Original articles

Acute Renal Failure in Children Undergoing Cardiopulmonary Bypass

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ABSTRACT

Objective: *To investigate the incidence, implicating factors and outcome of acute renal failure after cardiopulmonary bypass in patients admitted to a paediatric intensive care unit.*

Design: *Prospective observational pilot study.*

Setting: *A 14 bed paediatric intensive care unit in a university affiliated, tertiary care referral children's hospital.*

Patients: *One hundred and one children (less than sixteen years of age) admitted to the Pediatric Intensive Care Unit following cardiopulmonary bypass between June 2003 and May 2004.*

Interventions: *None*

Measurements and Main Results: *PRISM-III score was calculated on admission. Baseline admission urea (mmol/L) and creatinine (µmol/L) serum levels and highest urea and creatinine levels were measured. Urine output (mL/kg/hour) and frusemide dose (mg/kg/day) were also noted. A baseline inotrope score was calculated on admission and the highest inotrope score was noted based on maximum infused doses of inotrope in the first 36 hours. The surgical procedure was used to determine a Jenkins score. Eleven (11%) children developed acute renal injury (doubling of creatinine), one child (1%) developed acute renal failure (tripling of creatinine) and one child died (1%). No child required dialysis for acute renal failure and none developed chronic renal impairment. Low cardiac output was the only significant risk factor identified for developing acute renal injury or failure.*

Conclusions: *Acute renal injury is common and occurred in 11% of our children following congenital cardiac surgery, but acute renal failure requiring dialysis is uncommon.* (**Critical Care and Resuscitation 2005; 7: 286-291**)

Key words: Acute renal failure, epidemiology, paediatric, cardiopulmonary bypass, paediatric, outcome

Little is known about the epidemiology and risk factors for the development of acute renal failure (ARF) in children post cardiopulmonary bypass (CPB) for cardiac surgery. It is reported that ARF occurs frequently after CPB in children, but the actual incidence in these patients has not been well studied.[1] What is also uncertain is whether ARF directly contributes to the long-term morbidity and mortality of critically ill children.

Previous published reports have been retrospective and generally focused on children developing ARF as defined by the need for dialysis. This definition ignores most cases of acute renal injury and ARF which are treated without dialysis. This limited definition has meant that an understanding of factors contributing to ARF and therapeutic options to prevent progression of renal injury to ARF have received little attention.

Furthermore, our understanding and evaluation of new therapies is hindered by a lack of consensus on diagnostic criteria of renal dysfunction and ARF.

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Cognisant of this limitation, the Acute Dialysis Quality Initiative (ADQI) Group recently published consensus definitions of renal injury with the aim of standardising the reporting of ARF, and hence to enhance an understanding of both its prevention and treatment.[2] An important logical next step is to define the epidemiology and risk factors of ARF in children using the consensus definitions. It is only with this information that new therapies for prevention and treatment can be developed.

With this in mind and using the newly published guidelines, we designed this pilot study to prospectively evaluate the incidence, implicating factors and clinical course of ARF in children undergoing CPB. Based on our clinical experience and the scant reported literature, we hypothesised that renal injury would be common but ARF requiring dialysis would be uncommon.

MATERIALS and METHODS

This pilot study was approved by the Ethics Committee of the University of British Columbia. In our institution the cardiac science team manages all children undergoing cardiopulmonary bypass, including our study patients. The cardiac science team consists of cardiac surgeons, cardiologists, paediatric critical care specialists and paediatric cardiac radiologists. The full team conducts bedside rounds at least once daily and collaborates in the care of all children. The critical care specialists conduct further rounds at least two further times per day. Our hospital is the cardiac referral centre for a province with a population of 4.5 million people.

Data was prospectively collected on one hundred and one children between 38 weeks post conceptual age and 16 years of age during a 12-month period from June 2003 to May 2004. Five of the 101 children were less than 30 days of age at the time of surgery. The inclusion criteria consisted of; children less than 16 years of age, informed consent and children requiring CPB for surgical repair of their congenital cardiac lesion. Exclusion criteria consisted of pre-operative use of mechanical ventilation, extracorporeal life support or the use of pre-operative inotropes. During this time period there were a total of 10 children who under went CPB for whom data was not collected. Of these 10 children, 9 were excluded for lack of informed consent and 1 was excluded for the use of pre-operative mechanical ventilation. All but one child had normal baseline renal function based upon admission urea and creatinine. The one child with abnormal baseline creatinine was excluded from analysis.

