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ORIGINAL ARTICLE – OPEN ACCESS

The Efficacy of Continuous Venovenous Hemodiafiltration with Cytokine Filter on Sepsis

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ABSTRACT

Objective: Continuous renal replacement therapy is made with high biocompatibility membranes that have high current power by using diffusion and convection together or separately. The aim of the present study was to compare the EMIC-2 and AV600S filters used for continuous venovenous hemodiafiltration (CVVHDF) with respect to the effects on sepsis, the elimination of toxins that are elevated due to acute renal injury, and the effects on inflammatory mediators in severe sepsis.

Materials and Methods: The study included 38 patients who were diagnosed with severe sepsis and were treated with hemodiafiltration in the intensive care unit. Acute Physiology and Chronic Health Evaluation—2 (APACHE-2) and Sequential Organ Failure Assessment (SOFA) scores of the patients were calculated before CVVHDF starts. Hematocrit (Hct), white blood cell, blood pressure, heart rate, and body temperature values were measured and recorded. Procalcitonin (PCT), tumor necrosis factor alpha (TNF-α), interleukin (IL)-6, and IL-1 values on blood were also recorded before the process and at 8, 16, and 24 h of the process.

Results: When the AV600S filtered and EMIC-2 filtered groups are compared, TNF-α values are low in the EMIC-2 filtered group ($p<0.05$). There is no significant difference between the groups with respect to the measurements about APACHE-2, SOFA, IL-1β, IL-6, PCT, Hct, body temperature, mean blood pressures, and heart rate.

Conclusion: We think that the filters do not cause a significant change on the elimination of inflammatory cytokines, except TNF-α, on limited numbers of patients who have sepsis with acute renal injury undergoing CVVHDF with EMIC-2 and AV600S.

Keywords: Sepsis, acute kidney injury, inflammatory cytokine, continuous venovenous hemodiafiltration

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INTRODUCTION

Sepsis is usually related with acute kidney injury (AKI) according to acute tubular necrosis (1). Hypovolemia, hypotension, renal vasoconstriction, and toxic drugs (especially aminoglycosides) play roles in pathogenesis. Systemic hypotension is the preceding cause of the blamed factors for provoking kidney damage. Direct renal vasoconstriction and the release of cytokines, such as tumor necrosis factor alpha (TNF-α), can be counted as the other causes. Mortality increases in patients diagnosed with sepsis who develop renal failure (2). Among the factors that cause this is the release of proinflammatory mediators during hemodialysis as a result of leukocyte–dialysis membrane coactions. As preventing these interactions by using the biologically coherent membranes, it is possible to prolong the lifetime of the patient (3).

The treatment of a patient diagnosed with acute renal failure (ARF) is performed as a supportive treatment initially. This means renal replacement therapy (RRT) in patients with severe renal damage. The initiation of RRT in patients with AKI plays an important role in preventing other fatal complications associated with uremia and renal failure (4).

The time to onset of RRT and alterations in the treatment regimen affect clinical outcomes. Continuous renal replacement therapy (CRRT) means dialysis (solute excretion by diffusion) lasting 12–24 h including filtration (solute and water excretion via convection) or continuous administration of hemodiafiltration treatment. CRRT is better tolerated by patients than intermittent hemodialysis (IHD) because of the slower excretion of solute and fluid and the hemodynamic parameters are less affected (5). Continuous venovenous hemodiafiltration (CVVHDF) is a treatment that provides the opportunity for dialysis and ultrafiltration at a lower rate with a safe and sufficient solute clearance without confounding the hemodynamics of the patient, aiming to minimize the large-scale metabolic and volumetric changes due to dialysis in patients who are not suitable for IHD (6).

EMIC-2 is a CVVHDF polysulfone structure filter which is highly effective in infiltrating medium-sized molecules (~40 kDa) with high biocompatibility and running effectively even in low blood flow (7). On the other hand, the AV600S filter is a CVVHDF filter with an infiltrating threshold of molecule of 30 kDa, which preserves proteins, such as albumin and other large molecules, and cellular blood components (8). The molecular weight of TNF-α is 17 kDa, interleukin (IL)-6 is 26 kDa, IL-1β is 28 kDa, and procalcitonin (PCT) is 13 kDa (9).

