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Effect on Extrapulmonary Sepsis-Induced Acute Lung Injury by Hemoperfusion With Neutral Microporous Resin Column

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Abstract: The aim of this study was to investigate the effect of neutral microporous resin hemoperfusion on oxygenation improvement, removal of inflammatory cytokines in plasma and bronchoalveolar lavage, and mortality in acute lung injury induced by extrapulmonary sepsis. Forty-six patients with acute lung injury induced by extrapulmonary sepsis were randomized to HA type hemoperfusion treatment ($N = 25$) or standard therapy ($N = 21$). Those undergoing hemoperfusion treatment received HA330 hemoperfusion. We measured the plasma and bronchoalveolar lavage concentrations of TNF-α and IL-1, and the following parameters were compared between the control group and the hemoperfusion group on days 0, 3 and 7: lung injury measurements (arterial oxygen tension/fractional inspired oxygen ratio, lung injury score, chest X-ray score); interstitial edema of lung (extravascular lung water). Duration of mechanical ventilation, hospital, 28-day, and intensive care unit mortality were also observed. Patients treated with HA hemoperfusion showed a significant removal of plasma and bronchoalveolar lavage TNF-α and IL-1 over time while in the study. Patients in the HA group also demonstrated not only significant improvement of PaO_2/FiO_2, but also decreased Lung Injury Score and chest X-ray score at days 3 and 7. Furthermore, the measurements of the arterial oxygen tension/fractional inspired oxygen ratio, lung injury score and extravascular lung water (EVLWI) significantly correlated with and the concentration of cytokines in the plasma (all $P < 0.05$). The HA hemoperfusion treatment group had a significant reduction in duration of mechanical ventilation, length of intensive care unit stay, and intensive care unit mortality. Significant removal of inflammatory cytokines from circulation and lung by hemoperfusion treatment using the HA type cartridge may contribute to the improvement of lung injury and intensive care unit outcome in extrapulmonary septic patients. **Key Words:** Acute respiratory distress syndrome, Cytokine, Hemoperfusion, Sepsis.

Severe sepsis is defined as pathologic infection accompanied by a spectrum of physiologic abnormalities, originally described as systemic inflammatory response syndrome criteria in combination with acute organ dysfunction (1,2). Respiratory failure is the most frequent complications of severe sepsis, occurring in 85% of cases. The severe forms of lung failure, acute lung injury (ALI) and respiratory distress syndrome (ARDS), occur in 40% of patients with sepsis (3,4). The trademark symptom of ALI/ARDS is increased capillary permeability, which is characterized by the accumulation of extravascular lung water (EVLW) and manifests in the lungs as altered alveolar–capillary barrier function (5,6).

Inflammatory mediators play a key role in the pathogenesis of both ALI/ARDS and sepsis (7–9). The hallmark of pulmonary infiltration associated with septic ALI/ARDS is the presence of infiltrating leukocytes. Leukocyte migration is directed largely by inflammatory mediators. As the condition develops, leukocytes migrate into the pulmonary interstitium, and increased endothelial permeability leads to tissue edema and increased extravascular lung water (10). Investigations have been performed to assay markers of lung injury in the plasma and bronchoalveolar lavage (BAL) fluid, and suggested that cytokines in BAL and circulation are both

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thought to mediate the local host response and to play an important role the development of the lung injury in pneumonia-induced sepsis and extrapulmonary sepsis (11,12).

Recently, hemoperfusion has gradually developed for use in the treatment of patients with sepsis. Open-label clinical trials using polymyxin B immobilized fiber direct hemoperfusion (PMX-DHP) were conducted in Japan, demonstrating the safety of PMX in the treatment of septic shock and its capacity to decrease endotoxin levels; and in our previous study, we demonstrated that the HA330 resin cartridge significantly removed inflammatory cytokines (IL-6, IL-8) and improved the organ dysfunction such as respiratory failure and outcome in the treatment of sepsis and septic shock.

Such previous encouraging studies have prompted us to make further efforts to investigate the mechanism in the improvement of outcome in sepsis by HA330 hemoperfusion. Protective and anti-inflammatory effects of HA hemoperfusion on acute lung injury induced by sepsis perhaps is the key course of the treatment. Considering that the cytokines concentration of pneumonia-induced sepsis is obviously elevated both in lung and circulation, we investigated the effect of neutral microporous resin hemoperfusion on removal of inflammatory cytokines in circulation and BAL, clearance of extravascular lung water, and outcome only in acute lung injury (ALI) patients induced by extrapulmonary sepsis.

