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Serum Brain Natriuretic Peptide and Risk of Acute Kidney Injury After Cardiac Surgery in Children

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Abstract

Background—Acute kidney injury (AKI) after pediatric cardiac surgery is associated with poor outcomes and is difficult to predict. We conducted a prospective study to evaluate whether preoperative brain natriuretic peptide (BNP) levels predict postoperative AKI among children undergoing cardiac surgery.

Methods—This was a three-center, prospective study (2007–2009) of 277 children undergoing cardiac surgery (n=121 aged <2 years) with available preoperative BNP values. Preoperative BNP was measured and categorized into tertiles. The performance of BNP was evaluated alone and in combination with clinical factors. AKI was defined as doubling of serum creatinine or need for acute dialysis.

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Clinical Trial Registration at Clinicaltrials.gov as NCT00774137.

Results—Postoperative AKI occurred in 165 children (60%) with 118 (43%) being mild and 47 (17%) severe AKI. Preoperative BNP was not associated with increased risk of mild or severe postoperative AKI and did not significantly improve AKI risk prediction when added to clinical models. Preoperative BNP was however associated with several clinical outcomes including length of stay and mechanical ventilation. Results were similar when the analysis was repeated in the subset of children < 2 years of age or when evaluating the association of postoperative BNP and AKI.

Conclusions—Preoperative BNP levels did not predict postoperative AKI in this cohort of children undergoing cardiac surgery. Both pre- and postoperative BNP levels are associated with post-operative outcomes.

Keywords

kidney, renal failure; pediatric; surgery, complications

INTRODUCTION

Acute kidney injury (AKI) occurs in up to 42% of children after cardiac surgery (1). Mortality associated with postoperative AKI ranges from 20% to 79% for children requiring postoperative dialysis (2, 3). Risk factors for postoperative AKI in children are non-specific and include higher preoperative serum creatinine, younger age, cyanotic heart lesions, duration of cardiopulmonary bypass, and postoperative low cardiac output syndrome (1, 4, 5). Because these risk factors do not fully account for postoperative AKI risk, there is an interest in identifying biomarkers for use as predictors of postoperative AKI in children.

Brain natriuretic peptide (BNP) and its precursor N-terminal pro-B-type natriuretic peptide (NTproBNP) are natriuretic peptide biomarkers that have been studied in children and adults with cardiac disease (6, 7). Multiple studies in children undergoing cardiac surgery have demonstrated an association between elevated preoperative BNP and NTproBNP levels with poor outcomes. These adverse postoperative outcomes are also more frequent in children with postoperative AKI (8). Although it is possible that the associations between preoperative BNP or NTproBNP levels with these outcomes are partially due to their associations with postoperative AKI, there are limited published data available to confirm this premise. In a recent multicenter prospective study of high-risk adult patients undergoing cardiac surgery, preoperative BNP was associated with postoperative AKI, and its addition to models that included traditional risk factors for AKI resulted in moderate increases in their predictive abilities (9). Based on these findings, we sought to evaluate whether preoperative BNP also predicts the development of postoperative AKI and other clinical outcomes in a multicenter pediatric cardiac surgery cohort.

MATERIAL AND METHODS

Study Population

Pediatric patients older than 1 month and younger than 18 years of age undergoing surgery for congenital cardiac lesions at three academic medical centers in North America were prospectively enrolled between July 2007 and December 2009. These patients represent the

pediatric subset of the Translational Research Investigating Biomarker Endpoints in Acute Kidney Injury (TRIBE-AKI) (10). A history of prior renal transplantation or dialysis requirement were the only exclusion criteria. Written consent from the parents or legal guardians and assent when appropriate was obtained prior to enrollment, and the study was approved by each institution's research ethics board.

Definitions

Mild AKI was defined by creatinine criteria for Acute Kidney Injury Network (AKIN) stage 1 or higher: an absolute creatinine increase 0.3 mg/dL or a 50% relative increase (11). Severe AKI was defined by AKIN stage 2 or higher: either a doubling of creatinine or the requirement of acute renal replacement therapy. We evaluated length of stay in the intensive care unit (ICU) (> 2 days), length of stay in hospital (> 5 days) and duration of ventilation (> 2 days) as clinically relevant outcomes (with threshold above or below the median duration).

