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The effect of HA330 hemoperfusion adsorbent method on inflammatory markers and end-organ damage levels in sepsis: a retrospective single center study

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Abstract. – OBJECTIVE: **In this study, we aimed at evaluating the impact of HA330 hemoperfusion adsorbent application on inflammatory markers and end-organ damage markers in patients with sepsis/septic shock.**

PATIENTS AND METHODS: **Patients who were diagnosed with sepsis/septic shock and treated with HA330 hemoperfusion adsorbent in addition to the standard treatment were included in this retrospective study conducted at Inonu University Turgut Ozal Medical Center between January 1, 2019 and January 1, 2021.**

RESULTS: **A total of 150 patients were included in the study. The mean±SD age of the patients was 51.9±17.7 years. 102 patients (68%) were in septic shock. Mean±SD APACHE II scores were 15.3±4.8. The need for mechanical ventilation was noted in 64 patients (42.7%). WBC, neutrophil count, hemoglobin, platelet count, BUN, creatinine, AST, ALT, CRP and procalcitonin levels were measured before and after the procedure. Overall, 104 patients (69.3%) died median (min-max) 2.5 (1-114) days after the cytokine adsorption, while 46 patients (30.7%) recovered from sepsis and were discharged. The increase in BUN levels and decrease in platelet count after the procedure were statistically significant ($p \leq 0.001$, 0.041, respectively) in the overall study population. The laboratory findings in 46 survivors indicated significantly decreased AST and ALT levels after cytokine adsorption compared to baseline pre-treatment levels. WBC, neutrophil count, CRP, procalcitonin, BUN and creatinine values were also decreased after cytokine adsorption in survivors, whereas the change was not statistically significant. There was also a non-significant tendency for an increase in platelet count and hemoglobin levels after cytokine adsorption compared to pre-treatment values in these patients.**

CONCLUSIONS: **Although no effect of HA330 hemoperfusion application on inflammatory markers and end-organ damage markers was demonstrated in our study, we used the HA330 hemoperfusion adsorbent method as a last resort in terminal patients with a mortality rate of approximately 90% and for whom antibiotic treatment did not benefit. Therefore, multicenter, prospective studies are needed to clarify the effect of early HA330 hemoperfusion use in the treatment of sepsis.**

Key Words:
HA330 hemoperfusion adsorbent method, Sepsis, Septic shock, Inflammatory markers, End-organ damage markers.

Introduction

Sepsis has a clinical spectrum that ranges from infection and bacteremia to severe sepsis, organ dysfunction and septic shock. Patients with suspected or proven sepsis ordinarily present with tachycardia, hypotension, fever and leukocytosis[1].

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The estimates on the global incidence and mortality of sepsis in the 1995-2015 period revealed the annual incidence of sepsis to be 437 per 100,000 person-years with approximately 11 million deaths due to sepsis annually, accounting for 19.7 % of all global deaths[2].

Sepsis is a life-threatening condition with mortality rates which range from 10 to 52%[3-5]. Mortality rates significantly differ according to severity, as reported to be 10% for sepsis-related mortality and 40% for septic shock-related mortality[1].

Early initiation of fluids and antibiotics are the treatment priorities in sepsis. Besides the treatments with proven efficacy, there are also experimental treatment modalities. The use of hemadsorption together with cytokine and toxin inactivators is considered a promising adjunctive therapy in the treatment of sepsis[6,7].

Removal of inflammatory mediators by extracorporeal blood purification methods has been reported to be an effective treatment modality in patients with sepsis and septic shock[8,9]. HA330 hemoperfusion adsorbent application is a method used for cytokine apheresis that can extract cytokines and other medium molecular weight toxins from the circulation. It is a high flow, low resistance cytokine adsorbent containing polymer beads with a large adsorption surface[10].

Representing the largest case series in the literature on the efficacy of HA330 hemoperfusion adsorbent application in sepsis, the present study aimed to evaluate the changes in inflammatory markers and organ dysfunction in patients with sepsis/septic shock who received HA330 hemoperfusion adsorbent in our hospital for varying clinical reasons over 2 years.

