Epidural Labor Analgesia—Fentanyl Dose and Breastfeeding Success

A Randomized Clinical Trial

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ABSTRACT

Background: Breastfeeding is an important public health concern. High cumulative doses of epidural fentanyl administered for labor analgesia have been reported to be associated with early termination of breastfeeding. We tested the hypothesis that breastfeeding success is adversely influenced by the cumulative epidural fentanyl dose administered for labor analgesia.

Methods: The study was a randomized, double-blind, controlled trial of parous women at greater than 38 weeks gestation who planned to breastfeed, had successfully breastfed a prior infant, and who received neuraxial labor analgesia. Participants were randomized to receive one of three epidural maintenance solutions for labor analgesia (bupivacaine 1 mg/ml, bupivacaine 0.8 mg/ml with fentanyl 1 μg/ml, or bupivacaine 0.625 mg/ml with fentanyl 2 μg/ml). The primary outcome was the proportion of women breastfeeding at 6 weeks postpartum. Maternal and umbilical venous blood fentanyl and bupivacaine concentration at delivery were measured.

Results: A total of 345 women were randomized and 305 had complete data for analysis. The frequency of breastfeeding at 6 weeks was 97, 98, and 94% in the groups receiving epidural fentanyl 0, 1, and 2 μg/ml, respectively ($P = 0.34$). The cumulative fentanyl dose (difference: 37 μg [95% CI of the difference, −58 to 79 μg], $P = 0.28$) and maternal and umbilical cord venous fentanyl and bupivacaine concentrations did not differ between women who discontinued breastfeeding and those who were still breastfeeding at 6 weeks postpartum.

Conclusions: Labor epidural solutions containing fentanyl concentrations as high as 2 μg/ml do not appear to influence breastfeeding rates at 6 weeks postpartum. **(ANESTHESIOLOGY 2017; 127:614-24)**

BREASTFEEDING is an important public health concern, with documented maternal and infant health benefits.[1,2] Neuraxial labor analgesia is used in the majority of births in the United States,[3] but controversy exists as to whether neuraxial labor analgesia negatively impacts breastfeeding. A 2016 systematic review included 23 studies that investigated the association between neuraxial labor analgesia and breastfeeding outcomes.[4] Results were conflicting; half of the studies found no association between neuraxial analgesia and breastfeeding outcomes, while the other half identified negative associations, and one found a positive association. Most studies were observational trials; only three studies were randomized controlled trials. A possible explanation for these conflicting results is that many studies did not control for confounding variables known to influence breastfeeding success.[4,5] Some studies were underpowered, analgesia management in both the neuraxial analgesia and control groups differed or was not well described.

What We Already Know about This Topic

- There is controversy and disagreement between studies as to whether neuraxial analgesia for labor, particularly with fentanyl, affects postpartum breastfeeding

What This Article Tells Us That Is New

- A randomized parallel group study of three epidural solutions of bupivacaine with or without fentanyl showed that breastfeeding success at 6 weeks was not influenced by the epidural fentanyl concentration or the cumulative epidural fentanyl dose administered for labor analgesia
- Maternal and umbilical cord venous fentanyl and bupivacaine concentrations did not differ between women who discontinued breastfeeding (3 to 6%) and those who were still breastfeeding at 6 weeks postpartum

Opioids, such as fentanyl, are commonly used in combination with local anesthetics in epidural solutions used for labor analgesia. Two prospective randomized studies examining the effect of epidural fentanyl on breastfeeding success reported

This article is featured in "This Month in Anesthesiology," page 1A. Corresponding article on page 593.

Submitted for publication April 7, 2017. Accepted for publication June 19, 2017. From the Department of Anesthesiology, Memorial Hermann Memorial City Medical Center, Houston, Texas (A.I.L.); Department of Anesthesiology (R.J.M., P.T., M.J.J.) and Center for Healthcare Studies (P.T.), Northwestern University Feinberg School of Medicine, Chicago, Illinois (R.J.M., P.T.); Department of Nursing, Northwestern Memorial Hospital Chicago, Illinois (N.W.); and Department of Anesthesia, University of Iowa Carver College of Medicine, Iowa City, Iowa (C.A.W.)

 Anesthesiology 2017; 127:614-24

<zdoi;10.1097/ALN.0000000000001793>

conflicting results. Beilin *et al.*[6] reported that mothers who were randomized to receive a cumulative epidural fentanyl dose greater than or equal to 150 μg were more likely to stop nursing 6 weeks postpartum compared with mothers who received no fentanyl, or a cumulative epidural fentanyl dose less than150 μg. In contrast, Wilson *et al.*, in a secondary analysis of a large randomized trial, concluded that neuraxial analgesia, irrespective of epidural fentanyl administration, did not hinder breastfeeding, even at 12 months postpartum.[7]

The purpose of the current study was to evaluate the impact of intrapartum epidural fentanyl on breastfeeding success in the initial postpartum period, as well as at 6 weeks and at 3 months postpartum. The primary outcome was self-reported breastfeeding at 6 weeks postpartum. In this superiority study, we tested the hypothesis that 6-week breastfeeding success is adversely influenced by the cumulative epidural fentanyl dose administered for labor analgesia. Secondary outcomes were 1-min Apgar scores less than 7, day-1 LATCH (Latch, Audible swallowing, Type of nipple, Comfort, and Hold/help) breastfeeding assessments, the rate of mothers who discontinued breastfeeding at 3 months, and the reasons stated for discontinuation of breastfeeding.[8,9]

Materials and Methods

The study was approved by the Institutional Review Board of Northwestern University (Chicago, Illinois; STU00007275) and the protocol was registered at ClinicalTrials.gov (NCT01074190) on February 22, 2010. This manuscript adheres to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The study was a double-blind, randomized controlled trial conducted at Prentice Women's Hospital (Chicago, Illinois). Inclusion criteria were English-speaking parous women at greater than 38 weeks gestation who had successfully breastfed a prior infant for at least 6 weeks, expressed a desire to breastfeed for a least 3 months postpartum, and who planned to use neuraxial labor analgesia. Exclusion criteria included administration of a parenteral opioid prior to neuraxial labor analgesia, a history of chronic opioid therapy, or an expected delivery within 90 min of the request for analgesia.

