Rev Esp Cardiol. 2012;65(9):795–800

Original article

Evolution and Mortality Risk Factors in Children With Continuous Renal Replacement Therapy After Cardiac Surgery

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Article history:
Received 16 September 2011
Accepted 14 December 2011
Available online 25 April 2012

Keywords:
Cardiac surgery
Continuous renal replacement therapy
Children
Acute kidney injury
Critically ill children

ABSTRACT

Introduction and objectives: To study the clinical course of children requiring continuous renal replacement therapy after cardiac surgery and to analyze factors associated with mortality.
Methods: A prospective observational study was performed that included children requiring continuous renal replacement therapy after cardiac surgery. Univariate and multivariate analyses were performed to determine the influence of each factor on mortality. We compared these patients with other critically ill children requiring continuous renal replacement therapy.
Results: Of 1650 children undergoing cardiac surgery, 81 (4.9%) required continuous renal replacement therapy, 65 of whom (80.2%) presented multiple organ failure. The children who started continuous renal replacement therapy after cardiac surgery had lower mean arterial pressure, lower urea and creatinine levels, and higher mortality (43%) than the other children on continuous renal replacement therapy (29%) ($P = .05$). Factors associated with mortality in the univariate analysis were age less than 12 months, weight under 10 kg, higher pediatric risk of mortality score, hypotension, lower urea and creatinine levels when starting continuous renal replacement therapy, and the use of hemofiltration. In the multivariate analysis, hypotension when starting continuous renal replacement therapy, pediatric risk of mortality scores equal to or greaterer than 21, and hemofiltration were associated with mortality.
Conclusions: Although only a small percentage of children undergoing cardiac surgery required continuous renal replacement therapy, mortality among these patients was high. Hypotension and severity of illness when starting the technique and hemofiltration were factors associated with higher mortality.

Evolución y factores de riesgo de mortalidad en niños sometidos a cirugía cardiaca que requieren técnicas de depuración extrarrenal continua

Palabras clave:
Cirugía cardiaca
Técnicas de depuración extrarrenal continua
Niños
Insuficiencia renal aguda
Niños en estado crítico

RESUMEN

Introducción y objetivos: El objetivo fue estudiar la evolución de los niños que requieren técnicas de depuración extrarrenal continua tras la cirugía cardiaca y analizar los factores asociados con la mortalidad.
Métodos: Estudio prospectivo observacional. Se incluyó a los niños que requirieron técnicas de depuración extrarrenal continua tras la cirugía cardiaca. Se realizaron análisis univariable y multivariable para estudiar la influencia de cada factor en la mortalidad.
Resultados: De los 1.650 niños sometidos a cirugía cardiaca, 81 (4,9%) requirieron técnicas de depuración extrarrenal. Los niños que precisaron técnicas de depuración extrarrenal tras la cirugía cardiaca presentaban una presión arterial media y unos valores de urea y creatinina más bajos, y su mortalidad fue mayor (43%) que la del resto de los niños (29%) ($p = 0{,}05$). En el estudio univariable, los factores asociados con mortalidad fueron: edad < 12 meses, peso < 10 kg, hipotensión, puntuación elevada de riesgo de mortalidad infantil y valores bajos de creatinina al inicio de la técnica. En el estudio multivariable, la hipotensión en el momento del inicio de las técnicas de depuración extrarrenal continua, una puntuación puntuación elevada de riesgo de mortalidad infantil ≥ 21 y la hemofiltración fueron los factores asociados con la mortalidad.
Conclusiones: Aunque sólo un pequeño porcentaje de los niños sometidos a cirugía cardiaca precisan técnicas de depuración extrarrenal continua, su mortalidad es elevada. La hipotensión y la gravedad clínica al inicio de la técnica de depuración y la hemofiltración como técnica de depuración fueron los factores asociados con la mortalidad.

