Research Paper Medical Science

# Evaluation of Levobupivacaine and Bupivacaine Passage Into Breast Milk Following Epidural Anesthesia for Cesarean Delivery- A Randomized Control Trial

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**ABSTRACT**

Aim: to compare the passage of levobupivacaine and bupivacaine into breast milk following epidural anesthesia for cesarean delivery.

Methods: The study was conducted at Gujarat Adani Institute of Medical Science, Bhuj, Kutch, Gujarat. A total of 20 women undergoing optional cesarean delivery under epidural anesthesia were randomized to receive either 0.5% levobupivacaine or 0.5% racemic bupivacaine via an epidural catheter. Straight away before and 30 min, 1 h, 2 h, 6 h, 12 h and 24 h after administration of epidural local anesthetic, maternal blood and breast milk samples were taken concurrently. Drug concentrations in plasma and milk were determined via high-performance liquid chromatography.

Results: Both levobupivacaine and bupivacaine were found in breast milk 30 min after epidural administration. Concentrations of both agents showed stable and comparable decreases in milk and plasma and were nearly undetectable at 24 h. The milk/plasma ratios were 0.34 ± 0.13 for levobupivacaine and 0.37 ± 0.14 for bupivacaine.

Conclusion: Both levobupivacaine and bupivacaine pass into breast milk subsequent epidural administration. The concentration of both drugs was around three times lower in breast milk than in maternal plasma.

**KEYWORDS** Breast milk, Bupivacaine, Levobupivacaine, Plasma

## Introduction

Although it is suggested that infants are fed breast milk for at least the first six months of life,[1,2] some medications used by mothers during labor or breastfeeding can pass into breast milk and may be possible damaging to the infant.[3,4] Previous studies have revealed that local anesthetics, such as racemic bupivacaine, lidocaine and ropivacaine pass into breast milk,[5–7] although it has been recommended that the use of bupivacaine for epidural anesthesia is safe with regard to breastfeeding.[5] To our information, levobupivacaine transfer into human breast milk has not been studied. Therefore, present study was done with aim to investigate the degree to which levobupivacaine passes into breast milk following epidural anesthesia for elective cesarean delivery. Transfer of medications into breast milk depends on pharmacological properties such as protein binding and lipid solubility, lower protein binding being connected with greater transfer. Since protein binding of levobupivacaine is more than that of bupivacaine, we considered it might undergo less transfer into breast milk. Therefore, comparison is also done between the maternal plasma and milk concentrations of both drugs.

## Methods

The study was conducted at Gujarat Adani Institute of Medical Science, Bhuj, Kutch, Gujarat. Ethical approval was taken from institutional review board and ethical committee of the college and written informed consent was obtained from all participants. Study participants consisted of 18–40 years females with singleton full-term pregnancy undergo optional cesarean delivery under epidural anesthesia. Exclusion criteria were obstetric problems, cardiac, renal or metabolic disorders, allergy or sensitivity to local anesthetics and use of medications known to affect the metabolism of levobupivacaine and bupivacaine. All participants undergo pre-anesthetic assessment one day before surgery.

Participants were randomized to one of two groups, by using a random number table, to receive either 0.5% bupivacaine (Group B, n = 10) or 0.5% levobupivacaine (Group A, n = 10). Parturients were blinded to randomization. Each woman received intravenous famotidine 40 mg and metoclopramide 10 mg, 30–45 min before induction of epidural anesthesia. In the opration theater electrocardiogram, heart rate, non-invasive arterial blood pressure and peripheral oxygen saturation (SpO2) were incessantly monitored.

An 18-gauge venous catheter was inserted into the dorsum of one hand and lactated Ringer's solution 10 mL/kg was administered over 30 min before epidural anesthesia. An 18-gauge venous catheter was inserted into the dorsum of the other hand for blood sampling. An epidural catheter was inserted at the L3–4 vertebral level. The epidural space was identified using lossof- resistance to saline with an 18-gauge Tuohy needle. After a test dose of 2% lidocaine 3 mL, 0.5% levobupivacaine was administered to parturient in Group A, and 0.5% racemic bupivacaine to those in Group B. The study drugs were given as fractionated doses via the epidural catheter until a sensory block extending to T6 to pinprick was achieved. Motor block was evaluated by using a modified Bromage scale. The beginning of the administration of study medications was considered time 0 for evaluation of both sensory and motor blockade. When a T6 sensory block was achieved, surgery was permitted to start. If sufficient epidural anesthesia was not achieved, general anesthesia was administered and these parturient were excluded from succeeding analysis. The total quantity of local anesthetic required and the duration of sensory and motor blockade were recorded.