Patients and Methods

Patients who were diagnosed with sepsis or septic shock and treated with HA330 hemoperfusion adsorbent across different units [hematology ward, bone marrow transplantation unit, general intensive care unit (ICU), surgery ICU, reanimation ICU and COVID-19 ICU] of the Inonu University Turgut Ozal Medical Center Hospital were included in this retrospective study conducted between January 1, 2019, and January 01, 2021. This study was approved by the Inonu University Faculty of Medicine Ethics Committee (Date of Approval: 26/01/2021, Reference number: 2021/1567).

Sepsis was diagnosed according to the Third International Consensus Definitions for Sepsis and Septic Shock[1]. Septic shock was considered in patients who need for vasopressors to maintain mean arterial pressure ≥ 65 mm Hg and serum lactate levels above 2 mmol / L (> 18 mg/dL), despite adequate fluid therapy[1]. Severity of illness scores, using Acute Physiological and Chronic Health Assessment-II (APACHE-II) scoring system, was recorded to predict mortality in general ICU patients[11].

All patients received HA330 hemoperfusion adsorbent with HA330 resin cartridge once a day for 3 to 5 following days. A double-lumen catheter was inserted in the internal jugular or femoral vein for blood access. Each hemoperfusion session lasted from 2.5 to 3 hours. Enoxaparin was used as an anticoagulant. Treatment was carried out as outlined in the company's user manual. In this method, filters retain inflammatory mediators between 10-60 kilodaltons.

Data on inflammatory markers [procalcitonin (PCT) and C-reactive protein (CRP)] and organ dysfunction markers including blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST) levels were recorded before and after the procedure. Laboratory reference ranges were as follows: PCT (0-0.5 ng/mL), CRP (0-0.35 mg/dL), BUN (5.1-16.8 mg/dL), creatinine (0.57-1.25 mg/dL), ALT (0-55 U/L) and AST (5-34 U/L).

Statistical Analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was investigated by Shapiro-Wilk's test. The change in laboratory values before and after the procedure was analyzed with the Wilcoxon test. Data were expressed as mean ± standard deviation (SD), median (minimum-maximum) and percentage (%) where appropriate. $p<0.05$ was considered statistically significant.

Results

A total of 150 patients were included in the study. All patients received a median of 3 sessions and a total of 559 sessions of HA330 hemoperfusion. The baseline demographic and clinical characteristics of the patients are summarized in Table I.

Overall, 104 patients (69.3%) died median (min-max) 2.5 (1-114) days after the cytokine adsorption, while 46 patients (30.7%) recovered from sepsis and were discharged.

Table I. Baseline characteristics.

Age (years), mean ± SD	51.9 ± 17.7
Sex (Female/male), n	49/101
Body mass index (kg/m^2), mean ± SD	24.4 ± 4
Septic shock, n	102 (68)
APACHE II score, mean ± SD	15.3 ± 4.8
Infection site, n (%)	
Intra-abdominal	30 (20)
Pulmonary	80 (53.4)
Urinary tract	12 (8)
Skin and soft tissue	14 (9.3)
Other or unknown	14 (9.3)
Source of infection, n (%)	
Community-acquired	32 (21.3)
Hospital-acquired	118 (78.7)
Pathogen, n (%)	
Gram positive bacteria	28 (18.7)
Gram negative bacteria	31 (20.7)
Fungus	15 (10)
Virus	4 (2.6)
Mixed	41 (27.3)
Unknown,	31 (20.7)
Mechanical ventilation, n (%)	64 (42.7)

The increase in BUN level and decrease in platelet count after the procedure were statistically significant ($p \leq 0.001$, 0.041, respectively). The change of laboratory parameters before and after the application of cytokine adsorption in the overall study population is provided in Table II.

