Blood Purification

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The Clinical and Laboratory Efficacy of HA 330 Treatment Combined with Continuous Renal Replacement Therapy in Septic Shock Patients: A Case Series

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Keywords
Cytokines · HA 330 hemoperfusion · Septic shock · Critically ill patients · Intensive care

Abstract
Introduction: Blood purification therapy is a method used to enable cytokine removal and to improve disturbed immune homeostasis in patients with sepsis or septic shock. This study aimed to evaluate the impact of HA 330 treatment on biochemical and hemodynamic parameters and cytokine levels in adult patients with septic shock. ***Methods:*** Critically ill patients with septic shock who received continuous veno-venous hemodiafiltration and HA 330 treatment were included in this prospective observational study. Biochemical and hemodynamic parameters were followed throughout HA 330 treatment. Serum interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor (TNF)-α, high-mobility group box1 (HMGB-1) protein, IL-10 levels were analyzed by ELISA method, before and after each HA 330 session. ***Results:*** A total of 18 critically ill patients were included in this study. The median APACHE 2 score was 22.2 ± 7.49 and median SOFA score 9.6 ± 5.44 on intensive care unit admission. SOFA scores were significantly decreased on the 3rd day of HA 330 treatment, compared to 2nd day scores ($p = 0.017$). Median leukocyte value was significantly decreased ($p = 0.027$ and $p = 0.024$), while hemodynamic parameters remained unchanged throughout the HA 330 treatment. Median CRP and procalcitonin levels were significantly reduced at day 3 of HA 330 treatment compared to the baseline ($p = 0.015$ and $p = 0.033$, respectively). Serum IL-1 β, IL-6, IL-8, TNF-a, HMGB-1, and IL-10 levels decreased insignificantly by 11.5%, 26.4%, 11.4%, 37.9%, 0.02%, and 35.5%, respectively, at the end of the hemoperfusion treatment compared to the pre-treatment. ***Conclusion:*** The administration of HA 330-based hemoperfusion in septic shock patients revealed improvements in SOFA scores, leukocyte count, and CRP and procalcitonin levels. However, there was no statistically significant change in concentrations of inflammatory cytokines and hemodynamic parameters during HA 330 treatment.

Introduction

Sepsis is defined as a life-threatening organ dysfunction due to uncontrolled host response to infection [1]. The septic shock, the most severe form of

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Table 1. Participant demographic characteristic, clinical parameters, and clinical outcome

