Intrapartum Neuraxial Analgesia and Breastfeeding Outcomes: Limitations of Current Knowledge

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Although numerous studies have addressed the relationship between intrapartum neuraxial analgesia, particularly epidural fentanyl, and breastfeeding, substantial study design limitations have precluded the current literature from furnishing strong, clinically significant conclusions. Lack of randomized controlled trials, nonstandardization of breastfeeding evaluations across studies, and failure to control for confounding variables all pose significant problems. Further research is needed to elucidate the specific relationship between neuraxial opioids and breastfeeding and, if there are significant associations, whether these drugs act directly on neonatal brain tissue to attenuate exhibition of breastfeeding behaviors. In this review, I will detail the deficiencies of the current literature and make recommendations for future research. (Anesth Analg 2013;116:399–405)

Breastfeeding is associated with a decreased risk of numerous adverse outcomes, including sudden infant death syndrome, severe lower respiratory tract infections, nonspecific gastroenteritis, type 1 and 2 diabetes mellitus, and childhood acute lymphocytic and acute myelogenous leukemias. Exclusive breastfeeding may also decrease the incidence of allergic disease by reducing exogenous antigen exposure, promoting maturation of the gastrointestinal mucosa, and mediating various immunomodulatory effects. From a maternal health perspective, lactation has been associated with a decreased risk of breast cancer, ovarian cancer, and type 2 diabetes mellitus. Given the numerous benefits that breastfeeding may impart on children and mothers, it is critical to identify factors that affect breastfeeding outcomes.

It has been postulated that receiving intrapartum neuraxial analgesia decreases a woman’s likelihood of successfully breastfeeding her neonate. Studies define “breastfeeding success” differently, but most measure whether a woman is breastfeeding her infant, either as the only milk source (“exclusive breastfeeding”) or in addition to supplemental formula feeds (“partial breastfeeding”), at various time points up to 6 months postpartum. Many measure overall “breastfeeding duration,” defined as the total length of time after delivery that a woman continues to breastfeed in any capacity. Some studies also measure breastfeeding success on a much shorter time scale, that is, specifically during the postpartum hospital stay, either by using a standardized breastfeeding scoring system, such as the B-R-E-A-S-T Feeding Observation Form or the LATCH scoring system, or by simply quantifying the frequency with which neonates suckle at their mothers’ breasts during the first hours of life.

One proposed mechanism by which intrapartum neuraxial analgesia may decrease breastfeeding success is that women who remain unmedicated during labor experience a higher acute stress level, which subsequently prompts their neonates to organize neurobehaviors, including those tied to feeding, more rapidly and effectively during the immediate postpartum period. Those infants who feed most vigorously during their first days of life are, then, most likely to still be breastfeeding at 3 or 6 months. Another possibility is that neuraxial opioids, as highly lipophilic compounds, cross the placenta and, subsequently, the neonatal blood–brain barrier, in quantities substantial enough to result in depression of neonatal feeding behaviors.

This review discusses the limitations that have plagued studies of intrapartum neuraxial analgesia and breastfeeding and makes recommendations for future research. Because intrapartum neuraxial analgesia and breastfeeding are common worldwide, studies are needed to better elucidate the relationship between these 2 entities and identify whether neuraxial analgesia adversely affects breastfeeding outcomes.

REVIEW OF CURRENT LITERATURE

Intrapartum neuraxial analgesia is frequently implicated in adverse breastfeeding outcomes, although this association is not universal. Several retrospective studies have demonstrated significant associations between epidural analgesia and decreased likelihood of suckling at the breast within the first 4 hours of life, increased likelihood of the mother reporting “not having enough milk” during the postpartum hospital stay, increased likelihood of partial breastfeeding or formula feeding at hospital discharge and after 12 weeks, and decreased likelihood of 2 successful breastfeeding encounters by 24 hours of age (as measured by a LATCH breastfeeding assessment score of 7/10 or higher with 2/2 on the latch component of the score). Prospective cohort studies have yielded similar findings of increased breastfeeding difficulty and higher partial breastfeeding rates during the first week postpartum, decreased likelihood of massaging or sucking at the breast during the first 2 hours after delivery, less frequent sucking during the first feeding among female neonates, and lower breastfeeding rates at 2 and 6 months for the offspring of women.
who receive epidural analgesia as compared with control women who do not receive epidural analgesia.

