Comparison of Three Different Concentrations of Levobupivacaine for Epidural Labor Analgesia: Clinical Effect and Pharmacokinetic Profile

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Abstract

Background: The aim is to compare the clinical effect of three different concentrations of levobupivacaine (0.25%, 0.125%, and 0.0625%) on the sensory and motor block characteristics and mode of delivery during epidural labor analgesia. We also studied the pharmacokinetic profile of the three concentrations during labor. Materials and Methods: Sixty pregnant females undergoing normal vaginal delivery under epidural analgesia were divided into three groups according to the concentration of levobupivacaine used. All parturients received an epidural bolus dose of 15 ml of the desired concentration followed by a continuous infusion of the same concentration at 10 mL/h, each combined with fentanyl 2 µg/mL. Sensory block was assessed by the visual analog score (VAS), whereas motor block was evaluated by the Bromage score. Assessments were performed every 5 min in the first 20 min after initiation of epidural analgesia and then at 30 min interval. The incidence of instrumental delivery and cesarean section was also recorded. The total plasma concentrations of levobupivacaine were determined before the start of epidural analgesia, 5 and 10 min after starting the infusion, at infusion stop time, and 3–8 h after infusion termination. Results: The VAS was significantly lower with levobupivacaine concentrations of 0.25% and 0.125% than 0.0625%. Motor block in the form of Bromage score 1 was observed in 39% of parturients receiving levobupivacaine 0.25% of which 43% were converted to cesarean delivery. No motor block was observed with the other two concentrations. Levobupivacaine peak plasma concentrations increased with increasing the concentration of the local anesthetic. There was no difference in other pharmacokinetic parameters between the three groups. Conclusion: Levobupivacaine concentration of 0.125% is superior to other concentrations for epidural labor analgesia as it provides adequate analgesia without motor affection which reflects in a lower incidence of instrumental delivery or cesarean section.

Keywords: Bromage score, epidural analgesia, levobupivacaine, visual analog score

INTRODUCTION

Levobupivacaine is a pure S-enantiomer of bupivacaine. Clinical studies have shown that epidural levobupivacaine promotes sensory and motor block similar to bupivacaine with lower toxicity. These characteristics make levobupivacaine an attractive choice for obstetric anesthesia since pregnant women have a higher risk of toxicity due to physiological adaptations.

When using low concentrations of levobupivacaine, a differential neuraxial block is produced where sensory fibers are blocked with preservation of motor function. Block of the perineal or abdominal muscles from epidural local anesthetic may interfere with normal internal rotation of the fetal head. Minimizing motor block during labor may allow for normal progression of labor that may translate into fewer instrumental deliveries, although, this is controversial. The plasma concentration of levobupivacaine following therapeutic administration is determined by both the administered dose as well as the route of administration. Following epidural administration, levobupivacaine undergoes biphasic absorption; first, a small quantity of the drug is
rapidly absorbed into the circulation, this is followed by slower absorption of the remainder of the drug.\textsuperscript{[6]}

Different concentrations of levobupivacaine have been used for epidural analgesia for labor ranging from 0.0625% to 0.25%. However, the optimum concentration which provides adequate labor analgesia with avoidance of motor blockade and minimal side effects has not been clearly defined. Increasing the dose of a local anesthetic (increased concentration or volume) yields a faster onset of effect, a longer duration of action, and a greater depth of blockade.\textsuperscript{[7]} However, this may result in a higher plasma concentration of the local anesthetic agent which may increase the risk of toxicity.

This study was designed to compare the clinical effect of different concentrations of levobupivacaine (0.25%, 0.125%, and 0.0625%) for epidural labor analgesia. As a secondary outcome, we studied the pharmacokinetic profile of the different concentrations of levobupivacaine in pregnant females.

Materials and Methods

This study was conducted in Beni-Suef University hospital after obtaining the ethical committee approval and a written informed consent from the enrolled parturients. The study included 60 pregnant females who undergone normal vaginal delivery under epidural analgesia in the period from December 2015 to December 2016. The parturients were 20–40 years of age with vertex presentation and cervical dilatation <4 cm and having at least one contraction every 5 min, with gestational age >38 weeks. Nineteen of the enrolled parturients agreed for venous blood sampling for pharmacokinetic analysis. Parturients with hypertensive disorders of pregnancy or with a history of cardiac, liver, or kidney diseases were excluded from the study. Subjects with a history of allergy to amide local anesthetics were also excluded from the study.

