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Effect of Continuous Veno-Venous Hemodiafiltration Combined with Hem Perfusion on NLRP3 Levels and Prognosis in Children with Severe Sepsis

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ABSTRACT

Objectives: To explore the effect of continuous veno-venous hemodiafiltration (CVVHDF) + hemoperfusion (HP) on the level of nucleotide-binding oligomerization receptor protein 3 (NLRP3) and prognosis in children with severe sepsis.

Methods: This study is a prospective study. The research subjects are children with severe sepsis who were admitted to the Pediatric Intensive Care Unit (PICU) of the First Affiliated Hospital of Xinxiang Medical College from October 2021 to December 2023. The general information of the children, NLRP3 inflammasome levels in peripheral blood before and after treatment, Pediatric Sequential Organ Failure Assessment (pSOFA) score, incidence of sepsis-associated organ dysfunction (SAOD) during hospitalization, total hospital stays, PICU stay, and 28 Statistical analysis was performed on the prognosis of the day.

Results: Fifteen children underwent blood purification treatment (blood purification group) while another fifteen children underwent conventional treatment (conventional treatment group). After 72 hours, both groups showed a significant decrease in serum NLRP3 inflammasome levels ($p<0.01$), with the blood purification treatment group exhibiting a faster decline rate than the conventional treatment group. The pediatric sequential organ failure score (pSOFA) in the blood purification treatment group (CVVHDF+HP) decreased more than in the conventional treatment group. Additionally, the incidence of sepsis-associated organ dysfunction (SAOD) during hospitalization was lower in the blood purification treatment group compared to the conventional treatment group ($p=0.039$). Moreover, the hospitalization duration was significantly shorter in the blood purification treatment group than in the conventional treatment group ($p<0.05$).

Conclusion: Blood purification treatment (CVVHDF+HP) can reduce the early levels of NLRP3 in children with severe sepsis, reduce organ damage, and improve prognosis.

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Introduction

Sepsis represents a severe medical condition marked by dysfunction of organs, which is initiated by an infection and an unchecked immune reaction. Severe sepsis or septic shock, which can develop from sepsis, is primarily identified by low blood pressure leading to inadequate tissue perfusion and oxygen deprivation, along with cellular and metabolic disturbances. This condition is a significant global health concern and a leading cause of mortality [1]. The impact of sepsis in children is more severe compared to adults, with severe cases leading to multiple organ dysfunction, failure, and death. Sepsis is a major contributor to mortality and disability among children, particularly in less developed countries [2].

The NLRP3 inflammasome is a macromolecular protein complex responsible for orchestrating the body's immune response to various injuries. Activation of the NLRP3 inflammasome leads to the maturation and release of pro-inflammatory cytokines like interleukin-1β (IL-1β) and interleukin-18 (IL-18). Numerous studies have highlighted the pivotal role of the NLRP3 inflammasome in immune and inflammatory disorders associated with sepsis. Research specifically has shown that the activation of the NLRP3 inflammasome in cardiac fibroblasts during sepsis can induce the maturation and release of inflammatory cytokines like IL-1β, which subsequently results in direct damage to the myocardium [3]. Activation of the NLRP3 inflammasome during sepsis can result in differing levels of damage to various systems. Numerous studies have demonstrated that reducing inflammasome levels can effectively attenuate the inflammatory response in sepsis [4-6].

Conventional treatment of sepsis focuses on fluid resuscitation, removal of the source of infection, and use of antibiotics [7]. Blood purification (BP) can partially eliminate soluble pro-inflammatory mediators from the body and is considered a current extracorporeal adjunctive therapy for severe sepsis or septic shock

[8]. Hemoperfusion (HP) is a method of blood purification that utilizes adsorbent materials and polymer substances to eliminate inflammatory mediators from the body. The objective of this therapy is to reinstate immune balance by targeting both pro- and anti-inflammatory factors [9]. Studies have indicated that direct contact of blood with highly absorbent resins in extracorporeal circuits, known as hemoperfusion, may potentially be more effective than two other blood purification methods: dialysis or continuous venovenous hemodiafiltration (CVVHDF). This process aids in the clearance of inflammatory mediators, although current evidence supporting this approach remains inconclusive [10]. This study aims to investigate the effects of blood purification (CVVHDF+HP) on early NLRP3 levels and clinical outcomes in pediatric patients with severe sepsis.