Statistical Analyses

The cohort was categorized into tertiles using preoperative serum BNP levels. The linear trend was tested by the Cochran-Armitage test for binary outcomes and Jonckheere-Terpstra test for continuous outcomes. All continuous variables were compared between tertiles by Wilcoxon rank-sum test or Kruskal Wallis test and dichotomous variables are compared by Chi-square test. We estimated unadjusted and adjusted relative risk (RR) of AKI by using multivariate Poisson regression models with robust error variance method. Models were adjusted for covariates used in previous studies for prediction of AKI after cardiac surgery (1, 10), including age (per year), gender, race, surgery type (eg, elective or urgent and use of cardiopulmonary bypass), cardiopulmonary bypass time, Risk Adjustment in Congenital Heart Surgery (RACHS-1) score, percentile preoperative estimated glomerular filtration rate (eGFR) and site. Site was used as a fixed effect in these models. Similar models were used for non-AKI outcomes, including length of hospital stay, length of ICU stay, and duration of mechanical ventilation (all in days). We used the median to dichotomize each of these non-AKI outcomes: length of hospital stay more than 5 days, length of ICU stay more than 2 days, and ventilation more than 2 days. To evaluate the performance of pre-operative serum BNP, we used 3 methods: 1) the area under the receiver-operating characteristic curve (AUC), 2) the continuous net reclassification index (NRI) with preoperative serum BNP, and 3) the integrated discrimination improvement (IDI) index. DeLong test was used for the determination of increment in AUC after addition of BNP. A p-value < 0.05 was considered statistically significant. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Study cohort

We studied 277 children with available preoperative serum BNP levels. Of those, 135 (49%) were older than 2 years of age, 156 (56%) were male and 226 (82%) were white. Of those children, 273/277 (99%) underwent surgery requiring cardiopulmonary bypass and 22/277 (8%) required non-elective surgery. Baseline characteristics differed significantly across the 3 serum BNP tertiles (Table 1).

Outcomes

Mild postoperative AKI occurred in 118 children (43%). A higher proportion of children with mild postoperative AKI were in the highest tertile of preoperative serum BNP (Table 2), however there was no significant trend across the tertiles. Severe postoperative AKI occurred in 47 children (17%), and there was a non-significant trend towards a higher proportion of children with severe postoperative AKI across the 3 preoperative serum BNP tertiles (Table 2). Increase from preoperative serum BNP to postoperative serum BNP was not associated with a statistically significant increase in risk of postoperative mild or severe AKI (Table 2).

A total of 6 children (2%) died, of whom 5 required postoperative dialysis. The 6 deaths were equally distributed across the 3 preoperative serum BNP tertiles. Both mean hospital and ICU lengths of stay increased across the 3 preoperative serum BNP tertiles (Table 2; $p<0.001$). Only 43 children (16%) required postoperative mechanical ventilation >2 days and 12 children (5%) required postoperative mechanical ventilation >7 days. The proportion of children requiring mechanical ventilation for >2 days increased across the 3 preoperative serum BNP tertiles ($p=0.03$). Preoperative serum BNP in the third tertile was associated with increased ICU length of stay >2 days in unadjusted and adjusted analyses (Table 3). A preoperative serum BNP in the third tertile was associated with higher risk of postoperative mechanical ventilation >2 days and increased hospital length of stay in unadjusted analyses. However, this association did not persist in adjusted analyses (Table 3). While such trends were similar for preoperative serum BNP levels in the second tertiles, they did not reach statistical significance in adjusted or unadjusted analyses.

Diagnostic Testing and Risk Prediction

The ability of preoperative serum BNP to classify mild and severe AKI, length of ICU stay >2 days, length of mechanical ventilation >2 days or length of hospitalization >5 days was poor, with area under the receiver operating characteristics curve (AUC-ROC) values ranging from 0.55 (SE=0.04) for mild AKI to 0.67 (SE=0.03) for ICU length of stay >2 days (Table 4). The AUC-ROCs of the clinical models were generally higher, and adding preoperative serum BNP values to the clinical models did not significantly improve discrimination (Table 4). Preoperative serum BNP did not significantly impact risk prediction of any of the outcomes of interest as demonstrated by both the NRI and the IDI (Table 4).

COMMENT

In this large prospective study of children undergoing cardiac surgery, we did not find a statistically significant association between preoperative serum BNP levels and the incidence of mild and severe postoperative AKI. The ability of preoperative serum BNP levels to classify patients by AKI status was poor, and the addition of preoperative serum BNP levels to clinical models of AKI risk prediction did not significantly improve risk prediction. However, we found that increasing preoperative serum BNP levels were associated with prolonged length of intensive care unit and hospital stays, as well as the need for mechanical ventilation lasting more than two days. To our knowledge, this is the

first prospective study evaluating the association between preoperative serum BNP levels and AKI in children.

