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ORIGINAL RESEARCH

Association of Preoperative Diuretic Use With Early Acute Kidney Injury in Infants With Biventricular Hearts Following Cardiac Surgery

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BACKGROUND: Diuretics are used to manage congestive heart failure in infants with congenital heart disease. Adult data indicate that preoperative diuretic use increases the risk of cardiac surgery associated acute kidney injury (CS-AKI). We have sought to understand if preoperative diuretics in infants increases the risk of CS-AKI.

METHODS AND RESULTS: This is a single-center retrospective study of infants (1–12 months) who had CS requiring cardiopulmonary bypass between 2013 and 2018. The diagnosis and severity of CS-AKI was defined according to the Kidney Disease Improving Global Outcomes guidelines. Three hundred patients were included (mean 6 months, SD 2.4, range 1.2–12.9 months). A total of 149 (49.7%) patients were diagnosed with CS-AKI (stage 1: 80 [54%], stage 2: 57 [38%], stage 3: 12 [8%]). Logistic regression analysis showed preoperative diuretics were not associated with CS-AKI (odds ratio [OR], 0.79; 95% CI, 0.43–1.44; *P*=0.45). A diagnosis of tetralogy of Fallot was an independent risk factor for CS-AKI (OR, 3.49; 95% CI, 1.33–9.1, *P*=0.01). A diagnosis of tetralogy of Fallot (OR, 3.6; 95% CI, 1.28–10.22; *P*=0.02) and longer cardiopulmonary bypass (OR, 1.01; 95% CI, 1.0–1.02; *P*=0.04) time are risk factors for moderate to severe CS-AKI.

CONCLUSIONS: Preoperative diuretic use does not contribute to the risk of CS-AKI in infants early after surgery. A diagnosis of tetralogy of Fallot was the only risk factor for CS-AKI identified using multivariate analysis in our cohort. Furthermore, a diagnosis of tetralogy of Fallot and longer cardiopulmonary bypass time are risk factors for moderate to severe CS-AKI.

Key Words: congenital cardiac defect ■ diuretics ■ kidney

Diagnosis of cardiac surgery associated acute kidney injury (CS-AKI) is recognized as a significant complication in both pediatric and adult populations that is associated with increased morbidity and mortality.[1–5] Infants and neonates are at particularly high risk of CS-AKI following surgery for congenital heart disease with an incidence that is reported to be between 16% and 55%.[1–6] Surgical complexity, patient age, nephrotoxin exposure, preoperative ventilation, duration of cardiopulmonary bypass (CPB), and intraoperative hypotension are CS-AKI risk factors that have been previously described in children.[2,3,5,7–9]

Diuretic therapy is a mainstay in pre-operative medical management of congenital heart disease to control the symptoms of congestive heart failure (CHF) that are common in many lesions that require surgical repair in infancy.[10,11] The potential for nephrotoxicity of loop diuretics in critically ill pediatric patients has been previously demonstrated,[12] but this phenomenon has not been investigated in pediatric patients undergoing congenital heart surgery.

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CLINICAL PERSPECTIVE

What Is New?

- Cardiac surgery associated acute kidney injury is a common postoperative morbidity, and it is prudent for mechanisms to be in place to identify patients with cardiac surgery associated acute kidney injury, stratify them with respect to severity, and provide appropriate follow-up and consultation with nephrology.
- Given the routine use of diuretics in infants with congenital heart disease, understanding their impact on the risk of a postoperative acute kidney injury is important from the point of view of stratifying patients who may require closer monitoring of kidney function postoperatively.

What Are the Clinical Implications?

- Diuretic use in infants with congenital heart disease before cardiac surgery for management of congestive heart failure does not increase the risk of postoperative cardiac surgery associated acute kidney injury early after cardiac surgery.

Nonstandard Abbreviations and Acronyms

AKI	acute kidney injury
AVSD	atrioventricular septal defect
CPB	cardiopulmonary bypass
CS-AKI	cardiac surgery associated acute kidney injury
DORV	double outlet right ventricle
KDIGO	Kidney Disease Improving Global Outcomes Guidelines
SCr	serum creatinine
TOF	tetralogy of Fallot

A single large study in the adult population following CS has demonstrated that preoperative diuretic therapy is a risk factor for postoperative renal dysfunction.[13] The authors postulated that this may be because of intraoperative and postoperative hypotension and hypovolemia secondary to preoperative diuretic use. Furthermore, it has been postulated that aciduria caused by loop diuretics can cause nephrotoxic methemoglobin cast formation in the presence of hemolysis from cardiopulmonary bypass.[14] Despite the differences in the spectrum of heart disease in adult and pediatric patients, these hypotheses are applicable to both populations. The potential for nephrotoxicity of loop diuretics in critically ill pediatric patients has been previously demonstrated,[12] but this phenomenon has not been investigated in pediatric patients undergoing congenital heart surgery. Given the routine use of diuretics in patients with congenital heart disease, understanding the impact of these medications on the risk of a postoperative AKI is important from the point of view of stratifying patients who may require closer monitoring of kidney function and long-term renal follow-up.

