Long-term outcomes of children treated with continuous renal replacement therapy


Servicio de Cuidados Intensivos Pediátricos, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria, Hospital Gregorio Marañón, Madrid, Universidad Complutense de Madrid, Red de salud Maternoinfantil y del Desarrollo (Red SAMID), Madrid, Spain

Received 29 July 2014; accepted 29 December 2014
Available online 14 November 2015

KEYWORDS
Acute kidney injury; Acute renal failure; Continuous renal replacement therapy; Chronic renal failure

Abstract
Introduction: The objective of this study is to analyse long-term outcomes and kidney function in children requiring continuous renal replacement therapy (CRRT) after an acute kidney injury episode.

Patients and methods: A retrospective observational study was performed using a prospective database of 128 patients admitted to the paediatric intensive care unit between years 2006 and 2012 who required CRRT. The subsequent outcomes were assessed in those surviving at hospital discharge.

Results: Of the 128 children who required CRRT in the paediatric intensive care unit, 71 survived at hospital discharge (54.4%), of whom 66 (92.9%) were followed up. Three patients had chronic renal failure prior to admission to the PICU. Of the 63 remaining patients, 6 had prolonged or relapses of renal function disturbances, but only one patient with atypical hemolytic uraemic syndrome developed end-stage renal failure. The rest had normal kidney function at the last check-up.

Conclusions: Most of surviving children that required CRRT have a positive outcome, presenting low mortality rates and recovery of kidney function in the medium term.

© 2014 Asociación Española de Pediatría. Published by Elsevier España, S.L.U. All rights reserved.
Introduction

Acute renal failure (ARF) or acute kidney injury (AKI), which is currently the most used term, is a frequent complication in children who are in critical condition. Its incidence varies between 4.5% and 82%, according to the definition and characteristics of the studied population.1

AKI is associated with high rates of hospital mortality.2 Mortality rates differ according to studies,3–9 depending on the nature of the underlying disease and the severity of renal failure; it is higher in children under the age of two years.10

The aetiopathology of AKI differs between adults and children.11 The most common causes for AKI in children are tubular necrosis due to heart surgery, shock and/or sepsis, haemolytic uraemic syndrome and, less frequently, acute glomerulonephritis, urinary tract obstruction, toxins (including drugs) and renal parenchymal disease or renal parenchymal disease caused by complications of systemic disorders.12

In adults in critical condition 9.2% of patients with AKI who need renal replacement therapy (RRT) develop chronic renal failure (CRF) or develop it as the disease progresses.13 However, study results in adults cannot be extrapolated to children because, among other reasons, adults have more comorbidities.11

The severity of renal failure, the need for RRT and the number of episodes of AKI are associated with a poorer evolution.14

In addition, it has been observed that minor though severe changes in renal function can cause short-term and long-term complications, such as CRF.15

There are very few studies that have analysed the long-term evolution of AKI in children, and some of them have only analysed the prognosis of children with primary renal disease.16

The aim of this study is to analyse the long-term prognosis and renal function of children who have required RRT.

Patients and methods

A retrospective observational study was performed by reviewing the clinical records of patients included in a prospective database of children who required RRT during their admission to a paediatric intensive care unit (PICU) between 2006 and 2012. The study was approved by the local Ethics Committee.

All the patients between the age of one month and 18 years who were diagnosed with paediatric AKI according to KDIGO criteria17 and who were treated with continuous renal replacement therapy (CRRT) and survived after being discharged from the PICU were selected. The demographic data, the clinical severity scores from the Paediatric Risk of Mortality 2 index,18 the Paediatric Index of Mortality 219 and the Paediatric Logistic Organ Dysfunction,20 the characteristics of the CRRT during admission to the PICU, and progress after being discharged from the PICU were analysed. At each clinical examination, the following parameters were recorded: haemogram (haemoglobin, leukocytes, platelets), biochemistry (urea, creatinine, albumin, sodium, potassium, chloride, calcium, phosphate, magnesium) cystatin, glomerular filtration rate based on cystatin levels (estimated glomerular filtration rate)21, vitamin D, parathormone, arterial blood gas (pH, bicarbonate, base excess), lactic acid, renal ultrasound scan, number of admissions and their characteristics (cause, need and type of renal replacement therapy) and treatment during evolution (bicarbonate,
were male. The most frequent diagnosis was congenital cardio-
diopathy in 50 patients (70.4%) (39 patients after heart
surgery and seven after a heart transplant), followed by
septic shock in seven patients (9.8%). The other 14 patients
(19.7%) were admitted for other reasons (four after abdom-
inal surgery, one after respiratory tract surgery, one due to
haemolytic uraemic syndrome, two due to tumour lysis syn-
drome, three due to congenital metabolic diseases, one due
to peritonitis associated with a catheter for peritoneal dial-
ysis, one due to massive thrombosis of mitral prosthesis and
one due to glomerulonephritis [in a patient with Hodgkin
lymphoma]).