AKI occurs frequently after pediatric cardiac surgery, and even mild forms are associated with significant mortality (1, 8). Because of the inherent delay in serum creatinine rise, the traditional method to diagnose AKI, there has been an increasing interest in identifying biomarkers of AKI. Natriuretic peptides are a class of peptides studied in adults and children with cardiovascular and renal disease (6, 12). Elevated preoperative serum BNP levels were found to be associated with postoperative AKI in a series of 1139 high-risk adult patients undergoing cardiac surgery (9). The presumed pathophysiologic mechanism of this association is an increase in serum BNP concentration due to ventricular myocardial wall stress seen with volume overload, which is associated with increased venous pressure, and decreased renal perfusion and filtration (12, 13). We speculated that a similar mechanism would be present among children undergoing cardiac surgery. However, our findings did not support this theory, as we did not find a significant association between preoperative serum BNP levels and AKI.

In adults, serum BNP and NTproBNP elevations are associated with cardiac events and mortality in non-cardiovascular (14, 15) and cardiovascular operations (16, 17). In a prospective series of 40 children undergoing elective cardiac surgery, preoperative serum NTproBNP elevation was associated with increased risk of prolonged postoperative inotropic therapy even after adjusting for other risk factors, but there was no report of increased risk of AKI (18). Similar findings were reported in 38 children undergoing surgical repair of left ventricular volume loading lesions, where preoperative serum NTproBNP levels correlated with duration of mechanical ventilation and intensive care and hospital length of stay (19). We found a similar association between elevated preoperative serum BNP levels and prolonged intensive care unit and hospital length of stay in our cohort, but did not find a significant association with AKI. We mostly have to speculate as to why preoperative serum BNP levels in children would predict prolonged post-operative courses in a similar fashion than in adults, but fail to do the same for AKI. In adults, the range of preoperative serum BNP levels was significantly higher than in our cohort. In our cohort, the median preoperative BNP levels of the highest tertile (51.32 pg/ml) corresponded to the upper limit of the 2nd quintile of the adult cohort (56 pg/ml), that was not significantly associated with postoperative AKI (9). However, the overall rate of AKI in our cohort was high compared to other pediatric studies, suggesting that our patient population was at high risk of developing AKI. Another possible explanation for the difference in predictive ability of preoperative BNP levels in adults and children may be the mechanism of cardiac dysfunction. In adults with the highest NTproBNP levels and associated poor outcomes, left ventricular ejection fraction was <50% in 49% of cases, and 48% of patients had a history of prior myocardial infarction (20). Similarly, 48% of high-risk adult patients in whom an association between preoperative serum BNP levels and AKI was described underwent coronary artery bypass grafting, 26% had a diagnosis of heart failure and 21% had a left ventricular ejection fraction below 40% (9). In our pediatric cohort, the most common operations were closures of atrial, ventricular and atrio-ventricular septal defects, as well as replacement of pulmonary valves and right ventricular to pulmonary artery conduits. These lesions typically lead to volume overload of the ventricles with ventricular dilation.

Decrease in ventricular systolic function is less common and is rarely related to coronary ischemia. It is conceivable that these differences in pathophysiology lead to different BNP responses and thus different associations between BNP levels and AKI risk.

Multiple studies have evaluated natriuretic peptides in infants and young children, both with respect to diagnosis of cardiac disease (21) and management in particular of patent ductus arteriosus (22, 23). To rule out a potential association between BNP levels and AKI in this subset of children, we repeated our analysis limiting ourselves only to children <2 years of age. Again, we did not find a significant association between preoperative serum BNP levels and AKI, but elevated serum BNP levels were again associated with intensive care unit length of stay.