PATIENTS AND METHODS

Selection of patients and treatment

Of 52 potentially eligible patients who fulfilled the diagnostic criteria for extrapulmonary sepsis and acute lung injury, 48 were screened. A further two patients were withdrawn after standard therapy because of ineligibility, resulting in data being provided on 46 for primary outcome analysis. The flow chart is shown in Figure 1. Written informed consent was obtained from all participating subjects or their families before randomization whenever possible. When a patient was unable to give written consent, either witnessed verbal consent or relatives' assent was obtained. Sepsis was diagnosed according to the criteria of the members of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee (10). The source of extrapulmonary sepsis included abdominal infection (perforation of intestine or colon, infection of biliary tract, intra-abdominal abscess), urinary infection, blood and catheter infection (catheter-related bacteremia) and so on. Bacterial cultures were all positive in 46 patients and adequate antibiotic treatment was given. ALI was deemed to be present when the AECC criteria were met within 72 h of developing sepsis. These ALI criteria are as follows: acute onset of hypoxemia (arterial oxygen tension [PaO_2]/fractional inspired oxygen [FiO_2] ratio <300 mm Hg) with bilateral infiltrates on chest radiograph and pulmonary artery occlusion pressure ≤18mm Hg or no evidence of left atrial

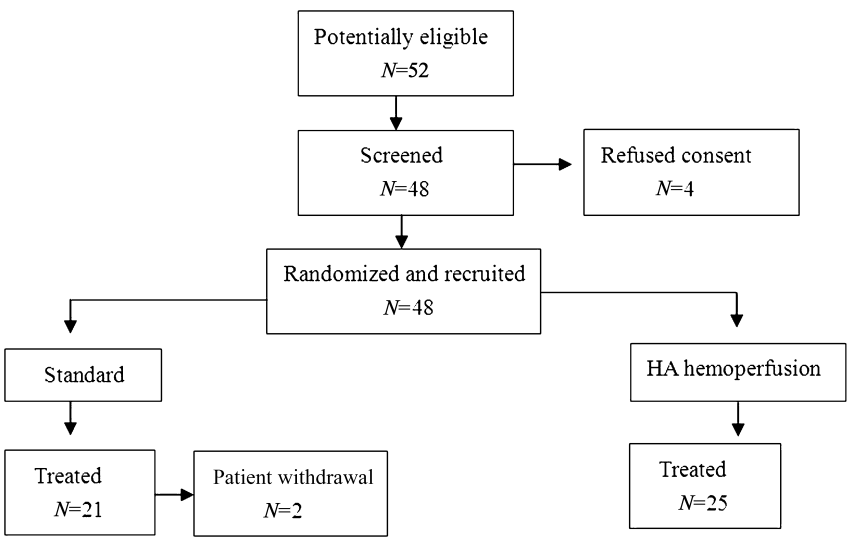

FIG 1. Flow chart of this study. Of 52 potentially eligible patients, 48 were screened and randomized. A further two patients in standard group were excluded after randomization because of withdrawing from the study.

TABLE 1. *Characteristics and severity of patients' disorders*

	HA group	Control group	*P*-value
Patients (*N*)	25	21	
Gender (%) (Male : female)	52 (13) : 48 (12)	42.8 (9) : 57.2 (11)	0.641
Age (mean year)	64.5 ± 13.1	66.4 ± 16.5	0.872
APACHE II score	26.1 ± 6.1	27.3 ± 5.5	0.392
SOFA score	8.2 ± 2.1	8.3 ± 1.9	0.792
Physiology at enrolment			
White blood cell count (cells × 10^9/L)	19.8 ± 6.3	21.6 ± 8.2	0.563
Cardiac index (L/min per m^2)	4.8 ± 1.7	4.7 ± 1.2	0.713
ITBV index (mL/m^2)	890 ± 202	915 ± 231	0.078
EVLW index (mL/kg)	11.2 ± 1.4	13.4 ± 2.6	0.081