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http://dx.doi.org/10.1016/j.rec.2012.04.009, Rev Esp Cardiol. 2012;65:785–7.
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doi:10.1016/j.rec.2011.12.010

Abbreviations

AKI: acute kidney injury
CRRT: continuous renal replacement therapy
CS: cardiac surgery
MAP: mean arterial pressure

INTRODUCTION

Advances in diagnosis, surgery, and postoperative treatment of children with congenital heart disease have led to a progressive increase in survival. However, children who require complex cardiac surgeries and those who suffer multiple organ failure after surgery have a high incidence of acute renal failure (ARF).[1–4] Children who are in the postoerative period of cardiac surgery (CS) have a high risk of renal function disorders due to the reduction in cardiac output, disorders caused by cardiopulmonary bypass, hemolysis, and infections.[1,4]

The incidence of ARF requiring continuous renal replacement techniques (CRRT) after CS in children varies between 1% and 17% according to the complexity of the surgery.[1–3,5,6]

There is little information on outcomes for children who require CRRT after CS[2,3] and there have been no studies analyzing the factors associated with survival. The objectives of this study are to analyze the clinical outcomes of children who require CRRT after CS and the factors associated with mortality.

METHODS

We carried out a prospective observational registry that included all critically ill children requiring CRRT at Gregorio Marañón University Hospital in Madrid.[7] The current study retrospectively analyzed patients with CRRT after CS. The study was approved by the hospital's ethics and research committee. During the study period (January 1996 to June 2009), 3 different monitors were used: BSM321C, Prisma, and Prismaflex (Hospal®, Madrid, Spain). We used 5-11 Fr catheters, depending on the child's age and weight.

The indication for CRRT was decided by the pediatric intensivist when there were criteria for ARF, defined as an increase in urea and creatinine of more than twice the normal levels for the patient's age, oliguria<0.5 mL/kg/h, or positive balance despite high doses of diuretics for 6 to 12 h.

The following parameters were recorded prospectively every 24 h throughout the CRRT therapy: age, weight, sex, diagnosis, and assessment of severity at the start of the clinical technique using the pediatric index of mortality (PIM) II,[8] pediatric risk of mortality (PRISM) II,[9] and pediatric logistic organ dysfunction (PELOD) score,[10] as well as the number of organ failures according to the criteria of the pediatric consensus[11]; mean arterial pressure (MAP), with hypotension defined as MAP<2 standard deviations for their age; dosage of vasoactive drugs; inotropic score; levels of lactic acid, pH and excess base, creatinine, urea, alanine aminotransferase and bilirubin; type of CRRT monitor used; type of technique (hemofiltration or hemodiafiltration); maximum dose of heparin; ultrafiltrate volume; filter half-life; complications related to CRRT, and mortality. We compared children (n=81) with CRRT after CS with children who required CRRT for other diagnoses.

The results are presented as frequencies and percentages or means ± standard deviation. The normality of the numerical variables was studied with the Kolmogorov-Smirnov test. To study the association between quantitative variables, we applied the Pearson chi-squared test or Fisher exact test depending on the sample size. For the comparison of numerical variables, we used the Student t-test or Mann-Whitney U test depending on normality.

The association between the diagnosis of heart disease and CRRT extending beyond 14 days was studied using logistic regression because it was a dichotomous variable. For the study of predictors of mortality, we applied Cox regression[12,13] and the results were expressed using the hazard ratio (HR) with its corresponding 95% confidence interval (95%CI). For each of the independent variables, we studied the verification of the hypothesis of proportional risks through the study of the ln(-lnS(t)) graphs, as a function of ln (survival) and martingale residuals (calculated from the Cox-Snell residuals), and Schoenfeld residuals. Once the suitability of the Cox regression was assessed, we included step-by-step in the multivariate model only those variables with P<.1, or variables with special clinical interest, such as predictors of mortality, excluding those that may be highly correlated with each other to avoid possible collinearity. We applied bilateral tests and considered results with P<.05 to be statistically significant. Statistical analysis was performed using the SPSS 18.0 program (SPSS Inc., Chicago, Illinois, United States).

