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

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Abstract

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 (increase in serum creatinine ≥50% from baseline within 72 hours of CPB) were excluded from analysis. NSAIDs were administered no sooner than 24 hours after CPB. NGAL levels were compared between children who received (n=146) and did not receive NSAIDs (n=64).

Results—The median age was 3.2 years in children who received NSAIDs and 2.5 years in children who did not receive NSAIDs (p=0.05). Prior to NSAID administration at 24 hours following CPB, median NGAL levels were 15 ng/ml in both groups (p=0.92). Following NSAID administration, median urinary NGAL levels increased to 83 ng/ml (IQR 45–95) at 72 hours after CPB in those receiving NSAIDs (p<0.001). In contrast, NGAL levels decreased to 10 ng/ml (IQR 5.4–15.9) at 72 hours after CPB in those who did not receive NSAIDs (p=0.01). In multivariable analysis, children receiving NSAIDs demonstrated a 5-fold elevation of urinary NGAL levels at 60–72 hours following CPB compared with children who did not receive NSAIDs (p<0.001).

Conclusion—NSAID administration was associated with a significant increase in urinary NGAL following CPB in children who did not develop clinical AKI. This indicates NGAL can detect NSAID-induced subclinical kidney injury in this population.

Keywords

neutrophil gelatinase-associated lipocalin; acute kidney injury; nephrotoxicity

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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 surgery (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 elevation of urine NGAL 2 hours post-operatively 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 (ADQI) consensus conference proposed utilizing 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 decreased kidney function (i.e., a rise in serum creatinine).⁷

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

Methods

This is a post-hoc analysis of a parent study that was aimed to determine the prognostic utility of urinary NGAL to predict AKI in children undergoing CPB. The methods and results of this parent study have been previously published.⁸ Briefly, the legal guardians of all patients <18 years of age undergoing cardiac surgery with CPB at Cincinnati Children's Hospital Medical Center (CCHMC) 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 CCHMC. Written informed consent was obtained from the legal guardian of each patient, and assent from the patient was obtained when appropriate. Children with pre-existing renal insufficiency (serum creatinine concentration >2 times age-adjusted reference range) were excluded. The complexity of cardiac surgery was classified according to the Risk Adjustment for Congenital Heart Surgery-1 (RACHS-1) consensus-based scoring system.⁹

For this study, 158 children who developed AKI (defined as a 50% increase in serum creatinine from pre-operative baseline values) within 72 hours following CPB were also excluded. The reason for this was twofold: 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 was up to 72 hours following CPB. Therefore, patients may have developed AKI after this time point. Children who received angiotensin-converting enzyme (ACE) inhibitors, aminoglycosides, or contrast agents (n=57) post-operatively were also 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, which were obtained pre-operatively 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 prior to batch measurement. Urine NGAL was assayed using a commercially available enzyme-linked immunoassay (NGAL ELISA Kit 036; Bioport, Grusbakken, Denmark) that specifically detects human NGAL. The intra- and inter-assay coefficients of variation were 2.1% and 9.1%, respectively.

Statistical Analysis

Descriptive analyses were reported as percentages for categorical variables, and median and interquartile ranges (IQR) were used for continuous variables. Baseline characteristics were compared between those children who received NSAIDs and those who did not receive NSAIDs post-operatively. Chi-square testing and the Wilcoxon rank-sum test were used to compare 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 levels 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 levels at each time point was investigated by including an interaction term (NSAID $\times$ 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-operator curve analyses (ROC) were conducted. Area under the curve (AUC) values were calculated along with cut-off values resulting in 80% sensitivity. Corresponding specificity, positive predictive values, and negative predictive values were also reported at the specified cut-off value. All analyses were conducted using SAS statistical software (version 9.3 SAS Institute, Cary, NC).

Results

A total of 210 children were included in the study, 146 (70%) of whom received NSAIDs following cardiac surgery. Of those who received NSAIDs, 88% received multiple doses. Demographic, clinical, and laboratory characteristics are shown in Table 1. Children who received NSAIDs were older and more likely to have undergone a previous surgery requiring CPB. The cardiothoracic surgeries of children who subsequently received NSAIDs tended to have lower RACHS-1 scores with a shorter bypass time. There were no differences in sex, race, or baseline serum creatinine.

