

Evaluation of the application of high volume hemofiltration in sepsis combined with acute kidney injury

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Abstract. – **OBJECTIVE:** To investigate the safety and effectiveness of the application of high-volume hemofiltration (HVHF) in children with sepsis combined with acute kidney injury.

PATIENTS AND METHODS: A total of 76 child patients were enrolled and randomly divided equally (n=38) into control and the observation groups respectively. The control group received conventional volume hemofiltration (the ultrafiltration rate of 35-50 ml/kg/h), and the observation group received HVHF (50-100 ml/kg/h).

RESULTS: The serum Interleukin-6 (IL-6), Tumor Necrosis Factor- α (TNF- α) and creatinine levels were significantly lower in the observation group than the control group at 6 h, 12 h, 24 h and 48 h of hemofiltration ($p<0.05$). The efficacy rate of treatment was improved. The mortality rate and incidence rate of complications were decreased, and the treatment course was significantly shortened ($p<0.05$).

CONCLUSIONS: The application of HVHF in children with sepsis combined with acute kidney injury has a better safety and effectiveness.

Key Words:

High volume hemofiltration (HVHF), Sepsis, Acute kidney injury.

sitive role in reducing the single treatment time and treatment course, decreasing complications, enhancing the treatment effect and improving the prognosis. Other studies^{4,5} have considered that HVHF can significantly ameliorate acute hemodynamic status, clear multiple inflammatory mediators in plasma, improve renal function, reduce oxidative stress and immune disorders and so forth. Many studies have focused on the analysis of its application in adult severe diseases, while reports of its application in child patients with sepsis combined with acute kidney injury are less^{6,7}. Children's body metabolic capability is weaker than in adults, and the disease tends to progress quickly, showing some difficulties in the treatment⁸. The current study aims at analyzing the safety and effectiveness of the application of HVHF in children with sepsis combined with acute kidney injury, to provide reference basis for improving the clinical prognosis of children with severe disease and extending the application indications of HVHF.

Introduction

Based on continuous veno-venous hemofiltration (CVVH), high volume hemofiltration (HVHF) increases the amount of displacement liquid in unit time, thereby further improving the convection to large and medium molecular solutes, as well as the adsorptive removal capacity, which has better application values in septic shock, severe trauma, severe acute pancreatitis, sepsis and multiple organ dysfunction syndrome (MODS)^{1,2}. A study³ confirmed that it plays a po-

Patients and Methods

Patients

A total of 76 child patients, who were admitted to our hospital and diagnosed as sepsis combined with acute kidney injury for the first time from June 2013 to June 2016, were continuously selected. Inclusion criteria: a) The diagnosis conformed to the diagnostic criteria which were formulated by the International Sepsis Definitions Conference of Washington and the diagnostic basis of acute kidney injury; b) There were application indications for hemofiltration, the treatment was expected to be effective, and the survival pe-

riod was at least 12.0 months; c) The treatment compliance was good, the clinical data were perfect, the study gained the informed consent of the children's guardians and obtained the approval of the Ethics Committee of our hospital.

Exclusion criteria: a) Patients with hereditary metabolic diseases, congenital diseases, autoimmune diseases, abnormal coagulation function, malnutrition, primary kidney diseases (such as polycystic kidney disease) and so forth; b) Patients with poor therapeutic effect of primary disease; c) Patients with other complications, such as heart, lung, liver, brain and other organ dysfunctions.

According to the order of admission, patients were divided into the control group and the observation group by using the random number method, with 38 cases in each group. Baseline data of the two groups were comparable (Table I).