Parturients were randomly assigned using randomized code into three groups according to the concentration of levobupivacaine administered for epidural analgesia:
- Group 1 ($n = 20$): received epidural levobupivacaine 0.25%
- Group 2 ($n = 20$): received epidural levobupivacaine 0.125%
- Group 3 ($n = 20$): received epidural levobupivacaine 0.0625%.

Before the performance of the epidural block, 15 ml/kg of lactated Ringer’s solution was infused over 30 min. The epidural space was identified in the sitting position in L3–L4 or L4–L5 level using the loss of resistance to air technique. A 20 gauge multiorifice catheter was secured in the epidural space using an 18 gauge Tuohy epidural needle and no test dose was given. Attempts to aspirate blood or CSF were done to exclude intravascular or intrathecal injection. Before insertion of the epidural catheter, the parturient was asked to quantify her score of pain on a visual analog score (VAS) of 0–10, with 0 being no pain and 10 being the worst imaginable pain. Parturients were positioned in the supine position, and the study drugs were started. Parturients were randomly assigned to receive 15 ml of levobupivacaine 0.25%, 0.125%, or 0.0625% (Chirocaine, Abbott, Queenborough, Kent, UK) with 2 µg/ml of fentanyl followed by continuous infusion of the same concentration at 10 ml/h. The study solutions were prepared in equal volumes of isotonic saline 0.9% by an anesthetist not directly involved in the patients’ care or data collection. Both patient and attending anesthetist who perform the block were blinded to the study drugs. Patient monitoring included electrocardiography, noninvasive blood pressure, and pulse oximetry.

The onset of sensory block determined by the time from injection of the epidural bolus dose till the occurrence of the first painless contraction and the achievement of VAS <3 was recorded. The degree of sensory block determined by theVAS, motor block and vital signs (heart rate [HR] and mean blood pressure) were recorded at the following time intervals; before the start of epidural analgesia, every 5 min in the first 20 min after initiation of epidural analgesia and then at 30 min interval till delivery. The motor block was assessed according to the modified Bromage scale; Bromage 0: the patient can move the hip, knee and ankle, Bromage 1: the patient cannot move the hip but can move the knee and ankle, Bromage 2: the patient cannot move the hip and knee but can move the ankle, Bromage 3: the patient is unable to move the hip, knee, and ankle. Hypotension defined as >20% drop of mean arterial pressure (MAP) from the baseline value or systolic blood pressure <90 mm Hg was treated by intravenous boluses of 10 mg ephedrine and crystalloid boluses of 250 ml. Bradycardia was defined as HR <50 beats/min or decrease in HR >25% of the baseline; it was treated by 0.3–0.5 mg atropine. The duration of delivery (part of the first stage of labor from starting the bolus dose and second stage of labor) was recorded. The incidence of instrumental delivery or conversion to cesarean section was also recorded.

Venous blood samples (2 ml) were collected from 19 parturients before the start of epidural analgesia, 5 and 10 min after starting the infusion, at infusion stop time, and 3–8 h after infusion termination. Blood samples were collected in EDTA tubes to avoid clotting and samples were centrifuged at 3000 R.P.M for 15 min to obtain plasma. The separated plasma tubes were stored at −20°C until assayed.

Assay

The total plasma concentrations of levobupivacaine were determined using a liquid chromatography (LC) mass spectrometry (MS) analysis method. The internal standard was mepivacaine. Plasma samples (250 µl) were mixed with 25 µl of a 5 ng/ml internal standard solution, and 750 µl methanol. The mixture was vortexed and centrifuged for 10 min. Aliquots from the supernatant (7.5 µl) were injected into a Waters Acquity Ultra-Performance LC MS/MS apparatus equipped with an auto-sampler, and reversed phase C18 column (2.1 × 150 mm²; a particle size of 1.7 µm). The mobile phase was a mixture of
methanol and 0.1% formic acid (90:10%v/v) and was delivered at a flow rate of 0.25 ml/min. Mass spectrometric detection was performed using Waters Acquity™ triple quadruple detector in multiple reactions monitoring mode. An electrospray ionization interface in positive ionization mode was used. The ion spray voltage was set at 3 kV. The gas temperature was 400°C and the gas flow rate was 500 L/h. Hardware control and data acquisition and treatment were carried out using MassLynx 4.1 SCN805 software (Waters Corp., Milford, MA, USA).