Several studies\textsuperscript{10,17–19} have addressed the relationship between specific doses of intrapartum neuraxial opioids and breastfeeding outcomes, with discordant results. Beilin et al.\textsuperscript{17} randomized parous women who had breastfed successfully in a previous pregnancy, to receive epidural bupivacaine analgesia with 1 of 3 epidural fentanyl groups (>150 µg, 1–150 µg, or 0 µg total dose). On postpartum day 1, mothers assigned to the high-dose fentanyl group were not significantly more likely to self-report difficulty breastfeeding than members of the other 2 groups ($P = 0.09$; intent-to-treat analysis), but the likelihood of a Type II error is high due to inadequate sample size. At 6 weeks postpartum, 14 women reported not breastfeeding; 10 were in the high-fentanyl group, 3 in the low-fentanyl group, and 1 in the no-fentanyl group ($P = 0.002$). In contrast, Wieczorek et al.\textsuperscript{,19} in their prospective observational cohort study of multiparous women who had previously breastfed successfully for >6 weeks, did not find a significant correlation between epidural fentanyl dose and breastfeeding rates at 6 weeks postpartum, although their extremely high breastfeeding success rates (92%–98%) left the study with insufficient power to detect differences. Radzyminski\textsuperscript{18} found no significant dose–response relationship for either epidural fentanyl or bupivacaine with respect to rooting, sucking, or swallowing, either at birth or 24 hours postpartum. Finally, in a secondary analysis of data from a randomized trial to assess the effects of neuraxial analgesia on mode of delivery, Wilson et al.\textsuperscript{11} assessed breastfeeding initiation and rates at 12 months postpartum with a mailed questionnaire. The response rates ranged from 73% to 78%. The authors found no significant differences regarding breastfeeding initiation or rates at 12 months postpartum among women who were randomly assigned to receive bupivacaine-only epidural analgesia, combined spinal-epidural analgesia with a mean fentanyl total dose of 107 µg, or epidural analgesia with a mean fentanyl dose 163 µg, as well as women who had elected not to receive neuraxial analgesia and were sequentially matched with each delivery in the randomized experimental groups. The exception was that the subgroup of women in the non-neuraxial analgesia group who received meperidine was significantly less likely to initiate breastfeeding compared with all other groups.

Some studies\textsuperscript{12,15,16} have addressed the association of intrapartum neuraxial opioids with neonatal Neurologic and Adaptive Capacity Scores (NACS), which do not specifically measure breastfeeding behaviors but rather the 5 general areas of adaptive capacity, passive tone, active tone, primary reflexes, and alertness/crying/motor activity.\textsuperscript{21} Just as for breastfeeding outcomes, NACS findings have been discordant across studies. Porter et al.\textsuperscript{20} randomized women to receive epidural bupivacaine with fentanyl (mean dose, 184 µg) or bupivacaine alone and found no significant association with NACS. Beilin et al.\textsuperscript{17} noted significantly lower scores when mothers’ epidural infusions contained >150 µg total epidural fentanyl compared with bupivacaine without fentanyl. Loftus et al.\textsuperscript{2} randomized women to receive either epidural bupivacaine only, bupivacaine and fentanyl (mean SEM dose, 137 ± 13 µg), or bupivacaine and sufentanil (mean SEM dose, 24 ± 2 µg) and found that neonatal NACS were significantly lower in the bupivacaine-fentanyl group than in the other 2 groups at 24 hours postpartum, although there were no significant between-group differences at 2 hours after birth. The bupivacaine-fentanyl group did not exhibit the improvement in neonatal composite NACS that typically occurs during the first 24 hours of life. The authors suggested low neonatal clearance of fentanyl, possibly secondary to immature liver enzymes, as a potential mechanism.

