Original Research Article

Effect of the combination of HA380 hemoperfusion with CVVHDF on inflammatory indices and microcirculation in early septic shock

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Abstract

Purpose: To determine the clinical efficacy of combining HA380 hemoperfusion with continuous veno-venous hemodialysis filtration (CVVHDF) in early-stage septic shock.

Methods: Data from 107 patients admitted to Affiliated Hospital of Jianghan University, China from January 2020 to January 2022 were analyzed. They were divided into control group (53 cases, on conventional treatment + CVVHDF) and study group (54 cases, on conventional treatment + CVVHDF + HA380 hemoperfusion). Changes in vital signs, renal function, inflammatory markers, microcirculatory indices and disease severity were compared before and after treatment. Adverse reactions and prognostic indicators were also recorded.

Results: In both groups, heart rate (HR), respiratory rate, urea nitrogen (BUN), blood creatinine (Scr), calcitoninogen (PCT), c-reactive protein (CRP), interleukin (IL)-1, tumor necrosis factor (TNF)-α, Sequential Organ Failure Assessment Score (SOFA) and Acute Physiology and Chronic Health Status Scoring System II (APACHE II) decreased after 7 days of treatment. These improvements were more significant in study group relative to control group. MAP, MFI and PPV showed an elevation in study group when compared to control group. Both groups showed no marked difference in the incidence of adverse reactions (7.55 vs. 12.96 %). The study group had shorter intensive care unit (ICU) stays, duration of mechanical ventilation and total hospital stays in comparison to control group (p < 0.05).

Conclusion: The combination of HA380 hemoperfusion and CVVHDF effectively improves renal function, controls septic shock, inhibits the inflammatory response, enhances microcirculation and improves short-term prognosis without significantly increasing adverse reactions. This treatment modality seems promising for early-stage septic shock pending outcomes of evaluating their long-term efficacy and prognosis.

Keywords: Septic shock, HA380 hemoperfusion, Venous hemodialysis filtration, Inflammatory index, Microcirculation

INTRODUCTION

Sepsis is an infection-related clinical state that is frequently brought on by burns, trauma, surgery, acute pancreatitis, etc. It is a threat to human health, possibly leading to substantial illness and death rates [1]. If prompt therapeutic intervention is not made, sepsis, a severe and quickly

developing illness that is frequently accompanied by pulmonary edema, cerebral edema, cardiac failure, fluid overload and other organ failure, can advance to septic shock and even result in death [2,3]. Septic shock remains one of the leading causes of death in critical care, even though patient mortality has dropped and treatment methods have improved. The disease's incidence continues to rise each year, with more than 18 million cases reported globally each year [4,5]. Consequently, septic shock has grown to be a significant worldwide health problem, and its efficient management can help conserve numerous medical resources.

The main course of treatment for septic shock patients is blood purification. Continuous veno-venous hemodialysis filtration (CVVHDF), which uses hemodialysis technology that is constantly improving, is frequently used in the clinical treatment of septic shock patients to remove small and medium-sized molecules, maintain hemodynamic stability and treat acid-base and water-electrolyte imbalances [5,6]. CVVHDF is generally effective in removing large molecules [7]. In contrast, hemoperfusion is more effective for macromolecules but less effective for correcting acid-base and water-electrolyte disorders [8]. Therefore, it was hypothesized that hemoperfusion combined with CVVHDF could achieve better efficacy in the early stage of septic shock. However, no clinical research has been reported on the effect of HA380 hemoperfusion integrated with CVVHDF on inflammatory markers and microcirculation in patients with early septic shock.

This research investigated the efficacy of HA380 hemoperfusion integrated with CVVHDF in early stages of septic shock and the effect on inflammatory indices and microcirculation.

METHODS

General patient data

A retrospective analysis was conducted on the clinical data of 107 patients admitted to Affiliated Hospital of Jianghan University in the early stage of septic shock between January 2020 and January 2022. The 107 patients in early stage of septic shock were allocated into control group (53 cases) and study group (54 cases) by the treatment regimen. This research was reported to the Ethics Committee of the Affiliated Hospital of Jianghan University and obtained approval for implementation (approval no. WHSHIRB-K-2021022). The research followed the protocols specified in the World Medical Association Declaration of Helsinki [10].