Pharmacokinetic analysis
A noncompartmental analysis of levobupivacaine plasma concentration-time data was performed to quantify pharmacokinetic parameters in the three treatment groups. To compute drug’s terminal half-life (t1/2), log-linear regression of postinfusion concentration–time data was performed. To estimate bioavailability normalized total clearance (CL/F), mean residence time (MRT), and bioavailability normalized distribution volume at steady state (Vss/F), a model-independent moment analysis was used. The parameters were calculated using the following formulae:

\[ \text{CL/F} = \frac{\text{Total dose}}{\text{AUC}_{0→∞}} \]

\[ \text{MRT} = \frac{\text{AUMC}_{0→∞}}{\text{AUC}_{0→∞}} - \frac{T}{2} \]

\[ \text{Vss/F} = \frac{\text{CL/F} \times \text{MRT}}{\text{T}} \]

Where T is infusion duration, AUC_{0→∞} and AUMC_{0→∞} denote total area under curve and area under moment curve, respectively. Calculation of the MRT is based on the assumption that levobupivacaine absorption rate from the epidural space to the systemic circulation is much faster than other pharmacokinetic processes. AUC_{0→∞} and AUMC_{0→∞} were calculated from the measured plasma concentration-time data using the linear trapezoidal rule followed by adjustment for the area of the terminal corner. The noncompartmental analysis was coded in R version 3.10 (R Core Team 2014).

Statistical analysis
To detect a clinically significant difference of sensory and motor blockade between the three groups, with the power of 80% and an alpha error of 5% using stratified random sampling with equal distribution to each group, the calculated sample size was 30 patients (10 patients in each group). This was increased to 60 patients (20 patients per group) for possible dropouts.

Data were coded and entered using the statistical package SPSS version 22 (Chicago, IL, USA). Data were presented as the mean and standard deviation (SD) for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using analysis of variance (ANOVA) with multiple comparisons post hoc test. For comparing categorical data; Chi square test was performed. The exact test was used instead when the expected frequency is <5. The values of P < 0.05 were considered to be statistically significant.

Type III ANOVA was used for statistical comparisons of the onset of sensory block and noncompartmentally determined pharmacokinetic parameters between the three treatment groups. ANOVA tests were performed after testing for normality and homogeneity of variance between the groups. Probabilities of achieving VAS score <3 and Bromage score >2 between the treatment groups at different times was analyzed using logistic regression models.

RESULTS
Sixty parturients were recruited to the study. Six cases of epidural failure were recorded (2 cases in each group). Three cases were delivered by cesarean section in group 1; all these cases were excluded from the study. Three cases were excluded from the pharmacokinetic study due to clotting of some blood samples and break of others during centrifugation.

The three groups were comparable regarding demographic data and duration of delivery, although the duration of delivery in Group 2 was slightly longer [Table 1].

MAP was comparable between the three groups; although, there was slightly lower MAP in group 1 than group 2 than group 3 but did not reach statistical significance (P > 0.05), no hypotension was observed [Table 2]. As regard to the HR, there

| Table 1: Demographic data |
|---------------------------|
| Group 1 (n=15) | Group 2 (n=18) | Group 3 (n=18) | P |
|-----------------|-----------------|-----------------|---|
| Age (year) | 25.07±3.634 | 27.13±4.838 | 25.07±3.636 | 0.274 |
| Weight (kg) | 77.10±10.333 | 72.70±11.461 | 70.00±7.860 | 0.293 |
| Height (cm) | 163.47±4.838 | 159.93±5.161 | 162.20±4.004 | 0.865 |
| Duration of delivery (min) | 118.00±50.029 | 174.33±72.429 | 133.00±72.600 | 0.064 |

