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Efficacy of HA330 Hemoperfusion Adsorbent in Patients Followed in the Intensive Care Unit for Septic Shock and Acute Kidney Injury and Treated with Continuous Venovenous Hemodiafiltration as Renal Replacement Therapy

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Keywords
HA330 hemoperfusion · Septic shock · Acute kidney injury · Continuous venovenous hemodiafiltration

Abstract
Introduction: Blood purification is an option for treatment of the source of sepsis when correcting patients' septic shock-induced clinical status. We investigated the efficacy of HA330 hemoperfusion adsorbent application with renal replacement therapy in patients with septic shock and acute kidney injury. ***Methods:*** This prospective observational study involved 23 patients diagnosed with sepsis who underwent continuous venovenous hemodiafiltration and HA330 hemoperfusion for 2 h once daily for 3 days. The patients' demographic data, comorbidities, lengths of intensive care unit and hospital stays, blood cell counts, blood biochemistry values, coagulation values, blood gas values, inflammatory markers, hemodynamic parameters, and inotropic medication use before and after each application of HA330 hemoperfusion were recorded. The effectiveness of HA330 hemoperfusion was evaluated by comparing the parameters on days 0 and 1, 1 and 2, and 2 and 3. ***Results:*** The pH increased significantly following the first application of HA330 hemoperfusion (p = 0.001), the C-reactive protein (CRP) and procalcitonin levels decreased significantly after the second application (p = 0.002 and 0.018, respectively), and the CRP level decreased significantly following the third application (p = 0.046). ***Conclusions:*** The application of HA330 hemoperfusion 2 h daily for 3 consecutive days improved level of CRP and heart rate, but had no effect on others or on the prognosis.

Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Septic shock is a form of sepsis in which underlying circulatory and cellular/metabolic abnormalities are sufficiently profound to substantially increase mortality [1].

The crude occurrence rates of sepsis, severe sepsis, and septic shock were 667, 103, and 91 cases per 100,000 population per year in Beijing from July 1, 2012 to June 30, 2014 [2]. Sepsis and septic shock affect 100–1000 per 100,000 person-years and 19 per 100,000 person-years, respectively, depending on the cohort studied [3]. Sepsis

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is the most important cause of morbidity and mortality in hospitalized patients worldwide, accounting for >50% of in-hospital deaths [4]. As sepsis is the most important cause of death in intensive care units (ICUs) worldwide, its management should be a primary topic of research [5].

Sepsis causes immune system defects due to prolonged infection [3, 6]. It may block several aspects of the host defense response to infection, which can lead to an excessive host response [3, 6]. Such excessive responses lead to the release of various cytokines [3, 7, 8], which damage organ systems [3, 9].

Sepsis continues to be a problem for clinicians; the mechanism by which microbial pathogens disrupt the host defense, the ability to cooperate in the invasive stage of infection, and the mechanism of interaction with microbial pathogens may be important for its treatment [3, 6].

An understanding of the pathophysiology of sepsis is important for the management of its treatment. Many studies have examined treatment strategies for cases in which cytokines are released, due to their important roles in the physiopathology of sepsis [10–13]. Those studies involved the use of antiendotoxin monoclonal antibodies and cytokine antagonists, which achieved partial responses in animal models; clinical success, however, remains elusive [10, 11]. In recent years, adsorbent-based hemoperfusion to eliminate cytokines from the blood has been proposed [14, 15]. The adsorbents used for hemoperfusion include HA330, CytoSorb, NKU-9, CYT-860-DHP, Lixelle, CTR-001, and MPCF-X [15, 16]. HA330 includes a neutral microporous resin that adsorbs bilirubin and inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, and IL-8 [11]. Moreover, HA330 hemoadsorbance may be beneficial for the treatment of septic shock [11].

Huang et al. [10] in a study which 44 patients with deep sepsis included in the study, 24 underwent HA330 hemoperfusion and 20 underwent standard intensive care treatment. The IL-6 and IL-8 levels were significantly lower than baseline in the HA330-treated group [11]. HA330 is used for the treatment of deep sepsis and septic shock in China, and this sepsis column has shown clinical utility and safety [11].

In patients who require treatment for both septic shock and acute kidney injury (AKI), it may be necessary to apply renal replacement therapy (RRT) and HA330 hemoperfusion adsorption columns together. The Prismaflex M100 hemofilter (Gambro Healthcare, Lakewood, CO, USA) and HA330 can be serially linked to enable simultaneous RRT and cytokine removal. This hemofilter is used for continuous venovenous hemodiafiltration (CVVHDF). It eliminates low- and medium-molecular-weight compounds, up to a certain weight. For example, it only partially eliminates beta 2-microglobulinin (12 kDa) and TNF-α (17 kDa) [17]. The HA330 hemoadsorbent efficiently eliminates 10–60-kDa molecules [18], including the cytokines IL-6 (6.5 kDa) and IL-8 (26 kDa) [10, 18]. Therefore, HA330 hemoadsorbent has a potential application for blood purification in patients with septic shock and AKI undergoing RRT.

