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Original Research

Bupivacaine Pharmacokinetics and Breast Milk Excretion of Liposomal Bupivacaine Administered After Cesarean Birth

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OBJECTIVE: To evaluate bupivacaine concentrations in maternal plasma and transfer into breast milk in women undergoing liposomal bupivacaine infiltration in the transversus abdominis plane after cesarean birth.

METHODS: Prospective cohort study of healthy pregnant women who underwent cesarean birth at term followed by a transversus abdominis plane block using 52 mg bupivacaine hydrochloride 0.25% (20 mL) and 266 mg liposomal bupivacaine 1.3% (20 mL). Simultaneous blood and milk samples were collected in a staggered fashion, three to four samples per patient at the following timepoints after block administration: 2, 6, 12, 24, 48, 72, and 96 hours. Quantification of bupivacaine was performed by liquid chromatography–tandem mass spectrometry. Neonatal drug exposure was modeled by calculating milk/plasma area under the curve (AUC) ratios, neonatal dosage, and relative neonatal dosage of bupivacaine at each sampling time.

RESULTS: Thirty patients were enrolled. Concentrations in breast milk peaked at 6 hours (mean 58 ng/mL), followed by constant and steady decline to low levels at 96 hours (mean 5.2 ng/mL). Maternal plasma concentrations had two peaks, first at 6 hours (mean 155.9 ng/mL) and then at 48 hours (mean 225.8 ng/mL), followed by steady decline. Milk/plasma $AUC_{0\text{-}t}$ ratios ranged between $AUC_{0\text{-}2}$ of 0.45 (80% CI 0.38–0.52) and $AUC_{0\text{-}96}$ of 0.15 (80% CI 0.14–0.17). Neonatal dosage ranged between a mean of 355.9 ng/kg at 0–2 hours and a mean of 15,155.4 ng/kg at 0–96 hours. Relative neonatal dosage was less than 1% at all time intervals. No serious adverse reactions occurred in any neonate.

CONCLUSION: Bupivacaine is excreted in breast milk after local infiltration of liposomal bupivacaine and bupivacaine hydrochloride mixture into transversus abdominis plane blocks after cesarean birth. Relative neonatal dosages of less than 1% (less than 10% is considered to be unlikely to be of clinical concern) suggest minimal risks for breastfeeding healthy, term neonates after the administration of this combination of local anesthetics to mothers.

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Effective pain management after cesarean birth promotes enhanced recovery, earlier patient mobilization, shorter time spent in postoperative care units, and reduced costs.[1–5] Untreated postpartum pain is associated with a risk of greater opioid use, postpartum depression, and development of persistent pain that may lead to chronic opioid use and misuse disorder (White K, Bou Zgheib N, Mitchell B. Decreasing narcotic use after cesarean section with enhanced recovery: a quality improvement project [28D] [abstract]. Obstet Gynecol 2018;131:48S.).[6,7] In

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2018, the American College of Obstetricians and Gynecologists recommended a stepwise approach to postcesarean pain management using a multimodal combination of agents including local anesthetics.[8] For decades bupivacaine has been used in obstetrics and nerve block procedures, but a major limitation is the relatively short duration of action (typically less than 8 hours).[9–11] Analgesia with liposomal bupivacaine on the other hand may be maintained for up to 96 hours after a single intraoperative administration into the surgical wound.[12–18] Liposomal bupivacaine infiltration has been shown to significantly reduce postsurgical pain and opioid consumption for up to 72–96 hours when administered through either local wound infiltration or using a transversus abdominis plane block in various procedures (Ang MJ, Silkiss RZ. The use of long-acting liposomal bupivacaine (Exparel) for postoperative pain control following enucleation or evisceration [letter]. Ophthalmic Plast Reconstr Surg 2018;34:599.),[19–22] including lower abdominal ones.[16–18,23] However, the clinical use of liposomal bupivacaine in patients undergoing cesarean birth has not been widespread for possible few reasons. First, efficacy has not been thoroughly investigated. Another reason could be cost, given the expense of liposomal bupivacaine. The last reason may be the lack of clinical data concerning breast milk transfer and neonatal safety. Therefore, in this study we evaluated bupivacaine concentrations in plasma and milk samples and modelled transfer to breast milk after liposomal bupivacaine transversus abdominis plane infiltration in low risk pregnant patients undergoing scheduled term cesarean birth.