The average stay at the PICU was 27 days (IQR: 16.5–47.5)
and the average duration of mechanical ventilation was 14
days (IQR 7.5–27.5). Twenty patients (28.1%) needed extra-
corporeal membrane oxygenation.

Analytical data before and after CRRT are shown in
Table 2. Only two patients (2.8%) needed dialysis techniques
at the time of discharge from the PICU (one had haemolytic
uraemic syndrome and another a previous CRF).

Subsequent follow-up

Fig. 1 summarises patients’ evolution. Sixty-six patients
(92.5%) were monitored after being discharged from the hos-
pital, with an average follow-up period of 40.4 months (IQR
18.4–64.8 months).

In three patients, kidney function alterations lasted over
one month and three other children had relapses or new AKI
episodes: their characteristics and evolution are shown in
Table 3. One of them, an infant with ARF who was later diag-
nosed with atypical haemolytic uraemic syndrome, suffered
from end-stage renal failure and was dialysis-dependant
for more than three months, which required renal transplanta-
tion.

Three patients had CRF before admission to the PICU.
The first had nail-patella syndrome with focal segmental
glomerulosclerosis. Subsequently, he underwent renal trans-
plantation and needed CRRT again after surgery, with
favourable progress. The second patient was readmitted for
a heart retransplant. His progress was favourable and did
not need CRRT. The third patient, diagnosed with lupus ery-
thematosus and associated nephropathy, was admitted due
to pneumococcal sepsis and needed CRRT. He progressed
well and is currently asymptomatic, with immunosuppress-
ant treatment. At the end of the study, none of the three
patients’ renal function had worsened compared with their
previous state.

The rest of the patients had normal renal function at the
time of the last follow-up visit.

The blood test results from the last check-up are shown in
Table 4. In 15 patients, urea levels were over 40, but
only three patients had creatinine levels over 1 mg/dl (one
of the patients with previous CRF who had 1.5 mg/dl crea-
tinine, an 18-year-old male with 1.1 mg/dl creatinine, which
was normal for his age, and a 23-year-old male with
a heart transplant undergoing immunosuppressant treat-
ment with tacrolimus who had 1.5 mg/dl creatinine). Fig. 2
shown the changes in creatinine. There were no signifi-
cant changes in creatinine after discharge from the PICU
(p=0.892). None of the patients had hyperpotassaemia

---

Table 1: General data from the 71 patients.

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>P25</th>
<th>P75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>51.1</td>
<td>6.0</td>
<td>99.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>15.0</td>
<td>6.0</td>
<td>25.0</td>
</tr>
<tr>
<td>PRISM 2 (mortality risk)</td>
<td>14.0</td>
<td>11.0</td>
<td>20.0</td>
</tr>
<tr>
<td>PIM 2% (mortality risk)</td>
<td>12.4</td>
<td>5.5</td>
<td>25.8</td>
</tr>
<tr>
<td>PELOD % (mortality risk)</td>
<td>16.2</td>
<td>1.3</td>
<td>24.8</td>
</tr>
<tr>
<td>Lactic (mEq/l)</td>
<td>1.7</td>
<td>1.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Total duration of technique (h)</td>
<td>158</td>
<td>85.0</td>
<td>293</td>
</tr>
</tbody>
</table>

P25: 25th percentile; P75: 75th percentile.
### Table 2 Biochemical data before and after CRRT.