Research Methods

The comprehensive therapies for primary disease were adopted according to the recommendation of the standard medical guide. Seeking for the source of infection, the effective anti-infection, the aggressive resuscitation, and the application of vasoactive agents and glucocorticoids (Yan-gtze Pharma Company Taizhou, Jiangsu, China) were needed. If necessary, assisted mechanical ventilation, sedation and analgesia, maintaining the stability of the internal environment, preventing the stress ulcer and deep venous thrombosis and others would be used. The treatment of hemofiltration was started within 12 h of admission. The control group received conventional volume hemofiltration, and the observation group received HVHF. After patients were treated with internal jugular vein indwelling catheter, CVVH mode was started, with blood flow volume of 180-200 ml/min, and the displacement liquid was normal saline (Biosharp, Hefei, China) 3000 ml + water for injection (Biosharp, Hefei, China) 1000 ml + 5% glucose (Biosharp, Hefei, China) 250 ml + 10% calcium chloride (Biosharp, Hefei, China) 10 ml + 50% magnesium sulfate (Biosharp, Hefei, China) 1.8 ml + 5% sodium bicarbonate (Biosharp, Hefei, China) 250 ml + 10% potassium chloride 15ml. For circulating anticoagulation, APTT was maintained as 1.5-2-fold of normal value. The continuous renal replacement therapy machine of German Diapact (Berlin, Germany) and the polysulfone membrane filter AV600 of German Fresenius (Bad Homburg, Germany) were adopted. The temperature was 37°C. The changes of vital signs were continuously monitored, the hemo-

filtration channels were maintained to be unobstructed, and the access pressure, return pressure and transmembrane pressure were continuously monitored. When the transmembrane pressure was more than 200 mmHg, the hemofilter and matching pipelines were needed to be replaced. The ultrafiltration coefficient of the control group was set as 35-50 ml/kg/h, 50-100 ml/kg/h of the observation group. The ultrafiltration was performed for continuous 12-18 h every day.

Observation Index

Two groups of serum IL-6, TNF- α and creatinine levels at 6 h, 12 h, 24 h and 48 h of hemofiltration were compared. The efficacy rates of treatment, the mortality rates and occurrence rates of complications as well as the treatment courses were also compared. The levels of IL-6 and TNF- α in peripheral elbow vein blood were detected by ELISA. The reagents were purchased from Jiangsu Beyotime Biotechnology Co., Ltd. (Jiangsu, China), and the steps were performed in accordance with the instructions. The serum creatinine levels were detected by conventional biochemical method using Hitachi 3700 fully automatic biochemical analyzer. The criterion for the efficacy rate of treatment was that the infection was controlled, the serum creatinine level was decreased by more than 50%, and the symptom was stable, no severe complications. Complications included hypotension, arrhythmia, electrolyte disturbance, cardiac dysfunction and other nonspecific symptoms, such as fatigue, soreness of waist, increased nocturia, anorexia, anemia, muscle spasm, itchy skin, etc. The treatment course referred to the time from the start of hemofiltration to the successful weaning. The weaning criteria were that the primary disease in patients with sepsis was controlled and improved, the symptoms were stable, and the serum creatinine levels were continuously decreased below one-fold of normal level, stable for at least 48 h, and no severe complications.

Statistical Analysis

SPSS20.0 software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. The measurement data were expressed as mean \pm standard deviation (SD). The repeated measures analysis of variance (ANOVA) followed by Post-Hoc Test (Least Significant Difference) was used to compare the serum IL-6, TNF- α and creatinine levels. The independent sample *t*-test was adopted to compare the treatment courses. The count data were expressed by the case or percentage, and

the chi-square test was used for the comparison between groups. $p < 0.05$ suggested that the difference was statistically significant.

Results

Comparisons of Serum IL-6, TNF- α , and Creatinine Levels

The serum IL-6, TNF- α and creatinine levels were significantly lower in the observation group than the control group at each time point, and the differences were statistically significant ($p < 0.05$) (Figure 1).

Comparisons of Efficacy Rates of Treatment, Mortality Rates, and Occurrence Rates of Complications

Compared with the control group, the efficacy rate of treatment of the observation group was improved, the mortality rate and occurrence rate of

complications were decreased, and the treatment course was significantly shortened. The differences were statistically significant ($p < 0.05$) (Table II).

Comparison of Treatment Courses

The treatment course of the control group was 3-8 d, with an average of (5.5 ± 1.6) d, and the treatment course of the observation group was 2-6 d, with an average of (4.3 ± 1.2) d. The treatment course was significantly shorter in the observation group than the control group, showing a statistically significant difference ($t = 5.264, p = 0.013$).

