Therapeutic Apheresis and Dialysis

Therapeutic Apheresis and Dialysis 14(6):596–602
doi: 10.1111/j.1744-9987.2010.00825.x

Removal of Humoral Mediators and the Effect on the Survival of Septic Patients by Hemoperfusion With Neutral Microporous Resin Column

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Abstract: The aim of this study is to evaluate the impact of neutral microporous resin hemoperfusion on hemodynamic improvement, removal of inflammatory cytokines, and mortality in critical care patients with severe sepsis. Forty-four patients with severe sepsis or septic shock were randomized to HA type hemoperfusion treatment ($N = 24$) or standard therapy ($N = 20$). Those undergoing hemoperfusion treatment received HA330 hemoperfusion. We measured the plasma concentrations of IL-6 and IL-8 at the start of every hemoperfusion treatment, and the following parameters were compared between the control group and the hemoperfusion group on days 3, 7, and 14: hemodynamics (cardiac index, systemic vascular resistance index, heart rate, and mean arterial pressure); change of hematology and coagulation function; organ function; and the sequential organ failure assessment (SOFA) score. Hospital, 28-day, and ICU mortality were also observed. Patients treated with HA hemoperfusion showed a significant removal of plasma IL-6 and IL-8 over time while in the study. Patients in the HA group also demonstrated significant increases in cardiac index, systemic vascular resistant index, fast withdrawal of vasoactive agents and decreases in heart rate compared with the controls at days 3 and 7. Although there was no significant difference between the groups in organ dysfunction as assessed by SOFA scores from day 0 (baseline) to day 7, significant improvement can be demonstrated in the hemoperfusion group at day 14. There was no significant difference between the groups in 28-day mortality, hospital mortality, or length of hospital stay, but ICU mortality and the length of ICU stay in the HA group were markedly reduced. Hemoperfusion treatment using the HA type cartridge in sepsis is safe and it may improve organ dysfunction, ICU mortality, and shorten the length of ICU stay. Clinical significant removal of inflammatory cytokines such as IL-6 and IL-8 from circulation by hemoperfusion may contribute to improving a patient's outcome in an ICU. **Key Words:** Absorption, Cytokine, Hemoperfusion, Severe sepsis.

Severe sepsis and septic shock continue to be the major causes of death in the medical and surgical intensive care unit (ICU), and often result in multiple organ dysfunction syndromes because of an inflammatory response by pro-inflammatory cytokines and activated neutrophils (1,2). Many clinicians have made great efforts to improve the prognosis of sepsis.

Recently, anti-endotoxin monoclonal antibodies and cytokine antagonists have been applied in controlling sepsis, but have proved unsuccessful in clinical trials, although many studies in animal models show some efficacy of treatment (3,4). In light of this situation, it is possible that the removal of endotoxins could represent a valuable treatment strategy for septic shock. Recently, 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 the indications for PMX have gradually been defined (5–7).

The HA type resin cartridge (Lizhu Industries, Zhuhai, China) 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 (8). The HA330 resin cartridge has the ability to absorb various medium-sized factors, including most inflammatory

Received November 2009; revised January 2010.
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cytokines (IL-1, IL-6, IL-8, TNF-α), and HA330 hemoperfusion is being newly developed for use in the treatment of patients with sepsis in China. Subsequently, many clinical case reports using HA in China have demonstrated the clinical benefit and safety of HA in the treatment of septic shock and severe sepsis (9). Since 2005, HA has been listed as a blood purification device in China and is reimbursed by the Chinese national health insurance. Such encouraging studies have prompted us to apply HA330 hemoperfusion to patient with sepsis, and this study is based on a two-year observation period and was performed to investigate its clinical benefit.

PATIENTS AND METHODS

Selection of patients and treatment

The study involved 44 patients who fulfilled the diagnostic criteria for severe sepsis. The patients consisted of 20 males and 24 females with a mean age of 74.9 years. 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). Patients under 18 or over 85 years of age were excluded. Those who had more than three failed organs were also excluded. Patients who fulfilled the indication criteria established by our hospital (i.e. those patients diagnosed with sepsis and with dysfunction of at least one organ) were randomized to receive standard therapy plus HA type hemoperfusion (HA group) or standard therapy only (control group). Patients in both groups received full intensive care management, including fluid resuscitation, vasopressors, antimicrobial therapy, and ventilatory support. Informed consent was obtained from all participating subjects or their families.