Materials and Methods

Patients In this prospective study, children with severe sepsis admitted to the Pediatric Intensive Care Unit (PICU) of the First Affiliated Hospital of Xinxiang Medical College from October 2021 to December 2023 were included. The inclusion criteria encompassed patients hospitalized in the PICU during the specified period, aged > 28 days and ≤ 14 years old, presenting with conditions such as respiratory failure, shock, emergency surgery, liver failure, kidney failure, and other diseases, without gender restrictions, Compliant with the 2020《Surviving Sepsis Campaign International Guidelines: Management of Septic Shock and Sepsis-Related Organ Dysfunction in Children》 The diagnostic criteria for septic shock and sepsis-related organ dysfunction are as follows: Septic shock manifests through cardiovascular dysfunction, which may involve hypotension, the requirement for vasoactive medication, or inadequate perfusion, and is a result of serious infection [11]. Sepsis-related organ dysfunction (SAOD) can encompass both cardiovascular and non-vascular issues arising from severe infections. A pSOFA score of 2 or higher indicates cardiovascular organ dysfunction. The following criteria are established for exclusion from this research: (1) pediatric patients with immunodeficiency disorders, autoimmune diseases, cancer, or serious cardiac conditions; (2) children with chronic renal failure requiring blood purification, liver failure indicated by a pSOFA score surpassing 0, and other significant chronic health issues; (3) instances of active or considerable bleeding linked to shock; (4) circumstances in which sepsis is unlikely to be the primary cause of shock; (5) minors whose families choose not to participate in the study; and (6) cases lacking complete clinical data. Ethics approval for this study was obtained from the Ethics Committee of the First Affiliated Hospital of Xinxiang Medical University (No. EC-022-184), and informed consent was obtained from the family members.

Grouping

The children were divided into two groups: conventional treatment group (conventional treatment) and blood purification treatment (CVVHDF+HP) group (conventional treatment+blood purification treatment) based on the treatment they received. The attending doctor determined the treatment plan after consulting with family members, taking into account the child's condition and financial status. Among the participants, the blood purification treatment group satisfied the criteria for continuous blood purification treatment [12]. These criteria include severe sepsis accompanied by acute kidney injury, fluid overload, life-threatening or ineffective electrolyte disorders, liver failure, and severe systemic inflammatory reactions. Patients who met the indications for blood purification but whose family members declined the treatment were classified into the conventional treatment group.

Treatments

Routine treatment is in accordance with the 2020□Surviving Sepsis Campaign International Guidelines: Management of Septic Shock and Sepsis-Related Organ Dysfunction in Children□ Standardized implementation includes (1)Regular care in the PICU involves observing heart rate, mean arterial pressure, respiration, transcutaneous oxygen saturation, along with a 24-hour assessment of fluid input and output. Furthermore, it is important to evaluate hemodynamic parameters like central venous pressure, cardiac output, bedside ultrasound for hemodynamic analysis, and variations in lactate levels. Maintaining body temperature, providing analgesia and sedation, and securing intravenous access are also crucial aspects of care; (2) Respiratory assistance: Either non-invasive ventilation or tracheal intubation is provided to pediatric patients suffering from acute respiratory distress syndrome due to sepsis, whereas tracheal intubation is particularly recommended for those with septic shock; (3) Fluid resuscitation: Deliver a fluid bolus ranging from 40 to 60 ml/kg per hour, divided into portions of 10 to 20 ml/kg for each administration, and stop the bolus once the desired cardiac output is reached or if signs of fluid overload appear; (4) Vasoactive agents: Administer epinephrine or norepinephrine as the primary medication, while dopamine should be utilized as the secondary option; (5) Provide a comprehensive treatment plan tailored to the child's condition, which may include early broad-spectrum antimicrobial therapy, management of fluid and electrolyte balance, maintenance of acid-base equilibrium, regulation of blood sugar levels, nutritional support, glucocorticoids, blood products, and human immunoglobulin when indicated [11].

Blood purification treatment is implemented according to the 2021《Adsorptive hemofiltration for sepsis management: expert recommendations based on the Asia Pacific experience》: a single double-lumen central venous dialysis catheter was inserted for venous access. The catheter size was selected based on the child's blood vessel diameter and our center's specifications for pediatric hemodialysis catheters: 5.0~7.0 Fr for newborns, 6.5 Fr for weights 3~30 kg [12]. The HP treatment was carried out with the HA330 neutral resin perfusion apparatus (Jafron Biomedical Co., Ltd., Zhuhai, China). Blood flow velocity was maintained at 3~5ml/kg/min. Hemoperfusion (HP) treatment was initiated for 2 hours upon admission to the Pediatric Intensive Care Unit (PICU), followed by sequential Continuous Veno-Venous Hemodiafiltration (CVVHDF) treatment for a minimum of 16 hours. The total duration of blood purification treatment exceeded 72 hours. Extracorporeal anticoagulation was achieved using 4% citrate (200ml: 8g) at a rate of 1.2 to 1.5 times the blood pump speed, with a 10% calcium gluconate injection speed set at approximately 6.1% of the citrate anticoagulant dose. Activated whole blood coagulation time (ACT) was maintained at 180~240 seconds, or activated partial thromboplastin time (APTT) at 60~80 seconds.