Inclusion criteria

Patients that meet the diagnostic criteria of septic shock [9], have complete clinical data, age between 18 - 70 years, time to onset < 24 h, and no history of cardiac disease.

Exclusion criteria

Patients with combined anaphylaxis, hemorrhagic shock, cardiogenic shock, etc.; combined malignancy; pregnant and lactating women; long-term use of immunosuppressive drugs; renal transplantation; active bleeding or bleeding tendency; use of glucocorticoids in the 3 months before enrollment; combined immune system diseases.

Treatments

All patients were given medical treatment such as anti-shock, anti-infection, nutritional support, mechanical ventilation, nutritional resuscitation and correction of electrolyte disturbance after admission. A 12F triple-lumen catheter was left in the femoral vein for control group's therapy, which included the use of a Prismaflex bedside hemodialysis machine, an AN69-M100 hemofilter and fluid replacement rates of 1000 and 180 – 220 mL/h for blood flow.

Time spent on the treatment was 4-6 hours. The overall treatment time was over three days and the filter was changed once every 72 h. According to each patient's unique condition, the appropriate anticoagulation medication was chosen. Patients with non-active bleeding received simple heparin. Along with the aforementioned treatments, study group received treatment with HA380 hemoperfusion: A hemofilter with a blood flow rate of 200 mL/min was coupled in series with the HA380 blood perfusion device. Hemoperfusion was carried out continuously for 6 h.

Once daily administration of CVVHDF + HA380 perfusion was carried out CVVHDF was continued following HA380 hemoperfusion therapy. Patients received ≥ 5 sessions of HA380 hemoperfusion treatments.

Evaluation of parameters/indices

Vital signs

Heart rate (HR), body temperature, mean arterial pressure (MAP) and respiratory rate were observed in the two groups before and after 7 days of treatment.

Renal function

Fasting venous blood (8 mL) was extracted from both groups before and after 7 days of treatment, centrifuged at 3500 rpm for 10 min and collected serum. The levels of urea nitrogen (BUN) and blood creatinine (Scr) were measured by Beckman Coulter AU5800 automatic biochemical analyzer, USA.

Inflammatory indices

The levels of calcitoninogen (PCT), C-reactive protein (CRP), interleukin (IL)-1 and tumor necrosis factor (TNF)-α were assayed by chemiluminescence, immunoturbidimetric, ELISA and radioimmunoassay in the two groups before and after 7 d of treatment, respectively. The above kits were provided by Shanghai Lightco Biotechnology Co. (XK-E10642, 11250-HNAH, 051A08.21, EM0183-HS).

Microcirculation indices

The microvascular flow index (MFI) and perfusion vascular ratio (PPV) of the two groups were determined before treatment and 7 days after treatment by Sidestream dark field detector from Microvision (Netherlands).

Severity

The severity of the disease in each group was assessed using the Sequential Organ Failure Assessment Score (SOFA) and the Acute Physiology and Chronic Health Status Scoring System II (APACHE II) before and after 7 days of treatment, respectively. The higher the score, the more severe the condition.

Adverse reactions

The occurrence of peptic ulcers, temporary hypotension and bleeding in both groups were counted.

Prognostic indicators

The duration of ICU stays, mechanical ventilation, and total hospital stay were recorded in both groups.

Statistical analysis

Statistic Package for Social Science (SPSS) 23.0 analysis software was utilized and the data are described by mean ± standard deviation (SD). The independent sample *t*-test and paired sample *t*-test were employed for comparison between two *groups* and intra-group comparison, respectively. A statistically significant difference is indicated by $p < 0.05$.

RESULTS

Baseline information

Body mass index, gender, age, type of primary disease and type of co-morbidities were similar between the two groups ($p > 0.05$) (Table 1).

Vital signs

Before treatment, the differences in HR, respiratory rate, and MAP did not show statistical significance between the two groups ($p > 0.05$); After 7 d of treatment, both groups showed a significant reduction in HR and respiratory rate, along with an elevation in MAP compared to their pre-treatment levels ($p < 0.05$). Furthermore, study group exhibited a notable decline in HR and respiratory rate, and a more pronounced increase in MAP when compared to control group ($p < 0.05$). Therefore, HA380 hemoperfusion in conjunction with CVVHDF exhibits a marked improvement in the vital signs in the early stage of septic shock as displayed in Figure 1.

