Neonatal Surgery for Noncardiac Congenital Anomalies: Neonates at Risk of Brain Injury

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Objective To evaluate the incidence of brain injury after neonatal surgery for noncardiac congenital anomalies using magnetic resonance imaging (MRI).

Study design An MRI was obtained in 101 infants at 7 days [range: 1-115] after neonatal surgery for major noncardiac congenital anomalies. Brain injury was assessed using T1, T2, diffusion weighted imaging, and susceptibility-weighted imaging.

Results Thirty-two preterm infants (<37 weeks of gestation) and 69 full-term infants were included. MRI abnormalities were found in 24 (75%) preterm and 40 (58%) full-term infants. Parenchymal lesions were noted in 23 preterm (72%) and 29 full-term infants (42%). These consisted of punctate white matter lesions (n = 45), punctate cerebellar lesions (n = 17), thalamic infarction (n = 5), and periventricular hemorrhagic infarction (n = 4). Nonparenchymal abnormalities were found in 9 (28%) preterm and 26 (38%) full-term infants. These included supra- and infratentorial subdural hemorrhages (n = 30), intraventricular hemorrhage grade II (n = 7), and asymptomatic sinovenous thrombosis (n = 1). A combination of parenchymal lesions was present in 21 infants. Of infants who had an MRI within 10 days after surgery, punctate white matter lesions were visible on diffusion weighted imaging in 22 (61%), suggestive of recent ischemic origin. Type of congenital anomaly and prematurity were most predictive of brain injury.

Conclusions Infants who have neonatal surgery for noncardiac congenital anomalies are at risk of brain injury, potentially accounting for the neurodevelopmental delay frequently observed in this population. Further research is warranted into potential mechanisms of brain injury and its timing of onset. Long-term neurodevelopmental follow-up is needed in this vulnerable population. *(J Pediatr 2017;182:335-41).*

Survival following neonatal surgery for major noncardiac congenital anomalies has improved to more than 95%.[1,2] In recent years, increasing concerns have been raised about the incidence of neurodevelopmental delay in children who underwent neonatal surgery for noncardiac congenital anomalies.[3,4] Although deficits can be ascribed to associated genetic syndromes (eg, Down syndrome) in some children, cognitive and motor problems also occur in up to 45% of children with isolated anomalies.[3]

The etiology of neurodevelopmental impairments is currently unknown, but several potential risk factors have been proposed.[5] Although the General Anaesthesia compared to Spinal Anaesthesia (GAS) study showed that a single episode of general anesthesia was not associated with 2-year neurodevelopmental outcomes,[6] multiple surgical procedures at a young age are associated with a significantly higher rate of behavioral problems in children.[7-9] Experimental studies have demonstrated increased apoptosis because of general anesthetics in the young animal brain.[10] Impaired cerebral autoregulation has been observed in full-term infants receiving anesthesia, increasing the risk for disturbances in cerebral perfusion. Preterm infants may be even more susceptible to cerebral hypoperfusion as a result of limited cerebral autoregulation because of immaturity.[10-13] As many as 73% of infants with critical congenital heart disease display brain lesions after neonatal surgical repair.[14] Severe postoperative brain injury was recently reported in a case series of 6 neonates who had elective surgery. The authors suggested that cerebral hypoperfusion from perioperative hypotension or hypocapnia may have contributed to a predominantly watershed pattern of injury.[15]

To date, there has not been a systemic evaluation of the incidence of brain injury after neonatal surgery for noncardiac congenital anomalies. At our institution, a clinical neuromonitoring program was initiated in 2013, including postoperative neuroimaging and perioperative cranial ultrasonography (cUS) in infants who needed neonatal surgery for noncardiac congenital anomalies. This offered an opportunity to study perioperative brain injury

CO_2	Carbon dioxide	SWI	Susceptibility-weighted imaging
cUS	Cranial ultrasonography	TE	Echo time
DWI	Diffusion-weighted imaging	TR	Repetition time
MRI	Magnetic resonance imaging	3D	3-dimensional

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in infants undergoing neonatal surgery. The aim of this study was to evaluate the incidence and pattern of brain injury following neonatal surgery for noncardiac congenital anomalies and to identify perinatal and perioperative risk factors.

Methods

In January 2013, magnetic resonance imaging (MRI) was implemented as clinical care after neonatal surgery for noncardiac congenital anomalies to evaluate brain injury. To detect recent ischemic injury, neuroimaging was performed, preferably within 10 days after surgery at the discretion of the attending physician in the neonatal intensive care unit. The Institutional Review Board of the University Medical Center Utrecht, The Netherlands, approved the use of the clinically acquired data for the purpose of the study and waived written parental informed consent. Exclusion criteria consisted of congenital anomalies of the central nervous system and critical congenital heart disease requiring surgical repair in the neonatal period.

cUS was performed upon admission to the neonatal intensive care unit before surgery, and repeated postoperatively. Serial bedside cUS was part of routine clinical care and images were included to assist in the evaluation of timing of injury. The attending neonatologist performed cUS according to a standard clinical protocol using a Toshiba Aplio Machine (Toshiba Medical Systems, Zoetermeer, The Netherlands). MRI was performed on a 3.0 Tesla whole-body Achieva system (Philips Medical Systems, Best, The Netherlands).