Our primary objective was to assess whether preoperative diuretic therapy in infants between the ages of 1 to 12 months increases the risk of CS-AKI early after CS. Secondary outcome measures include the incidence and severity of CS-AKI in infants and patient-related risk factors contributing to a diagnosis of CS-AKI.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Cohort and Clinical Data

This was a retrospective cohort study that included consecutive infants with biventricular hearts aged 1 to 12 months who underwent CS requiring CPB at British Columbia Children's Hospital between January 1, 2013 and December 31, 2018. This study was approved by the University of British Columbia Research Ethics Board (reference number H18-02333). The requirement for patient consent was waived. Patients were excluded from analysis if they previously had CS requiring CPB or single ventricle physiology. All surgical procedures were performed at a single center and CPB was performed according to standardized protocols by the same perfusion team. All patients underwent modified ultrafiltration following discontinuation of CPB. A preoperative ultrasound was performed in a subset of the population, and those who were identified as having a preexisting structural renal abnormality were also excluded from the study population. Both the risk adjustment for surgery for congenital heart surgery method and Aristotle comprehensive complexity score were used to risk stratify patients based on diagnoses, surgical procedure performed, and comorbidities.[15,16] AKI was defined as a rise in serum creatinine (SCr) >50% from preoperative baseline or <0.5 mL/kg per hour of urine output for any 6-hour period postoperatively as defined by the Kidney Disease Improving Global Outcomes Guidelines (KDIGO) classification, which is recommended for use in pediatric populations.[17,18] All patients had a baseline SCr within 1 week before surgery and a postoperative SCr within 24 hours after surgery. Further measurement of SCr beyond

postoperative day 1 was not routinely performed and done so at the discretion of the treating physicians. Urine output was measured over 6-hour intervals for the first 18 hours postoperatively in the cardiac intensive care unit while an indwelling catheter was in place. Patients who met the KDIGO criteria to have CS-AKI based on either the SCr or urine output criteria were further classified to have either mild (stage 1), moderate (stage 2), or severe (stage 3) AKI according to the KDIGO classification system (Table S1).[17,18] The severity of CS-AKI for each patient was classified based on the parameter that yielded the highest stage of severity.

Clinical data were obtained from medical records. Preoperative diuretic use in this study refers to any patient taking the loop diuretic furosemide as this was the preferential mode for management of infants with CHF at our center. The decision to start diuretics was at the discretion of the most responsible cardiologist for each patient based on the onset of symptoms that were consistent with CHF due to a hemodynamically significant left to right shunt. The dose range of furosemide was between 1 and 3 mg/kg per day divided 1 to 3 times per day and was administered orally in all cases. Most patients were concurrently taking spironolactone 1 to 2 mg/kg per day divided 1 or 2 times daily. Diuretic therapy was started at the discretion of the most responsible cardiologist at the onset of CHF symptoms in the preoperative period. Preoperative parameters included age and weight at surgery, cardiac diagnosis, risk adjustment for surgery for congenital heart surgery-1 classification, Comprehensive Aristotle Score, use of furosemide, shock, invasive or noninvasive ventilation, and extracorporeal life support. Intraoperative parameters included CPB time, aortic cross-clamp time, hypotension defined by mean arterial blood pressure <50 mm Hg for 2 or more readings,[7] and requirement for vasoactive agents (dopamine, epinephrine). Postoperative parameters included diagnosis of CS-AKI, CS-AKI severity (stage 1, 2, or 3), invasive or noninvasive ventilation, vasoactive agent use (epinephrine, dopamine, milrinone), arrhythmia or conduction abnormality (junctional rhythm, heart block, sinus node dysfunction, supraventricular tachycardia), cardiac arrest, extracorporeal life support, mortality, cardiac intensive care unit admission duration, and hospital admission duration.

