Original Article

Blood hemoperfusion with resin adsorption combined continuous veno-venous hemofiltration for patients with multiple organ dysfunction syndrome

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BACKGROUND: Blood hemoperfusion with resin adsorption can clean larger molecules that exceed the molecular weight cutoff of combined continuous veno-venous hemofiltration (CVVH). Hence blood hemoperfusion with resin adsorption combined CVVH (HP+CVVH) has higher ability of mediator clearance, and can improve clinical outcomes in theory. This study aimed to investigate the effect of blood hemoperfusion with resin adsorption combined continuous veno-venous hemofiltration (HP+CVVH) on plasma cytokines like TNF- α , IL-1 β , IL-6, cellular immunity and prognosis in patients with multiple organ dysfunction syndrome (MODS).

METHODS: This was a prospective, randomized clinical trial. A total of 30 patients who had been diagnosed with MODS were enrolled in this study. Patients were randomly allocated to routine treatment+HP+CVVH group (treatment group) and routine treatment+only CVVH group (control group). In the treatment group, patients received blood hemoperfusion with resin adsorption for 2 hours, and then received CVVH for 10 hours every day. In the control group, patients received CVVH for 12 hours only every day. The patients in the two groups received blood purification therapy for three days. The plasma of patients in the treatment group was obtained at 0, 2, 12, 24, 26, 36, 48, 50, 60 hours, 5th day, 7th day and 10th day, respectively. The plasma of patients in the control group was obtained at 0, 12, 24, 36, 48, 60 hours, 5th day, 7th day and 10th day, respectively. APACHE II score, T-lymphocytes subpopulations, blood lactate acid concentration, heart rate, breathing rate, and oxygenation index were observed.

RESULTS: Plasma cytokines like TNF- α , IL-1 β , IL-6 decreased markedly after HP ($P<0.01$); T-lymphocytes subpopulations CD3 $^{+}$, CD4 $^{+}$, CD8 $^{+}$, CD4 $^{+}$ /CD8 $^{+}$ increased after HP+CVVH or only CVVH. The plasma concentrations of TNF- α , IL-1 β and IL-6 in the two groups were not markedly different at 12, 36, and 50 hours. But on the 5th day, the plasma concentrations of TNF- α , IL-1 β and IL-6 in the treatment group were lower than those in the control group ($P<0.05$). On the 28th day, 5 patients died in the treatment group, and 6 patients in the control group.

CONCLUSIONS: Both HP+CVVH and CVVH can clean plasma cytokines like TNF- α , IL-1 β , and IL-6, and improve cellular immunity and clinical symptoms and signs of patients. Compared with only CVVH, the plasma concentrations of TNF- α , IL-1 β and IL-6 were lower on the 5th day, and patients have an increased survival rate on the 28 day in the HP+CVVH group.

KEY WORDS: Hemoperfusion with resin adsorption; Continuous veno-venous hemofiltration; Multiple organ dysfunction syndrome; Cytokines

World J Emerg Med 2012;3(1):44-48
DOI: 10.5847/wjem.j.1920-8642.2012.01.008

INTRODUCTION

Multiple organ dysfunction syndrome (MODS) and/or severe sepsis is the leading cause of morbidity and mortality in ICU. The pathophysiology of MODS is complicated, and several attempts for improving the outcomes of patients by targeting specific components have been proved unsuccessful.^[1] In recent years, researchers have found that continuous venovenous hemofiltration (CVVH) treatment can lower inflammatory cascade reaction and tissue damage, while regulating the balance of inflammatory/anti-inflammatory and immune system. Moreover the treatment can effectively regulate the volume and acid-base balance and improve symptoms, signs and eventual prognosis.^[2,3] CVVH plays a beneficial role in MODS and / or sepsis therapy, but the clearance of inflammatory cytokines is limited because of material and the diameter of the membrane. CVVH is not able to remove larger molecules such as lipopolysaccharide and mediators rich of proteins, but new resin adsorbents can resolve this problem. Blood hemoperfusion with resin adsorption can clean larger molecules exceeding the molecular weight cutoff of CVVH. Hence blood hemoperfusion with resin adsorption combined CVVH (HP+CVVH) has a higher ability of mediator clearance and can improve clinical outcomes in theory.^[3,4] In this study we observed the effect of HP+CVVH therapy on clearance of plasm cytokines like TNF- α , IL-1 β , IL-6, cellular immunity and prognosis in the MODS patients.