If intrapartum neuraxial opioids indeed exhibit a significant dose–response relationship with adverse neonatal neurobehavioral and breastfeeding outcomes, then the study of drug transfer from the epidural space into the maternal circulation, across the placenta, and across the neonatal blood–brain barrier becomes relevant, as direct action of these opioids on the neonatal brain may be the definitive physiologic mechanism that is responsible for the observed relationship. The uptake of fentanyl from the epidural space into the maternal plasma has been well documented. Among studies\textsuperscript{22–24} of women who received epidural fentanyl 100 µg combined with local anesthetic for cesarean delivery anesthesia, with and without epinephrine, the mean maternal plasma fentanyl concentration at the time of delivery ranged from 0.31 ng/mL\textsuperscript{22} to 0.58\textsuperscript{23} ng/mL. Several studies have demonstrated high placental transfer of fentanyl, with umbilical/maternal vein ratios of 0.89\textsuperscript{23} and 0.94,\textsuperscript{25} These quantities are notable because the mean (±SD) minimum effective analgesia concentration of fentanyl for adult postoperative analgesia was found to be as low as 0.63 ± 0.25 ng/mL.\textsuperscript{26} A current point of discord, however, is whether the fetus actually extracts a significant proportion of this fentanyl for uptake into the tissues. In one study\textsuperscript{27} of 16 mothers who received epidural fentanyl 100 µg before cesarean delivery, the authors measured umbilical arterial and venous fentanyl concentrations and calculated a fetal extraction ratio of 53% ± 19% (range 20%–83%). de Barros et al.\textsuperscript{28} administered epidural fentanyl 100 µg to 10 laboring women and found no significant differences in fentanyl concentration between the umbilical artery and vein, suggesting that fentanyl is neither taken up by fetal tissues, including the brain, nor metabolized by the fetus to any significant extent.

In summary, the current body of literature on intrapartum neuraxial analgesia and breastfeeding is fraught with incomplete answers and conflicting findings. These problems are attributable to a plethora of deficiencies in study design.

**STUDY DESIGN LIMITATIONS**

**Lack of Randomization**

Very few studies\textsuperscript{10,17} of neuraxial analgesia and breastfeeding have randomized women to different neuraxial opioid doses, and 1 of these\textsuperscript{16} was not designed with breastfeeding as a primary outcome measure. Although studies often include a control group that receives no neuraxial analgesia, no study has randomized women to this group, and investigators rarely control for systemic opioid analgesia. Elsewhere in the anesthesiology literature, studies have randomized women to a neuraxial analgesia versus a control group when addressing outcome measures other than breastfeeding, but these studies have been frequently...
plagued by high crossover rates. Self-selection into a neuraxial analgesia group is likely associated with other variables that confound breastfeeding outcomes, such as the general opinion of the mother regarding childbirth interventions (i.e., neuraxial analgesia versus unmedicated childbirth, formula feeding versus breastfeeding).

Institutional Breastfeeding Support
Hospitals vary widely regarding the amount of breastfeeding support they provide to mothers. It is likely that the type and amount of support affect the breastfeeding outcomes that are obtained in studies of intrapartum neuraxial analgesia. The Baby-Friendly Hospital Initiative (BFHI) is a program sponsored by the World Health Organization and United Nations Children’s Fund; its “Ten Steps to Successful Breastfeeding” include prenatal breastfeeding education, development of a written hospital policy on breastfeeding and appropriate staff training regarding its implementation, initiation of breastfeeding within 30 minutes of delivery, encouragement of the practice of rooming in during postpartum hospital stays, and referral of mothers to breastfeeding support groups after hospital discharge. A hospital receives BFHI accreditation when a trained external team documents that it is properly executing all 10 steps. A study of 17,359 mother–infant dyads found that BFHI-accredited hospitals had 10% higher rates of breastfeeding initiation than nonaccredited facilities, and another study found that babies born in a BFHI-accredited hospital were 28% more likely to be exclusively breastfeeding at 7 days postpartum. Some studies have also found that BFHI increases the overall duration of exclusive breastfeeding and any degree of breastfeeding to 6 months postpartum, although study quality has been poor overall with little control for potential confounding variables. Controlling for breastfeeding support in studies of neuraxial analgesia and breastfeeding is straightforward if researchers simply record BFHI accreditation status, but within the category of “non-BFHI-accredited hospitals,” the degree of breastfeeding support may still vary widely. A non–BFHI-accredited institution may fulfill multiple components of the Ten Step Program, such as encouraging “rooming in” during the postpartum hospital stay, or it may satisfy none at all. Future studies of neuraxial analgesia and breastfeeding should record an institution’s fulfillment of the individual components of the Ten Step Program during data collection, to optimally control for breastfeeding support and standardize data across studies. Even if a given study of neuraxial analgesia and breastfeeding is single center in design, such that the Ten Step data are assumed to be identical for all patients in that study, meaningful comparisons of breastfeeding outcomes across studies are limited if not controlled for between-institution differences in level of breastfeeding support.

