Urinary biomarkers and renal near-infrared spectroscopy predict intensive care unit outcomes after cardiac surgery in infants younger than 6 months of age

Matthew A. Hazle, MD,[a] Robert J. Gajarski, MD,[a] Ranjit Aiyagari, MD,[a] Sunkyung Yu, MS,[a] Abin Abraham,[b] Janet Donohue, MPH,[a] and Neal B. Blatt, MD, PhD[b]

Objective: To assess the ability of urinary acute kidney injury biomarkers and renal near-infrared spectroscopy (NIRS) to predict outcomes in infants after surgery for congenital heart disease.

Methods: Urinary levels of neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), and cystatin C were measured preoperatively and postoperatively in 49 infants younger than 6 months of age. Renal NIRS was monitored for the first 24 hours after surgery. A composite poor outcome was defined as death, the need for renal replacement therapy, prolonged time to first extubation, or prolonged intensive care unit length of stay.

Results: Forty-two (86%) patients had acute kidney injury as indicated by at least Acute Kidney Injury Network/Kidney Disease: Improving Global Outcomes (AKIN/KDIGO) stage 1 criteria, and 17 (35%) patients had poor outcomes, including 3 deaths. With the exception of KIM-1, all biomarkers demonstrated significant increases within 24 hours postoperatively among patients with poor outcomes. Low levels of NGAL and IL-18 demonstrated high negative predictive values (91%) within 2 hours postoperatively. Poor outcome infants had greater cumulative time with NIRS saturations less than 50% (60 vs 1.5 minutes; $P = .02$) in the first 24 hours.

Conclusions: Within the first 24 hours after cardiopulmonary bypass, infants at increased risk for poor outcomes demonstrated elevated urinary NGAL, IL-18, and cystatin C and increased time with low NIRS saturations. These findings suggest that urinary biomarkers and renal NIRS may differentiate patients with good versus poor outcomes in the early postoperative period, which could assist clinicians when counseling families and inform the development of future clinical trials. (J Thorac Cardiovasc Surg 2013;146:861-7)

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Acute kidney injury (AKI) is a common and potentially serious complication after surgery for congenital heart disease. Depending on the study population and criteria used to define AKI, contemporary studies report an incidence ranging from 5.5% to 50%, with associated mortality ranging from 20% to 61%.[1-3] Well-established risk factors include young age, low weight, increased duration of cardiopulmonary bypass (CPB), and postoperative hemodynamic instability.[1-3] Although they represent a high-risk population, infants often only comprise a small proportion of the study patients, and, because AKI is ill-defined in neonates, they are often entirely excluded.[4]

To standardize the definition of AKI, expert consensus groups have created the RIFLE (Risk, Injury, Failure, Loss, End-stage kidney disease) and AKIN (Acute Kidney Injury Network) scoring systems, which are based on changes in serum creatinine (S_{Cr}) and urine output.[5,6] Modification and application of the RIFLE criteria to pediatrics (pRIFLE) has been shown to predict morbidity and mortality in critically ill children.[7] In addition, a modified version of the AKIN criteria has also been shown to portend a poor clinical outcome in infants after surgery for congenital heart disease.[8] Although these systems represent important advancements in the standardization of AKI diagnosis, they have limited clinical utility in the perioperative period owing to delayed and unpredictable changes in S_{Cr} and urine output after CPB. Creatinine-based measures of AKI are particularly limited in neonates owing to the influence of maternal S_{Cr}, low glomerular filtration rates, and effect of serum bilirubin on the assay itself.[4]

Efforts to improve the sensitivity, accuracy, and timeliness of AKI diagnosis have resulted in the clinical testing

From the Divisions of Cardiology[a] and Nephrology,[b] Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, Mich.

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Address for reprints: Neal B. Blatt, MD, PhD, Division of Pediatric Nephrology, Department of Pediatrics & Communicable Diseases, University of Michigan, F6865 Mott/SPC 5297, 1500 E. Medical Center Dr, Ann Arbor, MI 48109-5297 (E-mail: nblatt@med.umich.edu).

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Abbreviations and Acronyms

AKI = acute kidney injury
AKIN = Acute Kidney Injury Network
CPB = cardiopulmonary bypass
ECMO = extracorporeal membrane oxygenation
ICU = intensive care unit
IL-18 = interleukin 18
KDIGO = Kidney Disease: Improving Global Outcomes
KIM-1 = kidney injury molecule-1
NGAL = neutrophil gelatinase-associated lipocalin
NIRS = near-infrared spectroscopy
pRIFLE = RIFLE criteria modified to pediatrics
RACHS-1 = Risk Adjustment for Congenital Heart Surgery 1
RIFLE = Risk, Injury, Failure, Loss, End-stage kidney disease
RRT = renal replacement therapy
rSO_2 = regional oxyhemoglobin saturation
S_{Cr} = serum creatinine

of renal injury biomarkers. The molecules neutrophil gelatinase-associated lipocalin (NGAL), interleukin 18 (IL-18), kidney injury molecule-1 (KIM-1), and cystatin C are increased in the blood and/or urine of critically ill adults and children with AKI in a variety of clinical settings.[9] After surgery for congenital heart disease, these biomarkers are elevated within 12 hours of CPB in patients in whom AKI develops by S_{Cr}.[10-13]

