Effect analysis of early bedside hemo-filtration in treatment of severe pneumonia with acute renal failure of children

G.-J. Qi1, Y.-L. Chao2, X.-Y. Xi1, K.-X. Liu1, W.-H. Li1

1Intensive Care Unit, Xuzhou Children’s Hospital, Xuzhou, Jiangsu, China
2Department of Severe Medicine, Affiliated Hospital of Xuzhou Medical College, Jiangsu, China

Abstract. – OBJECTIVE: To investigate the best opportunity for bedside continuous blood purification (CBP) to treat severe pneumonia with acute renal failure (ARF) of children and look for the sensitive marker to evaluate the clinical effects and prognosis.

PATIENTS AND METHODS: 54 children patients that were diagnosed as severe pneumonia with ARF by Pediatric Intensive Care Unit (PICU) were enrolled in our study as experimental group. In the meanwhile, 46 children patients that were diagnosed as severe pneumonia with ARF by PICU were enrolled as a normal control group. Patients in the experimental group started CBP treatment within 24 h after onset while patients in the control group started CBP treatment 24h after onset. The differences of clinical effects between two groups were compared for statistical significance.

RESULTS: The survival rates of the observation group in day 7, day 28 and 6 months were significantly higher than those in the control group. After treatment for 7 days, IL-6 and TNF-α, YKL-40 and Annexin A1 levels of the experimental group were significantly lower than those of the control group. 7-day infection-related organ failure score (SOFA) of the experimental group was significantly lower than that of the control group.

CONCLUSIONS: CBP therapy for treating severe pneumonia with acute renal failure of children within 24 hours could significantly improve the survival rate and reduce the inflammatory reactions.

Key Words: Continuous blood purification, Severe pneumonia, Acute renal failure, Cartilage glycoprotein 39, SOFA.

Introduction

Both “2008 Guidelines for the Diagnosis and Treatment of Severe Sepsis and Septic Shock” support 2B recommendation for treating septic acute kidney injury (AKI) by continuous blood purification (CBP) and 2D recommendation for assisted managing fluid balance of severe sepsis patients with unstable hemodynamics by CBP1,2. At present, CBP is not only applied in severe acute renal failure (ARF) but also in non-renal diseases such as liver failure, hyperbilirubinemia, acute respiratory distress syndrome, severe acute pancreatitis and crush syndrome, etc. CBP has been developed from a pure kidney replacement to a multi-organ system support therapy3. However, the intervention timing of CBP has been controversial4. A large number of studies have confirmed that early intervention of CBP can reduce the mortality of septic AKI. But the definition of “early” has been quite different, varying from 24-96 hours. There is still lack of a consensus on the optimal intervention time5,6. Based on this, we have compared and analyzed the differences on clinical effects and prognosis before and after 24 h and tried to find out a sensitive indicator to guide clinical treatment.

Patients and Methods

Patients

54 children diagnosed with severe pneumonia with ARF by PICU in our hospital from October, 2012 to October, 2014 were enrolled in our study as experimental group. In the meanwhile, 46 children patients diagnosed as severe pneumonia with ARF by PICU in our hospital from October, 2010 to October, 2012 were enrolled as control group. Diagnostic criteria (3) for severe pneumonia was with following symptoms -conscience disturbance, respiratory rate ≥ 30/min, less urine, urine volume < 20 ml/h or complicated by acute renal
failure and needed dialysis, arterial systolic pressure < 90 mmHg, $p_O_2 < 60$ mmHg, $p_O_2/FiO_2 < 300$, required mechanical ventilation therapy, bilateral or multiple pulmonary lobes were affected under chest X ray examination or lesions expanded for over 50% within 48 hours after admission, complicated by septic shock, respiratory failure, $p_O_2 < 60$ mmHg, $p_CO_2 > 50$ mmHg, $p_O_2/FiO_2 < 300$ under arterial blood gas analysis, digestive tract bleeding, convulsions, and extra-pulmonary infections, including sepsis, shock and disseminated intravascular coagulation. Diagnostic criteria for ARF (3) includes increase of serum creatinine ($Scr > 1.5$ times or urine volume $≤ 0.5$ ml/kg·h-1 after 48h for consecutive 6 hours. Patients with congenital immunodeficiency, inherited metabolic diseases, history of chronic renal insufficiency were excluded.