HA330 cartridge and hemoperfusion

Patients in the HA group received hemoperfusion with the HA330 resin cartridge (Lizhu Industries) once a day for three consecutive days after admission to the intensive care unit. This method was proven to be the most effective in our preliminary experiment. A double lumen catheter was inserted using Seldinger's method and maintained in the femoral vein for blood access. An Accura dialysis machine (Baxter, Deerfield, IL, USA) was used for hemoperfusion with the HA330 cartridge. The blood flow rate was permitted to be no less than 100 mL/min and no greater than 200 mL/min. Each individual session of hemoperfusion lasted for two hours. The anticoagulant used was enoxaparin; the activated clotting time was measured and the enoxaparin infusion was adjusted accordingly.

Evaluation of patients

The Acute Physiology and Chronic Health Enquiry (APACHE) II score was employed to assess of the severity of each patient's condition during the first 24 h of ICU admission. Expected mortality rates for APACHE II scores were computed using logistic regression calculations suggested in the original reports. The changes in the sequential organ failure assessment (SOFA) and Goris scores were assessed from baseline at day 0 to day 14 after the initiation of hemoperfusion. The vital signs were recorded frequently during the first 72 h, then every 8 h through to day 7. The following parameters were monitored during treatment: cardiac index (CI), systemic vascular resistance index (SVRI), heart rate (HR), and mean artery pressure were measured as hemodynamic parameters by pulse contour cardiac output (PiCCO; PULSION, Munich, Germany). The doses of vasoactive agents such as dopamine, dobutamine, and noradrenaline were monitored. The hemoglobin, white blood cell count, platelet count, and coagulation function index including prothrombin time (PT) and activated partial thromboplastin time (APTT) were measured. The mortality and length of stay in ICU and in hospital were also observed.

Serum IL-6 and IL-8 measurement

The two humoral mediators measured were IL-6 and IL-8, with the assays being done at a central laboratory (Guangzhou Medical College, Guangzhou, China). The blood samples for the measurement of these mediators were collected from a peripheral vein at 9 am on the day of treatment and immediately at the start of every hemoperfusion session. The serum was obtained by centrifugation at 4°C and $150 \times g$ for 10 min, and then stored at –80°C until analysis; then the serum levels of IL-6 and IL-8 were determined using a commercially available specific enzyme-linked immunosorbent assay kit for IL-6 and IL-8 (Otsuka Pharma, Tokyo, Japan) in accordance with the manufacturer's instructions.

Statistical analysis

The results are expressed as mean ± standard error. The unpaired Wilcoxon rank sum test or one-way analysis of variance was used to determine statistically significant differences. $P < 0.05$ was considered to be statistically significant.

RESULTS

Patient backgrounds

A total of 44 patients were enrolled, with 24 patients in the HA group and 20 patients in the

TABLE 1. *Patient demographics and the severity of their disorders*

	HA group	Control group
Male : Female (%)	13:11 (54.2:45.8)	11:9 (55:45)
Age (years)	75.2 ± 16.2	74.4 ± 13.9
APACHE II score	28.5 ± 5.4	29.1 ± 4.6
Number of failed organs	2.4 ± 0.6	2.6 ± 0.4
Shock and/or use of vasopressor	12 (50.0%)	10 (50.0%)
Endotracheal intubation and/or respiratory failure	24 (100.0%)	19 (95.0%)
Acute renal failure	14 (58.3%)	11 (55.0%)
Hepatic failure	4 (16.7%)	0 (0.0%)
Coagulation disorder	6 (25.0%)	3 (15.0%)

APACHE, Acute Physiology and Chronic Health Enquiry.

TABLE 2. *Etiology of infection*

Source	HA group	Control group
Abdominal cavity	6 (25.0%)	2 (10.0%)
Respiratory system	17 (70.8%)	16 (80.0%)
Others	1 (4.2%)	2 (10.0%)
Microorganism		
Gram-negative bacteria	10 (41.7%)	9 (45.0%)
Gram-positive bacteria	7 (29.2%)	4 (20.0%)
Fungus	2 (83.3%)	3 (15.0%)
Not detected or unknown	5 (20.8%)	4 (20.0%)

control group. No treatment was prematurely discontinued because of extracorporeal circuit clotting or high pressure problems. The demographics and baseline data of the patients' disorders are presented in Table 1. There was no significant difference between the two groups in baseline demographics, APACHE II score, or number of failed organs.