The pre- and post-procedural laboratory findings of patients who survived with early use (median 62 hours) of HA330 hemoperfusion are provided in Table III. The laboratory findings in 46 survivors indicated significantly decreased AST and ALT levels after cytokine adsorption compared to baseline pre-treatment levels. While WBC, neutrophil count, CRP, procalcitonin, BUN and creatinine values were also decreased after cytokine adsorption in survivors, the change was not statistically significant. There was also a non-significant tendency for increase in platelet count and hemoglobin levels after cytokine adsorption compared to pre-treatment values.

Discussion

Hemadsorption, a blood purification technique, represents a potentially useful therapeutic modality in the severe sepsis by removing inflammatory cytokines from the blood. The membranes used in this treatment modality have high adsorption capacity due to both high permeability and good biocompatibility of adsorption membranes, as well as the fast adsorption speed.

In a prospective study by Kaçar et al[12] on the results of HA330 hemoperfusion applied for 2 hours a day for 3 days in 23 patients with sepsis, a statistically significant decrease in CRP and procalcitonin levels was reported after the second application (p=0.002 and p=0.018, respectively)[12]. In our retrospective study, however, no significant changes were observed in CRP and procalcitonin levels after HA330 hemoperfusion (p=0.352 and p=0.927, respectively).

In a study by Huang et al[13] with 44 sepsis/septic shock patients who received either standard treatment (n=20) or standard treatment plus HA330 hemoperfusion (n=24), IL-6 and IL-8 levels were reported to be significantly lower in the standard treatment plus HA330 hemoperfusion group compared to standard treatment (control) group. The sequential organ failure assessment (SOFA) scores revealed no significant difference between treatment groups from the onset to the 7th day of treatment, whereas SOFA scores significantly improved in the standard treatment plus HA330 hemoperfusion group on the 14th day[13]. Since our study was retrospective and IL-6 and IL-8 were not analyzed, possible changes in these parameters could not be reported.

Table II. Laboratory parameters before and after cytokine adsorption overall.

Median (min-max)	Before cytokine adsorption	After cytokine adsorption	*p*-value
Platelet count (×10^9/L)	54 (3-647)	41 (2-588)	**0.041**
CRP (mg/L)	11.3 (0.3-125)	10 (0.3-45.9)	0.352
Hemoglobin (g/dl)	9.3 (5-15.9)	9.2 (5.5-14.9)	0.203
WBC (×10^9/L)	5.33 (0-116.67)	5.32 (0.01-139)	0.227
Neutrophil count (×10^9/L)	5 (0-94.3)	3.85 (0-95.8)	0.626
Procalcitonin (ng/mL)	2.49 (0.05-100.1)	2.21 (0.09-100)	0.927
BUN (mg/dl)	27.95 (3.03-167.84)	37.38 (3.03-125)	**< 0.001**
Creatinine (mg/dl)	0.91 (0.4-5.21)	0.9 (0.4-10.68)	0.057
AST (IU/L)	35 (3-3,885)	42 (6-4,202)	0.206
ALT (IU/L)	27 (6-2,171)	29 (5-4,013)	0.021

Table III. Laboratory parameters before and after cytokine adsorption in survivors.

Median (min-max)	Before cytokine adsorption	After cytokine adsorption	*p*-value
Platelet count (×10^9/L)	64 (3-647)	90 (2-368)	0.743
CRP (mg/L)	4.97 (0.3-32.2)	3.13 (0.3-31)	0.175
Hemoglobin (g/dl)	8.1 (5.9-14)	9.7 (7.1-14.9)	0.899
WBC (×10^9/L)	5.95 (0-51.7)	5.21 (0.03-50.5)	0.924
Neutrophil count (×10^9/L)	4.82 (0-46.6)	3.61 (0-47.4)	0.608
Procalcitonin (ng/mL)	1.08 (0.05-100.1)	0.74 (0.09-100)	0.201
BUN (mg/dl)	19.16 (3.03-115.07)	18.01 (3.03-124.29)	0.798
Creatinine (mg/dl)	0.83 (0.43-4.16)	0.74 (0.4-2.96)	0.154
AST (IU/L)	27 (7-3,177)	24 (6-289)	**0.024**
ALT (IU/L)	42 (6-1,662)	39 (5-241)	**0.017**