APACHE II, Acute Physiology and Chronic Health Evaluation II; EVLW, extravascular lung water; ITBV, intrathoracic blood volume; SOFA, Sequential Organ Failure Assessment.

hypertension. The severity of ALI was quantified using the Lung Injury Score (LIS). Table 1 describes the patients' characteristics. All patients were randomized to receive standard therapy plus HA type hemoperfusion (HA group) or standard therapy only (control group). The standard therapy included fluid resuscitation, vasopressors, antimicrobial therapy, ventilatory and so on. The anticoagulant of 40 mg nadroparin calcium was used at the start of every hemoperfusion session and the standard therapy group never received any anticoagulant. The total mortality of both groups was 39.1%, and the major causes were multiple organ dysfunction syndromes induced by acute respiratory distress syndrome and sepsis. The ethics committees of our hospital approved the study protocol.

Mechanical ventilation

Patients in both groups received tracheal intubation and mechanical ventilation. After tracheal intubation the lungs were subjected to volume-controlled ventilation with a tidal volume (*V*t) of 6–8 mL/kg and adjusting respiratory rate to aim at normocarbia, using an O_2-air mixture and positive end-expiratory pressure of 5 cm H_2O or more, when needed, and an inspiratory to expiratory ratio of 1:2. Patients on mechanical ventilation should be constantly screened for the possibility of weaning. The criteria on which a decision to wean should be considered. Though not foolproof, all patients who fit most of the criteria can undergo a formal spontaneous breathing trial (SBT). 1. Underlying disease process that necessitated ventilation has resolved or improved. $PaO_2/FiO_2 > 250$ (positive end-expiratory pressure (PEEP) < 5, $FiO_2 < 0.5$, pH > 7.25). 2. Conscious and coherent. 3. Stable cardiovascular function: (a) HR < 140/min; (b) absence of myocardial ischemia; (c) absence of vasopressors or low dose inotropes. 4. Hb > 8 g%. 5. Absence of respiratory acidosis.

HA330 cartridge and hemoperfusion

Patients in the HA group received hemoperfusion with the HA330 resin cartridge (Lizhu Industries, Zhuhai, China) once a day for three consecutive days after admission to the intensive care unit. Each individual session of hemoperfusion lasted for 2 h. The anticoagulant used was nadroparin; the activated clotting time was measured and the nadroparin infusion was adjusted accordingly. The blood flow rate was permitted to be no less than 100 mL/min and no greater than 200 mL/min. The detailed method was recorded in our previous study.

Evaluation of lung injury and outcome

The Acute Physiology and Chronic Health Enquiry (APACHE) II score was used to assess the severity of each patient's condition during the first 24 h of intensive care unit (ICU) admission. The changes in the lung injury score and chest X-ray scores were assessed from baseline at day 0 to day 7 after the initiation of hemoperfusion. The vital signs were recorded frequently during the first 72 h, then every 8 h through to day 14. The following parameters were monitored during treatment: Extravascular lung water (EVLW), the intrathoracic thermal volume (ITTV), the pulmonary thermal volume (PTV), global end-diastolic volume (GEDV), and intrathoracic blood volume (ITBV) were measured as hemodynamic parameters by pulse contour cardiac output (PiCCO; PULSION, Munich, Germany). In addition, chest radiograph score (number of quadrants with >50% involvement with an alveolar filling process), PaO_2/FiO_2 ratio, and ventilator settings were recorded daily. The lung permeability index was calculated as the ratio of EVLW

to ITBV, which was shown to reflect permeability of the alveolar–capillary barrier. Mechanical ventilation duration, mortality and length of stay in ICU were also observed. The status of patients admitted to an ICU should be revised continuously to identify patients who may no longer need ICU care. When a patient's physiologic status has stabilized and the need for ICU monitoring and care is no longer necessary, removal from the ICU would be taken to account.

BAL fluid analysis

Bronchoalveolar lavage fluid was obtained by fiberoptic bronchoscopy at 8 am on days 0, 3, and 7 of the study. The method of lavage was as described previously (13). The fluid was filtered through a nylon net to remove the mucous secretions, and centrifuged at 500 × *g* for 10 min to remove cells. The supernatant was kept in cryotubes at –80°C in aliquots of 0.5 mL. The method of lavage was as described in previous reports. The following criteria were used for an acceptable sample: (i) the procedure should be shorter than 1 min, while the saline retention time in the lungs should be less than 20 s; (ii) recovery of more than 50% of the saline used for the lavage; (iii) absence of obvious blood contamination in the BAL fluid; (iv) the level of urea in the BAL fluid should be more than 0.4 mmol. The urea level was used as an index of BAL fluid dilution.