Statistical Analysis

STATA statistical data analysis software v.14.2 (StataCorp LLC, College Station, TX) was used for calculation of descriptive statistics and to perform univariate analyses, and multiple logistic regression analyses. Descriptive statistics include mean and 95% CIs or range for patient variables. Univariate analysis included Fisher's exact test and chi-square analysis for categorical variables, and both 1-sample and 2-sample *t* tests for comparison of group means (2 tailed). Multiple logistic regression analyses were performed to determine the odds for a diagnosis of CS-AKI (defined as CS-AKI stages 1, 2, or 3; referent: no injury), with potential explanatory variables previously identified from univariate analysis. Multiple logistic regression analyses were also performed to determine the odds for a diagnosis of a moderate-to-severe diagnosis of CS-AKI (defined as CS-AKI stages 2 or 3; referent: mild [stage 1] CS-AKI or no injury), with potential explanatory variables previously identified from univariate analysis. A *P* value of <0.05 was considered statistically significant. Calculation of relative risk was performed using R ver. 3.6.2 and R Studio v 1.0.143 (R Foundation, Vienna, Austria).

RESULTS

Demographics

A total of 319 patients were assessed for inclusion in the study with a total of 300 meeting inclusion criteria. Among 319 infants between 1 and 12 months of age with biventricular physiology who underwent cardiopulmonary bypass for the first time, 7 patients were excluded because of a structural renal abnormality on ultrasound, and 12 patients were excluded because of missing data from the medical record. Diagnoses included tetralogy of Fallot (TOF), atrioventricular septal defect (AVSD), ventricular septal defect (VSD), double outlet right ventricle (DORV), tetralogy of Fallot (TOF) with multiple aortopulmonary collateral arteries total anomalous pulmonary venous return, TOF with AVSD, and "other" diagnoses that consisted of an additional 7% of the sample. Patient demographics along with those exposed to preoperative diuretics are displayed in Table 1. Further detail on the distribution of subtypes for patients with DORV and total anomalous pulmonary venous return and their respective exposure to preoperative diuretics is shown in Table S2.

A total of 157 (52%) of patients used furosemide before CS. The demographics, preoperative, operative, and postoperative parameters of all patients according to their exposure to preoperative diuretics are displayed in Table 1 along with results from univariate analysis. Variables with a significant association with no preoperative diuretic use included higher weight, older age at surgery, a diagnosis of TOF, higher Aristotle Complexity Score, and longer CPB time. There was a significant association between preoperative diuretic use and a diagnosis of either VSD or AVSD.

Table 1. Patient Demographics and Preoperative, Intraoperative, and Postoperative Parameters for the Entire Cohort According to Exposure to Preoperative Diuretics

Variable	All patients	Preoperative diuretic use	No preoperative diuretic use	*P* value
n	300	157	143	0.420
Sex, n (% male)	158 (53)	81 (52)	77 (54)	0.696
Age, mo, mean (95% CI)	5.98 (5.7–6.2)	5.4 (5.1–5.7)	6.7 (6.2–7.1)	<0.001
Weight, kg, mean (95% CI)	5.8 (5.7–6)	5.2 (5.1–5.4)	6.4 (6.2–6.7)	<0.001
Diagnosis, n (%)				
TOF	60 (20)	3	57	<0.001
AVSD	42 (14)	33	9	<0.001
Ventricular septal defect	137 (45.7)	102	35	<0.001
Double outlet right ventricle	21 (7)	8	13	0.286
TOF/multiple aortopulmonary collateral arteries	5 (1.7)	1	4	0.208
Total anomalous pulmonary venous return	12 (4)	4	8	0.266
TOF/AVSD	3 (1)	0	3	N/A
Other	20 (6.7)	6	14	0.072
Preoperative parameters				
Risk adjustment for surgery for congenital heart surgery				
1	1 (0.3)	0	1	N/A
2	202 (67.3)	105	97	0.575
3	89 (29.7)	49	40	0.343
4	8 (2.7)	3	5	0.517
Aristotle score, mean (95% CI)	8 (1.9)	7.7 (7.4–8)	8.3 (8–8.6)	0.007
Intraoperative parameters				
Cardiopulmonary bypass time, min, mean (95% CI)	90.2 (85.2–95.2)	81.2 (75.1–87.3)	100.4 (92.4–108.4)	<0.001
Cross-clamp time, min, mean (95% CI)	53.3 (50–56.6)	50.5 (45.8–55.2)	56.5 (51.7–61.3)	0.085
Hypotension, n (%)	62 (21)	35	27	0.449
Vasoactive agent use, n (%)	52 (17)	26	26	0.711
Postoperative parameters				
Ventilation (invasive/noninvasive), n (%)	71 (24)	30	41	0.052
Vasoactive agent use, n (%)	126 (42)	52	74	0.001
Junctional rhythm, n (%)	49 (16)	27	22	0.671
Heart block, n (%)	17 (5.7)	7	10	0.343
Cardiac arrest, n (%)	4 (1.3)	0	4	0.050
Extracorporeal life support, n (%)	4 (1.3)	1	3	0.351
Mortality, n (%)	3 (1)	1	2	0.607
Cardiac intensive care unit admission duration, d, mean, (95% CI)	2.8 (1.8–3.8)	2.2 (1.7–2.7)	3.5 (1.5–5.5)	0.190
Hospital admission duration, d, mean, (95% CI)	5.8 (4.8–6.8)	5 (4.5–5.5)	6.7 (4.6–8.8)	0.109