Data Collection

Baseline information of the children including age, gender, weight, pre-hospital illness course, symptoms (fever, cough, dyspnea, vomiting/diarrhea, convulsions, disturbance of consciousness) was collected. Acute Physiology and Chronic Health Score Assessment (APACHE II score) was conducted. Peripheral blood serum samples were collected on admission to the PICU and 72 hours post-treatment for ELISA testing of serum NLRP3 inflammasome levels. Pediatric Sequential Organ Failure Score (pSOFA) was calculated. ΔpSOFA was defined as the difference between 24-h and 72-h pSOFA scores. Various outcomes such as total hospital stay, PICU stay, mechanical ventilation time, 28-day mortality,

and incidence of sepsis-related organ dysfunction (SAOD) were recorded.

Statistical Analysis

Statistical analysis of the data was conducted using SPSS version 27.0. Measurement data that followed a normal distribution were represented as mean ± standard deviation (SD). For comparisons between two groups, t-tests were employed, while one-way analysis of variance was used for multiple group comparisons. Data that did not adhere to a normal distribution were presented as [M (P25, P75)], with the Mann-Whitney U test utilized for group comparisons. Categorical data were reported as rates [n (%)], with the chi-square test applied for group comparisons. A p-value of less than 0.05 was deemed statistically significant.

Results

Characteristics of the Patients

The study included a blood purification treatment group (19 cases,Among them, 5 cases were septic shock, 1 case was septic shock combined with multiple organ dysfunction, 5 cases were sepsis combined with acute respiratory distress syndrome, and the rest were sepsis combined with severe systemic inflammatory reaction) and a conventional treatment group (16 cases,Among them, 3 cases were septic shock combined with multiple organ dysfunction, 1 case was septic shock combined with acute liver failure, 2 cases were severe sepsis after surgery, 1 case was sepsis combined with acute renal failure, and 3 cases were sepsis combined with acute respiratory distress syndrome, and the rest were sepsis combined with severe systemic inflammatory reaction). However, 4 cases in the blood purification treatment group had a treatment time of less than 72 hours (3 cases were discharged automatically and 1 case died), and 1 case in the conventional treatment group also had a treatment time of less than 72 hours (automatic discharge). These cases were then included in the blood purification group (15 cases) and the conventional treatment group (15 cases). There were no statistically significant differences between the two groups in terms of age, gender, weight, pre-hospital disease course, symptoms on admission, and APACHE II score (all p> 0.05; Table 1).

Table 1: Baseline Demographic Characteristics of the Different Groups

Parameters	Blood purification treatment(n=15)	Conventional treatment(n=15)	F/χ^2	p value
Age, years	6.32±4.51	3.67±3.75	0.651	0.091
Gender(Male), n (%)	7(46.67)	10(66.67)	1.222	0.269
Weight,kg	26.62±17.86	17.43±12.53	1.724	0.114
Pre-hospital disease duration,days	4.23±3.26	4.41±4.91	0.124	0.907
Symptoms on admission				
Fever(%)	14(93.30)	12(80.0)	0.288	0.591
Cough(%)	6(40.0)	8(53.30)	0.536	0.464
Dyspnea(%)	0	5(33.30)	3.327	0.050
Vomiting/diarrhea(%)	11(73.30)	6(40.0)	3.394	0.065
Convulsions(%)	7(46.70)	5(33.30)	0.556	0.456
Disorder of consciousness(%)	12(80.0)	11(73.30)	0.186	1.000
APACHE-II score	22.60±4.61	17.67±4.61	0.02	0.063

Data are presented as % or as mean ± SD.

Blood Levels of NLRP3

Comparison between groups: Prior to treatment, the NLRP3 level in the blood purification treatment group showed a significantly higher value compared to the conventional treatment group ($p<0.01$). Post-treatment, there was no notable difference in the NLRP3 level between the blood purification treatment group and the conventional treatment group ($p>0.05$). Intra-group analysis: Within the conventional treatment group, the NLRP3 level post-treatment exhibited a significant decrease compared to pre-treatment, with a statistically significant difference ($p<0.01$). Similarly, within the blood purification treatment group, the NLRP3 level post-treatment also displayed a significant decrease compared to pre-treatment, with a statistically significant difference ($p<0.01$) (Table 2).