We hypothesized that the EMIC-2 filter could more eliminate the inflammatory cytokines in sepsis than the AV600S filter. In this prospective randomized, double-blind, controlled study, we aimed to compare the effects of the EMIC-2 filter used for CVVHDF in patients diagnosed with sepsis compared with the AV600S filter and to compare its effects on sepsis, elimination of elevated toxins due to AKI, and inflammatory mediators in sepsis.

MATERIALS and METHODS

The study was approved by the ethics committee (date: 12/04/2016, no.: 2016-04/05) and supported by the Scientific Research Projects Coordination Unit of the university. The research was performed in the intensive care unit (ICU). The study was conducted on 34 patients aged between 18 and 90 years who underwent CVVHDF using the 17 AV600S and 17 EMIC-2 filters. The study included 38 patients diagnosed with sepsis and who were treated with hemodiafiltration; 2 patients who developed deep hypotension during the treatment, 1 patient whose dialysis was terminated because of blood clotting in the dialysis set, and 1 patient who died during the treatment were excluded from the study. CVVHDF decision was made by the ICU clinician. Exclusion criteria included patients who started hemodiafiltration and developed hypotension during follow-up, patients who could not complete the dialysis lasting 24 h because of clotting in the dialysis set, and patients who died during the study. Patients with chronic renal failure and end-stage cancer were excluded from the study. Any other comorbidities were not considered, and randomization was done by closed envelop method.

Relatives of the patients were informed in detail about the work and process. Written informed consent was obtained from all patients. All of the informed consent forms were signed by the first-degree relatives of the patients who participated in the study. Data on age, sex, admission date, and admission to the ICU were recorded for all patients included in the study. Acute Physiology and Chronic Health Evaluation—2 (APACHE-2) and Sequential Organ Failure Assessment (SOFA) scores were calculated before starting CVVHDF. Hematocrit (Hct), white blood cell (WBC), blood pressure, heart rate (Drager Infinity Delta monitor), and body temperature (Covidien Genius 2) values were recorded. Additionally, PCT, TNF-α, IL-6, and IL-1 values were recorded.

During the CVVHDF, hemodynamic parameters (blood pressure, heart rate, and body temperature), PCT, Hct, WBC, TNF-α, IL-6, and IL-1 of the patient were measured, and APACHE-2 and SOFA scores were calculated and recorded at 0, 8, 16, and 24 h of hemodiafiltration. The patients included in the study were separated into two groups. The first group comprised hemodiafiltration (Fresenius Medical Care, Bad Homburg, Germany), filter blood flow rate 200 ml/min, using hemofiltration solution (Multibic Fresenius 2 mmol/l, with potassium), dialysate flow rate was set at 30 ml/kg/h, filter polysulfone structure AV600S (Fresenius Medical Care) 1.4 m^2 surface area, and 100 ml filling volume filter was used. In the second group, the dialysate flow rate was set at 30 ml/kg/h with similar hemodiafiltration device (Fresenius Medical Care), filter blood flow velocity 200 ml/min, filter polysulfone structure EMIC-2 (Fresenius Medical Care) 1.8 m^2 surface area, and a filter volume of 130 ml was adjusted using hemofiltration solution (Multibic Fresenius 2 mmol/l, potentiated).

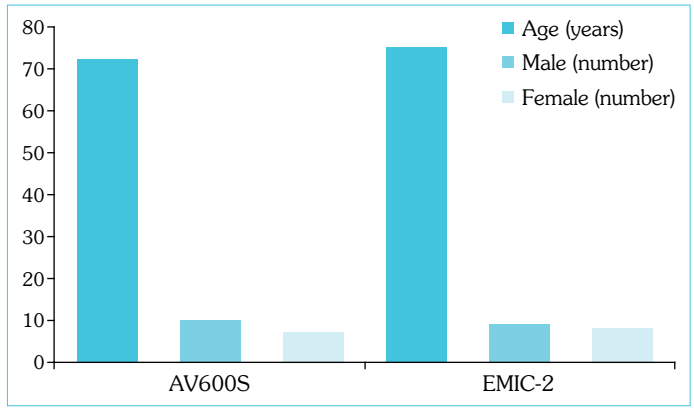

Figure 1. Age and gender distributions according to the groups

Blood samples were centrifuged at 4°C for 10 min and stored at –72°C before and after CVVHDF. TNF-α, IL-1β, and IL-6 biomarkers (DIAsource, Belgium) were performed by monoclonal antibodies directed against different epitopes of TNF-α, IL-1β, and IL-6 by a solid phase enzyme-amplified sensitivity immunoassay method performed on a microtiter plate. PCT biomarker (Getein 1100 Immunofluorescence Quantitative Analyzer) was used for immunofluorometric testing.