A convenience sample of eligible women were screened and approached shortly after admission to the labor and delivery unit. Screening included an assessment of the woman's prior breastfeeding history, and plans for labor analgesia use and breastfeeding with the current newborn. Women meeting inclusion criteria provided informed written consent for study participation. Recorded baseline maternal characteristics recorded included age, height, weight, gravidity/parity, and gestational age, and an assessment of the participants' motivation for breastfeeding using the Breastfeeding Motivational Measurement Scale.[10,11]

Participants were randomly allocated to one of three study groups defined by the solution used to maintain epidural analgesia: bupivacaine 1 mg/ml + fentanyl 0 μg/ml, bupivacaine 0.8 mg/ml + fentanyl 1 μg/ml, and bupivacaine 0.625 mg/ml + fentanyl 2 μg/ml. Prior to the study commencement, three-group block randomization (1:1:1) using randomly selected block sizes of 3, 6, and 9 was performed by an investigator (R.J.M.) using a computer-generated allocation list.[12] Group allocations were concealed in sequentially numbered opaque envelopes, which were opened by the research nurse at the time of request for neuraxial analgesia. Epidural solutions were prepared by pharmacy personnel not involved in the study. The research nurse obtained the epidural solution and concealed the contents by marking it as study drug. The research nurse was not blinded to group allocation. All other study personnel, including the anesthesiologist, lactation consultants, and research nurses performing follow-up assessments, and the study participants, were blinded to group allocation.

Labor analgesia was initiated using a combined spinal-epiduraltechnique with an intrathecal injection of bupivacaine 2.5 mg and fentanyl 15 μg, and an epidural test dose of 1.5% lidocaine with epinephrine 5 μg/ml (3 ml). An epidural catheter was sited and analgesia was maintained using patient-controlled epidural analgesia (PCEA). The nonblinded research nurse set up the PCEA pump. The initial settings for PCEA were a basal infusion rate of 8 ml/h, patient-administered epidural boluses of 8 ml with a lock-out interval of 10 min and a 1-h infusion limit of 32 ml. Breakthrough pain was managed by the anesthesia provider using manually administered boluses of bupivacaine 1.25 mg/ml without fentanyl.

Cervical dilation at the request for analgesia was recorded. Fifteen minutes following the intrathecal injection a verbal rating pain score (0 to 100-point scale), upper sensory analgesia level to ice and degree of motor blockade using the 4-point Bromage scale (none, partial, almost complete, complete) were assessed.[13] Motor block was assessed again at 2 h following intrathecal injection and at delivery. Samples of maternal venous blood and umbilical cord venous blood were collected from a double-clamped section of the umbilical cord into 3.0-ml spray-coated lithium heparin and polymer-separator gel tubes at delivery. Cells were removed by centrifugation and samples stored at −20°C until analysis.

Participants were queried shortly after delivery regarding satisfaction with labor analgesia using a 0 to 100-point scale. The mode of delivery, duration of the epidural infusion, total epidural infusate volume and manual bupivacaine bolus doses (for treatment of breakthrough pain) were recorded. Infant data included birth weight, umbilical cord blood gas values, 1-min Apgar score (assessed by labor nurses or neonatology team), and neonatal intensive care unit admission.

Breastfeeding was assessed by one of three lactation consultants, certified by the International Board of Lactation Consultant Examiners (Fairfax, Virginia), on the first postpartum day using the LATCH assessment tool, a validated tool routinely used at Prentice Women's Hospital.[8,9] Consultants observed mothers breastfeeding during the visit. Research nurses visited mothers prior to discharge and

queried them regarding the estimated percent contact time of maternal-to-infant skin during the first 24 h following delivery. At 6 weeks and at 3 months postpartum, follow-up phone calls were made by a blinded research nurse to assess the duration of breastfeeding. Mothers who reported discontinuation of breastfeeding were asked an open-ended question about the reason for discontinuation.

Plasma concentrations of fentanyl and bupivacaine were measured using high-performance liquid chromatography. Fentanyl and bupivacaine concentrations were determined by liquid chromatography-tandem mass spectrometry after sample preparation by solid-phase extraction using an API 3000 liquid chromatography-tandem mass spectrometry system (Applied Biosystems, Foster City, California) equipped with an Agilent 1100 series high-performance liquid chromatography system (Agilent Technologies, Wilmington, Delaware) as previously described.[14] The internal standard was alfentanil for fentanyl and mepivacaine for bupivacaine analysis. The plasma fentanyl standard curve was linear from 0.01 to 2.5 ng/ml with coefficients of variation of 15% or less throughout the entire concentration range. The linear range for the plasma bupivacaine standard curve was 1.0 to 100.0 ng/ml, with coefficients of variation of 15% or less throughout the entire concentration range.

Statistical Analysis

The primary outcome was the rate of breastfeeding at 6 weeks postpartum. The number of mothers who breastfed throughout the 6-week period in each group were compared using a chi-square statistic. A sensitivity analysis was performed assuming that participants lost to follow-up had discontinued breastfeeding. Differences and CI for the difference in the rate of breastfeeding among groups were calculated using the Pearson-Klopper method. Secondary outcomes were 1-min Apgar scores less than 7, day-1 LATCH breastfeeding assessments, the rate of mothers who discontinued breastfeeding at 3 months, and the reasons stated for discontinuation of breastfeeding.