Uğur et al[14] investigated the inflammatory blood parameters including copeptin, interleukin-6, procalcitonin, CRP, erythrocyte sedimentation rate (ESR), WBC count, and creatinine levels before and after Cytosorb administration in 34 patients diagnosed with sepsis. A significant decrease was reported in the copeptin, interleukin-6, procalcitonin, CRP and ESR levels after the procedure. The authors considered the decrease in inflammatory cytokines *via* Cytosorb administration in sepsis patients to be potentially helpful in preventing cytokine storm and enabling clinical improvement[14]. In our study, however, no significant changes were observed in inflammatory markers.

In a meta-analysis of 37 randomized controlled trials in 2,499 patients with sepsis or septic shock who received hemoperfusion, hemofiltration and plasmapheresis (as a blood purification technique) by Putzu et al[15], the authors concluded that, with very low-quality randomized evidence, use of hemoperfusion, hemofiltration or plasmapheresis can reduce mortality in sepsis or septic shock[15]. In a meta-analysis of 39 studies involving 2,729 sepsis patients treated with extracorporeal blood purification techniques by Snow et al[16], hemofiltration, endotoxin removal devices and non-specific adsorption devices were concluded to be associated with survival benefit. Cytokine removal or combined hemofiltration and adsorption processes were found not to be associated with survival benefit[16]. Since there was no control group in our study, the effect of HA330 hemoperfusion application on mortality could not be evaluated.

Although no significant effect of HA330 hemoperfusion application on inflammatory markers or end-organ damage markers was demonstrated in our study, we consider the use of HA330 hemoperfusion in the early period to be beneficial. In our patients, APACHE-2 scores were high, and end-organ damage due to sepsis probably developed prior to HA330 hemoperfusion in most of them. Therefore, we did not observe sufficient laboratory and clinical improvement in patients who underwent late procedures (>72 hours). No study to date investigated the effectiveness of the early use (first 72 hours) of HA330 hemoperfusion in the treatment of sepsis. In our study, we observed that patients who underwent HA330 hemoperfusion within 62 hours after the diagnosis of sepsis benefited from the treatment. Besides, there was a non-significant tendency for decrease in WBC, neutrophil count, CRP, procalcitonin, BUN and creatinine values in 46 surviving patients along with significantly decreased AST and ALT levels. In addition, albeit not significant, an increase was noted in platelet count and hemoglobin levels after the procedure among survivors.

Limitations

The major limitations of our study are its retrospective design, the absence of a control group, and the fact that the patient group was selected from a group with heterogeneous background high mortality. Prospective and randomized studies with larger numbers of patients are needed to clarify the effect of early HA330 hemoperfusion use in the treatment of sepsis.

Conclusions

Our findings revealed that the healing effect of HA330 hemoperfusion application on infection markers and end-organ damage markers (liver damage markers in particular) were observed in early use. This study may be valuable in demonstrating the benefit of early use of HA330 hemoperfusion therapy in sepsis.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Ethics Approval
This study was approved by the Inonu University Faculty of Medicine Ethics Committee (Date of Approval: 26/01/2021, Reference number: 2021/1567).

Authors' Contribution
Writing-review & editing: Ahmet Sarıcı, Ayşe Belin Özer, Mustafa Said Aydogan; Supervision: Mehmet Ali Erkurt, Ayşe Belin Özer, İrfan Kuku, Adem Kose, İlhami Berber; Validation: Mehmet Ali Erkurt; Visualization: Mehmet Ali Erkurt, Emin Kaya; Conceptualization: Ahmet Sarıcı, İlhami Berber; Data curation: Ahmet Sarıcı, İlhami Berber, Mustafa Özgül, Muhammed Furkan Keser; Investigation: Ahmet Sarıcı, Soykan Biçim, Volkan Ince, Emrah Otan, Mustafa Özgül, Muhammed Furkan Keser; Project administration: İrfan Kuku, Funda Memisoglu; Resources: İrfan Kuku, Adem Kose, Funda Memisoglu; Software: İrfan Kuku, Emin Kaya, İlhami Berber, Muhammed Furkan Keser; Formal analysis: Soykan Biçim, Volkan Ince, Emrah Otan; Methodology: Emin Kaya.