Patients	Gender	Age	BMI	Diagnosis at admission	Comorbidities	Source of sepsis	Antibiotics	Time to sepsis from admission, days	HA 330 treatment, *n*	Apache 2	SAPS 2	SOFA	28-Day mortality
1	M	71	26.37	Post-surgical peritonitis	HT	Abdominal sepsis	Vancomycin, colistin, anidulafungin	7.00	1	15	33	5	Yes
2	M	41	25.83	Pneumonia	HD	Pneumosepsis	Vancomycin, amphotericin B, meropenem	2.00	2	24	64	14	Yes
3	M	57	23.15	Pneumonia	CHF, HT	Pneumosepsis	Vancomycin, meropenem, trimethoprim-sulfamethoxazole	9.00	3	22	49	4	Yes
4	F	61	25.95	Major trauma	CHF, gut disease, MVR	Abdominal sepsis	Vancomycin, meropenem, colistin, anidulafungin	16.00	2	20	31	11	Yes
5	F	34	25.39	Septic shock	MS	Pneumosepsis	Vancomycin, meropenem, clarithromycin	0.00	1	20	43	9	Yes
6	M	50	24.69	Pneumonia	CVD	Pneumosepsis	Vancomycin, meropenem, trimethoprim-sulfamethoxazole, amphotericin B	2.00	2	23	63	14	Yes
7	M	81	31.25	Pneumosepsis	COPD, DM, HT	Pneumosepsis	Piperacillin/tazobactam, clarithromycin, linezolid	0.00	3	26	71	10	Yes
8	M	40	26.30	Major trauma		Pneumosepsis	Vancomycin, meropenem	2.00	3	15	57	9	Yes
9	F	66	31.25	Septic shock	CAD, DM	Unclear	Vancomycin, meropenem, clarithromycin	0.00	3	30	70	10	Yes
10	F	75	27.06	Septic shock	HT	Abdominal sepsis	Piperacillin/tazobactam, vancomycin, anidulafungin	0.00	2	28	98	14	No
11	M	81	26.30	Chronic liver disease	DM, HT	Catheter-related sepsis	Meropenem, anidulafungin	14.00	3	27	66	12	No
12	F	74	58.59	Major trauma	CHF, DM, HT	Wound infection-associated sepsis	Meropenem, colistin, daptomycin	15.00	2	20	43	7	Yes
13	F	80	33.30	Septic shock	CHF, HT, CAD	Pneumosepsis	Vancomycin, meropenem	0.00	1	38	94	14	Yes
14	F	72	27.68	Necrotizing fasciitis	CHF, DM, HT	Wound infection-associated sepsis	Piperacillin/tazobactam, metronidazol	0.00	3	31	62	11	No
15	F	66	24.69	Septic shock	CHF, DM, HT	Urosepsis	Vancomycin, meropenem	0.00	2	27	77	23	No
16	F	58	29.07	Pneumonia	CVD	Pneumosepsis	Vancomycin, meropenem	2.00	1	21	44	6	Yes
17	F	63	24.69	Pneumonia	CHF, DM	Pneumosepsis	Vancomycin, meropenem, clarithromycin	2.00	3	19	40	5	No
18	F	75	32.01	Pneumonia	CVD, CHF, DM	Pneumosepsis	Moxifloxacin, linezolid, meropenem	4.00	3	24	55	6	Yes

BMI, body mass index; CAD, coronery artery disease; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; DM, diabetes mellitus; F, female; HD, hematological disease; HT, hypertension; M, male; MS, multiple sclerosis; MVR, mitral valve replacement.

Table 2. Comparison of SOFA and biochemical parameters before and after HA 330 treatment

	Day 1 (n = 18)	Day 2 (n = 14)	Day 3 (n = 8)	p value	Difference between days
SOFA	15.0 (12.0–17.0)	14.5 (12.8–17.8)	11.5 (7.5–14.8)	**0.004**	1–3 (p = 0.013) 2–3 (p = 0.017)
Creatinine, mg/dL	3.58 (2.32–4.26)	2.71 (1.72–3.92)	2.01 (0.89–2.27)	0.368	
BUN, mg/dL	58.0 (42.2–90.0)	53.0 (44.8–80.3)	54.5 (37.8–65.3)	0.154	
AST, U/L	116.0 (51.3–701.2)	112.0 (34.3–1747.5)	93.5 (41.5–757.3)	0.243	
ALT, U/L	66.0 (21.0–522.8)	69.5 (30.8–752.8)	27.0 (23.3–980.5)	0.129	
Bilirubin, mg/dL	1.8 (0.4–8.3)	1.3 (0.3–9.2)	1.3 (0.4–2.2)	0.225	
Albumin, g/dL	2.5 (2.1–3.0)	2.2 (1.9–2.8)	2.5 (1.9–2.7)	0.290	
Leukocyte, 10^3/μL	14.0 (7.2–22.3)	12.6 (9.5–20.6)	11.7 (9.0–14.6)	**<0.001**	1–2 (p = 0.027) 2–3 (p = 0.024)
Platelet, 10^3/μL	103.0 (52.8–154.3)	93.0 (37.3–129.3)	96.0 (67.8–132.8)	0.082	
PT, s	17.0 (15.3–24.3)	19.5 (16.0–28.1)	16.0 (13.5–17.7)	0.071	
aPTT, s	41.3 (34.8–52.3)	65.5 (35.3–120.0)	40.3 (26.4–51.0)	0.202	
CRP, mg/L	208.0 (88.3–330.5)	98.5 (37.5–210.0)	98.0 (42.3–287.5)	**0.007**	1–3 (p = 0.015)
Procalcitonin, ng/mL	12.1 (3.4–22.8)	7.9 (4.5–9.9)	4.1 (2.1–6.6)	**<0.001**	1–3 (p = 0.033)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; PT, prothrombin time; sec, seconds; SOFA, sequential organ failure assessment.