Cardiorespiratory parameters were monitored (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 PICU admission to calculate a paediatric severity of illness score, PRISM III.[3] PRISM III is a paediatric scoring system used to estimate severity of physiologic derangements and is a predictor of morbidity and mortality in PICU's.

CPB time and surgical procedure were recorded for each patient. Based upon the surgical procedure, a Jenkins score was assigned.[4] The Jenkins score was 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 score.

The children were assessed for evidence of low output syndrome, as defined by Hoffman.[5] This diagnosis of low output syndrome includes a combination of clinical signs of poor perfusion, an increase in existing pharmacologic support or the addition of another 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 $\geq$ 30% difference in arterial-mixed venous oxygen saturation. In addition, an admission and highest inotrope score was calculated based upon data by Wernovsky.[6] The inotrope score was developed in an attempt to quantify inotropic support and is calculated as the sum of all inotrope agents, while correcting for potency [1 x (dopamine dose + dobutamine dose + amrinone dose) + 15 x (milrinone dose) + 100 x (epinephrine dose + norepinephrine dose)]. This score has been used in different studies to stratify the severity of myocardial dysfunction and identify low output syndrome.[6-8] The patients with renal injury were compared to those without renal injury with regards to their maximum inotrope score in the first 36 hours.

Definitions of acute renal failure and dysfunction were based upon the recent consensus guidelines developed by the ADQI.[2] Acute renal injury was defined as a doubling of baseline serum creatinine and or urine output less than 0.5 mL/kg/hour for 12 hours. Acute renal failure was defined as a tripling of the baseline serum creatinine, and or urine output less than 0.3mls/kg/hour for 24 hours or anuria for 12 hours or more. Serum creatinine level was measured using the enzymatic dry slide method (Vitros 900, OrthoDiagnostics, City, Country). The highest daily urea and creatinine and hourly urine output were measured and recorded as was total frusemide dose and whether dialysis was used. In addition, patients with renal injury were compared with those children without renal injury for length of stay.

All medical care of the children was left to the clinical judgment of the responsible physicians. The cardiac surgeons and perfusionists developed the CPB

technique used. A dedicated team of cardiac anesthetists performs cardiac anesthesia, and hence the techniques used in all children were similar. There were no specific renal protective strategies used. All critical care physicians at our institution follow a similar approach to the management of post-CPB patients, which includes optimisation of systemic oxygen delivery, and meticulous attention to preventing cerebral and other organ complications. Included in this management is the aggressive use of frusemide infusions for oliguria after the initial 24-hour postoperative period, with doses ranging from 0.1 - 1.0 mg/kg/hr. Frusemide infusions are our preferred treatment for oliguria or fluid overload in haemodynamically unstable patients, and are titrated to maintain a urine output based upon the individual patients overall fluid balance. The frusemide infusions were considered to have failed if urine output did not increase to the desired level, typically greater than 1 ml/kg/hour, despite maximum infusion rates, at which time other diuretics were added, such as spironolactone and metalozone.[9]

Statistical Analysis. Demographic data and study variables are expressed as mean ± SD, and as median. Our primary outcome was the development of acute renal injury or failure. Patients with renal injury were compared with those without renal injury using the Student t-test. Logistic regression analysis was used to estimate the probability of acute renal injury using age less than 30 days, CPB duration, and risk level based upon the Jenkins score for cardiac surgery, and low cardiac output as the independent variables, with 95% confidence intervals around the odds ratio. We chose these risk factors because they have been implicated in the development of ARF.[4,10,12]

RESULTS

We reviewed one hundred and one children who had CPB during the 12 month period from June 2003 to May 2004 Demographic data (mean ± standard deviation, median) for our study group are as follows: age (months) 42 ± 51, 17; bypass time (minutes) 142 ± 70, 135; cross clamp time (minutes) 62 ± 40, 64 PRISM III - 12 scores 10 ± 6,9; inotrope scores on admission 11 ± 10,10. Table 1 represents the number of cardiac procedures in each of the Jenkins Risk categories.