RESULTS

Of the 1650 patients who underwent CS between January 1996 and April 2009, 81 patients (4.9%) required CRRT, 18 of them after heart transplantation. Children in postoperative CS made up 46.5% of patients treated with CRRT in this period. The mean age of children with CRRT after CS was 50 (64) months, and 68% were male. Some 53% were under 1 year of age and 26% weighed less than 5 kg. Heart diseases, surgeries performed, and adjusted risk of the surgery are shown in Table 1. There were 13 patients who received extracorporeal membrane oxygenation.[14] The most frequent indications for CRRT were ARF with hypervolemia (37%), isolated ARF (36%), and hypervolemia refractory to diuretics (25%). The CRRT characteristics are shown in Table 2.

Table 3 shows the characteristics of the patients, their clinical severity, treatment received at the start of CRRT, and the comparison with other children treated with CRRT. Children who underwent CS showed greater risk of requiring CRRT treatment (4.9%) than other patients (1.6%; 93/5813). Some 80.2% of children with CRRT after CS suffered 3 or more organ failures. Children who were subjected to CS showed significantly lower MAP than the other patients, and 95% required vasoactive drugs. Their inotropic score was also greater. In contrast, levels of urea and creatinine at the start of CRRT were lower. The mean duration of CRRT filters was greater in children with CS, although the doses of administered heparin were also higher (Table 3).

Some 65% of children with CRRT after CS suffered complications. Table 4 shows the incidence of complications and the comparison with the rest of the patients. Only hypokalemia was greater in patients with CS.

The CRRT was required for more than 14 days by 22 children (27%), and for more than 21 days by 15 children (18.5%). In the logistic regression study, a diagnosis of heart disease increased the risk of needing prolonged CRRT (HR=1.49; 95%CI, 1.29-2.84; P=.01).

Mortality in children with CRRT after CS was greater than in children with CS who did not require CRRT (43% vs 4%, P<.001). Causes of death were multiple organ failure (46%), cardiogenic

Table 1
Surgeries and Risk Classification

Surgery	Patients, n (%)
Heart transplantation	18 (22.2)
Fontan surgery	12 (14.8)
Correction of tetralogy of fallot	10 (12.3)
Glenn surgery	9 (11.1)
Mitral valvuloplasty	7 (8.6)
Correction of atrioventricular canal	6 (7.4)
Correction of ventricular septal defect	5 (6.2)
Arterial switch surgery for transposition of the great arteries	5 (6.2)
Unifocalization surgery	3 (3.7)
Norwood surgery	2 (2.5)
Ross-Konno surgery in critical aortic stenosis	2 (2.5)
Aortic arch reconstruction	2 (2.5)
Total	81 (100)
*RACHS category**	
RACHS 2	24 (38.1)
RACHS 3	32 (50.8)
RACHS 4	3 (4.8)
RACHS 5	2 (3.1)
RACHS 6	2 (3.1)

RACHS: Risk Adjustment for Congenital Heart Surgery.
* The 18 patients with heart transplantation were not included.

Table 2
Characteristics of Continuous Renal Replacement Techniques in Children With Cardiac Surgery

Characteristics of the technique	
Vascular access	
Femoral vein	54 (67)
Jugular vein	13 (16)
Subclavian vein	6 (7)
Inserted in the ECMO circuit	3 (4)
Other accesses	5 (6)
Type of CRRT pump (Hospal®)	
Prisma	63 (77)
BSM32IC	15 (19)
Prismaflex	3 (4)
Catheter calibre, Fr	
5	8 (10)
6.5	42 (52)
7-9	13 (16)
10-11	10 (12)
Several	5 (6)
Inserted in the ECMO circuit	3 (4)
Surface area of the CRRT filter, m^2	
0.04	25 (31)
0.15	7 (8)
0.6	28 (35)
0.9	13 (16)
Several	8 (10)
Technique	
Hemofiltration	24 (30)
Hemodiafiltration	57 (70)
Flows	
Blood flow, mL/kg/min	4.3 [3.0-6.0]
Replacement fluid flow, mL/h	200 [100-400]
Dialysis fluid flow, mL/h	300 [163-750]
Total effluent flow, mL/kg/h	49 [39-64]
Total duration of treatment, h	115 [48-398]
Number of filters per patient	3 [2-8.5]
Filter half-life, h	39 [17-64]