Table 2: Comparison of NLRP3 Levels in Children with Severe Sepsis

Groups	n	NLRP3(ng/ml)				
		Before treatment	After treatment	ΔNLRP3	t	P
Blood purification treatment	15	188.67±26.54^{bf}	121.45±20.09^{be}	67.23±24.02	12.69	<0.01
Conventional treatment	15	162.44±16.57^{cf}	138.40±17.38^{ce}	24.04±11.94	4.537	0.012
t		4.951	3.200	6.237		
P		<0.01	0.119	<0.01		

All data are presented as mean ± SD, ng/ml.
bp <0.05 vs. Conventional treatment; ^{c}p <0.05 vs. Blood purification treatment; ^{e}p <0.05 vs. Before treatment; ^{f}p <0.05 vs. After treatment.

pSOFA Scores

Before the intervention, the pSOFA score in the blood purification treatment group was found to be higher compared to the conventional treatment group ($p < 0.05$). Additionally, the ΔpSOFA score of the blood purification treatment group was significantly higher than that of the conventional treatment group ($p < 0.05$). These differences were found to be statistically significant (Table 3).

Table 3: Sofa Score during Treatment

	Conventional treatment(n=15)	Blood purification treatment(n=15)	p value
Before treatment	6.87±1.92	9.13±3.13*	0.024
After treatment	5.13±2.17	5.47±3.36	0.749
ΔpSOFA	1.73±1.03	3.67±2.06*	0.003

All data are presented as mean ± SD, score.
* $p < 0.05$ vs. Conventional treatment.

Outcomes

The 28-day mortality rate in the blood purification treatment group was 6.7%, lower than the 13.3% in the conventional treatment group. However, the difference between the two groups was not statistically significant ($p > 0.05$). The incidence of SAOD in the blood purification treatment group during hospitalization (6.7%) was lower than that in the conventional treatment group (13.3%), with a statistically significant difference ($p < 0.05$).The average total hospitalization time for the conventional treatment group was 22.92 days, which was longer than the blood purification treatment group's average of 16.13 days. This difference was found to be statistically significant ($p < 0.05$). However, there was no significant difference in Pediatric Intensive Care Unit (PICU) hospitalization time between the two groups ($p > 0.05$) (Table 4).

Table 4: Comparison of the Two Primary Outcomes

Group	n	Death at 28 days(%)	SAOD(%)	Total length of hospital stay(days)	Total length of PICU stay(days)
Blood purification treatment	15	1(6.70)	1(6.70)	16.13±8.57	12.06±6.59
Conventional treatment	15	2(13.30)	7(46.70)	22.92±12.63	13.04±5.51
t/χ^2		0.370	6.136	5.359	1.330
P		1.000	0.039	<0.01	0.981

Data are presented as % or as mean ± SD.

Discussion

This research indicates that both standard therapy and blood purification therapy (CVVHDF+HP) are effective in lowering the serum levels of the NLRP3 inflammasome and the pSOFA score in pediatric patients suffering from severe sepsis. Nevertheless, the outcomes for the blood purification cohort are markedly better than those for the standard therapy cohort. While both cohorts demonstrate a decrease in the serum NLRP3 inflammasome levels, it is noteworthy that the blood purification cohort started with significantly elevated pre-treatment levels of the NLRP3 inflammasome compared to the standard therapy cohort. Furthermore, the change in pSOFA scores (ΔpSOFA) for the blood purification cohort was significantly greater than that observed in the standard therapy cohort, with statistical relevance ($p < 0.05$). This suggests that patients receiving blood purification therapy experienced a more pronounced decline in both serum NLRP3 levels and pSOFA scores relative to those undergoing standard treatment. Additionally, the rates of SAOD and the total duration of hospitalization for the blood purification cohort were significantly less than those of the standard treatment cohort, also reaching statistical significance ($p < 0.05$). No significant differences in 28-day mortality were observed between the two treatment groups. These results imply that, during the initial phases of severe sepsis in children, blood purification treatment (CVVHDF+HP) could facilitate a quicker decline in mortality rates as compared to standard therapy, thus mitigating organ damage and enhancing overall prognosis.

