Risk Factors Associated with Acute Kidney Injury in Neonates and Infants Following Open Heart Surgery

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Abstract

BACKGROUND: The complexity of surgical cardiac procedures is on the rise, resulting in prolonged cardiopulmonary bypass time and stay in the intensive care unit. One major complication of cardiac surgery is acute kidney injury. The aim of this study is to investigate the incidence and risk factors associated with acute kidney injury following open heart surgery.

METHODOLOGY: This is a retrospective cohort study that involved chart review of patients <1 year old who underwent open heart surgery from January 2012 to December 2017 in a tertiary cardiovascular referral center. Preoperative characteristics included age, gender, weight, cardiac diagnosis, baseline serum creatinine, history of mechanical ventilation and cardiac catheterization and pre operative medications given. Intra-operative characteristics included cardiopulmonary bypass and cross clamp time of cardiac surgery, and degree of hypothermia . Post operatively, urine output, systolic blood pressure, mean arterial pressure, highest serum creatinine and blood urea nitrogen were recorded.

RESULTS: Sixty one (61) patients were included in the study. Nine patients (15%) developed post-operative acute kidney injury, two of which underwent peritoneal dialysis. Lowest systolic blood pressure and lowest mean arterial pressure were noted to be significant in the development of acute kidney injury with odds ratio of 0.95 (p=0.049) and 0.93 (p=0.025), respectively. The duration of mechanical ventilation was also significantly increased in patients who developed acute kidney injury (p=0.028).

CONCLUSION: Lowest systolic blood pressure and lowest mean arterial pressure are significant risk factors for acute kidney injury in neonates and infants following open heart surgery.

KEYWORDS: acute kidney injury, acute renal failure, cardiac surgery in infants, congenital heart disease, cardiopulmonary bypass time

INTRODUCTION

The complexity of surgical cardiac procedures among children is increasing as a result of advances in surgical techniques.[1] This commonly results in prolonged cardiopulmonary bypass time and intensive care unit (ICU) stay, as well as an increase in mortality rate among the pediatric age group.

One major complication of cardiac surgery is acute kidney injury (AKI) during the post-operative state. AKI is seen in 5-33% of patients in pediatric post-cardiac surgery with an associated 20 79% mortality rate.[2] In the study by Rigden et al, acute renal failure was seen in 5.3% of children who underwent cardiopulmonary bypass. Long overall bypass time (>90 minutes) was significantly associated with development of acute renal failure.

Infants and neonates are recognized to have increased risk since they are the sickliest group of patients subjected to surgery, with reduced glomerular filtration rate (GFR) and renal blood flow.[1] Li et al reported that elevated preoperative serum creatinine, age <1 year, cyanotic lesions, prolonged cardiopulmonary bypass time and post-operative low cardiac output syndrome were risk factors for AKI after cardiac surgery.[2] There was also significant risk of AKI in patients who were categorized under Risk Adjustment for Congenital Heart Surgery (RACHS) 2 to 4. AKI developed in 68% of patients who had bypass time of more than 180 minutes. This may be secondary to ischemia, loss of pulsatile flow and progressive inflammation in the renal vasculature.[2,3] AKI was noted in 53% of patients within the first 24 hours, 97.7% within 48 hours and 42% within 72 hours from surgery.

In addition, median pediatric ICU and hospital stays were significantly prolonged in patients who developed AKI, resulting in increased use of hospital resources and overall health cost.[2] In the study of Aydinet al, acute renal failure was noted in 51% of children who underwent cardiac surgery.[4] Younger age, higher RACHS category and cardiopulmonary bypass time >55 minutes were independently associated with AKI. Immaturity of the renal tubules, low GFR, inability to adapt to inflammation and reperfusion injury on withdrawal to bypass increases the risk of AKI in neonates.[4] Lastly, early initiation of peritoneal dialysis after cardiac surgery in neonates and infants with AKI resulted in a significant decrease in mortality.[5]

The aim of this study is to investigate the incidence of AKI following cardiac surgery in neonates and infants in the past five years. In addition, the study also aims to determine the risk factors of AKI among neonates and infants following open heart surgery. Recognizing these factors will help in the management of patients in the critical care and post-operative care settings and may aid the development of relevant guidelines.

METHODOLOGY

This was a retrospective cohort study conducted at a pediatric surgical ICU of a tertiary cardiovascular referral center from September 1, 2018 to October 31, 2018. Inclusion criteria included all pediatric patients <1 year old who underwent open heart surgery over a 6-year period from January 2012 to December 2017. Exclusion criteria included those who had previous cardiac surgery and those with incomplete chart data.

