Subclinical Kidney Injury in Children Receiving Nonsteroidal Anti-Inflammatory Drugs After Cardiac Surgery

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Objective To investigate the association of nonsteroidal anti-inflammatory drug (NSAID) administration with urinary neutrophil gelatinase-associated lipocalin (NGAL) levels in children following cardiopulmonary bypass (CPB) who did not develop acute kidney injury (AKI).

Study design In this prospective observational study, urinary NGAL levels were investigated in 210 children who underwent cardiothoracic surgery requiring CPB. Children with clinical AKI (defined as an increase in serum creatinine ≥50% from baseline within 72 hours of CPB) were excluded from the analysis. NSAIDs were administered no sooner than 24 hours after CPB. NGAL levels were compared between children who received NSAIDs (n = 146) and those who did not receive NSAIDs (n = 64).

Results The median age was 3.2 years in the children who received NSAIDs and 2.5 years in those who did not receive NSAIDs ($P = .05$). Before NSAID administration at 24 hours following CPB, the median NGAL level was 15 ng/mL in both groups ($P = .92$). Following NSAID administration, the median urinary NGAL level increased to 83 ng/mL (IQR, 45-95 ng/mL) at 72 hours after CPB in those receiving NSAIDs ($P < .001$). In contrast, the median NGAL level decreased to 10 ng/mL (IQR, 5.4-15.9 ng/mL) at 72 hours after CPB in those who did not receive NSAIDs ($P = .01$). In multivariable analysis, children receiving NSAIDs demonstrated a 5-fold elevation of urinary NGAL levels at 60-72 hours following CPB compared with those who did not receive NSAIDs ($P < .001$).

Conclusion NSAID administration was associated with a significant increase in urinary NGAL in children who did not develop clinical AKI following CPB. This indicates that NGAL can detect NSAID-induced subclinical kidney injury in this population. *(J Pediatr 2017;189:175-80).*

Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed for postoperative pain. NSAIDs disrupt autoregulation of renal perfusion by opposing prostaglandin-mediated vasodilation of the renal vasculature.[1] When administered to children with decreased renal perfusion or cardiac output, NSAIDs can compromise renal blood flow and induce renal ischemia.[2] Children with congenital heart disease undergoing cardiopulmonary bypass (CPB) represent a population that may be at high risk for NSAID-induced acute kidney injury (AKI).

Neutrophil gelatinase-associated lipocalin (NGAL) is an early and sensitive urinary biomarker of AKI.[3] In children undergoing cardiac surgery, an elevated urine NGAL level 2 hours postoperatively can identify those who will develop AKI within 48 hours following CPB.[4,5] As the field of urinary biomarkers continues to develop, the 10th Acute Dialysis Quality Initiative consensus conference proposed the use of urinary biomarkers to improve the evaluation and treatment of patients with AKI. Specifically, urinary biomarkers can provide both diagnostic and prognostic information independent of conventional markers such as serum creatinine, thereby refining the clinical management of AKI.[6] One application is in the field of nephrotoxicity, where urinary biomarkers such as NGAL may identify subclinical kidney injury, when structural damage occurs without the development of decreased kidney function (ie, a rise in serum creatinine).[7]

In this study, we investigated the association of NSAID administration with urinary NGAL levels in a cohort of 210 children undergoing cardiac surgery with CPB who did not develop clinical AKI. We hypothesized that the children receiving NSAIDs would experience an increase in urinary NGAL concentration, indicating the presence of NSAID-induced subclinical kidney injury in this population.

AKI	Acute kidney injury
AUC	Area under the curve
CPB	Cardiopulmonary bypass
NGAL	Neutrophil gelatinase-associated lipocalin
NSAID	Nonsteroidal anti-inflammatory drug
ROC	Receiver operating characteristic

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Methods

This was a post hoc analysis of a parent study aimed at determining the prognostic utility of urinary NGAL level to predict AKI in children undergoing CPB. The methods and results of this parent study have been published previously.[8] In brief, the legal guardians of all patients aged <18 years undergoing cardiac surgery with CPB at Cincinnati Children's Hospital Medical Center were approached. Initial enrollment consisted of 425 children who underwent cardiac surgery between January 2004 and May 2007. Institutional Review Board approval was obtained from Cincinnati Children's Hospital Medical Center. Written informed consent was obtained from the legal guardian of each patient, and assent from the patient was obtained when appropriate. Children with preexisting renal insufficiency (defined as serum creatinine concentration >2 times the age-adjusted reference range) were excluded. The complexity of cardiac surgery was classified according to the Risk Adjustment for Congenital Heart Surgery-1 consensus-based scoring system.[9]