METHODS

We conducted a prospective cohort study. Institutional review board approval for this study was obtained from the University of Minnesota (STUDY00003258), and written informed consent was obtained for all participants. Recruitment occurred at the University of Minnesota Medical Center Women's Health Clinics and labor and delivery unit between March 2019 and October 2019. Participants were required to be American Society of Anesthesiologists physical status I or II, aged 18–40 years, with singleton uncomplicated full-term (37–42 weeks of gestation) pregnancies undergoing elective cesarean birth, planning to breastfeed, and considering postoperative transversus abdominis plane block for pain control. Exclusion criteria included obstetric complications (fetal anomaly, fetal growth restriction, hypertensive disorders of pregnancy, gestational diabetes, Rh incompatibility or congenital malformations), and maternal conditions including cardiac, renal, metabolic disorders, allergy or sensitivity to local anesthetics and use of medications known to affect the metabolism of bupivacaine. Maternal blood samples were collected at the day of the surgery before the cesarean birth procedure and considered to be time-point zero. Breast milk samples were not collected preoperatively. The study was designed in concordance with the 2019 U.S. Food and Drug Administration draft guidance.[24]

All aspects of anesthetic and obstetric care were according to hospital routine. A spinal anesthetic was performed with 150 micrograms morphine (eg, Duramorph) combined with 1.4–1.6 mL of 0.75% hyperbaric bupivacaine hydrochloride plus 15 micrograms intrathecal fentanyl. Within 30 minutes after the completion of the cesarean birth, all patients received a bilateral transversus abdominis plane blocks under ultrasound guidance performed using 52 mg bupivacaine hydrochloride 0.25% (20 mL) and 266 mg liposomal bupivacaine 1.3% (20 mL).

Simultaneously, 1 mL of blood and breast milk samples were collected at 2, 6, 12, 24, 48, 72, and 96 hours after the transversus abdominis plane block administration. Collection was done in the hospital during hospital stay and by a home-visit nurse after discharge. Participants were instructed to express the milk through pumping or hand expression, to mix the collected milk, and to remove 1 mL for the research study after expression. Maternal blood samples were centrifuged after collection and plasma was extracted. Both plasma and milk samples were stored at −20 °C until analyses.

Sparse sampling technique was used in which participants were randomly assigned to one of two groups. In the group that received an odd code, paired blood and milk samples were obtained at 2, 12, and 48 hours. In the group that received an even code, paired samples were obtained at 6, 24, 72, and 96 hours.

Quantification of bupivacaine in the collected blood and milk samples was performed by liquid chromatography–tandem mass spectrometry, which was performed using a Quattro Ultima triple quadrupole mass spectrometer coupled with a Waters Acquity Ultra Performance Liquid Chromatography system. Limit of quantification was determined empirically by standard methods and found to be 0.7 ng/mL.[25,26] Sample analysis was performed using MassLynx 4.1 software.

Our primary objectives were to evaluate bupivacaine concentrations in plasma and milk samples and to model bupivacaine transfer to breast milk and

neonates by calculating milk/plasma area under the curve (AUC) ratios, neonatal dosage, and relative neonatal dosage using the below formulae. The safety analysis included adverse events in all neonates of participating mothers from the time of informed consent through the study safety follow-up period (up to day 14 postpartum). While in the hospital, adverse events were monitored through chart review; while at home, a follow-up phone call was conducted at day 14 postpartum. During the call, the neonates' mothers were given the opportunity to report adverse events spontaneously, and a general prompt using open-ended questions was used. Neonatal adverse events of interest included central nervous system, gastrointestinal, respiratory, rash, seizures, and any reported hospital readmissions. No related maternal adverse events occurred throughout the study, however, these were not systematically sought as they have been thoroughly evaluated in prior studies.[27]

No formal sample size calculations were performed, as no statistical hypotheses were being tested. However, published literature for other local anesthetics, and for liposomal bupivacaine under other circumstances, had sample sizes ranging from 12 to 30 patients.[15,24,28,29] The planned sample size for our study was 30 mothers.

