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Therapeutic Effects of Hemoperfusion Combined with High Volume Hemofiltration on Acute Respiratory Distress Syndrome
Short Title: Treatment of ARDS

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Summary

We aimed to analyze the impacts of hemoperfusion (HP) plus high-volume hemofiltration (HVHF) on acute respiratory distress syndrome (ARDS). Eighty ARDS patients were randomly distributed into a control group and an HP combined with HVHF group (n=40). Both groups received HVHF treatment. On this basis, HP + HVHF group was given HP treatment. Arterial blood gas analysis was performed, and serum inflammatory mediators, peak airway pressure and lung compliance were detected. Period at ICU stay, duration of mechanical ventilation and 28-day mortality rate were recorded. The ICU stay time, mechanical ventilation time and number of HVHF treatments of HP + HVHF group were significantly less than those of HVHF group (P<0.05). There were considerable differences in APACHE II scores between two groups after 24 h and 72 h of treatment (P<0.05). The respiratory index and oxygenation index were significantly different after 72 h (P<0.05). In HP + HVHF group, the APACHE II score, respiratory index, oxygenation index, peak airway pressure and lung compliance were considerably improved after 24 h and 72 h (P<0.05). Such values of HVHF group after 72 h of treatment were also improved as compared with those before treatment (P<0.05). The levels of TNF-α, IL-6 and IL-8 in HP + HVHF group after 24 h and 72 h were significantly lower as compared to those before treatment (P<0.05). HP plus HVHF reduced the peak concentrations of cytokines affecting lung function, alleviated symptoms and improved prognosis of patients with ARDS.

Keywords: hemoperfusion; high volume hemofiltration; acute respiratory distress syndrome

1. Introduction

Acute respiratory distress syndrome (ARDS) is a type of acute respiratory failure, which is characterized by progressive dyspnea along with refractory hypoxemia, with high mortality rates. ARDS is mostly an uncontrollable systemic inflammatory response caused by direct or indirect lung injury (Bhatia, Zemans, & Jeyaseelan, 2012). Cytokines and inflammatory mediators play important roles in the occurrence and development of local and systemic inflammatory responses of ARDS. Low tidal volume ventilation, which can increase survival rate (Amato et al., 1998) has been combined with high positive end-expiratory pressure (PEEP) to decrease mortality rate (Meade et al., 2008). Although mechanical ventilation and protective pulmonary ventilation can elevate the success rates of rescue for patients suffering ARDS, the inflammatory lung injury of

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ARDS cannot be stopped, leading to high mortality rates (Bhatia et al., 2012). At the early stage of ARDS, continuous utilization of low-dose glucocorticoids can decrease the incidence rate of infection, level of C-reactive protein, systemic inflammatory response,
mechanical ventilation time and ICU stay time, as well as relieve intra- or extra-pulmonary organ dysfunction (Peter et al., 2008). Besides, restrictive fluid therapy has longer off-line time, fewer cases of neurological failure, and shorter ICU stay time (Benes, Giglio, Brienza, & Michard, 2014). Since the 1970s, extracorporeal membrane oxygenation has been used for the gas exchange of ARDS patients with ventilation failure. However, this technology can only improve the lung function and oxygenation of severe ARDS patients in the short term, and reduce mechanical ventilation support. Whether it decreases the mortality rate remains controversial. In combination with high cost, it is difficult to promote this technology in clinical practice (Peek et al., 2010).

High volume hemofiltration (HVHF) has become one of the key strategies to rescue critically ill patients in ICU from simple treatment of acute renal failure (Clark et al., 2014). In recent years, HVHF has been employed to control inflammatory responses such as toxic shock and multiple organ failure (Ronco et al., 2014). The plasma concentrations of cytokines barely decrease after HVHF alone, which may be related to the interaction of cytokines, charge together with hydrophilic and hydrophobic membrane sites. To increase the clearance of inflammatory mediators, haemofilter should be replaced more frequently or adsorbent should be introduced. On the other hand, the aim of hemoperfusion (HP) is to collect patient's blood via a single-needle double-lumen catheter, to remove endogenous and exogenous toxins by using a hemoperfusion machine through adsorption, and then to transfuse the purified blood back into the patient, finally realizing blood purification.

HVHF combined with HP can clear lung interstitial water, reduce pulmonary shunts, terminate the inflammatory cascade in an early and timely manner, improve the microcirculation and oxygen carrying capacity of cells, and increase the utilization of tissue oxygen, with obvious effects on removing some cytokines and inflammatory mediators. This combination can significantly reduce the peak concentrations of cytokines that affect lung function in the acute phase of ARDS, alleviate the severity, and improve the prognosis. In current investigation, we evaluated the impacts of HP in combination with HVHF on the respiratory function and prognosis of patients with ARDS.

