CHD

Clinically silent preoperative brain injuries do not worsen with surgery in neonates with congenital heart disease

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Objective: Preoperative brain injury, particularly stroke and white matter injury, is common in neonates with congenital heart disease. The objective of this study was to determine the risk of hemorrhage or extension of preoperative brain injury with cardiac surgery.

Methods: This dual-center prospective cohort study recruited 92 term neonates, 62 with transposition of the great arteries and 30 with single ventricle physiology, from 2 tertiary referral centers. Neonates underwent brain magnetic resonance imaging scans before and after cardiac surgery.

Results: Brain injury was identified in 40 (43%) neonates on the preoperative magnetic resonance imaging scan (median 5 days after birth): stroke in 23, white matter injury in 21, and intraventricular hemorrhage in 7. None of the brain lesions presented clinically with overt signs or seizures. Preoperative brain injury was associated with balloon atrial septostomy ($P = .003$) and lowest arterial oxygen saturation ($P = .007$); in a multivariable model, only the effect of balloon atrial septostomy remained significant when adjusting for lowest arterial oxygen saturation. On postoperative magnetic resonance imaging in 78 neonates (median 21 days after birth), none of the preoperative lesions showed evidence of extension or hemorrhagic transformation (0/40 [95% confidence interval: 0%–7%]). The presence of preoperative brain injury was not a significant risk factor for acquiring new injury on postoperative magnetic resonance imaging ($P = .8$).

Conclusions: Clinically silent brain injuries identified preoperatively in neonates with congenital heart disease, including stroke, have a low risk of progression with surgery and cardiopulmonary bypass and should therefore not delay clinically indicated cardiac surgery. In this multicenter cohort, balloon atrial septostomy remains an important risk factor for preoperative brain injury, particularly stroke. (J Thorac Cardiovasc Surg 2010;140:550-7)

Multiple studies using highly sensitive magnetic resonance imaging (MRI) have identified a high frequency of preoperative brain injury in neonates with congenital heart disease (CHD).[1-6] In particular, brain injuries such as stroke, white matter injury (WMI), and intraventricular hemorrhage (IVH) are seen in more than one third of term neonates with CHD scanned *before* surgery.[3,4,7] These lesions are typically clinically silent in the neonatal period and usually not identified by routine cranial ultrasound scans.[3,4] It is unknown whether heart surgery with cardiopulmonary bypass (CPB) and perioperative hemodynamic instability might worsen these areas of brain injury. Two studies published to date with preoperative and postoperative MRI noted worsening of a preoperative hemorrhagic lesion[2] in a single patient and worsening of periventricular leukomalacia in 2 patients.[1] In the latter cases, the authors did not distinguish between extension of existing WMIs or addition of new WMIs. Thus, the identification of these injuries poses a dilemma in the clinical care of these critically ill neonates: should heart surgery be delayed if brain injury is present preoperatively? The answer to this question must balance the need for and timing of life-saving surgery and the risk posed by exposing areas of injured brain to CPB and hemodynamic instability.

Most neonates with severe CHD, such as dextro-transposition of the great arteries (TGA), or single ventricle physiology, including the hypoplastic left heart syndrome, require open cardiac operations with CPB to correct or palliate their heart defect.[8] Neonates undergoing cardiac surgery are exposed to the risks of intraoperative ischemia, postoperative low cardiac output syndrome,[9] and anticoagulation required for CPB. Therefore, we hypothesized that preoperative brain injuries will be at significant risk of

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Abbreviations and Acronyms

BAS = balloon atrial septostomy
CHD = congenital heart disease
CI = confidence interval
CPB = cardiopulmonary bypass
IQR = interquartile range
IVH = intraventricular hemorrhage
MRI = magnetic resonance imaging
OR = odds ratio
RR = relative risk
Sa_{O_2} = arterial oxygen saturation
TGA = transposition of the great arteries
UBC = British Columbia Children's Hospital University of British Columbia
UCSF = University of California San Francisco Children's Hospital
WMI = white matter injury

progression from the preoperative to the postoperative scan, including hemorrhagic transformation of stroke or extension of WMI.

The objective of this study is to determine the frequency of progression of preoperative brain injuries with cardiac surgery in a prospective dual-center cohort of neonates with TGA and single ventricle physiology. This cohort also provides an opportunity to re-examine clinical risk factors previously identified for preoperative brain injury.

PATIENTS AND METHODS

Subjects

Between September 2001 and March 2008, this dual-center prospective cohort study enrolled term neonates (>36 weeks' gestation) with CHD delivered at or transferred to the University of California San Francisco Children's Hospital (UCSF) or British Columbia Children's Hospital University of British Columbia (UBC), both tertiary level cardiac referral centers. The research ethics board at each site approved the study protocol. The neonates were recruited and studied with the informed consent of their parents. Subgroups of this cohort were previously reported.[3-5,7] Term neonates with TGA or single ventricle physiology, including hypoplastic left heart syndrome, were included in this study. They were excluded if they had a congenital infection or genetic malformation syndrome.