In this study, we evaluated the efficacy of HA330 hemoadsorbent for cytokine adsorption applied during RRT in patients with septic shock and AKI in the ICU.

Materials and Methods

This prospective observational study was initiated after obtaining approval from the Clinical Research Ethics Board of Diyarbakir Gazi Yasargil Education and Research Hospital (No. 110, June 29, 2018). Calculations indicated that a minimum of 23 patients was needed to achieve a two-tailed alpha error of 0.05, a power of 0.95, and an effect size of 0.8 (G-Power version 3.1.9.4; Kiel University, Germany). Twenty-three patients who were hospitalized in the Anesthesiology and Reanimation ICU between July 7, 2018 and October 10, 2018, with septic shock, and who were scheduled to undergo HA330 hemoperfusion, were included in the study. This study was conducted in compliance with the 2008 Declaration of Helsinki, and written informed consent was obtained from all patients or their first-degree relatives.

Inclusion criteria were: diagnosis of septic shock, based on the 2017 guidelines of the European Society of Intensive Care Medicine and the Society of Critical Care Medicine [1]; and Patients undergoing RRT in CVVHDF mode and patients that Kidney Disease: Improving Global Outcome (KDIGO) is 2 and 3. The patients were administered HA330 hemoperfusion within the first 12 h following diagnosis.

Exclusion criteria were: patients with allergies to HA 330 (characterized by hypotension and/or tachycardia), age <18 or >85 years, and acute respiratory distress syndrome (ARDS) or history of septic shock for >12 h after diagnosis. Patients not treated with RRT. Patients in study received full intensive care management, including fluid resuscitation, vasopressor administration, antimicrobial therapy, and ventilatory support.

In all patients, electrocardiography, pulse oximetry assessment, and continuous invasive arterial pressure measurement after intra-arterial cannulation were performed using a BSM-9101K monitor (Nihon Kohden Europe GmbH, Rosbach, Germany).

In addition to the standard therapy, the patients diagnosed with septic shock underwent CVVHDF and HA330 hemoperfusion daily for 2 h for 3 consecutive days [8]. Blood samples were taken 2 h before CVVHDF and HA330 administration and 6 h after HA330 administration. Hemoperfusion was conducted by serially connecting the HA330 hemoperfusion cartridge to the Prismaflex M100 hemofilter system (Gambro Healthcare). Before HA330 administration, 5,000 IU unfractionated heparin was primed; during RRT, it was infused for 40–60 s as needed to maintain the activated partial thromboplastin time (aPTT). RRT was applied in

CVVHDF mode, with a 35–40-mL/kg/h dialysis dose and a blood flow rate of 100–200 mL/min. The HA330 hemoperfusion cartridge was serially connected before the Prismaflex M100 hemofilter system. We applied this method to avoid dialysis; we do not know whether Baxter has approved it.

The researchers who diagnosed septic shock were different from those who followed the patients. Data were collected from our institution's electronic medical records system and patient files.

Patients' demographic data, comorbidities, Acute Physiology and Chronic Health Enquiry (APACHE) II scores at the time of ICU admission, Sequential Organ Failure Assessment (SOFA) scores before and after HA330 hemoperfusion, existing organ failure at the time of HA330 hemoperfusion, lengths of ICU and hospital stays, and mortality data were recorded. All patients had acute renal failure, which developed in the ICU in 6 patients. Seventeen patients had the KDIGO score of 3 and 6 had the KDIGO score of 2. All patients underwent RRT for AKI.

The hemoglobin level (BC-6800 auto-hematology analyzer; Mindray, Shenzhen, China), blood cell counts (white blood cells [WBCs], neutrophils, lymphocytes, platelets; BC-6800 auto hematology analyzer, Mindray), blood biochemistry values (urea, creatinine, alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin; c702-502 autoanalyzer, Roche, Rosbach, Germany), coagulation parameters (prothrombin time [PT], aPTT, international normalized ratio [INR]; ACL TOP500 and ACL TOP700, Instrumentation Laboratory, Bedford, MA, USA), blood gas parameters (pH, arterial oxygen tension [PaO_2]/fraction of inspired oxygen [FiO_2], base excess [BE], lactate; Rapid Point 500 blood gas analyzer, Siemens, Berlin, Germany), inflammatory markers (C-reactive protein [CRP], Cobas c702 autoanalyzer, Roche; procalcitonin [PRC], Cobas e601 and COBAS e602 analyzers, Roche), hemodynamic parameters (mean arterial pressure, heart rate [HR]), and inotropic medication use were recorded 2 h before CVVHDF + HA330 and 6 h after HA330. The effectiveness of HA330 hemoperfusion was evaluated by comparing the parameters between days 0 and 1, 1 and 2, and 2 and 3. In addition, the parameters were compared between days 0 and 3. Blood samples were immediately transported to the laboratory. Blood, tracheal aspirate, urine, wound, rectal, and focal fixations were obtained from the patients with septic shock. Noradrenalin infusion dose recorded 2 h before and after 6 h of HA330 administration. The source of sepsis and the microorganisms cultured were recorded.

