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Association between Maternal Neuraxial Analgesia and Neonatal Outcomes in Very Preterm Infants

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Abstract

Background Although the use of neuraxial analgesia has been shown to improve uteroplacental blood flow and maternal and fetal hemodynamics related to labor pain, possibly improving immediate outcomes in term neonates, the association between neuraxial analgesia use and outcomes in preterm neonates remains unclear.

Objective The aim of this article was to evaluate the association between maternal use of neuraxial analgesia and neonatal outcomes in very preterm infants.

Methods This is a retrospective cohort study of women delivering singleton neonates between 23 and 32 weeks' gestation at a large academic center between 2012 and 2016. Outcomes of neonates born to women who used neuraxial analgesia for labor and/or delivery were compared to those whose mothers did not. Multivariable logistic regression was utilized to assess the independent associations of neuraxial analgesia use with neonatal outcomes after controlling for potential confounders, including gestational age, mode of delivery, and existing interventions to improve neonatal outcomes of prematurity.

Results Of 478 eligible women who delivered singleton very preterm neonates in this study period, 352 (73.6%) used neuraxial analgesia. Women who used neuraxial analgesia were more likely to have delivered at a later preterm gestational age, to have a higher birthweight, to have preeclampsia and/or hemolysis, elevated liver enzymes, low platelet count (HELLP), to have undergone labor induction, to have delivered by cesarean delivery, and to have received obstetric interventions such as magnesium prophylaxis for fetal neuroprotection, antenatal corticosteroids for fetal lung maturity, and antibiotics prior to delivery; they were less likely to have been diagnosed with a clinical abruption. Neuraxial analgesia was associated with decreased incidence of cord umbilical artery pH less than 7.0 (24.7 vs. 34.9%, $p = 0.03$), as well as decreased incidence of neonatal intensive care unit length of stay over 60 days (35.5 vs.

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48.4%, $p = 0.01$), although these associations did not persist on multivariable analysis. On multivariable analyses, neuraxial analgesia remained independently associated with decreased odds of necrotizing enterocolitis (adjusted odds ratio [aOR]: 0.28, 95% confidence interval [CI]: 0.12–0.62) and grade III/IV intraventricular hemorrhage (aOR: 0.33, 95% CI: 0.13–0.87). These associations remained significant on sensitivity analyses, which were performed between 10 and 90% of the overall cohort in order to control for outliers, as well as between the subgroup of patients who received obstetric interventions.

Conclusions Maternal neuraxial analgesia use may be associated with lower odds of adverse outcomes in very preterm infants, even after controlling for existing interventions for prematurity. Prior work has suggested such effects may be due to improved neonatal acid–base status from changes in placental perfusion and maternal pain management, but further work is required to prospectively investigate such associations.

Neuraxial analgesia is one of the safest and most common methods of pain management in labor, used by more than 70% of women who deliver in the United States.[1] These methods include spinal anesthesia, epidural analgesia, and combined spinal–epidural analgesia, and have been associated with improved neonatal outcomes in comparison to systemic opioids, including higher Apgar scores and lower incidence of naloxone administration for neonatal respiratory depression.[2]

The maternal and neonatal safety of neuraxial analgesia has been well established in both obstetric and anesthesia literature, with previous studies demonstrating that maternal use of neuraxial analgesia is not associated with an increase in neonatal morbidity in term neonates.[3–7] In a recent Cochrane review, neuraxial analgesia appeared to have no immediate adverse effect on neonatal status by Apgar scores or neonatal intensive care unit (NICU) admissions.[8] Many studies have shown similar results for neonatal outcomes regardless of the type of neuraxial analgesia used.[9]

Other studies have demonstrated a potential benefit of maternal neuraxial analgesia for neonates delivering at term.[2,10–13] This effect is hypothesized to be related to the association between labor pain and maternal hyperventilation, stress, and anxiety.[14] Maternal hyperventilation resulting from pain can lead to maternal hypoxemia and respiratory alkalosis, thus shifting the oxyhemoglobin dissociation curve leftward and increasing the affinity of oxygen for maternal hemoglobin, which subsequently impairs the placental transfer of oxygen to the fetus.[14] Maternal respiratory alkalosis can result in uteroplacental vasoconstriction, subsequently decreasing uterine blood flow and fetal oxygenation.[15] Neuraxial analgesia has been shown to alleviate the adverse hypoxemic effects associated with labor pain, resulting in improved fetal oxygen delivery.[16–18] Furthermore, increased maternal stress and anxiety due to labor pain may result in elevated levels of circulating maternal catecholamines, thereby lowering fetal oxygenation and increasing fetal acidosis.[19] Neuraxial analgesia has been shown to decrease maternal concentrations of circulating catecholamines.[20]