Clinical data thought to be potential predictors of brain injury or neurodevelopmental outcome were collected from the medical records at both sites as described previously[3-5,7] Specifically, the lowest preoperative arterial oxygen saturation (Sa_{O_2}) was obtained from the intensive care unit nursing record. Inasmuch as this was an observational study, the neonates received routine clinical care for their cardiac lesions, including surgery, irrespective of the MRI findings. However, at UCSF the operations on the first 2 neonates were delayed empirically for 1 week after preoperative brain injury was found on the MRI scan.

MRI Studies

MRI studies were performed as soon as the neonates were sufficiently stable to be transported to the scanner by trained personnel and with the use of a specialized MRI-compatible isolette and a dedicated neonatal head coil.[10,11] The transport team is composed of 2 intensive care nurses and a critical care physician at UCSF and of an intensive care nurse and a respiratory therapist at UBC. No adverse events occurred at either center with this scanning protocol. Neonates were examined by a pediatric neurologist, blinded to the MRI findings, within 24 hours of the MRI scan.

At UCSF, most subjects received pharmacologic sedation with pentobarbital (1–2 mg/kg per dose up to a total of 6 mg/kg) and/or morphine sulfate (0.05 mg/kg per dose up to a total of 0.2 mg/kg), according to the institution's sedation guidelines. MRI studies were carried out on a 1.5-tesla Signa Echo-Speed system (GE Medical Systems, Waukesha, Wis) as described previously[3-5] and included (TR/TE/FieldOfView/SliceThickness/Gap): (1) T1-weighted sagittal spin echo images (600/8/20 cm/3 mm/1 mm), (2) dual-echo T2-weighted spin echo (3000/60/120/8 × 13.5 cm/4 mm/2 mm), (3) coronal volumetric 3-dimensional gradient echo images with radiofrequency spoiling images (36/3.5/22 cm/1 mm/0), and (4) average diffusivity maps echo-planar acquisition (8000/150/36 × 27 cm/5 mm/0).

At UBC, MRI studies were carried out without pharmacologic sedation on a Siemens 1.5-tesla Avanto system using VB 13A software and included comparable imaging to that obtained at UCSF (TR/TE/FieldOfView/SliceThickness/Gap): (1) 3-dimensional coronal volumetric T1-weighted images (36/9.2/200 mm/1 mm/0) and (2) axial fast spin echo T2-weighted images (4610/107/160 mm/4 mm/0.2 mm). Average diffusivity maps were generated from diffusion tensor imaging acquired with a multirepetition, single-shot echo planar sequence with 12 gradient directions (4900/104/160 mm/3 mm/0), b = 0, 600 and 700 s/mm^2, and an in-plane resolution of 1.3 mm.

The MRI scans were reviewed by a neuroradiologist independently at each site (UCSF: A.J.B.; UBC: K.J.P.) blinded to the neonate's clinical condition except for gestational age. As previously described, the neuroradiologists scored each MRI scan for acquired injury (focal, multifocal, or global) or developmental brain abnormalities.[4] The severity of stroke, WMI, or IVH was recorded using previous scoring systems.[4] Single lesions in the white matter that measured 3 mm or less were classified as WMI, whereas larger lesions were considered stroke. The differentiation of these lesions is conceptual, with stroke resulting from occlusion of a vessel and being more likely to hemorrhage whereas WMI follows hypoxia–ischemia.[12] However, it is not clear that the two can be differentiated by MRI, and sensitivity analyses for the main findings were performed by reclassifying all lesions as either stroke or WMI. A single neuroradiologist (K.J.P.) reviewed all preoperative and postoperative MRI scans in neonates with preoperative injury, blinded to the original scores. In the 4 cases of discrepancy (all solitary white matter lesions), the size definition was applied and consensus reached in all cases. ''Progression'' from the preoperative to postoperative scans was defined as enlargement of the size of the injury, regardless of the presence of hemorrhage.

Anesthetic and CPB Management

Neonates in this cohort underwent anesthesia and CPB according to a uniform clinical practice at each institution. At UCSF, anesthesia consisted of fentanyl (25–150 mg/kg total dose), midazolam (0.25–3 mg/kg total dose), sevoflurane (up to 4% end-tidal concentration before and after CPB), and isoflurane (up to 3% in the bypass sweep gas during CPB). Pancuronium was used for neuromuscular blockade. CPB was established with aortic and bicaval cannulation. Patients were cooled by alpha-stat pH management to a minimum nasopharyngeal temperature of 28°C for full-flow bypass or 18°C for regional cerebral perfusion. The CPB prime included Normosol electrolyte solution, methylprednisolone, cefazolin, and albumin. Fresh whole blood or packed red blood cells and fresh frozen plasma were added to the prime to maintain hematocrit level at 24% to 27%. Flow was maintained at 150 mL · kg^{-1} · min^{-1} except in patients requiring aortic arch reconstruction. For regional cerebral perfusion, the aortic cannula was removed and the innomonate artery cannulated with a 2-mm olive-tipped arteriotomy cannula through an incision in the aorta. Flows of 30 to