Descriptive statistics were obtained for demographic variables. Plasma and milk concentrations are presented as mean with 80% CI. Milk and plasma AUCs were calculated using the trapezoidal method from time zero to the time of the last recorded concentration. Area under the curve calculations were performed using the noncompartment analysis module in Phoenix 8.1, and plots were created using R 3.4.2. milk/plasma $AUC_{0\text{-}t}$ ratios were determined. The average milk concentration is calculated by dividing the milk $AUC_{0\text{-}t}$ by the amount of time (t) over which the milk was collected. The weight–adjusted neonatal dosage (ng/kg) was calculated according to Equation 1:

$$\text{Infant dosage}(\text{ng/kg}) = \text{AUC}_{0\text{-t}},\text{milk}(\text{ng}\times\text{h/mL})/\text{t(h)} \times \text{milk volume ingested within t period}\left(\text{mL/kg}\right) \quad (1)$$

where $AUC_{0\text{–t}}$, milk=the AUC from time 0 to t for milk, and t=the amount of time over which the milk was collected. Because the actual volume of milk ingested by the neonate is not known, the average neonatal milk intake was assumed to be 150 mL/kg/d.[30–33] The mean with 80% CI of weight–adjusted maternal dosage (MD) (ng/kg) was calculated and used to calculate the relative neonatal dosage according to Equation 2:[24,30–32,34]

$$\text{Relative infant dosage}(\%) = \text{infant dosage (ng/kg)}/\text{MD (ng/kg)} \times 100\% \quad (2)$$

RESULTS

Between March 2019 and October 2019, a total of 30 healthy participants were enrolled (Table 1). All intended paired samples were obtained as planned except for one mother in the odd code group owing to low milk supply and the neonate's requiring milk supplementation. A total of 102 paired blood and milk samples were collected for the study. Reported adverse events (related or unrelated or both) were transient tachypnea of the newborn in two neonates (Table 1).

Bupivacaine was detected in all plasma and milk samples except for samples obtained before transversus abdominis plane block administration (Fig. 1). Concentrations in breast milk peaked at 6 hours (mean 58 ng/mL) followed by constant and steady decline to low almost undetectable levels at 96 hours (mean 5.2 ng/mL, Fig. 2). Maternal plasma concentrations had two peaks, first at 6 hours (mean 155.9 ng/mL) and then at 48 hours (mean 225.8 ng/mL) followed by steady decline (Fig. 2 and Table 2). Mean milk concentrations were measured at 44%, 36%, 28%, and 18% of mean plasma concentration at 2, 6, 12, and 24 hours, respectively, after liposomal bupivacaine infiltration (Table 2). Time intervals were 0-t (Table 3) and reflect bupivacaine exposure in plasma, breast milk, and milk/plasma ratios over that period of time, for example, milk/plasma $AUC_{0\text{-}72}$ of 0.17 reflects the ratio over the period of 3 days. The estimated milk/plasma AUC ratios ranged between $AUC_{0\text{-}2}$ of 0.45 (80% CI 0.38–0.52) and $AUC_{0\text{–}96}$ of 0.15 (80% CI 0.14–0.17) (Table 3). The estimated neonatal dosage ranged between a mean of 355.9 at 0–2 hours and a mean of 15,155.4 ng/kg at 0–96 hours (Table 4). Relative neonatal dosage was less than 1% at all time intervals (Table 4).

