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Original Article

Continuous veno-venous hemofiltration for septic shock

Zhi Hui[1], Zhe Li[2]

[1]*Intensive Care Unit,* [2]*The 1st Department of Cardiology, Cangzhou Central Hospital, Cangzhou City, Hebei Province, China*

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Abstract: Objective: To explore the efficacy of continuous veno-venous hemofiltration in the treatment of patients with septic shock. Methods: From January 2015 to January 2017, a total of 70 patients with sepsis admitted to the intensive care unit (ICU) of our hospital were recruited in the current study. The patients were randomly assigned to the conventional treatment group (control group) or the continuous veno-venous hemofiltration group (CVVH group). The patients in the control group were treated according to the International Guidelines for Management of Severe Sepsis and Septic Shock (2012) where as those in the CVVH group received hemofiltration with a polyflux 14 Shem of ilter (1.4 m^2 membrane area) in addition to all the above treatment given to the control group. The clinical outcomes including the cardiac, renal and hepatic functions, oxygen index (OI), vasopressor consumption and the serum lactic level were measured, the scores of the patients on the Acute Physiology and Chronic Health Evaluation II (APACHE II) and the Sepsis-related Organ Failure Assessment (SOFA) were also assessed and the changes in the plasma concentrations of TNF-α, IL-6, IL-8, IL-10, HMGB1, vWF and E-selectins were also measured by the enzyme-linked immunosorbent assay (ELISA) before treatment and at 72 h after treatment, respectively. Results: Before treatment, the two groups did not differ significantly inthe cardiac, renal and hepatic functions, OI, vasopressor dosage, serum lactic level, APACHE II scoreand SOFA score and other inflammatory mediators. After treatment, among the patients in the CVVH group, improvements in cardiac, renal and hepatic functions and OI, a decrease in vasopressor dosage, a decline in serum lactic levels, significant reductions in APACHE II and SOFA scores, substantial reductions in the levels of TNF-α, IL-6, HMGB1, vWF and E-selectinsbut marked rise in IL-8 and IL-10 levels were noted (All $P<0.05$). Conclusion: Continuous veno-venous hemofiltration is effective in improving the clinical, physiological and biochemical outcomes of patients with septic shock.

Keywords: Continuous veno-venous hemofiltration, septic shock, inflammatory cytokine

Introduction

Sepsis, a systemic inflammatory response syndrome (SIRS) which is caused by infection, can be subdivided into three grades of sepsis, severe sepsis, septic shock and multiple organ dysfunction syndrome (MODS), andit is one of the most important causes of mortality in the intensive care units (ICUs). The studieson the management of sepsis have revealed that the blood purification techniqueis effective in treating sepsis as it can, by reducing the levels of inflammatory cytokines in the blood stream, regulate the immune system and other mechanisms in a patient, there by effectively improving the patient's condition [1]. Continuous veno-venous hemofiltration (CVVH) is a blood purification method used extensively in clinical treatment of sepsis. CVVH, however, has shown to filter out anti-inflammatory cytokines (such as IL-8 and IL-10) in the removal of pro-inflammatory cytokines (such as IL-1β, IL-6 and TNF-α). In addition, production and metabolism of inflammatory cytokines is strikingly fast in the body. Never the less, several studies have demonstrated that CVVH has no effect on the levels of the above inflammatory cytokines, so CVVH is still questioned in clinical application [2, 3]. Therefore, this study was designed to make a comprehensive analysis on the effects of CVVH treatment on the clinical, physiological and biochemical outcomes of sepsis patients through the clinical and experimental observations, in order to provides up portive evidence for clinical treatment of sepsis.

