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Effectiveness of High Cut-Off Hemofilters in the Removal of Selected Cytokines in Patients During Septic Shock Accompanied by Acute Kidney Injury-Preliminary Study

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Background: In recent years there have been attempts to treat sepsis using various methods of extracorporeal blood purification in order to eliminate selected mediators of inflammation.

Material/Methods: This retrospective study assessed 28 patients (17 males, 11 females, age 60.3 ± 14.5 years) in septic shock, treated with continuous venovenous hemodialysis (CVVHD). Oligoanuric patients with acute kidney injury were qualified for 24-hour CVVHD using high cut-off (HCO) hemofilter. Before the start of dialysis and after 24 hours of treatment, the concentration levels of selected cytokines (IFN-α, IFN-γ, TNF-α, IL-1β, IL-2, IL-6, IL-10, IL-12) in serum were assessed. After 12 hours and 24 hours of treatment, the concentration of the same cytokines in the dialysis fluid was assessed. The aim of our study was to evaluate the effectiveness of HCO-CVVHD in the removal of selected cytokines.

Results: After 24-hour HCO-CVVHD treatment, IL-10 and IL-12 levels in serum were significantly lower. Concentrations of INF-α, IL-1β and IL-2 in dialysis fluid significantly increased during HCO-CVVHD, which corresponded with the parallel rise of related clearances. Clearance of IL-6 was approximately four times higher than IL-10. The rise of IL-6 during HCO-CVVHD significantly correlated with mortality due to sepsis.

Conclusions: Continuous venovenous hemodialysis using high cut-off hemofilter proved to be effective in the removal of IFN-α, IL-1β, IL-2 and IL-6, IL-10 and IL-12 from serum in patients during septic shock. The rise of IL-6 during HCO-CVVHD seems to be a marker of bad prognosis in septic shock patients.

MeSH Keywords: Acute Kidney Injury • Continuous Veno-Venous Hemodialysis • Cytokines • Hemofiltration • Renal Replacement Therapy • Sepsis

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Background

As the systemic inflammatory response to infection, sepsis is an important multidisciplinary clinical problem. Despite a long history associated with this condition, it is still a life-threatening disease with a poor prognosis. Severe sepsis, is defined as a systemic inflammatory response with accompanying multiple organ failure and tissue hypoperfusion and remains a major therapeutic challenge. The complex pathophysiology of sepsis results in treatment that includes the combination of antibiotic therapy, fluid therapy, corticosteroids, and vasoconstrictor drugs, increasing myocardial contractility [1]. In recent years, there have been attempts to treat sepsis using various methods of extracorporeal blood purification in order to eliminate selected mediators of inflammation [2]. Given the role of cytokines in the pathogenesis of sepsis, using high cut-off (HCO) dialysis membranes is particularly promising [3]. We present the impact of continuous venovenous hemodialysis (CVVHD) with the use of HCO dialyzer, on the removal of selected cytokines in the treatment of patients during septic shock with multiple organ failure, including acute kidney injury (AKI).

Material and Methods

This study involved 28 patients aged 26 to 84 years (17 males, 11 females, age 60.3±14.5 years) in septic shock who despite the use of optimal treatment regimen, including targeted antibiotic therapy, showed no signs of clinical improvement. In all patients, the SOFA (Sequential Organ Failure Assessment) score [4] was assessed (Table 1).

Additionally, based on the RIFLE (Risk, Injury, Failure, Loss, End-stage) criteria, characteristics of acute renal dysfunction at the level of Injury or Failure were observed. Due to the increase of organ dysfunction, including AKI, patients were subjected to 24-hour CVVHD using a HCO hemofilter with polyarylethersulfone (PAES) membrane, allowing for the removal of cytokines (Septex™, Gambro Lundia AB).

The blood flow through the dialyzer averaged 150 mL/minute, while the flow of the dialysis fluid averaged 1200 mL/hour. Ultrafiltration was of 100 mL/hour on average. For anticoagulatory support, the mean supply of predilution fluid was 250 mL/hour. The average weight of patients was 91.3 kg. Anticoagulation was performed using unfractionated heparin or, if severe coagulation disorders occurred by flushing with 0.9% NaCl. Before and after treatment the concentrations of cytokines in the serum were assessed. After 12 hours and 24 hours, the concentration of cytokines in the dialysis fluid was assessed. Whole blood was collected in tubes containing separating gel and a preparation to facilitate coagulation. After the blood formed a clot, tubes were centrifuged for 10 minutes at 3000 rev/minunte and the serum was separated. Samples of the serum and the dialysis fluid were frozen at –80° C. In order to assess the concentration of the following cytokines: interferon-α (IFN-α); interferon-γ (IFN-γ); tumor necrosis factor (TNF-α); Interleukin-1β (IL-1β); interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-12 (IL-12) we used Affymetrix Procarta Immunoassays, based on xMAP technology allowing us to detect and quantify numerous proteins in a sample volume. We used Serum Assay Buffer to dilute serum samples and Bodily Fluid Buffer as a dialysis fluid.