sepsis, is a very fatal condition that leads to mortality in 37–47% of cases in the setting of critical illness [2–4].

In septic shock, proinflammatory mediators are frequently promoted by pathogen-associated molecular patterns and damage-associated molecular patterns [5]. The conditions dominated by the cytokine storm with the highest levels of both the proinflammatory and the anti-inflammatory cytokine levels are known to be associated with very high mortality rates. Hence, blockade of cytokine overproduction is suggested to prevent sepsis and to improve poor clinical outcomes [6].

Blood purification therapies are considered a novel therapeutic method to enable cytokine removal and to improve disturbed immune homeostasis in sepsis [3]. HA 330 is a high-volume hemoperfusion cartridge with an electrically neutral microporous copolymer resin designed for critical clinical conditions associated with a cytokine storm [7, 8]. HA 330 resin cartridge has the capacity of adsorbing various medium-sized factors including inflammatory cytokines (interleukin [IL]-1, IL-6, IL-8, tumor necrosis factor [TNF-α]) with molecular weight of 6–26 kDa [9].

Hemadsorption, a complementary mechanism for removal of solutes, is based on direct binding of solutes to membranes or sorbent material inside the cartridge (adsorption unit) [8]. In contrast to other extracorporeal blood purification techniques (i.e., high-volume hemofiltration and high-threshold membranes), an important characteristic of sorbent materials is minimizing unwanted molecules loss (such as nutrients and antibiotics) [10–12].

Adsorption can be used alone or in combination with other renal replacement therapies. Several clinical case reports indicated the potential clinical benefit and safety of HA 330 in the treatment of septic shock and severe sepsis [8, 9, 13]. However, there is limited clinical evidence regarding the hemadsorption approaches, necessitating clarification of its clinical efficacy via further investigations [3]. This study aimed to evaluate the impact of HA 330 hemadsorption treatment on biochemical findings, hemodynamic parameters, and inflammatory cytokines (IL-1β, IL-6, IL-8, TNF-α, high-mobility group box1 [HMGB-1] protein, IL-10) in critically ill adult patients with septic shock.

Methods

This prospective observational study was conducted in patients diagnosed with septic shock who received HA 330 hemoperfusion treatment and continuous renal replacement therapy (CRRT) (continuous veno-venous hemodiafiltration, CVVHDF mode) in Anesthesiology and Reanimation and Medical ICU center. The study was performed in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by Erciyes University Ethics Committee (date of approval: January 09, 2019: Protocol No: 2019/09). Written informed consent was obtained from all patient or from parents/guardian/next of kin for all vulnerable participants.

Table 3. Comparison of the hemodynamic parameters before and after the cycle of HAA 330 treatment during follow-up