Results from univariate analysis are shown. Vasoactive agents include any of epinephrine, dopamine, and/or milrinone. AVSD indicates atrioventricular septal defect; and TOF, tetralogy of Fallot.

Preoperative Diuretic Use and Impact on CS-AKI

The distribution of CS-AKI in all patients and according to patient demographics and diagnoses is shown in Table 2. The incidence of CS-AKI in infants within 24 hours after CS was 49.7% (149/300) with 122 (41%) patients meeting the SCr criteria, 17 (6%) patients meeting the oliguric criteria, and 10 patients satisfying both criteria (Table 2 and Table S3). Among the patients who developed CS-AKI, the severity was stage 1 in 53.7% (80/149), stage 2 in 38.2% (57/149), and stage 3 in 8.1% (12/149). There were no patients who had a peritoneal dialysis catheter inserted following CS, and no patients in this cohort required continuous renal replacement therapy. The incidence of CS-AKI was equivalent between sexes with 50.3% incidence in female infants and 40.7% in male infants (P=0.3) (Table 2). Both older age and weight at the time of surgery were associated with an increased incidence of CS-AKI. Tetralogy of Fallot was the only diagnosis with

Table 2. Patient Demographics and Parameters Evaluated From Preoperative, Intraoperative, and Postoperative Course With Respect to the Presence or Absence of Postoperative Acute Kidney Injury

Variable	CS-AKI	No CS-AKI	*P* value
n (%)	149 (49.7)	151 (50.3)	0.91
AKI stage 1, n (%)	80 (54)	/	
AKI stage 2, n (%)	57 (38)	/	
AKI stage 3, n (%)	12 (8)	/	
Sex, n			
Male	74	84	0.3
Female	75	67	
Age, mo, mean (95% CI)	6.5 (6.1–6.9)	5.5 (5.1–5.9)	<0.001
Weight, kg, mean (95% CI)	6.1 (5.8–6.3)	5.6 (5.3–5.8)	0.02
Diagnosis, n (%)			
TOF	43 (72)	17 (28)	<0.001
AVSD	23 (55)	19 (45)	0.54
VSD	51 (37)	86 (63)	0.003
DORV	14 (67)	7 (33)	0.13
TOF/multiple aortopulmonary collateral arteries	3 (60)	2 (40)	0.65
Total anomalous pulmonary venous return	2 (17)	10 (83)	0.013
TOF/AVSD	3 (100)	0 (0)	N/A
Other	10 (50)	10 (50)	1
Preoperative parameters			
Risk adjustment for surgery for congenital heart surgery-1			
1	1	0	0.3
2	94	108	
3	50	39	
4	4	4	
Aristotle score, mean (95% CI)	8.3 (8.0–8.6)	7.7 (7.4–8.0)	0.004
Diuretic use, n			
All patients	65	92	0.03
AVSD+VSD+DORV	61	82	0.08
Intra-operative parameters			
Cardiopulmonary bypass time, min, mean (95% CI)	99.7 (91.4–108.0)	81.2 (75.5–86.0)	<0.001
Cross-clamp time, min, mean (95% CI)	58.7 (53.5–63.9)	48.1 (43.8–52.4)	0.002
Hypotension, n	28	34	0.44
Vasoactive agent use, n	29	23	0.33
Postoperative parameters			
Ventilation (invasive/noninvasive), n	37	34	0.64
Vasoactive agent use, n	69	57	0.13
Junctional rhythm, n	24	25	0.92
Heart block, n	11	6	0.2
Cardiac arrest, n	4	0	N/A
Extracorporeal life support, n	3	1	N/A
Mortality, n	3	0	N/A
Cardiac intensive care unit admission duration, d, mean (±SD)	2.9 (2.3–3.5)	2.8 (0.8–4.7)	0.89
Hospital admission duration, d, mean (±SD)	6.1 (5.4–6.8)	5.5 (3.6–7.5)	0.55

Results from univariate analysis are shown. Vasoactive agents include any of epinephrine, dopamine, and/or milrinone. AVSD indicates atrioventricular septal defect; CS-AKI, cardiac surgery associated acute kidney injury; DORV, double outlet right ventricle; TOF, tetralogy of Fallot; and VSD, ventricular septal defect.

a significantly increased risk of AKI among those operated on in our cohort (CS-AKI 43 [72%], no CS-AKI 17 [28%], *P*=0.0005).