METHODS

Inclusion criteria and exclusion criteria

Patients in ICU were enrolled according to the following criteria: >18 years old; male/female; serious injury or infection induced MODS with or without acute renal failure. The diagnostic criteria of MODS refer to the *Diagnosis and Treatment of MODS: the Effect of Integrated Traditional and Western Medicine on Mortality* prepared by the Research Group of Key Project of Beijing Municipal Sciences and Technology Commission in 2008,^[5] and the sepsis diagnostic criteria refer to guidelines issued at 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference.^[6] The patients were excluded from the study if they have poor prognosis, or have main causes of death such as severe craniocerebral injury and cerebral stroke, CPR, late stage of malignant tumor. Exclusion criteria also included death in less than 72 hours after treatment, automatic hospital discharge, failure to adhere to the

system of treatment.

All eligible patients with or without renal failure were subjected to blood purification. Patients were randomly allocated to a HP+CVVH group (treatment group) and a CVVH group (control group). In the HP+CVVH group, patients received blood hemoperfusion with resin adsorption for 2 hours, then received CVVH for 10 hours every day. In the CVVH group, patients received CVVH for 12 hours only every day. The patients of the two groups were subjected to blood purification for three days. Clinical data, ApacheII score, T-lymphocyte subpopulations, blood lactic acid, dosage of vasoactive drugs, heart rate, respiratory rate and oxygenation index of the patients were recorded.

The plasma of the treatment group was obtained at 0, 2, 12, 24, 26, 36, 48, 50, 60 hours, the 5th day, 7th day and 10th day, respectively. The plasma of the control group was obtained at 0, 12, 24, 36, 48, 60 hours, the 5th day, 7th day and 10th day, respectively. All plasma samples were stored in a - 60 °C refrigerator. TNF- α , IL-6, and IL-1 β were tested with radioimmunoassay in accordance with the instructions of the kits provided by the Beijing North Biotechnology Institute.

A double-lumen catheter (B/BRAUN, Haemocat R Signo, German) was inserted into the femoral vein or the jugular vein to establish vascular access. HP and CVVH were performed using the multi-functional hemopurifying machine-AQUARIUSTM (Edward Life Sciences Co, Ltd, German). Blood filter (HF-1200, Baxter, America) was used during CVVH. A resin cartridge (HA-330-I, Zhuhai Lizhu Group of Biological Material Co, Ltd. China) was used during hemoperfusion. Replacement fluid formula was: NS 3000 mL+ sterile water for injection 820 mL+5% GS 170 mL+25% magnesium sulfate injection 3.2 mL. Calcium chloride and potassium chloride were added according to the levels of serum potassium and serum calcium of the patients. Volume replacement was 3-4 L /h (40-65 mL/kg per hour). For anticoagulation, unfractionated heparin, heparin or heparin free was selected according to patients with/without bleeding tendency.

Statistical analysis

All data were expressed as means $\pm$ standard deviation, and analyzed with SPSS13.0 statistical software. The data were analyzed by repeated measures of ANOVA, and Student's *t* test. *P*<0.05 was considered of statistical significance.

RESULTS

General clinical data

In the HP+CVVH group, 9 patients were male and 6 female; their age ranged from 39 to 85 years. Eight patients had renal insufficiency, 4 had oliguria and anuria, and 14 received mechanical ventilation with Apache II 26.3 ± 8.7 . In the CVVH group, 9 patients were male and 5 female, and their age ranged from 26 to 78 years. Seven patients had renal dysfunction, 3 had oliguria and anuria, and 13 received mechanical ventilation, with Apache II 25.1 ± 10.3 . No significant differences were observed in general clinical data between the two groups. Five patients in the HP+CVVH group (5/15) and 6 patients in the CVVH group (6/15) died in 28 days.