2. Materials and Methods

Subjects

Ethics Committee of our hospital has approved this study and all patients have given their written consent as part of this study. Eighty ARDS patients treated in the ICU of our hospital from October 2016 to October 2017 were selected, who met the Berlin definition criteria for ARDS (Brower et al., 2004). Inclusion criteria: 1) Acute onset; 2) oxygenation index ≤200 mmHg; 3) bilateral patchy shadows disclosed by frontal X-ray; 4) pulmonary wedge pressure ≤18 mmHg.

These patients were randomly distributed into two groups: a treatment group (HP + HVHF) (n=40), including 20 males and 20 females with the mean age of (55.81 ± 4.17) years and APACHE II score of (25.90 ± 2.89) points before treatment; a control group (HVHF) (n=40), including 19 males and 21 females with the average age of (55.78 ± 4.43) years and APACHE II score of (25.87 ± 2.94) points before treatment. The age, gender and APACHE II scores of these two groups have similarity (P>0.05).

3. Treatment Methods

The two groups were treated in two independent wards in a double-blinded manner. First, all patients were routinely treated by using antibiotics, adrenocortical hormones and vasoactive drugs to maintain appropriate blood volume, water-electrolyte/acid-base balance, nutritional support, systolic BP >90 mmHg and mean arterial pressure ≤65 mmHg. Besides, they were all subjected to HVHF and mechanical ventilation. The HP + HVHF group was daily given 3 h of HP 3 days before HVHF treatment.

Mechanical ventilation: Both groups had basically the same modes, i.e. synchronized intermittent mandatory ventilation or bi-level positive airway pressure ventilation and PEEP ventilation. The protective lung ventilation strategy was used, and the tidal volume was maintained at 4-7 ml / Kg according to the body weight. The end inspiratory plateau airway pressure was controlled under 30 cm H_2O (Fan et al., 2017; Force et al., 2012), and hypercapnia was allowed. PEEP was started from 5 cmH_2O and increased by 2 cmH_2O each time, which was adjusted according to blood gas indices and

oxyhaemoglobin saturation. As a result, the arterial-oxygenation goal was to maintain an arterial oxyhaemoglobin saturation of 88 to 95 % or partial pressure of arterial oxygen of 55 to 80 mmHg (Fan et al., 2017). Sedative medications were given when necessary to maintain the synchronicity between patients and equipment. For patients with refractory life-threatening hypoxemia, the pulmonary recruitment maneuver was utilized during early ARDS to improve the oxygenation status.

Blood purification: The single-needle double-lumen catheter (ARROW) was retained in the femoral vein, internal jugular vein or subclavian vein according to individual conditions to establish a temporary vascular access. ACH-10 hemofiltration machine (B. Braun Avitum AG, Germany) was used. The replacement fluid was prepared by our hospital, and the pre-dilution method was employed. The flow rates of blood and replacement fluid were 200-250 ml/min and 35 ml/h/kg respectively. In addition, continuous slow-type polysulfone membrane hemofilter (Asahi Kasei Medical, Japan) was utilized, with the membrane area of 1.3 m2 for each 8-12 h of treatment. The dehydration volume was adjusted according to intake and output. The HVHF group received HVHF treatment. The HP + HVHF group was daily given 3 h of HP 3 days before HVHF treatment, using HA330 resin HP machine (Zhuhai Livzon Medical Biomaterial Co., Ltd., China). First, 500 mL of 5% glucose solution was used to flush the HP machine and channels which were then washed with 500 mL of normal saline containing 20 mg of heparin, 2,000 mL in total. Afterwards, the HP machine was connected with the channels, and the flow of blood was 200-250 ml/min. The machine was finally removed 3 h after HP to complete hemofiltration. Three days after intensive treatment, HVHF was stopped when the lung PO2/FIO2 exceeded 300 mmHg. However, for patients complicated with impaired renal function, HVHF was continued until the function recovered.

Use of anticoagulants: Each patient was treated with routine heparin (3,000-3,500 U of normal heparin for the first dose and 600-800 U/h for the maintenance dose), low-molecular-weight heparin (4,000 U of intravenous injection during filtration), heparin in vitro (30-50 mg of protamine was given after filtration to neutralize heparin) or heparin-free regimen (heparin was no longer used after withdrawal of HP machine in the HP + HVHF group; no heparin was used during treatment in the HVHF group). The filter was replaced if the ultra-filtration capacity declined or a large area of coagulation occurred during treatment.

4. Observation Indices

The vital signs, peak airway pressure, lung compliance and airway resistance were recorded before and after 24 h and 72 h of treatment respectively. Arterial blood gas analysis was conducted, serum inflammatory mediators were detected, and APACHE II score, respiration index and oxygenation index were calculated. Human TNF-α, IL-6 and IL-8 were measured by ELIA before and after 24 h and 72 h of treatment respectively.