Although use of neuraxial analgesia has been shown to improve uteroplacental blood flow and maternal and fetal hemodynamics related to labor pain, possibly improving immediate outcomes in term neonates, there is little existing literature on the association between neuraxial analgesia use and outcomes in preterm neonates. This raises a clinically important question as this high-risk population may benefit even more from the physiologic effects of neuraxial analgesia on improved uteroplacental blood flow, as compromised neonates are already at increased risk of hypoxemia in the setting of prematurity.[21,22] The objective of this study is to evaluate the association between maternal use of neuraxial analgesia for labor and/or delivery and neonatal outcomes in very preterm infants.

Materials and Methods

This was a retrospective cohort study of women delivering singleton neonates between 23 and 32 weeks' gestation at a large volume academic center between 2012 and 2016. Inclusion criteria included women who delivered singleton live births. Exclusion criteria included women with multifetal gestations, major fetal anomalies, no intent to resuscitate, intrauterine fetal demise, receipt of general anesthesia, and contraindications to neuraxial analgesia including disseminated intravascular coagulopathy.

Women who received neuraxial analgesia encompassed those who received epidural analgesia, spinal anesthesia, or combined spinal epidural analgesia for delivery. Neuraxial analgesia at our institution is typically initiated with combined spinal epidural technique using intrathecal bupivacaine and fentanyl. Maintenance labor analgesia is a standardized infusion of bupivacaine and fentanyl administered through the epidural catheter via either a continuous infusion or programmed intermittent epidural bolus. All data were abstracted from the electronic medical record and reviewed by the coauthors.

Maternal demographic and clinical characteristics were analyzed by maternal use of neuraxial analgesia before delivery. These characteristics included age at delivery, nulliparity, obesity as defined by body mass index more than or equal to 30 kg/m^2, maternal race and ethnicity, insurance status, gestational age at delivery, antepartum admission, preterm labor, preterm premature rupture of membranes, preeclampsia and/or hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, gestational diabetes or pregestational diabetes, delivery via cesarean including planned cesarean delivery, and need for emergent delivery. Additional characteristics included receipt of antibiotics prior to delivery for group B streptococcus prophylaxis, intra-amniotic infection, or preterm premature rupture of membranes; receipt of magnesium prophylaxis for fetal neuroprotection prior to delivery; receipt of a full course of antenatal corticosteroids for fetal lung maturity prior to delivery; neonatal sex; neonatal birthweight; clinical diagnosis of placental abruption; intra-amniotic infection; presence of meconium; and induction of labor.

Neonatal outcomes of very preterm neonates born to women who used neuraxial analgesia were compared to those born to women who did not receive neuraxial analgesia. These outcomes included cord umbilical artery pH less than 7.0; 1 minute Apgar score less than 7; 5 minute Apgar score less than 7; hypothermia (defined as core body temperature $<$ 36.5 degrees Celsius); need for vasopressors; NICU prolonged length of stay defined as greater than 60 days; blood transfusion needed in the first week of life; prolonged mechanical ventilation (defined as mechanical ventilation needed for more than 7 days); bronchopulmonary dysplasia; necrotizing enterocolitis (NEC); late onset sepsis (defined as culture positive sepsis after 3 days); severe grade III/IV intraventricular hemorrhage (IVH); and neonatal death after delivery.

