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Neonatal Opioids and Preschool Outcomes

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The cognitive, behavioral, neuromotor, and developmental outcomes of children born prematurely are worse than those born at term(1–3). Brain abnormalities in prematurity were previously conceptualized as ‘one-hit’ or ‘two-hit’ brain injuries resulting from perinatal or postnatal events. Emerging data, however, suggest widespread brain dysmaturation in prematurity with altered developmental trajectories for several cellular processes and structures, other than the clinical manifestations of white matter injury, intraventricular hemorrhage, or other ‘gross’ findings(4). Repetitive neonatal pain/stress appears to play a central role in promoting brain dysmaturation, altering development in myriad ways, and contributing significantly to the cognitive, perceptual, and behavioral difficulties of preterm-born children and adults(2, 5). Neonatal pain is associated with reduced fractional anisotropy in white matter tracts (e.g., in the long axis of corticospinal tracts), reduced N-acetyl-aspartate/choline ratios in subcortical gray matter, cortical thinning in frontal, parietal, or other regions, lowered functional connectivity in temporal areas, volumetric reductions in the thalamus, limbic system, and basal ganglia, and the altered background cortical rhythmicity associated with visual-perceptual deficits(6).

Because premature neonates have the most prolonged exposures to repetitive pain(7), opioid analgesia was investigated for ventilated preterm neonates(8–10). Concurrently, however, experimental studies showed anesthesia-induced neurotoxicity in 7-day-old rats(11), raising concerns that opioids may produce similar effects in the preterm brain(12). Though the clinical applicability of animal data was refuted(13, 14) and large multicenter studies have dismissed most of the concerns for anesthetic neurotoxicity(15–18), lingering doubts about the long-term effects of early opioid therapy continue to worry some clinicians. Follow-up studies of preterm neonates enrolled in large placebocontrolled multicenter trials of opioid analgesia were never funded, therefore the question of whether prolonged opioid exposures or repetitive unrelieved pain are more damaging to preterm brain development must rely on observational studies with concurrent or historical controls.

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After implementing a standardized analgesia/sedation protocol in two NICUs, Diendl and colleagues found 6–7-fold increases in opioid exposures but no effects on their in-hospital morbidity or mortality(19), slightly lower behavior rating scores at 1 year(20) and 3 years(21), but no differences in their long-term mental, psychomotor, or behavioral development compared to historical controls(19–21). Steinbauer et al. now report their preschool outcomes from cognitive, neuromotor, and behavioral assessments performed at age 5–6 years in the protocol-treated cohort and historical controls(22). Other than slightly increased autism spectrum features and withdrawn behavior in the protocol-treated group, or oppositional defiant behaviors and sleep problems in the control group, they again found no differences in the cognitive, neuromotor, or behavioral outcomes between the two groups(22). Though reassuring, these results must be interpreted with caution because of substantial weaknesses in their study design.

Results from a single-center, observational, retrospective case-control study with historical controls are highly susceptible to selection bias, temporal trends in patient population, prenatal or perinatal management, personnel or administrative changes, other assessment or management approaches, and a variety of unknown confounding factors.

Additionally, between NICU discharge and the 1-year evaluation, 108 infants were lost to follow-up in the protocol group and 119 infants in the control group, with further attritions occurring at the 3-year and 5-year follow-up evaluations. Thus, only 27% of the 367 VLBW survivors contributed to these results(23). Also missing from prior or current descriptions of this cohort are the clinical indications for using opioids(19–22). This is critically important because opioids given in the presence of pain are much less likely to alter brain development as compared to opioids given in the absence of pain(24).

First, cognition was evaluated using the simultaneous processing and sequential processing scales in the Kaufman Assessment Battery for Children (KABC). KABC and other cognitive scales are based on the Cattell-Horn-Carroll dominant structural model of mental abilities, and the validity of using selected subscales appears questionable and incomplete(25). *Second*, neuromotor evaluations were based on Amiel-Tison's neurological assessment and recorded in the clinic chart; these were simply classified as normal vs. abnormal disregarding the finer details of gross motor skills, fine motor skills, muscle tone, reflexes, or the neurological soft signs(26) that may underlie subtle differences. *Third*, though the parent-reported Child Behavior Checklist (CBCL) is widely used in clinical practice, it does not account for important factors in the social ecology of early childhood. Parents and caregivers, for example, may be more inclined to report "problematic" behaviors in preschool children than to divulge personal difficulties, family dynamics, or household dysfunction.

Given these methodological as well as the other limitations discussed Steinbauer et al., how will busy clinicians interpret the findings from this study? The results of this study are unlikely to dispel the opiophobia in some NICUs, or excess opioid use in others(27). Clinical use or avoidance of opioid analgesia has achieved a cult-like status in some NICUs, with every new finding interpreted to support strongly held views on opposite sides of this divide. Those who prescribe opioids will suggest that protocol-driven neonatal analgesia/

sedation, with routine assessments of pain/distress using validated scales, will not lead to adverse outcomes even at preschool age, whereas those who avoid opioids may be concerned about their reported association with autism spectrum features and withdrawn behaviors(22). CBCL scores of children in this study were included in 12 logistic regression analyses using a penalized likelihood approach designed for maximum likelihood estimation of rare events, reporting 96 p-values with no correction for multiple testing. The higher odds for autism spectrum and withdrawn behaviors (p=0.03) resulted from 4 subjects in the intervention group and none in the historical controls. Even if one child in the control group or one less in the intervention group had a positive screen for these behaviors, then the reported group differences would have disappeared.

Clinical decision-making in medicine rests heavily on weighing trade-offs. For clinicians faced with the decision of treating moderate/severe and/or prolonged neonatal pain, the potential risks for long-term neurodevelopmental sequelae from opioids should not be considered in the risk-benefit equation(28). Just like changes in the gut microbiome or associations with future inflammatory bowel disease do not enter into the decisions for neonatal antibiotic use(29), similarly, concerns about anesthetic-related neurotoxicity in animals(24, 30) or humans(15, 31), or subtle findings from population-based studies of neurodevelopmental outcomes(6, 21, 22, 28, 31) should not interfere with evaluating the clinical need for opioid analgesia in that moment for any individual patient.

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