Maternal characteristics, breastfeeding history and plan and motivational assessment in the current pregnancy, labor analgesia and infant outcomes, and breastfeeding during the hospital stay were compared among study groups. Continuous and interval data were compared among groups using the Kruskal-Wallis H test. *Post hoc* comparisons were made using Dunn's test with Bonferroni correction for 6 comparisons ($P < 0.008$). Nominal data were compared using a chi-squared test. All statistical tests were two-tailed and a P value less than 0.05 was required to reject the null hypothesis.

Because the independent variable of interest, cumulative epidural fentanyl dose, was dependent on both the epidural solution fentanyl concentration and the duration of labor analgesia, the cumulative fentanyl dose, and the maternal and umbilical cord venous plasma fentanyl concentrations were compared among groups and between women who did and did not continue breastfeeding at 6 weeks using the Mann-Whitney U test. Differences in medians and CI of median differences were calculated using a 10,000-sample bootstrap.

Maternal characteristics, breastfeeding history and plan and motivational assessment in the current pregnancy, labor analgesia and infant outcomes, and LATCH breastfeeding assessments during the hospital stay also were compared between women who did and did not continue breastfeeding at 6 weeks using the Mann-Whitney U test or a chi-square test. Risk factors identified on univariable analysis to be associated with discontinuation of breastfeeding at 6 weeks postpartum ($P < 0.2$) were entered into a multivariable logistic regression model to adjust estimates of risk for main effects. Prior to multivariable modeling, multicollinearity was assessed by evaluating the tolerance, variance inflation factor, and the condition index of the variables for inclusion. Tolerance greater than 0.1, a variance inflation factor less than 10 or a condition index less than 30 were considered acceptable to enter the variable into the logistic regression model. Measures of effect in the multivariable model are reported as an adjusted odds ratio and 95% confidence limits. The accuracy of the logistic regression model was evaluated by the area under the receiver operator characteristics curve and 95% CI.

Based on the study by Beilin *et al.*,[6] the incidence of failed breastfeeding at 6 weeks was estimated to be 2, 6, and 19% in study groups in the current study. Using a chi-square test with 2 degrees of freedom, significance level of 0.05, and beta of 0.2, a sample of 183 participants was necessary to demonstrate an effect size (Cramér's ω) of 0.23 using a superiority study design. Beilin *et al.* also reported that the rate of ineffective sucking during the immediate postpartum period was 3, 7, and 12%, respectively.[6] Using these estimates, the effect size is 0.14; a total sample size of 492 would be needed to achieve 80% power to detect a difference in sucking among groups. However, using the LATCH assessment tool, we anticipated greater sensitivity in detecting early postpartum differences in infant sucking and estimated an effect size (Cramér's ω) of 0.175.[9] Using these assumptions, a total sample size of 315 achieved 80% power to detect a difference among groups using a chi-square test with 2 degrees of freedom and a significance level of 0.05. We elected to recruit an additional 10 participants per study group to account for loss to follow-up, thus the planned total sample size was 345.

Statistical analysis was performed using RStudio version 1.0.136, release date December 21, 2016 (Integrated Development for R; RStudio, Inc., USA) and R version 3.3.3, release date March 6, 2017 (The R Foundation for Statistical Computing, Austria). Sample size analysis was performed using PASS 2005 (NCSS, LLC, USA).

Results

Between February 2010 and January 2015, 956 women were assessed for eligibility, and 345 were enrolled in the study. Twenty-six participants were lost to follow-up prior

to the 3-month follow-up assessment. The flow of study participants is shown in figure 1. Maternal characteristics are shown in table 1. The maternal breastfeeding history, plan to breastfeed following the current pregnancy, and breastfeeding motivational assessment did not differ among any pair of epidural infusion groups.

There was no difference in the breastfeeding rate at the 6-week and the 3-month follow-up period among the groups (table 2). The frequency of breastfeeding at 6 weeks was 97, 98, and 94% in the bupivacaine 1 mg/ml + fentanyl 0 μg/ml, bupivacaine 0.8 mg/ml + fentanyl 1 μg/ml and bupivacaine 0.625 mg/ml + fentanyl 2 μg/ml groups, respectively (P = 0.34). Sensitivity analysis assuming that participants lost to follow-up had discontinued breastfeeding at 6 weeks did not change the results (P = 0.97). The stated reason for breastfeeding discontinuation did not differ among groups (P = 0.72). Most women discontinued breastfeeding prior to 3 months for maternal rather than infant reasons.

Labor analgesia outcomes are described in table 3. More women in the bupivacaine 1 mg/ml + fentanyl 0 μg/ml group had motor block at the time of delivery than the bupivacaine 0.625 mg/ml + fentanyl 2 μg/ml group (difference 14% [99.2% CI, 2 to 26%], P < 0.001). The cumulative fentanyl and bupivacaine doses, and maternal plasma concentrations at the time of delivery, varied among groups. The verbal rating score for analgesia satisfaction did not differ among groups and there was no difference in the mode of delivery.