Maternal and neonatal characteristics and outcomes were compared using the Student's *t* test or Mann–Whitney *U* test where applicable for continuous variables, and χ^2 or Fisher's exact test where applicable for categorical variables. Multivariable linear and logistic regression were used to assess the independent association between maternal receipt of neuraxial analgesia and neonatal outcomes after adjusting for demographic and clinical characteristics that were significant at *p*-value less than 0.05 on bivariable analysis. Two sensitivity analyses were performed. In the first, propensity score analysis was performed between 10 and 90% of the overall cohort in order to evaluate for outcomes data after controlling for outliers. In the second, the same analyses were performed in the subgroup of patients who received obstetric interventions, defined as the receipt of magnesium prophylaxis for fetal neuroprotection, a full course of antenatal corticosteroids for fetal lung maturity, and antibiotics prior to delivery. All tests were two-tailed and *p*-value less than 0.05 denoted significance. All statistical analyses were performed with SPSS Statistical software (Version 22; IBM Corp, Armonk, NY). This study was approved by the Institutional Review Board of Northwestern University.

Results

A total of 478 eligible women delivered very preterm singleton neonates during this 4-year study period. Of these, 352 (73.6%) received neuraxial analgesia prior to delivery. Women who had neuraxial analgesia were more likely to deliver at a later preterm gestational age, to have developed preeclampsia and/or HELLP, to have a higher neonatal birthweight, to have undergone induction of labor, and to have delivered via cesarean delivery, and were less likely to have a clinical diagnosis of abruption. These women were also more likely to have received magnesium prophylaxis for fetal neuroprotection, a full course of antenatal corticosteroids, and antibiotics prior to delivery (►**Table 1**). There were otherwise no differences in the remaining maternal demographic and clinical characteristics between the two groups.

On bivariable analysis of neonatal outcomes, infants born to women who used neuraxial analgesia had a decreased incidence of NEC, severe grade IVH, cord umbilical artery pH less than 7.0, and NICU length of stay for more than 60 days (►**Table 2**). After adjusting for maternal demographic and clinical characteristics, use of maternal neuraxial analgesia remained independently associated with a decreased odds of NEC (adjusted odds ratio [aOR]: 0.28, 95% confidence interval [CI]: 0.12–0.62) and grade III/IV IVH (aOR: 0.33, 95% CI: 0.13–0.87). These associations remained significant even after adjusting for cesarean delivery, which was considered a clinically and statistically significant confounder, as all patients who underwent cesarean delivery received neuraxial anesthesia (►**Table 2**).

Finally, on sensitivity analysis that was performed on 10 to 90% of the overall cohort to further control for outlier data, neuraxial analgesia remained significant in predicting decreased incidence of NEC (aOR: 0.17, 95% CI: 0.03–0.84) and grade III/IV IVH (aOR: 0.29, 95% CI: 0.02–0.89). An additional sensitivity analysis was performed for the 83.8% of patients who received obstetric interventions. Neuraxial analgesia remained significantly associated with decreased odds of NEC (aOR: 0.41, 95% CI: 0.14–0.77) and grade III/IV IVH (aOR: 0.43, 95% CI: 0.12–0.84) in this restricted population of women for whom precipitous delivery did not occur. Neuraxial analgesia did not remain significantly associated with decreased incidence of cord umbilical artery pH less than 7.0 or NICU length of stay for more than 60 days on either of the sensitivity analyses performed.

Comment

Neuraxial analgesia is one of the most commonly employed techniques for pain control in labor, and understanding its role in the very preterm parturient is essential. In this observational study of women who delivered before 32 weeks, maternal use of neuraxial analgesia may be associated with improved neonatal outcomes, such as decreased odds of NEC and severe grade IVH, even after controlling for existing interventions for prematurity and mode of delivery. Prior work has suggested such effects may be due to improved neonatal acid–base status from changes

Table 1 Cohort demographic and clinical characteristics associated with receipt of neuraxial analgesia