	Day 1			Day 2			Day 3			Pre- vs. post-treatment		
	before	after	*p* value	before	after	*p* value	before	after	*p* value	pre-treatment	post-treatment	*p* value
Pulse	98.0	101.0	0.546	90.5	96.0	0.649	84.0	90.5	0.327	98.0	90.5	0.432
	(80.0–102.0)	(77.0–112.3)		(83.8–112.3)	(81.5–105.0)		(57.3–93.8)	(74.3–96.5)		(80.0–102.0)	(74.3–96.5)	
MAP, mm Hg	67.0	66.5	0.067	67.0	67.0	0.556	71.0	78.0	0.483	67.0	78.0	0.483
	(60.5–72.5)	(60.8–74.5)		(59.0–77.5)	(65.0–82.0)		(63.5–84.5)	(71.5–83.0)		(60.5–72.5)	(71.5–83.0)	
Vasopressor support,	0.30	0.30	0.330	0.30	0.20	0.113	0.28	0.23	0.180	0.30	0.23	0.833
mcg/kg/min	(0.13–1.00)	(0.04–1.00)		(0.00–0.75)	(0.09–0.73)		(0.00–0.48)	(0.00–0.48)		(0.13–1.00)	(0.00–0.48)	
pH	7.31	7.31	0.704	7.33	7.37	0.265	7.41	7.35	0.362	7.31	7.35	0.599
	(7.19–7.37)	(7.26–7.39)		(7.26–7.45)	(7.23–7.43)		(7.28–7.45)	(7.27–7.46)		(7.19–7.37)	(7.27–7.46)	
pCO_2, mm Hg	33.5	33.0	0.861	33.5	37.0	0.969	32.0	36.0	0.674	33.5	36.0	1.000
	(28.3–40.3)	(27.0–37.8)		(26.8–40.6)	(27.0–39.5)		(27.3–42.8)	(28.0–41.8)		(28.3–40.3)	(28.0–41.8)	
HCO3	17.2	17.4	0.756	19.8	18.0	0.080	21.0	19.5	0.261	17.2	19.5	0.205
	(12.8–21.1)	(14.0–19.3)		(16.0–26.0)	(15.5–21.5)		(17.0–25.3)	(13.3–24.0)		(12.8–21.1)	(13.3–24.0)	
Lactate, mmol/L	5.0	4.7	0.344	4.4	3.7	0.814	3.9	3.5	0.236	5.0	3.5	0.575
	(4.0–6.5)	(3.9–10.0)		(3.7–6.7)	(3.3–5.6)		(3.4–4.9)	(3.1–4.8)		(4.0–6.5)	(3.1–4.8)	
paO_2/FiO_2	205.0	230.0	0.256	247.5	272.0	0.701	180.0	240.0	0.063	205.0	240.0	0.866
	(135.0–336.5)	(162.0–354.3)		(177.5–377.5)	(182.5–347.5)		(151.8–249.8)	(203.0–268.0)		(135.0–336.5)	(203.0–268.0)	

Study Participants

The inclusion criteria were as follows: (1) 18–80 years of age, (2) the diagnosis of septic shock at ICU based on "the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)" [1] criteria, (3) receiving full ICU treatment including fluid resuscitation, vasopressor treatment, antibiotic treatment, and mechanical ventilatory support, (4) having Kidney Disease Improving Global Outcome (KDIGO) scores ≥2, (5) receiving HA 330 hemoperfusion treatment and renal replacement therapy in the CVVHDF mode. Pregnant women, patients who had cardiopulmonary resuscitation within previous 24 h of the ICU admission, patients with cardiogenic shock, HIV positivity, thrombocytopenia, previous organ transplantation, advanced stage malignancy with ongoing chemotherapy or radiotherapy, stage 5 or more chronic renal failure or end-stage liver failure, and those under immunosuppressive therapy with drugs other than corticosteroids were excluded from the study.

Data Collection

On Admission

Data on patient demographics (i.e., age, gender, body mass index), reason for ICU admission, source of sepsis, and presence of comorbidity were recorded. Clinical assessment on ICU admission was based on acute physiology and chronic health evaluation (APACHE) 2 score, sequential organ failure assessment (SOFA) score, and simplified acute physiology (SAPS) 2 score.

During Follow-Up

SOFA score, hemodynamic parameters (pulse, mean arterial pressure [MAP]), blood gas analysis (pH, pCO_2, HCO_3, paO_2/FiO_2), lactate levels, and therapy of vasopressor and antibiotic were followed during study period. Creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, albumin, leukocyte count, platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), C-reactive protein (CRP), and procalcitonin levels were daily recorded. Length of hospital/ICU stay and 28-day mortality data were recorded.