The data were analyzed using SPSS software (version 16.0 for Windows; SPSS Inc., Chicago, IL, USA). Numerical data are reported as means and SDs, and categorical data are presented as frequencies and percentages. The normality of the data was evaluated using a skewness test, and normally distributed variables were analyzed using parametric tests (paired-sample *t* test and analysis of variance). The Tukey post hoc test was also applied. *p* values ≤0.05 were considered to indicate significance.

Table 1. Demographic data and clinical features of patients

	Mean ± SD
Age, years (*n* = 23)	42.30±19.09
Length of stay in ICU, day	67.82±124.40
Length of stay in hospital, day	100.70±156.72
APACHE II	24.43±7.79
Gender, *n* (%)	
Female	14 (60.9)
Male	9 (39.1)
Comorbidity, *n* (%)	
–	13 (56.5)
Diabetes mellitus	3 (13)
İmmunocompromised	2 (8.7)
Cancer	2 (8.7)
Others	3 (13)
Number of organs with failure, *n* (%)	
1	6 (26.1)
3	6 (26.1)
4	7 (30.4)
5	4 (17.4)
Acute renal failure, *n* (%)	
+	23 (100)
–	0 (0)
KDIGO 2, *n* (%)	14 (60.87)
KDIGO 3, *n* (%)	9 (39.13)
Liver failure, *n* (%)	
+	6 (26.1)
–	17 (73.9)
Coagulation defect, *n* (%)	
+	6 (26.1)
–	17 (73.9)
Respiratory failure, *n* (%)	
+	22 (95.7)
–	1 (4.3)
Shock, *n* (%)	
+	23 (100)
–	0 (0)
Mortality, *n* (%)	
+	9 (39.1)
–	14 (60.9)
Total, *n* (%)	23 (100)

APACHE, Acute Physiology and Chronic Health Enquiry II Score; KDIGO, Kidney Disease Improving Global Outcomes.

Results

Twenty-three patients hospitalized in the ICU and diagnosed with septic shock were included in this study. Fourteen (60.9%) of the patients were female and 9 (39.1%) were male (mean age 42.30 ± 19.09 years). The mean length of ICU stay was 67.82 ± 124.40 days, and the mean length of hospital stay was 100.70 ± 156.72 days. Nine (39.1%) patients died in the ICU and 14 (60.9%) were transferred from the ICU to other services (Table 1).

The mean APACHE II score on ICU admission was 24.43 ± 7.79, and the mean SOFA score before HA330

Table 2. Source of sepsis, blood culture growth, and filter-type data of the study patients

Study patient	Reason for hospitalization in ICU	Source of sepsis	Bacterial growth in blood	Gram	Filter
1	Exacerbation of KOAH	Urosepsis	*K. pneumoniae*	–	M100
2	Pneumonia	Pneumosepsis	*S. epidermidis*	+	M100
3	Polytrauma	Wound infection-associated sepsis	*P. aeruginosa*	–	M100
4	Polytrauma	Wound infection-associated sepsis	*S. epidermidis*	+	
5		Urosepsis	*A. baumannii*	–	M100
6		Pneumosepsis	*S. hominis ssp hominis*	+	M100
7	Polytrauma	Catheter-related sepsis	*S. hominis ssp hominis*	+	M100
8	Polytrauma	Catheter-related sepsis	*E. faecium*	+	M100
9	Polytrauma	Catheter-related sepsis	*S. aureus*	+	M100
10		Pneumosepsis	*A. baumannii*	–	M100
11	Gunshot injury	Abdominal sepsis	*Enterobacter spp.*	–	M100
12	Pneumonia	Pneumosepsis	*P. aeruginosa*	–	M100
13	Pneumonia	Pneumosepsis	*S. aureus*	+	M100
14	Polytrauma	Catheter-related sepsis	*S. haemolyticus*	+	M100
15	Gunshot injury	Unclear	Unclear	Unclear	M100
16	Gunshot injury	Abdominal sepsis	*Enterobacter spp.*	–	M100
17	Polytrauma	Wound infection-associated sepsis	*P. aeruginosa*	–	M100
18	Polytrauma	Catheter-related sepsis	*S. hominis ssp hominis*	+	M100
19	Pneumonia	Unclear	Unclear	Unclear	M100
20	Gunshot injury	Abdominal sepsis	*A. baumannii*	–	M100
21	Pneumonia	Unclear	Unclear	Unclear	M100
22	Gunshot injury	Pneumosepsis	*A. baumannii*	–	M100
23	Pneumonia	Pneumosepsis	*P. aeruginosa*	–	M100

ICU, intensive care unit.

hemoperfusion was 10.52 ± 4.59. No additional disease was detected in 13 (56.5%) patients; diabetes mellitus was noted in 3 (13%) patients (Table 1).

Six (26.1%) patients had single organ failure, 6 (26.1%) had 3 failed organs, 7 (30.4%) had 4, and 5 (17.4%) had 5 failed organs. In addition, 23 (100%) patients developed AKI, 6 (26.1%) had liver failure, 6 (26.1%) had coagulation defects, 22 (95.7%) had respiratory failure, and 23 (100%) were in shock (Table 1).