Gram-negative bacteria were detected between days 0 and 7 in 9 (45%) of the controls and 10 (41.7%) of the HA group patients (Table 2). There were no significant differences in antibiotic administration at baseline. Respiratory system infection was the main cause leading to severe sepsis in both groups.

Effect on hemodynamics

There were no significant differences in hemodynamic variables at baseline between the groups (Table 3). In the HA group, the mean arterial pressure (MAP) increased significantly from baseline to day 3. The CI, MAP, and SVRI were significantly greater in the HA group than in the control group at days 3 and 7 ($P = 0.02$, 0.04, 0.01, respectively). Further, in the HA group, the heart rate decreased from baseline to day 7, but significantly increased in the control group ($P = 0.04$).

In fact, dopamine is generally the first choice of vasoactive/inotropic agent in our unit; however, once the dopamine infusion exceeds 10 μg/kg/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 3 in the HA group, but increased in the control group ($P = 0.01$). No patients developed threatening hypotension during hemoperfusion therapy.

Hematology and coagulation function

In the HA group, the white blood cell counts increased from baseline to day 7 and were greater than those in the control group on day 7 ($P = 0.03$). Platelet counts decreased significantly by HA hemoperfusion at day 3, but improved quickly and were greater than those in the control group at day 7 ($P = 0.01$). The prothrombin time (PT) remained unchanged between the values at baseline and after treatments in both groups. The activated partial

TABLE 3. *Changes in hemodynamics and hematocyte, coagulation function during hemoperfusion treatment*

	HA group			Control group		
	Baseline	Day 3	Day 7	Baseline	Day 3	Day 7
MAP (mm Hg)	70.3 ± 14.5	84.2 ± 9.5*	94.8 ± 22.7*	72.1 ± 11.7	71.3 ± 10.2	78.2 ± 21.4
Heart rate (beats/min)	116.7 ± 25.6	108.9 ± 16.7	106.1 ± 21.6*	109.0 ± 31.2	110.6 ± 21.1	121.1 ± 23.4
Cardiac index (L/min/m^2)	4.6 ± 1.8	4.2 ± 1.7*	4.4 ± 1.5*	4.1 ± 1.1	3.4 ± 1.7	2.9 ± 2.1
SVRI (dyne.s/cm^5.m^2)	1056 ± 411	1452 ± 370*	1689 ± 395*	1142 ± 501	1011 ± 370	981 ± 452
Dose of dopamine (μg/kg/min)	12.0 ± 11.5	10.7 ± 10.2*	5.1 ± 5.0*	11.2 ± 10.8	15.3 ± 12.6	16.2 ± 3.4
Dose of dobutamine (μg/kg/min)	4.1 ± 3.1	3.7 ± 3.6	2.5 ± 2.4	4.1 ± 3.5	4.2 ± 2.3	3.1 ± 2.1
Dose of noradrenaline (μg/kg/min)	0.31 ± 0.25	0.29 ± 0.11	0.11 ± 0.10*	0.21 ± 0.12	0.43 ± 0.31	0.64 ± 0.21
Hemoglobin (g/L)	92.2 ± 12.5	75.3 ± 5.6*	94.7 ± 10.9*	89.1 ± 15.4	86.1 ± 21.3	72.1 ± 13.6
White blood cell count (×10^9/L)	13.4 ± 4.2	12.4 ± 5.1	10.1 ± 5.1*	14.1 ± 4.5	14.1 ± 3.4	14.6 ± 4.1
Platelet count (×10^9/L)	81.9 ± 23.1	54.9 ± 13.2*	75.6 ± 29.8*	87.1 ± 67.1	71.2 ± 37.6	64.1 ± 41.6
PT (s)	12.2 ± 1.3	14.9 ± 3.1	13.4 ± 1.5	13.1 ± 1.5	15.5 ± 2.0	15.6 ± 3.1
aPTT (s)	29.2 ± 4.3	70.6 ± 17.9*	33.1 ± 4.5	26.5 ± 4.2	36.4 ± 4.1	39.4 ± 3.3

*$P < 0.05$ vs. control group. aPTT, activated partial thromboplastin time; MAP, mean arterial pressure; PT, prothrombin time; SVRI, systemic vascular resistance index.

