Neonatal Morphine Exposure in Very Preterm Infants—Cerebral Development and Outcomes

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Objective To investigate the association of morphine exposure in very preterm infants with cerebral volumes and neurodevelopmental outcome from birth through middle childhood.

Study design Observational study of very preterm infants in the Victorian Infant Brain Study cohort. A total of 230 infants born <30 weeks' gestational age or <1250 g were recruited from all admissions to the neonatal intensive care unit of the Royal Women's Hospital. Fifty-seven (25%) infants received morphine analgesia during their neonatal intensive care unit stay at the attending physician's discretion. Primary outcomes were regional brain volumes at term and 7 years; neurobehavioral performance at term; and cognitive, motor, emotional, behavioral, communication, and executive function scores at age 2 and 7 years. Linear regressions were used to compare outcomes between participants who did and did not receive morphine.

Results At term, preterm infants who received morphine had similar rates of gray matter injury to no-morphine infants, but a trend toward smaller cortical volumes in the orbitofrontal (*P*left = .002, *P*right = .01) and subgenual (*P*left = .01) regions. At 7 years, cortical volumes did not differ between groups. At 2 years, morphine-exposed children were more likely to show behavioral dysregulation (*P* = .007) than no-morphine children, but at 7 years no detrimental impacts of morphine on neurobehavioral outcome were observed.

Conclusions Low-dose morphine analgesia received during neonatal intensive care was associated with early alterations in cerebral structure and short-term neurobehavioral problems that did not persist into childhood. *(J Pediatr 2015;166:1200-7)*.

Preterm infants are highly susceptible to the harmful effects of pain and stress to which they are routinely exposed in the neonatal intensive care unit (NICU).[1,2] NICU patients receive a daily average of 5-15 procedures classified as uncomfortable, painful, or stressful.[3] Exposure to a greater number of stressors in the NICU has been reported to result in smaller frontal and parietal brain widths, altered connectivity in the temporal lobes, and abnormal neurobehavior at term equivalent.[4] Consistent with these findings, higher neonatal exposure to procedural pain is associated with reduced white matter (WM) volume and subcortical gray matter (GM) maturation by 40 weeks, as determined by diffusion magnetic resonance imaging (MRI) and magnetic resonance (MR) spectroscopy.[5] To ameliorate the consequences of painful neonatal procedures, the administration of opioid analgesics is a common NICU practice.[6]

Morphine is one of the more common and well-studied opioids administered to preterm infants in the NICU, but concerns over the neurologic consequences of morphine exposure remain.[2] In animal studies of opioid exposure, alterations in neuronal proliferation and survival have been detected. Chronic exposure to morphine produced neuronal degeneration,[7] and perinatal exposure reduced cortical neuron number and density,[8] reduced basilar dendritic growth,[9] and decreased metabolic activity in motor areas of the brain.[10] These alterations were often accompanied by behavioral changes. Rats exposed prenatally to a long-acting opiate demonstrated more reference and working memory errors in the radial arm maze,[11] and postnatal morphine exposure impaired reward-mediated learning in adulthood.[12]

In human studies, reports on the neurologic consequences of morphine exposure have been inconsistent. Neonatal exposure to continuous morphine infusions to reduce pain did not result in neurodevelopmental benefit,[13,14] and

CRIB	Clinical Risk Index for Babies
FOV	Field of view
GM	Gray matter
IVH	Intraventricular hemorrhage
MR	Magnetic resonance
MRI	Magnetic resonance imaging
NICU	Neonatal intensive care unit
PMA	Postmenstrual age
TE	Echo time
TR	Repetition time
WM	White matter

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concerns have been raised for subtle neurobehavioral differences at term in those exposed to morphine.[15] At age 5-7 years, children randomized to continuous morphine infusions during the NICU period had smaller head circumferences and body size, in addition to poorer performance on tests of short-term memory and a higher likelihood of social problems than those given a placebo infusion.[16] However, in a separate trial, 5-year-olds who received morphine as preterm infants performed similarly on tests of movement, behavior, and intelligence compared with children who had received no morphine.[17] In this study, we aimed to compare the short- and long-term outcomes of very preterm infants with and without exposure to low-dose morphine. Short-term outcomes include brain volumes and neurobehavior performance at term equivalent age, and longer term outcomes include cognitive and behavioral outcomes at 2 and 7 years and brain volumes at 7 years.