Near-infrared spectroscopy (NIRS) uses an infrared light source to measure regional oxyhemoglobin saturation (rSO_2) continuously and noninvasively 1.5 to 2 cm into the tissue bed of interest.[14] It has the advantage of being noninvasive, real time, and specific to the organ of interest. Saturation values obtained from cerebral and flank NIRS probes are correlated with invasive mixed venous oxygen saturations after surgery for congenital heart disease.[15] In addition, low rSO_2 values have been correlated with injury to the brain, gut, and kidney after CPB in children.[16-18]

To date, urinary biomarkers and renal NIRS have not been simultaneously evaluated after surgery for congenital heart disease and correlated with outcome. We hypothesized that infants with perioperative kidney injury identified by elevated urinary biomarkers or low renal NIRS values would have comparatively poorer clinical outcomes.

METHODS

This prospective study was approved by the Institutional Review Board at the University of Michigan. Infants under 6 months of age undergoing cardiac surgery with CPB between July 2009 and July 2010 were eligible for enrollment. Fifty families were approached, and 1 family declined participation in the study. Premature infants less than 35 weeks' gestation were excluded. After parental or guardian informed consent was obtained, patient demographic and surgical information was collected. Surgical complexity was ranked according to the Risk Adjustment for Congenital Heart Surgery 1 (RACHS-1) scoring system.[19] Postoperative hemodynamic status was estimated by calculation of a daily maximum vasoactive–inotropic score (VIS) for the first 3 days after surgery as per the equation below[20]:

$$\begin{aligned}\text{VIS} = {} & \text{dopamine dose } (\mu g \cdot kg^{-1} \cdot min^{-1}) \\ & + \text{dobutamine dose } (\mu g \cdot kg^{-1} \cdot min^{-1}) \\ & + 100 \cdot \text{epinephrine dose } (\mu g \cdot kg^{-1} \cdot min^{-1}) \\ & + 10 \cdot \text{milrinone dose } (\mu g \cdot kg^{-1} \cdot min^{-1}) \\ & + 10,000 \cdot \text{vasopressin dose } (\text{units} \cdot kg^{-1} \cdot min^{-1}) \\ & + 100 \cdot \text{norepinephrine dose } (\mu g \cdot kg^{-1} \cdot min^{-1})\end{aligned}$$

All patients received routine standard of care during the study period, which included the use of dextrose-containing crystalloid solutions (75-100 mL $\cdot$ kg^{-1} $\cdot$ d^{-1}) during the first 24 to 48 hours postoperatively, followed by the initiation of total parenteral nutrition. Patients were started on bolus furosemide (1 mg/kg per dose every 6 hours) within the first 24 hours postoperatively. One of the study patients had a peritoneal drain placed for mild abdominal compartment syndrome. Primary providers were aware that the patients were enrolled in a study looking at AKI and outcomes.

Biomarkers

Preoperative urine samples were collected from a bag specimen or indwelling catheter placed in the operating room before initiation of CPB. Postoperative urine samples were obtained from the Foley catheter on admission to the intensive care unit (ICU) and at 2, 6, 12, and 24 hours. The samples were centrifuged (2000 rpm, 5 minutes), divided into aliquots, and stored (−80°C) until analysis. Urinary concentrations of NGAL, IL-18, KIM-1, and cystatin C were measured using commercially available enzyme-linked immunosorbent assay kits from R&D Systems (Minneapolis, Minn).

Near-Infrared Spectroscopy

After arrival in the ICU, a Somanetics (Troy, Mich) INVOS Pediatric NIRS sensor was placed over the right flank and continuous rSO_2 was recorded in 30-second intervals for the first 24 hours after surgery. The primary caregivers were blinded to the data during the collection period and no clinical interventions were made on the basis of the NIRS values. Faulty NIRS probes were discovered in 2 patients after completion of the observation period. Because of the impact of extracorporeal membrane oxygenation (ECMO) on oxygen saturation, in 6 patients NIRS data were censored from analysis.

Acute Kidney Injury

S_{Cr} was measured preoperatively and postoperatively, then once daily as part of routine daily laboratory studies. AKI was defined using criteria proposed by the Acute Kidney Injury Network and Kidney Disease Improving Global Outcomes group, and recently validated in a study of infants with congenital heart disease.[6,8,21] Infants had AKI if they met AKIN stage 1 criteria, defined as an increase in S_{Cr} by either 0.3 mg/dL or more or a 50% rise from preoperative baseline within the first 3 days postoperatively.

Outcome Measures

Owing to the relatively small size of our patient population and our low mortality and renal replacement therapy (RRT) rates, a composite poor