<table>
<thead>
<tr>
<th></th>
<th>Initial value</th>
<th>Final value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>P25</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>72.0</td>
<td>25.5</td>
</tr>
<tr>
<td>Uric (mg/ml)</td>
<td>8.0</td>
<td>6.4</td>
</tr>
<tr>
<td>Potassium (mEq/l)</td>
<td>4.0</td>
<td>3.4</td>
</tr>
<tr>
<td>Platelets</td>
<td>156,500</td>
<td>84,750</td>
</tr>
</tbody>
</table>

### Table 3 Characteristics of patients with prolonged alteration of renal function and/or relapse.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (months)</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Progress</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>Female</td>
<td>Atypical haemolytic-uraemic syndrome</td>
<td>ESKD. Renal transplantation</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>Male</td>
<td>Congenital cardiopathy</td>
<td>New AKI that required CRRT following surgery. Complete recovery of renal function. Died after one year due to cardiac arrest caused by brain death.</td>
</tr>
<tr>
<td>3</td>
<td>180</td>
<td>Male</td>
<td>Glomerulonephritis. Hodgkin lymphoma</td>
<td>New moderate AKI due to meningococcal sepsis, no CRRT required. Full recovery</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>Female</td>
<td>Meningococcal sepsis</td>
<td>Moderate 3-month RF that does not require RRT. Full recovery</td>
</tr>
<tr>
<td>5</td>
<td>84</td>
<td>Male</td>
<td>Congenital cardiopathy</td>
<td>Readmission due to PTE that required CRRT.</td>
</tr>
<tr>
<td>6</td>
<td>99</td>
<td>Male</td>
<td>Congenital cardiopathy</td>
<td>Prolonged 7-month RF that required CRRT.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Full recovery.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>After heart transplant</td>
</tr>
</tbody>
</table>

AKI: acute kidney injury; RF: renal failure; ESKD: end-stage kidney disease; CRRT: continuous renal replacement therapy, PTE: pulmonary thromboembolism.

### Table 4 Haemogram, arterial blood gas and biochemistry at last check-up.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Median</th>
<th>P25</th>
<th>P75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>65</td>
<td>13.2</td>
<td>11.6</td>
<td>14.3</td>
</tr>
<tr>
<td>Leukocytes (cells/mcl)</td>
<td>65</td>
<td>7.7</td>
<td>5.3</td>
<td>10.9</td>
</tr>
<tr>
<td>Platelets (cells/mcl)</td>
<td>65</td>
<td>211,000</td>
<td>149,500</td>
<td>262,500</td>
</tr>
<tr>
<td>pH</td>
<td>15</td>
<td>7.30</td>
<td>7.30</td>
<td>7.40</td>
</tr>
<tr>
<td>Bicarbonate (mmol/l)</td>
<td>15</td>
<td>25.7</td>
<td>21</td>
<td>28</td>
</tr>
<tr>
<td>BE</td>
<td>13</td>
<td>0.6</td>
<td>-2.2</td>
<td>2.7</td>
</tr>
<tr>
<td>Lactic acid (mmol/l)</td>
<td>6</td>
<td>1.9</td>
<td>1.3</td>
<td>2.9</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>64</td>
<td>33</td>
<td>27</td>
<td>39</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>64</td>
<td>0.4</td>
<td>0.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Sodium (mEq/l)</td>
<td>64</td>
<td>138</td>
<td>136</td>
<td>141</td>
</tr>
<tr>
<td>Potassium (mEq/l)</td>
<td>71</td>
<td>4.2</td>
<td>3.6</td>
<td>4.6</td>
</tr>
<tr>
<td>Chloride (mEq/l)</td>
<td>50</td>
<td>102</td>
<td>99.7</td>
<td>104</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>51</td>
<td>9.4</td>
<td>9.0</td>
<td>9.8</td>
</tr>
<tr>
<td>Phosphorus (mg/ml)</td>
<td>48</td>
<td>4.3</td>
<td>3.6</td>
<td>4.8</td>
</tr>
<tr>
<td>Magnesium (mEq/l)</td>
<td>48</td>
<td>1.9</td>
<td>1.7</td>
<td>2.2</td>
</tr>
<tr>
<td>Vitamin D (ng/ml)</td>
<td>12</td>
<td>32.3</td>
<td>17.0</td>
<td>38.2</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>6</td>
<td>71.5</td>
<td>34.0</td>
<td>111.7</td>
</tr>
<tr>
<td>GFR (ml/min/1.73 m²)</td>
<td>25</td>
<td>85</td>
<td>66</td>
<td>126</td>
</tr>
<tr>
<td>Cystatin</td>
<td>25</td>
<td>1.0</td>
<td>0.7</td>
<td>1.2</td>
</tr>
</tbody>
</table>

BE: base excess; GFR: estimated glomerular filtration rate; PTH: parathormone.
and only four patients had mild metabolic acidosis. The rest of the analytical parameters were normal. In 52 (78.7%) patients who underwent follow-up a renal ultrasound scan was performed, which was normal in 35 (67.3%). Ten (19.2%) had cortical hyperechogenicity, two (3.8%) had an associated uropathy and five (9.6%) other non-relevant findings.