Changes of cytokines in 3-day treatment via HP+CVVH and CVVH

TNF- α , IL-1 β , and IL-6 were not different between the two groups before HP+CVVH and CVVH. TNF- α , IL-1 β , and IL-6 decreased markedly after HP (2 h vs. 0 h, 26 h vs. 24 h, 50 h vs. 48 h, $P < 0.01$). Plasma concentration of IL-6 continued to decline (2 h vs. 12 h, 36 h vs. 26 h, 60 h vs. 50 h) after CVVH for

10 hours ($P < 0.05$). But the plasma concentrations of TNF- α and IL-1 β were not decreased after CVVH. TNF- α , IL-1 β , and IL-6 decreased after CVVH for 12 hours in the CVVH group (12 h vs. 0 h, 36 h vs. 24 h, 60 h vs. 48 h, $P < 0.05$). TNF- α , IL-1 β , and IL-6 were not significantly different between the groups at 12, 36, and 50 hours (at the end of each blood purification therapy) (Table 1).

Changes of cytokines after HP+CVVH and CVVH

Plasma concentrations of TNF- α , IL-1 β and IL-6 were observed continuously on the 5th, 7th and 10th day at the end of blood purification. On the 5th day, the concentrations of TNF- α , IL-1 β and IL-6 in the treatment group (HP+CVVH) were lower than those in the control group ($P < 0.05$). On the 7th and 10th day, the concentrations of TNF- α , IL-1 β and IL-6 were not different significantly between the two groups (Table 2).

Changes of T-lymphocytes subpopulations after HP+CVVH and CVVH

T-lymphocytes subpopulations CD3+, CD4+, CD8+, CD4+/CD8+ (reagent from BD company, united

Table 1. Plasma concentrations of TNF- α , IL-1 β , and IL-6 before and within 3-day blood purification (mean $\pm$ SD, $n=15$)

Time points (h)	TNF- α (mol/L)		IL-6 (ng/L)		IL-1 β (ng/L)	
	Treatment group	Control group	Treatment group	Control group	Treatment group	Control group
0	20.30 $\pm$ 8.73	21.04 $\pm$ 4.63	60.23 $\pm$ 22.34	58.58 $\pm$ 21.80	0.14 $\pm$ 0.06	0.12 $\pm$ 0.03
2	15.98 $\pm$ 5.11*		58.65 $\pm$ 23.10*		0.09 $\pm$ 0.05*	
12	16.05 $\pm$ 6.33	18.70 $\pm$ 4.65 $^{\Delta}$	42.32 $\pm$ 21.57 $^{\#}$	44.74 $\pm$ 20.31 $^{\Delta}$	0.09 $\pm$ 0.05	0.09 $\pm$ 0.02 $^{\Delta}$
24	18.52 $\pm$ 8.58	18.25 $\pm$ 6.20	59.27 $\pm$ 20.65	54.73 $\pm$ 31.80	0.15 $\pm$ 0.05	0.16 $\pm$ 0.02
26	15.62 $\pm$ 6.67*		56.23 $\pm$ 24.31*		0.11 $\pm$ 0.05*	
36	13.31 $\pm$ 4.53	16.19 $\pm$ 6.23 $^{\Delta}$	48.03 $\pm$ 20.14 $^{\#}$	46.05 $\pm$ 29.79 $^{\Delta}$	0.11 $\pm$ 0.05	0.11 $\pm$ 0.04 $^{\Delta}$
48	15.41 $\pm$ 6.52	17.00 $\pm$ 4.81	55.45 $\pm$ 26.14	62.89 $\pm$ 43.58	0.13 $\pm$ 0.05	0.09 $\pm$ 0.05
50	12.89 $\pm$ 6.19*		54.13 $\pm$ 22.10*		0.09 $\pm$ 0.03*	
60	15.59 $\pm$ 9.18	15.27 $\pm$ 4.65 $^{\Delta}$	50.12 $\pm$ 18.14 $^{\#}$	44.58 $\pm$ 21.83 $^{\Delta}$	0.09 $\pm$ 0.03	0.08 $\pm$ 0.04 $^{\Delta}$

