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A single-center experience with resin adsorption hemoperfusion combined with continuous veno-venous hemofiltration for septic shock patients

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Abstract
Our primary goal was to investigate whether treatment of CVVH-HP in patients with septic shock caused decreased vasoconstrictor and inotropic drug requirements. As a secondary objective, to determine whether CVVH-HP had an effect on inflammatory biomarkers and mortality. 11 septic shock patients who received CVVH-HP treatment within 12 months were included in the study. The following parameters were taken from patients' medical records; hemodynamic parameters, infection markers, inotropes and vasopressors use. Also, Intensive care mortality and duration of ICU stay were assessed. The survival rate after the 24 hours from the start of treatment was 63.6% and 28 days survival rate was 36.4%. Four of the remaining seven survivors at the 24 hours were discharged home. CVVH- HP treatment was associated with an increase of mean arterial pressure, reduction of vasoconstrictor/ionotropic requirement, reduction of C-reactive protein and procalcitonin levels. In our retrospective study, we found that patients treated with CVVH-HP treatment had approximately 40% reduction in norepinephrine and dopamine requirement in the first 24 hours and patients had higher mean arterial pressures.

Keywords: Adsorption, hemofiltration, hemoperfusion, septic shock

Introduction

Sepsis is the most leading cause of death in the intensive care units (ICU) resulting from the injury triggered by the body infection [1-3]. High mortality and morbidity rates of sepsis reveal the necessity of a serious clinical approach [4]. Response induced by the proinflammatory, anti-inflammatory cytokines and the activated immune cells generally result in multiple organ dysfunction [2,5]. Moreover, the level of this inflammation is also closely related to sepsis mortality [6,7]. While the mortality associated with septic shock rises to 54%, this rate reaches up to 80% with the increasing need for vasopressor and organ dysfunction [8]. Such high mortality has forced the clinicians to search for different and innovative treatment methods. Methods which reduce endotoxin and cytokine levels are thought to possibly be effective on treatment of septic shock. Anti-endotoxin monoclonal antibodies, cytokine antagonists, coupled plasma filtration adsorption (CPFA) and Polymyxin B immobilized direct hemoperfusion (PMX-DHP) are a few of these treatment methods [2,3]. Classical hemoperfusion is the direct contact of blood with the sorbents in the extracorporeal system [1]. Being a new hemoperfusion method, "HA 330 type resin cartridge" is produced from a polymer material and removes mediators, molecular toxins and cytokines by using neutral micro-porous resin according to the adsorption principles [2,3]. While HA 330 type resin cartridge can be used alone using a device in sepsis patients for hemoperfusion, it can also be used in renal failure by integrating into the CVVH treatment. Moreover, it is offered as a therapeutic option for sepsis as CVVH removes -at low amounts though- tumor necrosis alpha and some proinflammatory cytokines [6]. In theory, hemoperfusion combined with CVVH (CVVH-HP) can remove higher amounts of mediators and cytokines, as a result, can positively affect the clinical results. Use of HA 330-type resin cartridge is a new method in hemoperfusion treatment and there are only a limited number of clinical studies on its clinical effectiveness and reliability.

This study aimed to investigate the effectiveness of the CVVH-HP method in patients with septic shock. The primary goal of the study was to investigate whether treatment of CVVH-HP method caused decreased vasoconstrictor and inotropic drug requirements

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in septic shock patients. As a secondary objective, the study aimed to determine whether CVVH-HP had an effect on inflammatory biomarkers and mortality.

Materials and Methods

This retrospective, single-center study was conducted on all the patients who received HA-type resin cartridge combined with CVHH for hemoperfusion within the first 12 months (January 2016 – December 2016) of the start of the use of HA 330 type resin cartridge in Adana Numune Hospital. The study was approved by the Ethics and Scientific Board of Adana Numune Hospital with the Dossier No of ref:51.

In our clinic, the decision of hemoperfusion begins with the decision of the intensive care specialist and the following written standard protocols are applied. Firstly all patients diagnosed with sepsis receives an appropriate treatment regarding last Sepsis Surviving Campaign guidelines including [10] ;

1-Initial fluid resuscitation aiming; Central venous pressure (CVP) 8–12 mm Hg b) MAP ≥ 65 mm Hg c) Urine output ≥ 0.5 mL/kg/hr d) Central venous oxygen saturation ≥ 70

2- Administration of effective intravenous antimicrobials as soon as recognition of septic shock

3- a) Norepinephrine as the first choice vasopressor as needed to target a mean arterial MAP of 65 mm Hg b) Epinephrine or dopamine when an additional agent is needed to maintain adequate blood pressure.