Cytokine measurement

The blood samples for the measurement of these mediators were collected from a peripheral vein at 08:00 hours on days 0, 3, and 7. The assay method for cytokine measurement was the same for plasma and BAL fluid samples. Determination of plasma and BAL fluid cytokines and adhesion molecules was done with the solid phase ELISA methodology based on the quantitative immunometric sandwich enzyme immunoassay technique. Reagents for the various cytokines were obtained from several sources (kits from R&D, Minneapolis, MN, USA for TNF-α, IL-1) and were used according to manufacturer's instructions. All the measurements were done within 6 months of the sample collection. Intra-assay and inter-assay reproducibility was checked and found to be more than 90%.

Statistical analysis

The results are expressed as mean ± standard error. The unpaired Wilcoxon rank sum test or Student's *t*-test of variance was used to determine statistically significant differences. The Spearman's rank order correlation coefficient was used to determine correlation between the cytokines and the various other parameters measured. $P < 0.05$ was considered to be statistically significant.

RESULTS

Severe sepsis study population

A total of 46 patients with acute lung injury induced by extrapulmonary sepsis were enrolled after development of organ dysfunction requiring ICU admission, with 25 patients in the HA group and 21 patients in the control group. No treatment was prematurely discontinued because of extracorporeal circuit clotting or high pressure problems. Demographic and physiologic characteristics are presented in Table 1. Baseline characteristics and physiology for severe sepsis patients in both groups were similar. There were no significant differences in fluid balance or cardiac function (ITBV index and extravascular lung water index [EVLWI]) between the two groups.

Gram-negative bacteria were detected between days 0 and 7 in eight (38.1%) of the controls and nine (41.7%) of the HA group patients (Table 2). There were no significant differences in antibiotic administration at baseline. Abdominal cavity infection was the main cause leading to extrapulmonary sepsis in both groups.

Effect on improvement of lung injury

Compared to baseline, the measurement of PaO_2 and oxygenation index elevated obviously, and the FiO_2, LIS, chest X-ray score, EVLW decreased significantly on day 7 of the study both in the control group and the HA group. Moreover, the patients in both groups receiving mechanical ventilation had an obvious decrease of PEEP and plateau pressure at the 7th day of treatment ($P = 0.001$, 0.002 in HA group; $P = 0.02$, 0.04 in control group), while the tidal volume was similar ($P = 0.31$, 0.67).

There was no significant difference of every variable in baseline between the control group and HA group. However, at day 3, FiO_2 of ventilation was significantly downregulated in the patients of the HA group compared with the control group. Moreover, LIS, chest X-ray score, and EVLW also declined, PaO_2 and oxygenation index improved in the HA group slightly at day 3, although the difference had no statistical significance. At day 7, the marked differences between two groups (seven variables) were observed ($P = 0.005$, 0.000, 0.02, 0.04, 0.03, 0.02, 0.03) (Table 3).

Effect on hemodynamics

Dopamine is generally the first choice of vasoactive/inotropic agents in our unit; however,

TABLE 2. *Comparisons of Etiology of infection in the patients between HA group and Control group*

Source	HA group	Control group	*P*-value
Abdominal cavity (%)	127 (48)	12 (57.1)	0.815
Perforation of intestine and colon	6	5	
Biliary tract	3	5	
Intra-abdominal abscess	3	2	
Urinary tract (%)	8 (32)	6 (28.6)	0.805
Blood/catheter (%)	3 (12)	1 (4.8)	0.636
Others (%)	2 (8)	2 (9.5)	0.223
Micro-organism			
Gram-negative bacteria (%)	9 (41.7)	8 (38.1)	0.668
Gram-positive bacteria (%)	9 (29.2)	7 (33.3)	0.053
Fungus (%)	2 (8.3)	3 (14.3)	0.881
Mixed (%)	5 (20.8)	3 (14.3)	0.542

once the dopamine infusion exceeds 10 mg/kg per min or low systemic vascular resistance is identified by PiCCO, our policy is to initiate noradrenaline and taper the dopamine. In this study, both the dose of dopamine and noradrenaline were significantly decreased from baseline to day 7 in the HA group, but increased in the control group ($P = 0.032$), despite fluid management and cumulative water balance being similar between the two groups.

