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ORIGINAL ARTICLE

Predictors of acute kidney injury post-cardiopulmonary bypass in children

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Abstract
Objective To investigate the incidence, implicating factors and outcome of acute kidney injury (AKI) after cardiopulmonary bypass (CPB) in patients admitted to a pediatric cardiothoracic intensive care unit (ICU).
Materials and methods *Design:* A retrospective review study. *Setting:* A 10-bed cardiothoracic ICU. *Patients:* One hundred and twenty-four children (<18 years of age) admitted to the cardiothoracic ICU following CPB between January 2007 and December 2009. *Methods:* Age, sex, diagnosis, baseline and post-surgery hemoglobin, total leukocyte count, platelet count and biochemistry were recorded. Baseline and postoperative urea (mg/dl), creatinine (mg/dl), urine output (ml/kg/h) and inotrope dose were also recorded daily. The duration of CPB was noted. Postoperative cardiac, renal, hepatic, neurologic and respiratory dysfunctions were recorded.
Results Seven (5%) children developed AKI stage I, five children (4%) developed AKI stage II and two children developed AKI stage III (2%). All patients with AKI had a longer stay in hospital and increased mortality. Two children required dialysis for AKI and none developed chronic renal impairment. All patients with AKI stage III died during the ICU stay. Using stepwise regression, younger age (<1 year), weight <10 kg, pump failure, sepsis and duration of CPB >90 min were significant risk factors identified for developing AKI.
Conclusions AKI is common and occurred in 11% of our patients following CPB; however, AKI requiring renal replacement therapy is uncommon.

Keywords Acute kidney injury · Acute renal failure · Cardiac surgery · Congenital heart disease · Pediatric intensive care · Cardiopulmonary bypass

Introduction

Cardiac surgery with cardiopulmonary bypass (CPB) is the most frequent major surgical procedure performed in hospitals worldwide, with well over a million operations undertaken each year. Acute kidney injury (AKI) is a common and serious complication encountered in 30–40% of adults and children after CPB [1–4]. AKI requiring dialysis occurs in up to 5% of these cases, in whom the mortality rate approaches 80% [2–4]. However, even minor degrees of postoperative AKI as manifested by only a 0.2–0.3 mg/dl rise in serum creatinine from baseline, and often thought to be clinically unimportant, portend a significant increase in morbidity and mortality [5–7].

AKI is associated with increased morbidity and mortality, extended stay in the intensive care unit (ICU), and higher treatment costs [8–11]. Despite improvements in surgical procedures and intra- and postoperative supportive care for children operated on for congenital heart disease,

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mortality due to postoperative complications and multi-organ dysfunction including AKI remains high [12–15]. Complexity of the underlying heart disease and surgical procedure [e.g. RACHS-l score (Risk Adjusted Classification for Congenital Heart Surgery)], duration of CPB, circulatory arrest, postoperative low cardiac output syndrome, use of adrenaline and isoprenaline, and young age have previously been shown to be associated with postoperative AKI and mortality [16–19].

We retrospectively analyzed the variables from the cardiothoracic ICU database of all consecutive children undergoing CPB for congenital heart diseases at our unit between January 2007 and December 2009 to identify the incidence of AKI in post-CPB patients, and examine the risk factors for AKI and mortality in this group of patients. This is the first ever study from Asia on pediatric CPB.

Materials and methods

Data was retrospectively collected on 124 children (<18 years old) from January 2007 to December 2009 at the cardiothoracic ICU, the Post Graduate Institute of Medical Education and Research, and the associated RML Hospital, New Delhi. The inclusion criteria consisted of children <18 years of age requiring CPB for surgical repair of their cardiac lesion. Exclusion criteria consisted of preoperative use of mechanical ventilation, extracorporeal life support or the use of preoperative inotropes and pre-existing renal dysfunction. All children had a normal baseline renal function.

Cardiorespiratory parameters were recorded (heart rate and rhythm, invasive blood pressure, central venous pressure, and pulmonary artery pressure for children at risk of pulmonary hypertensive crises), as were physiologic variables at the time of ICU admission. CPB time and surgical procedure were recorded for each patient. Based upon the surgical procedure, a Jenkins' score was assigned. The Jenkins' score has been developed as a method of risk adjustment to allow comparisons of in-hospital mortality between different cardiac centers. More complex lesions and surgery in the first 30 days of life have a higher Jenkins' score [20].