All patients received noradrenaline before and after HA330 administration 23 (100%) (Table 1).

The reasons for hospitalization in the ICU, the source of sepsis, and the microorganisms cultured are listed in (Table 2).

Significant decreases were detected in the hemoglobin, WBC, neutrophil, platelet, creatinine, BE, and HR values ($p = 0.018$, 0.013, 0.011, 0.005, 0.033, 0.015, and 0.027, respectively) between baseline and 1 day after HA330 hemoperfusion. A significant increase was detected in the pH ($p = 0.001$). No significant difference was observed between baseline and 1 day after HA330 hemoperfusion in the lymphocyte, CRP, PRC, urea, ALT, AST, bilirubin, PT, aPTT, INR, lactate, PaO_2/FiO_2, or mean arterial pressure value, or in the noradrenaline infusion dose needed (Table 3).

The CRP, PRC, ALT, INR, and HR values decreased significantly between days 1 and 2 after HA330 hemoperfusion ($p = 0.002$, 0.018, 0.023, 0.035, and 0.016, respectively). However, no significant difference was observed in the hemoglobin, WBC, neutrophil, lymphocyte, platelet, urea, creatinine, AST, bilirubin, PT, aPTT, pH, BE, lactate, PaO_2/FiO_2, or mean arterial pressure value, or in the noradrenaline infusion dose needed (Table 4).

A significant decrease in the CRP level ($p = 0.046$) was detected between days 2 and 3 after HA330 hemoperfusion. No significant difference was observed in any other vital parameter or biochemical value (Table 5).

Significant decreases in the hemoglobin, platelet, CRP, creatinine, ALT, aPTT, and HR values ($p = 0.003$, 0.05, 0.002, 0.012, 0.037, 0.043, and 0.006, respectively) were observed between baseline and after the third HA330 hemoperfusion application. No significant difference was observed in any other vital parameter or biochemical

Table 3. Effectiveness of sepsis column on values in first day

	Day 0	Day 1	*p* values
Hemoglobin	10.06±2.46	9.31±2.13	0.018*
WBC	19.18±9.40	16.02±7.99	0.013*
Neutrophil	15.01±7.00	12.55±5.77	0.011*
Lymphocyte	1.30±0.77	1.29±0.14	0.353
Platelet	169.26±118.96	136.82±149±57	0.005*
CRP	217.80±95.69	197.31±94.35	0.319
Procalcitonin	68.05±59.15	50.61±43.39	0.138
Urea	103.60±64.22	92.50±58.72	0.180
Creatinine	2.74±2.24	2.50±1.98	0.033*
ALT	319.31±598.23	259.95±538.28	0.193
AST	413.09±721.61	365.59±708.76	0.299
Bilirubin	1.57±2.01	1.81±2.50	0.160
PT	15.41±3.75	15.15±3.14	0.545
aPTT	52.43±32.22	44.02±14.48	0.149
INR	1.70±0.71	1.73±0.72	0.616
pH	7.30±0.131	7.36±0.107	0.001*
BE	–4.98±7.28	–2.76±5.54	0.015*
Lactate	3.70±3.66	3.18±3.77	0.500
PO_2/FiO_2	176.11±97.30	187.28±124.75	0.601
MAP	74.31±19.96	78.04±14.69	0.199
HR	112.40±30.49	103.95±24.46	0.027*
NİD	0.80±0.38	0.89±0.49	0.408

* Statistically significant ($p \leq 0.05$).

WBC, white blood cell; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; aPTT, activated partial thromboplastin time; INR, international normalized ratio; pH, power of hydrogen; BE, base excess; PaO2/FiO2, arterial oxygen tension/fractional inspired oxygen rate; MAP, mean arterial pressure; HR, heart rate; NİD, noradrenalin infusion dose.

Table 4. Effectiveness of sepsis column on values in second day

	Day 1	Day 2	*p* value
Hemoglobin	9.31±2.13	9.06±1.66	0.292
WBC	16.02±7.99	17.45±12.31	0.404
Neutrophil	12.55±5.77	12.23±7.20	0.978
Lymphocyte	1.29±0.14	1.40±0.62	0.127
Platelet	136.82±149±57	131.52±112.53	0.574
CRP	197.31±94.35	161.34±96.82	0.002*
Procalcitonin	50.61±43.39	38.75±41.63	0.018*
Urea	92.50±58.72	93.28±69.94	0.918
Creatinine	2.50±1.98	2.35±1.92	0.427
ALT	259.95±538.28	196.27±426.61	0.023*
AST	365.59±708.76	272.77±546.68	0.194
Bilirubin	1.81±2.50	1.84±2.53	0.846
PT	15.15±3.14	16.75±2.60	0.570
aPTT	44.02±14.48	41.09±16.25	0.099
INR	1.73±0.72	1.53±0.66	0.035*
pH	7.36±0.107	7.37±0.09	0.686
BE	–2.76±5.54	–1.46±6.29	0.084
Lactate	3.18±3.77	2.87±3.72	0.423
PO_2/FiO_2	187.28±124.75	201.68±121.97	0.236
MAP	78.04±14.69	77.59±17.17	0.841
HR	103.95±24.46	95.68±21.23	0.016*
NİD	0.89±0.49	0.65±0.33	0.166

* Statistically significant ($p \leq 0.05$).