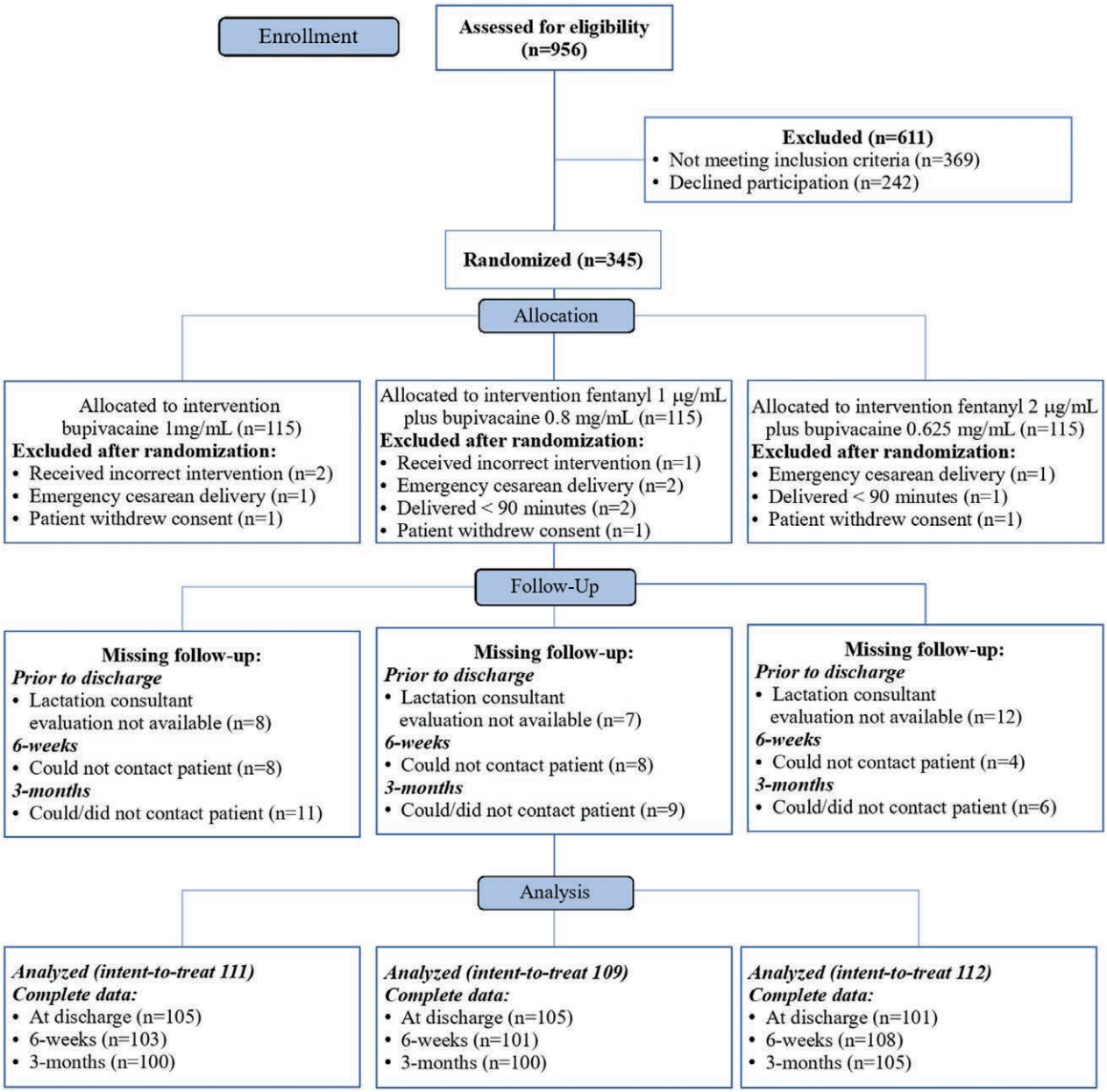

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

Table 1. Maternal Characteristics, Breastfeeding History and Plan, and Motivational Assessment

	Patient-controlled Epidural Analgesia Solution*			
	Bupivacaine 1 mg/ml + fentanyl 0 μg/ml (n = 111)	Bupivacaine 0.8 mg/ml + fentanyl 1 μg/ml (n = 109)	Bupivacaine 0.625 mg/ml + 2 μg/ml fentanyl (n = 112)	*P* Value
Age (yr)	33 (31 to 37)	34 (32 to 36)	34 (31 to 36)	0.94
Body mass index (kg/m^2)	28 (26 to 31)	28 (26 to 31)	29 (26 to 31)	0.81
Gravidity	3 (2 to 3)	3 (2 to 3)	2 (2 to 3)	0.08
Parity	1 (1 to 2)	1 (1 to 2)	1 (1 to 2)	0.32
Gestational age (d)	277 (273 to 280)	276 (274 to 281)	276 (273 to 279)	0.88
Assessment of breastfeeding history with prior child				0.37
< 3 months	9 (8)	6 (6)	9 (8)	
3 to 6 months	20 (18)	31 (28)	30 (27)	
> 6 months	82 (74)	72 (66)	73 (65)	
Reason for discontinuing, n (%)				0.50
Return to work	35 (31)	30 (28)	36 (32)	
Perceived time to stop	22 (20)	22 (20)	20 (18)	
Lack of time	3 (3)	2 (2)	9 (8)	
Pregnancy	10 (9)	9 (8)	9 (8)	
Inadequate milk production	11 (10)	19 (17)	14 (12)	
Child eating solid foods/teething	21 (19)	17 (16)	19 (17)	
Difficulty with breastfeeding	9 (8)	10 (9)	5 (5)	
Support for breastfeeding, n (%)				0.25
Weak	0	2 (2)	1 (1)	
Moderate	9 (8)	13 (12)	18 (16)	
Strong	101 (92)	94 (86)	93 (83)	
Used an assistive device/nipple shield, n (%)	19 (17)	22 (20)	18 (16)	0.71
Skin-to-skin contact in first 24 h*, n (%)				0.25
Did not remember	2 (2)	3 (4)	2 (2)	
0 to 25%	35 (31)	33 (30)	43 (28)	
25 to 50%	28 (34)	41 (37)	39 (35)	
50 to 75%	23 (21)	27 (25)	25 (22)	
75 to 100%	13 (12)	5 (5)	3 (3)	
Time from delivery to initial breastfeeding, n (%)				0.53
Did not remember	4 (4)	2 (2)	5 (5)	
0 to 1 h	90 (81)	80 (73)	79 (70)	
1 h to 3 h	9 (7)	19 (17)	16 (14)	
4 h to 10 h	4 (4)	4 (4)	5 (5)	
> 10 h	4 (4)	4 (4)	7 (6)	
Took a breastfeeding class or received breastfeeding education, n (%)	62 (56)	52 (48)	62 (55)	0.40
Planned breastfeeding with current pregnancy and breastfeeding motivational assessment				
Planned duration of breastfeeding, n (%)				0.03
< 3 months	7 (6)	1 (1)	10 (9)	
3 to 6 months	41 (37)	32 (29)	42 (37)	
> 6 months	63 (57)	76 (70)	60 (54)	
Breastfeeding motivational measurement scale				
Interest/enjoyment (maximum 30)	24 (20 to 27)	24 (20 to 27)	24 (20 to 26)	0.60
Perceived competence (maximum 30)	23 (20 to 26)	22 (19 to 25)	22 (20 to 25)	0.07
Effort/importance (maximum 25)	23 (20 to 25)	23 (20 to 25)	23 (20 to 25)	0.46
Pressure/tension (maximum 25)	22 (19 to 25)	20 (18 to 23)	21 (18 to 24)	0.02
Value/usefulness (maximum 30)	30 (30 to 30)	30 (30 to 30)	30 (29 to 30)	0.93
Total score (maximum 140)	119 (111 to 127)	117 (109 to 124)	117 (110 to 124)	0.28