Social Support
Social support is well established in the literature as an important determinant of the initiation and duration of breastfeeding. Mothers’ decisions to breastfeed are heavily influenced by perceived pressure from members of their social networks, especially their partners. One study of 26,325 mothers in England revealed that single women are less likely to initiate breastfeeding than women with husbands or partners (odds ratio [OR], 0.57) and in a study of 100 primiparous women presenting to an inner-city prenatal clinic, women were significantly more likely to breastfeed if they reported having support from a partner (OR, 20.48) or family members or peers (OR, 6.08). Another study found that receiving breast pump education from friends or relatives was positively associated with longer breastfeeding duration (OR, 1.70). In light of this evidence, studies of neuraxial analgesia and breastfeeding should control for marital status and other indicators of social support, but many have failed to do so. Researchers could pose the question, “Do you feel you have support for breastfeeding from any of the following people in your life?” and list “partner,” “other family members,” and “friends” as response options.

Maternal Body Mass Index
A maternal body mass index (BMI) in the overweight or obese range is associated with significantly worse breastfeeding outcomes than a normal BMI. Sebire et al. retrospectively studied 287,213 mother–baby dyads and found that women with BMI between 25 kg/m² and 30 kg/m² were significantly less likely to breastfeed at the time of hospital discharge than their normal BMI counterparts, with OR 0.86 and 0.58, respectively. In another retrospective study of 13,234 mother–baby dyads, mothers with prepregnancy BMI > 29.0 kg/m² were significantly less likely (P < 0.01) to initiate breastfeeding and had a significantly shorter breastfeeding duration than women with BMI between 19.8 kg/m² and 26.0 kg/m² (11.8 vs 13.6 weeks, respectively). Wojcicki reviewed 13 studies and found that 10 of them identified an association between higher prepregnancy BMI categories and decreased breastfeeding duration, but for some studies, this association was significant only for particular racial or ethnic groups, or in conjunction with other comorbidities. Observed associations between maternal BMI and breastfeeding success may not be attributable to a direct causative mechanism but rather to the fact that obesity is associated with other factors that worsen breastfeeding outcomes, such as low socioeconomic status or chronic or gestational diabetes. Four of the studies reviewed by Wojcicki either excluded women with chronic or gestational diabetes, or controlled for it, and all still found that high maternal BMI was associated with early breastfeeding cessation or failure to initiate. Maternal BMI is a potential confounder of breastfeeding outcomes for which many studies of neuraxial analgesia and breastfeeding have neglected to control.

Oxytocin Augmentation of Labor
Failure to account for oxytocin augmentation of labor is problematic, because IV intrapartum oxytocin infusion has been shown to decrease a woman’s endogenous serum oxytocin concentration on the second day postpartum in a dose-dependent fashion, which may subsequently impair milk release and decrease breastfeeding success. Multiple studies have demonstrated that recipients of epidural analgesia have higher rates of oxytocin augmentation than nonrecipients. One retrospective study associated oxytocin augmentation with delayed initiation of breastfeeding.
(OR, 3.28) and increased likelihood of formula feeding during the postpartum hospital stay (OR, 2.15), although induced labor may also be associated with other confounders that worsen breastfeeding outcomes, such as preexisting maternal disease. All studies of neuraxial analgesia and breastfeeding should account for oxytocin augmentation.