As shown in Figure 1, urine NGAL levels in all patients were low prior to surgery, ranging from 0 – 51 ng/ml. During the first 24 hours following CPB, during which no NSAIDs were administered to either group, no differences in NGAL levels were evident. Both groups demonstrated a mild but significant rise in urine NGAL that peaked at 6 hours after surgery and then declined until 24 hours post-operatively. After 24 hours, when NSAIDs were administered, a divergence in urinary NGAL levels was observed. In those who received NSAIDs, urinary NGAL levels increased from 15 ng/ml (IQR 5–30) at 24 hours to 83 ng/ml (IQR 45–95) at 72 hours following CPB ($p<0.001$). In contrast, in those who did not receive NSAIDs, NGAL levels decreased from 15 ng/ml (IQR 5–25) at 24 hours to 10 ng/ml (IQR 5.4–15.9) at 72 hours following CPB ($p=0.01$). In these patients, urinary NGAL decreased to levels that were not significantly different from pre-operative values. At all time points after 24 hours, urinary NGAL levels were significantly higher in those who received NSAIDs (all $p<0.001$).

The association of urine NGAL levels with NSAID administration was investigated at each time point in multivariable analysis (Table 2), adjusting for all clinical and demographic characteristics in Table 1. NGAL levels 60–72 hours after CPB were more than 5-fold higher in children who received NSAIDs compared with those who did not. To determine the ability of NGAL to identify patients who received NSAIDs, ROC analyses were performed for each time point 36 hours after CPB. AUCs (95% confidence interval) for urine NGAL at each time point were as follows: 36 hours, 0.88 (0.83–0.93); 48 hours, 0.95 (0.93–0.98); 60 hours, 0.96 (0.93–0.98); 72 hours, 0.96 (0.93–0.98). At 48 hours, an NGAL threshold of 39 ng/ml had a sensitivity of 81% and specificity of 98% to identify NSAID administration. Therefore, 118/146 children who received NSAIDs had an NGAL level $\geq$ 39 ng/ml, while only 1/64 children who did not receive an NSAID had an NGAL level $\geq$ 39 ng/ml. The corresponding positive predictive value using this cutoff was 99%, with a negative predictive value of 69%.

To determine if repeated doses of NSAIDs have a cumulative effect on increasing NGAL levels, urinary NGAL levels were compared in patients receiving one dose ($n=18$) to those receiving multiple doses of NSAIDs ($n=128$). As seen in Figure 2, NGAL levels increased from 24 to 48 hours following CPB in both groups. However, a divergent pattern of NGAL levels was observed after 48 hours: NGAL levels decreased in patients receiving only 1 dose of NSAIDs, whereas levels progressively increased in children who continued to receive repeated doses. At 72 hours after CPB, median (IQR) of NGAL levels were 24.5 ng/ml (15–33) in patients who received only 1 dose, compared with 85 ng/ml (65–97.5) in those receiving multiple doses of NSAIDs ($p<0.001$). To determine the ability of NGAL to discriminate between one vs. multiple NSAID doses, ROC analyses were performed including only the 146 subjects who received NSAIDs. The AUCs (95% confidence interval) for urine NGAL to identify children who received multiple NSAID doses were 0.92 (0.88–0.97) at 60 hours and 0.94 (0.90–0.98) at 72 hours.

Discussion

In this cohort of children undergoing cardiac surgery and CPB who did not develop clinical AKI, NSAID administration was associated with a significant increase in urinary NGAL

levels. The increase in NGAL was first detected within 12 hours after NSAID administration and remained persistently elevated in those who received repeated doses. These results indicate that NSAID use in critically ill children is associated with subclinical kidney injury that occurs despite normal kidney function.