WBC, white blood cell; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; aPTT, activated partial thromboplastin time; INR, international normalized ratio; pH, power of hydrogen; BE, base excess; FiO2, arterial oxygen tension; FiO_2, fractional inspired oxygen rate; MAP, mean arterial pressure; HR, heart rate; NİD, noradrenalin infusion dose.

value (Table 6). No patient developed an allergy or similar side effect or complication necessitating treatment termination.

Discussion

The HA330 hemoadsorbent is a cytokine adsorbent used to treat sepsis, septic shock, and inflammatory diseases [10]. We investigated the effects of HA330 hemoperfusion on the blood cells, blood biochemistry, inflammatory markers, and clinical status of patients with septic shock and AKI.

The mean length of ICU stay was 67.82 ± 124.40 days (Table 2). All patients were hospitalized due to polytrauma, gunshot injury, or pneumonia. No patient was admitted to the ICU due to sepsis. Sepsis and subsequent septic shock developed during follow-up in the ICU.

The clinical benefit of HA330 hemoperfusion in patients with septic shock has been reported [10, 13, 19–21]. HA330 is also effective in patients with hepatitis and pancreatitis [18, 22]. Moreover, HA330 hemoperfusion eliminates itching in patients receiving dialysis [23]. HA330 has high biocompatibility, and its use in hemoperfusion does not cause cytotoxic or other side effects [24]. Many studies have documented the clinical benefits of HA330 treatment for septic shock [10, 13, 19–21]. In this study, we observed no side effect or complication related to HA330.

We applied CVVHDF with HA330 hemoperfusion in all patients in this study; we did not include a control group. The molecular weight of creatinine is 113 Da [25]. The Prismaflex M100 hemofilter (Gambro Healthcare) is used for CVVHDF. It eliminates low- and medium-molecular-weight compounds, up to a certain weight. For example, it only partially eliminates beta

Table 5. Effectiveness of sepsis column on values in third day

	Day 2	Day 3	*p* value
Hemoglobin	9.06±1.66	8.62±2.09	0.090
WBC	17.45±12.31	17.34±16.63	0.945
Neutrophil	12.23±7.20	11.96±8.90	0.748
Lymphocyte	1.40±0.62	1.53±0.87	0.437
Platelet	131.52±112.53	129.53±108.35	0.809
CRP	161.34±96.82	129.21±92.56	0.046*
Procalcitonin	38.75±41.63	37.24±65.83	0.930
Urea	93.28±69.94	86.04±58.94	0.200
Creatinine	2.35±1.92	2.18±1.83	0.124
ALT	196.27±426.61	179.52±443.79	0.534
AST	272.77±546.68	284.04±618.82	0.842
Bilirubin	1.84±2.53	1.84±2.66	0.806
PT	16.75±2.60	13.99±2.18	0.190
aPTT	41.09±16.25	39.88±18.22	0.352
INR	1.53±0.66	1.45±0.88	0.500
pH	7.37±0.09	7.33±0.16	0.151
BE	–1.46±6.29	–2.99±8.85	0.209
Lactate	2.87±3.72	3.64±5.45	0.243
PO_2/FiO_2	201.68±121.97	208.17±125.13	0.763
MAP	77.59±17.17	76.86±19.41	0.803
HR	95.68±21.23	93.09±24.21	0.442
NİD	0.65±0.33	0.60±0.43	0.428

* Statistically significant ($p \leq 0.05$).

WBC, white blood cell; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; aPTT, activated partial thromboplastin time; INR, international normalized ratio; pH, power of hydrogen; BE, base excess; FiO2, arterial oxygen tension; FiO2, fractional inspired oxygen rate; MAP, mean arterial pressure; HR, heart rate; NİD, noradrenalin infusion dose.

2-microglobulinin (12 kDa), TNF-α (17 kDa), IL-6 (26 kDa), and IL-10 (30 kDa) [17]. Regarding pore size, the HA330 resin cartridge specifically absorbs inflammatory cytokines with molecular weights of 6–26 kDa, such as IL and TNF [10].