Data are presented as mean±SD. Group 1=Levobupivacaine 0.25%, Group 2=Levobupivacaine 0.125%, Group 3=Levobupivacaine 0.0625% (all with fentanyl 2 µg/ml). SD=Standard deviation.

| Table 2: Mean arterial pressure measurements throughout the study period |
|-----------------------------|
| Group 1 (n=15) | Group 2 (n=18) | Group 3 (n=18) | P |
|-----------------|-----------------|-----------------|---|
| MAP base line reading | 90.50±7.990 | 84.90±7.880 | 90.80±4.894 | 0.129 |
| MAP after 5 min | 87.33±6.597 | 78.33±17.224 | 84.73±9.153 | 0.115 |
| MAP after 10 min | 85.87±8.601 | 89.93±8.892 | 86.67±9.663 | 0.436 |
| MAP after 15 min | 78.07±11.423 | 82.47±6.323 | 85.87±7.809 | 0.062 |
| MAP after 30 min | 81.87±5.651 | 85.80±5.979 | 83.47±9.568 | 0.396 |
| MAP after 60 min | 83.20±6.971 | 83.57±4.879 | 85.07±6.108 | 0.686 |
| MAP after 90 min | 84.18±11.686 | 86.43±5.302 | 92.08±5.230 | 0.051 |
| MAP after 120 min | 89.12±6.813 | 83.42±7.549 | 90.55±10.093 | 0.119 |
| MAP after 150 min | 77.00±2.67 | 88.80±3.271 | 89.80±11.967 | 0.753 |
| MAP after 180 min | 78.00±0.000 | 85.00±4.093 | 83.00±17.578 | 0.263 |

Data are presented as mean±SD. Group 1=Levobupivacaine 0.25%, Group 2=Levobupivacaine 0.125%, Group 3=Levobupivacaine 0.0625% (all with fentanyl 2 µg/ml). SD=Standard deviation, MAP=Mean Arterial Pressure.
was no statistically significant difference between the groups throughout the procedure except at 10, 15, and 30 min, where the HR was significantly lower in group 1 than group 2 than group 3 (P < 0.05). No bradycardia was observed [Table 3].

The VAS was statistically significant between the three groups at 5, 10, 15, 120, and 180 min (P < 0.05), being lower in groups 1 and 2 than group 3 [Table 4]. The VAS decreased gradually compared to the baseline score in the first 60 min, then started to increase gradually till delivery but still lower in groups 1 and 2 than group 3 and lower in groups 1 and 2 than their corresponding baseline score. The time needed to reach VAS score ≤3 was shorter in group 1 (8 ± 3.162 min) than group 2 (8.33 ± 4.082 min) than group 3 (15.67 ± 6.510 min). The duration of analgesia (VAS score ≤3) was longer in group 1 (median 115 min) than group 2 (median 105 min) than group 3 (median 95 min).

No motor block was observed in groups 2 and 3 as all parturients could freely move the lower limbs, but in group 1, motor block occurred in 7 parturients (39%) in the form of bromage score 1 (cannot flex the hip joint), three of them delivered by cesarean section. Motor block bromage score of 2 or 3 was not observed in any of the groups [Table 5].

Pharmacokinetic parameters associated with the three concentration groups are depicted in Table 6. The ANOVA analysis failed to detect a statistically significant difference between pharmacokinetic parameters of any of the groups (P > 0.05).

Levobupivacaine plasma concentration-time profiles in the 0.0625%, 0.125%, and 0.25% concentration groups are shown in Figure 1. The mean ± SD peak plasma concentration (Cmax) was 0.09 ± 0.02, 0.19 ± 0.1, and 0.28 ± 0.1 µg/mL for the 0.0625%, 0.125%, and 0.25% groups respectively. For the area under concentration time curve calculated from zero to last observation time (AUC0–tlast), the mean ± SD values were 0.49 ± 0.26, 1.2 ± 0.94, and 1.1 ± 0.69 µg·h/mL, respectively.

