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Analysis of the effects of ha-330 hemo adsorption column application on mortality and morbidity of adult patients with sepsis in general intensive care unit

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Abstract

Sepsis is a leading cause of mortality and morbidity in critical care units. The objective of this study is to evaluate if using the HA-330 Sepsis Adsorption Column in the intensive care unit reduces mortality and morbidity in patients with sepsis. This study was designed as a retrospective study evaluating demographic and laboratory parameters in the General Intensive Care Unit. The study involved 200 sepsis patients who were followed in the critical care unit between June 2019- December 2020 and were treated with the HA-330 Sepsis Adsorption Column. The length of hemoperfusion in patients who died was statistically significantly longer than in patients who recovered. The mean lactate and the hemoperfusion time/day value had a weak but significant negative correlation. In the recovery and death observations, the improvements in repeated C-reactive protein and Procalcitonin measurements were statistically significantly different. The differences in repeated pH and lactate measurements in the recovery and mortality observations were statistically identical, according to the observations. Sepsis-related deaths are a severe issue in critical care units. HA-330 Sepsis Adsorption Column, it can be thought that it can be an inexpensive, useful, and effective method that can be used in the prognosis of the patients. In antibiotic-resistant sepsis, hemoperfusion may be recommended.

Keywords: Sepsis adsorption column, sepsis, hemoadsorption, intensive care, mortality, morbidity

Introduction

Sepsis is described as a life-threatening organ failure induced by a dysregulated immune response to infection in the host [1, 2]. Septic shock is defined as the necessity for vasopressors to maintain mean arterial pressure above 65 mmHg and a serum lactate level of more than 2 mmol/L despite sufficient fluid resuscitation [2]. If the systemic inflammatory response (SIRS) is not suppressed, severe sepsis, septic shock, and multi-organ failure develop, and mortality and morbidity increase [3].

Sepsis is a catastrophic medical condition that affects immunocompromised patients, children, newborns, and the elderly, and is caused by the immune system's destructive response to infections [4]. Despite significant advances in contemporary medicine such as immunization, the use of powerful antibiotics, and effective intensive care procedures, the prevalence of sepsis has increased dramatically [5, 6].

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The patient's sepsis response is a complicated process including inflammatory and anti-inflammatory processes, cellular and humoral reactions, and circulatory system abnormalities [7]. Due to the nonspecific and highly unpredictable nature of the clinical signs and symptoms associated with sepsis, researchers are still looking for a quick test to diagnose and assess sepsis severity. Biomarkers are regarded to be valuable in this respect since they may indicate the absence, presence, or severity of sepsis, be used to do a clinical follow-up on patients, be classified, and predict sepsis prognosis. Biomarkers can also be used to manage antibiotic therapy, assess patient response to treatment and recovery from sepsis, distinguish between bacterial, viral, and fungal infections, and distinguish systemic from local infections [8, 9].

Hundreds of biomarkers have been investigated to determine whether they can be utilized to diagnose sepsis. Among these biomarkers; C-reactive protein (CRP), interleukins, procalcitonin (PCT), lactate, presepsin, and tumor necrosis factor-alpha are particularly notable [8, 10].

CRP is a pentameric acute-phase protein of hepatic origin found in the blood. CRP has the potential to attach to certain molecular configurations that are prevalent on the surfaces of pathogens or occur during apoptosis or necrosis, resulting in increased plasma

concentrations during inflammation. It has been suggested that CRP contributes to defense, especially with the innate immune response, due to its increased synthetic ability within hours following infection or inflammation [11].

PCT is the 116-amino-acid precursor protein of the calcitonin hormone, which is normally released by the thyroid gland's medullary neuroendocrine C cells in response to elevated calcium levels in the blood [12]. PCT is a chemokine that modulates the migration of monocytes to infection sites throughout the body. Furthermore, during sepsis, it promotes the generation of pro-inflammatory cytokines [13].