The children were assessed for evidence of low output syndrome or pump failure, as defined by Hoffman et al. [21]. This diagnosis of pump failure includes a combination of clinical signs of poor perfusion, an increase in existing pharmacologic agent to treat low cardiac output, an increase in lactate of 0.22 mmol/l on two successive arterial blood gases or a metabolic acidosis with an increase in base deficit of >4, with or without a >30% difference in arterial-mixed venous oxygen saturation. AKI was defined as 'an abrupt (within 48 h) reduction in kidney function defined as an absolute increase in serum creatinine of ≥0.3 mg/dl, an increase in serum creatinine of ≥1.5-fold from baseline, or reduction in urine output (oliguria of <0.5 ml/kg per h for >6 h)'. Staging of AKI was based upon the recent consensus guidelines developed by the AKI Network (AKIN) [22]. Hematologic dysfunction was defined as a platelet count <80,000/mm^3 or a decline of 50% in the platelet count from the highest value recorded over the last 48 h. Hepatic dysfunction was defined as alanine transaminase level 2× upper limit of the normal. Prolonged ventilatory requirement was defined as the need for invasive ventilation for >48 h. Prolonged ionotropic requirement was defined as the need for ionotropes for >48 h.

The cardiac surgeons and perfusionists developed the CPB technique used. All critical care physicians at our institution follow a similar approach to the management of post-CPB patients, which includes optimization of systemic oxygen delivery, and meticulous attention to preventing cerebral and other organ complications. This includes aggressive fluid therapy and central venous pressure monitoring.

Statistical analysis

Demographic data and study variables are expressed as mean ± SD. Our primary outcome was the development of AKI. Patients with AKI were compared with those without kidney injury using the standard statistical tests.

Multiple logistic regression analyses to compute odds ratios were analyzed to find the independent predictors of AKI. We included the following risk factors in the analysis: gender, age group (<1, >1 year), body weight (<10, >10 kg), Jenkins' score, duration of CPB, pump failure, prolonged ionotrope requirement, prolonged ventilator requirement and development of sepsis. Adjusted odds ratios were calculated allowing for gender, age group, body weight, Jenkins' score and CPB time.

Results

We reviewed 124 Indian children who underwent CPB for their cardiac lesion during the 36-month period from January 2007 to December 2009. Demographic data for the study group is shown in Table 1. No patient had clinical evidence of a significant chromosomal abnormality.

The mean age of the children was 120.3 months with the majority being male (55.6%). The mean duration of CPB was 106.7 min. All patients had a normal baseline renal function as assessed by Schwartz formula (100.4 ± 12.3 ml/min/1.73 m^2) and urinary protein/creatinine ratio (0.11 ± 0.06). There was no evidence of an underlying renal disorder. Mean ICU stay was 2.2 days.

Table 1 Basic demographic data of children undergoing cardiopulmonary bypass

Age (months), mean ± SD	120.3 ± 75.1
Males (%)	69 (55.6)
Weight (kg), mean ± SD	26.1 ± 16.3
Cardiopulmonary bypass time (min), mean ± SD	106.7 ± 67.3
Baseline urea (mg/dl), mean ± SD	19.5 ± 8.4
Baseline creatinine (mg/dl), mean ± SD	0.63 ± 0.16
eGFR (Schwartz) (ml/min/1.73 m^2)	100.4 ± 12.3
ICU stay (days), mean ± SD	2.2 ± 2.0

Table 2 Procedures performed and Jenkins' risk scores

Jenkins' risk score	Number of patients
1	30
2	49
3	44
4	1
5	0
6	0

Procedures performed in risk class 1: atrial septal defect surgery (including atrial septal defect secundum, sinus venous atrial septal defect), partial anomalous pulmonary venous connection surgery

Procedures performed in risk class 2: aortic valvotomy or valvuloplasty at age >30 days, subaortic stenosis resection, ventricular septal defect repair, ventricular septal defect, ventricular septal defect closure and pulmonary artery band removal, total repair of tetralogy of Fallot, repair of total anomalous pulmonary veins at age >30 days, Glenn shunt, repair of pulmonary artery stenosis

Procedures performed in risk class 3: aortic valve replacement, mitral valvotomy or valvuloplasty, mitral valve replacement, tricuspid valve replacement, repair of double outlet right ventricle with or without repair of right ventricular obstruction, arterial switch operation

Procedures performed in risk class 4: atrial switch operation with ventricular septal defect closure

Table 2 presents the underlying cardiac abnormality and the number of cardiac procedures in each of the Jenkins' risk categories. The majority of the procedures belonged to Jenkins' risk class 1–3.