Immediately before and 30 min, 1 h, 2 h, 6 h, 12 h and 24 h after administration of epidural drugs, 2 mL samples of maternal blood and 2 mL samples of breast milk were taken all together. Breast milk samples were collected with a milking pump Blood samples were centrifuged straight away after collection and the plasma extracted. Plasma and milk samples were stored at -20$^0$C until analyses. Quantification of levobupivacaine and racemic bupivacaine was performed. Levobupivacaine and bupivacaine solutions were prepared at methanol concentrations of 0.2, 0.4, 0.8, 1.6 and 2.4 lg/mL.

**Statistical analysis**
Data are presented as median or mean ± standard deviation (SD) as appropriate. Data were analyzed using the Mann–Whitney U test, the chi-square test and the Wilcoxon signed-rank test using SPSS version 15.0). statistically significance was set at 5% p value.

**Results**
Patient characteristics were comparable among groups (Table 1). Epidural anesthesia was sufficient in all patients and there was no requirement of general anesthesia. There were no differences between groups in the characteristics of epidural anesthesia (Table 2). Nausea was observed in two patients in Group A and two patients in Group B; nausea and vomiting was observed in one patient in Group B. Levobupivacaine was found in both maternal plasma and breast milk 30 min following epidural administration. However, concentrations of levobupivacaine in breast milk were just about three times inferior to those in plasma. Plasma and milk concentrations of levobupivacaine showed steady and comparable declines and were nearly untraceable 24 h after drug administration. The course of both plasma and breast milk concentrations of bupivacaine was analogous to that of levobupivacaine. As with levobupivacaine, the concentrations of racemic bupivacaine in breast milk were almost one-third of those in maternal plasma. There were no significant differences between the mean concentrations of levobupivacaine and bupivacaine in either plasma or breast milk at all evaluation points.

**Table 1: Demographic data of study population**

| | Group A N=10 | Group B N=10 |
|---|---|---|
| Age | 24.8 ± 6.0 | 27.6 ± 6.5 |
| Height (cm) | 161 ± 6.5 | 158 ± 4.2 |
| Weight (kg) | 68.9 ± 9.4 | 72.1 ± 2.9 |
| ASA Physical Status Class I/II | 9/1 | 8/2 |

**Table 2 Characteristics of epidural anesthesia**

| | Group A | Group B |
|---|---|---|
| Total dose of local anesthetic (mg) | 79.9 ± 10.7 | 81.9 ± 12.7 |
| Time to achieve T6 block (min) | 15.9 ± 3.0 | 14.8 ± 3.4 |
| Maximum modified Bromage scale score | 3 | 3 |
| Duration of sensory block (min) | 319 ± 58 | 331 ± 67 |
| Duration of motor block (min) | 143 ± 92 | 136 ± 104 |

**Discussion**
Present study confirmed that levobupivacaine, like racemic bupivacaine, passes into breast milk. The concentration of levobupivacaine was roughly three times inferior in breast milk than in plasma. The amount of both drugs in plasma and breast milk constantly decreased and was nearly undetectable 24 h after administration. Previous studies have shown that bupivacaine is transferred into breast milk[5,6]. Although breast milk is an best food for infants, spread of medicines used by the mother to breast milk can potentially cause adverse effects in infants. Therefore, when a new medicine is given to a nursing mother, there is worry about exposure through milk. It has been suggested that medications can be effortlessly transferred to milk, especially during the first two weeks postpartum because gaps between mammary cells are not yet closed during that period.[4]

Previous studies have shown that some local anesthetics can be transferred to breast milk[5, 7, 9] In the present study, we have established that levobupivacaine too passes into breast milk. The passage of drugs into breast milk frequently occurs via passive diffusion proportional to the concentration of drug in maternal plasma. In addition, physicochemical characteristics such as molecular weight, lipid solubility, protein-binding and pKa are important.[4,10] High rates of transfer of levobupivacaine to breast milk may be anticipated because of its low molecular weight, lipophilicity, weak basic structure and ease of transport to the central nervous system.[11] However, in the current study, levobupivacaine was detected in breast milk at around one-third of the concentration in maternal plasma. This might be because levobupivacaine is 97% bound to plasma proteins. Only non-ionized portions of compounds that are not bound to plasma proteins can be shift to breast milk.