DISCUSSION

We evaluated breast milk transfer of bupivacaine after liposomal bupivacaine infiltration in transversus abdominis plane in patients undergoing cesarean birth. Bupivacaine was detected in breast milk shortly after infiltration and peaked at 6 hours, with a mean concentration of 58 ng/mL, which was 36% of mean plasma concentration at that time-point. Milk levels decreased slowly over the next 4 days to almost undetectable levels. Bupivacaine was transferred into

Table 1. Patient Characteristics

Mothers (n=30)	Value
Age (y)	33 (21–40)
Parity	
Nulliparous	3 (10)
Multiparous	27 (90)
Ethnicity	
Caucasian	16 (53)
Black	7 (23)
Latina	4 (13)
Asian	3 (10)
Measurements at delivery	
Weight (kg)	81.9 (60–132)
Height (cm)	163 (152–167)
BMI category at delivery	
Underweight	0 (0.0)
Normal	3 (10)
Overweight	14 (47)
Obese	13 (43)
Gestational age at delivery (wk)	39.2 (37.42)
Cesarean birth	
Primary	3 (10)
Repeat	27 (90)
Neonates (n=30)	
Sex	
Male	15 (50)
Female	15 (50)
Birth weight (g)	3,480 (2,900–5,190)
Age of milk intake start (d)	1 (1–1)
Required supplementing with formula or donor milk	1 (3)
Length of hospital stay (d)	3 (3–4)
Weight change at discharge (%)	6 (2–11)
Neonates with related or unrelated AEs	2 (7)*
Required hospital readmission within follow-up period	0 (0.0)

BMI, body mass index; AE, adverse event.
Data are median (range) or n (%).
* Both admissions were for transient tachypnea of the newborn.

mother's milk such that an exclusively breastfeeding neonate would ingest less than 1% (relative neonatal dosage) of the maternal dose. None of the neonates of the enrolled mothers had clinically significant adverse events within the study follow up period, which was 14 days postpartum.

Prior reports have evaluated the transfer of the standard racemic bupivacaine into breast milk with reported milk/plasma AUC_{0-12} of 0.34 with no reported calculated neonatal dosage or relative neonatal dosage.[29,35] However standard bupivacaine has a relatively short duration of action up to 8 hours if used for wound infiltration.[36] Liposomal bupivacaine plasma pharmacokinetics have been well established by prior studies.[15] In our study, plasma kinetics were consistent with those reports indicating a bimodal release

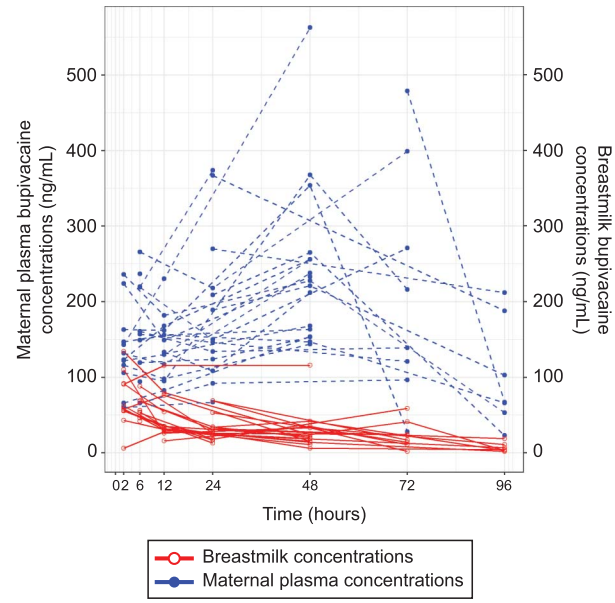

Fig. 1. Plots of maternal plasma and breast milk bupivacaine concentration over time for each participant.

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profile with first peak within few hours and second between 12 and 36 hours of liposomal bupivacaine local infiltration. Although not systematically sought in our study, it is unknown whether systemic plasma