Lactate measurement is not a predictive factor, although it is an excellent predictor of multiple organ failure and mortality, especially in septic shock patients [14].

The study's goal is to examine whether treating patients with sepsis using the HA-330 Sepsis Adsorption Column lowers mortality and morbidity while they are being monitored in the critical care unit. For this main purpose, the relationship between serum CRP, PCT, pH, and lactate parameters in sepsis patients who underwent HA-330 Sepsis Adsorption Column was investigated.

Materials and Methods

This study was designed as a retrospective study evaluating demographic and laboratory parameters in the General Intensive Care Unit. The study involved 200 sepsis patients who were followed in the critical care unit between June 2019 - December 2020 and were treated with the HA-330 Sepsis Adsorption Column. Exclusion criteria for the study were individuals under the age of 18 and above the age of 80, patients with bleeding diathesis, and patients with neurodegenerative disorders.

The study protocol was permitted by Ethics Committee and the Ministry of Health. Number was given 2019/27-14 by Ethics Committee. The study was completed according to the mandates of the Helsinki Declaration. Conscious patients and legal guardians of unconscious patients were given complete information about the study, and their agreement to use their data was obtained.

Study protocol

HA-330 (HP, HA cartridge, Jafron Biomedical Co Zhuhai, China) in combination with HP / Continuous Renal Replacement Therapies (CRRT) was initiated. Before the onset of HP CRRT, the patients have oliguria (urine 400 cm 3 in 24 hours). After HA-330, the urine output of the patients reaches 1100 cm^3 in 24 hours, the CRRT mode used is as follows; continuous veno venous hemofiltration (CVVH) pre- dilution and post -dilution every 2 hours, blood flow 200-250 mL / minunte, substitution flow 25 cm 3/kg/UF, rate 20 cm^3 / heparin 10 U/kg/ hour, patient weight 70 kg. The HP cartridge was added to the CRRT circuit simultaneously with the start of CRRT, and HP and CRRT were started simultaneously. After 6 hours, the HP cartridge was removed from the CRRT circuit, and CRRT was continued. After 20 hours, the second HP cartridge was added to the CRRT circuit, and it was used for 6 hours and then removed. The fluid balance was maintained neutral[15].

Data collection method

The laboratory tests and evaluations obtained before and after the application of the HA-330 Hemoadsorption Sepsis Column were collected from the patients who were followed up in accordance with the sepsis criteria by the responsible investigators working in the intensive care unit. The data for the study's sample of sepsis patients was initially gathered from patients who were followed up on according to sepsis criteria by the relevant investigators in the critical care unit. Biochemical and specific sepsis parameters known to be effective on patient prognosis were assessed as part of the patients' laboratory examinations. Furthermore, patient demographic data (age, gender, disease information, risk factors, etc) was collected from patient files on a regular basis and recorded into a Microsoft Office Excel file.

Definitions

Systemic Inflammatory Response Syndrome (SIRS) [16]: SIRS includes 2 or more of the following: Temperature greater than 38 C or less than 36 C, Heart rate greater than 90 beats per minute, Tachypnea greater than 20 breaths per minute or PaCO2 less than 32 mm Hg, White blood cell (WBC) count greater than 12,000 per cubic millimeter or fewer than 4000 per cubic millimeter, or greater than 10% immature (band) forms

Sepsis: SIRS as the result of an infection

Severe Sepsis: Sepsis associated with organ dysfunction (1 or more), hypo-perfusion abnormality, or sepsis-induced hypotension; Hypo-perfusion abnormalities may include but are not limited to lactic acidosis, oliguria, or acute change in mental status

Septic Shock Sepsis-induced hypotension despite adequate fluid resuscitation

Statistical analysis

In the statistical analysis of the data obtained in the study, SPSS (23.0 Version) program was used. The suitability of the data to normal distribution was examined with the Kolmogorov Smirnov test, Student's t-Test was used to compare normally distributed features in two independent groups, and the Mann-Whitney U Test was used to compare non-normally distributed features in two independent groups. The features that did not show a normal distribution at repetitive times were corrected with the Friedman Test and the Post-hoc Test and examined with the Wilcoxon Test. Differences of repeated measurements in prognosis and exitus groups were examined by two-way ANOVA test in repeated measurements. The relationship of categorical features with groups was examined using the Chi-square Test. As descriptive statistics, mean ± standard deviation, median for numerical variables and number and % values for categorical variables are given. In statistical analysis, $p<0.05$ value was accepted as significant.

