Interleukin-8 and Tumor Necrosis Factor Predict Acute Kidney Injury After Pediatric Cardiac Surgery

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Background. **Inflammation is a key component of both acute kidney injury (AKI) and response to cardiopulmonary bypass. Because AKI poses risks to children after cardiac surgery, we investigated the value of inflammatory biomarkers interleukin-8 (IL-8) and tumor necrosis factor alpha (TNFα) for predicting AKI and other complications.**

Methods. **We enrolled 412 children between the ages of 1 month and 18 years undergoing cardiopulmonary bypass for cardiac surgery. We collected blood both preoperatively and postoperatively (within 6 hours postsurgery) and measured plasma IL-8 and TNFα.**

Results. **IL-8 and TNFα did not predict AKI in children <2 years, but were strongly associated with AKI in children ≥2 years. There were significant associations between biomarker levels and age (<2 or ≥2 years). In children ≥2 years, patients in the highest tertile of preoperative IL-8 and postoperative TNFα had 4.9-fold (95% CI: 1.8-13.2) and 3.3-fold (95% CI: 1.2-9.0) higher odds of AKI compared with those in the lowest tertile. Children <2 years with higher biomarker levels also had higher odds of AKI, but the difference was not significant. We also found that postoperative TNFα levels were significantly higher in patients with longer hospital stays, and that both postoperative IL-8 and TNFα levels were significantly higher in patients with longer ventilation lengths. There was no evidence that biomarker levels mediated the association between AKI and length of ventilation; they appear to be independent predictors.**

Conclusions. **Preoperative IL-8 and postoperative TNFα are significantly associated with higher odds of AKI and greater lengths of hospital stays and ventilator use in children 2 years and older.**

(Ann Thorac Surg 2017;104:2072–9)

Every year, 40,000 children are born with congenital heart disease in the United States. About 25% of these children require cardiac surgery [1]. Unfortunately, acute kidney injury (AKI) is a common complication of these procedures and is associated with morbidity. As a patient's blood flows through the extracorporeal circuit during bypass, the body reacts by mounting an immune response. This inflammation contributes to the development of AKI, which in turn propagates further inflammation [2]. Because of these close relationships between AKI, cardiopulmonary bypass (CPB), and inflammation, we chose to investigate the association between inflammatory biomarkers and AKI in pediatric patients undergoing CPB.

The present investigation is a sub-study of the Translational Research Investigating Biomarker Endpoints in Acute Kidney Injury (TRIBE-AKI) Consortium. The goal of this multi-center prospective observational study is to investigate novel biomarkers as potential tools to help detect early AKI in patients post-cardiac surgery.

Accepted for publication April 14, 2017.

*Additional members of the TRIBE-AKI Consortium appear at the end of this article.

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The Supplemental Tables can be viewed in the online version of this article [http://dx.doi.org/10.1016/j.athoracsur.2017.04.038] on http://www.annalsthoracicsurgery.org.

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2017.04.038

Ultimately, TRIBE-AKI aims to improve outcomes and safety associated with cardiac surgery. Since 2007, over 1,500 patients across 9 North American sites have participated in the cohort. This group consists of both adult and pediatric patients enrolled in parallel. Three of the 9 sites conducted the pediatric arm of the cohort, enrolling 412 children over the course of the study. Many studies examining the extensive set of resulting data on the pediatric cohort have been published so far. Some of these key findings include that serum brain natriuretic peptide helps risk-stratify patients for AKI, that postoperative neutrophil gelatinase–associated lipocalin and interleukin-18 help predict AKI, and that chronic kidney disease and hypertension are common 5 years after cardiac surgery [3–5]. In the present study, we are extending the analysis of TRIBE-AKI pediatric data to two additional promising biomarkers of AKI.