	Neuraxial analgesia ($n = 352$)	No neuraxial analgesia ($n = 126$)	*p*-Value
Maternal age (years)	30.37 ± 6.53	31.36 ± 5.93	0.13
Nulliparous	198 (56.3%)	62 (49.2%)	0.18
Obese (BMI ≥ 30 kg/m^2)	139 (39.5%)	44 (34.9%)	0.36
Race/ethnicity			0.16
Non-Hispanic White	122 (34.7%)	44 (34.9%)	
Non-Hispanic Black	115 (32.7%)	29 (23.0%)	
Hispanic	47 (13.4%)	21 (16.7%)	
Other/unknown	68 (19.3%)	32 (25.4%)	
Public insurance	213 (60.5%)	77 (61.1%)	0.91
Gestational age (weeks)	29.38 ± 2.30	28.9 ± 2.52	0.05
Preeclampsia/HELLP	111 (31.5%)	24 (19.0%)	0.008
Gestational or pregestational diabetes	23 (6.5%)	8 (6.3%)	0.94
Antepartum admission	285 (81.0%)	94 (74.6%)	0.13
Antibiotics received before birth	331 (94.0%)	110 (87.3%)	0.015
Magnesium prophylaxis	320 (90.9%)	100 (79.4%)	< 0.001
Full betamethasone course	310 (88.1%)	98 (77.8%)	0.005
Preterm labor	102 (29.0%)	38 (30.2%)	0.80
PPROM	120 (34.1%)	47 (37.3%)	0.52
Induction of labor	66 (18.8%)	8 (6.3%)	< 0.001
Cesarean delivery	154 (43.8%)	0 (0.0%)	< 0.001
Emergent delivery	22 (6.3%)	6 (4.7%)	0.76
Clinical diagnosis of abruption	40 (11.4%)	29 (23.0%)	< 0.001
Intra-amniotic infection	37 (10.5%)	10 (7.9%)	0.41
Meconium	16 (4.5%)	4 (3.2%)	0.51
Male infant	176 (50.0%)	56 (44.4%)	0.23
Birthweight (grams)	$1{,}348.47 \pm 481.44$	$1{,}256.56 \pm 388.58$	0.05

Abbreviations: BMI, body mass index; HELLP, hemolysis, elevated liver enzymes, low platelet count; PPROM, preterm premature rupture of membranes.
Data reported as *n* (%) or mean ± standard deviation.

in maternal physiology as a result of adequate labor analgesia.[16–18]

Although there were some differences in clinical characteristics between women who used neuraxial analgesia and those who did not, the majority of these differences in potential confounders can be clinically explained. As expected, all women who underwent cesarean delivery received neuraxial epidural or spinal anesthesia as general anesthesia was excluded in this study. Neuraxial analgesia use is also expected to be higher in women undergoing induction of labor compared to those who present in active spontaneous labor. Women admitted to the antepartum service with a planned iatrogenic preterm delivery may be encouraged to ask for neuraxial analgesia during induction of labor in anticipation of prolonged labor or need for emergent cesarean delivery. Furthermore, antepartum patients who have the time to receive neuraxial analgesia prior to delivery may have longer labor courses allowing time for more neonatal protective measures such as the administration of antibiotics, magnesium, and corticosteroids. Although women who received neuraxial analgesia were less likely to have a clinical diagnosis of abruption, this is likely because abruption may preclude epidural use due to concern for disseminated intravascular coagulation, even if not overtly diagnosed.

Neuraxial analgesia may also be recommended by providers to women with preeclampsia or HELLP without coagulopathy, as it is generally preferred over general anesthesia due to the potential for difficult airways from soft tissue or laryngeal edema in patients with hypertensive disorders of pregnancy.[23] Patients with preeclampsia or HELLP may be encouraged to ask for epidural analgesia earlier in their labor course due to the risk of developing more severe forms of coagulopathy as the disease progresses.

Table 2 Neonatal outcomes associated with maternal receipt of neuraxial analgesia

	Neuraxial analgesia ($n = 352$)	No neuraxial analgesia ($n = 126$)	*p*-Value	aOR[a]	95% CI
Cord umbilical artery pH < 7.0	87 (24.7%)	44 (34.9%)	0.03	0.70	0.44–1.13
1 minute Apgar score < 7	191 (54.3%)	80 (63.5%)	0.07		
5 minutes Apgar score < 7	75 (21.3%)	37 (29.4%)	0.07		
Hypothermia (core temperature < 36.5 °C)	18 (5.1%)	7 (5.6%)	0.85		
Need for vasopressors	18 (5.1%)	10 (7.9%)	0.25		
NICU length of stay > 60 days	125 (35.5%)	61 (48.4%)	0.01	0.59	0.33–1.05
Blood transfusion needed during 1st week of life	76 (21.6%)	36 (28.6%)	0.11		
Mechanical ventilation > 7 days	57 (16.2%)	27 (21.4%)	0.19		
Bronchopulmonary dysplasia	86 (24.4%)	36 (28.6%)	0.36		
Necrotizing enterocolitis	16 (4.5%)	16 (12.7%)	0.002	0.28	0.12–0.62
Late onset sepsis	18 (5.1%)	9 (7.1%)	0.40		
Grade III/IV IVH	11 (3.1%)	11 (8.7%)	0.01	0.33	0.13–0.87
Neonatal death	10 (2.8%)	5 (4.0%)	0.53		