Exposure to diuretics preoperatively did not increase the risk of AKI postoperatively early after CS (Table 2). This was demonstrated using separate analyses for the entire cohort of patients as well as a subgroup consisting of diagnoses that commonly have a hemodynamically significant left to right shunts (VSD, AVSD, and DORV). Univariate analysis that included all patients in the cohort shows a significantly higher number of patients who developed CS-AKI postoperatively who were not exposed to diuretics preoperatively (AKI 65/149 [44%], no AKI 92/151 [61%], *P*=0.03). The same analysis on the subgroup with left to right shunts showed that there was no statistically significant difference in the incidence of CS-AKI between patients who were exposed to preoperative diuretics and those who were not (AKI 61/149 [41%], 82/151 [54%], *P*=0.08). A similar result was found on assessment of the relative risk for CS-AKI following preoperative diuretic use. The relative risk of CS-AKI after exposure to preoperative diuretics in all patients is 0.71 (95% CI, 0.56–0.89) and 0.92 (95% CI, 0.69–1.22) in patients with a diagnosis of VSD, AVSD, or DORV. Multiple logistic regression was performed that included all patients to assess for significant risk factors for a diagnosis of CS-AKI. A regression model was created that includes the variables and results displayed in Table 3. This analysis demonstrated that preoperative diuretic use is not associated with an increased risk of CS-AKI early after CS (OR, 0.72; 95% CI, 0.41–1.28; *P*=0.27), and a diagnosis of TOF is the only independent variable associated with an increased risk of CS-AKI (OR, 3.89; 95% CI, 1.55–9.77; *P*=0.004).

Risk Factors for Moderate to Severe CS-AKI

Patients who developed an AKI were categorized into having either a mild AKI (stage 1) or moderate to severe (stage 2 or stage 3) according to the KDIGO

Table 3. Multiple Logistic Regression Analysis Assessing the Association Between a Diagnosis of Cardiac Surgery Associated Acute Kidney Injury and Potential Explanatory Variables

Explanatory variable	OR (95% CI)	SE	*P* value
Tetralogy of Fallot (referent: all other diagnoses)	3.89 (1.55–9.77)	1.82	0.004
Ventricular septal defect/atrioventricular septal defect/double outlet right ventricle (referent: all other diagnoses)	1.90 (0.80–4.48)	0.83	0.14
Preoperative diuretics (referent: no diuretics)	0.72 (0.41–1.28)	0.21	0.27
Aristotle score	1.11 (0.95–1.29)	0.09	0.21
Cardiopulmonary bypass time, min	1.01 (0.99–1.01)	0.01	0.33
Cross-clamp time, min	1.00 (0.99–1.01)	0.01	0.95
Intraoperative hypotension (referent: no hypotension)	0.73 (0.39–1.34)	0.23	0.31
Postoperative heart block (referent: no heart block)	1.40 (0.47–4.18)	0.78	0.55

Dependent variable: diagnosis of postcardiac surgery acute kidney injury (defined as any severity [stage 1, 2, or 4] vs no injury). OR indicates odds ratio.

classification[18] (Table 2, Table S1). A total of 69 patients were diagnosed with moderate to severe CS-AKI. Univariate analysis demonstrated that the diagnosis of moderate to severe CS-AKI relative to no AKI or stage 1 AKI is significantly associated with Aristotle Complexity Score, CPB time, cross-clamp time, heart block, cardiac arrest, postoperative extracorporeal life support, and mortality. Preoperative diuretic use was significantly associated with mild or no CS-AKI (Table 4). Multiple logistic regression showed that a diagnosis of TOF and longer CPB time are associated with an increased risk of moderate to severe CS-AKI (Table 5).

DISCUSSION

Our study sheds new light on our understanding of CS-AKI in infants by demonstrating that preoperative diuretic use does not increase the risk of early onset CS-AKI. This is in contrast to what has been shown in adults[13] and is of particular interest to pediatric cardiologists as they strive to optimize preoperative CHF using diuretics without contributing to postoperative morbidity and mortality. Bandeali[13] et al showed with a logistic regression model that in a large cohort of adults undergoing CPB grafting and/or valve surgery, preoperative diuretic use is significantly associated with postoperative renal dysfunction and atrial fibrillation (OR, 1.44; 95% CI, 1.28–1.63).