HA330 hemoperfusion decreased the WBC and neutrophil counts between days 0 and 1, the CRP and PRC levels between days 1 and 2, and the CRP level between days 2 and 3 (Tables 2–4). We also detected a significant decrease in the CRP level between days 0 and 3 (Table 5). Huang et al. [10] reported a significant decrease in the WBC count between days 0 and 7. They concluded that the anti-inflammatory effect of HA330 hemoperfusion persisted beyond completion of the 3-day treatment. In our study, these parameters were checked on day 3 to evaluate the anti-inflammatory effect of HA330 hemoperfusion. Their measurement over a longer period may be beneficial to determine the degree of permanence of the anti-inflammatory effect of HA hemoperfusion. Administration of HA330 hemadsorption to patients with septic shock over 3 days decreased the WBC, neutrophil, CRP, and PRC values. CRP has a molecular weight of 115 kDa, and PRC has a molecular weight of 14.5 kDa [26, 27]. The decrease in the PRC level was likely associated with elimination by HA330 and CVVHDF, and the decrease in the CRP level was associated with a decrease in inflammation. The CVVHDF and HA330 cartridges cannot absorb CRP (which has a molecular weight of up to 115 kDa). As the host response is mediated by cytokines, absorption of cytokines by the HA330 cartridge reduces inflammation and the CRP level [6].

HA330 hemoperfusion decreased the INR between days 1 and 2 (Table 3) and significantly decreased the aPTT between days 0 and 3 (Table 6). Huang et al. [10] reported that the aPTT increased significantly after each hemoperfusion treatment. They used enoxaparin as the anticoagulant; in contrast, we used heparin and did not detect an increase in the aPTT. Additionally, high aPTT values had decreased significantly, to within normal limits, by the end of day 3. Therefore, the anticoagulation performed during the operation was sufficient and effective.

HA330 hemoperfusion increased the pH and decreased the BE value, but did not increase the PaO_2/FiO_2 ratio, between days 0 and 1 (Table 2). HA330 reportedly improves lung function, resulting in improved PaO_2/FiO_2 values [19, 20]. The reason for the difference from our work is that the previous studies were conducted with patients with ARDS. In accordance with the Berlin criteria, patients with ARDS were excluded from our study.

We found that HA330 hemoperfusion decreased the HR, but had no effect on the need for inotropic medication (Tables 3, 4). Moreover, HA330 hemoperfusion significantly decreased the HR, but did not significantly affect the need for inotropic medication, between days 0 and 3 (Table 6). HA330 reportedly has beneficial effects on hemodynamic parameters, but it had no effect on hemodynamics in one study [10, 19]. We believe that HA330 can have beneficial hemodynamic effects secondary to its anti-inflammatory activity.

The crude population mortality rates of sepsis, severe sepsis, and septic shock are 137, 27, and 77 cases per 100,000 population per year, respectively. These figures represent 831,674 deaths from sepsis, 156,057 deaths from severe sepsis, and 447,219 deaths from septic shock nationally, although this extrapolation is

Table 6. Comparison of the values before and after the application of sepsis column

	Day 0	Day 3	*p* value
SOFA score	10.52±4.59	8.95±4.09	0.107
Hemoglobin	10.06±2.46	8.62±2.09	0.003*
WBC	19.18±9.40	17.34±16.63	0.549
Neutrophil	15.01±7.00	11.96±8.88	0.084
Lymphocyte	1.30±0.77	1.53±0.87	0.273
Platelet	169.26±118.96	129.53±108.35	0.05*
CRP	217.80±95.69	129.21±92.56	0.002*
Procalcitonin	68.05±59.5	37.24±65.83	0.298
Urea	103.60±64.22	86.04±58.94	0.089
Creatinine	2.74±2.24	2.18±1.83	0.012*
ALT	319.31±598.23	179.52±443.79	0.037*
AST	413.09±721.61	284.04±618.82	0.185
Bilirubin	1.57±2.01	1.84±2.66	0.276
PT	15.41±3.75	13.99±2.18	0.118
aPTT	52.43±32.22	39.88±18.22	0.043*
INR	1.70±0.71	1.45±0.88	0.122
pH	7.30±0.131	7.33±0.16	0.501
BE	–4.98±7.28	–2.99±8.85	0.276
Lactate	3.70±3.66	3.64±5.45	0.947
PO_2/FiO_2	174.11±97.30	208.17±125.13	0.295
MAP	74.31±19.96	76.86±19.41	0.561
HR	112.40±30.49	93.09±24.21	0.006*
NİD	0.80±0.38	0.60±0.43	0.340

* Statistically significant ($p \leq 0.05$).

SOFA, The Sequential Organ Failure Assessment score; WBC, white blood cell; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; aPTT, activatedpartialthromboplastin time; INR, international normalized ratio; pH, power of hydrogen; BE, base excess; PaO_2, arterial oxygen tension; FiO_2, fractional inspired oxygen rate; MAP, mean arterial pressure; HR, heart rate; NİD, noradrenalin infusion dose.

speculative [2]. Clinically, a patient with septic shock can be identified by the requirement for a vasopressor to maintain a mean arterial pressure ≥65 mm Hg and a serum lactate level >2 mmol/L (>18 mg/dL) in the absence of hypovolemia; the in-hospital mortality rate among such patients is >40% [7]. In our ICU, the mortality rate was 39.1% (Table 1), which is in agreement with this rate.