Study Protocol

All patients received CRRT combined with hemadsorption treatment and standard ICU treatment. CRRT was applied in CVVHDF (Fresenius or Gambro) mode for treatment of renal failure in the ICU. Unfractionated heparin was used as the anticoagulant. HA 330 (Jafron, Zhuhai, China) hemoperfusion column was attached to CVVHDF and replaced every 24 h. Vascular access was obtained with Seldinger technique via double lumen catheter through the jugular vein or femoral vein. Ultrafiltration was set at a rate of 30–35 mL/kg/h and blood flow rate at 100–200 mL/min. Standard and invasive arterial pressure was monitored in all study patients. HA 330 was applied for at least once in each participant and for a maximum of 3 days and 2 h per day [14].

Analysis of Inflammatory Cytokines

A 3-mL peripheral blood sample was collected two times including 1 h before and 1 h after each administration of HA 330 hemoperfusion. Collected blood samples were centrifuged at 4°C and 150 × *g* for 10 min to obtain serum. Serum was stored at −80°C until analysis. The concentration of IL-1β, IL-6, IL-8, TNF-α, HMGB-1 proteins, and IL-10 were determined using commercial

sandwich ELISA kits according to the manufacturer's instructions (Bioassay Technology Laboratory; E0143Hu, E0089Hu, E0082Hu, E0099Hu, E1635Hu, and E0119Hu, respectively). The measured protein concentrations were evaluated using the calibrated standard curve.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics software, version 26.0. Continuous data were expressed as mean ± standard deviation," median (25q-75q, interquartile) according to normality distribution using Shapiro-Wilk test. Categorical data were presented as number (%). To compare two dependent groups, Wilcoxon test was used. Kruskal-Wallis test was used for comparison of three dependent groups. A $p < 0.05$ value was considered as statistically significant.

Results

The mean age of patients was 63.6 ± 14.53 years. The mean APACHE 2 score of study sample was 22.2 ± 7.49, mean SAPS 2 score was 56.8 ± 20.99, and mean SOFA score was 9.6 ± 5.44. The median length of HA 330 treatment was 2.0 (1.0–3.0) days. All patients received invasive mechanical ventilation support throughout the whole process of sepsis column treatment. Demographic and clinical characteristics and clinical outcomes of the study patients are listed in Table 1 in detail.

SOFA score was significantly decreased on the 3rd day of HA 330 treatment ($p = 0.013$ for day 1 and day 3, $p = 0.017$ for day 2 and day 3). A significant decrease was noted in median leukocyte value of patients starting from the onset of HA 330 therapy ($p = 0.027$ and $p = 0.024$). During follow-up, median CRP and procalcitonin levels were significantly decreased on the 3rd day of HA 330 treatment ($p = 0.015$ and $p = 0.033$, respectively) (Table 2).

As summarized in Table 3, no significant change was noted in MAP values after HA 330 treatment compared to pre-treatment value ($p = 0.432$). Pre-treatment and post-treatment values for vasopressor dose, lactate levels, and pO2/FiO2 value were also similar ($p = 0.833$, $p = 0.575$, $p = 0.866$, respectively) (Table 2). Although not statistically significant, there was a tendency for decrease in serum IL-1β, IL-6, IL-8, TNF-a, HMGB-1 levels during the course of HA 330 treatment, by 11.5%, 26.4%, 11.4%, 37.9%, and 0.02%, respectively ($p = 0.417$, $p = 0.096$, $p = 0.809$, $p = 0.493$, and $p = 0.102$, respectively) (Fig. 1) (Table 4).

Serum IL-10 levels were decreased by 35.5% during HA 330 treatment session (Fig. 1). However, there was no significant difference between the pre- and post-HA 330 therapy all days of sepsis column session ($p = 0.937$) (Table 4).