Methods

In this longitudinal cohort study, we enrolled 230 infants born at <30 weeks' gestation or <1250 g at the Royal Women's Hospital between July 2001 and December 2003. Patients were recruited consecutively from all eligible admissions to the hospital. Details of subject eligibility, recruitment, and follow-up at term, 2-years of age, and 7-years of age are available in the **Figure** (available at www.jpeds.com). Newborns received morphine analgesia at the attending physician's discretion; no other form of pharmacologic sedation or analgesia, including benzodiazepines, were employed in the NICU, with the exception of intraoperative anesthesia. Ethical permission was granted for each stage of the study by the Human Research Ethics Committees of the Royal Women's and Royal Children's Hospitals. Parents of participants provided written informed consent.

Term Equivalent MRI

Brain MRI was performed without sedation between 38 and 42 weeks' postmenstrual age (PMA) using a 1.5 T General Electric Signa System (GE Healthcare, Little Chalfont, United Kingdom), with the following sequences: (1) a 3-dimensional spoiled gradient recalled sequence (1.2 mm coronal slices, flip angle 45°, repetition time (TR) 35 ms, echo time (TE) 9 ms, field of view (FOV) 21 × 15 cm^2, matrix 256 × 192); (2) a double-echo (proton density and T2-weighted) spin-echo sequence (2 mm axial slices, TR 4000 ms, TE 60 and 160 ms, FOV 22 × 16 cm^2, matrix 256 × 192, interpolated 512 × 512, interleaved acquisition); and (3) a linescan sequence (4-6 mm axial slices with a 0.5-1 mm gap, TR 2139 ms, TE 78 ms, FOV 22 cm, matrix 128 × 128, 2 images at b = 5 s/mm^2, 6 images at b = 700 s/mm^2. The diffusion gradients for b = 700 s/mm^2 were oriented in 6 directions). Qualitative MR images were classified according to degree of intraventricular hemorrhage (IVH), cerebellar hemorrhage, WM abnormality, and GM abnormality as has been previously reported.[18]

Quantitative volumetric MR analysis was undertaken by a single operator. The methods for total brain and hippocampal segmentation have been described previously.[19,20] For total brain segmentation, brain tissue was separated into myelinated and unmyelinated WM, cortical and deep nuclear GM, and cerebrospinal fluid. Volumes were automatically parcellated into 8 cortical regions per hemisphere, as described in Shah et al.[21]

Seven-Year MRI

Data at age 7 years were obtained on a Megnetom Trio 3T imaging system (Siemens, Erlangen, Germany) using a 32-channel, phased array radiofrequency head coil. The acquisition included a 3D MPRAGE T1-weighted sequence (TR 30 ms, TE 4.1 ms, flip angle 8°, 256 × 256 matrix; 0.9-mm isotropic voxels).

Cortical reconstruction and volumetric segmentation were performed with the Freesurfer v 4.4 analysis suite (Laboratory for Computational Neuroimaging, Charlestown, Massachusetts) according to the procedure reported in Desikan et al.[22] The output was manually edited by 3 operators, with an inter-rater reliability of 0.98. Freesurfer generated 34 subregions for each hemisphere using the Desikan-Killian Atlas. These subregions were then grouped into 18 hemispheric regions (**Table I**; available at www.jpeds.com).

Neurodevelopmental Assessment

At term equivalent PMA, neurobehavior was evaluated with the Hammersmith Neonatal Neurologic Examination.[23] At 24 months' corrected age, survivors were assessed by examiners blinded to the infant's birth weight and gestational age. Clinical assessment included outcomes such as cerebral palsy and other neurologic impairments. Cognitive and motor development were assessed with the Mental Development Index and the Psychomotor Development Index of the Bayley Scales of Infant Development, 2nd Edition.[24] The prepublication version of the Infant-Toddler Social and Emotional Assessment is a parent report questionnaire that was used to measure emotional and behavioral problems.[25] Communication skills were evaluated using the Communication Symbolic Behavior Scale Developmental Profile infant-toddler checklist, also completed by parents.[26] Executive function, specifically inhibition and working memory, was assessed with the delayed alternation task[27,28] and the Behavior Rating Inventory of Executive Function, Preschool Version.[29]

At 7 years of age, participants underwent detailed cognitive, educational, and behavioral assessment by trained examiners blinded to gestational age and clinical outcomes. General intelligence was measured with the Wechsler Abbreviated Scale of Intelligence,[30] motor functioning with the Movement Assessment Battery for Children, 2nd edition,[31] emotional and behavioral problems with the Strengths and Difficulties Questionnaire,[31,32] language skills with the Clinical Evaluation of Language Fundamentals, 4th edition,[33] executive function with the parent report form of the Behavior Rating Inventory of Executive Function,[29] and basic educational skills with the Wide Range Achievement Test-4.[34] The variables of interest are summarized in **Table II** (available at www.jpeds.com).