascular system. It has also been reported to cause less motor blockade. [16,19,20]

The aim of this study was to evaluate the analgesic efficacy of continuous epidural infusion of levobupivacaine, to compare it 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. [21]

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. [22,23] Levobupivacaine is thought to be a good alternative to racemic bupivacaine for epidural labor analgesia because the S (-) enantiomer has less affinity for the sodium channels and thus has fewer depressant effects on the cardiovascular and central nervous system than the R (+) enantiomer. Although levobupivacaine has been used for labor analgesia in some countries, [24] we found that an optimal concentration of levobupivacaine not been studied by reviewing textbooks and literature describing levobupivacaine for epidural labor analgesia. Numerous studies have been performed to determine whether or not levobupivacaine is suitable for labor analgesia and to determine whether it is superior to bupivacaine.

**Stereospecificity and Structure:**
Enantiomers exist in two different spatial configurations, like right- and left-handed gloves, and are present in equal amounts in a racemic solution. They are optically active and can be differentiated by their effects on the rotation of the plane of a polarized light into dextrorotatory [clockwise rotation (R+)] or levorotatory [counterclockwise rotation (S-)] stereoisomers. The physicochemical properties of the two enantiomeric molecules are identical, but the two enantiomers can have substantially different behaviors in their affinity for either the site of action or the sites involved in the generation of side effects. R(+) and S(-) enantiomers of local anaesthetics have been demonstrated to have different affinity for different ion channels of sodium, potassium, and calcium; this results in a significant reduction in central nervous system (CNS) and cardiac toxicity (cardio toxicity) of the S(-)-enantiomer as compared with the R (+)-enantiomer. [25]

**Mechanism of Action:**
Levobupivacaine causes reversible inhibition of sodium ion influx, and thereby blocks impulse conduction in nerve fibres. This action is potentiated by dose-dependent inhibition of potassium channels. [27] Levobupivacaine is less lipophilic than bupivacaine and is less likely to penetrate large myelinated motor fibers; therefore, it has selective action on
the pain-transmitting $A\beta$ and C nerves rather than $A\beta$ fibres, which are involved in motor function.

**MATERIALS AND METHODS**

After obtaining Institutional Ethics Committee approval and written informed consent, 100 Primigravida were recruited to this double-blind, randomized trial. The study was carried out in the Kamineni Institute of Medical Sciences for about two years. 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 >100 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. A 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 (MCA) 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 an 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 (group L) or 0.125% bupivacaine (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 10 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 10-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 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 $Spo_2$ 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. 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. 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, 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 0.050 two-sided significance level, a sample size of 50 in each group was required. Fifty 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 interquartile 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 a covariate. The following inferential tests were applied according to the type of variables: Fisher’s exact test for categorical variables, one-way ANCOVA for continuous variables and Kruskal-Wallis test for ordinal values. Whenever treatment effect was statistically significant (P < 0.05), a post-hoc test was applied using the Bonferroni method for adjusting for multiple comparisons. The last observation carried forward (LOCF) approach was applied to the VAS pain scores measurements after the second hour. The level of significance was predefined at 5% two-tailed.

**RESULTS**

100 women were recruited to the study. Four were excluded; two from group B and two from group L. One woman in group B was failed to achieve a VAS <4 cm and one reported a metallic taste after the initial dose and requested to leave the study. In group L one woman gave birth 40 min after the epidural was sited and one failed to achieve a VAS <4 cm. Patients’ demographic data and pre block characteristics were similar (Table 1).

<table>
<thead>
<tr>
<th>Particulars</th>
<th>Group L (n = 50)</th>
<th>Group B (n = 50)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>22.30 (4.0)</td>
<td>22.28 (2.9)</td>
<td>0.949</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61 (9)</td>
<td>62 (9)</td>
<td>0.110</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38.44 (1)</td>
<td>38.28 (1)</td>
<td>0.991</td>
</tr>
<tr>
<td>Cervical dilatation at epidural placement (cm)</td>
<td>2.7 (0.7)</td>
<td>2.4 (1.0)</td>
<td>0.346</td>
</tr>
<tr>
<td>Baseline pain score, (VAS 0–100 mm) mean</td>
<td>[95%CI] 86.3</td>
<td>[82–90] 81.5</td>
<td>0.320</td>
</tr>
</tbody>
</table>