Charts and Medtrak entries of subjects included were reviewed. AKI was defined using the Risk, Injury, Failure, Loss, End-stage Kidney Disease (RIFLE) criteria (Appendix).[6] Pre operative characteristics, including age, gender, weight, cardiac diagnosis, pre-operative serum creatinine, GFR, pre-operative medications, and pre-operative history of mechanical ventilation and cardiac catheterization were collected and tabulated. Cardiac surgery risk was categorized using RACHS-1.[2,7] Cardiopulmonary bypass, cross clamp time of cardiac surgery, duration of mechanical ventilation and degree of hypothermia were recorded. In the immediate post-operative course, urine output in the first six hours, 24 hours and 48 hours from surgery; lowest and mean systolic blood pressure (SBP); mean arterial pressure (MAP) from 48 to 72 hours after surgery; highest serum creatinine; blood urea nitrogen and post-operative infections were all recorded and tabulated. The length of ICU stay and hospital stay were also collected.

The study was conducted in compliance with the ethical principles of the Declaration of Helsinki. Prior to study initiation, the study protocol and subsequent amendments were reviewed by an independent Institutional Ethics Review Board. Since the study was retrospective and involved review of charts, the investigator requested approval of a waiver for obtaining informed consent due to difficulty in securing individual authorization, since the patients were already discharged. The investigator ensured anonymity and preserved the privacy and confidentiality of all patients whose records were reviewed in the study.

SAMPLE SIZE CALCULATION[8] AND STATISTICAL ANALYSIS

A minimum of 62 patients was required for this study based on 7.57 odds ratio of having AKI among patients who had cardiopulmonary bypass time >3 hours compared to those patients who had <1 hour bypass time.[2] This computation also accounted for 1.1160 effect size,[9] 5% level of significance and 80% power.

Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion were used for categorical variables while median and interquartile range (IQR) were used for non-normally distributed continuous variables. Mean and standard deviation were used for normally distributed continuous variables. Independent sample T-test, Mann-Whitney U test and Fisher's exact/Chi-square test were used to determine the difference of mean, rank and frequency, respectively, between patients with and without AKI. Odds ratio and corresponding 95% confidence intervals from binary logistic regression were computed to determine significant predictors of AKI. All statistical tests were two tailed. Shapiro-Wilk was used to test the normality of the continuous variables. Missing variables were neither replaced nor estimated. Null hypothesis was rejected at 0.05 α-level of significance. STATA 13.1 was used for data analysis.

RESULTS

Sixty-one patients met the inclusion and exclusion criteria and were included in the study. Pre-operative characteristics of included patients are reported in Table 1. There was a 2:1 male:female ratio in both groups ranging from 62-67% male and 33 39% female patients. Majority of the patients were RACHS-1 category 3 with no patients in category 1 and 5. Nine (15%) patients met the RIFLE criteria for AKI. There were no significant differences in all pre-operative characteristics between those who developed AKI vs those without AKI.

Table 1. Pre-operative Characteristics of Neonates and Infants with or without AKI

	Non-AKI (n=52)	**AKI (n=9)**	**p-value**
Age in months median (IQR)	2 (0.82 to 4.5)	1 (0.1 to 1)	0.070
Gender frequency (n,%) Male Female	 32 (61.5) 20 (38.5)	 6 (66.7) 3 (33.3)	0.770
Weight in kg (mean + SD)	4.02 ± 1.16	3.41 ± 0.63	0.149
RACHS Category frequency (n,%) 1 2 3 4 5 6	 0 13 (25.0) 26 (50.0) 13 (25.0) 0 0	 0 1 (11.1) 7 (77.8) 0 0 1 (11.1)	0.427
Baseline serum creatinine in mmol/L (median (IQR)	0.04 (0.03 to 0.04)	0.04 (0.03 to 0.04)	0.818
Cardiac catherization prior surgery frequency (n,%)	3 (5.8)	2 (22.2)	0.123
Pre-operative mechanical ventilation frequency (n,%)	8 (15.4)	3 (33.3)	0.209
Pre-operative antibiotic frequency (n,%) Cefuroxime Vancomycin Amikacin	 9 (17.3) 42 (80.8) 42 (80.8)	 1 (11.1) 7 (77.8) 8 (88.9)	 0.646 0.835 0.564
Pre-operative medications frequency (n,%) Prostaglandin Dopamine Digoxin Furosemide Captopril Spironolactone Others*	 11 (21.2) 2 (3.9) 18 (34.6) 28 (53.9) 6 (11.5) 9 (17.3) 15 (28.9)	 4 (44.4) 0 0 2 (22.2) 1 (11.1) 0 2 (22.2)	 0.146 0.097 0.970 0.683

*Other medications included anticonvulsants (e.g., phenobarbital), sedatives (e.g., morphine), pulmonary vasodilators (e.g., milrinone and iloprost) and antibiotics (e.g., meropenem, ceftriaxone, ampicillin, cefepime and cotrimoxazole).