Compared with before HP, * $P < 0.01$; compared before with after CVVH, $^{\#}P < 0.05$; compared with before and after CVVH in the control group, $^{\Delta}P < 0.05$

Table 2. Plasma concentrations of TNF- α , IL-1 β and IL-6 after blood purification (mean $\pm$ SD, $n=15$)

Time points	0	24 h	48 h	5th day	7th day	10th day
TNF- α (mol/L)						
Treatment group	20.30 $\pm$ 8.73	18.52 $\pm$ 8.58	15.41 $\pm$ 6.52	11.91 $\pm$ 4.32	12.20 $\pm$ 3.90	11.66 $\pm$ 3.44
Control group	21.04 $\pm$ 4.63	18.25 $\pm$ 6.20	17.00 $\pm$ 4.81	15.60 $\pm$ 4.73*	14.89 $\pm$ 4.45	13.27 $\pm$ 4.49
IL-6 (ng/L)						
Treatment group	60.23 $\pm$ 22.34	59.27 $\pm$ 20.65	55.45 $\pm$ 26.14	46.12 $\pm$ 22.16	47.10 $\pm$ 29.90	40.12 $\pm$ 19.23
Control group	58.58 $\pm$ 21.80	54.73 $\pm$ 31.80	55.89 $\pm$ 43.58	49.63 $\pm$ 25.43*	44.70 $\pm$ 19.82	39.42 $\pm$ 24.76
IL-1 β (ng/L)						
Treatment group	0.14 $\pm$ 0.06	0.15 $\pm$ 0.05	0.13 $\pm$ 0.05	0.13 $\pm$ 0.11	0.08 $\pm$ 0.05	0.10 $\pm$ 0.05
Control group	0.12 $\pm$ 0.03	0.16 $\pm$ 0.02	0.09 $\pm$ 0.05	0.16 $\pm$ 0.04*	0.10 $\pm$ 0.03	0.14 $\pm$ 0.09

Compared with the control group on the 5th day, * $P < 0.05$.

Table 3. The influence on T-lymphocytes subpopulations after HP+CVVH and CVVH (mean±SD, n=15)

Groups	CD3(%)	CD4(%)	CD8 (%)	CD4/CD8
Treatment				
0	45.01±27.01	26.68±12.58	21.32±7.35	1.76±0.95
10th day	51.03±15.01*	30.23±8.64*	26.46±9.32*	1.95±0.98*
Control				
0	46.65±10.35	27.23±6.48	20.89±6.81	1.56±0.87
10th day	50.26±14.42 [#]	30.64±9.25 [#]	24.68±7.28 [#]	1.89±0.92 [#]

After CVVH+HP, CD3+, CD4+, CD8+, CD4+/CD8+ increased in the treatment group, **P*<0.05; after CVVH, CD3+, CD4+, CD8+, CD4+/CD8+ increased in the control group, [#]*P*<0.05

Table 4. Blood lactate acid concentration, heart rate, breath rare, oxygenation index on the 5th day and 10th day (mean±SD)

Groups	Norepinephrine (μg/min)	Blood lactate acid (mmol/L)	HR (beat/min)	Oxygenation index (mmHg)	RR (rate/min)
Treatment					
0	28.3±11.7	3.31±3.61	121.5±20.45	100.5±42.31	35.21±9.43
5th day	10.6±8.7	2.14±1.65	94.25±18.73	151.3±32.37	27.24±6.74
10th day	8.9±8.2	1.35±1.52	92.14±16.26	187.4±55.16	24.12±8.75
Control					
0	31±15.6	4.02±2.10	130.5±28.14	105.2±45.24	33.62±10.57
5th day	9.3±7.9	2.45±1.54	91.33±19.21	172.1±53.26	26.41±9.38
10th day	7.8±6.2	1.15±2.61	89.45±36.15	183.3±66.23	23.54±7.11

state; flow cytometry, PARTEC German) increased after HP+CVVH or only CVVH (*P*<0.05). Differences of T-lymphocytes subpopulations were observed between the two groups on the 10th day (Table 3).

Clinical symptoms and signs during HP+CVVH and CVVH

Blood lactate, heart rate, respiratory rate, oxygen index and other indicators were improved after HP+CVVH or CVVH, but the improvement was not different between the two groups (Table 4).