**DISCUSSION**

The aim of modern obstetric analgesia is to provide adequate relief of pain resulting from cervical dilatation and uterine contractions while minimizing motor block of the pelvic and lower limb muscles.

The study revealed that in full-term parturients undergoing normal vaginal delivery under epidural analgesia with levobupivacaine, increasing the concentration of levobupivacaine from 0.0625% to 0.125% to 0.25% improves the sensory block characteristics and provides a longer lasting analgesia with decreased requirement of rescue analgesics. However, using a concentration of 0.25% was associated with

| Table 3: Heart rate throughout the procedure |
|---------------------------------------------|
| Group 1 (n=15) | Group 2 (n=18) | Group 3 (n=18) | P |
|----------------|----------------|----------------|---|
| HR base line | 91.3±12.412 | 94.9±7.573 | 100.8±10.589 | 0.068 |
| HR after 5 min | 90.2±8.319 | 91.4±6.651 | 95.8±8.193 | 0.145 |
| HR after 10 min | 84.8±10.063 | 87.9±8.506 | 94.6±4.881 | 0.007 |
| HR after 15 min | 85.4±10.357 | 87.0±10.562 | 97.3±4.523 | 0.004 |
| HR after 30 min | 90.4±7.058 | 90.6±10.026 | 96.5±3.796 | 0.001 |
| HR after 60 min | 87.7±6.912 | 93.8±6.717 | 97.5±5.579 | 0.862 |
| HR after 90 min | 93.0±7.979 | 86.6±8.170 | 95.4±3.619 | 0.112 |
| HR after 120 min | 89.1±8.887 | 89.5±5.535 | 94.3±4.111 | 0.118 |
| HR after 150 min | 77.0±7.93 | 86.8±6.611 | 93.8±14.822 | 0.386 |
| HR after 180 min | 78.0±6.000 | 89.5±6.391 | 95.6±27.574 | 0.090 |

Data are presented as mean±SD. P<0.05 were considered as statistically significant. Group 1=Levobupivacaine 0.25%, Group 2=Levobupivacaine 0.125%, Group 3=Levobupivacaine 0.0625% (all with fentanyl 2 µg/ml). HR=Heart rate, SD=Standard deviation

| Table 4: Visual analogue score throughout the procedure |
|---------------------------------------------|
| Group 1 (n=15) | Group 2 (n=18) | Group 3 (n=18) | P |
|----------------|----------------|----------------|---|
| VAS base line | 5.70±0.675 | 5.10±0.876 | 5.90±0.876 | 0.092 |
| VAS after 5 min | 3.87±0.743 | 3.73±0.884 | 4.80±0.775 | 0.001 |
| VAS after 10 min | 2.67±0.724 | 2.67±0.816 | 3.73±0.704 | 0.000 |
| VAS after 15 min | 1.73±0.594 | 1.73±0.799 | 2.80±0.561 | 0.000 |
| VAS after 30 min | 1.73±0.594 | 1.67±1.67 | 2.13±0.516 | 0.200 |
| VAS after 60 min | 1.60±0.910 | 1.86±1.167 | 2.21±0.579 | 0.208 |
| VAS after 90 min | 2.09±0.701 | 2.71±1.684 | 3.17±0.835 | 0.116 |
| VAS after 120 min | 2.75±0.463 | 3.77±1.787 | 5.27±1.348 | 0.002 |
| VAS after 150 min | 4.00±0.000 | 3.60±1.265 | 5.60±1.517 | 0.021 |
| VAS after 180 min | 5.00±0.000 | 4.22±1.202 | 6.33±1.155 | 0.022 |

Data are presented as mean±SD. P<0.05 were considered as statistically significant. Group 1=Levobupivacaine 0.25%, Group 2=Levobupivacaine 0.125%, Group 3=Levobupivacaine 0.0625% (all with fentanyl 2 µg/ml). VAS=Visual analogue score, SD=Standard deviation