Data from patients with severe sepsis and septic shock included in a 2011 study conducted by Herrán Monge et al. [28] were compared with those obtained in a similar study conducted in 2002. In 2002, the average APACHE II score was 25.5, and the ICU mortality rate was 48.8%; in 2011, the respective values were 21.9 and 27.2%. Niewinski et al. [29] reported in 2014 that the mortality rates of nonoperative patients with severe sepsis and septic shock in the ICU were 29% for those with APACHE II scores of 20–24 and 37% for those with scores of 25–29. In our study, the mean APACHE II score at the time of first ICU admission was 24.43 ± 7.79, and the rate of mortality in the ICU was 39.1% (Table 1). This mortality rate is comparable to those observed in some, but not all, previous studies.

Lie et al. [30] reported that the overall 28-day mortality rate in patients with sepsis and severe sepsis was 22%; rates ranged from 7% for those with a SOFA score of 2 to 39% for those with scores >6 at the time of ICU admission. Khwannimit et al. [31] reported that the overall 30-day mortality rate for patients with septic shock and a SOFA score of 9 was 45.1%. In our study, the mean SOFA score before HA330 hemoperfusion was 10.52 ± 4.59, and the rate of mortality in the ICU was 39.1% (Tables 1, 6). Moreover, no significant difference in the SOFA score was observed between days 0 and 3 after HA330 hemoperfusion (Table 6). These results are comparable with those reported in the literature and show that our treatment did not alter the SOFA score.

Huang et al. [10] found no significant difference in the NID between days 0 and 3, as in this study.

Conclusion

The HR, but not the NID, decreased significantly between days 0 and 1. The CRP and PRC levels and the HR decreased significantly, despite the decrease in the NID, between days 1 and 2. Compared with day 2, only the CRP level was significantly lower on day 3; the NID did not decrease. The CRP level and HR, but not the NID, decreased significantly. The application of CVVHDF and HA330 hemoperfusion adsorbent for 3 consecutive days did not reduce the NID, but reduced the CRP level and the HR. These effects are likely attributable to cytokine adsorption via CVVHDF and HA330 administration.

Limitations

This study was conducted during CVVHDF and did not include a control group. We evaluated the effects of the first, second, and third applications of HA330 hemoperfusion on laboratory and clinical parameters. We did not compare the parameters on days 7 and 14 with those on day 0. We recommend that future studies involve the monitoring of these parameters for longer periods after

HA330 application. This study examined only the effectiveness of HA330 hemoperfusion; a randomized, controlled, prospective, double-blind study is required to validate our results. Moreover, we did not determine whether HA330 hemoperfusion decreased the levels of cytokines such as TNF-α, IL-1β, IL-6, and IL-8. Studies of the effect of HA330 hemoperfusion on the levels of these cytokines are scheduled.

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Statement of Ethics

This study was initiated after obtaining approval (No. 110, dated June 29, 2018) from the Diyarbakir Gazi Yasargil Education and Research Hospital Clinical Research Ethics Board. Patient's parents or guardians have given their written informed consent and that the study protocol was approved by the institute's committee on human research. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

C.K.K.: writing, analyzed the data. O.U.: analyzed the data. D.K.: data collection. A.K.Y.: writing, study design, analyzed the data, edited the final version of the manuscript.