Effect on removal of cytokines in BAL fluid and plasma

Figure 2 shows IL-1 and TNF-α levels measured in BAL fluid and plasma in the control group and the HA group following treatment over time. There was no difference of cytokine levels in plasma or BAL fluid at day 0 between the two groups. But the values in the subsequent days showed that IL-1 and TNF-α concentration in BAL fluid decreased obviously in the HA group versus the control group at day 3 ($P = 0.02$, 0.04), and this difference was the most marked at day 7 ($P = 0.001$, 0.000). Likewise, plasma IL-1 and TNF-α levels also dropped more significantly in the HA group than those in the control group, while the lowest value of cytokines in the HA group was just at the end of HA hemoperfusion for 3 days ($P = 0.001$, 0.002) and the levels rose again partly on day 7 ($P = 0.07$, 0.06). However, in the control group the cytokine levels in plasma and BAL fluid both showed a tendency to decrease during the study from baseline to day 3 and day 7, but this change was not statistically significant ($P > 0.05$).

TABLE 3. *Relationship between cytokines and measures of oxygenation, EVLWI (r value)*

	BAL		Plasma	
	TNF-α	IL-1	TNF-α	IL-1
PaO_2/FiO_2	–0.438*	–0.699*	–0.408*	–0.582*
LIS	–0.635*	–0.574*	–0.382*	–0.622*
EVLW index	0.433*	0.512*	0.158	0.147

*$P < 0.05$. BAL, broncholalveolar lavage; EVLW, extravascular lung water; IL, interleukin; LIS, lung injury score; TNF, tumor necrosis factor.

Correlations of the studied cytokines

Plasma levels of IL-1 and TNF-α were significantly positively correlated to EVLW index (r = 0.572, 0.366, $P < 0.05$), and were negatively correlated to PaO_2/FiO_2 (r = –0.408, –0.582, $P < 0.05$) and LIS (r = –0.382, –0.622, $P < 0.05$) (Table 4). Similarly, BAL IL-1 and TNF-α levels also were markedly correlated to PaO_2/FiO_2(r = –0.438, –0.699, $P < 0.05$), LIS (r = –0.635, –0.574, $P < 0.05$), while they had a poor correlation to EVLW index (r = 0.158, 0.147, $P > 0.05$).

Mortality distribution and organ function

As shown in Table 5, the HA treatment group had a significant reduction in length of ICU stay, ICU mortality and 28-day mortality ($P = 0.04$, 0.02). Among the survivors, a trend toward significant reduction in duration of mechanical ventilation (13.6 ± 3.2 vs 9.2 ± 2.3, $P = 0.01$) and mechanical ventilation-free days to day 28 (14.7 ± 5.5 vs 9.6 ± 4.7, $P = 0.03$) in the HA group was observed. Similarly, duration of continuous renal replacement therapy was further shortened significantly by HA hemoperfusion treatment ($P = 0.005$). The Sequential Organ Failure Assessment (SOFA) scores on day 14 also showed a similar decrease in the HA group ($P = 0.047$).