Table 1: Comparison of baseline data

Baseline data		Control group	Study group
Sex	Male	29	31
	Female	24	23
Age (years)		56.19±5.77	55.80±5.62
Body mass index (kg/m^2)		24.03±2.36	23.76±2.14
Type of primary disease	Abdominal infection	19	18
	Pulmonary infection	24	27
	Urinary infection	7	6
	Other	3	3
Type of comorbid disease	Hypertension	15	18
	Diabetes	13	14
	Coronary heart disease	8	10

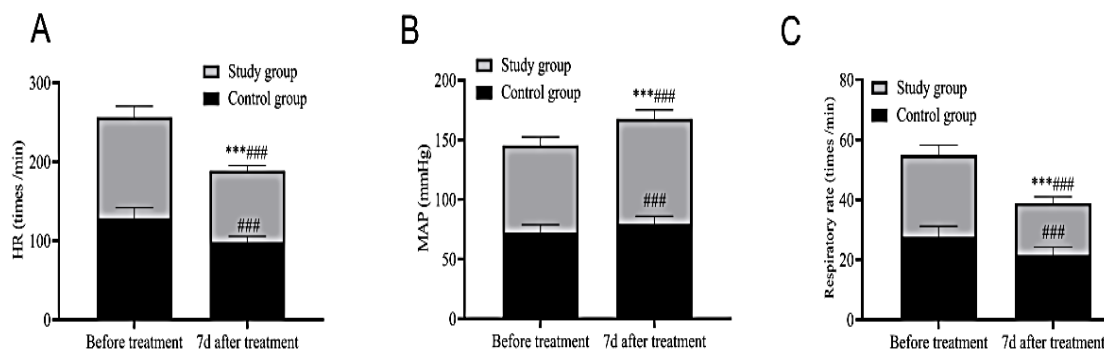Data are presented by n and mean ± SD

Figure 1: Effect of HA380 hemoperfusion combined with CVVHDF on early vital signs in septic shock. HA380 perfusion combined with CVVHDF significantly reduces (A) HR, and (C) respiratory rate levels and increases (B) MAP levels in patients in early septic shock. **Note:** ***$P < 0.001$ vs. control group; ###$p < 0.001$ vs. within the same group

Table 2: Comparison of renal function

Group	BUN (mmol/L)		Scr (μmol/L)	
	Before treatment	After 7 days of treatment	Before treatment	After 7 days of treatment
Control group (n = 53)	18.25±2.55	8.36±1.32###	198.65±18.54	81.67±8.35###
Study group (n = 54)	18.82±2.64	6.67±1.02***###	197.24±20.03	62.57±6.22***###

Note: ***$P < 0.001$ vs. control group; ##$p < 0.001$ vs. within the same group

Renal function

Before treatment, both groups showed comparable renal function indices with no statistically significant differences ($p > 0.05$); the serum BUN and Scr levels in both groups were significantly lower than those before treatment after 7 d of treatment, and the BUN and Scr levels in study group were markedly lower in comparison to control group after 7 d of treatment ($p < 0.05$). It is suggested that HA380 hemoperfusion in conjunction with CVVHDF can greatly improve the renal function of patients in the early stage of septic shock. The result is presented in Table 2 below.

Inflammatory indices

Before treatment, both groups exhibited comparable inflammatory indices with no statistically significant differences ($p > 0.05$). The serum levels of PCT, *CRP,* IL-1 and TNF-α were significantly lower in both groups after 7 d of treatment than before treatment. Furthermore, study group had markedly lower serum levels of PCT, CRP, IL-1 and TNF-α in comparison to control group after 7 d of treatment ($p < 0.05$). This result suggests that HA380 hemoperfusion combined with CVVHDF can greatly decrease serum inflammatory factor levels in patients with early septic shock. (Figure 2).
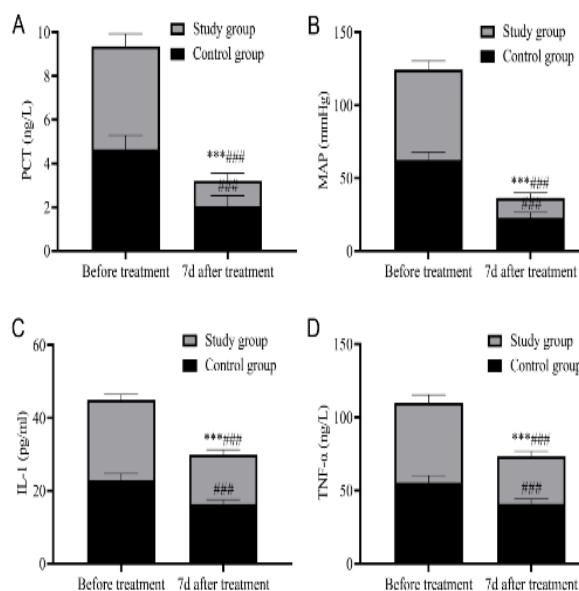