Table 1: Patient demographics and labor characteristics

<table>
<thead>
<tr>
<th>Particulars</th>
<th>Group L</th>
<th>Group B</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose bolus mg</td>
<td>12.5</td>
<td>12.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Additonal dose mg</td>
<td>12.5</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>Onset of analgesia</td>
<td>20 min [15-30]</td>
<td>20 min [15-20]</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Group L (n = 50)</th>
<th>Group B (n = 50)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of supplemental doses</td>
<td>1 [1–1]</td>
<td>1 [1–1]</td>
<td>0.849</td>
</tr>
<tr>
<td>Total dose of local anesthetic (mg)</td>
<td>30</td>
<td>32.5</td>
<td>0.158</td>
</tr>
<tr>
<td>Duration of epidural infusion (min)</td>
<td>120</td>
<td>155</td>
<td>0.051</td>
</tr>
</tbody>
</table>

Table 3: Local anesthetic used during the continuous epidural infusion

Data are mean and standard deviation unless stated.

Group L: levobupivacaine 0.125%; group B: bupivacaine 0.125%; Group L (n = 50) Group B (n = 50) P
Group L: levobupivacaine 0.125%; group B: bupivacaine 0.125%; IQR: interquartile range
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) (Table 2). Analgesia was effective during the first stage of labor in all two groups, with VAS scores <40 mm at all measurement periods. When VAS between groups was compared, significant differences were found (Table-3).

Figure 1: Blood pressures in bupivacaine group:

Figure 2: Blood pressure Levobupivacaine group

Figure 3: Comparison of arterial pressures group-L and group-B

Table 4: Labor and Neonatal outcomes

<table>
<thead>
<tr>
<th>Mode of delivery</th>
<th>Group L (n=50)</th>
<th>Group B (n=50)</th>
<th>P value n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous vaginal</td>
<td>20 (40)</td>
<td>19 (38)</td>
<td></td>
</tr>
<tr>
<td>Instrumental vaginal</td>
<td>8 (16)</td>
<td>11 (22)</td>
<td></td>
</tr>
<tr>
<td>Caesarean delivery</td>
<td>22 (44)</td>
<td>20 (40)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>50</td>
<td>47.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[22.5-68.7]</td>
<td>[31.2-70.2]</td>
<td></td>
</tr>
<tr>
<td>Birth weight (g), mean (SD)</td>
<td>3006 (403)</td>
<td>3029 (463)</td>
<td>0.938</td>
</tr>
<tr>
<td>Birth height (cm), mean (SD)</td>
<td>50 (1)</td>
<td>49 (1)</td>
<td>0.108</td>
</tr>
<tr>
<td>Apgar score &lt;7 at 1 min, n (%)</td>
<td>1 (3.1)</td>
<td>1 (3.2)</td>
<td>0.546</td>
</tr>
</tbody>
</table>

Group L = levobupivacaine 0.125%; Group B = bupivacaine 0.125%; Time: Mean VAS (mm) Group L Group B

Figure 1 Mean VAS scores for pain during labor. Group L: levobupivacaine 0.125%; group B: bupivacaine 0.125%; group Full dil: full dilution.

*Significant differences between group L – group B (P < 0.05) at all time periods.
DISCUSSION

We have demonstrated that levobupivacaine 0.125%, bupivacaine 0.125% are effective when given as a continuous epidural infusion during the first stage of labor. With each infusion VAS were less than 4cm throughout the study. The design of our study was based on previous work demonstrating the relative potency of levobupivacaine to bupivacaine was 0.98. [26] From this we considered that the two agents would be similar when used for epidural analgesia in labor. [27] We chose the infusion regimens because they have previously been reported in the literature, [26,27] 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. [28] 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 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 [26,27] 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 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 had higher pain scores than those in the other group; this difference was statistically significant. Other studies have found levobupivacaine to be of similar potency when used for epidural analgesia, with a relative potency of 0.98. [28] Supandji et al demonstrated that boluses of 0.2% levobupivacaine, bupivacaine provided equally effective analgesia. [29] These studies suggest that levobupivacaine has less potent that racemic bupivacaine.

We found that motor block was greater in the women who received bupivacaine compared to levobupivacaine. This has previously been reported by others, [30] 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. [31] However other studies have found no differences in motor block between levobupivacaine and bupivacaine. [32,33] 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
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, 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**

To conclude, we found that 0.125% levobupivacaine, 0.125% bupivacaine 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, bupivacaine are necessary to determine the optimal dose of levobupivacaine administered in continuous infusion for labor epidural analgesia.

**ACKNOWLEDGEMENTS**

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