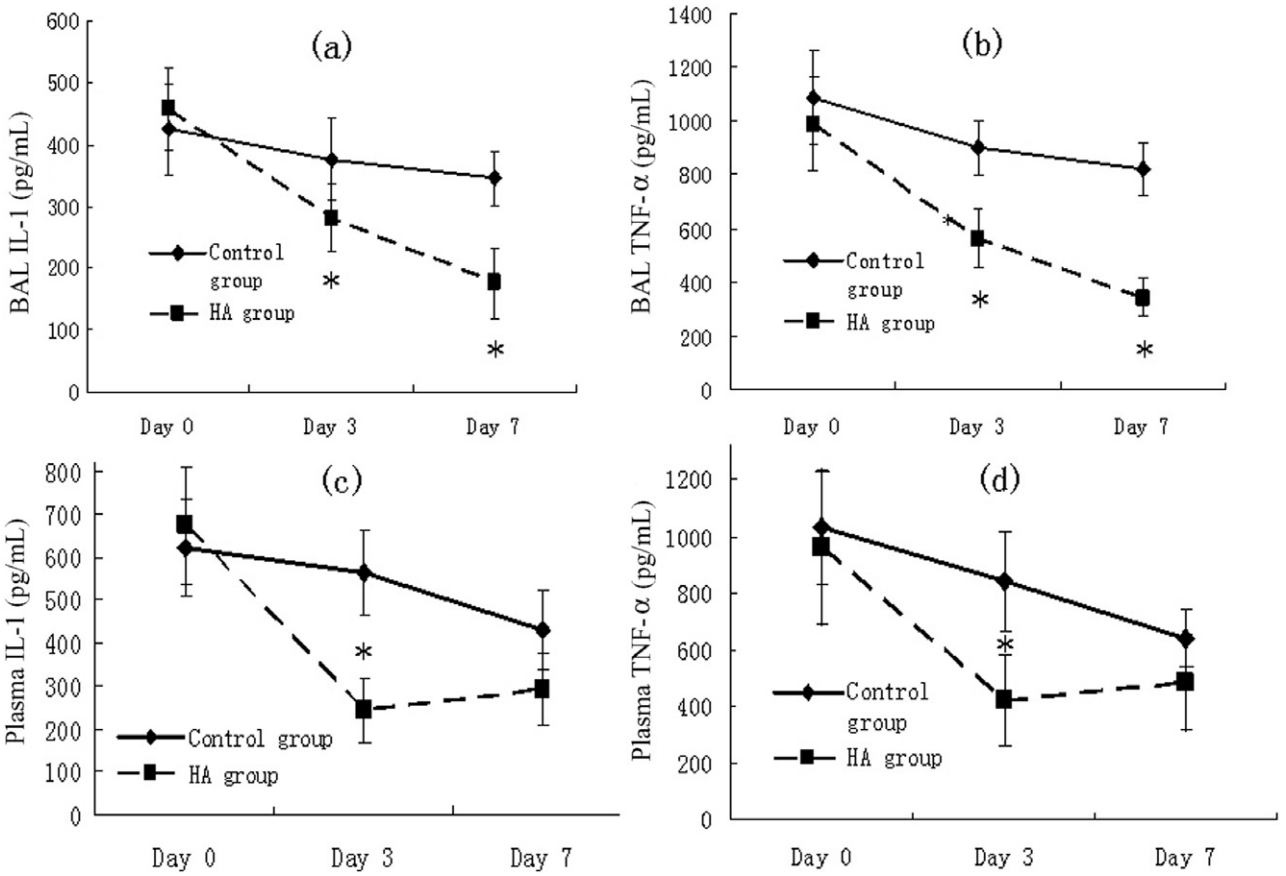

FIG 2. Trends of IL-1 and tumor necrosis factor (TNF)-α in bronchoalveolar lavage (BAL) fluid (a,b) and plasma (c,d) in the two groups of patients during the study stage. * $P < 0.05$, vs control group.

TABLE 4. *Effect on oxygenation, mechanical ventilation, creatinine and hemodynamics of hemoperfusion*

