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Original Article

Serum Neuronal Biomarkers in Neonates With Congenital Heart Disease Undergoing Cardiac Surgery

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ABSTRACT

BACKGROUND: Newborns with congenital heart disease have associated brain damage that affects short-and long-term neurodevelopment. Several neuronal biomarkers exist that could predict brain damage. We investigated the pattern of neuron-specific enolase (NSE) and s100B levels after cardiopulmonary bypass surgery in neonates with congenital heart disease. **METHODS:** We completed a prospective observational study of neonates with congenital heart disease who were undergoing cardiopulmonary bypass surgery. NSE and s100B levels were measured from serum samples obtained preoperatively, immediately postoperatively, and once daily on post-operative days one to seven. Cranial ultrasounds were obtained preoperatively and postoperatively and findings were scored using an internally developed scoring system. **RESULTS:** Eighteen neonates were included. Immediate postoperative and peak levels of both NSE (58.0 [21.6] and 68.1 [55.7] μg/L) and s100B (0.14 [0.3] and 0.14 [0.3] μg/L) were significantly increased when compared with preoperative levels (34.0 [21.6] μg/L; $P < 0.01$ and 0.08 [0.1] μg/L; $P < 0.02$). By postoperative day seven, NSE and s100B levels were lower than preoperative levels: NSE (18 [5.7]; $P = 0.09$) and s100B (0.03 [0.05]; $P < 0.01$). Postoperative s100B levels were negatively correlated with age at surgery and positively correlated with circulatory arrest time. Although there was no significant correlation between either NSE or s100B levels and intensive care unit length of stay, hospital length of stay, and pediatric cerebral performance category score, there was a negative correlation between postoperative levels of NSE and ventriculomegaly. **CONCLUSIONS:** NSE and s100B levels increase after bypass surgery and return below preoperative baseline levels by postoperative day seven. The levels of s100B were positively correlated with circulatory arrest time and negatively correlated with age at time of surgery. This finding may be supportive of pre-existing prenatal brain injury that could be enhanced by longer surgical times but also of some brain protection effect associated with longer wait until surgery.

Keywords: neonatal, congenital heart disease, neurodevelopmental outcomes, pediatric, neuron-specific enolase, s100B, biomarkers, cranial ultrasound

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Introduction

Congenital heart disease occurs in 5 to 8 per 1000 births per year and is a significant cause of childhood morbidity and mortality. Up to half of the surviving children will have impaired neurodevelopmental outcomes.[1] These neurodevelopmental deficits encompass many diverse domains, including, but are not limited to academic achievement, fine motor function, visual-spatial skills, executive function, and language.[2,3] Surgical practice advances have led to improved mortality, and therefore research focus has shifted to advancing perioperative care to limit postnatal brain injury.[4] A key to this advance is identification of brain injury biomarkers that can be used to direct interventions, gauge treatment effects, and provide prognostic information in this population.

Recently there is a growing body of evidence for use of these brain injury biomarkers in cardiac surgery; however, the vast majority of this information is in the adult population. Two neuronal biomarkers, neuron-specific enolase (NSE) and s100B, have been correlated with brain injury after heart surgery in adults. NSE is a 78 kDa dimeric glycolytic enzyme localized to neuronal cytoplasm.[5,6] It has been shown to be increased in both cerebrospinal fluid (CSF) and serum after cardiac surgery using deep hypothermic cardiac arrest, normothermic cardiopulmonary bypass, and off-pump cardiac surgery.[6] In adults undergoing coronary bypass surgery, NSE was demonstrated to be a reliable marker for adverse neurological outcomes.[7-9] The s100B protein is a 21 kDa protein belonging to a multigenic family of calcium-mediated proteins. The s100B dimer is secreted into the CSF by astrocytes after CNS injury and is detected in the serum as a marker of blood-brain barrier dysfunction. It is believed to be involved in neuronal and glial growth, proliferation, and activation. Increases in s100B levels have been correlated with stroke, increased mortality, longer hospital stay, and development of delirium, neuropsychological outcomes, and memory decline after cardiac surgery in adults.[5,6]

In a study conducted at our institution, neither NSE nor s100B was independently associated with neurological outcomes in pediatric patients undergoing cardiac surgery.[10] However, these studies only measured levels at baseline, immediately after surgery, and at 16 hours postoperatively. Although the half-life of s100B is only 25 minutes, the half-life of NSE is 24 hours and it may be beneficial to measure these levels for a longer time period.