Identification of nephrotoxin-mediated kidney injury is an emerging application of urinary NGAL. This was first demonstrated in a murine model of cisplatin nephrotoxicity, where NGAL was detectable in the urine prior to other biochemical indicators of kidney injury.¹⁰ Clinical studies investigating the association of urinary NGAL with nephrotoxins have primarily been limited to intravenous contrast agents. In children and adults undergoing cardiac catheterization with angiography, urinary NGAL is an early predictor of contrast-induced nephropathy.^{11, 12} Similar to our results, NGAL levels are also elevated following contrast administration in patients who do not develop a significant increase in serum creatinine.^{13, 14} Nephrotoxic injury caused by cisplatin and cyclosporine exposure may also be identified by urinary NGAL.^{15, 16} In a recent study, chronic NSAID exposure in adults with spondyloarthritis was associated with a significant rise in urinary NGAL.¹⁷ To our knowledge, our study is the first to demonstrate subclinical kidney injury associated with the use of a nephrotoxic medication in hospitalized children.

Critically ill children are exposed to numerous nephrotoxic medications, which contribute to 16–25% of all cases of AKI.^{18–20} The development of AKI is associated with longer hospital stay, prolonged mechanical ventilation, and increased patient mortality. Furthermore, increasing severity of AKI confers an incremental increase in the risk of adverse outcomes.^{21–23} Considering that there are no effective treatments to reverse AKI, early identification and management of nephrotoxic medication-associated kidney injury is therefore paramount. Our results indicate that urinary NGAL can detect NSAID-mediated tubular injury at the initial stage of kidney injury, when structural damage has occurred despite any appreciable increase in serum creatinine.

Diagnostic accuracy of urinary NGAL to identify children who received NSAIDs was excellent, with an AUC of 0.95–0.96 at 24–48 hours following NSAID administration. Moreover, urinary NGAL accurately discriminated between those receiving one versus multiple doses of NSAIDs. Urinary NGAL levels continued to increase in patients receiving multiple doses of NSAIDs, whereas NGAL levels declined in the absence of repeated dosing. Taken together, these findings indicate that urinary NGAL is a highly sensitive marker for the initiation and progression of NSAID-mediated kidney injury. Considering that NSAIDs account for 2.7–6.6% of AKI in hospitalized children,²⁴ routine measurement of urinary NGAL levels may be an option to mitigate renal complications in this population. For example, serial NGAL monitoring in children receiving scheduled NSAIDs could identify those with progression of subclinical kidney injury as indicated by rising NGAL levels. Such an approach would provide clinicians with a window of opportunity to proactively prevent the development of overt AKI with functional impairment. Therapeutic interventions may include dose reduction or discontinuation of nephrotoxic medications and optimization of intravascular volume. However, because NSAIDs are usually well-tolerated in healthy patients, biomarker testing would likely need to be combined with a clinical risk

stratification scheme to optimize diagnostic accuracy by identifying those patients at significant risk for AKI.

Children with AKI during the study period were excluded from our analysis to remove subjects who had elevated NGAL levels associated with CPB-induced kidney injury. We were therefore unable to assess prognostic ability of NGAL to predict the clinical occurrence of NSAID-induced AKI, as defined by a rise in serum creatinine. However, this study design permitted a targeted assessment of NSAID-induced subclinical kidney injury by studying children in whom NGAL levels were comparable to normative values prior to NSAID administration.²⁵ Although we did not investigate clinical outcomes, the significance of our findings can be inferred by interpreting our results in the context of previous studies. At 72 hours following CPB, the median range of urinary NGAL in children receiving NSAIDs was 82 ng/ml, which is within previously recommended threshold values of 50–200 ng/ml to predict AKI.^{5, 8, 26} Furthermore, urinary NGAL levels > 100 ng/ml were evident in 16% of those who received NSAIDs at the end of the study period, all of whom received repeated doses. Therefore, it is possible that these patients incurred a degree of nephrotoxic injury that placed them at risk of clinical AKI.