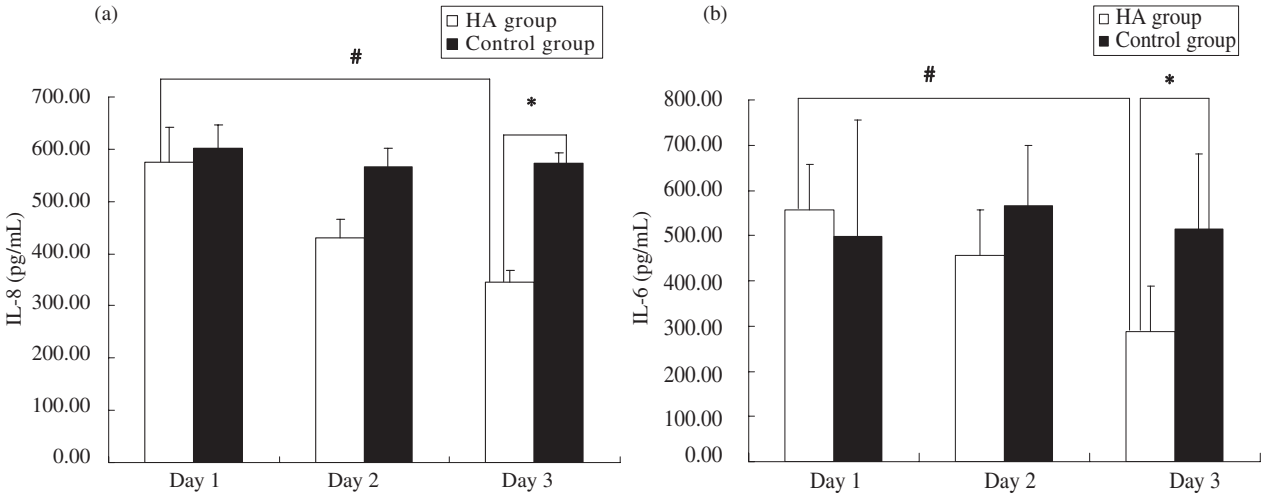

FIG. 1. Changes of circulating (a) interleukin (IL)-8, and (b) IL-6 between the HA group and the control group. The level of circulating IL-6 and IL-8 decreased post hemoperfusion compared with the baseline. In the control group the levels showed a tendency to increase during the study between the values at baseline and on day 2; however, this was not statistically significant ($P = 0.32, 0.67$). *There were statistically significant differences in the IL-6 and IL-8 levels between the two groups at day 3 ((a) $P = 0.03$; (b) $P = 0.01$). #Compared to the first day, the concentration of IL-6 and IL-8 reduced significantly at day 3 ((a) $P = 0.04$; (b) $P = 0.03$).

thromboplastin time (APTT) was significantly prolonged at the end of every hemoperfusion session ($P = 0.003$), but improved at day 7. There were no significant differences in PT and APTT at day 7 between the two groups ($P = 0.81, 0.56$, respectively).

Changes in IL-6 and IL-8

IL-6 and IL-8 were detected continuously in all patients. The change in serum IL-6 and IL-8 during the study are shown in Fig. 1. The baseline IL-6 and IL-8 levels were similar in both groups. IL-6 and IL-8 showed a significant fall in concentration post hemoperfusion than at baseline. However, in the control group the levels showed a tendency to increase during the study between the values at baseline and day 2, but this was not statistically significant ($P = 0.43$). There were statistically significant differences in the IL-8 and IL-6 levels between the two groups at day 3 ($P = 0.03, 0.01$, respectively).

Effect on organ dysfunction

Organ dysfunction assessed by the SOFA and Goris scores at baseline was similar in both groups (Table 4). There was no difference in the platelet count on day 14 from the baseline in the HA group, but it decreased significantly in control group. Further, P_aO_2/F_iO_2 was greater in the HA group at day 14 than in the control group ($P = 0.02$), and creatinine was lower. The SOFA and Goris scores on day 14 also showed a similar change ($P = 0.03, 0.01$, respectively).