It is well recognized that postoperative AKI following CS in children is a common complication that is associated with morbidity, mortality, and prolonged hospitalization.[1–5] Operative factors such as surgical complexity, CPB time, cross-clamp time, and use of inotropes have been described to contribute to the risk of postoperative AKI along with an increased risk of developing chronic kidney disease (CKD).[2,3,5,7–9]

Although some risk factors for postoperative AKI have been identified in prior studies,[2,3,5,7–9] there are no data describing the risk of preoperative diuretic use on postoperative AKI in the pediatric population undergoing CS. Diuretics are an essential component in the management of CHF in infants before operative intervention for a variety of congenital heart lesions, but the impact of this practice on the postoperative risk for AKI and CKD long term is unknown. We chose to investigate infants between 1 and 12 months of age because this population includes a large proportion of patients requiring regular diuretic therapy to manage CHF in the context of hemodynamically significant left to right shunts that require surgical intervention. We found from univariate analysis that preoperative diuretic use does not increase the risk of postoperative AKI in this population early after CS. This conclusion holds true whether we investigate the entire cohort or only the subset of diagnoses that are most likely to develop CHF and require diuretic therapy. This group included patients diagnosed with VSD, AVSD, or DORV. Although the relative risk indicated a significantly lower risk of AKI when exposed to preoperative diuretics when considering all diagnoses, this is unlikely to represent a true protective effect of diuretics in this context. Rather, we postulate that this is a reflection of the increased surgical complexity and CPB time that we found in our patients who are not exposed to preoperative diuretics as shown in Table 1. The large proportion of patients with a diagnosis of TOF that are within this segment of the cohort is the most likely explanation for this finding. An alternative explanation that could contribute to this observation is that appropriate preoperative management of CHF using diuretics produces a more optimal surgical candidate that will experience fewer risk factors for developing a CS-AKI such as a prolonged bypass time and/or aortic cross-clamp time.

The significant association between both older age and greater weight at the time of surgery to increased risk of AKI are likely a reflection of the greater age at the time of surgery in patients with TOF relative to patients with a VSD in our cohort (Table S4). This is further supported by our observation that

Table 4. Distribution of CS-AKI Severity, Comparing Patients With Moderate to Severe CS-AKI With Those With a Mild or No CSI-AKI According to Preoperative, Intraoperative, and Postoperative Parameters

Variable	CS-AKI severity		
	No CS-AKI or Stage 1	Stage 2 or 3 CS-AKI	*P* value
n	231	69	
Aristotle score, mean (95% CI)	7.8 (7.6–8.1)	8.5 (8.13–8.92)	0.007
Diuretic use, n (%)	133 (57.6%)	24 (34.8%)	0.001
Cardiopulmonary bypass time (min), mean (95% CI)	84.5 (79.5–89.4)	109 (95.8–123.8)	<0.001
Cross-clamp time, min, mean (95% CI)	51.1 (47.4–54.7)	60.9 (52.7–69.1)	0.016
Ventilation (invasive/noninvasive), n (%)	51 (22.1%)	20 (29.0%)	0.236
Postoperative vasoactive agent use, n (%)	43 (18.6%)	9 (13.0%)	0.283
Junctional rhythm, n (%)	37 (11.2%)	12 (17.4%)	0.786
Heart block, n (%)	9 (3.9%)	8 (11.6%)	0.015
Cardiac arrest, n (%)	0 (0%)	4 (5.8%)	0.003
Extracorporeal life support, n (%)	1 (0%)	3 (4.3%)	0.001
Mortality, n (%)	0 (0%)	3 (4.3%)	0.012
Cardiac intensive care unit admission duration (d) mean, (±SD)	2.6±9.9	3.5±4.5	0.470
Hospital admission duration (d) mean, (±SD)	5.5±10.0	6.8±5.1	0.318

Results from univariate analysis for each parameter are shown. Vasoactive agents include any of epinephrine, dopamine, and/or milrinone. CS-AKI indicates cardiac surgery associated acute kidney injury.

patients who were not exposed to diuretics, which includes the vast majority of patients with TOF, were significantly older and had a greater weight at the time of surgery (Table 1). We recognize that patients with TOF, in general, do not typically require diuretics to manage symptoms of CHF. We chose to retain patients with TOF in our analysis as there is a small population of patients with TOF and a net left to right shunt because they have only a mild right ventricular outflow tract obstruction. There were 3 patients in this cohort with a diagnosis of TOF and a net left to right shunt and they included 1 patient with only mild right ventricular outflow tract obstruction resulting in a predominant left to right shunt across the VSD, 1 patient who had a right ventricular outflow tract stent placed as a neonate and developed symptoms of CHF owing to an unobstructed right ventricular outflow tract, and 1 patient with both TOF and an aortopulmonary window. To address the confounding effect of including patients with TOF on our analysis, we constructed a multiple logistic regression model. By incorporating the diagnoses of TOF and those with either VSD, AVSD, or DORV as separate groups into a model with variables that were identified by univariate analysis as significant or nearly significant, TOF was found to be the only independent risk factor for CS-AKI in our cohort, and preoperative diuretic use was not found to either increase or decrease the risk for CS-AKI.