Our hemoperfusion therapy is performed only patients who give no response to the septic shock treatment applied by the ICU physician according to the Sepsis Surviving Campaign (SSC) Goal-Directed Protocol [10]

If there is no response to conventional treatment, hemoperfusion is initiated in the following situations.

1- Use of high-dose vasopressor or dual vasopressor,

2- Dysfunction of 2 organs ≥ ,

3- Presence of suspected or proved gram-negative infection.

Hemoperfusion method is performed using HA 330 resin cartridge (Jafron Biomedical Co., Ltd Zhuhai, Guangdong, China) by following the use instructions. Hemoperfusion is performed once a day for three consecutive days. Dual lumen catheter 12 F is placed in the right jugular vein or femoral vein with the Seldinger method. CVVH-HP is performed using the same hemodiafiltration (HDF) machine. Blood filter (HF-1200, Baxter, America) is used for CVHH. The CVVHH procedure is performed on the patients simultaneously using the prismaflex device. Blood flow rate is adjusted at 100 ml/min-150ml/min. Each hemoperfusion procedure lasts at least 2 hours. Hemofiltration continues after the hemoperfusion. Hemofilter is replaced once in 72 hours or whenever occluded by coagulation. Anticoagulation is achieved using citrate.

Hemoperfusion and hemofiltration may be applied separately or together. In our clinic, all hemoperfusion therapy are applied together with hemofiltrations. Even if hemofiltration is not performed before hemoperfusion, it is wanted to continue until the filter is clogged because of the blood purification effect it provides.

Patient Evaluations

Since lactic acid level could not be measured in our intensive care in the concerned date interval, septic shock was diagnosed as the case which is characterized by the circulation failure accompanied by persistent arterial hypotension which cannot be explained by another reason [9].

Following parameters were collected from the medical records of the patients. The Acute Physiology and Chronic Health Enquiry (APACHE) 2 score of each patient, (measured in the first 24 hours of stay in the ICU) was used to evaluate the severity of the disease. Changes in the sequential organ dysfunction assessment (SOFA) score were recorded before the hemoperfusion treatment and at the 24th and 72nd hours after completion of the treatment. Heart rate (HR), systolic blood pressure, diastolic blood pressure and mean artery pressure (MAP) were recorded. Dopamine, dobutamine and noradrenaline infusion dosages; leucocytes and thrombocytes counts; procalcitonin and CRP levels; and arterial pH; pO2/FiO2 rate were measured on daily basis. ICU mortality and the duration of stay in the ICU were evaluated.

Statistical Analysis

Statistical analyses were performed using SPSS 20.0 software (SPSS Inc. Chicago, IL, USA). Student's independent and paired t-test was applied for the parametric data and Mann-Whitney U test for the non-parametric data. Results are presented with "mean +standard deviation". Statistical significance was set at $P<0.05$.

Results

7 male and 4 female, totally 11 septic shock patients (age 51.3± 21.7 years) were included in the study scope. Most frequent reasons for ICU stay were found to be pneumonia and head trauma. Basic and clinical features of the patients are presented in Table 1. While gram-negative bacteria was isolated most, the most frequent source of sepsis was respiratory system infections (Table 2.) In 5 patients (45.5 %), gram-negative bacteria and Candida spp. were isolated together. Each patient was administered 2.18±0.9 hemoperfusion treatment on average.

Table 1. Patient demographics and the severity of their disorders

Male:Female (%)	7:4 (63.6:36.4)
Age (years)	51.3± 21.7
Number of failed organs	3.09±0.8
Acute renal failure (%)	7 (63.6)
Apache† II score	31.4±11.3
Diagnosis at ICU admission	
Traumatic brain injury (%)	4 (36.4)
Pneumonia (%)	4 (36.4)
Intra-abdominal sepsis (%)	2 (18.2)
Acute renal failure (%)	1 (9.1)

†APACHE Acute Physiologic and Chronic Health Evaluation; ‡ Intensive Care Unit

Table 2. Etiology of the infections

Source	
Abdominal cavity (%)	1 (9.1 %)
Respiratory system (%)	9 (81.8 %)
Urosepsis (%)	3 (27.3%)
Central venous catheter-related blood infection (%)	2 (18.2 %)
Causative microorganism	
Gram-negative bacteria (%)	9 (81.8%)
Acinetobacter baumannii (%)	8 (72.7%)
Gram-negative bacteria+fungus (%)	5 (45.5 %)
Gram-negative bacteria+fungus+gram-positive bacteria (%)	3 (27.3%)
Unrecognized	2 (18.2%)