Table 4. Comparison of the primary end points on before and after in the cycle of HA 330 treatment

	Day 1			Day 2			Day 3			
	before	after	*p* value	before	after	*p* value	before	after	*p* value	*p* value[a]
IL-1, pg/L	1510.5 (1121.5–1906.5)	1362.0 (1005.0–1681.0)	0.879	1648.0 (1248.0–2312.0)	1679.0 (871.0–2619.0)	0.182	1293.0 (943.0–1779.0)	1337.0 (1091.0–2151.0)	0.866	0.417
IL-6, pg/mL	144.2 (89.6–167.2)	142.3 (85.8–154.4)	0.139	128.6 (94.4–174.5)	116.8 (78.8–172.5)	0.248	148.1 (71.2–239.3)	106.2 (69.2–243.6)	0.612	0.096
IL-8, pg/mL	229.1 (170.6–301.4)	224.5 (140.2–292.9)	0.472	274.7 (184.0–292.2)	215.2 (172.6–277.5)	0.657	202.5 (179.4–377.9)	203.0 (139.5–481.0)	0.499	0.809
TNF-alfa, pg/mL	229.5 (134.1–272.5)	211.0 (116.2–258.8)	0.207	239.5 (118.2–311.0)	229.0 (103.9–266.3)	0.722	161.0 (112.8–236.0)	142.5 (109.1–354.0)	0.345	0.493
HMGB-1, ng/mL	26.6 (21.7–38.3)	26.5 (18.5–42.3)	0.145	22.3 (18.8–34.4)	26.2 (21.4–36.5)	0.998	30.1 (25.5–41.3)	26.2 (18.0–47.3)	0.176	0.102
IL-10, pg/mL	247.2 (151.5–274.8)	188.7 (171.8–271.5)	0.845	216.4 (162.1–331.8)	206.0 (163.5–324.3)	0.534	172.0 (114.2–366.5)	159.4 (133.2–251.1)	0.933	0.937

p: before versus after HA 330 treatment. [a]*p*: comparison among day 1, day 2, and day 3.