Statistical Analysis

Data obtained from the study were analyzed using SPSS 22.0 program (SPSS Inc., Chicago, IL, USA). Kolmogorov–Smirnov test was used to test the normality of data. Student's t test was used for parametric test assumptions and variance analysis. Bonferroni test was used for repeated measurements. Mann–Whitney U, Friedman, Wilcoxon, and chi-square tests were used when the assumptions could not be fulfilled. The error level was accepted as 0.05. When we considered α=0.05, β=0.20, and 1–β=0.80 in the present study, it was decided that 17 individuals were assigned into each group and the strength of the test was 0.80970.

RESULTS

The ages of the individuals were 72.76±15.93 years in the AV600S group and 75.76±8.25 years in the EMIC-2 group. When the groups were compared with respect to age, the difference was insignificant ($p>0.05$). While 58.8% of the individuals in the AV600S group were male and 41.2% were female, 52.92% of the individuals in the EMIC-2 group were male and 47.1% were female (Fig. 1). When the groups were compared with respect to gender, the difference was not significant ($p>0.05$).

The causes of sepsis are shown in Table 1. Patients were distributed to the groups according to their sepsis etiologies (Table 1).

When the IL-1β values measured at different times were compared between the two groups, the difference between the beginning (0 h) values was significant ($p<0.05$). The difference between IL-1 values measured at 8, 16, and 24 h was statistically insignificant ($p>0.05$). In the AV600S and EMIC-2 groups, when the IL-1β values measured at different times for each group were compared, the difference between the measurements was statistically insignificant ($p>0.05$) (Table 2).

Table 1. Causes of sepsis

Causes of sepsis	Patient number (n)		Ratio (%)
	Group AV600S	Group EMIC-2	
Pneumosepsis	6	6	35.2
Urosepsis	5	5	29.4
Wound infection	2	2	11.7
Catheter sepsis	2	2	11.7
Cholangiosepsis	1	1	5.8
Necrotising fasciitis	1	1	5.8

Table 2. Variation of IL-1β values by hours

Hour	Group AV600S (n=17)	Group EMIC-2 (n=17)	p
0 hour	3.66±2.45	2.14±1.50	0.040*
8th hour	3.72±2.70	2.82±2.48	0.260
16th hour	3.81±2.35	2.96±2.41	0.130
24th hour	3.15±1.75	2.63±2.38	0.230
p value	0.850	0.500	

IL-1β: Interleukin-1β; *p<0.05: significant

The difference between the groups was statistically insignificant with respect to PCT values measured at 0 (beginning), 8, 16, and 24 h in both groups (p>0.05). In the AV600S and EMIC-2 groups, when the measured PCT levels were compared at different times in each group, the difference between the measurements was not statistically significant (p>0.05) (Table 3).

When the TNF-α values of the subjects in both groups were compared at different times, the difference was insignificant with respect to the values measured at 0 and 8 h, whereas the difference between the groups at 16 and 24 h was statistically significant (p<0.05). As stated in the table, measurements were found to be lower in the EMIC-2 group (Table 4).

In the AV600S group, when the IL-6 values were measured in separate periods, the difference between the measurements was statistically significant (p<0.05). When the IL-6 values measured in the EMIC-2 group at different times were compared, the difference between the measurements was found to be statistically insignificant (p>0.05) (Table 5).

Hemodynamic parameters and APACHE-2 and SOFA values are given in Tables 6 and 7, respectively.

DISCUSSION

We compared the EMIC-2 filter and AV600S filter with respect to hemodynamic parameters and cytokine levels in our study. The EMIC-2 filter in the CVVHDF caused more decrease in the TNF-α value than the AV600S filter. We think that TNF-α and IL-6 mediators do not have sufficient and effective elimination with the AV600S filter (Tables 4 and 5). However, there is an increase in

Table 3. Changes in PCT values according to time

Hour	Group AV600S (n=17)	Group EMIC-2 (n=17)	p
0 hour	10.90±19.43	4.83±5.65	0.230
8th hour	12.35±15.12	6.69±8.21	0.730
16th hour	13.80±14.50	8.91±15.36	0.380
24th hour	15.83±19.73	7.16±9.60	0.200
p value	0.180	0.950	