Four (4) of 11 patients (41.7 %) lost their lives within 24 hours by completing only one CVVH+HP treatment. Survival rate at the 24th hour of treatment start was found to be 63.6 % and survival rate in 28 days to be 36.4 %. Table 3 shows the comparison of the pre-hemoperfusion clinical and laboratory parameters of the surviving patients. Evaluation of the hemodynamic parameters shows similarities between the mean arterial pressure and pulse rate of the non-survivors and the survivors. Compared to the survivors, non-survivors had statistically significantly higher procalcitonin values (25.5±31.5 vs. 2.8±3 p=0.03), SOFA scores (14.4±3.6 vs. 8.2±3.6 p=0.042) and APACHE 2 scores (38.4±7.2 vs. 19.2±1.7 p=0.006). Meanwhile, non-survivors had statistically the significantly lower number of leucocytes (10.1±5 vs. 18.3±4.9, p=0.042) and arterial pH values (7.13±0.1 vs. 7.37±0.07, p=0.012).

Table 3. Comprasion of clinical and laboratory parameters between survivors and non-survivors before hemoperfusion

	Survivors (n=4)	Non Survivors (n=7)	P value
Mean blood pressure, (mm Hg)	78.1±12.4	73±7.5	0.648
Heart rate (beat/min)	88.5±18.7	107.3±24.2	0.164
Platelet count (x109/L)	337.2±124.1	139.4±131.6	0.073
White cell blood count (x 109/ L)	18.3± 4.9	10.1±5	0.042*
CRP† (mg/dL)	25.5±13.3	27±12.9	0.570
PCT ‡ (ng/ml)	2.8±3	25.5±31.5	0.012*
pH	7.37±0.07	7.13±0.1	0.012*
PaO2/FiO2	226.7±170	131.5±114	0.109
SOFA§ score	8.2±3.8	14.4±3.6	0.042*
Dose of dopamine (µg/kg/min)	15±12.9	14.3±6.7	0.927
Dose of noradrenaline (µg/kg/min)	0.42±0.39	0.41±0.21	0.923
APACHE # II score	19.2±1.7	38.4±7.2	0.006*

Data in the table are presented as mean ± SD. Survivors vs. Non Survivors ($p < 0.05$) ,
† CRP C-reactive protein; ‡ PCT Procalcitonin, # APACHE Acute Physiologic and Chronic Health Evaluation;
§ SOFA Sequential Organ Failure Assessment

Reduction of the procalcitonin and CRP values after the CVVH-HD treatment are presented in Figure 1. Procalcitonin value was measured as 18.3 ±28.7 before the treatment, started to decrease to 7.04±7.8 on the first day and measured as 2.4±3.3 on the 7th day after the treatment. The decrease recorded in the procalcitonin levels of the surviving patients at the 1st day after the treatment was found to be statistically insignificant (2.8±3 vs. 0.74 ±0.28 p=0.285). Similarly, a comparison of the pre- and post-CRP values of the surviving group produced no statistically significant difference (26.9±12.9 vs. 18±11.22, p=0.075).

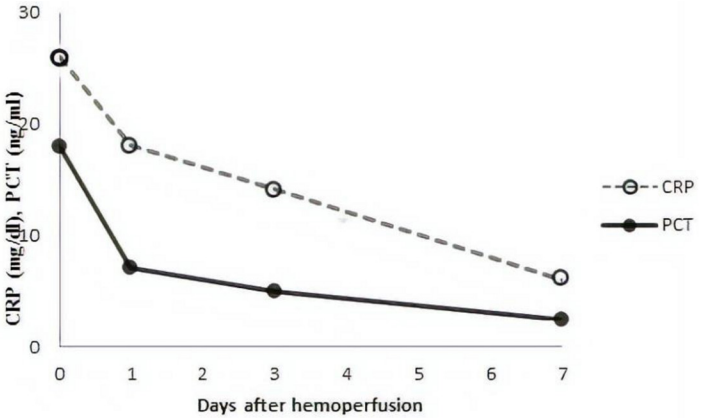

Figure 1. The changes of biomarkers after hemoperfusion. C-reactive protein and procalcitonin daily reduced after resin adsorption theraphy.