**Figure 1:** Levobupivacaine plasma concentration time profiles following epidurial administration of 0.25%, 0.125% and 0.0625% concentrations. The points and error bars represent the mean and standard deviation, respectively, at each time point.
In the present study, time to onset of sensory block was more rapid in groups 1 and 2 than group 3 and the duration of analgesia (VAS score ≤3) was longer in group 1 (median 115 min) than group 2 (median 105 min) than group 3 (median 95 min). Requirement of postoperative rescue analgesics was less in groups 1 and 2 than group 3. The VAS score was lower in groups 1 and 2 than group 3 throughout the study period. The sensory level was nearly the same in the three groups at T10 with slightly higher in group 1 to T9. It has been assumed that the occurrence of excessive motor block during epidural labor analgesia may result in failure in the normal progress of labor as a result of a decrease in the tone of the pelvic muscles which may reflect in a higher incidence of instrumental vaginal delivery or even conversion to cesarean section. However, this hypothesis remains controversial.

The effect of local anesthetics injected into the epidural space depends on achieving a concentration gradient between the extraneural and the intraneural spaces which allows the local anesthetic to diffuse into the nerve. For the local anesthetic to achieve the desired effect, a critical length of the nerve fiber has to be blocked. Thick, long motor fibers have twice the critical blocking length of thin, short pain fibers. Motor block requires using high concentrations of local anesthetics while using lower concentrations of local anesthetic is associated with a lower incidence of motor blockade because the total amount of local anesthetic inside the nerve is insufficient.

In our study, there was no motor affection with levobupivacaine concentrations of 0.125% or 0.0625%. However, when using a concentration of 0.25%, motor block was recorded in 7 cases (39%) in the form of bromage score 1; three of these parturients (43%) were delivered by cesarean section.

Lacassie et al.\(^{[10]}\) studied the minimum local anesthetic concentration (MMLAC) required for motor block for each of bupivacaine, levobupivacaine, and ropivacaine in labor. Each patient received an epidural bolus of 20 mL of each of the three local anesthetics determined by the MMLAC model. Assessment of motor block was achieved using a 4 point bromage score. The primary outcome in this study was the degree of muscle strength in the legs at 30 min after injection of the study drugs. The MMLAC detected in their study with the 95% confidence intervals was as follows: 0.26% (0.22–0.30) for bupivacaine; 0.30% (0.25–0.36) for levobupivacaine; and 0.34% (0.29–0.38) for ropivacaine. This was in agreement with our study that found motor affection in 39% of cases in 0.25% group of levobupivacaine.

Burke et al.\(^{[11]}\) compared the clinical effect of levobupivacaine 0.25% with bupivacaine 0.25% for epidural labor analgesia. An initial bolus of 10 mL of each of the two study drugs was administered followed by top up doses of 10 mL each. Both drugs produced equivalent pain relief, similar spread of sensory analgesia and similar degree of motor block. Motor block occurred in their levobupivacaine group in 16% of parturients after the initial bolus dose which was increased to 34% after the first top-up dose compared to 17% and 37% in the bupivacaine group. This was close to our finding of 39% motor affection with levobupivacaine 0.25%. The higher percentage of motor block observed in our study may be due to
the higher initial bolus of 15 ml we used which was followed continuous infusion of 10 ml/h. This may have resulted in a higher concentration of local anesthetic in the nerve fibers.

At 10, 15, and 30 min, we found a decrease in HR in groups 1 and 2 than group 3 but not to the degree of defined bradycardia, this may be explained by parturient satisfaction as the pain score was lower in groups 1 and 2 than group 3.

Levobupivacaine pharmacokinetics following epidural administration has been investigated in youth and elderly patients undergoing variable surgical operations excluding obstetrics and during maternity as Simon et al. investigated the effect of the systemic absorption and disposition of levobupivacaine 0.5% after epidural administration in surgical patients.

To the best of our knowledge, this is the first study to evaluate the pharmacokinetics of levobupivacaine concentrations lower than 0.5% in women during labor. Plasma concentration-time profiles shown in Figure 1 suggest large inter-individual variability in levobupivacaine pharmacokinetics. At the medium and large concentrations [Figure 1], terminal phase plasma levels deviate positively from standard exponential decay behavior consistent with a biphasic absorption process (rapid and slow) that happens following epidural administration of levobupivacaine, as previously suggested by Simon et al. who investigated the effect of age on the clinical profile and systemic absorption and disposition of levobupivacaine after epidural administration.