After obtaining the approval of our hospital Ethic Committee and the informed consents of the patients’ custodians, children in the observation group started CBP treatment within 24h after onset while patients in the control group started CBP treatment 24h after onset. The experimental group includes 29 cases of male and 25 cases of females, with patients aged from 5-16 years old and on average age of 9.5±3.4; course of disease from 1h-4d and on average 1.4±0.5d; weight from 15-53 kg and on average 36.4±7.8 kg; Scr 654-1243 μmol/l and on average 823.9±76.5 μmol/l; CBP opening time from 8-23h and on average 14.2±3.3 h; 22 cases in 12h and 32 cases in 12h-24h.

The control group includes 25 cases of male and 21 cases of females, with patients aged from 4-15 years old and on average age of 9.7±3.5; course of disease from 3h-6d on average 1.7±0.4 d; weight from 16-52 kg on average 37.2±6.3 kg; Scr 686-1108 μmol/l and on average 805.4±92.7 μmol/l; CBP time from 30-68h and on average 45.5±6.7 h; 27 cases in 12h-24h and 19 cases over 48h. Differences on gender, weight, course of disease and Scr level between the two groups of patients had no statistical significance ($p > 0.05$).

**CBP Therapy**

All of the children patients were given standard medical treatments, such as antibiotics, fluid infusion, nutritional support, body temperature control, and prevention of complications of heart, brain, liver and other organs, etc. CBP treatment includes

1. Central venous catheter: 6.5-11.5 F single needle double cavity tube was used and puncture sites were located in bilateral femoral vein according to the patients’ age and weight.

2. Line and filter model: BaxBM25 model CBP machine (Baxter, Deerfield, FL, USA); child-sized line; polysulfone membrane; 0.2-0.4 m² membrane area for patients less than 20 kg, 0.4-0.8 m² membrane area for patients of 20-30 kg, 0.8-1.0 m² membrane area for patients over 30 kg.

3. Blood priming and return: Total volume of blood path and filter was kept within 10% of the total blood volume of patients. If it’s over 10%, whole blood priming should be applied appropriately priming by albumin or fresh frozen plasma for patients over 15 kg and had no anemia; priming by normal saline for patients below 15 kg and had no anemia; returned the blood completely if the patients were over 10kg and their hearts could tolerate.

4. Anticoagulation: Heparin sodium was used to anticoagulant. First dose was 0.25-0.5 mg/kg and maintenance dose was 0.05-0.3 mg/kg. The coagulation was monitored for once every 2-4 hours and activated coagulation time (ACT) was controlled at 180-220 seconds or controlled activated partial thromboplastin time (APTT) at 60-80s. Patients with abnormal coagulation and bleeding tendency were treated with heparin-free and monitored for coagulation function. If coagulation disorder occurred upon CBP withdrawal, protamine was used for neutralization.

5. Displacement fluid: used improved PORTS replacement fluid, regularly monitored blood gas analysis and timely adjusted the formula of replacement fluid. Selected sodium bicarbonate formula, took calcium as B solution and input it through another line.

6. Treatment mode and parameter setting: applied continuity vein-vein hemofiltration (CVVH), kept blood flow speed at 3-5 ml/min/kg, generally no more than 100 ml/min. Set the replacement fluid at 20-50 ml/h/kg.

7. Indications for machine withdrawal: body temperature dropped to normal range; organ function improved significantly; water, electrolyte, acid-base were balanced; urine volume ≥ 1 ml/kg·h; Scr and BUN returned to normal range; ALT ≤ 300 U/L; lung exudation of ARDS patients were alleviated and oxygenation index ≥ 300 mm Hg; consciousness was recovered.

8. Treatment shall be suspended under the following circumstances: low blood volume shock can not be corrected within 1 hour; se-
were bleeding, which could not be controlled by supplement of blood platelet and plasma as well as by suspension of heparin; no significant improvement in symptoms after 48 h treatment.