The strengths of our study include its prospective nature, multi-institutional data source, and the use of standardized definition of AKI (11). We also specifically evaluated the isolated outcome of AKI, rather than include symptoms of impaired renal function in a broader definition of postoperative low cardiac output syndrome (24). The limitations of our study are primarily related to the study cohort. Overall serum BNP levels, while abnormal, were significantly lower than in the adult population suggesting that thresholds for normal values likely differ among adults and children. Assuming an adult upper limit of normal serum BNP value of 25pg/ml, 80% of adult patients had elevated preoperative serum BNP levels in the only adult study reporting an association between BNP and AKI (9). This is in contrast to our study where 75% of children two years of age or older had a preoperative BNP level <22.2pg/ml, and 75% of children younger than two years of age had a preoperative BNP level <47.5pg/ml. It is conceivable that the inclusion of children with higher preoperative serum BNP levels might have allowed us to identify an association between higher preoperative BNP values and AKI, and that our study was underpowered to unmask an association between lower levels of preoperative BNP with AKI. This assumption is supported by the fact that there was a trend towards increased odds of AKI across the 3 preoperative BNP tertiles. Details of the cardiopulmonary bypass procedure including the use of modified ultrafiltration was not collected as part of this study, and the majority of children enrolled underwent elective, lower risk surgeries, as evidenced by a RACHS score of 3 or less in 96% of the cohort and. Thus, our findings may not be generalizable to children undergoing higher complexity cardiac surgeries including neonates (<1 month of age), who were excluded from the original study due to their dynamic baseline kidney function and the lack of normative data for AKI biomarkers.

In summary, our study supports previous reports that elevated preoperative serum BNP levels are associated with postoperative outcomes in children undergoing elective cardiac surgery. In contrast to the adult TRIBE population, we did not observe an association with AKI, which constitutes a new finding in this patient population that may reflect differences in the physiology of cardiac dysfunction or BNP levels across the age spectrum.

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Table 1Patient Characteristics by Preoperative Serum Brain Natriuretic Peptide.^a

	All (N=277)	Tertile 1 (N= 91)	Tertile 2 (N= 94)	Tertile 3 (N= 92)	P
		(< 5.5 pg/ml)	(5.5 - 26.8 pg/ml)	(>26.8 pg/ml)	
Demographics					
Age, years	3.8 (4.5)	4.6 (4.66)	4.0 (4.39)	2.8 (4.28)	<.001
Male	156 (56%)	53 (58%)	48 (51%)	55 (60%)	0.44
White Race	226 (82%)	73 (80%)	78 (83%)	75 (82%)	0.89
Pre-operative variables					
Pre-op eGFR, ^b median[IQR], mL/min per 1.73m ²	88.11 [72.79, 104.9]	93.61 [76.7, 107.9]	90.86 [80.95, 108.41]	80.88 [62.23, 96.71]	<0.001
Pre-op eGFR percentile	56 [20, 86]	46 [21, 85]	66.5 [31, 87]	52.5 [15, 85]	0.23
Pre-op ACE inhibitors	50 (18%)	17 (19%)	13 (14%)	20 (22%)	0.36
Pre-op Beta Blockers	9 (3%)	1 (1%)	3 (3%)	5 (5%)	0.26
Pre-op Aspirin	31 (11%)	13 (15%)	9 (10%)	9 (10%)	0.48
Operative variables					
Palliative Surgery	37 (13%)	16 (18%)	10 (11%)	11 (12%)	0.34
RACHS Score					
1	17 (6%)	10 (11%)	7 (8%)		0.02
2	134 (49%)	41 (46%)	51 (55%)	42 (46%)	0.02
3	112 (41%)	36 (40%)	30 (32%)	46 (50%)	0.02
4	12 (4%)	3 (3%)	5 (5%)	4 (4%)	0.02
CPB time, minutes	106.48 (62.46)	97.95 (62.03)	104.03 (64.5)	117.41 (59.79)	0.01
Cross clamp time, minutes	47.99 (45.65)	37.57 (39.59)	49.82 (47.04)	56.52 (48.25)	0.01

eGFR: estimated glomerular filtration rate, BNP brain natriuretic peptide, IQR interquartile range CPB cardiopulmonary bypass, RACHS-1, risk adjustment for congenital heart surgery, SD standard deviation, ACE angiotensin converting enzyme.

^aValues are mean(SD) or N (%).

^bEstimated GFR (glomerular filtration rate) was calculated by the Schwartz formula. For percentiles of estimated GFR, normative values from children with normal renal function were used for percentile derivation (25, 26)

