European Review for Medical and Pharmacological Sciences 2015; 19: 4795-4800

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

G.-J. QI[1], Y.-L. CHAO[2], X.-Y. XI[1], K.-X. LIU[1], W.-H. LI[1]

[1]Intensive Care Unit, Xuzhou Children's Hospital, Xuzhou, Jiangsu, China
[2]Department 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" and "2012 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 CBP[1,2]. 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 therapy[3]. However, the intervention timing of CBP has been controversial[4]. 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 time[5,6]. 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 -consciousness disturbance, respiratory rate ≥ 30/min, less urine, urine volume < 20 ml/h or complicated by acute renal

Corresponding Author: Weihua Li, MD; e-mail: liweihua1975@126.com

failure and needed dialysis, arterial systolic pressure < 90 mmHg, pO_2 < 60 mmHg, pO_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, pO_2 < 60 mmHg, pCO_2 > 50 mmHg, pO_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) > 0.3 mg/dl (26.5 μmol/l), 7d 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 female being aged from 4-15 years old and on average 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 opening 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-typed line; polysulfone membrane; 0.2-0.4 m^2 membrane area for patients less than 20 kg, 0.4-0.8 m^2 membrane area for patients of 20-30 kg, 0.8-1.0 m^2 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 applicated 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 one 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-

vere 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 l100 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 (pO_2/FiO_2) ≥ 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) ≥ 150×10^9/L was defined as 0 point, < 150×10^9/L as 1 point, < 100×10^9/L as 2 points, < 50×10^9/L as 3 points, < 20×10^9/L as 4 points. Liver (bilirubin) < 20 μmol/l was defined as o 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 ug/kg·min was defined as 2 points, > 5 ug/kg·minas 3 points, > 15 ug/kg·minas 4 points. Epinephrine dose ≤ 0.1 ug/kg·min was defined as 3 points, > 0.1 ug/kg·min as 4 points; norepinephrine dose ≤ 0.1 ug/kg·min as 3 points, > 0.1 ug/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 μmol/l was defined as 0 point, 110-170 μmol/l as 1 point, 171-299 as 2 points, 300-440 μmol/l as 3 points, > 440 μmol/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 X^2 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-

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

Group	Case	7d	28d	6 months
Control group	46	28 (60.87)	22 (47.83)	20 (43.48)
Experimental group	54	43 (79.63)	37 (68.52)	35 (64.81)
X^2		4.246	4.397	4.569
p		0.039	0.036	0.033

tion" has mentioned the indications and timing for severe sepsis treatment, but has not touched upon the best time for CBP Intervention. Tian et al[8] studied meta-analysis of 414 patients undergoing CBP therapy from 11 randomized controlled trials and found that CBP could remove inflammatory factors, reduce white blood cells, stabilize hemodynamics, shorten average length of stay in hospital, but it cannot reduce mortality. Study has pointed out that survival rates (20%-39%) of patients under early intervention of CBP (BUN 42.6 mg/dl) were higher than those under late intervention of CBP (BUN 94.5 mg/dl), but there was no difference in the length of hospital stay[9]. Van Bommel advocated early CBP indication as less urine above 24 hours and no urine above 12 hours (adult < l00 ml/8h), and held that early CBP could reduce mortality[10].

In our study, we have selected 24h as the cut-off time point and consulted the definition of "early" in adult septic AKI as the damage stage in RIFLE grading criteria formulated by acute dialysis quality initiative group in 2002[9]. Karvellas et al[11] have made a meta-analysis, which shows that early CBP intervention could reduce death rate according to RIFLE criteria. Chon et al[12] have taken the time from entering into ICU to performing CBP as grouping criteria and divided the patients into two groups: early group-before 24h and late group-after 24h. The results of their study showed that 28 days death rates of early group and late group were 19.4% and 47.4%, respectively and difference was statistically significant ($p < 0.05$). Besides, late CBP intervention 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[13].

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 II. Comparison on IL-6 and TNF-α, YKL-40 and Annexin A1protein level.

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

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[14]. Annexin A1 is a member of ca-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[15]. 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[9,16-17] 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

1) Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL; International Surviving Sepsis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; World Federation of Societies of Intensive and Critical Care Medicine. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock. Crit Care Med 2008; 36: 296-327.

2) Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R; Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 2013; 39: 165-228.

3) Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC. The epidemiology of severe sepsis in children in the United States. Am J Respir Crit Care Med 2003; 167: 695-701.

4) Lu B, Li MQ, Cheng SL. Clinical effectiveness of continuous blood purification in combination with ulinastatin in treating thermoplegia. Eur Rev Med Pharmacol Sci 2014; 18: 3464-3467.

5) Payen D, Mateo J, Cavaillon JM, Fraisse F, Floriot C, Vicaut E; Hemofiltration and Sepsis Group of the Collège National de Réanimation et de Médecine d'Urgence des Hôpitaux extra-Universitaires. Impact of continuous venovenous hemofiltration on organ failure during the early phase of severe sepsis: a randomized controlled trial. Crit Care Med 2009; 37: 803-810.

6) Piccinni P, Dan M, Barbacini S, Carraro R, Lieta E, Marafon S, Zamperetti N, Brendolan A, D'Intini V, Tetta C, Bellomo R, Ronco C. Early isovolaemic haemofiltration in oliguric patients with septic shock. Intensive Care Med 2006; 32: 80-86.

7) Seabra VF, Balk EM, Liangos O, Sosa MA, Cendoroglo M, Jaber BL. Timing of renal replacement therapy initiation in acute renal failure: a meta-analysis. Am J Kidney Dis 2008; 52: 272-284.

8) Hongliang T, Rong Z, Xiaojing W, Rao S, Lun L, Jinhui T, Nong C, Kehu Y. The effects of continunous blood purification for SIRS/MODS patients: a systematic review and meta-analysis of radomized controlled trails. ISRN Hematology 2012; 2012: 986795.

9) Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative workgroup. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004; 8: R204-212.

10) van Genderen ME, Engels N, van der Valk RJ, Lima A, Klijn E, Bakker J, van Bommel J. Early peripheral perfusion-guided fluid therapy in patients with septic shock. Am J Respir Crit Care Med 2015; 191: 477-480.

11) Karvellas CJ, Farhat MR, Sajjad I, Mogensen SS, Leung AA, Wald R, Bagshaw SM. A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis. Crit Care 2011; 15: 72-81.

12) Chon GR, Chang JW, Huh JW, Lim CM, Koh Y, Park SK, Park JS, Hong SB. A comparison of the time of the time from sepsis to inception of continuous renal replacement therapy versus RIFLE criteria in patients with septic acute kidney injury. Shock 2012; 38: 30-36.

13) Wu VC, Ko WJ, Chang HW, Chen YS, Chen YW, Chen YM, Hu FC, Lin YH, Tsai PR, Wu KD. Early renal replacement therapy in patients with postoperative acute liver failure associated with acute renal failure: effect on postoperative outcomes. J Am Coll Surg 2007; 205: 266-276.

14) Shiao CC, Wu VC, Li WY, Lin YF, Hu FC, Young GH, Kuo CC, Kao TW, Huang DM, Chen YM, Tsai PR, Lin SL, Chou NK, Lin TH, Yeh YC, Wang CH, Chou A, Ko WJ, Wu KD; National Taiwan University Surgical Intensive Care Unit-Associated Renal Failure Study Group. Late initiation of renal replacement therapy is associated with worse outcomes in acute kidney injury after major abdominal surgery. Crit Care 2009; 13: R171.

15) Carl DE, Grossman C, Behnke M, Sessler CN, Gehr TW. Effect of timing of dialysis on mortality in critically ill, septic patients with acute renal failure. Hemodial Int 2010; 14: 11-17.

16) Zhang XH, Dong Y, Chen YD, Zhou P, Wang JD, Wen FQ. Serum N-terminal pro-brain natriuretic peptide level is a significant prognostic factor in patients with severe sepsis among Southwest Chinese Population. Eur Rev Med Pharmacol Sci 2013; 17: 517-521.

17) Sakamoto Y, Mashiko K, Matsumoto H, Hara Y, Kutsukata N, Yokota H. Selection of acute blood purification therapy according to severity score and blood lactic acid value in patients with septic shock. Indian J Crit Care Med 2010; 14: 175-179.