Figure 2: Effect of HA380 hemoperfusion combined with CVVHDF on the levels of inflammatory indices in the early stage of septic shock. HA380 hemoperfusion combined with CVVHDF significantly reduced the levels of (A) PCT, (B) CRP, (C) IL-1 and (D) TNF-α in patients with early septic shock. **Note:** ***$P < 0.001$ vs. control group. ###$P < 0.001$ vs the same/within group

Microcirculatory indices

Before treatment, both groups exhibited comparable microcirculatory indices with no statistically significant differences ($p > 0.05$); After 7 d of treatment in both groups, MFI and

Table 3: Comparison of microcirculatory indices

Group	MFI		PPV (%)	
	Before treatment	**After 7 days of treatment**	**Before treatment**	**After 7 days of treatment**
Control group (n = 53)	1.67±0.82	2.34±0.87###	32.59±2.36	39.42±3.34###
Study group (n = 54)	1.75±0.79	2.85±1.03***###	32.85±2.41	46.35±3.67***###

***$P < 0.001$ vs control group; ###$P < 0.001$ vs. within the same group

Table 4: Comparison of the severity of the disease

Group	SOFA		APACHE II	
	Before treatment	*After 7 days of treatment*	*Before treatment*	*After 7 days of treatment*
Control group (n = 53)	10.26±1.67	8.45±1.24###	17.56±2.14	14.87±1.64###
Study group (n = 54)	10.01±1.55	6.24±1.06***###	17.31±2.06	11.74±1.55***###

***$P < 0.001$ vs. control group; ###$p < 0.001$ vs. within the same group

Table 5: Comparison of adverse reactions

Group	Gastrointestinal ulcer	Transient hypotension	Hemorrhage	Total
Control group (n = 53)	2 (3.77)	1 (1.89)	1 (1.89)	4 (7.55)
Study group (n = 54)	3 (5.56)	2 (3.70)	2 (3.70)	7 (12.96)

Table 6: Comparison of prognostic indicators

Group	ICU length of stay	Duration of mechanical ventilation	Total length of stay
Control (n = 53)	12.69±1.46	2.19±0.56	19.26±2.11
Study (n = 54)	9.88±1.34***	1.44±0.47***	15.84±1.86***

***$P < 0.001$ vs. control group

PPV were markedly higher than before treatment, and the serum PMFI and PPV were significantly higher in study group relative to control group after 7 d of treatment ($p < 0.05$). This suggests that HA380 hemoperfusion in conjunction with CVVHDF can greatly improve the microcirculation in patients with early septic shock (Table 3).

Severity of condition

Before treatment, both groups exhibited no statistically significant differences in the severity of the disease ($p > 0.05$). Both groups showed reduced SOFA and APACHE *II* scores after 7 days of treatment, with study group exhibiting much lower scores than control group ($p < 0.05$) (Table 4).

Adverse reactions

Before treatment, the incidence of adverse reactions in both groups (7.55 vs. 12.96 %) did not show statistically significant difference ($p > 0.05$) (Table 5).

Prognostic indicators

During hospitalization, there were no deaths in either group. Study group showed shorter duration of ICU stay, shorter duration of mechanical ventilation, and shorter total hospital stay compared to control group ($p < 0.05$). This result suggests that HA380 hemoperfusion in conjunction with CVVHDF can significantly improve the prognosis of patients with early septic shock (Table 6).

DISCUSSION

The pathogenesis of sepsis is complex. It has been found that the onset of sepsis arises from a large number of pathogenic bacteria and the production of toxins, inducing an excessive inflammatory response in the body. This then results in immune system, coagulation system and metabolic microcirculation disorders, which in turn causes septic shock or multi-organ dysfunction [11-13].