5. Statistical Analysis

SPSS 16.0 was used to analyse the data. The measurement data were expressed as mean ± SD. Inter-group comparisons were carried out by the independent t test, and intra-group comparisons were performed with the paired t test. Inter-group comparisons at different points were carried out by the repeated measurement analysis of variance, and those at each time point were performed with the independent t test. The time differences between two groups were compared by the SNK-q test. $P<0.05$ is considered statistically important.

6. Results

Apache Ii Scores, Oxygenation Indices, Respiratory Indices, Peak Airway Pressures and Lung Compliances Before and After Treatment

All the 80 patients completed this study. There were huge differences in APACHE II scores between the two groups after 24 h and 72 h of treatment ($P<0.05$). The respiratory index and oxygenation index were significantly different after 72 h of treatment ($P<0.05$). In the HP + HVHF group, the APACHE II score, respiratory index, oxygenation index, peak airway pressure and lung compliance were significantly improved after both 24 h and 72 h of treatment ($P<0.05$). Such values of the HVHF group after 72 h of treatment were all considerably improved as compared to values before treatment ($P<0.05$) (Table 1).

TNF-α, IL-6 and IL-8 Levels Before and After Treatment

The levels of TNF-α, IL-6 and IL-8 in the two groups were similar before treatment ($P>0.05$). After 24 h and 72 h of treatment, the levels of the HP + HVHF group were significantly lower than those of the HVHF group ($P<0.05$). The levels of TNF-α, IL-6 and IL-8 after 24 h and 72 h of treatment in the HP + HVHF group were significantly lower than those before treatment ($P<0.05$). Such levels significantly decreased in the

HVHF group after 72 h of treatment compared with those before treatment (P<0.05) (Table 2).

ICU Stay Time, Mechanical Ventilation Time and Number of HVHF Treatments

The ICU stay time (d), mechanical ventilation time (d) and number of HVHF treatments of the HP + HVHF group were significantly less than those of the HVHF group (16.50 ± 2.50 vs. 18.00 ± 2.00; 8.00 ± 1.50 vs. 13.50 ± 2.00; 6.75 ± 1.20 vs. 9.25 ± 1.50, all P<0.05) (Table 3).

28-Day Mortality Rates

In the HP + HVHF group, 32 cases were relieved and 8 died. In the HVHF group, 22 cases were alleviated, 14 died and 4 were unrecovered. The 28-day mortality rates of the two groups have similarities (P>0.05) (Table 4).

7. Discussion

As one of the most devastating diseases in ICU, ARDS occurs and progresses along with the aggravation of cytokine-induced inflammatory responses. The resulting immunosuppression causes an imbalance of the immune system, finally leading to systemic multiple organ failure. It is well-established that IL-6, IL-8 and TNF-α are involved in inflammatory responses (Aisiku et al., 2016; Volpin et al., 2014). Especially, TNF-α, as a key inflammatory factor, can stimulate the generation of various pro-inflammatory cytokines. On the other hand, the production and increase of IL-6 and IL-8 have been significantly correlated with the prognosis (Kawasumi et al., 2014). Therefore, we herein aimed to recover the homeostasis by adsorbing and eliminating cytokines and inflammatory mediators with different molecular weights in the blood through HP in combination with HVHF.

HVHF has become one of the important strategies for rescuing critically ill patients in ICU to control inflammatory responses such as toxic shock and multiple organ failure. Continuous blood purification for non-kidney indications can remove inflammatory mediators such as IL-6, IL-8, plasminogen activator and neutrophil elastase, as well as mitigate inflammatory responses and damage of vascular endothelial cells (Calfee et al., 2015). During ARDS treatment, early blood purification can relieve inflammatory responses, decrease pulmonary capillary blood flow and extravascular lung water, improve lung compliance and increase alveolar ventilation, thereby improving the oxygenation and prognosis safely and reliably. Meanwhile, the cardiac function or circulation was not affected. HVHF eliminates inflammatory mediators through convection and adsorption, which is capable of reducing the interference of circulation, raising the removal rates of solutes and inflammatory mediators, improving tissue perfusion and oxygenation, and providing nutritional support. Nevertheless, the plasma concentrations of cytokines barely drop after HVHF alone, probably because of interactions between them, charge, membrane hydrophilic and hydrophobic sites, together with the binding of cytokines to proteins (Chung et al., 2017). To effectively control inflammatory responses, it is feasible to increase the total amount of replacement fluid and to use large-area filtration membrane for better removal of cytokines. However, convection only contributes slightly to the overall elimination performance of filtration membrane, so hemofilter must be replaced frequently or adsorbent must be introduced.