PCT: Procalcitonin

Table 4. Variation of TNF-α values by hours

Hour	Group AV600S (n=17)	Group EMIC-2 (n=17)	p
0 hour	21.80±12.85	21.76±9.89	0.781
8th hour	22.14±12.10	15.70±6.80	0.082
16th hour	29.75±16.36	17.83±8.16	0.020*
24th hour	29.31±18.47	18.44±6.91	0.024*
p value	0.007*	0.002*	

TNF-α: Tümör nekrozis faktör-alfa; *p<0.05: significant

Table 5. Variation of IL-6 values by time

Hour	Group AV600S (n=17)	Group EMIC-2 (n=17)	p
0 hour	383.59±417.06	509.21±394.93	0.190
8th hour	465.39±499.37	559.74±460.68	0.221
16th hour	574.34±559.55	450.97±359.73	0.955
24th hour	686.91±562.03	462.15±396.02	0.203
p value	0.011*	0.370	

IL-6: Interleukin 6; *p<0.05: significant

TNF-α values in the AV600S group. We also think that the reasons for this condition may be the degree of deterioration in tissue perfusion of patients with severe sepsis and the response to antibiotherapy and vasopressors differs according to the patient. Owing to these differences, it is hard to standardize patients with severe sepsis in groups.

All the parameters, except IL-1β, were insignificant between the groups at 0 h in spite of the age, sex, and causes of sepsis are similar in the groups. This situation is probably due to comorbidities of the patients.

Many biomarkers are used to identify the occurrence of sepsis in intensive care patients. The frequently preferred biomarkers are TNF-α, IL-1β, and IL-6 (10, 11). The mortality of septic acute renal injury varies between 20.9% and 56.8% according to the severity of damage (12, 13). AKI may occur in approximately 35% of patients in the ICU. Sepsis and septic shock are among the most important causes of >50% of developing AKI in ICU patients. The

Table 6. Hematocrit, white blood cell, and mean arterial pressure values by hours

Hour	Group AV600S	Group EMIC-2	p
0th Hct	29.77±6.73	27.64±3.67	0.51
8th Hct	31.90±6.14	28.70±2.53	0.21
16th Hct	31.31±5.83	28.14±2.46	0.13
24th Hct	29.77±5.54	27.59±3.04	0.57
0th Wbc	18.62±10.10	15.27±7.11	0.36
8th Wbc	21.06±11.29	15.47±7.22	0.14
16th Wbc	21.07±11.80	15.45±7.27	0.22
24th Wbc	19.53±11.01	15.02±6.88	0.23
0th Map	75.11±10.52	73.82±13.00	0.75
8th Map	78.05±8.66	75.41±15.62	0.54
16th Map	78.35±13.02	73.70±14.13	0.32
24th Map	79.05±19.13	79.41±14.45	0.95

Hct: Hematocrite; Wbc: White blood cell; Map: Mean arterial pressure

Table 7. APACHE-2 and SOFA scores change by time

Hour	Group AV600S		Group EMIC-2	
	APACHE-2	SOFA	APACHE-2	SOFA
0 hour	29.00±8.73	11.35±3.98	33.35±6.97	13.82±3.76
24th hour	25.70±8.35	10.23±4.17	29.76±8.04	11.82±3.84
p value	0.002*	0.003*	0.014	0.002*

APACHE-2: Acute Physiology and Chronic Health Evaluation—2; SOFA: Sequential Organ Failure Assessment; *p<0.05: significant

percentage of development of AKI is 15%–20% of the patient receiving treatment in the ICU (14, 15). Our study was performed on 34 patients with severe sepsis.

ARF is a clinical manifestation of a loss of function of the kidney due to a decrease in glomerular filtration rate, which develops within hours, days, or weeks (15, 16).

The development of the ARF association with the septic table has been demonstrated in many studies in patients followed up in the ICU (12, 13). In common with the development of ARF with the existence of sepsis, although the development of ARF in sepsis is a common condition, sepsis may develop in patients with ARF, especially in intensive care follow-up and after mechanical therapy (17).

