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ORIGINAL ARTICLE

Risk factors associated with acute renal failure in pediatric patients after cardiac bypass surgery

Factores de riesgo asociados a insuficiencia renal aguda postoperatoria en niños intervenidos de cirugía cardíaca

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Abstract

Introduction: Acute renal failure (ARF) is a complication associated with cardiac surgery with cardiopulmonary bypass (CPB) with an impact on morbidity and mortality. **Objective:** To identify risk factors associated with postoperative IRA according to pediatric Risk, Injury, Failure, Loss, End-Stage Renal Disease scale in children undergoing cardiac surgery with CPB. **Patients and Method:** A nested case-control study was conducted. We included children under 16 years of age attended postoperative for CBP in a pediatric intensive care unit over a period of 18 months. The cases were those who developed ARF according to the classification pediatric Risk, Injury, Failure, Loss, End-Stage Renal Disease scale during their stay in the pediatric intensive care unit. Controls were those who did not develop this complication. Logistic regression analysis was performed and adjusted odds ratio (OR) and confidence intervals at 95% (95% CI) were calculated. **Results:** 91 patients (31 cases and 60 controls) with a median age of 20 months and predominance of males (53.8%) were analyzed. Independent risk factors for ARF were the intraoperative lactate level > 6 mmol/l (OR = 4.91; 95% CI 1.26-19.05; p = .02) and cyanotic heart disease (OR = 3.62; 95% CI 1.11-11.63; p = .03). **Conclusions:** This study identified that pediatric patients with lactate levels >6 mmol/l during CPB and those with cyanotic congenital heart disease are a subgroup of high risk to develop ARF after heart surgery and should be closely monitored to prevent, detect and/or treat this complication timely manner.

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Introduction

Congenital heart disease is a group of diseases characterized by the presence of structural abnormalities of the heart of large intrathoracic vessels from the embryonic period and it represent the most common congenital malformations in newborns with a prevalence that oscillates around 1%[1,2].

Advances in the perioperative management of these heart diseases have resulted in a significant decrease in mortality even for the most severe heart defects. However, postoperative morbidity of these patients remains high[3].

Acute renal failure (ARF) is a complication that can occur between 5% and 46% of pediatric patients undergoing cardiac surgery and it is associated with longer stays in intensive care, as well as increased risk of nosocomial infections and high mortality (27-70%) postsurgical[4-9].

Studies that have used different methods to classify ARF have been described as risk factors associated with ARF to patients younger than one year of age, with history of kidney damage, time of cardiopulmonary bypass, elevated serum lactate levels during the immediate postoperative period, cyanogenic heart disease and metabolic acidosis[4,10–14].

Recently, the Pediatric Risk, Injury, Failure, Loss, End-Stage Renal Disease scale (pRIFLE) has been proposed as an easy-to-apply and highly sensitive tool for identifying and staging the severity of ARF in children (Table 1)[13-17].

Cardiopulmonary bypass time (CBC) has been described as an independent risk factor for postoperative ARF in children undergoing cardiac surgery[18,19]. The underlying mechanism is multifactorial and it is related to renal hypoperfusion, a combination of ischemia-reperfusion phenomena, pulsatile flow loss and severe systemic inflammatory response caused by CPB[20].

There are few studies that have described the risk factors associated with ARF assessed by pRIFLE in the subgroup of high risk children to develop such complication as are those patients undergoing cardiac surgery requiring support with CPB[12,15,21].

The aim of the present study was to identify the risk factors associated with postsurgical ARF according to the pRIFLE scale in children undergoing cardiac surgery with CPB.

Patients and Methods

A nested case-control study was conducted. We included in the cohort all patients younger than 16 years who were admitted after being operated on cardiac surgery that required CPB during the period from January 1, 2014 to July 1, 2015 in the Pediatric Intensive Care Unit (PICU) of the Pediatric Hospital Siglo XXI, which is a unit with a high level of resolution capacity in Mexico City. The cases were those patients who developed some degree of ARF according to the pRIFLE scale (Tabla 1)[13]; whereas, the controls corresponded to those patients who did not develop it. No patient was excluded.

The variables studied were: gender, age at surgery < 1 year (yes/no), type of cardiopathy (cyanogenic/acyanogenic), maximum serum lactate level during CPB ≥ 6 mmol/l, metabolic acidosis during CPB (mild: pH 7.34 - 7.30, moderate: pH 7.29-7.21, severe: pH < 7.2), time of CPB ≥ 140min (yes/no), low cardiac output syndrome (uresis < 0.5 ml/kg/h, central venous saturation < 60% and/or lactate > 3 mmol/l) (yes/no) and aortic clamping (yes/no). The frequency of mortality of patients during their stay in the PICU was determined.