Materials and methods

Study population

This study obtained approval from the Hospital Ethics Committee and each patient or family

Table 1. General characteristics of the patients

Variable	Control (n=35)	CVVH (n=35)
Sex, male, n (%)	25 (71.4)	26 (74.3)
Age ($\bar{x}$ ±s)	56.3±12.5	58.4±15.6
Ventilator use, n (%)	19 (54.3)	21 (60.0)
Hypertension, n (%)	8 (22.9)	7 (20.0)
Diabetes mellitus, n (%)	4 (11.4)	3 (8.6)
Chronic renal insufficiency, n (%)	6 (17.1)	5 (14.3)

provided written informed consent. It was conducted by recruiting sepsis patients admitted to the ICU in our hospital between January 2015 and January 2017. All the eligible patients metthe diagnostic criteria for severe sepsis specified in the International Guidelines for Management of Severe Sepsis and Septic Shock (2012).

The patients who were 18-75 yearsold were eligible for this study if they met the diagnostic criteria for sepsis shock and hospital stay was longer than 24 hours. Those were excluded if they were unable to receive hemofiltration due to hemodynamic disorders, associated with other autoimmune disease and cardiacinjury, expected deaths with in 72 h after admission, contra indicated to hemodialysis or had previous hemofiltration. As a result, 70 eligible patients were finally included in this study.

Group assignment

The patients, in terms of the computer-generated random numbers, were randomly assigned to the conventional treatment group (control group) or to the continuous hemofiltration group (CVVH group). The patients in the control group were given treatment in accordance with the International Guidelines for Management of Severe Sepsis and Septic Shock (2012), and those in the CVVH group received hemofiltration with a polyflux 14 S hemofilter (1.4 m^2 membrane area) apart from concurrent treatment according to the International Guidelines (2012).

CVVH protocol

Hemofiltration device: The patients under went CVVH immediately after they were confirmed as having sepsis shock by three senior physicians in our hospital. CVVH was performed with the use of polyflux 14 S hemofilter (1.4 m^2 membrane area) and matched tubes via the insertion of tri-lumen deep venous catheters (ARROW, USA) into the internal carotidveins or femoral veins every 24 hours for a period of 72 hours. Filtrate was replaced in a pre-dilution mode at a rate of 40 ml/kg/h. The blood flow rate was 200 ml/min. Heparin was utilized for anticoagulation. The hemofilter was prewashed with washing solution (mixture of 3000 ml of normalsaline and 20 mg of heparin) for 30 min. The intravenous infusion of heparin was initiated at a dose of 3000 IU, then at 500 IU/h. Heparin consumption was regulated with the alternations in coagulation indexes. For the patients with a tendency of potential bleeding, non-heparin treatment was performed.

Fluid resuscitation formula: The formula for fluid resuscitation was the one provided by the Nanjing General Hospital of Nanjing Military Region, which states: 3000 ml of isotonic normal saline + 170 ml solution containing 5% glucose + 820 ml of water for injection + 6.4 ml solution containing 10% calcium chloride + 1.6 ml solution containing 50% magnesium sulfate. The mixed fluid produced based on the above formula put into an infusion bag (A fluid) and 250 ml containing 5% sodium bicarbonate (B fluid) were concurrently delivered through the same pathway, but B fluid was not infused into A fluid to preclude the precipitation of calcium ions.

Outcomes measures

The vasopressor consumption out come included consumption of dopamine and norepinephrine after admission, before treatment and at 72 h, respectively.

Biochemical outcomes included the results of blood tests regarding the hepatic, cardiac and renal functions, biochemical indicators, and serum lactic levels of patients before treatment and at 72 h after treatment respectively, as well as the plasma concentration of TNF-α, IL-6, IL-8, IL-10, HMGB1, vWF and E-selectins (Immuno Way, US), as measured by the enzyme-linked immunosorbent assay (ELISA). The ELISA was conducted as follows: the anti-coagulation blood specimens were centrifuged at 3000 rpm for 15 min, followed by abstraction of serum used for ELISA. Details of the experimental procedure were referred to the instruction.

Septic shock severity outcomes comprised APACHE II score and SOFA score before treatment and at 72 h after treatment, respectively.