Discussion

At present, sepsis is the main cause of death in children during the admission in ICU; the incidence rate of sepsis combined with acute kidney injury is from 50% to 80%, and the continuous blood purification (CBP) is an important method

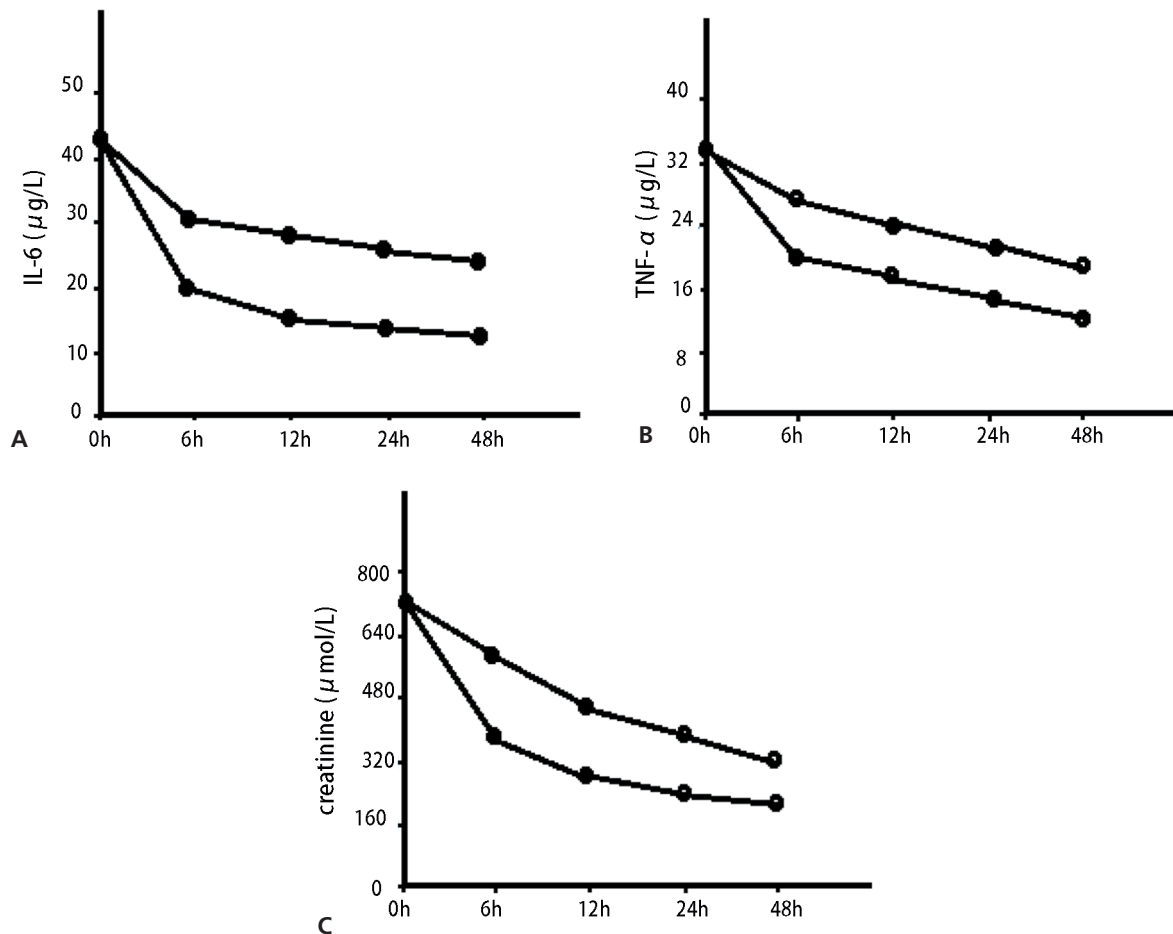


Figure 1. Comparisons of serum IL-6, TNF- α and creatinine levels.

Table I. Comparisons of baseline data between the two groups.

| Groups | Cases | Male/ Female | Age (y) | Course of the disease (h) | Weight (kg) | APACHE II | Serum creatinine ($\mu\text{mol/L}$) | Severe pneumonia | Intracranial infection | Digestive tract infection and others |
|----------------------|-------|-----------------|---------------|------------------------------------|----------------|----------------|--|---------------------|---------------------------|---|
| Control group | 38 | 20/18 | 6.6 \pm 2.4 | 10.5 \pm 3.6 | 19.6 \pm 3.5 | 16.5 \pm 2.4 | 765.8 \pm 123.4 | 31 | 5 | 2 |
| Observation group | 38 | 21/17 | 6.3 \pm 2.2 | 11.2 \pm 3.7 | 20.4 \pm 3.7 | 16.8 \pm 2.6 | 772.4 \pm 152.6 | 28 | 7 | 3 |
| t/χ^2 | | 0.053 | 0.265 | 0.312 | 0.185 | 0.252 | 0.421 | 0.682 | | |
| p | | 0.818 | 0.786 | 0.669 | 0.923 | 0.867 | 0.687 | 0.409 | | |