The strengths of our study include a large sample size with a prospective study design, and a rigorous protocol with frequent urine NGAL measurements. We were therefore able to determine the precise temporal relationship between NSAID administration and urinary NGAL. Urine NGAL was measured using a standardized laboratory platform, which has demonstrated consistent performance and broad agreement in clinical cutoff values to predict AKI.²⁷ Nevertheless, several limitations deserve consideration. First, our study was conducted in a homogenous cohort of children undergoing cardiac surgery, with minimal comorbidities including pre-existing kidney disease. We cannot be certain that our findings are generalizable to more diverse populations where NGAL performance can be variable, such as children in the non-cardiac intensive care unit.^{28, 29} Compared with the pediatric population, the performance NGAL in adults following CPB is also inferior,^{30–32} possibly due to the presence of comorbid conditions. Second, the cause of AKI is often multifactorial, and we cannot exclude the presence of additional insults that may have affected NGAL levels. For example, some patients may have experienced acute tubular injury secondary to post-operative hemodynamic instability, which may have affected NGAL levels. However, the strong associations observed between NSAID administration and urinary NGAL levels were unlikely to be markedly affected by possible unidentified confounding variables. Third, serum creatinine levels were not obtained reliably after the study period ended. Therefore, correlation of NGAL levels at 72 hours following CPB with subsequent development of clinical AKI could not be determined. Finally, we were unable to evaluate the association of subclinical kidney injury with patient outcomes. Previous studies in adult patients have demonstrated that subclinical kidney injury is associated with increased risk of adverse events, including longer hospital stay, initiation of renal replacement therapy, and patient death.^{33, 34} Our cohort of pediatric patients represented a lower-risk population, as none of the patients died or required renal replacement therapy during hospitalization. Therefore, although subclinical kidney injury has emerged as a new diagnosis with promise to improve management of AKI,³⁵ the severity and clinical significance of this condition is unknown.

Further research is needed refine the diagnosis of subclinical AKI by establishing NGAL thresholds that correlate with patient outcomes.⁶

Acknowledgments

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Abbreviations

AKI	acute kidney injury
AUC	area under the curve
CPB	cardiopulmonary bypass
IQR	interquartile range
NGAL	neutrophil gelatinase-associated lipocalin
NSAID	non-steroidal anti-inflammatory drug
RACHES-1	Risk Adjustment for Congenital Heart Surgery-1
ROC	receiver operator curve

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Figure 1. Urine NGAL levels in children following CPB, stratified by NSAID administration
 Children who received NSAIDs (n=146) are represented by the solid line, children who did not (n=64) are represented by the dashed line. NGAL levels graphed as median (dots) and interquartile ranges (vertical bars).

Figure 2. Urine NGAL levels in children receiving NSAIDs following CPB, stratified by NSAID dose

Children who received multiple NSAID doses (n=128) are represented by the solid line, children who received only a single NSAID dose (n=18) are represented by the dashed line. NGAL levels graphed as median (dots) and interquartile ranges (vertical bars).

Table 1

Demographic, clinical, and laboratory characteristics

	No NSAID (N= 64)	Received NSAID (N=146)	P value
Age, years	2.5 (0.35, 5.3)	3.2 (0.8, 6.4)	0.05
Male	61% (39)	55% (80)	0.41
Caucasian	84% (54)	88% (129)	0.43
Bypass time, minutes	95.5 (72.5, 165)	83.5 (62, 116)	0.02
Hospital stay, days	4 (3, 9.5)	5 (4, 7)	0.36
Baseline S _{cr}	0.45 (0.4, 0.55)	0.4 (0.4, 0.6)	0.41
% S _{cr} change	0 (0, 18.88)	0 (0, 15)	0.76
History of prior bypass	23% (15)	42% (62)	0.01
RACHS-1 score			0.01
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)	

For continuous variables, median (interquartile range) are reported; for categorical variables, % (n) are reported. Scr, serum creatinine (mg/dl).

Table 2

Multivariable analysis of NSAID administration and urine NGAL levels

Time point	% increase in NGAL between groups ^a	95% Confidence Interval	P-value ^b
24 hours	-12	(-31, 13)	0.32
36 hours	206	(141, 288)	<0.001
48 hours	367	(267, 493)	<0.001
60 hours	532	(398, 703)	<0.001
72 hours	561	(420, 739)	<0.001

All variables in Table 1 were included as covariates in the multivariable analysis. Prior CPB was mildly significant ($p=0.04$) and was associated with a mean (95% confidence interval) increase in NGAL levels of 23% (1, 50). All other variables were not significant at the $p<0.05$ level.

^a represents the mean percentage increase in urine NGAL levels in those receiving NSAIDs compared to those who did not receive NSAIDs at each time point following CPB.

^b p-value for interaction term of NSAID administration with each corresponding time point.