Data reported as median (interquartile range) or n (%) of group.
*Estimated by mother.

Infant weight, umbilical cord blood gas values (data not shown), the incidence of 1-min Apgar scores less than 7, and neonatal intensive care unit admissions did not differ among study groups (table 3). Umbilical cord venous fentanyl and bupivacaine concentrations varied among groups. LATCH scores, the number of women observed breastfeeding by the lactation consultant, and the estimated percent of infant-to-maternal skin contact time in the first 24 h following delivery were similar among groups.

Table 2. Infant and Breastfeeding Outcomes at Follow-up Assessments

	Patient-controlled Epidural Analgesia Solution			
	Bupivacaine 1 mg/ml + fentanyl 0 μg/ml (n = 111)	Bupivacaine 0.8 mg/ml + fentanyl 1 μg/ml (n = 109)	Bupivacaine 0.625 mg/ml + 2 μg/ml fentanyl (n = 112)	*P* Value
6-week follow-up				
Delivery follow-up interval (d)	42 (41 to 44)	42 (41 to 45)	42 (41 to 47)	0.06
Breastfeeding*				0.34†
Yes	100 (97)	99 (98)	102 (94)	
No	3 (3)	2 (2)	6 (6)	
Lost to follow-up	8	8	4	
3-month follow-up				
Delivery follow-up interval (d)	91 (89 to 93)	91 (90 to 95)	91 (90 to 95)	0.76
Breastfeeding*				0.10†
Yes	94 (94)	96 (96)	93 (88)	
No	6 (6)	4 (4)	12 (12)	
Lost to follow-up	11	9	7	
Reason stated for discontinuation				0.72
Maternal†	4 (67)	3 (75)	10 (83)	
Infant‡	2 (33)	1 (25)	2 (17)	

Data presented as median (interquartile range) or n (%) of group.

*Rate of breastfeeding and *P* value for comparison based on participants with complete follow-up. †Maternal reasons: return to work (n = 7), breast pain/mastitis (n = 4), perceived low supply (n = 4), overactive letdown (n = 1), maternal cerebral vascular accident (n = 1). ‡Infant reasons: infant did not latch well (n = 2), infant did not tolerate milk/colicky (n = 2), newborn had infection and physician instructed mother to stop (n = 1).

Cumulative fentanyl dose, maternal and umbilical cord venous fentanyl and bupivacaine concentrations did not differ in participants who discontinued breastfeeding compared with those who were still breastfeeding at 6 weeks and 3 months (table 4). Planned duration of breastfeeding, the use of a device/nipple shield with prior breastfeeding, the LATCH score assessed by the lactation nurse, and the 15-min verbal rating pain score were associated with discontinuation of breastfeeding within 6 weeks of delivery ($P < 0.2$) in the univariable analysis. The only variable associated with continued breastfeeding at 6 weeks was planned duration of breastfeeding (table 5). The area under the receiver operating characteristics curve for the logistic regression model was 0.82 (95% CI, 0.69 to 0.95). The adjusted odds ratio for discontinuation of breastfeeding less than 6 weeks per 25 μg in cumulative epidural fentanyl received was 1.05 (95% CI, 0.89 to 1.24, $P = 0.57$).

Discussion

The important finding of this study was the lack of association between the cumulative epidural fentanyl dose and discontinuation of breastfeeding within 3 months postpartum in motivated women who had successfully breastfed in a prior pregnancy. Overall, 93% of the women who completed study follow-up were still breastfeeding at 3 months postpartum; maternal factors were cited for discontinuation by 77% of women who had stopped breastfeeding. These findings suggest that epidural solutions containing fentanyl in concentrations as high as 2 μg/ml do not interfere with subsequent breastfeeding.

Worldwide, health organizations have been crusading to increase breastfeeding rates because of the myriad of associated health benefits.[1,15] Children who are breastfed have improved immunity and mothers who breastfeed have a lower incidence of breast and ovarian cancers and diabetes.[1,15] According to a U.S. Centers for Disease Control National Immunization Survey, 80% of mothers started breastfeeding after birth and 51% were still breastfeeding at 6 months in 2012 compared with 71 and 38%, respectively, in 2002.[16] The rate of women who use neuraxial labor analgesia is increasing.[3,17] As medical practitioners, it is important to ensure our anesthetic interventions do not impede the mother's or infant's ability to breastfeed.