Adverse events

Only one hemoperfusion patient had a treatment-emergent adverse event, which was considered to be possibly device related (fever). None of the adverse events occurred during HP treatment, and the adverse events reported during the study were not indicative of resin toxicity. There were no significant differences in red blood cell or platelet counts

TABLE 4. *Changes of organ function during hemoperfusion treatment*

	HA group			Control group		
	Baseline	Day 7	Day 14	Baseline	Day 7	Day 14
P_aO_2/F_iO_2	230.7 ± 108.4	259.3 ± 110.3	308.1 ± 131.2*	219.2 ± 67.2	200.1 ± 25.3	189.1 ± 39.1
Creatinine (μmol/L)	316.1 ± 98.2	311.2 ± 51.6	204.6 ± 60.7*	234.5 ± 45.2	351.1 ± 128.4	458.3 ± 200.1
Platelet count ($\times 10^9$/L)	81.9 ± 23.1	75.6 ± 29.8	80.6 ± 33.7*	87.1 ± 67.1	71.2 ± 37.6	64.3 ± 24.2
SOFA score	8.1 ± 2.1	7.5 ± 3.2	6.2 ± 4.1*	8.3 ± 2.5	8.1 ± 3.4	8.9 ± 2.4
Goris score	7.6 ± 3.1	6.1 ± 3.6	5.3 ± 3.9*	7.1 ± 2.5	7.3 ± 3.1	8.2 ± 1.1

*$P < 0.05$ vs. control group. SOFA, sequential organ failure assessment.

TABLE 5. *Duration of length of ICU and hospital stay; ICU and hospital mortality*

Variables	HA group ($N = 24$)	Control group ($N = 20$)	P value
Length of ICU stay (days)	12.4 ± 3.1*	19.5 ± 4.0	0.03
Length of hospital stay (days)	27.9 ± 6.7	29.4 ± 4.4	0.76
ICU mortality	3 (12.5%)*	9 (45.0%)	0.02
Hospital mortality	9 (37.5%)	10 (50.0%)	0.81
28-day mortality	11 (45.8%)	11 (55.0%)	0.47
SOFA score at ICU admission			
>8	9/15 (60.0%)	8/13 (61.5%)	0.91
<8	2/9 (22.2%)*	3/7 (42.9%)	0.02

*$P < 0.05$ vs. control group. ICU, intensive care unit; SOFA, sequential organ failure assessment.

between the baseline and day 7. Despite the administration of heparin (bolus plus continuous administration), no adverse events due to bleeding were observed during or after HA hemoperfusion treatment.

Mortality distribution

As shown in Table 5, the hemoperfusion treatment group had a significant reduction in ICU mortality, but no trend toward significant reduction in hospital or 28-day mortality was observed. However, the 28-day mortality was lower in the hemoperfusion group compared with the control group only in the patients with a SOFA score of <8 at the time of admission to the ICU. In addition, among the survivors, the hemoperfusion treatment group had a significant reduction in the duration of ICU stay, but the length of hospital stay showed no difference between the two groups.

DISCUSSION

This randomized controlled trial investigate the efficacy and safety of a hemoperfusion cartridge (HA330) designed to remove cytokines from the septic patient's circulation. Regarding specific pore size, the HA330 resin cartridge has the specific absorption of medium-sized inflammatory cytokines, and the molecular weight of most inflammatory cytokines, such as the interleukin family and TNF, ranges from 6 kDa to 26 kDa. Regarding the absorption characteristics, in our study we chose IL-6 (6.5 kDa) and IL-8 (26 kDa) as representative molecules for the verification of the ability of the HA330 resin cartridge to remove cytokines. This study evaluated the effect of HA hemoperfusion treatments on the removal of cytokines IL-6 and IL-8, and on the biological and physiologic responses related to inflammation.

Our chosen mediators—IL-6 and IL-8—belong to a supergene family of host defense molecules characterized by potent neutrophil activation in vitro (11). They can be produced by several types of cells, including macrophages, lymphocytes in response to a variety of stimuli such as endotoxin and other cytokines such as IL-1 or TNF. In the present study, they both acted as the marker for systemic inflammation in sepsis. Results obtained showed that the levels of plasma IL-6 and IL-8 decreased quickly after the initiation of hemoperfusion treatment and presented a significant reduction over time. It perhaps indicated that inflammatory cytokines, including IL-6 and IL-8, could be removed effectively through the absorption of HA resin. So, we hypothesize that the inhibitory effect of HA hemoperfusion on cytokines, which are the key mediators of inflammatory reactions, may contribute to improvement in organ dysfunction and patient outcome.