HA330 resin HP machine uses neutral macroporous polymers obtained from styrene-divinylbenzene as the adsorbent. It works by competing with plasma protein to bind toxins when the blood flows through the resin surface. It has the advantages of rapid adsorption as well as high adsorption capacity, specificity and mechanical strength. As a result, inflammatory mediators with high molecular weights can be well eliminated and damages to organs can be alleviated. In the meantime, the damaged cells can be repaired and regenerated (Rello, Valenzuela-Sánchez, Ruiz-Rodriguez, & Moyano, 2017). In this study, the APACHE II scores of the two groups were significantly different after 24 h and 72 h of treatment (P<0.05). Besides, the respiratory index and oxygenation index were significantly different after 72 h of treatment (P<0.05). The HP + HVHF group had significantly improved APACHE II score, respiratory index, oxygenation index, peak airway pressure and lung compliance after 24 h of treatment (P<0.05). In contrast, such indices of the HVHF group were all significantly improved after as long as 72 h of treatment. Hence, HVHF alone exerted therapeutic effects later than HP in combination with HVHF did. Given that IL-6, IL-8 and TNF-α levels of the HP + HVHF group decreased more significantly compared with those of the HVHF group after 24 h and 72 h of treatment, the combination therapy was superior to HVHF alone in eliminating inflammatory mediators. We postulated that the peak concentrations of cytokines plummeted due to HP in the process of ARDS. Simultaneously,

inflammatory mediators in the blood, alveoli and alveolar gaps were removed directly or indirectly. When the concentrations of inflammatory mediators dropped to critical points, the inflammatory cascade was blocked, and inflammatory responses were attenuated, which benefited the rapid recovery of human body to a balanced state. Furthermore, HP in combination with HVHF shortened the time of mechanical ventilation and decreased the number of HVHF treatments, thus markedly reducing the hospitalization expenditure.

In summary, the combination therapy can significantly decrease the peak concentrations of cytokines affecting lung function, mitigate the symptoms and improve the prognosis of ARDS patients. Regardless, the sample size herein is small, so further studies with larger sample sizes are ongoing in our group to validate the findings.

8. Conflict of Interest

There is no conflict of interest.

9. Acknowledgements

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Table 1. **APACHE II Scores, Oxygenation Indices, Respiratory Indices, Peak Airway Pressures and Lung Compliances of Two Groups**

	HP + HVHF			HVHF		
Time	Before treatment	24 h	72 h	Before treatment	24 h	72 h
APACHE II score	25.91±2.89	20.10±2.49*#	15.75±1.96*#	25.75±2.96	22.85±1.44	18.95±2.01#
Respiratory index	4.73±0.17	3.49±0.16*#	3.09±0.19*#	4.72±0.17	4.02±0.18	3.44±0.15#
Oxygenation index	153.15±6.55	190.50±8.80#	242.95±8.58*#	152.90±5.09	155.35±8.89	179.90±5.31#
Peak airway pressure	35.40±1.97	33.26±1.98*#	31.51±1.04*#	35.46±1.56	35.44±1.55	34.34±1.54#
Lung compliance	39.85±1.39	42.16±1.40*#	43.41±1.36*#	39.87±1.17	39.89±1.18	41.99±1.19#

*Compared with HVHF group at the same time point, P<0.05; #compared with the same group before treatment, P<0.05.

Table 2. **TNF-α, IL-6 and IL-8 Levels Before and After Treatment (*Compared with HVHF Group at the Same Time Point, P<0.05; #Compared with the Same Group Before Treatment, P<0.05.)**

	HP + HVHF			HVHF		
Time	Before treatment	24 h	72 h	Before treatment	24 h	72 h
TNF-α (pg/ml)	570.18±19.00	540.10±18.41*#	520.15±19.56*#	574.05±21.96	569.85±19.44	547.95±19.01#
IL-6 (pg-ml)	237.01±6.11	211.49±6.16*#	193.79±6.19*#	234.22±6.17	229.02±6.18	213.44±6.15#
IL-8 (pg-ml)	98.47±2.55	65.50±1.80#	35.15±1.58*#	98.40±2.09	95.35±2.89	70.90±2.32#

*Compared with HVHF group at the same time point, P<0.05; #compared with the same group before treatment, P<0.05.

Table 3. **ICU Stay Time, Mechanical Ventilation Time and Number Of HVHF Treatments**

	HP + HVHF	HVHF	t	P
Number of survivals (case)	32	26		
Mechanical ventilation time (d)	8.00±1.50	13.50±2.00	11.96	<0.01
ICU stay time (d)	16.50±2.50	18.00±2.00	2.45	<0.05
Number of HVHF treatments	6.75±1.20	9.25±1.50	7.05	<0.01

Table 4. **28-Day Mortality Rates**

	HP + HVHF	HVHF	χ2	P
Relieved (case)	32 (80.0%)	22 (55%)	2.26	>0.05
Died (case)	8 (20%)	14 (35%)		
Unrecovered (case)	0 (0.0%)	4 (10.0%)		