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HELLP, hemolysis, elevated liver enzymes, low platelet count; IVH, intraventricular hemorrhage; NICU, neonatal intensive care unit.
Note: Data reported as *n* (%) or mean ± standard deviation.
[a]Adjusted for factors with $p < 0.05$ on bivariable analyses, including gestational age, preeclampsia/HELLP, antibiotics received before birth, magnesium prophylaxis received before birth, full betamethasone course received before birth, birthweight, clinical diagnosis of abruption, induction of labor, and cesarean delivery.

Importantly, maternal use of neuraxial analgesia remained independently associated with decreased odds of NEC and grade III/IV IVH in very preterm neonates after controlling for differences in clinical characteristics and mode of delivery on multivariable analysis, and remained significant on sensitivity analyses, which were performed to attempt to limit the effects of outliers or the potential unmeasured confounding introduced by precipitous delivery. As discussed previously in the literature on term neonates, maternal neuraxial analgesia may improve neonatal outcomes such as Apgar scores by alleviating maternal pain-related hypoxemia and improving fetal oxygenation. These hemodynamic benefits may extrapolate to even more clinically relevant outcomes in preterm neonates as this population may be more predisposed or at higher risk of hypoxemia due to the etiology and/or consequences of their prematurity.[21,22]

This study is unique in that it is one of the first to address the association between maternal neuraxial analgesia and outcomes in very preterm neonates. A strength of this analysis is that it was performed at a large academic center with a diverse, high-risk patient population. Additionally, antepartum care for women at risk of delivering very preterm neonates is managed via standardized protocols with regard to use of existing interventions to improve neonatal outcomes of prematurity, such as administration of antenatal corticosteroids, magnesium prophylaxis for fetal neuroprotection, and intrapartum antibiotics. Moreover, unlike large-scale population databases, our data include highly granular details about parturients and their neonates, with the ability to corroborate all details directly from the electronic medical record.

Our study must be examined within the context of its limitations. This study was conducted at a large academic center with around the clock in-house availability of obstetric anesthesia services, and thus may not be generalizable to different practice settings. Because this is an observational study, it is impossible to fully account for all potential confounders. While we attempted to control for potential confounders, such as receipt of existing interventions for prematurity, gestational age at delivery, and mode of delivery, it is possible that there are other factors that we did not account for which may improve neonatal outcomes independently of maternal neuraxial analgesia use. For example, although there was no difference in emergent delivery for maternal or fetal compromise between the two groups, it is possible that mothers who did not use neuraxial analgesia delivered more compromised neonates due to precipitous preterm labor or inadequate prenatal and antenatal care. Consequently, women who did not use neuraxial analgesia may have been less likely to receive magnesium prophylaxis, complete a full course of antenatal corticosteroids, and receive antibiotics due to precipitous preterm delivery as a potential unmeasured confounder, which we attempted to account for in our sensitivity analysis. Furthermore, the effect of neuraxial analgesia may also be influenced by unmeasured clinical characteristics such as the overall duration of preterm labor, the etiology of preterm birth, the degree of maternal pain, and the use of additional analgesic therapies such as intravenous opioids. Additionally, there was limited power to detect

differences in some rare outcomes. Finally, as a retrospective cohort study, an inherent limitation of this work lies in its inability to determine a causal relationship between these factors. Nonetheless, since randomization of women with elevated risk of very preterm birth to receive versus not receive neuraxial analgesia would likely be unacceptable, we propose that this observational investigation represents an important perspective on an important unanswered question, despite these limitations.

Further research is required to prospectively investigate this association in very preterm neonates, although the known relationship between neuraxial analgesia and improved uteroplacental blood flow suggests there may be a physiological benefit for neonatal oxygenation. Our study provides initial support for the potential added benefit of neuraxial analgesia on improved neonatal outcomes in this high-risk population.

Note

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Conflict of Interest

None declared.

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