Statistical analysis was performed using the statistical program *SPSS version 21*. A descriptive analysis of the variables of interest was performed by calculating frequencies and percentages for categorical variables. Quantitative variables distribution was determined with the Shapiro-Wilk test considering as non-parametric distribution those variables that resulted in a

Table 1. Pediatric-modified RIFL E (pRIFLE) criteria. (13)

	Estimated CCI	Urine output
Risk	eCCl decrease by 25%	< 0.5 ml/kg/h for 8 h
Injury	eCCl decrease by 50%	< 0.5 ml/kg/h for 16 h
Failure	eCCl decrease by 75% or eCCl < 35 ml/min /1.73 m^2	< 0.3 ml/kg/h for 24 h or anuric for 12 h
Loss of function	Persistent failure > 4 weeks	-
End-stage renal disease	End-stage renal disease (persistent failure > 3 months.	-

eCCl, estimated creatinine clearance; pRIFLE, pediatric risk, injury, failure, loss and end-stage renal disease.

p-value lower than 0.05; For those who resulted with nonparametric distribution were calculated medians and ranges; For those with parametric distribution, means and standard deviations were determined. Odds ratio (OR) and 95% confidence intervals (95% CI) were calculated. Subsequently, an unconditional logistic regression analysis was performed, where it was adjusted for age, gender and CPB time longer than 140 min. The low expenditure syndrome and the aortic clamping time, although they had a p-value lower than 0.05, could not be included in the final logistic regression analysis in order to avoid the homoscedasticity phenomenon since a correlation greater than 30% was observed in the correlation matrix analysis.

The protocol was approved by the Local Committee on Ethics and Health Research with the number: 2015-3603-66.

Results

During the study period, 321 cardiac surgery patients were admitted, who entered for post-surgical care in the PICU. From these, a total of 91 patients had been operated for cardiac surgery with CPB, being included in the present analysis (Figure 1). Cyanogenic heart disease accounted for 54.9% and 53.8% (n = 49) were males. The median age was 20 months, being a 26.4% younger than one year.

Thirty-one patients (34%) developed ARF according to the pRIFLE scale and they were included in the *case* group, while 60 patients who did not develop this complication during their stay in PICUs formed the *control* group. Regarding the severity of ARF by pRIFLE, fourteen patients had *kidney injury* and seventeen presented a *failure,* starting this complication during the first 72 hours after surgery.

There were no statistically significant differences between the *case* group and the *control* group in terms of gender (p = 0.45) and age (p = 0.41), but for the length of stay in intensive care, which was higher in the group of cases (median 10 days, range: 2-33) compared to the *control* group (median 4 days, range: 1-22) (p < 0.001).

Table 2 shows the results of the bivariate analysis between the different risk factors studied for the development of postsurgical ARF and where it was observed that cyanogenic heart disease, a maximum serum lactate level during CPB greater than 6 mmol/l, metabolic acidosis and a CPB time longer than 140 min had an OR greater than 2.

Later, in the logistic regression analysis adjusted by gender, patient age and CPB time longer than 140 min, two independent risk factors associated with ARF development in the studied population were identified:

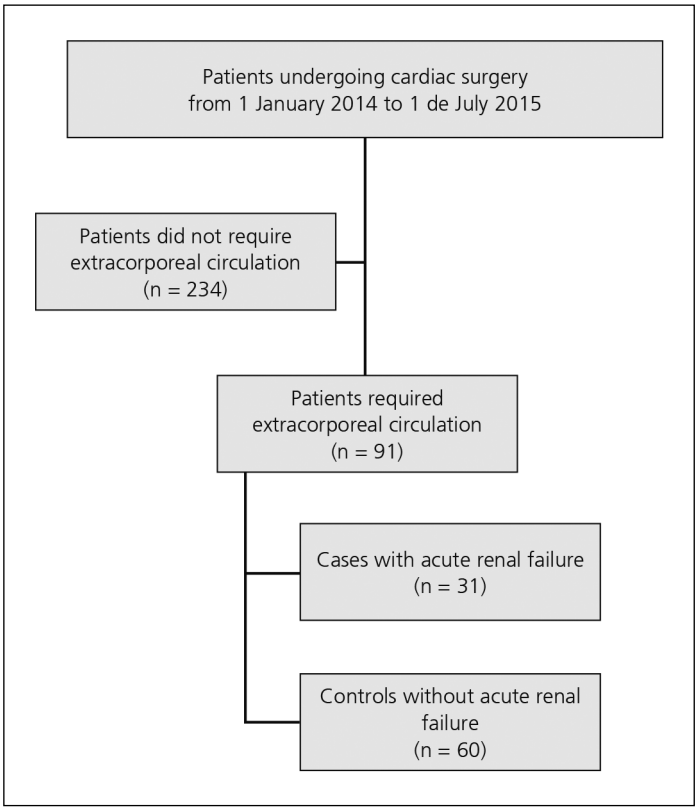

Figure 1. Flow chart of study participants selection.

cyanogenic heart disease (p = 0.03), and moderate-severe degree of hyperlactatemia (p = 0.02) (Table 3).

Eight patients who developed ARF died during their stay in the PICU. None of the patients in the *control* group died (Figure 2). There was no difference in gender (p = 0.81) compared to patients who did not die. Seven patients had cyanogenic heart disease, two had a CPB time ≥ 140 min, four had a peak serum lactate level during CPB ≥ 6 mmol / l (p = 0.04). Their total was between 4 months and 4 years of age (median: 13.5 months), which had developed low cardiac output syndrome and had a prolonged aortic clamping time (longer than 25 min). Regarding the pRIFLE classification, six patients had been identified with *failure (F).* The direct causes of death according to that reported in death certificates were septic shock (n = 4), cardiogenic shock (n = 2) and multiple organ dysfunction (n = 2).

Discussion

The frequency of IRF measured by pRIFLE observed in the present study (34%) in pediatric heart surgery patients with CPB was high considering the frequency reported by Skippen (11%), where the fre-

Table 2. Clinical characteristics of patients included in the study according to the development of acute renal failure during their stay at intensive care unit after cardiac surgery with cardiopulmonary bypass

Variable	Total of patientes included in the study		Acute Renal Failure				OR (CI 95%)
			Yes (n = 31)		No (n = 60)		
	N = 91	%	N	%	N	%	
Sex							
Male	49	53.8	15	48.4	34	56.7	0.77 (0.30-1.71)
Female	42	46.2	16	51.6	26	43.3	
Type of heart disease							
Cyanogen	50	54.9	25	80.6	25	41.7	5.8 (2.08-16.3)
Acyanogen	41	45.1	6	19.4	35	58.3	
Maximal hyperlactatemia during CPB							
Mild (3-5 mmol/l)	70	76.9	15	48.4	55	91.7	
Moderate and Severe (≥ 6mmol/l)	21	23.1	16	51.6	5	8.3	11.7 (3.69-37.24)
Metabolic acidosis							
Mild (ref.)	22	24.2	3	9.7	19	31.7	-
Moderate	34	37.4	10	32.3	24	40.0	2.63 (0.63-10.95)
Severe	35	38.5	18	58.1	17	28.3	6.70 (1.67-26.82)
Time of CBP							
< 139.9 min	75	82.4	19	61.3	56	93.3	8.84 (2.54-30.72)
≥ 140 min	16	17.6	12	38.7	4	6.7	
Low Cardiac Output Syndrome							
Yes	85	93.4	31	100	54	90	1.57 (1.34-1.84)
No	6	6.6	0	----	6	10	
Aortic Clamping							
Yes	85	93.4	31	100	54	90	1.57 (1.34-1.84)
No	6	6.6	0	----	6	10	

CBP: Cardiopulmonary Bypass.

Table 3. Logistic regression analysis to identify independent risk factors associated with acute renal failure after pediatric cardiac surgery

Risk Factors	OR	CI 95%	p*
Cyanogenic Congenital Heart Disease	3.62	1.11 - 11.63	0.03
Moderate and severe hyperlactemia (≥ 6 mmol/L)	4.91	1.26 - 19.05	0.02

Adjusted for age, sex and cardiopulmonary bypass time >140 minutes.

quency of ARF was determined based on the baseline serum creatinine or that reported by Setti (11.29%) using the guidelines developed by the Acute Kidney Injury Network[5,19]. However, it is similar to that reported by Zappitelli et al. (35.9%) in which the pRIFLE scale was used and who had studied a total of 390 patients, of whom 337 had been operated with CPB[21].