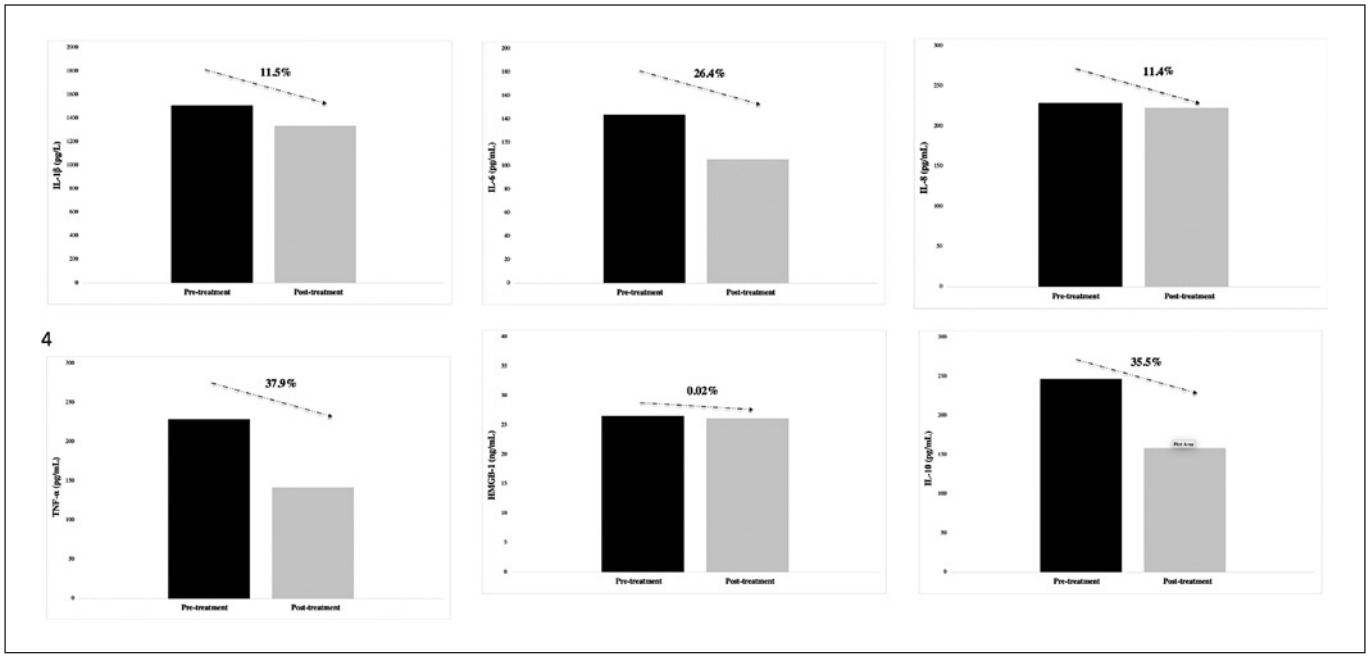

Fig. 1. Change of serum inflammatory cytokine values between pre- and post-HA 330 treatment. It shows concentrations of serum IL-1B, IL-6, IL-8, TNF-a, HMGB-1, and IL-10 during HA 330 treatment.

The median number of days with MV support of patients was 5.5 (1.8–13.5) days. The median length of ICU and hospital stay was 11.5 (4.8–21.8) and 18.5 (10.0–29.0) days, respectively. The 28-day all-cause mortality rate of study sample was 72.2% (Table 1).

Discussion

Our findings revealed the administration of HA 330 treatment was associated with a significant decrease in SOFA scores, leukocyte count, CRP, and procalcitonin levels in patients who were admitted to ICU with septic shock or who develop septic shock during their ICU stay. During the course of HA 330 treatment, a nonsignificant decrease was found in serum IL-1β, IL-6, IL-8, TNF-a, HMGB-1, and IL-10 levels. However, no statistically significant difference was found in the hemodynamic parameters (pulse, MAP).

Extracorporeal cytokine hemadsorption is a novel therapeutic approach applied in clinical conditions such as the septic shock including disturbed immunoregulation and cytokine storm. Although there is insufficient amount of evidence on hemadsorption use in routine practice, the clinical efficacy remains debated [15]. After HA 330 treatment started, SOFA scores of the study patients decreased at a statistically significant level during the follow-up. Moreover, concentrations of some inflammatory markers (WBC, CRP, and procalcitonin) decreased significantly at post-HA 330 treatment compared to the pre-HA 330 treatment. Similarly, in a recent prospective study by Kacar et al. [16], the use of HA 330 hemadsorption for 3 days in patients with septic shock was reported to be associated with reduction in inflammatory parameters including WBC, neutrophil counts, CRP, and procalcitonin levels. Another study found that there was relationship between HA 330 treatment and reduced SOFA, PCT, and CRP levels in critically ill patients [17]. Cytosorb [18–20], as well as HA 330 [9, 21], is frequently used in removal of cytokines via hemoperfusion in patients with sepsis/septic shock. Cytosorb hemoadsorption was also indicated to be associated with improvement of inflammatory syndrome along with marked decrease of WBC count and serum levels of CRP and procalcitonin [22].

Present study exhibited no statistically significant difference in hemodynamic parameters and vasopressor dose throughout HA 330 treatment. Likewise, in a study conducted with severe sepsis or septic shock patients, use of HA 330 treatment plus standard treatment versus standard treatment alone reported similar

hemodynamic parameters [9]. In addition, HA 330 treatment was reported to reveal no improvement of vasopressor usage in critically ill patients [16].