Results

The distribution of demographic and clinical characteristics of the patients included in the study is given in Table 1.

Table 2 shows the results of a comparison of laboratory parameters based on the duration of hemoperfusion and length of stay in the intensive care unit of the patients in the study.

Table 1. Distribution of demographic and clinical characteristics of the patients

	Median	Mean±SD	Min-max
Age	71	68.61±14.29	20-103
Hemoperfusion duration	7	5.69±1.89	1-11
Intensive care stay (day)	16.5	31.34±47.35	2-425
Comorbidity number	3	2.45±1.15	0-4
Male n (%)	122 (61)		
Comorbidity 1	188 (94)		
Comorbidity 2	156 (78)		
Comorbidity 3	104 (52)		
Comorbidity 4	41 (21)		
Exitus / Recovered	145/55 (72.5/27.5)		

n=200

A moderate positive correlation was found between PCT mean and Lactate baseline levels, as indicated in Table 2 (r=0.461,p=0.001). The mean lactate and the hemoperfusion time/day value had a weak but significant negative correlation (r=-0.307,p=0.001).

In Table 3, the recovered and death patients' parameters are compared. The age and length of stay in the intensive care unit of patients who recovered and died had no statistically significant differences (p>0.05). The length of hemoperfusion in patients who died was statistically significantly longer than in patients who recovered, as shown in Table 3 (p=0.001).

The change in repeated CRP measurements in the observations with recovery and death was statistically significant, according to the findings of a two-way repeated ANOVA analysis (p<0.05). In other words, the variation in repeated CRP tests is an essential component in recovery and mortality.

Table 2. Results of comparing the hemogram parameters of the patients according to the duration of hemoperfusion and length of stay in the intensive care unit

Parameters		PCT (initial)	pH (initial)	Lactate	Hemoperfusion duration/day	Intensive care unit duration	Comorbidity number
CRP (initial)	r	-.023	.130	-.001	-.009	-.054	-.050
	p	.751	.076	.993	.905	.459	.498
	n	188	188	188	188	188	188
PCT (initial)	r	1	-.025	.178*	-.012	-.052	.009
	p		.721	.012	.869	.466	.903
	n	200	200	200	200	200	200
pH (initial)	r		1	.026	.043	.030	.049
	p			.713	.544	.671	.495
	n		200	200	200	200	200
Lactate (initial)	r			1	-.167*	-.076	-.026
	p				.018	.282	.710
	n			200	200	200	200
CRP (mean)	r	-.041	.077	.057	-.250**	-.060	-.162*
	p	.564	.277	.424	.000	.399	.022
	n	200	200	200	200	200	200
PCT (mean)	r	.730**	-.027	.461**	-.158*	-.115	-.063
	p	.000	.701	.000	.025	.105	.372
	n	200	200	200	200	200	200
pH (mean)	r	-.019	.521**	.041	.051	.120	.050
	p	.794	.000	.569	.469	.092	.486
	n	200	200	200	200	200	200
Lactate (mean)	r	-.013	-.034	.652**	-.307**	-.151*	.039
	p	.850	.628	.000	.000	.033	.584
	n	200	200	200	200	200	200
CRP (7. day)	r	.045	-.200*	-.049	.112	-.162	-.012
	p	.658	.038	.614	.250	.095	.903
	n	101	108	108	108	108	108
PCT (7. day)	r	-.179	.170	-.009	-.016	-.165	.035
	p	.075	.081	.930	.872	.090	.719
	n	100	107	107	107	107	107
pH (7. day)	r	.153	-.089	-.025	.035	.070	-.112
	p	.128	.363	.796	.720	.473	.250
	n	100	107	107	107	107	107
Lactate (7. day)	r	-.113	-.231*	-.021	.015	.048	.098
	p	.263	.017	.827	.876	.622	.316
	n	100	107	107	107	107	107