Several experimental studies have reported on the beneficial hemodynamic effects of hemoperfusion in sepsis (12–14). In a recent clinical observation, hemoperfusion showed a significant improvement in hemodynamic parameters, such as the dopamine dose, CI, MAP, and SVRI. In our study, we also demonstrated that hemoperfusion contributed significantly to the improvement of systemic hemodynamic parameters compared to the general infusion therapy, including markedly increased values of CI, and SVRI, and the withdrawal of dopamine infusion. Hirasawa et al. reported that hemodynamics in patients with sepsis or septic shock was improved by the removal of a variety of humoral mediators, including IL-6 and others (15). There also was a significant decline in IL-6 and IL-8 levels after the initiation of hemoperfusion, accompanied by an improved hemodynamic change in the present study. Therefore, it is confounded that the observed improvement in hemodynamics was perhaps related

to the inhibition of the production of inflammatory mediators and consequent suppression of systemic inflammation by HA hemoperfusion. In addition, the favorable effects of HA on cardiac function may be secondary to the elimination of myocardial-depressant mediators. Further clinical studies are needed to investigate the exact mechanisms involved in HA treatment.

Results of hematological tests on white blood cell and platelet counts were evaluated as follows. There was a slight reduction in the platelet count and hemoglobin with the absorber; however, this did not require any treatment and no signs of hemolysis could be detected. This HA resin adsorbent material exhibited favorable biocompatibility features in the study and is thus a promising candidate for future clinical hemoperfusion studies in septic patients (16,17). In addition, based on the continuous decrease in white blood cell counts over time in the study, the anti-inflammatory effect of HA hemoperfusion was proven to be potent and persisted for a longer period after the end of treatment.

Anticoagulation remains a major problem with the use of hemoperfusion; however, in our study, the temporary prolongation of activated partial thromboplastin time (aPTT) with heparin has been effectively controlled by an appropriate anticoagulation protocol and reduced bleeding complications and morbidity during hemoperfusion. Hemoperfusion was not associated with any bleeding complications and no serious adverse events were mentioned. On the contrary, coagulation dysfunction including prolonged aPTT and PT due to severe sepsis may have occurred more frequently in the control group. We demonstrated that HA hemoperfusion is a safe procedure.

For severity assessment, we performed serial measurements of the SOFA and Goris scores, which have been reported to be useful in the assessment of the severity of sepsis (18). In the present study, the severity score and organ function parameters, including hemodynamics, hematology parameters, and oxygenation indices all improved in HA patients at day 7 compared to baseline and the control group, showing the significant effect of HA hemoperfusion on improvement in organ dysfunction. It is possible that the removal and inhibition of the production of inflammatory mediators by hemoperfusion mainly contributes to this effect.

In this study, the hemoperfusion treatment group significantly improved the outcome of sepsis in an ICU, but had no obvious effect on the reduction of hospital mortality or 28-day mortality. We have commented that it might not be appropriate to justify the effect of hemoperfusion therapy by the 28-day mortality and hospital mortality in our study. Patients with severe sepsis or septic shock had a high mortality rate, and spent prolonged periods of time in the ICU (19). With the requirements of advanced technologies and skilled personnel, intensive care is among the most expense of all hospital care and cost-containment in health care is a major issue in today's practice of medicine (20). In our developing country, this fact requires the careful analysis of the indication for ICU admission, as well as necessitating early discharges from ICU and shortened ICU therapy. For these reasons, we concluded that inadequate intensive therapy resulted in the increased mortality of patients away from the ICU, and that a properly prolonged ICU stay would likely benefit severely septic patients. In addition, it was demonstrated that mortality was lower in the hemoperfusion group compared with the control group only in patients with a SOFA score <8 at ICU admission. It showed that an early and non-delayed hemoperfusion treatment may effectively improve the prognosis of septic patients. Additionally, the small sample size in this study may be another key leading to no significant difference in hospital mortality between the two groups. Study limitations are attributed primarily to the small sample size and so a larger randomized trial will be necessary to support the mortality findings of this study.

CONCLUSIONS

The above results demonstrated that HA hemoperfusion elicited the following effects: improvement of hemodynamics; a possible anti-inflammatory effect by the removal of inflammatory cytokines; and the improvement of organ dysfunction (by severity assessment) and ICU outcome. In recent years, the indication of HA hemoperfusion is a still matter of debate, and the favorable results with HA hemoperfusion unfortunately lack multicenter evaluation and inclusion in randomized controlled trials. Several problems remain for future studies, which should be assessed in multiple centers over an effective time period and with an appropriate number of HA hemoperfusion cycles, as well as examining other mediators, such as TNF-α and other interleukins.

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