AKI, acute kidney injury; IQR, interquartile range; SD, standard deviation.

Table 2 shows the intra-operative characteristics of neonates and infants who underwent cardiac surgery. The duration of cardiopulmonary bypass time and cross clamp time as well as the rates of hypothermia did not significantly differ between those with or without AKI.

There was a significant difference between the mean lowest SBP of patients who developed AKI (56.8 ± 20.0 mmHg) and those without AKI (68.8 ± 15.1 mmHg; p=0.049) (Table 3). The mean lowest MAP was also significantly lower in those with AKI compared to those without (39.8 ± 15.1 vs 49.9 ± 10.4 mmHg, respectively; p=0.025). The median duration of mechanical ventilation of patients with AKI was eight days (IQR 1 to 3 days), which was significantly longer compared to those without AKI (2 days; IQR 1 to 4 days). Two patients who developed AKI received peritoneal dialysis. There were no significant differences between the two groups in terms of median highest serum creatinine, median highest blood urea nitrogen, mean urine output, infection rate, and length of hospital and ICU stays.

Table 2. Intra-operative Characteristics of Neonates and Infants Who Underwent Open Heart Surgery

	Non-AKI (n=52)	**AKI (n=9)**	**p-value**
Cardiopulmonary bypass time (n, %) < 60 minutes	1 (1.9)	0	0.121
60-120 minutes	25 (48.1)	3 (33.3)	
> 120 minutes	26 (50.0)	6 (66.7)	
Mean + SD	160.8 ± 73.2	204.4 ± 77.8	
Cross clamp time (n, %) < 60 minutes	7 (13.5)	2 (22.2)	0.151
60-120 minutes	25 (48.1)	2 (22.2)	
> 120 minutes	20 (38.5)	5 (55.6)	
Mean + SD	103.3 ± 42.7	127.3 ± 58.7	
Hypothermia (n, %) Mild (28-34 oC)	41 (78.9)	7 (77.8)	0.467
Moderate (20-28oC)	11 (21.6)	1 (11.1)	
Deep (14-20 oC)	0	1 (11.1)	
Profound (<14 oC)	0	0	

AKI, acute kidney injury; SD, standard deviation.

Table 3. Post-operative Characteristics of Neonates and Infants Who Underwent Open Heart Surgery

	Non-AKI (n=52)	**AKI (n=9)**	**Crude Odds Ratio (95% CI)**	**p-value**
Highest serum creatinine in mmol/L median (IQR)	0.06 (0.03 to 0.07)	0.09 (0.07 to 0.15)		0.080
Highest BUN in mmol/L median (IQR)	6.1 (2.2 to 11.6)	11.1 (5.3 to 36.8)		0.086
Urine output in ml/kg/hr (mean + SD) • first 6 hours • 24 hours • 48 hours	2.93 ± 2.64 2.80 ± 1.75 3.35 ± 1.24	2.2 ± 3.00 1.64 ± 1.54 2.42 ± 1.61		0.473 0.057 0.093
Systolic blood pressure in mmHg (mean + SD) • Lowest • Average	68.8 ± 15.13 87.6 ± 12.83	56.8 ± 19.97 79.4 ± 18.82	0.95 (0.91 to 1.0)	**0.049** 0.116
Mean arterial blood pressure in mmHg (mean + SD) • Lowest • Average	49.9 ± 10.45 62.8 ± 8.75	39.8 ± 15.10 55.8 ± 13.17	0.93 (0.87 to 0.99)	**0.025** 0.055
Presence of infection frequency (n,%)	8 (15.38)	3 (33.33)		0.209
Peritoneal Dialysis frequency (n,%)	0	2 (22.22)		
Duration of mechanical ventilation in days median (IQR)	2 (1 to 4)	8 (1 to 13)		**0.028**
ICU stay in days median (IQR)	6 (3 to 9.5)	8 (3 to 19)		0.079
Hospital stay in days median (IQR)	16 (10.5 to 28.5)	15 (12 to 25)		0.805

AKI, acute kidney injury; IQR, interquartile range; SD, standard deviation.