Infants were sedated per clinical protocol and placed in a vacuum fixation pillow. For hearing protection Minimuffs (Natus Medical Incorporated, San Carlos, California) and Earmuffs (Ems for kids, Brisbane, Australia) were used. A neonatologist or physician assistant monitored the infant throughout the examination. Routine protocol included coronal 3-dimensional (3D) T1-weighted and T2-weighted imaging (3D T1-weighted repetition time [TR] 9.5 ms; echo time [TE] 4.6 ms; slice thickness 1.2 mm and T2-weighted TR 4847 ms; TE 150 ms, slice thickness 1.2 mm), as well as diffusion-weighted imaging (DWI) (including a DWI-derived apparent diffusion coefficient map and single-shot echo planar imaging in 3 orthogonal directions; 33 slices; slice thickness 3 mm; TR 5270 ms; TE 108 ms; b-values of 0 and 800 mm^2/s, no gap). Additional sequences, including susceptibility-weighted imaging (SWI) (3D gradient-echo sequence with flow compensation, multishot echo-planar imaging; TR 52 ms; TE 30 ms, slice thickness 2 mm and echo-planar imaging factor 3), magnetic resonance venography (3D/magnetic resonance venography TR 18.4, TE 6.377, voxel size 0.90 mm, slice/dis 2/1 mm, phase contrast 15 cm/s, slices 130), and magnetic resonance angiography were performed based on imaging findings on the T2-, T1- , and DWI images if considered necessary.

Two neonatologists systematically evaluated and scored the cUS images. Two neonatologists, with more than 10 years of experience in the interpretation of neonatal brain MRI, evaluated all scans. The following abnormalities were systematically scored: parenchymal lesions including punctate white matter lesions defined as <6 or ≥ 6 and described as cluster, linear, or mixed lesion pattern,[16] cerebellar hemorrhage, thalamic, and/or cortical infarction, and periventricular hemorrhagic infarction. Nonparenchymal abnormalities were defined as subarachnoid and subdural hemorrhage, grade I-III intraventricular hemorrhage, classified according to the grading system of Papile et al,[17] and sinovenous thrombosis without associated intracranial lesions.

Anesthesia

All patients were subjected to a standardized anesthesia protocol. For the induction of anesthesia sevoflurane (6%-8% inspired concentration) was used with a 40%-100% fraction of inspired oxygen. Muscle relaxation was applied with atracurium besylate (0.5 mg/kg), rocuronium (0.6 mg/kg), or suxamethonium (1-2 mg/kg), and the patient was intubated. Pain medication consisted of sufentanil, morphine, or bupivacaine by epidural. Dosages varied at the discretion of the attending pediatric anesthesiologist (**Table I**). Blood samples were taken every 30 minutes as part of routine clinical care. Ventilation settings and depth of anesthesia were adapted to maintain individual values of arterial oxygen saturation, end tidal carbon dioxide (CO_2), heart rate, and mean arterial blood pressure.

Statistical Analyses

Statistical procedures were performed using IBM SPSS Statistics software package v 20 (IBM Corporation, Armonk, New York). Data are presented as mean ± SD or as median and range when indicated. First, differences in clinical characteristics between the subgroups, defined as preterm and full-term infants, were tested using the Mann-Whitney *U* test. The 2 subcohorts were tested for differences in the incidence of brain lesions with the Fisher exact test. The significance level was set at an alpha *P* value of < .05. The Mann-Whitney *U* test was used to assess the association between findings of brain lesions and several clinical risk factors.

Results

From January 2013 to December 2015, 114 infants with noncardiac congenital anomalies were admitted to the neonatal intensive care unit for neonatal surgery. Thirteen infants were not eligible for inclusion in this study because no postoperative MRI was available for the following reasons: death (n = 2), metal jaw screws (n = 1), logistic reasons (n = 5), and no parental consent to MRI (n = 5). This resulted in a final sample of 101 infants enrolled in the study (**Tables I** and **II**; **Table II** available at www.jpeds.com). Of all patients, 51% were transported from other centers. Inborn or outborn status was not related to the neuroimaging findings (parenchymal injury $\chi 2^2 = 4.464$, $P = .11$; nonparenchymal injury $\chi 2^2 = 1.491$, $P = .47$).

The number of postoperative days until MRI acquisition was not statistically different between preterm and full-term infants (**Table I**). Preoperative and postoperative cUS images were available in 99 (98%) and 96 (95%) infants, respectively.