DISCUSSION

Inflammatory mediators such as complement C3a/C5a, cytokines (TNF-α, IL-1, IL-6, IL-8 etc.), receptors for cytokines, chemokines, platelet activating factors, myocardial depressant factors can be removed some extent by hemofiltration.^[4-7] CVVH improves clinical symptoms and signs of patients, and plays a beneficial role in treatment of MODS. For large molecules such as endotoxin (106×10³ molecular weight) and some inflammatory mediators with lipid solubility, high protein binding capacity couldn't be removed by hemofiltration.

Resin adsorption can clear large molecular toxins and inflammatory mediators.^[8] In the present study,

the plasma concentrations of TNF-α, IL-1β, and IL-6 decreased markedly after blood hemoperfusion with resin adsorption. This finding indicated that it can effectively remove the inflammatory cytokines like TNF-α, IL-1β and IL-6. Unfortunately, at the beginning of the study, we didn't use endotoxin test and failed to observe endotoxin concentrations. The plasma concentrations of TNF-α, IL-1β and IL-6 in the HP+CVVH group were lower than those in the control group on the 5th day (36 hours after blood purification) (*P*<0.05). HP+CVVH or CVVH improved oxygenation and hemodynamics, gradually increased blood pressure, reduced vasoactive drugs dosage and resuscitation volume, and alleviated edema. This was also observed in our previous studies.^[9,10] The present study showed that the above-mentioned results were related to myocardial depressant factor, inflammatory cytokine removal, and endothelial cell injury.^[11,12]

We also found that the scavenging capacity of cytokines like TNF-α, IL-1β and IL-6 using HP+CVVH is not more powerful than using CVVH alone. First, this may be related to the design of the study. The hemoperfusion with HA330-I was removed after 2-hour adsorption saturation, and cytokines like TNF-α, IL-1β, IL-6 decreased markedly after HP (*P*<0.01). Followed with CVVH for 10 hours after HP, TNF-α, IL-1β, IL-6 didn't change significantly compared with CVVH for 12 hours. This was related to hemoperfusion HA330-1 with only once in 24 hours and cytokine metabolism characteristics (two compartment model, the blood chamber and a liquid chamber);^[13,14] Second, CVVH used a HF-1200 filter with a large hole diameter, and a molecular weight cut-off point for 55×10³. The molecular weight of TNF-α monomer and trimer, IL-1β and IL-6 was 17×10³, 51×10³, 17×10³, 26×10³, respectively. All of them can be cleared by CVVH through the filter. On the 5th day after three blood purifications, the plasma concentrations of TNF-α, IL-1β and IL-6 in the HP+CVVH group were lower than those in the CVVH group (*P*<0.05). Possibly, large molecular inflammatory mediators like endotoxin were removed partly through HP, and thus inflammatory cascade response decreased. This result indicated that HP+CVVH was more effective to clear various inflammatory mediators than CVVH, and the patients had a longer period of blood purification.

Lin et al^[15] found that when excessive inflammatory response occurs, the anti-inflammatory response also starts, and inflammatory/anti-inflammatory response tends to be balanced, followed by the declined monocytic function and immunodeficiency, and this can cause the

increase of fatality rate. Obviously the treatment of anti-inflammatory or immune stimulation is not adequate to reverse the inflammatory/anti-inflammatory and immune function disorder. This study showed that both HP+CVVH and CVVH can improve immune function disorder, and are helpful to the reconstruction of the human immune system.

In our study, 5 patients in the HP+CVVH group (5/15) and 6 patients in the CVVH group (6/15) died in 28 days ($P>0.05$). The number of patients in this study was small. Moreover hemoperfusion was used only once in 24 hours. The HA-330-I cartridge was saturated after 2-2.5 hour adsorption, while various inflammatory mediators by autocrine and/or paracrine fashion secreted constantly from various tissue cells. Increased resin adsorption time (using 2-3 HA-330-I cartridge/24h), increased replacement volume or prolonged CVVH might lead to more satisfactory results. Further, it was too late to start blood purification (patients were transferred to ICU late), and the enrolled patients were in critical situation (Apache II scores of the HP+CVVH group and CVVH group 26.3 ± 8.7 and 25.1 ± 10.3 , respectively).