References

1 Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international concensus definition for sepsis and septic shock. JAMA. 2016 Feb; 315(8):801–10.
2 Zhou J, Tian H, Du X, Xi X, An Y, Duan M, et al.; for China Critical Care Clinical Trials Group (CCCCTG). Population-Based Epidemiology of Sepsis in a Subdistrict of Beijing. Crit Care Med. 2017 Jul;45(7):1168–76.
3 Honore PM, Hoste E, Molnár Z, Jacobs R, Joannes-Boyau O, Malbrain ML, et al. Cytokine removal in human septic shock: where are we and where are we going? Ann Intensive Care. 2019 May;9(1):56.
4 Paoli CJ, Reynolds MA, Sinha M, Gitlin M, Crouser E. Epidemiology and Costs of Sepsis in the United States-An Analysis Based on Timing of Diagnosis and Severity Level. Crit Care Med. 2018 Dec;46(12):1889–97.
5 Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med. 2013 Aug;369(9): 840–51.
6 van der Poll T, Opal SM. Van der poll T, Opal SM. Host-pathogen interactions in sepsis. Lancet Infect Dis. 2008;8(1):32–43.
7 Delano MJ, Ward PA. The immune system's role in sepsis progression, resolution, and long-term outcome. Immunol Rev. 2016 Nov; 274(1):330–53.
8 Lelubre C, Vincent JL. Mechanisms and treatment of organ failure in sepsis. Nat Rev Nephrol. 2018 Jul;14(7):417–27.
9 Houschyar KS, Pyles MN, Rein S, Nietzschmann I, Duscher D, Maan ZN, et al. Continuous hemoadsorption with a cytokine adsorber during sepsis – a review of the literature. Int J Artif Organs. 2017 May;40(5):205–11.
10 Huang Z, Wang SR, Su W, Liu JY. Removal of humoral mediators and the effect on the survival of septic patients by hemoperfusion with neutral microporous resin column. Ther Apher Dial. 2010 Dec;14(6):596–602.
11 Zhang J, Peng Z, Maberry D, Volpe J, Kimmel JD, Federspiel WJ, et al. Effects of hemoadsorption with a novel adsorbent on sepsis: in vivo and in vitro study. Blood Purif. 2015; 39(1-3):239–45.
12 Gotts JE, Matthay MA. Sepsis: pathophysiology and clinical management. BMJ. 2016 May;353:i1585.
13 Rello J, Valenzuela-Sánchez F, Ruiz-Rodriguez M, Moyano S. Sepsis: A Review of Advances in Management. Adv Ther. 2017 Nov; 34(11):2393–411.
14 Hinz B, Jauch O, Noky T, Friesecke S, Abel P, Kaiser R. CytoSorb, a novel therapeutic approach for patients with septic shock: a case report. Int J Artif Organs. 2015 Aug;38(8): 461–4.
15 Chen J, Han W, Chen J, Zong W, Wang W, Wang Y, et al. High performance of a unique mesoporous polystyrene-based adsorbent for blood purification. Regen Biomater. 2017 Feb;4(1):31–7.
16 Taniguchi T. Cytokine adsorbing columns. Contrib Nephrol. 2010;166:134–41.
17 Thomas M, Moriyama K, Ledebo I. AN69: evolution of the world's first high permeability membrane. Contrib Nephrol. 2011;173: 119–29.
18 Ankawi G, Fan W, Pomarè Montin D, Lorenzin A, Neri M, Caprara C, et al. A New Series of Sorbent Devices for Multiple Clinical Purposes: Current Evidence and Future Directions. Blood Purif. 2019;47(1-3):94–100.
19 Xu X, Jia C, Luo S, Li Y, Xiao F, Dai H, et al. Effect of HA330 resin-directed hemoadsorption on a porcine acute respiratory distress syndrome model. Ann Intensive Care. 2017 Aug;7(1):84.
20 Huang Z, Wang SR, Yang ZL, Liu JY. Effect on extrapulmonary sepsis-induced acute lung injury by hemoperfusion with neutral microporous resin column. Ther Apher Dial. 2013 Aug;17(4):454–61.
21 Ankawi G, Neri M, Zhang J, Breglia A, Ricci Z, Ronco C. Extracorporeal techniques for the treatment of critically ill patients with sepsis beyond conventional blood purification therapy: the promises and the pitfalls. Crit Care. 2018 Oct;22(1):262.
22 Sun S, He L, Bai M, Liu H, Li Y, Li L, et al. High-volume hemofiltration plus hemoperfusion for hyperlipidemic severe acute pancreatitis: a controlled pilot study. Ann Saudi Med. 2015 Sep-Oct;35(5):352–8.
23 Li WH, Yin YM, Chen H, Wang XD, Yun H, Li H, et al. Curative effect of neutral macroporous resin hemoperfusion on treating hemodialysis patients with refractory uremic pruritus. Medicine (Baltimore). 2017 Mar;96(12): e6160.

24 Pomarè Montin D, Ankawi G, Lorenzin A, Neri M, Caprara C, Ronco C. Biocompatibility and Cytotoxic Evaluation of New Sorbent Cartridges for Blood Hemoperfusion. Blood Purif. 2018;46(3):187–95.
25 Thongprayoon C, Cheungpasitporn W, Kashani K. Serum creatinine level, a surrogate of muscle mass, predicts mortality in critically ill patients. J Thorac Dis. 2016 May;8(5):E305–11.
26 Okemefuna AI, Stach L, Rana S, Buetas AJ, Gor J, Perkins SJ. C-reactive protein exists in an NaCl concentration-dependent pentamer-decamer equilibrium in physiological buffer. J Biol Chem. 2010 Jan;285(2):1041–52.
27 Samsudin I, Vasikaran SD. Clinical Utility and Measurement of Procalcitonin. Clin Biochem Rev. 2017 Apr;38(2):59–68.
28 Herrán-Monge R, Muriel-Bombín A, García-García MM, Merino-García PA, Martínez-Barrios M, Andaluz D, et al. Epidemiology and Changes in Mortality of Sepsis After the Implementation of Surviving Sepsis Campaign Guidelines. J Intensive Care Med. 2019 Sep;34(9):740–750.
29 Niewiński G, Starczewska M, Kański A. Prognostic scoring systems for mortality in intensive care units – the APACHE model. Anaesthesiol Intensive Ther. 2014 Jan-Mar;46(1):46–9.
30 Lie KC, Lau CY, Van Vinh Chau N, West TE, Limmathurotsakul D; for Southeast Asia Infectious Disease Clinical Research Network. Utility of SOFA score, management and outcomes of sepsis in Southeast Asia: a multinational multicenter prospective observational study. J Intensive Care. 2018 Feb;6(1):9.
31 Khwannimit B, Bhurayanontachai R, Vattanavanit V. Comparison of the accuracy of three early warning scores with SOFA score for predicting mortality in adult sepsis and septic shock patients admitted to intensive care unit. Heart Lung. 2019 May - Jun;48(3):240–4.