**Observation index**

Blood was drawn from the radial artery end and centrifuged for 10 min at 4°C, plasma was obtained with EDTA, and preserved at -70°C. The levels of IL-6 and TNF-α were measured with ELISA (Shenzhen Jingmei Bio Engineering Company). Adopted Metra™YKL-40EIA kit (provided by Quidel Company, San Diego, CA, USA) and ELISA was used to measure the concentration of YKL-40 in plasma.

Survival rates were compared and analyzed for 7d, 28d, and 6 m. As well as IL-6 and TNF-α, YKL-40 and Annexin A1 expression levels, as well as SOFA scores was compared between the two groups of patients.

**Measurement of Annexin A1**

3 ml of blood was drawn and separated peripheral blood mononuclear cell (PBMC) by single nuclear cell separation fluid according to density gradient centrifugation, quantitate proteins by 2D-QUANT methods (GE Health Care, Montreal, QC, Canada) followed by 2D gel electrophoresis and finally images were taken with UMAX PowerLook II 100 projection scanner, analyzed the images by PDQuest7.1.0 software package. Identified differentially expressed protein by mass-spectrography and verified by western blot.

**SOFA scoring included (7)**

Breathing (pO₂/FiO₂) ≥ 400 mmHg was defined as 0 point, < 400 mmHg as 1 point, < 300 mmHg as 2 points, < 200 mmHg and could be supported by ventilator as 3 points, < 100 mmHg and could be supported by ventilator as 4 points. Coagulation (platelet) ≥ 150×10⁹/L was defined as 0 point, < 150×10⁹/L as 1 point, < 100×10⁹/L as 2 points, < 50×10⁹/L as 3 points, < 20×10⁹/L as 4 points. Liver (bilirubin) < 20 μmol/l was defined as 0 point, 20-32 μmol/l as 1 point, 33-101 μmol/l as 2 points, 102-204 μmol/l as 3 points, > 204 μmol/l as 4 points. Circulation was either of (mean arterial pressure ≥ 70 mmHg was defined as 0 point, < 70 mmHg as 1 point. Dopamine dose ≤ 5 μg/kg·min was defined as 2 points, > 5 μg/kg·min as 3 points, > 15 μg/kg·min as 4 points. Epinephrine dose ≤ 0.1 μg/kg·min was defined as 3 points, > 0.1 μg/kg·min as 4 points; norepinephrine dose ≤ 0.1 μg/kg·min as 3 points, > 0.1 μg/kg·min as 4 points. The use of dobutamine was defined as 2 points; nerve (GCS scoring) in 15 as 0 point, between 13-14 as 1 point; between 10-12 as 2 points; in 6-9 as 3 points, < 6 as 4 points. Kidney was either of (creatinine < 110 m mol/l was defined as 0 point, 110-170 m mol/l as 1 point, 171-299 as 2 points, 300-440 m mol/l as 3 points, > 440 m mol/l as 4 points; 24h urine volume within 200-500 ml as 3 points, < 200 ml as 4 points). Daily assessment was based on the more diseased condition value and adrenergic drug used for 1h. The higher the scores was, the poorer the prognosis was.

**Statistical Analysis**

SPSS 20.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis, data was presented by means ± standard deviation and t test was applied in comparisons between groups; enumeration data was presented by percentage (%) and X² test was applied in comparisons between groups. The p < 0.05 was considered as statistical significance.

**Results**

**Comparisons on Survival Rate**

The survival rates of the observation group in day 7, day 28 and 6 months were significantly higher than those in the control group, and the difference was statistically significant (p < 0.05) as shown in Table I.

**Comparison on the levels of IL-6 and TNF-α, YKL-40 and Annexin A1**

After treatment for 7 days, IL-6 and TNF-α, YKL-40 and Annexin A1 levels of the observation group were significantly lower than those of the control group (p < 0.05) as shown in Table II.

**Comparison on SOFA score**

7 day Sequential Organ Failure Assessment (SOFA) score of the experimental group was significantly lower than that of the control group and the difference was statistically significant (13.4 ± 3.6): (20.7 ± 4.2).