An important characteristic of septic shock or severe sepsis is the presence of persistent hemodynamic instability, which is associated with high mortality, treatment costs, and morbidity. Research has shown that the mortality rate among hospitalized patients can reach as high as 40% [7,13]. The pathogenesis of sepsis is intricate, with the inflammatory response playing a crucial role. Programmed pyroptosis is identified as one of the contributors to multi-organ dysfunction in sepsis. Pyroptosis, a pro-inflammatory programmed cell death, is characterized by the release of numerous inflammatory factors and cellular contents, leading to an 'inflammatory factor storm.' The NLRP3 inflammasome, a cytoplasmic multi-protein heteromeric complex, when activated, can generate mature IL-1 and interleukin-18 (IL-18), thus initiating pyroptosis [14]. The activation of the NLRP3 inflammasome promotes the onset of an early inflammatory response in sepsis, exacerbating tissue damage. Excessive pro-inflammatory cytokines can cause endothelial damage and systemic inflammatory response syndrome (SIRS), which may escalate to multiple organ failure and fatal outcomes in severe cases [15]. Recent studies have indicated that hemoperfusion can effectively mitigate dysregulated inflammatory responses in children with refractory septic shock, multiorgan dysfunction, hyperendotoxemia, and hypercytokinemia (notably elevated IL-6 levels). The findings of this study reveal that within 3 days of admission to the Pediatric Intensive Care Unit (PICU) for children with severe sepsis or septic shock, the levels of NLRP3 inflammasome were significantly reduced in both the blood purification treatment group and the conventional treatment group. However, the ΔNLRP3 in the blood purification treatment group exhibited a higher reduction compared to the conventional treatment group. This difference was statistically significant ($p < 0.05$), demonstrating that blood purification treatment (CVVHDF+HP) can rapidly and substantially decrease the level of NLRP3 inflammasome in children with severe sepsis.

The research indicated that the mortality rate at 28 days for the severe sepsis blood purification treatment cohort was less than that of the conventional treatment cohort; nonetheless, the difference in mortality rates between both cohorts was not statistically significant ($p > 0.05$). Moreover, the occurrence of SAOD during hospitalization in the blood purification treatment cohort was significantly lower than that in the conventional treatment cohort ($p = 0.039$), and the duration of hospitalization was also notably shorter in comparison with the conventional treatment cohort ($p < 0.05$). However, no significant differences were observed in the lengths of PICU stays or mechanical ventilation times between the two cohorts ($p > 0.05$). These findings suggest that blood purification treatment may enhance the prognosis of children with sepsis. Nonetheless, results from various clinical studies on blood purification technology in sepsis patients have shown inconsistencies. A large retrospective study from Japan contradicts the aforementioned findings, as it reported that patients

who underwent 1-2 hemoperfusion treatments did not exhibit a significantly lower mortality rate compared to sepsis patients who received conventional treatment [16]. Ruixiang Zhou et al [17]. conducted a randomized double-blind controlled experiment with 74 patients diagnosed with severe sepsis. Patients were randomly assigned to two groups: a control group and a treatment group. The control group underwent standard treatment, whereas the treatment group received standard treatment in addition to blood purification therapy. The results indicated a significant decrease in mortality rate in the treatment group compared to the control group. Furthermore, the group receiving treatment demonstrated a notable decrease in both the duration of mechanical ventilation and the length of time spent in the intensive care unit (ICU). The lack of a difference in mortality rates between the groups in this research may be linked to the greater severity of disease observed in the blood purification group when contrasted with the conventional treatment group. Furthermore, factors such as the smaller sample size and various confounding variables (complications, surgeries, inflammation intensity, etc.) may have influenced the outcomes. Therefore, larger multicentre prospective randomized studies are necessary to further investigate the impact of hemoperfusion on clinical outcomes in pediatric patients with sepsis.

Limitations

The limitations of this research include a comparatively small number of samples and an absence of statistical evaluation regarding the upstream and downstream elements of the NLRP3 inflammasome, such as caspase-1, IL-1, TNF-α, etc., which may not fully capture the level of NLRP3 inflammasome activation. Additionally, the economic disparities among children may result in only those from wealthier families receiving CVVHDF+HP treatment, leading to limitations in the generalizability of the research findings.

Conclusion

CVVHDF+HP can quickly decrease the concentration of NLRP3 inflammasome in the peripheral blood of children with severe sepsis at an early stage, leading to a reduction in organ damage and improved prognosis. Nonetheless, it is crucial to recognize that treatments for blood purification might not substantially influence the decrease of mortality rates in pediatric patients.

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Disclosure Statement

The authors declare that they have no conflict of interests.

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