CRRT, continuous renal replacement techniques; ECMO, extracorporeal membrane oxygenation.
Data are expressed as no. (%) or median [interquartile interval].

shock (40%), brain death (3%), and withdrawal of care due to the irreversibility of the underlying disease (11.4%).

Table 5 shows the univariate analysis of risk factors for mortality in children with CRRT after CS and their comparison with the other patients.

The age of the children who underwent CS and died was lower (30 months) than those who survived (64 months) (P=.026). Patients who died had higher PRISM (18 vs 14, P=.007) and PELOD (21 vs 17, P=.046) scores than the survivors. The mortality of children with hypotension at the start of the CRRT was significantly higher than for normotensive children (51.1% vs 25.8%, P=.03). Children treated with hemodiafiltration showed lower mortality than those who only received hemofiltration.

In the multivariate analysis, the factors related to mortality in children with CRRT after CS were hypotension at the start of CRRT, a PRISM score≥21, and the use of hemofiltration (Table 6).

DISCUSSION

In our study, 4.9% of children subjected to CS required CRRT. These figures are similar to those reported by other authors.[15] A significant percentage of children were under 12 months of age and a quarter weighed less than 5 kg. In the younger children, CRRT is more complicated due to the difficulty of venous cannulation, the small calibre of vascular accesses and the major hemodynamic repercussion of CRRT due to the fact that the extracorporeal circuit represents a high percentage of blood volume.

Low cardiac output is the main factor for onset of ARF in the postoperative period of CS. Patients with CRRT after CS showed a greater frequency of hypotension and greater need for inotropic drugs than other critically ill children who required CRRT, although there were no differences in clinical severity scores. This fact indicates that hemodynamic alteration is one of the fundamental factors in the need for CRRT. In heart transplantation, the toxicity of immunosuppressants such as tacrolimus also contributes to renal damage, and may explain the high need for CRRT in these patients.

The timing of CRRT initiation is very important.[16] Several studies have shown that one of the most important prognostic factors is a positive fluid balance prior to starting CRRT.[17,18] In our opinion, it is important that CRRT be started early. In our patients, urea and creatinine levels at the start of CRRT were low, since the technique was initiated once a positive fluid balance was detected. The technique involved increasing the dose of diuretics, regardless of urea and creatinine readings.

Children subjected to CS required CRRT for almost twice as long as the other patients. In the logistic regression study, CS significantly increased the risk of prolonged CRRT, which probably reflects slower recovery of the renal disorder in low cardiac output conditions.

The incidence of complications related to CRRT was high, which coincides with reports from other authors,[18] although the majority of complications were not significant.

Few studies have analyzed the mortality of patients who require CRRT. The need for CRRT in adults varies between 30% and

Table 3
Comparison Between Children With Continuous Renal Replacement Techniques After Cardiac Surgery and the other Critically ill Children Treated With Continuous Renal Replacement Techniques