The elimination of septic biomarkers with conventional hemodialysis filters is not possible. It is not presumptive to eliminate the solute load and other substances >5000 Da with these filters (18). The presence of hemodynamic instability in intensive care patients is a problem with respect to hemodialysis. However, it has been reported that treatment can be performed with RRT even in hemodynamic unstable patients (19). In addition, Gedmintas et al. reported that there is no hemodynamic change with prolonged daily diafiltration (20). Tamme et al. investigated the effects of high volume hemodiafiltration on inflammatory response in septic patients and found that CRRT has no adverse effect on hemodynamic parameters (21). In our study, hemodynamic parameters were stable in both groups in the treatment of CRRT using the AV600S and EMIC-2 filters (Table 6).

With the filters used in RRT, the elimination of solutes and other substances between 30,000–50,000 Da is provided (22). In the study conducted by Hladik et al. on 40 burn patients, they reported that the elimination capacity of CRRT for inflammatory mediators can vary depending on the membrane used, but it can clear mediators with molecular weights in the range of 30,000–50,000 Da and this is more prominent, especially with CVVHDF administration (23).

Kade et al. investigated the elimination of PCT, C-reactive protein (CRP), and selected cytokines during CVVHDF in patients with sepsis and AKI using high flux. They studied CRP, PCT, TNF-α, IL-1β, IL-6, IL-12, and IL-17 at the beginning and at 24 h of hemodiafiltration. They found a significant decrease in PCT, CRP, and cytokine levels and concluded that the decrease in PCT was more significant than the decrease in CRP (24). In our study, we found a statistically significant decrease in the EMIC-2 group in the TNF-α values (Table 4). Although the PCT values were 10.90 in the AV600S group and 4.83 in the EMIC-2 group, no statistically significant decrease was found in PCT values in both groups when comparing the two filters in other measurement times (Table 3).

In the study conducted by Eichorn et al. investigating the elimination of selected plasma cytokines by using the ultraflux EMIC-2 filter against the ultraflux AV1000S filter with continuous venovenous dialysis, also evaluating the elimination of IL-6, IL-8, IL-1β, and TNF-α, in 30 patients with ARF using high sensitivity continuous venovenous hemofiltration with high cut-off filters (CVVH-HCO) versus standard filters, they found that the mean plasma cytokine concentrations decrease in time for all cytokines without perceptible differences for treatment modalities (25).

Atan et al. researched the effect of the hemodiafiltration with high flux filters against standard hemofiltration on plasma cytokines; during the hemodiafiltration made with standard filter and high flux filter lasting 72 h of treatment, IL-6, TNF-α, IL-8, and IL-1β levels were measured. They found that IL-6 was decreased in both treatments, none of the other cytokines were stable during 72 h of treatment, and there was no significant difference between the two groups with respect to plasma cytokine levels. With all these conclusions, they deduced not to promote using CVVH-HCO to reduce the cytokines in critical patients with ARF (26).

In the study by Balgobin et al. in patients with ARF at the ICU comparing continuous venovenous high flux (EMIC-2) hemodialysis and CVVHDF, they approved that there is no significant difference between the levels measured before and after the CVVHDF of the proinflammatory cytokines (TNF-α, IL-1α, IL-1β, IL-2, IL-6, and IL-8) and anti-inflammatory cytokines (IL-4 and IL-1β) (27). In our study, changes between the levels of IL-1β and IL-6 were not significantly measured before and after the CVVHDF using two different filters comparing two groups and values in each group.

In the study by Peng et al. in 2010, searching for the effect of venovenous hemofiltration on monocytes, leukocytes, antigens, and plasma cytokines in septic patients, they did not find a significant difference on APACHE-2 score before and after hemofiltration (28).

In the early diagnostic criteria study and venovenous hemofiltration in patients with critical ARF made by Gjyzari et al., there was no any significant difference between APACHE-2 scores between the living and dead patients before and after the treatment (29).

We aimed to compare the effects of the EMIC-2 filter against the AV600S filter used for CVVHDF in patients with severe sepsis with respect to the elimination of elevated toxins due to AKI and inflammatory mediators in sepsis. No significant difference was found between the groups; APACHE-2 and SOFA scores; IL-1β, IL-6, PCT, and Hct values; and hemodynamic parameters. In the CVVHDF performed with the EMIC-2 and AV600S filters in a limited number of patients with sepsis with ARF, we concluded that the filters did not cause any significant change other than TNF-α cytokines on the elimination of inflammatory cytokines. We think that more studies on this subject are required.

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Conflict of Interest: The authors have no conflict of interest to declare.

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