The results of previous studies are inconsistent, but most of the data are from observational trials. A 2016 systematic review identified only three randomized controlled trials. Beilin *et al.*[6] randomized women to three groups with cumulative doses of epidural fentanyl of 0, 1 to 150 μg, and greater than 150 μg. The primary outcome was "breastfeeding difficulty" (none, mild, moderate, severe) as assessed by the mother on postpartum day one. There was a trend toward increased difficulty in the high-dose fentanyl group, but the difference was not significant. The lactation consultants identified no differences in breastfeeding difficulty on postpartum day one among groups. At 6 weeks postpartum, more women in the high-dose fentanyl group had discontinued breastfeeding than those in the low-, or no-fentanyl groups (17, 5, and 2%, respectively). Wilson *et al.*[7] performed a secondary analysis of a randomized controlled trial in three groups of women randomized to receive different neuraxial analgesic techniques. The control group received

Table 3. Labor Analgesia Outcomes, Mode of Delivery, Maternal and Umbilical Cord Fentanyl and Bupivacaine Levels, Infant and Breastfeeding Outcomes during Hospital Stay

	Patient-controlled Epidural Analgesia Solution			
	Bupivacaine 1 mg/ml + fentanyl 0 μg/ml (n = 111)	Bupivacaine 0.8 mg/ml + fentanyl 1 μg/ml (n = 109)	Bupivacaine 0.625 mg/ml + 2 μg/ml fentanyl (n = 112)	*P* Value
Cervical dilation at labor analgesia request (cm)	3 (3 to 4)	3 (2 to 4)	3 (2.5 to 4)	0.14
VRPS (0 to 100) 15 min following intrathecal drug administration	2 (0 to 6)	3 (1 to 9)	3 (0 to 9)	0.15
Upper level of sensory analgesia to ice 15 min following intrathecal drug administration				
Left	T_6 (T_8 to T_5)	T_6 (T_7 to T_5)	T_6 (T_7 to T_5)	0.84
Right	T_6 (T_8 to T_5)	T_6 (T_7 to T_5)	T_6 (T_7 to T_5)	0.97
Motor block assessment* n (%)				
15 min following intrathecal injection				0.61
None	106 (95)	105 (97)	110 (98)	
Partial	4 (4)	3 (3)	2 (2)	
Almost complete	1 (1)	0	0	
Complete	0	0	0	
2 h following intrathecal injection				0.70
None	106 (95)	105 (96)	108 (96)	
Partial	4 (4)	4 (4)	4 (4)	
Almost complete	1 (1)	0	0	
Complete	0	0	0	
At delivery				0.03
None	92 (82)	100 (91)	108 (96)	
Partial	14 (13)	5 (5)	4 (4)	
Almost complete	4 (4)	4 (4)	0	
Complete	1 (1)	0	0	
Duration of epidural infusion (min)	207 (149 to 298)	216 (165 to 327)	197 (133 to 319)	0.37
Total epidural infusion volume (ml)	56 (40 to 85)	63 (46 to 94)	62 (41 to 98)	0.49
Manual bupivacaine boluses for breakthrough pain, n (%)	14 (13)	21 (19)	24 (21)	0.20
Cumulative fentanyl dose (μg)	15 (15 to 15)	78 (60 to 109)	139 (97 to 210)	< 0.001
Cumulative bupivacaine dose (mg)	58 (40 to 86)	55 (37 to 81)	42 (25 to 61)	< 0.001
Plasma bupivacaine concentration (ng/ml)	228 (159 to 306)	173 (118 to 257)	144 (108 to 230)	< 0.001
Plasma fentanyl concentration (ng/ml)	0.01 (0.007 to 0.02)	0.07 (0.05 to 0.09)	0.13 (0.09 to 0.18)	< 0.001
Verbal rating score for analgesia satisfaction (0 to 100)	91 (76 to 97)	91 (76 to 99)	86 (74 to 96)	0.38
Mode of delivery, n (%)				
Vaginal	111 (100)	107 (98)	110 (98)	
Assisted vaginal	0	1 (1)	2 (2)	0.73
Cesarean	0	1 (1)	0	
Infant weight (kg)	3.54 (3.32 to 3.77)	3.61 (3.28 to 3.91)	3.57 (3.31 to 3.87)	0.39
Umbilical vein plasma bupivacaine concentration (ng/ml)	63 (48 to 82)	50 (31 to 72)	44 (27 to 67)	< 0.001
Umbilical vein plasma fentanyl concentration (ng/ml)	0.005 (0.005 to 0.10)	0.03 (0.02 to 0.04)	0.06 (0.04 to 0.09)	< 0.001
Apgar score < 7 at 1 min, n (%)	1 (4)	2 (4)	0 (0)	0.36
Neonatal intensive care unit admission, n (%)	1 (1)	2 (2)	2 (2)	0.81
Breastfeeding at lactation consultant assessment, n (%)				0.12
Yes	98 (88)	96 (88)	98 (87)	
No	8 (7)	9 (8)	3 (3)	
Consultant not available	5 (5)	4 (4)	11 (10)	

(*Continued*)

Table 3. (Continued)

	Patient-controlled Epidural Analgesia Solution			
	Bupivacaine 1 mg/ml + fentanyl 0 μg/ml (n = 111)	Bupivacaine 0.8 mg/ml + fentanyl 1 μg/ml (n = 109)	Bupivacaine 0.625 mg/ml + 2 μg/ml fentanyl (n = 112)	*P* Value
LATCH score (0 to 2 for each factor)				
Latch	2 (2 to 2)	2 (2 to 2)	2 (2 to 2)	0.59
Audible swallowing	2 (1 to 2)	2 (1 to 2)	2 (1 to 20	0.38
Type of nipple	2 (2 to 2)	2 (92 to 20)	2 (2 to 2)	0.63
Comfort (breast/nipple)	2 (1 to 2)	2 (1 to 20)	2 (1 to 2)	0.88
Hold (positioning)	1 (1 to 2)	1 (1 to 2)	1 (1 to 2)	0.63
Total score (maximum 10)	8.5 (8 to 9)	8 (8 to 9)	9 (8 to 9)	0.35
Skin-to-skin contact during first 24 h†, n (%)				0.12
0 to 25%	72 (68)	70 (69)	71 (70)	
25 to 50%	19 (18)	28 (26)	17 (17)	
50 to 75%	9 (9)	8 (7)	11 (11)	
75 to 100%	5 (5)	0 (0)	2 (2)	

Data presented as median (interquartile range) or n (%) of group.