Levobupivacaine C and AUC increased almost linearly with the administered concentration level. This finding, together with the fact that levobupivacaine pharmacokinetic parameters [Table 6] are basically the same in the three groups, refers to dose independent disposition. This finding is in agreement with a previous finding by Mather et al. on their study of the systemic and regional pharmacokinetics of levobupivacaine and bupivacaine enantiomers in sheep (dose escalation study).

The mean levobupivacaine clearance and distribution volume parameters estimated in our study [Table 6] are approximately two folds larger than the corresponding values reported in the literature for non-pregnant adults by Simon et al. On an average, levobupivacaine clearance increases from 360 to 737 mL/min, and distribution volume increases from 72 to 124 L during pregnancy. Although one can argue that discrepancies in clearance and volume values may be attributed to bioavailability adjustment made in our study, the fact that levobupivacaine is completely absorbed following epidural administration (i.e., epidural bioavailability is 100%) nullifies the preceding argument.

Unlike clearance and distribution volume, average half-life and MRT values estimated in our study, 276 and 208 min, respectively [Table 6], are comparable to values reported in nonpregnant adults (t0.5: 180–296, and MRT: 175–273 min Simon et al.)

Levobupivacaine is extensively metabolized in the liver by CYP3A4 and CYP1A2 isomers to the inactive metabolites, desbutyl-levobupivacaine, and 3-hydroxy levobupivacaine, respectively, as concluded by Bajwa and Kaur on their systematic review about clinical profile of levobupivacaine in regional anesthesia.

It is generally accepted that hepatic clearance depends on metabolic enzyme activity, plasma protein binding, and liver blood flow. Pregnancy is associated with profound changes in the three determinants of hepatic extraction. Studies of CYP3A4 metabolized drugs suggest that CYP3A4 activity increases during pregnancy by Anderson since levobupivacaine is >97% bound to plasma protein, mostly to alpha-1 acid glycoprotein, its disposition is probably sensitive to alterations in plasma protein levels.

Alpha-1 acid glycoprotein concentration decreases during pregnancy as concluded by Perucca and Crema on their study of plasma protein binding of drugs in pregnancy, thus increasing the fraction of free drug that is available for hepatic extraction. In addition, total hepatic blood flow increases significantly after 28 weeks of gestation. Similarly, pregnancy-related modifications justify the increased distribution volume in this study. The decrease in alpha-1 acid glycoprotein level during pregnancy Perucca and Crema is expected to increase the fraction of drug that can distribute to the extravascular space.

Moreover, approximately 80% of the body weight gained during pregnancy is attributed to the accumulation of extravascular body water as concluded by Krauer and Krauer on their study of drug kinetics in pregnancy that certainly increases the dilution of the drug in the body.

A limitation of our study is that we employed assessment of lower extremities muscle tone for evaluating the effect of epidural local anesthetics on motor function and its relation on the mode of delivery. The tone of the pelvic and abdominal muscles would be more important for the progress of labor. However, it is difficult to assess pelvic muscle tone clinically, and hence we used the lower limbs muscle tone as a surrogate for pelvic muscle blockade, similar to what was followed in most previous studies.

Conclusion

Our data indicate that levobupivacaine concentration of 0.125% is superior to other concentrations for epidural labor analgesia as it provides adequate analgesia during labor without motor affection or the need for instrumental vaginal delivery or conversion to cesarean section. Concentration of 0.25% is the least desirable as its analgesic effects are comparable to 0.125% while increasing the incidence of motor block which may result in higher incidence of instrumental and cesarean deliveries. It was also associated with higher plasma concentrations potentially increasing the risk of toxicity.
Levobupivacaine $C_{\text{max}}$ and AUC$_{0\rightarrow t_{\text{last}}}$ increased almost linearly with the administered concentration level and other pharmacokinetic parameters did not significantly change between the three concentration levels referring to dose-independent pharmacokinetics.

It seems that levobupivacaine faster clearance and larger distribution volume observed in this study is understandable in the light of pregnancy-induced alterations in human physiology. However, more studies are needed to confirm this.

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Conflicts of interest
There are no conflicts of interest.

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