r: Spearman correlation coefficient; * p <0.05; ** p <0.001

Table 3. The comparison of recovered and death patients' parameters

	Recovered Avg±SD	Death Avg±SD	p
Age (median)	69.52±13.67 (73)	66.18±15.66 (68)	0.103
Intensive Care Unit duration (median)	45.88±3.141 (16)	46.73±7.308 (17)	0.168
Hemoperfusion duration/ (median)	5.36±2.00 (6)	6.56±1.21 (7)	0.001
Comorbidty number	2.52±1.11 (3)	2.21±1.25 (2)	0.114
Gender (n:%)			
Male	90 (62.1)	32 (58.2)	0.614
Female	55 (37.9)	23 (41.8)	
Comorbidity (n:%)			
Comorbidity 1	138 (95.2)	50 (90.9)	0.257
Comorbidity 2	118 (81.4)	38 (69.1)	0.061
Comorbidity 3	79 (54.5)	25 (45.5)	0.254
Comorbidity 4	31 (21.4)	10 (18.2)	0.617
CRP (median)			
T1	190.22±97.56 (184.2)	208.26±80.57 (194.6)	0.199
T2	176.67±90.77 (172.3)	184.57±80.20 (172.7)	0.573
T3	158.35±81.88 (148.1)	146.71±64.32 (129.5)	0.441
T4	143.28±79.36 (136.5)	116.46±53.85 (107.6)	0.030
T5	135.06±85.48 (125.6)	102.90±55.02 (92.2)	0.037
T6	127.87±79.96 (117.5)	86.46±50.83 (75.6)	0.002
T7	120.71±72.41 (105.3)	82.93±50.23 (77.7)	0.009
	40.014	40.001	
PCT (median)			
T1	13.29±20.98 (4.6)	15.41±20.76 (5.9)	0.335
T2	13.67±22.88 (5.9)	11.26±16.58 (4.5)	0.788
T3	12.44±20.73 (5.4)	6.44±7.42 (2.9)	0.086
T4	8.71±14.42 (4.1)	6.78±17.49 (3.1)	0.053
T5	7.05±9.43 (3.5)	4.40±7.85 (2.7)	0.039
T6	4.65±6.77 (2.4)	3.25±7.07 (1.3)	0.061
T7	4.61±5.72 (2.4)	2.26±4.26 (1.1)	0.006
	40.001	40.001	
pH (median)			
T1	110.12±871.46 (7.4)	7.44±0.12 (7.5)	0.273
T2	60.90±628.53 (7.4)	7.46±0.09 (7.5)	0.013
T3	66.29±666.06 (7.4)	7.47±0.08 (7.5)	20.006
T4	72.02±689.76 (7.4)	7.47±0.07 (7.5)	0.017
T5	7.41±0.15 (7.5)	7.47±0.07 (7.5)	0.029
T6	189.90±1161.30 (7.4)	7.48±0.07 (7.5)	0.003
T7	7.38±0.42 (7.4)	7.48±0.06 (7.5)	0.019
	40.628	40.595	
Lactate (median)			
T1	2.27±0.42 (7.4)	1.74±1.06 (1.6)	0.001
T2	2.19±1.75 (1.8)	1.63±0.81 (1.5)	0.015
T3	2.15±1.46 (1.9)	1.47±0.70 (1.3)	<0.001
T4	2.12±1.80 (1.7)	1.34±0.69 (1.2)	0.001
T5	2.44±2.37 (1.9)	1.34±0.76 (1.2)	0.001
T6	2.00±1.61 (1.7)	1.29±0.62 (1.2)	0.001
T7	2.03±1.64 (1.5)	1.27±0.69 (1.1)	0.001
	40.109	40.001	

[1]Student's t-Test; [2]Mann-Whitney U Test; [3]Chi Square (Yates) Correction; [4]Friedman Test, *According to the initial value, it shows statistical significance according to the Friedman post hoc test ($p < 0.05$].