Informed Consent
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Data Availability
The data supporting this article are available from the corresponding author on reasonable request.

References

1) Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, Poll TVD, Vincent JL, Angus DC. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016; 315: 801-810.
2) Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, Angus DC, Reinhart K. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. Am J Respir Crit Care Med 2016; 193: 259-272.
3) Winters BD, Eberlein M, Leung J, Needham DM, Pronovost PJ, Sevransky JE. Long-term mortality and quality of life in sepsis: a systematic review. Crit Care Med 2010; 38: 1276-1283.
4) Epstein L, Dantes R, Magill S, Fiore A. Varying estimates of sepsis mortality using death certificates and administrative codes—United States, 1999-2014. MMWR 2016; 65: 342-345.
5) Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. Crit Care Med 2007; 35: 1244-1250.
6) Cruz DN, Antonelli M, Fumagalli R, Foltran F, Brienza N, Donati A, Malcangi V, Petrini F, Volta G, Pallavicini FMB, Rottoli F, Giunta F, Ronco C. Early use of polymyxin B hemoperfusion in abdominal septic shock: the EUPHAS randomized controlled trial. JAMA 2009; 301: 2445-2452.
7) Iwagami M, Yasunaga H, Doi K, Horiguchi H, Fushimi K, Matsubara T, Naoki Y, Eisei N. Postoperative polymyxin B hemoperfusion and mortality in patients with abdominal septic shock: a propensity-matched analysis. Crit Care Med 2014; 42: 1187-1193.
8) Honore PM, Hoste E, Molnár Z, Jacobs R, Joannes-Boyau O, Malbrain ML, Forni LG. Cytokine removal in human septic shock: Where are we and where are we going? Ann. Intensive Care 2019; 9: 1-13.
9) Klein D, Foster D, Walker P, Bagshaw S, Mekonnen H, Antonelli M. Polymyxin B hemoperfusion in endotoxemic septic shock patients without extreme endotoxemia: a post hoc analysis of the EUPHRATES trial. Intensive Care Med 2018; 44: 2205-2212.
10) Zhang J, Peng Z, Maberry D, Volpe J, Kimmel JD, Federspiel WJ, Kellum JA. Effects of hemoadsorption with a novel adsorbent on sepsis: in vivo and in vitro study. Blood Purif. 2015; 39: 239-245.
11) Ho KM, Dobb GJ, Knuiman M, Finn J, Lee KY, Webb SA. A comparison of admission and worst 24-hour Acute Physiology and Chronic Health Evaluation II scores in predicting hospital mortality: a retrospective cohort study. Crit Care 2005; 10: 1-8.
12) Kaçar CK, Uzundere O, Kandemir D, Yektaş A. 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. Blood Purif 2020; 49: 448-456.

13) 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; 14: 596-602.
14) Uğur BK, Çiçek H, Kul S, Mete Ö, Yılmaz M. Effect of a novel extracorporeal cytokine apheresis method on endocan, copeptin and interleukin-6 levels in sepsis: An observational prospective study. Transfus Apher Sci 2020; 59: 102919.
15) Putzu A, Schorer R, Lopez-Delgado JC, Cassina T, Landoni G. Blood purification and mortality in sepsis and septic shock: a systematic review and meta-analysis of randomized trials. Anesthesiology 2019; 131: 580-593.
16) Snow TA, Littlewood S, Corredor C, Singer M, Arulkumaran N. Effect of Extracorporeal Blood Purification on Mortality in Sepsis: A Meta-Analysis and Trial Sequential Analysis. Blood Purif 2020: 1-11.