Sepsis and hematologic dysfunction (thrombocytopenia) were the most common complications. The mean ICU stay was 2.2 ± 2.0 days. Nine patients died following surgery (7.2%). The cause of death was pump failure in 7 patients, and sepsis in the two remaining patients.

Using the consensus definitions developed by AKIN, 14 children developed AKI. The stages of AKI and the mortality are shown in Table 3.

Two children had AKI-III and required peritoneal dialysis. The indications for peritoneal dialysis in both cases were complete anuria with azotemia; however, both children with AKI-III died.

The comparison of all demographic variables and outcome in AKI and non-AKI patients is shown in Table 4.

Table 3 AKI staging and mortality in the patients

AKI stage	*n* (%)	Mortality (%)
AKI-I	7 (50.0)	5 (71.4)
AKI-II	5 (35.7)	2 (40)
AKI-III	2 (14.3)	2 (100)
Total	14	9

The AKI patients were found to be younger than 12 months, weight <10 kg, increased duration of CPB procedure, and more postoperative complications. The mortality and morbidity rate related to ICU stay was higher in patients with AKI.

Logistic regression analysis was used to examine risk factors for AKI allowing for potential confounding factors. Overall, in-hospital mortality was 7.2% (9/124). Mortality of AKI patients was 64.3% compared to 0% among non-AKI patients. The risk of AKI was strongly increased when the body weight was ≤10 kg, age was <12 months, the duration of CPB was >90 min, presence of pump failure, prolonged ionotropic and ventilator requirement, and sepsis postoperatively. The odds ratio and adjusted odds of developing AKI in these groups is shown in Table 5. The risk of AKI post-CPB was higher with age <12 months, postoperative pump failure, duration of CPB >90 min and sepsis.

Discussion

In the present study, the following independent risk factors for AKI were identified in children having surgical procedures: age <12 months, postoperative pump failure, duration of CPB >90 min and sepsis. Children with AKI stayed substantially longer in the ICU than non-AKI patients, and had a significantly higher mortality rate.

We undertook this study in our cardiothoracic ICU as there is no data from Asia and a lack of data from developing countries on incidence, risk factors, and outcome of renal impairment postoperatively following CPB. We found AKI to be fairly common, but AKI requiring renal replacement therapy is rare.

The diagnosis of AKI is strongly influenced by the criteria used for its definition, the patient population studied, as well as variables related to individual cardiac surgical units. We followed standard definitions as developed by the AKIN group [22].

Risk factors for the development of AKI in critically ill children and adults are in many cases similar, and include sepsis, hypotension, and nephrotoxic medication, such as antibiotics. In addition, both children and adults undergoing cardiac surgery are at risk from procedure-related factors that include invasive devices, the cardiac surgical procedure,

Table 4 Comparison of demographic variables in AKI and non-AKI patients

	AKI ($n = 14$)	Non-AKI ($n = 110$)	p value
Age (months)	57.8 ± 22.9	128.2 ± 6.7	0.05
Weight (kg)	16.6 ± 4.2	27.3 ± 1.5	0.03
Weight <10 kg (%)	8 (57.1)	14 (12.7)	<0.001
Age <12 months	10 (71.4)	5 (4.5)	<0.001
Males (%)	7 (50)	63 (57.2)	NS
Cardiopulmonary bypass time (min), mean ± SD	221.6 ± 94.9	92.0 ± 46.1	<0.001
Cardiopulmonary bypass time >90 min	14 (100)	49 (44.5)	<0.001
Sepsis (%)	11 (78.6)	29 (26.4)	<0.001
Respiratory complications (%)	5 (35.7)	10 (9.1)	0.01
Hepatic complications (%)	7 (50)	20 (18.2)	0.01
Hematological complications (%)	8 (57.1)	34 (30.9)	0.05
Pump failure (%)	7 (50)	–	<0.001
Prolonged ionotrope requirement (%)	8 (57.1)	19 (17.3)	0.002
ICU stay (days), mean ± SD	5.8 ± 4.5	1.7 ± 1.4	0.005
Mortality (%)	9 (64.3)	–	<0.001