Need for dopamine infusion decreased from 14.54±9.07 mcg/kg/min in the pre-CVVH-HP period to 8.8±11.5 mcg/kg/min at the 1st day and to 1±2.4 mcg/kg/min at the 3rd day after the treatment. Similarly, norepinephrine need was reduced from 0.41±0.27 mcg/kg/min in the pre-treatment period to 0.25±0.31 mcg/kg/min at the 1st day and to 0.2±0.31 mcg/kg/min at the 3rd day after the treatment. Unlike the decrease in the vasoconstrictor requirement, MAP value progressively increased from the pre-treatment value of 75.2±0.4 to 82±19.1 on the 3rd day after the treatment. PaO2/FiO2 ratio started to increase just after the CVVH- HP treatment.

Thrombocyte count of the patients who survived after the first 24 hours decreased firstly and then started to rise again. It decreased from 211.9±196.14 to 170.14±123.3 at the 24th hour after the treatment and then increased up to 229.8±165.9 on the 7th day after the treatment.

Discussion

This retrospective study presents CVVH+HP procedure as a rescue treatment for 11 septic shock patients who did not respond to the goal-oriented treatment and who required vasopressor. It was observed that the norepinephrine and dopamine need of the patients decreased by 40% and their mean arterial pressure (MAP) values increased within the first 24 hours following the CVVH+HP treatment. Moreover, CVVH-HP treatment was shown by this study to improve hemodynamic parameters, to decrease

vasopressor requirement and to improve oxygenation in patients who did not respond to the conventional treatment [11].

Similarly, a study which used resin adsorption revealed a 60% decrease in the norepinephrine and dopamine need and improved mean arterial pressure values [2]. Restoration of hemodynamic stability by the HA 330 hemoperfusion treatment can be partially explained by the reduced pro- and anti-inflammatory mediators the blood thanks to the treatment, which resulted in less vasodilation. By this way, manipulation of the mediators via removal may lead to downregulation of systemic inflammation and restoration of homeostasis of the organism [5]. In patients who were subjected to a resin adsorption procedure, IL-6 and IL-8 levels were observed to decrease approximately by 50% on the 3rd day of the procedure [2]. Similarly, among the proinflammatory mediators, IL-6 ve TNF-alpha levels were found to be statistically significantly lower in the group receiving HP treatment in the scope of the peritoneal sepsis model developed. Moreover, after the treatment, compared to the other group, the HP group produced a lower number of bacteria colonies [5]. 28-day hospital mortality rate of the present study was recorded to be lower than the mortality rate estimated by the APACHE 2 score (which was 73.3%). However, the mortality rate varies in 20.9%-45% range in the blood purification methods [2,8,12]. Compared to the previous studies, the present study produced higher mortality rates, which may have resulted from four main reasons. Firstly, the patients of the present study had higher APACHE 2 scores. Secondly, nearly all of the present study patients developed a gram-negative infection. In addition to the gram-negative organisms, they developed fungal-polymicrobial infections at higher rates. Besides, the rate of intra-abdominal infection, on which blood purification techniques are thought to be more effective, was low in the patient group of the present study. Rather, this study had a higher rate of pneumonia-induced sepsis (recorded as 81%). Finally, in terms of exclusion criteria, this study included all patients who were administered hemoperfusion while the compared studies are observed to have excluded some patients with prospective bad prognosis. Hemoperfusion treatment is actually known to be more effective when initiated at early stages. It may be less effective in late cases with prospective bad prognosis. This difference in patient selection may be the reason behind the high mortality rates recorded in the present study. Since CVVH-HP treatment is not a widely-accepted treatment at the moment, it is referred to as the last option in the study clinic in line with the regulations of the Ministry of Health and ethical rules. Rather than this practice, if the patients who were estimated to die at early stages (for instance within the first 24 hours) were excluded from the scope of this study, as done in the compared studies, the 28-day mortality rate would be 36.4%, a rate comparable with the other studies. Procalcitonin is known to be helpful in prognosis in presence of systemic bacterial infection [13]. Compared to the CRP, procalcitonin is a better marker in both diagnosing serious sepsis and mortality. Both CRP and procalcitonin values decreased after the treatment both in non-survivors and survivors. However, while the procalcitonin value was statistically significantly higher in the patients to have lost their lives within the first 24 hours, it was observed to be still high, not at a statistically significant level though, in the patients who lost their lives at later periods when compared to the survivors.