*Motor block definitions: None = full leg movement, full flexion of knees and ankles; Partial = inability to raise extended legs, just able to flex knees, full ankle flexion; Almost complete = inability to flex knees, some flexion of ankles possible; Complete = no movement possible (unable to move legs or feet). †Estimated by mother.

LATCH = Latch, Audible swallowing, Type of nipple, Comfort, and Hold/help; VRPS = verbal rating pain score.

epidural bupivacaine without fentanyl. The second and third groups received epidural and combined spinal-epidural analgesia, respectively, both initiated with bupivacaine and fentanyl and maintained with epidural bupivacaine/fentanyl.[7] The mean cumulative fentanyl doses in the epidural and combined spinal-epidural groups were 163 μg and 107 μg, respectively. A matched comparison group that received no analgesia or systemic opioid analgesia (*i.e.*, meperidine) also was recruited. The control group that received meperidine analgesia had a lower breastfeeding initiation rate than women who received neuraxial analgesia or no analgesia. A mail questionnaire sent one year after delivery assessed breastfeeding outcomes (overall number of responders was 1,043). The overall mean duration of breastfeeding was 15 weeks, and there were no differences among the neuraxial study groups and the matched control group and no difference in the proportion of women still breastfeeding at one year. In a randomized controlled trial reported in Chinese with an English abstract, no differences in time of initiation of lactation were found between women randomized to ropivacaine epidural analgesia (no opioid) and a control group without analgesia.[18]

The addition of opioids to local anesthetics for the maintenance of epidural analgesia has several advantages. Neuraxial local anesthetics and opioids work synergistically to provide analgesia.[19] The combination of the two types of drugs allows the use of lower doses of both drugs, thus decreasing the rate and severity of adverse effects of both drugs. One of the adverse effects of neuraxial local anesthetics is motor block. The density of motor blockade is directly associated with the neuraxial local anesthetic dose. Motor block is uncomfortable for parturients because it restricts mobility. Furthermore, a 2013 meta-analysis of studies comparing low- to high-concentration local anesthetic solutions for maintenance of labor analgesia found that high compared to low-concentration techniques are associated with an increased risk of instrumental vaginal delivery.[20] The finding that neuraxial opioids do not adversely affect breastfeeding is important, because removal of opioids from the epidural solution would require an increase in local anesthetic concentration and its associated adverse effects.

There are several limitations to our study design and conclusions. In the current study, the number of women exposed to a cumulative epidural fentanyl dose greater than 150 μg was low (19%). The median fentanyl dose administered in the high-dose fentanyl group in the study by Beilin *et al.* was 200 μg compared to 139 μg in the current study.[6] This difference is, in part, due to the inclusion of fentanyl in the epidural initiation bolus dose and in the bolus doses administered for breakthrough pain in the Beilin *et al.* study.[6] Additionally, the median duration of labor analgesia was longer in their study. In our study, the rate of continued breastfeeding at 6 weeks in women who received less than 150 μg of fentanyl was 96.4% (95% CI, 93.5 to 95.5%) compared with 96.7% (95% CI, 88.6 to 99.1%) in women who received greater than or equal to 150 μg. Therefore, we cannot rule out noninferiority of cumulative epidural fentanyl greater than or equal to 150 μg at a margin of noninferiority of 5%. In addition, we found a rate of discontinuation of breastfeeding of 10.2% in women exposed to a cumulative fentanyl dose greater than or equal to 150 μg prior to 3 months compared with 6.5% of those who received less than 150 μg (difference 3.7% [95% CI of the difference, −4 to 12%], $P = 0.31$). At the level of difference observed at 3 months, a sample size of 1,542 participants (771 per group) would be required to have 80% power to detect this difference at an alpha of 0.05, if it were real.

Table 4. Fentanyl and Bupivacaine Exposure for Women Breastfeeding and Not Breastfeeding

	6-week Follow-up				3-month Follow-up			
	Breastfeeding (n = 301)	Not Breastfeeding (n = 11)	Median Difference (95% CI)	*P* Value	Breastfeeding (n = 283)	Not Breastfeeding (n = 22)	Median Difference (95% CI)	*P* Value
Cumulative epidural fentanyl dose (μg)	72 (15 to 119)	109 (15 to 149)	37 (–58 to 79)	0.28	71 (15 to 118)	107 (15 to 155)	36 (–5 to 75)	0.10
Maternal venous bupivacaine (ng/ml)	186 (121 to 267)	235 (129 to 272)	49 (–62 to 86)	0.74	181 (120 to 266)	230 (148 to 274)	49 (–19 to 77)	0.25
Maternal venous fentanyl (ng/ml)	0.07 (0.02 to 0.12)	0.10 (0.01 to 0.18)	0.03 (–0.06 to 0.1)	0.32	0.07 (0.02 to 0.12)	0.11 (0.1 to 0.18)	0.04 (–0.03 to 0.1)	0.15
Umbilical vein bupivacaine (ng/ml)	53 (32 to 74)	47 (41to 74)	–6 (–21 to 15)	0.80	53 (32 to 73)	49 (41 to 74)	–4 (–11 to 12)	0.88
Umbilical vein fentanyl (ng/ml)	0.03 (0.01 to 0.05)	0.05 (0.01 to 0.07)	0.02 (–0.02 to 0.04)	0.13	0.03 (0.01 to 0.05)	0.05 (0.01 to 0.07)	0.02 (–0.01 to 0.04)	0.14

Data presented as median (interquartile range).