According to the results of two-way repeated ANOVA analysis, it was observed that the change of repeated PCT measurements in the observations with recovery and death was statistically significantly different ($p<0.05$). In other words, the change of PCT repeated measurements is an effective factor in recovery and mortality.

The change of repeated pH measurements in the observations with recovery and death was statistically similar ($p>0.05$), according to the results of two-way repeated ANOVA analysis.

The change of repeated lactate measurements in the observations of recovery and mortality was statistically similar ($p>0.05$), according to the results of two-way repeated ANOVA analysis.

Discussion

Since there is currently no effective pharmacological treatment for sepsis, early diagnosis, resuscitation, and emergency treatment with appropriate antibiotics are crucial to reducing the disease's burden. In many countries, the attention focused on national or regional screening and quality improvement programs emphasizing on early diagnosis and emergency treatment has resulted in decreased sepsis rates of morbidity and mortality. Although early diagnosis and advanced treatment of acute episodes are essential steps in reducing sepsis-related mortality and disability in the treatment of persistent sepsis, a significant decrease in sepsis-related disease burden requires efforts across the health system.

There are studies in the literature that show varied results on male and female gender ratios in sepsis patients. As in this study, there are research that demonstrate the male gender is 54-62 percent greater than the female gender [17-19].

A decline in physiological capability and reaction to stress stimuli is a predicted effect of the lifetime accumulation of molecular and cellular damage produced by aging, which raises the risk of becoming critically ill in elderly patients [20]. The average age of sepsis patients in most studies is over 60 [19, 21]. The average age of sepsis patients was found to be 71 years old in this study.

Within the scope of the research, hemoperfusion applied to patients with sepsis is a blood purification technology with excellent efficacy in critical diseases, and early prevention and clearance of inflammatory mediators are of great importance in the treatment of critical diseases. Hemoperfusion (HP Jafron HA330) can specifically and effectively cleanse inflammatory mediators and regulate body immunity. Thus, it shows excellent efficacy in the treatment of critical diseases by allowing the injured organs to repair quickly and the patient's symptoms to disappear [22]. HA330 adsorption treatment has been proven in the studies to improve in the recovery of organ functionality in sepsis patients [23, 24]. According to the study's findings, the hemoperfusion duration found in those who recovered was statistically significantly higher in those with exhausted patients.

All inflammatory processes, including infections and sepsis, raise CRP levels in the blood [25]. CRP synthesis in the liver begins after a stimulus that occurs within 6 hours after the initiation of inflammation or tissue injury, peaks in 48 hours, and has an 18-hour plasma half-life [26]. Furthermore, elevated CRP levels in septic patients are associated to organ failure and higher mortality risk [27]. According to the findings of our research, the change in repeated CRP measures in recovery and mortality observations was statistically significant. As a consequence, the change in CRP over time may be determined to be a significant determinant in recovery and mortality. Therefore, CRP is a crucial test in the diagnosis of sepsis.

Procalcitonin (PCT) level has been used frequently to diagnose acute bacterial infection in previous years [2]. Simon et al. discovered that the PCT level had an 88 percent sensitivity and an 81 percent specificity in determining bacterial infection[28]. According to recent studies, a high PCT level supports the diagnosis in patients with a suspected bacterial infection, while a bacterial infection cannot be ruled out in individuals with low PCT levels. Although low PCT levels do not exclude the diagnosis of bacterial infection, it can give an idea that the current infection is not very serious [29]. According to the results of our study, it was observed that the change in PCT measurements repeated in recovery and mortality, and observations was statistically significant. Therefore, it is possible to conclude that the variation in PCT repeated measurements is an important determinant in recovery and mortality.