**Neuraxial Drugs and Doses**

The drugs most commonly used for intrapartum neuraxial analgesia include the amide local anesthetics, bupivacaine, ropivacaine, and levobupivacaine, and the lipid-soluble opioids, fentanyl and sufentanil. The doses of these drugs vary within and among studies, and all of these drugs cross the placenta to a variable degree. The failure of some studies12,13,15 to control for the precise pharmacologic composition of the epidural infusion is problematic because it becomes impossible to ascertain whether any observed association of epidural analgesia with breastfeeding outcomes is attributable to one specific drug administered at certain doses or is intrinsic to the general condition of receiving an epidural infusion. Investigators should report the identities and doses of all neuraxial drugs administered over the course of each subject’s labor and delivery. Additionally, the mode of delivery (e.g., bolus versus continuous infusion) and the proportion of drug(s) administered by bolus or infusion may influence maternal absorption of drug from the epidural space and, subsequently, fetal exposure to the drug. The 10 volunteer subjects of one study43 received, on separate days, epidural fentanyl either as a bolus (30 µg, then 100 µg after 210 minutes) or an infusion (30 µg/hour, then 100 µg/hour after 210 minutes for an additional 200 minutes). Compared with the bolus administration, the infusion resulted in a significantly higher peak plasma fentanyl concentration, greater area under the time-concentration curve, and longer time to maximal concentration. In another study25 of 10-mL/hour continuous epidural infusions containing 0.125% bupivacaine and 2 µg/mL fentanyl, neither drug’s mean umbilical vein concentration correlated with total infusion time, but further research with larger sample sizes is needed.

**Maternal Temperature Elevation**

Low-risk nulliparous women who receive epidural analgesia are more likely than nonrecipients to experience intrapartum maternal temperature increase >100.4°F (19.2% vs 2.4%) of subjects in a study of 3209 mothers44 and 14.5% vs 1.0% in a study of 1657 mothers,45 and this temperature increase is predictive of multiple adverse neonatal outcomes. Among the epidural analgesia recipients in the 3209-mother study,14 maximal maternal temperature > 99.5°F was positively, significantly correlated with risk of the following neonatal outcomes: assisted ventilation, 1-minute and 5-minute Apgar scores <7, hypotonia, and early-onset seizures. When maternal temperature exceeded 101°F, the risk of all of these outcomes increased 2-fold to 6-fold. Of note, epidural analgesia without maternal temperature increase was not associated with increased risk of neonatal adverse outcomes. In a retrospective cohort study of 11,246,042 singleton live births,46 intrapartum fever was a risk factor for assisted ventilation, neonatal seizures, meconium aspiration syndrome, and hyaline membrane disease. It is reasonable to suspect that maternal temperature increase may worsen breastfeeding outcomes if it also increases the risk of the adverse neonatal outcomes described above; therefore, investigators should control for maternal temperature in studies of neuraxial analgesia and breastfeeding; virtually all studies to date6,10,11,13,16,17,19 have failed to do so.

**Time to Initiation of Breastfeeding**

Frequently, studies of neuraxial analgesia and breastfeeding11,17,19 do not record the specific time point after delivery at which the first breastfeeding attempt occurred. In a study of 1085 women who prenatally had intended to breastfeed their infants for more than 2 months, cessation of breastfeeding before 6 weeks postpartum was more likely if the first breastfeeding encounter was not initiated until more than 1 hour after delivery than if it was initiated within the first hour (OR, 2.4).65 Conversely, Rowe-Murray and Fisher48 found that a shorter time to initiation of breastfeeding was not significantly associated with likelihood of breastfeeding at 8 months postpartum (P = 0.64), although the authors noted varying attrition rates among the different hospitals in their study and that more mothers of lower socioeconomic status had been lost to follow-up. A Cochrane systematic review49 also found no difference in breastfeeding rates at 12 weeks postpartum (OR, 0.73) when breastfeeding was initiated within 30 minutes of birth compared with 4 hours to 8 hours. Although the current data are conflicting regarding whether later initiation of breastfeeding is associated with poorer outcomes, future studies should control for this factor.

**Skin-to-Skin Contact**

In a prospective study of 21,842 mothers in 19 hospitals,50 the likelihood of exclusive breastfeeding throughout the hospital stay was positively correlated with the number of minutes of skin-to-skin contact during the first 3 hours postpartum, even after controlling for intention to breastfeed at the time of hospital admission. Lack of control for skin-to-skin contact is a limitation of numerous studies,12,13,16,17 because this variable may confound the assessment of the relationship between neuraxial analgesia and breastfeeding outcomes.