For this study, 158 children who developed AKI (defined as a 50% increase in serum creatinine from preoperative baseline values) within 72 hours following CPB were also excluded. The reason for this was 2-fold: (1) to remove the confounding presence of increased urinary NGAL levels due to AKI associated with CPB, and (2) to permit the evaluation of NSAID-induced subclinical kidney injury. Serum creatinine values were not routinely obtained after the study period, which extended up to 72 hours following CPB; therefore, patients may have developed AKI after this time point. Children who received angiotensin-converting enzyme inhibitors, aminoglycosides, or contrast agents (n = 57) postoperatively also were excluded, leaving a final cohort of 210. The primary predictor variable was NSAID administration, which was prescribed no sooner than 24 hours following CPB. The primary outcome variable was urine NGAL levels measured preoperatively and at 2, 6, 12, 24, 36, 48, and 72 hours following surgery.

Laboratory Analysis

Urine samples were obtained and stored in aliquots at −80°C before batch measurement. Urine NGAL was assayed using a commercially available enzyme-linked immunoassay (NGAL ELISA Kit 036; Bioporto, Grusbakken, Denmark) that specifically detects human NGAL. The intra-assay and interassay coefficients of variation were 2.1% and 9.1%, respectively.

Statistical Analyses

Descriptive analyses are reported as percentage for categorical variables and as median and IQR for continuous variables. Baseline characteristics were compared between those children who received NSAIDs and those who did not receive NSAIDs postoperatively. The χ^2 test and Wilcoxon rank-sum test were used to compare between-group differences for categorical and continuous variables, respectively. NGAL levels were compared at each time point using the Wilcoxon rank-sum test (between groups) and Wilcoxon signed-rank test (within the same group) as appropriate. A multivariable analysis was then performed to determine the independent association of NSAID exposure with urine NGAL level at each time point while adjusting for clinical characteristics. To account for the repeated nature of the data and within-subject correlation, generalized linear mixed modeling was used with study subject as a random effect. The association of NSAID use with serum NGAL level at each time point was investigated by including an interaction term (NSAID × time) in the model. NGAL levels were log-transformed to fulfill the assumptions of linear regression modeling. To determine the ability of urinary NGAL to identify children who received NSAIDs, conventional receiver operating characteristic (ROC) curve analyses were conducted. Area under the curve (AUC) values were calculated along with cutoff values resulting in 80% sensitivity. Corresponding specificity, positive predictive values, and negative predictive values also were reported at the specified cutoff value. All analyses were conducted using SAS version 9.3 (SAS Institute, Cary, North Carolina).

Results

Of the 210 children included in the study, 146 (70%) received NSAIDs following cardiac surgery. Of those who received NSAIDs, 88% received multiple doses. Demographic, clinical, and laboratory characteristics of the study participants are summarized in **Table I**. The children who received NSAIDs were older and more likely to have undergone a previous surgery requiring CPB. Their cardiothoracic surgeries tended to have lower Risk Adjustment for Congenital Heart Surgery-1 scores with shorter CPB times. There were no between-group differences in sex, race, or baseline serum creatinine concentration.

As shown in **Figure 1**, urine NGAL levels in all patients were low before surgery, ranging from 0 to 51 ng/mL. During the first 24 hours following CPB, during which no NSAIDs were administered to either group, no between-group differences

Table I. Demographic, clinical, and laboratory characteristics

Characteristics	No NSAIDs (n = 64)	NSAIDs (n = 146)	*P* value
Age, y, median (IQR)	2.5 (0.35-5.3)	3.2 (0.8-6.4)	.05
Male sex, % (n)	61 (39)	55 (80)	.41
White race, % (n)	84 (54)	88 (129)	.43
CPB time, min, median (IQR)	95.5 (72.5-165)	83.5 (62-116)	.02
Hospital stay, d, median (IQR)	4 (3-9.5)	5 (4-7)	.36
Baseline serum creatinine, mg/dL, median (IQR)	0.45 (0.4-0.55)	0.4 (0.4-0.6)	.41
% serum creatinine change, median (IQR)	0 (0-18.88)	0 (0-15)	.76
History of previous CPB, % (n)	23 (15)	42 (62)	.01
RACHS-1 score, % (n)			.01
1	9 (6)	17 (25)	
2	39 (25)	45 (66)	
3	34 (22)	34 (50)	
4	13 (8)	3 (5)	
5	3 (2)	0 (0)	
6	2 (1)	0 (0)	