**Discussion**

“Expert consensus on treatment of children with severe sepsis by continuous blood purifica-
and SOFA score were the independent risk factors of 28-day death rate (RR were 3.106 and 1.410, respectively). If grouping by RIFLE criteria, difference on death rate of early group (RIFLE-I) and late group (RIFLE-F) was not statistically significant. Therefore, it was speculated that to define the time from entering into ICU to perform CBP as early period could better improve the prognosis of patients than RIFLE. From clinical practice, we found that time from the onset of disease to CBP start up could better reflect the outcomes and that 24h death rate of ARF on children has reached up to 20-30%, after 24 hours, death rate began to decrease.

The results of our study showed that the survival rates of experimental group in day 7, day 28 and 6 months were significantly higher than those in the control group. Further subgroup analysis showed that differences on the homochronous survival rates in 12h and in 12-24h were not statistically significant, which indicated that started CBP therapy in 24 hours might be the best. After treatment for 7 days, IL-6 and TNF-α, YKL-40 and Annexin A1 levels of the observation group were significantly lower than those of the control group (Table II). IL-6 and TNF-α are inflammatory factors of sepsis, which plays an important role in sepsis or multiple organ failures, immune disorders and inflammatory response unbalances secondary to ARF.

CBP can not only remove small molecule toxic substances, such as creatinine, urea nitrogen, and potassium ion, but also effectively remove inflammatory mediators and endotoxin, reduces

<table>
<thead>
<tr>
<th>Group</th>
<th>Case</th>
<th>7d</th>
<th>28d</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>46</td>
<td>28 (60.87)</td>
<td>22 (47.83)</td>
<td>20 (43.48)</td>
</tr>
<tr>
<td>Experimental group</td>
<td>54</td>
<td>43 (79.63)</td>
<td>37 (68.52)</td>
<td>35 (64.81)</td>
</tr>
<tr>
<td>X²</td>
<td></td>
<td>4.246</td>
<td>4.397</td>
<td>4.569</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>0.039</td>
<td>0.036</td>
<td>0.033</td>
</tr>
</tbody>
</table>

Table I. Comparisons on survival rate [case (%)].

<table>
<thead>
<tr>
<th>Group</th>
<th>IL-6 (ng/L)</th>
<th>TNF-α (ng/L)</th>
<th>YKL-40 (µg/L)</th>
<th>Annexin A1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>242.26 ± 76.35</td>
<td>195.64 ± 55.47</td>
<td>123.57 ± 46.22</td>
<td>2654.39 ± 165.74</td>
</tr>
<tr>
<td>Observation group</td>
<td>84.53 ± 30.26</td>
<td>60.38 ± 19.57</td>
<td>52.41 ± 21.35</td>
<td>649.52 ± 96.35</td>
</tr>
<tr>
<td>t</td>
<td>5.748</td>
<td>6.324</td>
<td>5.627</td>
<td>6.127</td>
</tr>
<tr>
<td>p</td>
<td>0.016</td>
<td>0.012</td>
<td>0.019</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Table II. Comparison on IL-6 and TNF-α, YKL-40 and Annexin A1 protein level.
the series cascade inflammatory factors in the circulation of the patients, reduce damages on heart, lung, liver and other organs, improve organ functions and adjust the immune homeostasis. YKL-40 does not exist in normal mononuclear cells. It only increases significantly in the late stage of infection and could be regarded as an inflammatory acute phase protein, whose sensitivity may be superior than high sensitive C reactive protein. Annexin A1 is a member of calcium-dependent-phospholipid-binding protein superfamily. As an important inflammation regulatory protein, Annexin A1 plays quite an important role in the production of inflammatory metabolites and the adhesion process of neutral granulocyte/monocyte and endothelial cells. 7 days SOFA score of the observation group was significantly lower than that of the control group and the difference was statistically significant. Study results showed that SOFA was an effective predictor for the prognosis of patients that accepted blood purification.

Conclusions

CBP therapy for treating severe pneumonia with acute renal failure of children within 24 hours could significantly improve the survival rate and reduce the inflammatory reactions.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References