The incidence of AKI in this population of infants undergoing CS was found to be 49.7%. This represents a high proportion of AKI cases in this population but is within the range of previously published reports.[4] One factor that likely contributes to the relatively high incidence of CS-AKI in our cohort is, in part, the inclusion of both serum creatinine and oliguria in our definition of AKI. Cases of CS-AKI meeting criteria based on oliguria alone constitute 11% (17/149) of

Table 5. Multiple Logistic Regression Analysis Assessing the Association Between a Moderate-to-Severe Diagnosis of CS-AKI and Potential Explanatory Variables

Explanatory variable	OR (95% CI)	SE	*P* value
Tetralogy of Fallot (referent: all other diagnoses)	3.6 (1.28–10.22)	1.92	0.02
Ventricular septal defect/Atrioventricular septal defect/double outlet right ventricle (referent: all other diagnoses)	1.84 (0.66–5.14)	0.96	0.24
Preoperative diuretics (referent: no diuretics)	0.64 (0.32–1.29)	0.23	0.22
Aristotle score	1.12 (0.93–1.34)	0.1	0.23
Cardiopulmonary bypass time, min	1.01 (1.0–1.02)	0.01	0.04
Cross-clamp time, min	0.99 (0.97–1.01)	0.01	0.3

Dependent variable: diagnosis of a moderate-to-severe CS-AKI (defined as stage 2 or 3; vs no or mild [stage 1] CS-AKI). CS-AKI indicates cardiac surgery associated acute kidney injury; and OR, odds ratio.

our total number of cases (Table S3). Further understanding of why our incidence is higher than other reports would require multicenter comparative analysis or prospective analysis of systematic changes within our own practice over time. The distribution of AKI severity included 54% stage 1, 38% stage 2, and 8% stage 3. Acute kidney injury of any severity during a critical illness in children has been demonstrated to be a risk factor for CKD later in childhood.[6,18] Limited studies investigating the risk of CKD relative to increasing severity of AKI suggests that patients with a diagnosis of moderate to severe AKI have a greater risk for CKD than those with mild AKI. Given that 46% of our cohort fell within this category of diagnosis we explored added risk factors for a diagnosis of moderate to severe CS-AKI in infants. Multiple logistic regression using variables that were found to be significant from univariate analysis demonstrated that a diagnosis of TOF and longer CPB time are significantly associated with an increased risk of moderate to severe CS-AKI in infants compared with patients diagnosed with mild CS-AKI or no CS-AKI. Evaluation of risk factors affecting CS-AKI severity demonstrated that diuretic use did not increase the risk of moderate to severe CS-AKI relative to patients with no or mild CS-AKI. Postoperative heart block, extracorporeal life support, cardiac arrest, and mortality were all found to be significantly associated with a diagnosis of moderate to severe CS-AKI from univariate analysis but were not included in the multiple model because of the small number of patients who had these postoperative complications.

Our results suggest that preoperative diuretics do not increase the risk of postoperative AKI early after CS in infants with no history of renal dysfunction. This is contrary to data in the adult population.[13] We are unable to provide an explanation for why our results differ from those found in an adult population, but we can hypothesize that the difference between the 2 groups of patients with respect to the presence of comorbid diabetes, hypertension, and reduced ventricular function in the adult population may have contributed to an increased vulnerability to develop CS-AKI. Based on our results, diuretic therapy should be provided to infants with no history of renal dysfunction as required to manage CHF related to left-to-right shunt lesions leading up to CS without concern for increasing the risk of postoperative AKI. Despite the finding that diuretic therapy is not associated with an increased risk of postoperative AKI, our data reaffirm the high prevalence of this complication following CS in infants that ranges in severity from mild to severe. Given that long-term follow-up studies in children with AKI following both CS and other critical care admissions show an increased risk of CKD regardless of AKI severity,[4–6,18] routine screening for CS-AKI along with long-term follow-up of these patients according to KDIGO guidelines is prudent.[17,18] The general recommendation from the KDIGO guideline for patients diagnosed with AKI of any severity includes a 3-month evaluation post-AKI to assess for resolution or worsening of renal function. In addition, it would be beneficial for these patients to receive education on nephrotoxin avoidance, medication reconciliation to minimize or eliminate nephrotoxic agents, and documentation in their records that indicate a history of kidney injury.[17,18] Further investigations and nephrology consultation should be considered in cases of moderate to severe CS-AKI.[17]