**Breastfeeding Scoring System**

The methodology used by research studies in assessing breastfeeding encounters during the postpartum hospital stay is far from standardized. Many studies10,12,16 do not use any sort of objective breastfeeding scoring scale. Among those that do, the chosen scoring system varies widely. Beilin et al.15 used the 12-point B-R-E-A-S-T Feeding Observation Form3 as completed by certified lactation consultants, whereas other studies8,13 have used the LATCH scoring system,4 whose 5 components measure quality of latch, audible swallows, type of nipple, maternal comfort with breastfeeding, and need for staff assistance to properly position one’s infant for breastfeeding. LATCH scores have high interrater reliability51 and are positively correlated with duration of breastfeeding.52 The Preterm Infant
Breastfeeding Behavior Scale (PIBBS) is another scoring system. It was initially designed to assess premature neonates but has also shown good interrater reliability with full-term neonates. The PIBBS examines neonatal rooting, latching, sucking, and swallowing behaviors as well as general activity level, producing a comprehensive picture of breastfeeding interactions. Postulating that a higher PIBBS should be associated with greater milk consumption by the neonate secondary to increased effectiveness of feeding behaviors, Radzyminski weighed each neonate in the study immediately before and after breastfeeding encounters, attributing the weight change to the volume of breast milk that the neonate had just ingested. The study found that PIBBS scores were significant \((P = 0.0001)\) predictors of the amount of weight gain, further supporting the strength of the PIBBS as a breastfeeding scoring tool. Some studies also include NACS among their outcome measures. These scores do not specifically measure feeding behaviors, but rather the 5 general areas of adaptive capacity, passive tone, active tone, primary reflexes, and alertness/crying/motor activity. The limited literature that exists regarding NACS reliability indicates that both simultaneous and test-retest reliability are poor. The various tools score breastfeeding interactions in different amounts of detail, for instance, the B-R-E-A-S-T Observation Form separately analyzes the positioning of the infant’s lips, tongue, and cheek as well as the presence of the rooting reflex, while LATCH encompasses all aspects of the latching behavior in 1 single score of 0, 1, or 2. These differences among assessment tools render the comparison of findings across studies difficult. The use of the PIBBS for the assessment of neuraxial analgesia and breastfeeding may have advantages compared with other tools, because it accounts for both general neurologic effects that the analgesia may produce in the infant (which NACS aims to accomplish but without evidence of high reliability) and examines individual components of neonatal breastfeeding behavior in detail.

Time to Follow-Up

Some studies do not address breastfeeding outcomes at all during the immediate postpartum period, relying solely on questionnaires mailed to mothers months after delivery, which may generate unreliable data. After hospital discharge, many new factors, such as a mother’s need to return to work or lack of social support, begin to confound the picture of breastfeeding success. While assessment of long-term breastfeeding outcomes is clinically relevant, short-term outcomes should also be measured to ascertain the actual etiology of decreased breastfeeding rates. If intrapartum neuraxial medications potentially mediate some physiologic effect on breastfeeding, and the half-life of lumbar epidural fentanyl is 126 ± 40 minutes in the maternal circulation, then breastfeeding should be studied during the immediate postpartum period, by using the PIBBS to score the first breastfeeding encounter that occurs after delivery. If dose–response relationships are identified between neuraxial opioid medications and breastfeeding outcomes, then further research should investigate the behavior of these opioids in the neonatal circulation, including placental transfer and subsequent use by neonatal brain tissue, in an attempt to establish a definitive physiologic mechanism that is responsible for this association.

CONCLUSIONS AND RECOMMENDATIONS

Due to the study deficiencies described above, the current body of literature on intrapartum neuraxial analgesia and breastfeeding is insufficient to enable clinicians to make evidence-based recommendations to mothers regarding this important topic. Future studies should be randomized and control for all of the potential confounding variables described in this review, such as maternal temperature increase and the degree of structured breastfeeding support available at the study institution. Ideally, studies will measure breastfeeding success not only in the long term, for instance, by following up with mothers regarding total breastfeeding duration, but also during the immediate postpartum period, by using the PIBBS to score the first breastfeeding encounter that occurs after delivery. If dose–response relationships are identified between neuraxial opioid medications and breastfeeding outcomes, then further research should investigate the behavior of these opioids in the neonatal circulation, including placental transfer and subsequent use by neonatal brain tissue, in an attempt to establish a definitive physiologic mechanism that is responsible for this association.

DISCLOSURES

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