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Evaluation of the relationship between opioid exposure in extremely low birth weight infants in the neonatal intensive care unit and neurodevelopmental outcome at 2 years

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ABSTRACT

Background: Extremely low birth weight (ELBW) infants are exposed to many painful procedures while in the neonatal intensive care unit (NICU), such as catheter insertion and endotracheal intubation. Exposure of ELBW infants to repetitive pain and stress in the NICU can lead to cardiovascular instability and may alter neuronal and synaptic organization. Opioid analgesics are administered to reduce pain, stress and to potentially reduce poor neurologic outcomes. They may also be utilized as sedation for mechanically ventilated ELBW infants. There is limited data in regards to neurodevelopmental outcomes of preterm infants exposed to opioids, and available studies have conflicting results.
Objective: To examine the relationship between cumulative opioid dose in ELBW infants in the NICU and neurodevelopmental outcomes at 20 months corrected age (CA).
Study design: 100 ELBW infants who had complete neurodevelopmental assessments at 20 months CA were categorized by cumulative opioid exposure during the NICU stay (high vs. low/no opioid). Outcome measures included cognitive, motor and language scores from the Bayley Scales of Infant and Toddler Development-III (BSITD-III). Multiple regression analyses adjusted for the impact of social and neonatal risk factors on outcome.
Results: There were 60 patients with high and 40 with low/no opioid exposure. Infants in the high dose group had a higher number of median ventilator days (53.5 vs. 45.6 days, $p = 0.046$) and a higher incidence of necrotizing enterocolitis (5% vs. 21.7%, $p = 0.022$). There were no significant differences in BSITD-III scores between the two opiate groups. In multivariate analysis cumulative opioid dose was associated with lower cognitive scores on the BSITD-III even after adjusting for social and neonatal risk factors ($\beta = -0.247$, $p = 0.012$).
Conclusion: Cumulative opioid dose is associated with worse cognitive scores at 20 months CA even after adjusting for social and neonatal risk factors.

1. Introduction

Throughout their stay in the neonatal intensive care unit (NICU), extremely low birth weight (ELBW; birth weight < 1000 g) infants undergo numerous painful procedures including venous or arterial catheter insertion, endotracheal intubation or suctioning and lumbar puncture [1–3]. Compared with older pediatric age groups, newborns may experience a greater sensitivity to repetitive pain and are more susceptible to the long-term effects of painful stimulation [1–3]. In addition to abnormalities in respiration, heart rate and blood pressure, neonatal pain may alter neuronal and synaptic organization [1–3]. Animal studies have shown that untreated repetitive pain and stress can lead to activation of N-methyl-D-aspartate (NMDA) receptors, augmenting hypoxia-induced glutamate release and excitotoxicity [4]. Opioid analgesics such as morphine and fentanyl are administered to critically ill neonates in an effort to reduce pain, stress and potentially reduce neurologic injury. Fentanyl is generally the preferred agent in this patient population primarily because of its decreased gastrointestinal effects and histamine release when compared to morphine [5]. Alternate theories suggest that opioids may be detrimental due to their depressive effects and potential to cause apoptotic neurodegeneration [6].

Additionally, ELBW infants may be started on continuous infusions of opioid for sedation to provide comfort while on mechanical

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ventilation, although literature regarding this indication is controversial. Some studies have shown that blood pressure fluctuations and periods of hypoxemia are reduced in ventilated infants receiving opioids [7,8]. Conversely, opioids have been associated with prolonged ventilation [9]. A meta-analysis showed no differences in duration of mechanical ventilation but increased time to reach full enteral feeding in infants receiving opioids for sedation [10]. Most institutions recommend against routine use of opioids for sedation during mechanical ventilation.

There is limited data in regards to neurodevelopmental outcomes of ELBW infants exposed to opioids, and available studies have had conflicting results [11–16]. Early studies primarily focused on short-term outcomes including mortality rates, neonatal morbidities such as intraventricular hemorrhage and periventricular leukomalacia, and neuroimaging findings such as decreased orbitofrontal and subgenual volumes [11–13]. The literature is sparse with respect to neurodevelopmental outcomes associated with opioid exposure in preterm infants born after 2000 [13,15,16]. This is relevant as perinatal management has changed such that opioid exposure may or may not have as significant an impact on long-term neurologic outcome as in prior decades. To our knowledge only one study has evaluated a recent cohort of VLBW (very low birth weight; BW < 1500 g) using the 3rd edition of the Bayley Scales of Infant and Toddler Development (BSITD-III) and found no association between cumulative fentanyl dose and BSITD-III scores at a median of 9 months corrected age (CA) [16,17]. We therefore sought to determine the relationship between opioid exposure and neurodevelopmental outcome in a contemporary cohort of ELBW infants at 20 months CA.

2. Methods

2.1. Patient population and opioid data

This is a retrospective chart review of all ELBW infants born in 2008–2010 who were cared for in the Rush University Medical Center (RUMC) NICU and who had complete neurodevelopmental assessments at 20 months CA in the Rush Neonatal High-Risk Follow-up Clinic. Infants who were transferred to RUMC after 7 days of age, those who had major malformations, genetic syndromes, hypoxic ischemic encephalopathy or death prior to discharge were excluded from this study.