Our study results showed that although not statistically significant, serum IL-1β, IL-6, IL-8, TNF-a, HMGB-1, and IL-10 levels decreased by 11.5%, 26.4%, 11.4%, 37.9%, 0.02%, and 35.5%, respectively, during HA 330 treatment. In a prospective study in 44 critically ill ICU patients with severe sepsis or septic shock by Huang et al. [9], it was analyzed efficiency of HA 330 resin cartilage in two groups, critically ill patients receiving only standard ICU treatment (full ICU care composed of fluid resuscitation, vasopressor treatment, antibiotic therapy, and ventilation support) and critically ill patients receiving in combination with the standard ICU treatment plus hemoperfusion treatment. Patients who received hemoperfusion treatment had statistically significant decreased serum IL-6 and IL-8 levels [9]. In a recent prospective study in 32 critically ill patients receiving HA 330 therapy by Koc et al. [17], serum IL-6, IL-8, IL-10, and TNF-a levels were reported to significantly decrease with hemoadsorption treatment. Our findings revealed a nonstatistically significant slightly lower decrease in inflammatory cytokines in patients treated with HA 330 than reported in the abovementioned studies, which seems to be related to larger sample size of these studies as well as the higher mortality rate. On the other hand, a study performed in 96 septic shock patients found that there was no statistically significant difference between serum IL-6 levels of patients with and without cytokine adsorption. Moreover, mortality was higher in the cytokine adsorption group (HR: 1.82, 95% CI: 1.03–3.2, $p = 0.038$) (control: 20 [42%], cytokine adsorption: 32 [67%], $p = 0.024$) [23]. Zuccari et al. [24] reported that only plasma IL-8 levels were decreased in the first 24 h of cytosorb adsorber treatment, with no statistically significant change in plasma TNF-a, IL 1-β, IL-6, and IL-10 levels in 10 patients with sepsis or septic shock receiving cytosorb adsorber. Moreover, our results showed no statistically significant change in serum inflammatory markers unlike CRP and procalcitonin. We believe that these results were due to our small size of study sample.

This study has some limitations. First, the lack of control group treated with CRRT alone seems to be the major limitation, given the likelihood of concomitant CRRT and antibiotic treatment also to decrease the inflammatory markers. Second, our study is case series; therefore, study sample was small size. Third, lack of data on certain hemodynamic parameters such as preload, afterload, and cardiac output is another limitation.

In conclusion, our findings revealed that use of HA 330 treatment and CRRT was associated with significant decrease in SOFA score and inflammatory markers including WBC, CRP, and procalcitonin levels, with no significant alteration in inflammatory cytokine levels, hemodynamic parameters, and vasopressor treatment. The efficacy of HA 330 needs to be further investigated in larger sample randomized controlled studies with a longer-term follow-up.

Statement of Ethics

The study was performed in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by Erciyes University Ethics Committee (date of approval: January 09, 2019: Protocol No: 2019/09). Written informed consent was obtained from each participant or from his/her legal guardian.

Conflict of Interest Statement

The authors declare no competing interests.

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Author Contributions

Sevda Onuk, Aynur Karayol Akin, Ali Sari, Kursat Gundogan, Gulden Baskol, Kudret Dogru, and Murat Sungur designed the study, contributed to the interpretation of the results, and critically revised the manuscript. Sevda Onuk, Aynur Karayol Akin, Kursat Gundogan, and Murat Sungur performed the statistical analysis, drafted the manuscript, and interpreted the data. Sevda Onuk and Ali Sari made a substantial contribution to the acquisition of the data. Sevda Onuk, Aynur Karayol Akin, Kursat Gundogan, Kudret Dogru, and Murat Sungur made a substantial contribution to the study design. Sevda Onuk, Ali Sari, and Gulden Baskol gave an important contribution in statistical revision and data interpretation. All authors had full access to the data, take responsibility for the integrity of the data and the accuracy of the analysis, and have read and approved of the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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