It is also important to quantify infant drug exposure, for which M/P ratio is the most commonly used parameter. This can be calculated using several formulae.[12] Ortega et al.[5] reported the M/P ratio for bupivacaine as 0.34 for women undergoing cesarean delivery, which was dependent on the $AUC_{0-12}$ values for bupivacaine when administered epidurally. Santos et al.[13] administered levobupivacaine, racemic bupivacaine and ropivacaine to pregnant ewes intravenously. Following administration, they found these drugs in fetal plasma and tissues. Bader et al.[14] administered levobupivacaine and bupivacaine epidurally to women undergoing voluntary cesarean delivery. They determined that concentrations of these two drugs in umbilical venous blood samples taken during delivery were one-third lower than those in the maternal plasma. These two studies reveal that both levobupivacaine and bupivacaine cross the placenta to the fetus. Therefore, it should be taken into report that, in addition to breast milk, infants are exposed to local anesthetic drugs via the placental pathway.

**Conclusion**
Both levobupivacaine and racemic bupivacaine pass into breast milk subsequent epidural administration. In both groups, maternal plasma and milk concentration–time profiles were similar.

**References**

1. Kramer MS, Kakuma R. Optimal duration of exclusive breastfeeding. Cochrane Database Syst Rev 2012;8:CD003517.
2. Breastfeeding and the use of human milk. American Academy of Pediatrics Work Group on Breastfeeding. Pediatrics 1997;100:1035–9.
3. Ito S, Lee A. Drug excretion into breast milk – overview. Adv Drug Deliv Rev 2003;55:617–27.
4. Spencer JP, Gonzales LS 3rd, Barnhart DJ. Medication in the breast-feeding mother. Am Fam Physician 2001;64:119–26.
5. Ortega D, Viviand X, Lorec AM, Gamerre M, Martin C, Bruguerolle B. Excretion of lidocaine and bupivacaine in breast milk following epidural anesthesia for cesarean delivery. Acta Anaesthesiol Scand 1999;43:394–7.
6. Baker PA, Schroeder D. Interpleural bupivacaine for postoperative pain during lactation. Anesth Analg 1989;69:400–2.
7. Matsota PK, Markantonis SL, Fousteri MZ, et al. Excretion of ropivacaine in breast milk during patient-controlled epidural analgesia after cesarean delivery. Reg Anesth Pain Med 2009;34:126–9.
8. Papini O, Mathes AC, Cunha SP, Lanchote VL. Stereoselectivity in the placental transfer and kinetic disposition of racemic bupivacaine administered to parturients with or without a vasoconstrictor. Chirality 2004;16:65–71.
9. Giuliani M, Grossi GB, Pileri M, Lajolo C, Casparrini G. Could local anesthesia while breast-feeding be harmful to infants? J Pediatr Gastroenterol Nutr 2001;32:142–4.
10. Hale TW. Maternal medications during breastfeeding. Clin Obstet Gynecol 2004;47:696–711.
11. McLeod GA, Burke D. Levobupivacaine. Anaesthesia 2001;56:331–41.
12. Fleishaker JC. Models and methods for predicting drug transfer into human milk. Adv Drug Deliv Rev 2003;55:643–52.
13. Santos AC, Karpel B, Noble G. The placental transfer and fetal effects of levobupivacaine, racemic bupivacaine, and ropivacaine. Anesthesiology 1999;90:1698–703.
14. Bader AM, Tsen LC, Camann WR, Nephew E, Datta S. Clinical effects and maternal and fetal plasma concentrations of 0.5% epidural levobupivacaine versus bupivacaine for cesarean delivery. Anesthesiology 1999;90:1596–601.