Lactate in critically ill patients has been investigated extensively in the literature. Although lactate levels are related to tissue perfusion disorders, they are not a direct indicator of tissue hypoxia [2]. Lactate is a molecule excreted mostly by the liver and to a lesser extent by the kidneys as a result of pyruvate metabolism. Especially in liver dysfunction, an increase in lactate levels can be seen [2, 29]. When the metabolic steps are reviewed, it is discovered that energy is acquired by turning pyruvate into lactate, which is unable to enter the oxygen cycle in anaerobic glycolysis. This is a normal metabolic process in hypoxic tissues, and it causes lactate to increase [30]. Furthermore, elevated adrenaline in stressful situations activates the Na/K/ATPase pump, generating a rise in pyruvate and lactate via glycogenolysis and glycolysis independent of tissue hypoxia [2]. In Acute Respiratory Distress Syndrome (ARDS), lactate may be released from the lungs. There are studies showing that lactate production increases in stress situations in the brain and heart cells and that the cells located here use lactate as an energy source. Lactate levels can also be affected by pyruvate dehydrogenase enzyme dysfunction and protein catabolism [2, 30].

Different threshold values have been examined in different studies regarding lactate values at the time of admission in sepsis and septic shock. Serial lactate measurement was used in most studies, and lactate values recorded after treatments were used instead of the lactate value at application, and the lactate level was combined with hypotension or other clinical data to make the interpretation [30-34]. In the "Sepsis-3" study published in 2016, lactate was not used in the definition of sepsis. It is only recommended within the definition of septic shock [1, 17, 31]. In a multicenter retrospective study conducted by Cristopher W. Seymour et al., When the qSOFA score was added to the qSOFA score and re-evaluated by adding lactate 2 mmol / L, it has been observed that there was a significant change in predicting the outcome of death or CU hospitalization days ≥3 days in patients who were considered sepsis at presentation [17, 35, 36]. According to the results of the study, the observation that the change of repeated lactate measurements in recovery and

death observations are statistically similar to the results of the study.

In ProCESS (Protocolized Care for Early Septic Shock) and ARISE (The Australasian Resuscitation in Sepsis Evaluation) studies, where the early targeted treatment protocol was compared with standard or conventional therapies and present evidence of departure from the early targeted treatment protocol, in addition to the SIRS criteria, fluid therapy-unresponsive hypotension and lactate 4 mmol / L are the limit values in defining early septic shock [32, 33]. When evaluated prognostically using Caseserly et al.'s "Surviving Sepsis Campaign" data, the relationship between lactate 4mmol/L and hypotension was found to be a good predictor. According to the same study, lactate levels at admission had a low prognostic value, but according to the same study, serial lactate measurements and adjusting treatment accordingly reduced the mortality rate of patients hospitalized in the intensive care unit due to septic shock [34].

As a result, since there are statistically significant differences in the CRP and PCT values of laboratory parameters in sepsis patients followed in the intensive care unit and treated with the HA-330 Sepsis Adsorption Column, it can be thought that it can be an inexpensive, useful, and effective method that can be used in the prognosis of the patients. Sepsis-related deaths are a severe issue in critical care units. In antibiotic-resistant sepsis, hemoperfusion may be recommended.

Conclusion

There are certain drawbacks to this research. There are just a few patients. Randomized, controlled, multicenter studies with larger numbers of patients are needed to identify criteria with higher sensitivity and specificity values to diagnose sepsis and predict prognosis more accurately.

Conflict of interests
The authors declare that they have no competing interests.

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Ethical approval
Ethics committee approval was obtained (Ethical Permision No: 2019/27-14)

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