Cardiac surgery with CPB generates a state of systemic inflammatory response, hypoflow with loss of renal autoregulation, among other effects, all related in some way to a greater kidney damage. In this regard, it has been reported in pediatric patients that the longer the exposure to CPB, the greater the risk of postoperative ARF[19,22-24]. In our study, CPB time was longer than 140 minutes, a pH < 7.29, a serum lactate level > 6 mmol/l during CPB and the low-expenditure syndrome, similar to those previously reported in other studies research[19,25-27]. Elevated lactate levels translate tissue hypoperfusion[28]. Complex cardiac lesions, increased cardiopulmonary bypass time, and lower patient age are associated with a higher lactate level reflecting the magnitude of tissue hypoperfusion status during CPB[26].

On the other hand, cyanogenic cardiopathies were

an independent risk factor for ARF, which agrees with Dittrich (2000) and Ruf (2015) who have indicated that patients with this type of heart disease may develop glomerular and tubular damage post-surgery that may even be exacerbated by poorly hydrated patients[29,30].

It should be noted that none of the patients that we analyzed had a history of ARF, but we do not know if any had glomerular lesions secondary to cyanosis, since hypoxia, low compliance and tubular ischemia during reperfusion have been reported in this group and overheating during CPB. For this reason, it would be advisable that the pre-surgery evaluation include determination of levels of proteinuria and albuminuria, in order to detect those that require a perioperative surveillance and care that is narrower to prevent and/or detect postoperative ARF[29].

In our study, we also observed that patients who developed ARF had a longer intensive care stay and higher mortality. Among the patients who died, 50% had sepsis, which has been described as frequent comorbidity and increases the risk of dying in children who develop postoperative ARF[31]. This highlights the need to implement preventive measures for postoperative infection in these children.

As limitations in our study, we must consider its retrospective nature, so that the absence of bias cannot be guaranteed. However, our study provides an overview of this postoperative complication in children undergoing cardiac surgery who required CPB and gives guidelines for the design of new studies, such as: (1) Prospective studies aiming to reduce risk by modifying susceptible variables (time of cardiopulmonary bypass and/or time of aortic clamping); (2) cost-benefit evaluation studies on implementation of early diagnostic tools, and (3) studies that investigate the importance of a patient with risk factors for postoperative ARF, being withdrawn from the operating room with a dialysis catheter, reducing the risk of a second surgical procedure and early initiation of kidney function replacement therapy.

Conclusions

ARF is a frequent complication in pediatric patients exposed to cardiac surgery with CPB treated in a PICU. The present study allowed the identification of some independent risk factors associated with the development of postsurgical ARF such as having presented maximum lactate levels during CPB > 6 mmol / l and those patients with cyanogenic congenital heart disease, which should be monitored in a special way for the purpose of prevent, detect and/or treat in a timely manner said complication.

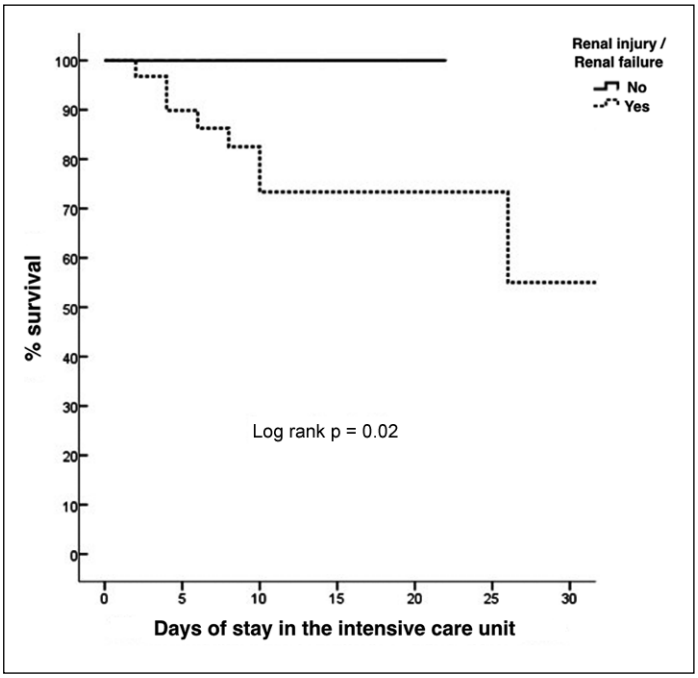

Figure 2. Kaplan Meier survival analysis for the duration of stay at the intensive care unit bypass according to the development of renal injury/failure by using the pRIFLE scale after pediatric cardiac surgery with cardiopulmonary.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

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Conflicts of Interest

Authors state that any conflict of interest exists regards the present study.

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