Data on opiate exposure was collected from the medication record in the electronic chart and included cumulative morphine or fentanyl dose in intravenous (IV) morphine equivalent (ME) in mg/kg. A ratio of 0.1:10 was used to convert IV fentanyl to IV ME [18]. Patients were stratified to no/low dose and high dose groups. The no/low dose group included ELBW infants who had a cumulative exposure of <1 mg/kg IV ME.

2.2. Maternal, neonatal and socio-demographic data

Maternal data collected included the following: age at delivery, in-utero drug exposure, antenatal steroid exposure, mode of delivery and medical insurance type. Infant data collected included the following: gestational age (GA), birth weight (BW), gender, race, small for gestation status, head ultrasound abnormalities, treatment for patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), culture-proven sepsis, ventilator exposure, bronchopulmonary dysplasia (BPD, defined as oxygen dependence at 36 weeks CA), exposure to postnatal steroids, surgical procedures and length of NICU stay.

2.3. Neurodevelopmental follow-up data

During the period of study it was the policy to evaluate all ELBW infants in the Neonatal High Risk Follow-up Clinic, a multidisciplinary clinic which monitors the growth, neurologic and developmental status of infants cared for in the NICU. The primary outcome of this study was to compare the cumulative dose of opioid received throughout the NICU stay to BSITD-III cognitive, language and motor index scores at 20 months CA. Secondary outcomes included comparing rates of subnormal BSITD-III index and subscale scores between the two opiate exposure groups. Subscale scores included cognitive, expressive and receptive language, and fine and gross motor scores. The BSITD-III mean for index scores is 100 ± 15 and for subscale scores is 10 ± 3. All scores > 1 standard deviation below the mean (<85 for index scores and <7 for subscale scores) were classified as subnormal [17]. Social–emotional scores on the BSITD-III were not included as an outcome in this study as they are not routinely assessed at RUMC.

2.4. Statistical analysis

A univariate linear regression analysis was performed separately for BSITD-III cognitive, language, and motor scores as outcomes using cumulative IV ME in mg/kg as the predictor. For outcomes with a statistically significant correlation to the predictor, a multivariate linear regression model was created. Covariates found to have a linear relationship with the outcome at $p < 0.1$ were included the model. To compare outcomes in the no/low dose and high dose groups, a Chi-square, Fisher's exact or Mann–Whitney U test were used when appropriate. Double sided p-values <0.05 were considered significant. Statistical analysis was performed with SAS version 9.

The study was reviewed by and approved the Institutional Review Board of Rush University Medical Center.

3. Results

One hundred ELBW infants (median birth weight 795 g, median gestational age 26 2/7 weeks) who met study criteria were included in the analysis (Table 1). This comprised approximately 70% of eligible infants. There were 40 ELBW infants in the no/low dose group and 60 ELBW infants in the high dose group. Infants in the low dose group received a median of 0.81 mg/kg (range 0–0.91 mg/kg) IV ME as compared to those in the high dose group who received a median of 82.44 (range 5.19–789 mg/kg) IV ME. The majority of maternal and ELBW infant characteristics and neonatal morbidities were similar between the two groups with the exception of days of ventilator exposure ($p < 0.046$) and rates of NEC ($p = 0.022$) which as expected were higher in the high dose group as compared to the no/low dose group (Tables 1 and 2). There also was a trend toward an increased incidence of surgical procedures in the high dose group ($p = 0.052$) (Table 2).

In univariate analyses a significant correlation was found between cumulative opioid dose and cognitive score. For every 1 mg/kg increase in cumulative IV ME, the cognitive index score decreased, on average, by

Table 1
Maternal and infant baseline characteristics between opiate groups.

	No/low dose N = 40	High dose N = 60	P-value
Median (range) or N (%)			
Maternal age, years	25.5 (20–41)	29.5 (16–41)	0.058
Birth weight, grams	763 (725–990)	808 (485–990)	0.581
Male gender	20 (50)	27 (45)	0.624
Caucasian	10 (25)	18 (30)	0.275
GA at birth	26 3/7 (25 1/7–30 1/7)	26 2/7 (23–34)	0.683
Public insurance	31 (78)	38 (63)	0.133
Small for gestation	10 (25)	11 (18)	0.423
Antenatal steroids	33 (83)	48 (80)	0.755
Vaginal delivery	10 (25)	19 (32)	0.472
Length of NICU stay	93.5 (45–101)	102 (45–231)	0.433
Ventilator days	45.6 (3–51)	53.5 (1–175)	0.046
Cumulative IV ME, mg/kg	0.81(0–0.91)	82.44(5.19–789.3)	
Midazolam	3 (8)	7 (12)	0.736
CGA at discharge, weeks	40 5/7 (35 2/7–41 1/7)	40 (35 3/7–69 4/7)	0.746