Table 5 Odds ratio and adjusted odds ratio for AKI post-cardiopulmonary bypass

Risk factor	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)	p value
Age <12 months	52.5 (12.6–219.3)	50.7 (10.8–221.9)	<0.001
Weight <10 kg	9.1 (2.8–29.2)	8.7 (3.2–32.0)	0.001
Cardiopulmonary bypass time > 90 min	10.4 (1.6–63.9)	12.2 (2.3–74.1)	<0.001
Pump failure	20.7 (2.4–46.0)	20.2 (2.3–48.0)	<0.001
Prolonged ionotrope requirement	6.3 (2.0–19.8)	6.1 (3.2–22.4)	0.002
Sepsis	10.24 (2.8–36.4)	10.1 (3.4–44.2)	<0.001
Hematological complications	2.9 (0.9–8.9)	2.6 (1.4–9.4)	0.05
Hepatic dysfunction	4.5 (1.4–13.8)	4.1 (1.6–14.1)	0.01
Prolonged ventilatory requirement	5.5 (1.6–19.1)	5.3 (1.8–19.4)	0.01

Adjusted odds ratios calculated allowing for age group, body weight, Jenkins' score and CPB time

CPB, circulatory arrest, transfusions and cardiac catheterization. However, there are also significant differences between children and adults with regard to risk factors for the development of AKI. Infant kidneys are more dependent on the renin−angiotensin system than are adult kidneys, and may respond to hypotension and ischemia differently [7, 23, 24]. Another contributing factor is the case mix of admissions to a pediatric ICU, with more cases of congenital cardiac and other lesions, more chromosomal conditions, and less cases of chronic illness [7, 24–27]. The most common risk factors for the development of AKI identified in children undergoing CPB have been neonatal age group, cyanotic heart disease, CPB duration, low cardiac output and hypotension in the perioperative period, as well as certain specific complex cardiac lesions [7, 15, 24, 27–29]. The previous results are consistent with our study.

There is accumulating evidence that the development of AKI in critically ill adult patients independently contributes to their high mortality. In children, the mortality rate in those receiving dialysis following CPB is reported to range between 46 and 67%. In a recent prospective study, the contribution of each organ dysfunction included in the PELOD (Pediatric Logistic Organ Dysfunction) score was statistically related to mortality. Neurologic, cardiovascular and renal dysfunctions accounted for 46%, 35% and 13% of the PELOD score variance, respectively [30]. Mortality appears to be even greater in patients requiring dialysis, despite full support with either hemodialysis or continuous renal replacement therapy [31].

Our pilot study suffers from a small sample size and from being a single–institution study. Our results, performed by multiple logistic regression on a small sample size, need to be validated by a prospective study with larger numbers. We also recognize that cardiac centers who perform surgical procedures for hypoplastic left heart syndrome and have a higher number of children who

undergo surgery when they are <30 days of age may have a different incidence of AKI, as these children are at greater risk of postoperative pump failure, and hence are at a higher risk of AKI.

Previous published reports have been retrospective and generally focused on children developing acute renal failure as defined by the need for dialysis. This definition ignores most cases of AKI which are treated without dialysis. This limited definition does not include the factors contributing to AKI and therapeutic options to prevent progression of injury.

The diagnosis of AKI after an insult such as CPB is currently delayed and inaccurate. Recent studies have uncovered biomarkers such as neutrophil gelatinase-associated lipocalcin, interleukin-18, liver-type fatty acid-binding protein, kidney injury molecule-1 and cystatin C. It is anticipated that a panel of strategically selected candidates may prove optimal for early rapid diagnosis of AKI and its clinical outcomes [1, 3, 4, 7].

Conclusions

In summary, we report an incidence of AKI of 11% in a population of 124 children who underwent CPB. The two patients who developed AKI-III and required peritoneal dialysis both succumbed. All the deaths were in AKI patients. Further large multicenter epidemiologic studies are required to determine the true incidence of AKI and its impact upon survival.

Conflict of interest None.

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