Table 2. Changes in dosage of dopamine and norepinephrine and in the serum lactic levels before and after treatment among the patients

Parameter \ Group	Before treatment		After treatment	
	Control	CVVH	Control	CVVH
Dopamine (μg/kg/min)	7.9±4.3	6.5±3.9	4.3±2.3*	1.3±1.9*,#
Norepinephrine (μg/kg/min)	0.52±0.36	0.48±0.32	0.37±0.25*	0.12±0.20*,#
Lactic acid (μg/L)	5.02±2.1	4.93±1.96	3.49±1.59*	1.46±1.13*,#

Note: *P<0.05 for comparison before and after treatment, there was significant difference; #P<0.05 for comparison between the CVVH group and the control group, there was significant difference.

Table 3. Changes of APACHE II and SOFA scores before and after treatment

Parameter \ Group	Before treatment		After treatment	
	Control	CVVH	Control	CVVH
APACHE II	26.8±7.0	27.3±7.1	25.3±6.6*	16.7±4.4*,#
SOFA	30.2±7.8	29.7±7.7	24.8±6.5*	18.3±4.8*,#

Note: *P<0.05 for comparison before and after treatment, there was significant difference; #P<0.05 for comparison between the CVVH group and the control group, there was significant difference.

Table 4. Changes in biochemical parameters of patients before and after treatment

Parameter \ Group	Before treatment		After treatment	
	Control	CVVH	Control	CVVH
TBIL	55.4±11.08	57.65±11.53	52.79±10.56	30.56±6.11*,#
DBIL	50.09±10.02	45.77±9.15	46.67±9.33	33.26±6.65*,#
Cr	192.2±38.44	193.1±38.62	147.2±29.44*	56.3±11.26*,#
BUN	23.54±4.71	22.37±4.47	10.99±0.40*	4.78±0.96*,#
CysC	1.18±0.24	1.21±0.24	0.5±0.10*	0.31±0.06*,#
Tn	0.63±0.13	0.48±0.10	0.3±0.06*	0.16±0.03*,#
OI	197.6±39.52	216.5±43.30	226.4±45.28	296.6±59.32*,#

Note: *P<0.05 for comparison before and after treatment, there was significant difference; #P<0.05 for comparison between the CVVH group and the control group, there was significant difference.

Statistical analysis

All the statistical data were represented as $\bar{x}\pm s$ and analyzed with the use of the SPSS software package, version 19.0. The independent t-test was used for comparisons of measurement data between the groups and the differences before and after treatment, whereas comparisons of the differences with in the same group before and after treatment were made with the paired t-test. The χ^2 test was applied for comparisons of count data between the groups. P<0.05 was set to be statistically significant difference.

Results

General characteristics of the patients before treatment

Before treatment, no significant differences between the CVVH group and the control group were found concerning gender and age, previous hypertension, diabetes mellitus or chronic renal insufficiency. The rate of ventilator use ranged from 54.3% to 60.0%, without striking difference between the two groups (**Table 1**).

Dosage of vasopressor agents and serum lacticlevels

Dopamine and norepinephrine are commonly used for blood pressure control in patients. Inthe current study, dopamine and norepinephrine consumption varied in significantly between the two groups before treatment (P=0.853, 0.922), but they reduced substantially in CVVH group after treatment (P=0.042, 0.000), and less than those of the control group (P=0.007, 0.019); moreover, comparisons of the changes in dopamine consumption before and after treatment revealed a significant benefit for the patients in the CVVH group (P=0.023). In significant differences in the serum lactic levels were found between the two groups before treatment (P=0.745), but after treatment the levels fell considerably in the CVVH group (P=0.042), and lower than those of the control group (P=0.021, **Table 2**).