Therefore, although the results of the current study cannot entirely rule out an association between high-dose epidural fentanyl and breastfeeding success, our data suggest that if an association exists, the effect is small in motivated women when epidural infusions contain fentanyl 2 μg/ml or less and epidural fentanyl is not administered for breakthrough pain.

A further limitation of the current study is that we did not study nulliparous women. Several factors are known to influence breastfeeding success, including institutional breastfeeding support and the mother's social support system.[5] We elected to study parous women who had previously successfully breastfed to minimize variability in other factors known to influence this outcome. Beilin *et al.* also studied this population, allowing our results to be directly compared.[6] Additionally, we anticipated that it would be more difficult to enroll nulliparous women in a randomized controlled trial. Although we cannot conclude that epidural fentanyl does not affect breastfeeding success in first-time mothers, from a pharmacokinetic and -dynamic standpoint, it is unlikely given the results of the current study. Our study was a single-center study in an urban population and results may differ in other environments with less support of breastfeeding. The overall rate of exclusive breastfeeding at discharge at Prentice Women's Hospital in 2014 was 59%.[21] During the time period of the study, the hospital was pursuing Baby Friendly status.[22] A final limitation is that both the fentanyl and bupivacaine concentrations changed in the three epidural study solutions. We intentionally designed the study to administer equieffective analgesic concentrations of epidural solution to women in the three study groups; thus, the lower-concentration fentanyl solution contained a higher concentration of bupivacaine. There is no credible evidence that epidural local anesthetic influences neonatal outcomes, but lactation outcomes have not been studied. It is possible that we observed minimal differences between groups because both fentanyl and bupivacaine negatively influence lactation.

In conclusion, among motivated parous women with a previous history of successful breastfeeding, epidural analgesia maintained with an analgesia solution that contains fentanyl did not have adverse effects on breastfeeding outcomes.

Acknowledgments

The authors acknowledge the contributions of Michael J. Avram, Ph.D., Northwestern University Feinberg School of Medicine, Chicago, Illinois (contribution analysis of bupivacaine and fentanyl concentrations); Deborah Flores, R.N., I.B.C.L.C., and Donna Stanton, R.N., I.B.C.L.C., Northwestern Memorial Hospital, Chicago, Illinois (contribution breastfeeding assessments); Rene Gora, R.N., and Yvonne Jekels, R.N., Northwestern Memorial Hospital, Chicago, Illinois (contribution subject recruitment and follow-up).

Research Support

This study was supported in part by the Evergreen Invitational Grant of the Northwestern Memorial Foundation and Department of Anesthesiology at Northwestern University Feinberg School of Medicine (Chicago, Illinois). The funding

Table 5. Multivariable Analysis of Total Fentanyl Expose Adjusted for Potential Confounders ($P \leq 0.2$) on Likelihood of Discontinuation of Breastfeeding within 6 Weeks

	Breastfeeding (n = 301)	Not Breastfeeding (n = 11)	*P Value**	β	Odds Ratio	95% CI of Odds Ratio	*P Value*†
Cumulative epidural fentanyl dose (μg)	72 (15 to 119)	109 (15 to 149)	0.28	0.05	1.05‡	0.89 to 1.24	0.57
LATCH score (max 10)	9 (8 to 9)	8 (7 to 9)	0.08	−0.35	0.70	0.45 to 1.09	0.11
Used an assistive device/nipple shield	50 (16)	5 (45)	0.03	0.88	2.40	0.59 to 9.84	0.22
VRPS (0 to 100) 15 min following intrathecal injection	3 (1 to 8)	4 (1 to 11)	0.12	0.05	1.05	0.99 to 1.11	0.10
Planned duration of breastfeeding							
< 3 months	14 (5)	4 (36)		2.50	12.14	2.07 to 71.19	0.02
3 to 6 months	103 (34)	4 (36)	< 0.001	0.71	2.02	0.42 to 9.71	0.006
> 6 months	184 (61)	3 (28)			1	Reference	0.38
Constant				−0.77	0.46		0.68

Data reported as median (interquartile range) or n (%).

*Unadjusted uni-variable *P* value. †Confounder adjusted for main effects multi-variable *P* value. ‡Odds for 25 μg change in cumulative epidural fentanyl. Area under the receiver operating characteristics (ROC) curve for the logistic regression model 0.82 (95% CI, 0.69 to 0.95).

LATCH = Latch, Audible swallowing, Type of nipple, Comfort, and Hold/help; VRPS = verbal rating pain score.

organization had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Competing Interests

The authors declare no competing interests.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Paine's Celery Compound: Celery Seed Bracer or Cocaine Elixir?

Around 1874, a Yale medical graduate and Dartmouth professor, Edward Elisha Phelps, Sr., M.D., L.L.D. (1803 to 1880), compounded a remedy based on the celery seed (note the head of celery in the logo above). He eventually allowed his favorite compounding pharmacist, Milton Kendall Paine (1834 to 1896) to market the popular panacea as "The Best Remedy in the World—Paine's Celery Compound." In 1887 Paine sold his rights to Wells, Richardson & Company of Burlington, Vermont. That firm may have "enhanced" the compound with traces of cocaine and marketed it as "The True Medicine for Lost Nervous Strength." After regulations in 1906, the compound likely joined Coca Cola in dropping cocaine from its formulation. Besides celery seed, the manufacturer's later booklets listed Paine's botanical slurry as comprising calisaya bark, cascara sagrada, senna leaves, prickly ash bark, hops, black haw, and chamomile flowers—all of which were added to the roots of sarsaparilla, ginger, dandelion, mandrake, gentian, black cohosh, and yellow dock. The American Medical Association categorized Paine's compound as belonging "to the 'bracer' type of nostrums; that is, it is a preparation whose most potent and active drug is alcohol." (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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