	Cardiac surgery	Other patients	*P*
Patients	81	93	
Age, months	50±64	55±64	.62
PRISM, %M	21±22	20±25	.17
PIM, %M	9±14	12±17	.36
PELOD, %M	20±29	25±28	.16
Number of organ failures	3.1±0.7	2.9±1.5	.21
Lactate, mmol/L	3.1±3.6	3.1±3.7	.44
Arterial pH	7.35±0.1	7.29±0.1	.06
MAP, mmHg	55±14	66±23	<.001
Inotropic Score	75.6±141.9	55.1±90.1	<.001
Adrenaline dose, μg/kg/min	0.6±1.5	0.4±0.8	<.001
Dopamine dose, μg/kg/min	10±6	8±7	<.001
Initial creatinine, mg/dL	1.1±0.8	1.9±1.7	<.001
Initial urea, mg/dL	70±46	98±68	<.001
ALT, UI/L	223±764	181±642	.63
Bilirubin, mg/dL	2.1±2.8	1.6±1.4	.60
Maximum doses of heparin, U/kg/h	17±11	13±10	.04
Total effluent flow, mL/kg/h	53±19	62±33	.51
Filter half-life, hours	50±48	36±31	.02
Treatment duration	271±357	148±188	.02
Sex (males)	55 (68)	50 (54)	.06
Mechanical ventilation	78 (98)	67 (73)	<.001
Dialysis technique (hemodiafiltration)	57 (70)	72 (77)	.29
Vasoactive drugs	77 (95)	59 (63)	<.001
Initial Hypotension	45 (59)	27 (34)	<.001

%M, percentage of mortality; MAP, mean arterial pressure; PELOD, pediatric logistic organ dysfunction; PIM, pediatric index of mortality; PRISM, pediatric risk of mortality.
Inotropic score (μg/kg/min): dopamine+dobutamine+(adrenaline×100)+noradrenaline×100)+isoproterenol×100)+(milrinone×15).
Data are expressed as mean ±standard deviation or no. (%).

Table 4
Complications of the Renal Replacement Technique. Comparison Between Children With Cardiac Surgery and the Other Patients

	Cardiac surgery	Other patients	*P*
Catheterization complications	5 (6.3)	8 (8.7)	.54
Hemorrhage	10 (12.5)	8 (8.7)	.41
Hypotension during CRRT connection	27 (33.8)	26 (28.3)	.43
Hyponatremia, Na<130mEq/L	4 (9.3)	6 (15)	.42
Hypocalcemia, total Ca<8mg/dL	0	4 (10.3)	.07
Hypokalemia, K<3mEq/L	3 (7)	2 (4.9)	.55
Hypomagnesemia, Mg<1.5mg/dL	2 (5)	1 (2.9)	.89
Hypophosphatemia*	20 (42.6)	19 (47.5)	.64
Thrombocytopenia<100 000/μL	13 (27.7)	11 (23.4)	.67

CRRT, continuous renal replacement techniques.
**P*<4 mg/dL in children under 6 years of age and *P*<3 mg/dL in those over 6 years of age.
Data are expressed as no. (%).

70%.[15,19,20] Factors associated with mortality in adults with CRRT are poor ventricular function, diabetes mellitus, peripheral vascular disease, need for urgent surgery, and preoperative creatinine values.[10–13] In our study, mortality in children with CRRT after CS was 43%. There is only one retrospective study that has studied the outcomes of children (n=25) with CRRT after CS.[3] In that study, initial mortality during CRRT was 32% and final mortality was 76%.[3]

Some studies have analyzed the prognostic factors of critically ill children who suffer ARF or require CRRT. Clinical severity scores, hemodynamic disorders, number of organ failures, and positive fluid balance before starting CRRT are the main factors associated with the prognosis.[17,18,21,22]

In our study, children under 1 year old and those that weighed less than 10 kg had higher mortality, which coincides with findings from other authors.[18,23] However, in the multivariate logistic regression study, age was not a factor that increased mortality risk.

Scores for clinical severity assessment, mortality risk, PRISM, PIM, and PELOD were significantly greater in children who died than in the survivors.[7,24] However, the 3 scales underestimated the mortality risk.[25,26]

In the multivariate study, risk factors associated with mortality were the hemodynamic disorder (hypotension) when starting CRRT, clinical severity score, and the use of hemofiltration.[5,7] Although there are few variables in critically ill patients that are truly independent, our results indicate that the prognosis of critically ill children that require CRRT after CS is not directly related to the degree of renal failure or replacement technique, but rather depends on the clinical severity and, in particular, hemodynamic disorders.