Septic shock should be actively and effectively treated in the early stages of the condition in order to stop the patient's illness from worsening, according to research by Piton [14] and other

researchers. Septic shock is an important process in the progression of sepsis into multiple organ failure.

The results of this research showed that study group exhibited lower HR, respiratory rate, serum BUN, Scr levels and SOFA, APACHE II score, ICU length of stay, duration of mechanical ventilation and total hospital stay in comparison to control group after treatment, while showed higher MAP in contrast to control group ($p < 0.05$). It is suggested that in the early stages of septic shock, HA380 hemoperfusion combined with CVVHDF is beneficial in enhancing renal function, controlling the condition and enhancing short-term prognosis. This is because CVVHDF removes small and medium-sized molecules from the blood and maintains hemodynamic stability and acid-base and water-electrolyte balance through a hemofilter with high biocompatibility and high permeability [15,16]. Also, CVVHDF removes toxic metabolites from the blood by convective and diffusive clearance of solutes, improving immune function as well as prognosis [17]. However, Constantinescu *et al* [18] found that CVVHDF is not effective against large molecules such as inflammatory cytokines. Blood perfusion is an effective approach to remove large molecules such as inflammatory mediators, and the HA380 hemoperfusion apparatus used in this study has a powerful adsorption capacity to remove inflammatory mediators such as CRP and IL-6, reduce the inflammatory response, block the waterfall effect of inflammatory factors and thus control the condition as well as promote recovery [19-21]. However, blood perfusion is not effective in maintaining the stability of the internal environment [22]. HA380 hemoperfusion combined with CVVHDF for early septic shock has a synergistic effect with complementary advantages to further enhance the clearance effect, which can effectively remove inflammatory cytokines, toxins and metabolites, maintain the stability of the internal environment, block the inflammatory waterfall effect and promote the balance of immune function.

The involvement of inflammatory response is widely recognized as a significant factor in the onset of septic shock [23,24]. Inflammatory mediators can cause damage to pathogen-infected target organs in addition to spreading to other organs and tissues through blood circulation and inducing neutrophils and macrophages to release large amounts of proteases and derivatives of arachidonic acid. This results in abnormal blood flow distribution,

tissue and organ ischemia and eventually the development of reperfusion in the affected area [25,26]. Thus, it is clear that correcting microcirculatory abnormalities and lowering the intensity of the inflammatory response in patients in the early stages of septic shock is crucial for improving their conditions and maximizing the therapeutic effects. The measurement of inflammatory disorders benefits greatly from the large molecular weight of PCT, a molecule that is a precursor to calcitonin. Its level can increase with the intensity of the inflammatory reaction. CRP is a large molecule acute phase protein that reflects the degree of inflammatory response.

An agent that starts the inflammatory response is IL-1. By removing IL-1, it is possible to effectively stop the amplification and clustering of inferior inflammatory factors, preventing the waterfall effect of inflammatory factors and inhibiting the inflammatory response. TNF-α is a mononuclear factor secreted by activated macrophages and monocytes, inducing systemic inflammatory responses. The results of this research revealed that study group had lower serum levels of PCT, CRP, IL-1 and TNF-α in comparison to control group after 7 d of treatment, while exhibiting higher MFI and PPV compared to control group ($p < 0.05$). This indicates that HA380 hemoperfusion combined with CVVHDF effectively suppresses inflammatory response and improves microcirculation, which is beneficial to improve the prognosis of patients in early septic shock. In addition, this study found that the two groups exhibited relatively similar incidence of adverse reactions ($p > 0.05$), again showing that HA380 hemoperfusion combined with CVVHDF is a safe and effective treatment modality.

Limitations of this study

This research was restricted to a single-center retrospective analysis with a small sample size, which may have skewed the results.

CONCLUSION

The combination of HA380 hemoperfusion with CVVHDF in patients with early septic shock effectively improves renal function, suppresses inflammatory response, enhances microcirculation and improves short-term prognosis with a good safety profile. Future research should focus on evaluating the long-term efficacy and prognosis of HA380 hemoperfusion combined with CVVHDF for early septic shock.

DECLARATIONS

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Both Guochao Zhu and Jing Zhang contributed equally to this work and should be considered as equal first coauthors.

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