DISCUSSION

There is limited literature regarding the development of AKI in pediatric patients who undergo cardiac surgery. With the increasing complexity of cardiac diagnosis and surgical procedures in recent years in the institution where the study took place, AKI and renal failure are continually seen in the post-operative state, specifically in infants and neonates. Most patients are diagnosed with acute renal failure when there is increasing serum creatinine or declining urine output, necessitating dialysis. The concern is the timing of insertion of the dialysis catheter and initiation of dialysis.

In this study, the incidence of AKI was 15% in neonates and infants following open heart surgery. This was lower compared to the incidence cited in other literature wherein AKI was seen in 42% to 51% of pediatric patients who underwent cardiac surgery.[1-4] Two patients who were diagnosed with AKI had peritoneal dialysis.

Lowest SBP and lowest MAP were identified as significant risk factors for developing AKI in this study. SBP and MAP were not included as risk factor for developing AKI in previous studies. However, in the study by Li et al, post-operative low cardiac output syndrome was mentioned as a risk factor.[2] Such patients would manifest with low SBP and MAP, resulting in renal hypoperfusion and, ultimately, AKI. Additional studies are recommended to investigate the influence of these conditions on the risk of AKI to help develop guidelines in the post-operative care of neonates and infants who undergo open heart surgery.

The duration of mechanical ventilation was also significantly longer in patients who developed AKI. This was also seen in previous studies with AKI following cardiac surgery.[2,10] According to the study by Li et al, patients with AKI were mechanically ventilated longer because of fluid retention and possible interstitial edema, leading to a restrictive lung disease.[2]

Although patients who developed AKI were younger, the difference in age between the two groups was not statistically significant. Previous studies have shown that children aged <1 year have increased risk of AKI because of their vulnerability to ischemic and inflammatory insults, since maximal GFR is not reached until two years of age.[11]

Longer cardiopulmonary bypass time was not significantly associated with AKI in this study. This is in contrast with other studies, which showed that increased cardiopulmonary bypass time raised the likelihood of AKI, which was attributed to various mechanisms, including inflammation, ischemia and loss of pulsatile flow.[1-4] It is also considered an indicator of complexity and severity of the congenital heart disease.

A review of literature revealed that other factors related to AKI in neonates and infants include young age and prematurity, pulmonary hypertension, hemoconcentration, hemodilution and postoperative anemia.[12-19] Among these, anemia is a modifiable risk factor that may be addressed through appropriate blood transfusion and administration of human erythropoietin, which as bee associatred with improved outcomes.[20,21]

One of the limitations of this study was the inability to achieve the target sample size. This is primarily due to the incomplete data of patients who underwent open heart surgery during the study period. Studies with bigger sample size, preferably prospective or randomized control studies, are recommended. The study also did not consider the indication for surgery, which is related to the retrospective nature of the study. This information is important as different congenital heart diseases differ in prognosis and outcomes according to the stage and severity of the disease as well as other comorbid medical problems. Hence, it is recommended that this information be specified in medical records for future studies and for improved patient follow-up.

CONCLUSION

The incidence of AKI in neonates and infants following open heart surgery was 15%. Lowest SBP and lowest MAP were significant risk factors for AKI in these patients. The duration of mechanical ventilation was also significantly longer in patients who developed AKI.

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APPENDIX
Neonatal and Pediatric Risk, Injury, Failure, Loss, End-stage Kidney Disease (nRIFLE & pRIFLE) Criteria[11]

	Serum Creatinine	**Urinary Output (Neonatal)**	**Urinary Output (Pediatric)**
Risk	Increased creatinine x 1.5 or GFR decreases >25%	<1.5ml/kg/hr for 24 hours	≤0.5ml/kg/hr for 8 hours
Injury	Increased creatinine x 2 or GFR decreases >50%	<1ml/kg/hr for 24 hours	<0.5ml/kg/hr for 12 hours
Failure	Increased creatinine x 3 or GFR decreases >75%	< 0.7ml/kg/hr for 24 hours or anuria for 12 hours	<0.3ml/kg/hr for 24 hours or anuria for 12 hours
Loss	Persistent failure > 4 weeks		
End-stage	Persistent failure >3 months		