Namely, we focused on interleukin-8 (IL-8) and tumor necrosis factor alpha (TNFα). IL-8 is a chemokine produced by macrophages, neutrophils, fibroblasts, and epithelial cells. This protein is a key mediator of inflammation that assists in neutrophil recruitment and degranulation [6]. TNFα is a proinflammatory cytokine produced primarily by monocytes but also by lymphocytes and endothelial cells. TNFα acts on neutrophils and macrophages leading to cytokine secretion and cytotoxicity, and is one of the cytokines that drive the acute phase reaction [7]. Both IL-8 and TNFα have been associated with AKI in adult patients with various diseases. Elevated IL-8 levels have been tied to AKI risk in patients undergoing liver transplants, patients in septic shock, and patients with acute lung injury [8–11]. Elevated TNFα levels have been associated with AKI risk in patients developing sepsis and in patients having cardiovascular surgery [12, 13]. Only one previous study has been performed measuring IL-8 and TNFα in children undergoing cardiac surgery and it showed that IL-8 was associated with increased risk of AKI. The association of TNFα with AKI was inconclusive, however, and that study was also very small, with only 18 AKI and 21 non-AKI patients [14]. Thus, further evidence is needed.

Patients and Methods

Patients were part of the pediatric cohort of the TRIBE-AKI multi-center study. This sub-study consisted of 412 patients between the ages of 1 month and 18 years who were enrolled prospectively from July 2007 to December 2010. Three medical center were involved, namely, the Cincinnati Children's Hospital Medical Center, the Montreal Children's Hospital, and the Yale-New Haven Children's Hospital. Informed consent was obtained from all patient guardians and patients themselves when appropriate. All 412 patients received CPB surgery to correct congenital heart defects [15]. This study was approved by the ethics board of each medical center.

Sample Collection

We collected blood specimens both preoperatively and postoperatively (first sample within 6 hours after surgery). Plasma aliquots were then stored at –80°C until biomarker measurement.

Biomarker Measurements

All samples were measured using the Meso Scale Discovery platform (Meso Scale Discovery, Gaithersburg, MD). IL-8 was able to be detected at a range of 0.047 to 516 pg/mL, and TNFα at a range of 0.04 to 311 pg/mL. Personnel responsible for biomarker measurements were blinded to clinical outcomes.

Outcome Definitions

The two main outcomes analyzed in this study were "any AKI" and "severe AKI." We defined any AKI as the development of at least stage 1 AKI (composite of stage 1, stage 2, and stage 3 AKI). Severe AKI was defined as only patients with stage 2 or greater AKI. Our stage 1 AKI definition was based on the Kidney Disease: Improving Global Outcomes standard, namely, a 50% or greater (or 0.3 mg/dL) increase in serum creatinine during the first postoperative week relative to the baseline serum creatinine concentration [16]. Stage 2 AKI was defined as at least a doubling of the serum creatinine level from the baseline preoperative value; stage 3 AKI was defined as a tripling or receipt of acute dialysis. We also measured other outcomes including length of hospital stay, length of intensive care unit (ICU) stay, and number of days on a ventilator.

Variable Definitions

In order to categorize the complexity of surgery, we used the Risk Adjustment for Congenital Heart Surgery 1 (RACHS-1) consensus-based scoring system and definitions of the Society of Thoracic Surgeons [17]. Preoperative estimated glomerular filtration rate (eGFR) was determined using the updated Schwartz equation [18]. Percentiles for eGFR values were obtained based on previously published data on normal pediatric renal function [19, 20].

Statistical Analysis

For comparisons of continuous variables, we used the two-sample t test or the Wilcoxon rank sum test. For comparisons of dichotomous variables, we used the χ^2 test or Fisher's exact test. For most analyses, we prespecified stratifying the results by age (<2 years or ≥ 2 years), as the kidney does not fully mature until about age 2 years. There is also precedent for this stratification in previous studies [4, 21]. In addition, the interaction p values between biomarker levels and age (<2 or ≥ 2 years) were all less than 0.05.

To examine associations between biomarkers and AKI, we divided patients into tertiles based on IL-8 and TNFα levels for the entire cohort, and then stratified by age. We examined the association between biomarkers and development of any or severe AKI via logistic regression and estimating adjusted odds ratios (aORs) of AKI. We also assess the discrimination of IL-8 and TNFα for AKI by calculating the area under the receiver operating characteristics curve (AUC-ROC) [22]. We examined the