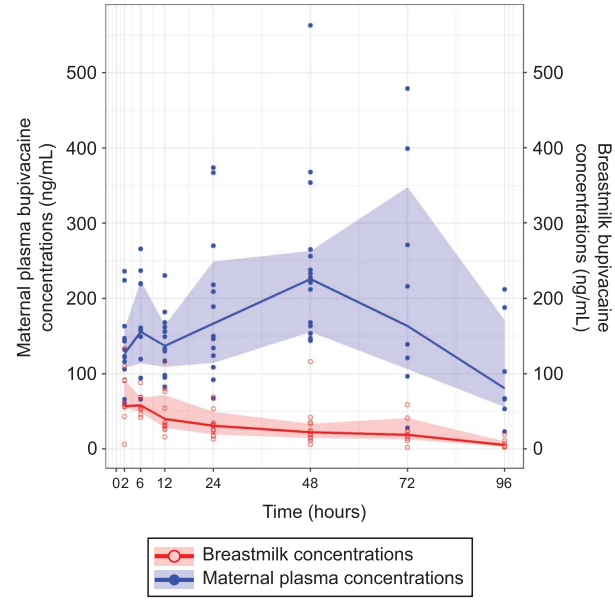

Fig. 2. Mean maternal plasma and breast milk bupivacaine concentration over time. The *shaded area* represents 80% CI. The *dots* represent observed concentrations.

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Table 2. Bupivacaine Concentrations in Breast Milk and Maternal Plasma

Time (h)	n	Milk Concentrations (ng/mL)	Range (ng/mL)	n	Maternal Plasma Concentrations (ng/mL)	Range (ng/mL)
2	11	56.9 (41.5–78.2)	6–134	12	126.9 (108.1–149.1)	60–236
6	8	58 (51.4–65.4)	42–88	10	155.9 (128.4–189.2)	66–266
12	12	39.9 (32–49.8)	16–115.6	14	137.3 (124.2–151.7)	82.5–230.3
24	12	30.8 (25–37.9)	13–69	13	166.8 (137.4–202.5)	67–374
48	15	22.4 (17.7–28.4)	6–116	17	225.8 (198.9–256.3)	144–563
72	9	18.8 (11.8–29.9)	2–58.9	8	163.4 (135.6–196.9)	28–479
96	7	5.2 (3.4–8.1)	2–19	7	80.6 (49.1–132.3)	23–212

Data are geometric mean (80% CI) unless otherwise specified.

concentrations of bupivacaine correlate with local efficacy, despite evidence suggesting analgesia up to 72 hours after single dose local infiltration as compared with bupivacaine hydrochloride or placebo.[12–14,16–18] By obtaining plasma samples, we were able to calculate milk/plasma $AUC_{0\text{-}t}$ ratios, which ranged between 0.3 at day 1 and 0.15 at day 4 postinfiltration. These ratios indicate that very little plasma bupivacaine is transferred into breast milk and that bupivacaine does not accumulate in breast milk.

Passage of drugs into breast milk primarily occurs through passive diffusion in proportion to the drug's concentration in maternal plasma, although this passage depends on different factors including lipophilicity, protein binding, molecular weight, and pKa.[33,34] Our calculated milk/plasma $AUC_{0\text{-}t}$ ratios correlate well with bupivacaine's protein binding characteristics of 85–95%.[37–39] Calculated neonatal dosage values ranged between a mean of 355.9 ng/kg at 0–2 hours and 15,155.4 ng/kg at 0–96 hours. As explained above, these time intervals reflect drug exposure in breast milk over that time period. Neonatal dosage was calculated based on the average daily milk intake of 150 mL/kg/d in an exclusively breastfed neonate.[31] Milk intake varies with age of the neonates and among patients. Nevertheless, the value of 150 mL/kg/d is well established in the pharmacokinetic literature and provides a standard by which drugs can be compared with each other. Once neonatal dosage is calculated, it can be compared with the standard neonatal or infant dosage for the drug, if it is known. However, to circumvent the problem caused by a lack of known neonatal and infant dosages for many maternal drugs, the World Health Organization Working Group and others proposed calculation of relative neonatal dosage as we have done.

Relative neonatal dosage calculations have some pitfalls, which include the effect of variations in administered medications dosages, postnatal age, and milk volume. However, it is generally well accepted as a measure of safety of medication use during breastfeeding.[30,40] Relative neonatal dosage is classified into acceptable if less than 10% of maternal dosage, caution if 10–25% of maternal dosage, and unacceptable if greater than 25% of maternal dosage.[24] In our study, values were all less than 1% at all time intervals. Because bupivacaine is metabolized primarily in the liver, a neonate's absorption will likely be even lower given the first-pass effect.