Severity of septic shock of the patients before and after treatment

The Acute Physiology and Chronic Health Evaluation II (APACHE II) and the Sepsis-related

Table 5. Changes in inflammatory cytokines before and after treatment

Group / Parameter	Before treatment		After treatment	
	Control	CVVH	Control	CVVH
TNF-α (ng/L)	758.6±129.3	733.6±130.2	650.8±124.1	296.4±94.4*,#
IL-6 (ng/L)	256.5±46.9	256.6±39.4	224.0±52.5*	105.6±32.4*,#
IL-8 (ng/L)	158.9±45.6	149.8±38.7	247.6±81.5*	458.9±52.2*,#
IL-10 (ng/L)	115.6±32.3	113.8±33.1	197.2±46.4*	290.5±55.2*,#
HMGB1 (ng/ml)	42.9±9.5	46.7±10.2	40.5±8.6	30.7±7.6*,#

Note: *P<0.05 for comparison before and after treatment, there was significant difference; #P<0.05 for comparison between the CVVH group and the control group, there was significant difference.

Table 6. Changes in Levels of vWF and E-selectins of the patents before and after treatment

Group / Parameter	Before treatment		After treatment	
	Control	CVVH	Control	CVVH
vWF	28.8±8.12	27.8±7.85	22.1±6.4*	14.9±4.5*,#
E-selectins	34.6±9.62	34.0±9.52	27.6±7.8*	18.3±5.4*,#

Note: *P<0.05 for comparison before and after treatment, there was significant difference; #P<0.05 for comparison between the CVVH group and the control group, there was significant difference.

Organ Failure Assessment (SOFA) are the scales used to assess the severity of septic shock and the degree of organ dysfunction, respectively. In our current study, we found no substantial differences in APACHE II score and SOFA score between the two groups before treatment (P=0.855, 0.754). After treatment, the APACHE II score and SOFA score reduced markedly in the CVVH group (P=0.023, 0.041), and lower than those in the control group (P=0.015, 0.024; **Table 3**).

Biochemical parameters of the patients before and after treatment

In this study, before treatment, the hepatic biochemical parameters (the levels of ALT, AST, TBIL and DBIL), myocardial enzymes Tn and CK-MB, andthe renal function parameters (the levels of Cr, BUN and CysC), andthe oxygen index (OI) were not statistically different between the two groups (**Table 4**). After treatment, the levels of TBIL, DBIL, Cr, BUN, CysC and Tnre duced significantly in the CVVH group (P=0.000, 0.002, 0.000, 0.000, 0.003, 0.027), and were even lower than those in the control group (P=0.000, 0.004, 0.014, 0.021, 0.043, 0.023); OI in the CVVH group was substantially higher than that before treatment, and the value was substantially greater than that in the control group (P=0.042). There were no marked differences in other parameters between the two groups (**Table 4**).

Inflammatory cytokines of the patients before and after treatment

The findings indicated no striking differences in the serum levels of TNF-α, IL-6, IL-8, IL-10 and HMGB1 between the two groups before treatment. After treatment, significant reductions in the serum levels of TNF-α, IL-6, and HMGB1 were seen in the CVVH group (P=0.000, 0.000, 0.012), and lower than those in the control group (P=0.000, 0.000, 0.014); in contrast, the levels of IL-8 and IL-10 rose substantially in the CVVH group (P=0.000, 0.000) and higher than those in the control group (P=0.000, 0.000; **Table 5**).

Levels of vWF and E-selectins of the patents before and after treatment

This study demonstrated that no significant differences were seen in the levels of vWF and E-selectins between the two groups before treatment. After treatment, both vWF and E-selectins levels decreased considerably in the CVVH group (P=0.025, 0.014), and substantially lower than those in the control group (P=0.023, 0.021; **Table 6**).

Discussion

The extremely highmortality of severe sepsis may bethe causes that the invaded pathogenic organisms are recognized by the immune system, which produces inflammatory cytokines and induces inflammation; the vascular endothelial cells are vulnerable to stimulation from a variety of inflammatory mediators released by different cells, thereby activating cascade reactionsto the coagulation and fibrinolytic systems, which results in an interaction between the injuries as a result of the coagulation and fibrinolysis and inflammation [4, 5]. The widely-

used techniques for treatment of severe sepsis focus on the clearance of inflammatory mediators, among which CVVH is one of the currently-recognized effective therapies for clearance of inflammatory mediators [6, 7]. The effect of CVVH on severe sepsis, however, remains uncertain. Therefore, we made a comprehensive analysis on the efficacy and other mechanisms of CVVH in the treatment of severe sepsis in a large-sample, randomized trial.