Twenty children (20%) met the definition of low cardiac output following CPB, similar to that reported in the paper by Hoffman.[5] Six of the children who developed acute renal injury met our definition of low cardiac output. Using stepwise regression, low cardiac output was the only significant predictor of developing a renal injury. However, the ability of the presence of low cardiac output to predict the development of an acute renal injury in any individual case was poor, with only 30% of those children with low cardiac output developing renal injury. There was no difference in the maximum inotrope score of patients with renal injury and those with out (mean ± standard deviation, median) 16 ± 11, 14 vs. 12 ± 13, 11 respectively ($p > 0.05$). One child died of low cardiac output following an atrioventricular septal defect repair, but was not in renal failure at the time of death.

Table 1. Procedures performed and Jenkins risk scores

Jenkins risk score	*Number of patients*
1	12
2	41
3	44
4	4
5	0
6	0

Procedures performed in risk class 1. Atrial septal defect surgery (including atrial septal defect secundum, sinus vensous atrial septal defect, patent foramen ovale closure), partially anomalous pulmonary venous connection surgery.

Procedures performed in risk class 2. Aortic valvotomy or valvuloplasty at age > 30 days, subaortic stenonsis resection, pulmonary valve replacement, ventricular septal defect repair, ventricular septal defect closure and pulmonary valvotomy or infundibular resection, 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 valvotomy or valvuloplasty, tricuspid valve replacement, right ventricular to pulmonary artery conduit, repair of double outlet right ventricle with or without repair of right ventricular obstruction, Fontan procedure, repair of transitional or complete atrioventricular canal with or without valve replacement, atrial switch operation, arterial switch operation.

Procedures performed in risk class 4. Konno procedure, repair of total anomalous pulmonary veins at age ≤ 30 days, atrial switch operation with ventricular septal defect closure, repair of truncus arteriosus.

Using the consensus definitions developed by ADQI, eleven children developed acute renal injury. The highest creatinine level was recorded in most cases by 48 hours post CPB. There was no difference in admission creatinine (30.3 ± 10 vs. 38.2 ± 14 μmoles/L). None of the children met the ADQI definition of renal injury or failure based on urine out put. The urine out put in the first 36 hours (1.72 vs. 1.89 mL/kg/hr) for children with and without a renal injury was similar. However the dose of frusemide was higher in patients with renal injury when compared with patients without renal injury (5.0 ± 5.8 mg/kg/day, 1.3 vs. 2.8 ± 3.0 mg/kg/day, 1.0). One child developed ARF based upon the ADQI definition of tripling of baseline

creatinine, but did not require dialysis. This child also had a low cardiac output and was managed successfully by optimising cardiac function and oxygen delivery. Patients with renal injury had a longer mean LOS (days compared with those without a renal injury (mean ± standard deviation, median) 12.9 ± 10.7, 9 vs. 4.4 ± 3.3,3 respectively ($p < 0.05$).

Five children had a dialysis catheter placed in the operating room by the cardiac surgeon in anticipation of postoperative fluid overload and renal problems. Dialysis catheters were placed in the operating room in anticipation of possible postoperative low cardiac output, generally at the discretion of the cardiac surgeon but usually following discussion with the critical care physician.

DISCUSSION

We undertook this pilot study because of the lack of data on the incidence, risk factors and outcome of renal impairment postoperatively following CPB. We found acute renal injury to be fairly common, but ARF rare. Our findings are difficult to compare with previous reports. A major stumbling block faced in the PICU has been a lack of consensus for the diagnostic criteria used to define ARF. The diagnosis of ARF following CPB is strongly influenced by the criteria used for its definition, the patient population studied, as well as variables related to individual cardiac surgical units. For instance, many investigators have defined ARF as the need for dialysis, while others have defined ARF as a rise in creatinine above a certain threshold (e.g. 170 mmol/L). These criteria ignore mild or moderate renal insufficiency that might lead to morbidity. Another drawback is inconsistency in defining oliguria which ranges from < 1 mL/kg/min for 4 hours[1] to < 0.5 mL/kg/hr in the ADQI consensus statement.[2] Another pitfall in determining the true incidence of ARF following CPB has been the inclusion of cardiac and non cardiac patients in reports, although it appears to range from 1.6% if the diagnosis includes the need for dialysis, up to 17% for less stringent criteria such as a doubling of creatinine.[1,5,10-15] Our strict criterion circumvents these confounding factors and is likely the true incidence of ARF post CPB.