	Day 0		Day 3		Day 7	
	HA group	Control group	HA group	Control group	HA group	Control group
PaO_2 (mm Hg)	83.4 ± 13.5	86.7 ± 15.6	89.1 ± 17.3	89.7 ± 16.6	101.2 ± 15.5*,**	92.2 ± 14.7**
$PaCO_2$ (mm Hg)	29.2 ± 14.4	31.3 ± 15.1	33.9 ± 12.0	36.4 ± 13.6	37.2 ± 9.8	36.2 ± 7.9
FiO_2 (%)	54.8 ± 19.3	52.8 ± 19.0	45.5 ± 17.1*,**	49.3 ± 16.3	40.1 ± 11.2*,**	47.9 ± 10.2**
PaO_2/FiO_2	155.7 ± 53.6	163.5 ± 58.7	195.4 ± 43.1**	181.4 ± 48.0**	276.2 ± 47.8*,**	195.1 ± 51.1**
LIS	2.7 ± 0.5	2.9 ± 0.3	2.5 ± 0.4	2.7 ± 0.5	1.7 ± 0.3*,**	2.4 ± 0.3**
Chest X-ray score	2.7 ± 0.8	3.0 ± 0.4	2.5 ± 0.5	2.8 ± 0.9	2.1 ± 0.3*,**	2.7 ± 0.6**
Tidal volume (mL)	443 ± 43.3	454 ± 52.3	421 ± 51.1	489.1 ± 65.1	422 ± 34.1	452 ± 37.7
PEEP (cmH_2O)	11.2 ± 3.2	10.7 ± 2.9	8.7 ± 1.2*,**	10.7 ± 1.9	4.3 ± 1.2*,**	8.3 ± 2.2
Plateau pressure (cmH_2O) 31.6 ± 6.1		29.2 ± 5.1	27.6 ± 9.5	28.3 ± 4.2	25.2 ± 5.6**	27.3 ± 3.3
EVLW index (mL/kg)	11.2 ± 1.4	13.4 ± 2.6	8.9 ± 1.2**	11.2 ± 3.1	7.7 ± 0.9*,**	10.7 ± 4.2**
Cumulative fluid balance (mL)	–	–	3756 ± 342	4387 ± 412	6564 ± 892	7012 ± 1011
Dopamine (mg/kg per min)	11.0 ± 4.3	10.9 ± 7.8	6.7 ± 1.2*,**	15.1 ± 6.6	5.1 ± 1.0*,**	15.9 ± 4.7
Noradrenaline (mg/kg per min)	0.41 ± 0.15	0.36 ± 0.09	0.26 ± 0.13	0.43 ± 0.31	0.12 ± 0.04*,**	0.55 ± 0.21
Creatinine (μmol/L)	174.5 ± 32.5	191.2 ± 17.2	148.1 ± 18.4	298.3 ± 21.5**	111.9 ± 15.8*	274.2 ± 35.6**

*$P < 0.05$ vs. control group; **$P < 0.05$, vs. day 0. EVLW, extravascular lung water; LIS, lung injury score; PEEP, positive end-expiratory pressure.

TABLE 5. *Duration of mechanical ventilation and length of stay in survivors; ICU and 28-day mortality*

Variables	Control group	HA group	*P*-value
Duration of mechanical ventilation, days	13.6 ± 3.2	9.2 ± 2.3	0.01
Mechanical ventilation-free days to day 28	14.7 ± 5.5	19.6 ± 4.7	0.03
Duration of CRRT, hours	65.7 ± 14.6	18.6 ± 5.1	0.005
Length of ICU stay, day	19.4 ± 3.1	15.5 ± 4.0	0.04
ICU mortality No. (%)	12/21 (57.14)	6/25 (24)	0.02
28-day mortality No. (%)	14/21 (66.7)	7/25 (28)	0.009
SOFA at 14 day	8.9 ± 2.5	6.1 ± 1.2	0.047

CRRT, continuous renal replacement therapy; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

DISCUSSION

In our previous study, we investigated the efficacy and safety of a hemoperfusion cartridge (HA330) designed to remove cytokines from the septic patient's circulation during a randomized controlled trial.

The HA type resin cartridge (Lizhu Industries) is an extracorporeal hemoperfusion device that uses neutral microporous resin, and it has been proven to specifically absorb different mediators such as bilirubin and cytokines. The HA330 resin cartridge has the ability to absorb various medium-sized factors, including most inflammatory cytokines (IL-1, IL-6, IL-8, TNF-α), ranges from 6 kDa to 26 kDa. The previous results demonstrated that HA hemoperfusion elicited significant improvement of outcome and organ dysfunction by the removal of inflammatory cytokines in severe sepsis. In order to investigate the mechanism in the improvement, we go a step further to focus on the overall effect of HA hemoperfusion on the protection of sepsis-induced lung injury by this randomized controlled trial.