In our current study, after 72 hours of treatment, as compared to those in the control group, the serum lactate levels were significantly lower among the patients in the CVVH group. Accumulation of lactic acid in the bloodstream of patients with severe sepsis was caused by anaerobic glycolysis triggered by hypoxia [8, 9]. The serum lactic level is not a high-precision biomarker for the tissue metabolism, but hyperlactacidemia is an important biomarker for prognosis of septicaemia in patients. In the current study, the serum lactic levels lowered substantially in the CVVH group, suggesting that CVVH improves tissue hypoperfusion during early resuscitation.

CVVH is associated with significantly improved hepatic, renal and cardiac functions, and OI of patients. The determinants of the OI level include cardiac output, oxygen demand, hemoglobin, and arterial oxygen saturation [10]. The decrease in OI in septic patients requires active intervention to increase delivery of tissue oxygen and reduce the vital indications of sepsis-induced tissue hypo-perfusion. In the resuscitation of sepsis, the arterial oxygen which fails to deliver to the tissues flows back to the vein, resulting in elevated OI level. This does not mean achievement of sufficient resuscitation.

We found in our current study that CVVH ultimately reduced the APACHE II scoreand SOFA score of the patients and controlled their disease conditions. There were four major mechanisms for CVVH in the treatment of sepsis. First, the peak concentration hypothesis (with regard to inflammatory cytokines) by Ronco et al. who held that CVVH decreased the concentrations of inflammatory cytokines in early sepsis to prevent inflammation storm as a result of excessive inflammation, reduce damages to a large number of organs and improve the prognosis of patients [6, 11]. Second, the thre shold hypothesis (regarding regulation of the immune system) by Honore et al. who argued that after inflammatory cytokines in the bloodstream had been removed by means of CVVH, the levels of inflammatory cytokines in interstitium were higher than thosein the bloodstream; then some inflammatory cytokines in interstitium moved to the bloodstream to achieve hemodynamic balance, inflammatory cytokines in the bloodstream were removed by CVVH again, inflammatory cytokines in interstitium moved to the bloodstream until the levels reached the threshold where the inflammatory cytokines made no damages to the body [12, 13, 18]. This hypothesis demonstrates that CVVH does not decrease the concentrations of inflammatory cytokines at all time points. Third, the inflammatory cytokine transfer hypothesis by Di Carlo et al. and Olszewski who believed that CVVH promoted the transfer of inflammatory cytokines from interstitium into the bloodstream, which could remove the inflammatory cytokines continuously, keeping the condition of the patients under control [14, 15, 19]. Fourth, the immune cell function regulation hypothesis by Peng and colleagues who held that CVVH regulated the functions of a variety of immune cells after the removal of inflammatory cytokines, so as to restore the normal functioning of the immune system [16, 17, 20]. In our present study, after treatment, significant changes in the levels of inflammatory mediators were also observed among patients in the CVVH group, with significantly lowerthe levels of TNF-α, IL-6, HMGB1, vWF, and E-selectins, but strikingly higher levels of inflammatory cytokines IL-8 and IL-10, as compared with those in the control group, thereby realizing disease control.

In conclusion, CVVH improved the clinical, physiological and biochemical outcomes, the immunefunctions and prognosis of sepsis patients through various mechanisms, and played an active role in the treatment of sepsis.

Disclosure of conflict of interest

None.

Address correspondence to: Zhe Li, The 1st Department of Cardiology, Cangzhou Central Hospital, No. 16, Xinhua West Road, Cangzhou City 061001, Hebei Province, China. Tel: +86-15132796060; E-mail: lizhe66628@163.com

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