Funding: None.

Ethical approval: The study was approved by the Ethical Committee of Yu-huangding Hospital, Yantai, Shandong Province, China.

Conflicts of interest: The authors declare that there is no conflict of interest.

Contributors: Liu LX composed and wrote the paper. All authors read and approved the final version of the manuscript.

REFERENCES

- 1 Vincent JL, Sun Q, Dubois MJ. Clinical trials of immunomodulatory therapies in severe sepsis and septic shock. *Clin Infect Dis* 2002; 34: 1084-1093.
- 2 Lee PA, Matson JR, Pryor RW, Hinshaw LB. Continuous arteriovenous hemofiltration therapy for *Staphylococcus aureus* induced septicemia in immature swine. *Crit Care Med* 1993; 21: 914-924.
- 3 Bellomo R, Tipping P, Boyce N. Continuous veno-venous hemofiltration with dialysis removes cytokines from the circulation of septic patients. *Crit Care Med* 1993; 21:522-526.
- 4 Ronco C, Inguaggiato P, D'Intini V, Cole L, Bellomo R, Poulin S, et al. The role of extracorporeal therapies in sepsis. *J Nephrol* 2003; 16: 34-41.
- 5 Heering P, Morgera S, Schmitz FJ, Schmitz G, Willers R, Schultheiss HP, et al. Cytokine removal and cardiovascular hemodynamics in septic patients with continuous venovenous hemofiltration. *Int Care Med* 1997; 23: 288-296.
- 6 Honore PM, Jamez J, Wauthier M, Lee PA, Dugernier T, Pirenne B, et al. Prospective evaluation of short-term, high-volume isovolemic hemofiltration on the hemodynamic course and outcome in patients with intractable circulatory failure resulting from septic shock. *Crit Care Med* 2000; 28: 3581-3587.
- 7 Ronco C, Bellomo R, Homel P, Brendolan A, Dan M, Piccinni P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomized trial. *Lancet* 2000; 356: 26-30.
- 8 Tian S, Li T, Luo LQ, Du Z. Study on the adsorption of endotoxin and proinflammatory cytokines with HB-H-7 resin in vitro. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue* 2009; 21: 179-182.
- 9 Yao LQ, Jin ZC, Ji MS, Xia CY, Yu ZX, Liu J, et al. Effect of continuous renal replacement therapy started at different time on patients with multiple organ dysfunction syndrome. *Zhonghua Yi Xue Za Zhi* 2011; 91: 1663-1667.
- 10 DiCarlo JV, Alexander SR, Agarwal R, Schiffman JD. Continuous veno-venous hemofiltration may improve survival from acute respiratory distress syndrome after bone marrow transplantation or chemotherapy. *J Pediatr Hematol Oncol* 2003; 25: 801-805.
- 11 Li CM, Chen JH, Zhang P, He Q, Yuan J, Chen RJ, et al. Continuous veno-venous haemofiltration attenuates myocardial mitochondrial respiratory chain complexes activity in porcine septic shock. *Anaesth Intensive Care* 2007; 35: 911-919.
- 12 Honore PM, Ioannes-Boyau O, Gressens B. Blood and plasma treatments: The rationale of high-volume hemofiltration. *Contrib Nephrol* 2007; 156: 387-395.
- 13 Joannidis M. Continuous renal replacement therapy in sepsis and multisystem organ failure. *Semin Dial* 2009; 22: 160-164.
- 14 Honore PM, Matson JR. Extracorporeal removal for sepsis: acting at the tissue level - the beginning of a new era for this treatment modality in septic shock. *Crit Care Med* 2004; 32: 896-897.
- 15 Cooperative Group of Immunomodulatory Therapy of Sepsis, Lin HY. Clinical trial with a new immunomodulatory strategy: treatment of severe sepsis with Ulinastatin and Maipuxin. *Zhonghua Yi Xue Za Zhi* 2007; 87: 451-457.

Received October 5, 2011

Accepted after revision February 6, 2012