Table II. Comparisons of efficacy rates of treatment, mortality rates and occurrence rates of complications [case (%)].

| Groups | Cases | Efficacy rate | Mortality rate | Occurrence rate of complications |
|-------------------|-------|---------------|----------------|----------------------------------|
| Control group | 38 | 27 (71.1) | 10 (26.3) | 14 (36.8) |
| Observation group | 38 | 34 (89.5) | 3 (7.9) | 6 (15.8) |
| χ^2 | | 4.070 | 4.547 | 4.343 |
| p | | 0.044 | 0.033 | 0.037 |

to reduce renal injury and prolong the time of treatment⁹. The occurrence of sepsis involves infection, inflammatory response, oxidative stress, immune disorder and other mechanisms¹⁰. Multiple studies suggest that the ultrafiltration rate (20-50 ml/kg/h) of conventional renal replacement therapy is mainly to correct the azotemia, while the treatment dose (50-100 ml/kg/h) of sepsis can quickly and effectively remove a variety of inflammatory mediators¹¹.

Our study indicated that the serum IL-6, TNF- α and creatinine levels in the observation group were significantly decreased after hemofiltration, the efficacy rate of treatment was improved, the mortality rate and occurrence rate of complications were decreased, and the treatment course was significantly shortened, suggesting that the application of HVHF in children with sepsis combined with acute kidney injury had a better safety and effectiveness. Through many animal models and clinical trials of sepsis¹²⁻¹⁵, it confirms that by using high biocompatibility and high permeability filter, HVHF continuously clears multiple large and medium molecular inflammatory mediators, such as IL-1 β , IL-6, IL-8, and TNF- α , multiple complements (C3a and C5a), prostaglandin, leukotriene, as well as, active oxygen free radical, platelet activating factors, nitric oxide, etc. As a pro-inflammatory factor, TNF- α can promote the activation of multiple inflammatory cells and the release and expression of other inflammatory mediators, which is the key to participate in re-

gulating the waterfall-like cascade reaction of inflammation. IL-6 is a sensitive index in the early stage of inflammatory reaction, which is closely related to the severity and prognosis of the disease. IL-8 mainly exerts the role in chemotaxis of neutrophils and it enhances the activity and phagocytosis of lysozyme, which is an important member of the inflammatory reaction network. Some scholars also believed that only HVHF can effectively remove multiple inflammatory factors in plasma, considering the reason that the inflammatory mediator passing through the filter is increased in unit time and the clearance rate of convection is increased¹⁶⁻¹⁷. Moreover, the increase of transmembrane pressure makes the solute easy to enter the deep layer of the membrane, and the effective adsorption area is increased. However, some study also suggests that using CBP in the treatment of sepsis is not obviously related to the efficiency of removing inflammatory factors, and the inflammatory factor levels in peripheral blood of some patients with sepsis are not significantly increased¹⁸. The theory of immune imbalance considers that the occurrence and development of sepsis experiences immune activation, immune suppression, immune type transformation and other aspects, of which the decrease of the expression of human leukocyte DR antigenic site is of great significance to judge the progression and prognosis of disease¹⁹. The early application of HVHF in patients with sepsis can significantly reduce the levels of inflammatory mediators in

plasma, and for the latter stage, it can improve the secretion of monocytes and antigen presentation function as well as ameliorate the immune suppression state and rebuild the immune homeostasis²⁰. The study finds that only HVHF can continuously improve the reactivity of monocytes and regulate the body's immune function, while the treatment effect of traditional CVVH is poor²¹.

Conclusions

Our study proposes that the application of HVHF in children with sepsis combined with acute kidney injury has a better safety and effectiveness. The limitation is that the sample size is small and sensitive and specific observation indexes are insufficient. The specific mechanism of its application in improving clinical outcomes remains to be further studied.

Conflict of interest

The authors declare no conflicts of interest.

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