In this study, we chose the patients with acute lung injury induced by the extrapulmonary sepsis as subjects investigated in order to exclude the effect of pneumonia itself on lung inflammation and injury. We found that compared with general supporting treatment, HA hemoperfusion therapy proved effective for improving the measurement of clinical apparent lung injury including elevated PaO2 and oxygenation index, and reduced lung injury score and chest X-ray score. In addition, by assessing the measurement of extravascular lung water by an invasive monitor (PiCCO), our data show that HA hemoperfusion contributed to not only more alleviated symptoms of lung injury, but also significantly decreased extravascular lung water. As we all know, the trademark symptom of acute lung injury is increased capillary permeability, which is characterized by the accumulation of EVLW and manifests in the lungs as altered alveolar–capillary barrier function (14,15). Other findings also indicate that there is a direct relationship between independently measured pulmonary permeability and EVLW ratios during extrapulmonary sepsis, independently of fluid loading and the plasma colloid osmotic pressure (16,17). Thus, these results confirmed greater possibility that HA hemoperfusion perhaps might play an important role in the improvement of in juried alveolar–capillary barrier permeability and damaged diffusion pathway of oxygen and oxygenation in extrapulmonary sepsis-induced lung injury.

Experimental and human studies both have indicated a potential role for inflammatory cytokines in the development of severe sepsis induced acute lung injury. As demonstrated by several researchers, the increase in bronchoalveolar concentrations of IL-1, IL-8 and TNF-α have been observed in sepsis patients with ARDS or at risk for ARDS (18–20). In this study, we observed the clearance of inflammatory cytokines not only in circulation but in BAL during the treatment of HA hemoperfusion. Results obtained showed that the levels of IL-1 and TNF-α both in BAL and circulation decreased quickly at the end of hemoperfusion treatment for 3 days and presented significant reduction over time. Furthermore, though the plasma cytokines rise again after the termination of hemoperfusion, the cytokines levels in BAL fluid continued the tendency of reduction. The most likely explanation is that the increased TNF-α and IL-1 levels found in the BAL fluid of our patients were produced by activated pulmonary macrophages or other cells. These cells are located in lung interstitium, alveolar space and capillaries in humans. Absorption of HA resin effectively alleviated the activation of local inflammatory by removal of cytokines and endotoxin in circulation. Moreover, the results supporting the hypothesis that BAL fluid cytokine measurement appears to be useful not only to predict inflammation status in lung but also to evaluate the therapeutic effect on respiratory injury of hemoperfusion treatment.

In addition, the severity of lung injury (PaO_2/FiO_2, LIS) seems to be related negatively with IL-1, TNF-α in BAL fluid. The same was true for plasma IL-1,

TNF-α. It is probable that these cytokines are closely related to the extension of lung tissue damage and respiratory failure. Effective removal of cytokines plays a key role in improvement of inflammatory injury and respiratory dysfunction. However, we observed a poor correlation between EVLWI and plasma IL-1, TNF-α, but a close correlation between EVLWI and BAL fluid IL-1, TNF-α. It might indicate that accumulation of cytokines in lung was the direct contribution to interstitial edema and damaged oxygenation. Thus, effective clearance of inflammatory cytokines in lung by HA hemoperfusion treatment might be the key role in the improvement of injuried alveolar–capillary barrier permeability.

In this RCT of patients with acute lung injury induced by extrapulmonary sepsis, HA hemoperfusion therapy proved effective for shortening duration of mechanical ventilation and length of ICU stay, improving ICU survival and 28-day survival. These findings are in agreement with those of other studies and our previous studies in diverse populations. This RCT demonstrates that HA hemoperfusion, when added to conventional medical therapy, was effective in improving lung injury and respiratory outcomes in a targeted population with acute lung injury caused by extrapulmonary sepsis.

This study has some limitations: we enrolled few patients, and a larger randomized trial will be necessary to support the findings of this study. The high mortality of the control group exceeded our expectations, these situations can perhaps be attributed to high percentages of renal injury of our selected study population at enrollment and rapid incidence of acute renal failure within 3 days. Hemoperfusion treatment could have a marked effect on the protection of renal function and decrease the mortality, which has been supported by our previous study.

CONCLUSION

In our randomized controlled trial, we investigated that HA hemoperfusion therapy proved effective for improving respiratory dysfunction and outcome, removal of inflammatory cytokines such as IL-1 and TNF-α from BAL fluid and circulation by absorption of HA resin perhaps played a important role in the improvement. Further investigation is required to confirm these findings and to determine the effect of HA hemoperfusion therapy as a protection of lung injury in patients with pneumonia-induced sepsis.

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