Table 2

Outcomes by preoperative serum Brain Natriuretic Peptide.^a

	All (N=277)	Tertile 1 (N= 91)	Tertile 2 (N= 94)	Tertile 3 (N= 92)	P
MILD AKI ^b	118 (43%)	37 (41%)	34 (36%)	47 (51%)	0.11
Severe AKI ^c	47 (17%)	12 (13%)	15 (16%)	20 (22%)	0.29
Length of ICU stay, days	3.9 (5.8)	2.55 (2.39)	3.41 (5.86)	5.67 (7.43)	<.001
Length of hospital stay, days	7.66 (8.45)	6.61 (6.8)	6.7 (9.22)	9.6 (8.81)	<.001
Dialysis	5 (2%)	1 (1%)	2 (2%)	2 (2%)	0.83
Mortality	6 (2%)	2 (2%)	2 (2%)	2 (2%)	0.99
Dialysis or mortality	6 (2%)	2 (2%)	2 (2%)	2 (2%)	0.99
Ventilation >2 days	43 (16%)	8 (9%)	14 (15%)	21 (23%)	0.03
Ventilation >7 days	12 (5%)	2 (2%)	2 (2%)	8 (9%)	0.03

^aValues are mean(SD) or N (%).

^bMild AKI was defined by creatinine criteria for Acute Kidney Injury Network (AKIN) stage 1 or higher: an absolute creatinine increase 0.3 mg/dL or a 50% relative increase.

^cSevere AKI was defined by AKIN stage 2 or higher: either a doubling of creatinine or the requirement of acute renal replacement therapy.

Table 3

Association of Preoperative Serum Brain Natriuretic Peptide with Outcomes

	RR (95% CI)	BNP tertile ^a			P
		T1 (<5.5 pg/ml)	T2 (5.5-26.8 pg/ml)	T3 (>26.8 pg/ml)	
Mild AKI^b	Unadjusted	ref	0.89 (0.62, 1.28)	1.26 (0.91, 1.73)	0.11
	Adjusted	ref	0.76 (0.54, 1.07)	1 (0.73, 1.38)	
Severe AKI^c	Unadjusted	ref	1.21 (0.6, 2.44)	1.65 (0.86, 3.17)	0.29
	Adjusted	ref	0.88 (0.44, 1.77)	1.32 (0.72, 2.43)	
Length of ICU stay >2 days	Unadjusted	ref	1.17 (0.78, 1.76)	2.15 (1.54, 3.01)	0.11
	Adjusted	ref	1.22 (0.84, 1.75)	1.92 (1.42, 2.6)	
Length of hospital stay >5 days	Unadjusted	ref	1.03 (0.7, 1.52)	1.55 (1.1, 2.16)	0.29
	Adjusted	ref	1.04 (0.73, 1.48)	1.32 (0.95, 1.84)	
Ventilation >2 days	Unadjusted	ref	1.69 (0.75, 3.84)	2.6 (1.21, 5.56)	0.11
	Adjusted	ref	1.37 (0.6, 3.15)	1.67 (0.76, 3.69)	

^a AKI acute kidney injury, RR relative risk, 95% CI 95% confidence interval

^b Mild AKI was defined by creatinine criteria for Acute Kidney Injury Network (AKIN) stage 1 or higher: an absolute creatinine increase 0.3 mg/dL or a 50% relative increase.

^c Severe AKI was defined by AKIN stage 2 or higher: either a doubling of creatinine or the requirement of acute renal replacement therapy.

Table 4
Areas Under the Receiver-Operating Characteristics curve, Continuous Net Reclassification Index (NRI), and Integrated Discrimination Improvement (IDI) of Preoperative Brain Natriuretic Peptide for Outcomes

	Mild AKI	Severe AKI	Length of ICU stay >2 days	Length of hospital stay >5 days	Ventilation >2 days
Area under the ROC curve, (SE)					
Serum BNP	0.55 (0.04)	0.57 (0.05)	0.67 (0.03)	0.59 (0.04)	0.66 (0.05)
Clinical Model ^a	0.79 (0.03)	0.84 (0.03) 0	.82 (0.03)	0.81 (0.03)	0.76 (0.04)
Serum BNP+Clinical Model ^a	0.79 (0.03)	0.84 (0.03)	0.84 (0.03)	0.82 (0.03)	0.77 (0.04)
Reclassification Indices					
NRI (SE) ^b	-0.04 (0.12)	0.07 (0.16)	-0.35 (0.42)	-0.15 (0.39)	0.12 (0.17)
IDI (SE) ^b	0.0009 (0)	0.017 (0.03)	0.03 (0.01)	0 (0.01)	0.03 (0.03)

NRI Continuous Net Reclassification Index, IDI Integrated Discrimination Improvement

^aClinical model includes age, male gender, Caucasian race, surgery type, cardiopulmonary bypass time, RACHS-1 score, percentile pre-op estimated glomerular filtration rate and site.

^b All p-values not significant