Table 5
Univariate Cox Regression Analysis of Factors Associated With Mortality in Children With Continuous Renal Replacement Techniques After Cardiac Surgery and the Other Patients Who Required Continuous Renal Replacement Techniques

	After cardiac surgery		Other patients	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Age≤12 months	1.99 (1-3.98)	.05	1.51 (0.70-3.25)	.30
Weight<10 kg	2.31 (1.13-4.74)	.02	1.57 (0.72-3.41)	.25
PRISM≥21	2.18 (0.99-4.80)	.05	3.01 (1.37-6.61)	<.01
Hypotension	2.25 (1-5.08)	.05	4.17 (1.68-10.4)	<.01
Adrenaline dose≥0.6	1.91 (0.91-4.04)	.08	3.42 (1.51-7.72)	<.01
Initial creatinine≥1.4	0.28 (0.11-0.73)	.01	0.59 (0.26-1.36)	.21
Dialysis technique (hemofiltration)	8.36 (3.25-21.5)	<.01	2.19 (0.91-5.30)	.08

HR, hazard ratio; 95%CI, 95% confidence interval; PRISM, pediatric risk of mortality.
Risk>1 indicates greater mortality.
Only those factors with *P*<.1 are shown.

Table 6
Adjusted Multivariate Cox Regression Analysis of Factors Associated With Mortality in Children With Continuous Renal Replacement Techniques After Cardiac Surgery and in the other Patients With Continuous Renal Replacement Techniques

Factor	After cardiac surgery		Other patients	
	HR (95%CI)	*P*	HR (95%CI)	*P*
PRISM≥21	2.78 (1.16-6.67)	.02		
Dialysis technique (hemofiltration)	12.90 (4.2-40)	<.01		
Hypotension	2.87 (1.02-8.08)	.04	6.36 (2.6-17.1)	<.01
Adrenaline dose≥0.6			5.00 (1.9-13)	<.01

95%CI, 95% confidence interval; HR, hazard ratio; PRISM, pediatric risk of mortality.

In the univariate and multivariate studies, the use of hemofiltration compared to hemodiafiltration was a factor associated with mortality. The type of replacement technique used probably does not affect the prognosis by itself. It is more likely that a selection bias occurred in our study between the two therapies. The association between hemofiltration and mortality was due to the fact that CRRT was initiated early in the most seriously ill patients due to hypervolemia and hemodynamic failure, without their presenting increased creatinine. However, prospective studies are needed to systematically compare the two techniques.

Limitations

Our study had some limitations. First, it was an observational study, which precludes establishing clear cause-and-effect relationships and ruling out confounding factors. Second, the sample size was too small, relatively, to allow for sufficient statistical power to analyze some variables. Lastly, due to the lengthy duration of the study, we cannot rule out that improvements in the treatment of critically ill children may have affected the results.

Prospective studies are needed to analyze whether new renal damage markers that allow for early diagnosis of renal disorders in children during the postoperative period of CS are useful to establish early indications for CRRT.[27,28] Randomized studies are also needed to determine whether early initiation of CRRT and hemodiafiltration improve the prognosis.

CONCLUSIONS

Although only a small percentage of the children subjected to CS required CRRT, their mortality was high and greater than that of the other children treated with CRRT. Hypotension and clinical severity when starting CRRT and hemofiltration as replacement techniques were factors associated with mortality.

ACKNOWLEDGEMENTS

We would like to thank the nurses and physicians of the Paediatric Intensive Care Department of the *Hospital General Universitario Gregorio Marañón* of Madrid for their collaboration in the study.

CONFLICTS OF INTEREST

None declared.

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