The primary outcome of this study is to describe the pattern of NSE and s100B levels after bypass surgery in neonates with complex congenital heart disease. Secondary outcomes include determining whether a link exists between increased NSE and s100B levels and abnormal cranial ultrasound findings, cardiac intensive care unit (CICU) length of stay (LOS), hospital LOS, neurological event (such as stroke or seizure), discharge destination (home versus rehabilitation), and pediatric cerebral performance category (PCPC) score.

Methods

Subjects

Infants who were diagnosed prenatally or postnatally with congenital heart disease requiring early (≤30 days of life), palliative, or corrective surgery on cardiopulmonary bypass and admitted to the pediatric CICU were eligible for inclusion. Inclusion criteria also included intravascular access placed as part of routine medical management (central venous catheter, peripherally inserted central catheter, long-term central venous catheter, arterial catheter, and so forth). Patients were excluded if family was unwilling to consent or if patients had undergone previous surgical intervention including extracorporeal membrane oxygenation therapy. Parents of eligible participants provided written informed consent for all patients. The Institutional Review Board approved the study. All data were collected according to the Health Information Portability and Accountability Act regulation. Patients were provided with standard postoperative intensive care regardless of participation within the study.

Measurements

Data collection

Demographic information and pertinent perinatal history were collected from the neonatal records. Intensive care LOS, hospital LOS, age at surgery, cardiopulmonary bypass and cross clamp times, status at final disposition, and neurodevelopmental status at hospital discharge, measured by the PCPC scale, were also collected.

NSE and s100B determinations

Serum samples were collected once preoperatively (within 24 hours of bypass surgery), once immediately on CICU admission, and once daily on postoperative days 1 to 7. These time points coincided with routine clinical laboratory monitoring. Samples were centrifuged at 6000 rotations per minute and supernatants were stored at −20°C. NSE and s100B levels were determined by enzyme-linked immunosorbant assay developed by Banyan Biomarkers from 25 μL of serum for each assay. NSE and s100B levels are reported in microliters.

Cranial ultrasound

Cranial ultrasound was performed preoperatively and postoperatively as part of standard of care. The serial cranial ultrasounds were performed as part of the institutional protocol for clinical ultrasound by technologists all of whom are credentialed as Registered Diagnostic Medical Sonographer. A General Electric (GE) Logic 9 ultrasound machine was used with multiple compatible transducers. The transducers used for conducting cranial ultrasound were GE 9L MHz and GE 6 to 15 MHz linear transducers. A pediatric neuroradiologist who was masked to the clinical data and biomarker results reviewed and scored the images using an internally developed scoring system. Brain ultrasounds were scored using 10 image findings and a structural abnormality score with a score range of 0 to 11 (higher values indicate more structural abnormalities). Our ultrasound scoring system was based on the prior literature (Supplementary material).[11-16]

Data analysis

Descriptive statistics are presented as median (interquartile range) and frequencies (%) for continuous and categorical variables, respectively. Paired *t* tests were used when the data were normally distributed, and the nonparametric Wilcoxon signed rank test was used when the data failed to meet the normality assumption for the paired *t* test. For correlations, the nonparametric Spearman rank order correlation was used. Statistical analyses were performed with SAS (SAS Institute, Cary NC).

Results

Eighteen neonates were studied. Seventeen (95%) were term. Patient characteristics and cardiac lesions are listed in Table 1.

Four children (22%) developed clinical seizures postoperatively. These four patients were also noted to have a stroke on a subsequent magnetic resonance imaging. Most patients were discharged home and had only mild disability