The use of liposomal bupivacaine in transversus abdominis plane block after cesarean birth provides a promising alternative in controlling pain and reducing opioid use, which will further reduce nausea, vomiting, delayed mobilization, and bowel

Table 3. Area Under the Curve Values for Milk and Plasma and Milk/Plasma Ratios

Time Interval (h)	Milk AUC (ng·h/mL)	Plasma AUC (ng·h/mL)	Milk/Plasma Ratio
0–2	56.9 (41.5–78.2)	126.9 (108.1–149.1)	0.45 (0.38–0.52)
0–6	286.8 (227.2–365.4)	692.5 (581.1–825.6)	0.41 (0.39–0.44)
0–12	580.4 (477.3–711)	1,571.9 (1,339–1,848.1)	0.37 (0.36–0.38)
0–24	1,004.5 (819–1,237.4)	3,396.4 (2,909–3,973)	0.30 (0.28–0.31)
0–48	1,643.1 (1,331.5–2,033.2)	8,107.6 (6,945–9,478.2)	0.20 (0.19–0.21)
0–72	2,137.3 (1,685.4–2,732.5)	12,777.9 (10,959.5–14,916.3)	0.17 (0.15–0.18)
0–96	2,424.9 (1,866.9–3,188.3)	15,706.2 (13,176.7–18,865.9)	0.15 (0.14–0.17)

AUC, area under the curve.
Data are geometric mean (80% CI).

Table 4. Neonatal Daily Dose and Relative Neonatal Dose

Time Interval (h)	Neonatal Dosage (ng/kg) (80% CI)	Relative Neonatal Dosage (%) (80% CI)
0–2	355.9 (259.1–488.9)	0.009 (0.006–0.013)
0–6	1,792.4 (1,419.1–2,283.9)	0.047 (0.035–0.062)
0–12	3,627.6 (2,983.2–4,443.7)	0.095 (0.074–0.121)
0–24	6,278.1 (5,118.5–7,733.9)	0.164 (0.128–0.211)
0–48	10,269.4 (8,321.9–12,707.6)	0.268 (0.208–0.347)
0–72	13,357.9 (10,533.7–17,077.8)	0.349 (0.263–0.467)
0–96	15,155.4 (11,667.9–19,926.8)	0.396 (0.291–0.545)

Data are geometric mean (80% CI).
Neonatal dosage (ng/kg) calculated using the formula: AUC_{0-t}, milk (ng·h/mL)/t (h)×average milk volume ingested within t period (mL/kg). Average milk volume ingested in 24 hours: 150 mL/kg.
Relative neonatal dose (%) was calculated using the formula: neonatal dosage (ng/kg)/maternal dosage (ng/kg)×100%.

malfunction, all of which can improve enhanced recovery after surgery.[41] However, studies evaluating the clinical benefit of liposomal bupivacaine intraincisional infiltration in patients undergoing cesarean birth had conflicting results. Although a retrospective case–control study of 80 patients showed significant reduction in postoperative opioid use,[42] a prospective single-blind randomized controlled trial of 80 participants showed no significant differences in opioid use or pain scores in the first 48 hours postoperatively.[43] More clinical data are needed on the benefit of its clinical use.

We acknowledge the limitations to our study, including that no mothers of preterm neonates were enrolled given that such analysis would have been outside the scope of this study. Drug effect on milk supply was not assessed in our study given the complexity of factors affecting breast milk supply including medical, obstetric, physiologic, and psychosocial. However, in our study only one mother was assessed for low milk supply for which the newborn received milk supplementation.

In conclusion, our study findings suggest that, after liposomal bupivacaine infiltration, the level of bupivacaine ingested by the sucking neonate is acceptable and compatible with breastfeeding.

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Authors' Data Sharing Statement

Will individual participant data be available (including data dictionaries)? *No.*

What data in particular will be shared? *Not available.*

What other documents will be available? *Not available.*

When will data be available (start and end dates)? *Not applicable.*

By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)? *Not applicable.*

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