During follow-up visits, 59 (89.4%) patients needed to be admitted to hospital. Out of the total of readmissions, 180 (43.5%) were due to heart conditions and 41 (9.9%) due to renal conditions (most of the readmissions were for patients who had end-stage renal failure and needed renal transplantation).

Discussion

In adults, AKI is associated with a higher risk of CRF, and a high number of patients who need RRT after an AKI episode evolves into CRF. In a study performed by Lowell in 703 patients with AKI and RRT, 65 (9.2%) developed CRF.

There are several elements that seem to be associated with the development of CRF after an AKI episode: older age, comorbidities, clinical duration and acuteness, number of AKI episodes, partial recovery of renal function after the acute episode, renal disease aetiology and the existence of previous CRF.

There are very few studies that have analysed the long-term evolution of children with ARF; some have analysed patients with AKI and, others, like ours, only those who had required RRT. Our work is one of the studies that analyses the long-term evolution of a higher number of paediatric patients (71 children) who needed CRRT for a long period (seven years).

Askenazi et al. studied 174 children who survived an ARF episode for 3–5 years. Sixteen developed CRF after the acute episode, and only 29 of the remaining 126 could be followed-up. Six of these had hyperfiltration and two microalbuminuria, and were the only ones who needed RRT in the acute episode.

Mammen et al. prospectively monitored for three years the renal function of 126 children who had had AKI, although only 22 had needed RRT. All the patients survived the AKI episode and recovered their previous renal function, except for one who progressed to dialysis dependency. During follow-up, 10% developed CRF and 38% had a slight decrease in renal function. Another 3.2% developed hypertension and 8.2% hyperfiltration, which are long-term risk factors for CRF. In this study, the need for acute dialysis was significantly associated with the development of CRF.

Spizzirri et al. analysed the evolution of 118 children with haemolytic uraemic syndrome who were monitored for at least 10 years. Of these, 3.4% developed end-stage renal failure and 37% a slight decrease in clearance, hypertension or urine protein.

In our study, most of the children who needed CRRT regained long-term renal function. Only six patients presented prolonged alterations or relapses, and just one of them, with atypical haemolytic-uraemic syndrome, developed end-stage renal failure. Our results contrast with those of other paediatric studies, which found that a higher number of children with AKI subsequently evolved into CRF. This could be because most of our patients had AKI of non-renal origin, caused by cardiogenic shock after heart surgery or by septic shock. When these patients develop multiple organ failure, mortality rates are high, but if they survive, they regain their renal function completely. Children with AKI of renal origin, meanwhile, have lower mortality rates, but the long-term evolution of renal function is worse. This is also the case for adults.

The percentage of readmissions in our study is very high (89.4%). However, it must be taken into consideration that both the initial AKI episode and the readmissions were caused by the underlying pathology of the patient, mostly congenital cardiopathies, and not by the renal problem. Only nine of our patients died after being discharged from the hospital and none of the deaths were caused by renal alterations.

Our study has some limitations. The main one is that it is a retrospective analysis that has prevented us from obtaining all renal function parameters, since there was no programmed follow-up of the patients. Therefore, it has not been possible to detect minor alterations in renal functions, such as urine protein, microalbuminuria or hyperfiltration, which can predict the risk of developing long-term CRF.

On the other hand, there was no record of diuresis prior to initiating CRRT in our database, nor of the percentage of patients who met AKI criteria due to diuresis alterations and/or creatinine levels. Thus, it is possible that some of the patients who were included in the study had been treated only for diuretic-resistant hypervolemy. Consequently, our study only shows the evolution of patients who needed treatment with CRRT and it is not possible to analyse the association between the evolution of the long-term renal function with diuresis or the severity of the renal alteration before treatment.

Lastly, this is a unicentric study, with a high percentage of children who developed AKI due to cardiogenic shock after heart surgery, and it is possible that it does not represent the general population.

For these reasons, it is necessary to perform multicentric prospective studies that analyse the evolution of children who have had AKI with a specific renal function follow-up protocol.
Conclusions

Most of the children who need CRRT and survived the acute episode regained renal function in the medium term, and are now making good progress.

Conflict of interests

The authors declare that there are no conflicts of interest.

References