The changes recorded in the oxygenation, thrombocyte count and vasopressor requirement by this study were observed to be similar with those recorded in the previous studies conducted by using different methods and filters. In parallel with the similar studies, the PaO2/FiO2 rate increased immediately after the treatment [2,14,15]. This improvement in oxygenation may have resulted from the decrease in the extravascular lung water (16). CVVH-HP treatment may create the estimated result (in the mechanism of the ARDS induced by the gram-negative bacteria) of reducing the alveolocapillary permeability caused by the activated immune cells by removing endotoxin and key mediators in the blood [17]. Further search should be made to find the reason behind oxygenation improvement. While the thrombocyte count decreased immediately after the treatment, it was observed to re-increase up to the pre-treatment levels. Although the literature presents no explanation for this result, it may have resulted from the direct contact of thrombocytes with the cartridge in the extracorporeal system. It does not seem to be the Heparin-Induced Thrombocytopenia (HIT), moreover, since the CVVH treatment was performed using citrate; HIT seems to be a low probability. It should be noted that serious thrombocytopenia and leukopenia developed in the first hemoperfusion applications [16]. With the introduction of the biocompatible coating systems offered by the technological developments, on the other hand, no serious thrombocytopenia is observed anymore. Still, it should be considered before the treatment that it will reduce thrombocyte count of the patients with thrombocytopenia or bleeding disorder.

Sepsis is the leading reason for acute renal failure and death in the ICU [1]. Acute renal failure increases alone the mortality and morbidity [13]. ICU patients with acute renal failure should be treated with CRRT (Continuous Renal Replacement Therapies). CRRT treatment restores fluid and electrolyte balance in the hemodynamically unstable patients. Moreover, continuous fluid removal ensures sufficient calorie intake. Despite all these advantages, CRRT has a little or no clinical effectiveness as a blood purification method. Although hemofiltration does not decrease mortality alone, it has been observed to further increase the effectiveness of hemoperfusion[11].

In a meta-analysis where 16 studies were analyzed, approximately 15% decrease was recorded in the mortality rate (35.7% vs. % 50.1) of the patients who were treated with a blood purification method [7]. Blood purification therapy techniques ensure non-specifically removal of many inflammatory mediators from the blood by using extracorporeal device [5]. Different blood purification methods have been developed for sepsis. Some of them are high volume hemofiltration, high adsorption hemofiltration, high cut-off membrane hemofiltration, plasma exchange, and hybrid systems like coupled plasma filtration adsorption. Blood purification methods have diversified in parallel with the technological developments and, mortality decreased has been achieved in the literature studies; however, it has not started to be used widely. In the scope of this study, a new hemofiltration filter “HA 330” was used in integration with the CVVH treatment in the study clinic.

Recently, an international guideline for the management of sepsis and septic shock was published, and sepsis campaign recommends initiation of fluid resuscitation, source control and administration of timely antibiotics (within 1 hour of suspected sepsis) if the refractory use of vasoactive agents [18]. While CVP is no

longer recommended alone in the evaluation of fluid therapy. It is proposed to take into account dynamic measurements such as passive leg raise.

This study has some limitations which have to be pointed out. Firstly, the small patient population, no control group and the retrospective nature of the study do not allow us to figure out a conclusion about the effectiveness of CVHH-HP. Secondary, at the beginning of the study, lactate measurement could not be effectively performed in our intensive care unit, which is now an important parameter for diagnosis and follow-up.

Conclusion

The mean APACHE II scores of the patients in our study were 31.4±11.3. Mortality rate with CVVH-HP treatment lower than the mortality rate estimated by the APACHE II score was observed. it was concluded that these findings need to be tested with multicenter prospective randomized controlled trials. Sepsis is a complex disease and blood purification is a complex intervention. Factors of the host, as well as the pathogenic factors, are effective on the course of sepsis. Sepsis factors may vary from one center to the other. For this reason, it may not be right to generalize the blood purification methods. Moreover, as well as the epidemiological factor, antibiotic preferences may also differ between the centers. Blood purification methods can have some effects on this situation. primary goal was to investigate whether treatment of CVVH-HP in patients with septic shock caused decreased vasoconstrictor and inotropic drug requirements. As a secondary objective, to determine whether CVVH-HP had an effect on inflammatory biomarkers and mortality.

Competing interests
The authors declare that they have no competing interest

Financial Disclosure
The financial support for this study was provided by the investigators themselves.

Ethical approval
The study was approved by the Ethics and Scientific Board of Adana Numune Hospital with the Dossier No of ref:51.

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