Limitations in this study should be considered. First, this is a retrospective single-center study without long-term follow-up. A diagnosis of AKI was assessed based on urine output and SCr according to the KDIGO classification, but this was applied only to the period of time when patients were monitored in the intensive care unit in the early postoperative period while a Foley catheter was in place. We assessed early AKI only within this first 24 hours after CS and the onset of AKI beyond the first postoperative day was not assessed. As a result, the association with early CS-AKI and CKD was not assessed with respect to preoperative diuretic therapy. Second, a preoperative ultrasound to screen for structural renal abnormalities was not performed in every patient given the inherent limitations of the retrospective design, which could have resulted in inclusion of patients with undiagnosed structural renal abnormalities.

CONCLUSIONS

We have found that preoperative use of diuretics in infants with no history of renal dysfunction for management of CHF does not increase the risk of postoperative CS-AKI early after CS. The only independent variable that increases the risk of CS-AKI is a diagnosis of TOF. With respect to CS-AKI severity, a diagnosis of TOF and longer CPB time are both risk factors for moderate to severe CS-AKI. It is apparent from our cohort and others that CS-AKI is a common postoperative morbidity, and it is prudent for mechanisms to be in place to identify patients with CS-AKI, stratify them with respect to severity, and provide appropriate follow-up and consultation with nephrology according to existing guidelines.

ARTICLE INFORMATION

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Supplementary Material
Tables S1–S4

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Supplemental Material

Table S1. KDIGO definition of AKI and AKI severity according to serum creatinine and urine output.

Stage	Serum Creatinine	Urine output
1	1.5-1.9 times baseline Or ≥26.5 μmol/l increase	<0.5 ml/kg/h for 6-12 h
2	2-2.9 times baseline	<0.5 ml/kg/h for ≥ 12 hr
3	3 times baseline Or Increase serum creatinine more than 353.6 μmol/l Or Initiation of renal replacement therapy Or Decrease in eGFR <35 ml/min per 1.73 m^2	<0.3 ml/kg/hr for ≥ 24 hr Or Anuria for ≥ 12 hr

Table S2. Distribution of double outlet right ventricle (DORV) and total anomalous pulmonary venous return (TAPVR) patients along with the use of pre-operative diuretics.

Diagnosis	Pre-operative diuretic use	No pre-operative Diuretic use
DORV		
Subaortic VSD/TOF	1	7
Subaortic VSD/Unobstructed	7	3
Subaortic VSD/PA	0	2
Non-committed VSD	0	1
Doubly committed VSD	0	0
Sub-pulmonary VSD	0	0
TAPVR		
Supracardiac	0	5
Cardiac	3	2
Infracardiac	0	0
Mixed	1	1

Subaortic VSD/TOF, Tetralogy type double outlet right ventricle; Subaortic VSD/Unobstructed, ventricular septal defect type double outlet right ventricle; Subaortic VSD/PA, tetralogy type double outlet right ventricle with pulmonary atresia; VSD, ventricular septal defect

Table S3. Distribution of AKI severity relative to the KDIGO criteria that was met to diagnose AKI.

CS-AKI severity	n	Oliguria	SCr	Oliguria/SCr
All	149	17	122	10
Stage 1	80	15	57	8
Stage 2	57	2	53	2
Stage 3	12	0	12	0

CS-AKI, cardiac surgery associated acute kidney injury; SCR, serum creatinine.

Table S4. Mean age at surgery for each diagnosis.

Diagnosis	Mean age at surgery m, (Stdev)
TOF	6.9 (2.0)
AVSD	5.9 (2.1)
VSD	5.5 (1.9)
DORV	7.2 (2.6)
TOF/MAPCAs	5.7 (2.6)
TAPVR	3.4 (1.5)
TOF/AVSD	11.4 (0.4)
Other	6.3 (3.9)

AVSD, atrioventricular septal defect; DORV, double outlet right ventricle; TOF, tetralogy of Fallot; TAPVR, total anomalous pulmonary venous return; TOF/AVSD, tetralogy of Fallot with atrioventricular septal defect; TOF/MAPCAs, tetralogy of Fallot with pulmonary atresia and multiple aortopulmonary collaterals; VSD, ventricular septal defect.