Risk factors for the development of ARF in critically ill children and adults are in many cases similar, and include sepsis, hypotension, and nephrotoxic medications, 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, CPB, circulatory arrest, transfusions, and cardiac catheterisation. However, there are also significant differences. Infant kidneys are more dependent on the rennin angiotensin system than are adult kidneys, and may respond to hypotension and ischaemia differently.[16] Many adult kidneys have coexisting atherosclerosis and require higher perfusion pressures. Another contributing factor is the casemix of admissions to a PICU differs, with more congenital cardiac and other lesions, more chromosomal conditions, and less chronic illness. The difference in case mix and confounding factors may explain the higher incidence of renal failure in adult cardiac surgical patients compared with children.[17-19] The most common risk factors for the development of ARF identified in children undergoing cardiac surgery previously identified have been neonatal age group, cyanotic heart disease, CPB duration, low cardiac output and hypotension in the perioperative period,[10,11,15] as well as certain specific complex cardiac lesions.[4] In our study, low cardiac output was the only risk factor, but this is probably explained by the fact that many of the other reported risk factors contribute to low cardiac output.

The general approach followed by our team towards managing low cardiac output involves optimising cardiac filling using 5% albumin or blood products as needed to support a central venous pressure of 10 - 12 mmHg and inotropes (milrinone, dopamine and epinephrine) to optimise contractility. In addition, haemoglobin levels are optimised depending on the child's cardiac lesion and cardiac function. For example, cyanotic babies would have a desirable haemoglobin level above 130 gm/L. Our ventilation strategy consists of using positive end expiratory pressure of at least 5 cm H_2O and tidal volumes of 10mls/kg exhaled (monitored at the endotracheal tube) to maintain a pH of 7.4 - 7.45 and arterial saturations > 95%, designed to avoid elevations in pulmonary vascular resistance. We avoid temperature above 37.5ºC in order to reduce the risk of arrhythmias and as a simple approach to cerebral protection.

We attempt to maintain control of fluid balance and avoid fluid overload, and are liberal in our use of frusemide infusions. In children developing renal injury and oliguria, we used frusemide infusions because of our clinical experience, supported by the literature of the benefits of a gradual and controlled diuresis, greater absolute urine output, and greater haemodynamic stability due to less fluctuation in intravascular volume and reduced electrolyte losses.[9] Peritoneal dialysis was used when complex surgery was performed in an infant and it was anticipated that low cardiac output might develop in the postoperative period.

While no child in our study died because of ARF, there is accumulating evidence that the development of ARF in critically ill adult patients independently contributes to their high mortality. In a multidiscip-

linary adult ICU, mortality has recently been demonstrated to be greater in patients with ARF compared with those patients that do not develop ARF during their ICU admission, even after adjustment for severity of illness.[17] Conlan found in adult patients who underwent coronary artery bypass grafting and who developed ARF, a mortality of 14% compared with 1% among those who did not, based upon diagnostic criteria of an increase of creatinine of 85 mmol/L above baseline or need for dialytic therapy.[18] Chertow found that ARF was independently associated with early mortality following cardiac surgery in adults after adjustment for co-morbidity and postoperative complications, based upon a diagnosis of ARF as the need for dialysis within 30days following surgery.[19] Whether ARF is an independent predictor of mortality in critically ill children is unclear. In children, the mortality rate in those requiring dialysis following CPB is reported to range between 46 - 67%. In a recent prospective study during the validation of an organ dysfunction score in children, ARF accounted for 13% of overall mortality in those children developing multiorgan failure.[20] Mortality appears to be even greater in those patients requiring dialysis, despite full support with either haemodialysis or continuous renal replacement therapy.[21] Additionally, neither the APACHE III nor PRISM scoring system, as in our study, correlates with outcomes in patients with ARF. [22]

Our pilot study suffers from a small sample size, from a single institution. Neither the inotrope score nor the Jenkins score has been validated, but no better method of comparing inotrope doses or surgical procedures exists at present. In addition, we have not compared the severity of illness or surgical complexity of patients in this study with other similar centers. We also recognise that paediatric 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 renal injury, as these children are at greater risk of postoperative low cardiac output syndrome than most others, and hence are at a higher risk of renal injury.

Conclusions

In summary, we report an incidence of acute renal injury of 11% in a population of 101 children who underwent CPB. Only one child developed ARF (1%), but did not require dialysis, and made a complete recovery. It remains unclear whether acute renal failure contributes to long-term outcome or mortality of critically ill children. Further large multicentre epidemiologic studies are required to determine the true incidence of acute renal failure and its impact upon survival.

Received: 19 July 2005
Accepted: 10 August 2005

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