The xMAP technology consists of stained fluorescent microspheres and the Luminex apparatus 100 with parameters similar to a flow cytometer. In a kit designed to assess a panel 10 of cytokines, there were 10 different microspheres differing in the level of fluorescence and the type of antibodies on its surface. In the first phase, merging of a corresponding antibody and a cytokine occurred. Then biotinylated antibodies were added allowing for the detection of the target complex using Streptavidin, R-phycoerythrin Conjugate (SAPE). Fluorescence readout was performed with two laser beams in the flow cell chamber of Luminex 100 analyzer, which measured the intensity of phycoerythrin (PE) fluorescence on every microsphere. For each series of measurements, we adjusted an 8-point standard curve in two repetitions for every type of cytokine. Assigning the corresponding concentrations of the assessed cytokine was performed by readouts from the appropriate standard curve. The detection limit of concentrations of individual cytokines was as follows: IFN-α 2.48–40700 pg/mL; INF-γ 6.01–6650 pg/mL; TNF-α 4.74–14200 pg/mL; IL-1β 0.36–23150 pg/mL; IL-2 0.2–13700 pg/mL; IL-6 1.66–27 200 pg/mL; IL-10 0.61–10 050 pg/mL; IL-12 1.14–18 650 pg/mL.

The study was carried out according to the Declaration of Helsinki and the protocol of the study was approved by the local bioethics committee. Due to the observational nature of the analysis that used only anonymised parameters, no individual written consent was required.

Statistical analysis

The Statistica 12 (StatSoft Inc.) software was used. In-group differences between examined variables were analysed with the Wilcoxon test as determined by missing the condition of normal distribution. The differences between the groups were investigated with U Mann-Whitney test. Relations between initial concentration of IL-6 and its change during the dialysis were tested with Spearman's correlation test and univariate regression analysis. The ROC analysis was used to estimate the best cut-off point value.

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Table 1. Characteristics of recruited patients.

Initial cause of sepsis	Age	SOFA score
Pneumonia	74	15
	64	17
	35	6
	82	7
	80	19
	67	15
	56	9
	84	8
Oncologic chemotherapy	62	6
	69	19
	63	17
	43	13
	62	19
Skin infection	69	9
	58	15
	41	17
	62	19
	50	16
Cardiothoracic surgery	52	13
	58	15
	63	17
	61	18
Urinary tract infection	77	10
	26	16
Vascular surgery	35	14
Acute pancreatitis	56	18
Multiorgan damage (traffic accident)	73	13
Unknown	66	17

Results

Mean value of SOFA score was 14.18±4.17. Eighteen patients died due to the septic shock, and three patients due to other reasons (myocardial infarction, pneumonia, pulmonary embolism) during hospitalization. Median time from HCO-CVVHD to discharge or death was eight days (ranged from 0 to 70). Results of serum concentrations of cytokines: INF-α, INF-γ, TNF-α, IL-1 β, IL-2, IL-6, IL-10, IL-12, before and after 24 hours of HCO-CVVHD treatment are shown in Table 2.

Initial, as well as after 24-hour HCO-CVVHD treatment, concentrations of INF-α INF-γ, TNF-α, IL-1β and IL-2 were below or on the level of the detection limit. Concentrations of IL-6, IL-10 and IL-12 were elevated before HCO-CVVHD, and we found a significant decrease of IL-10 and IL-12 after 24 hours of procedure. Surprisingly, in the whole group, concentration of IL-6 did not change during the treatment.

In dialysis fluid, concentrations of INF-α, IL-1β and IL-2 significantly increased during HCO-CVVHD, which corresponded with

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Table 2. Average cytokine concentrations in serum, initially and after 24 hours of treatment.

Cytokine	C_0 [pg/ml]	C_{24} [pg/ml]	p-Value (C_0: C_{24})
INF-α	2.49*±0.00	2.49*±0.00	n/a*
INF-γ	6.01*±0.0	6.01*±0.0	n/a*
TNF-α	4.74*±0.0	4.74*±0.0	n/a*
IL-1β	0.36*±0.00	0.36*±0.00	n/a*
IL-2	0.20*±0.0	0.20*±0.0	n/a*
IL-6#	78.73 [1.66; 2634.98]	141.17 [1.66; 2177.41]	0.340
IL-10#	39.22 [0.61; 156.88]	10.07 [0.61; 144.15]	0.004
IL-12	7.64±6.18	6.86±4.63	0.043

C_0 – concentration before HCO-CVVHD; C_{24} – concentration and after 24hrs of HCO-CVVHD; n/a – non-available;
median; * concentrations below or on the level of the detection limit.

Table 3. Concentrations of cytokines in the dialysis fluid and their clearances during HCO-CVVHD.

Cytokine	CF_{12} [pg/ml]	CF_{24} [pg/ml]	CL_{12} [ml/min]	CL_{24} [ml/min]	p-Value
INF-α	3.60±1.41	5.22±1.62			<0.001
			37.31±14.65	54.17±16.85	<0.001
INF-γ	6.01*±0.0	6.01*±0.0	n/a*	n/a*	n/a*
TNF-α	4.74*±0.0	4.74*±0.0	n/a*	n/a*	n/a*
IL-1β	0.61±0.25	1.88±0.94			<0.001
			43.89±17.67	134.73±67.42	<0.001
IL-2	1.00±0.77	2.30±1.80			<0.001
			129.44±98.99	296.60±151.87	<0.001
IL-6#	288.65 [19.33; 37375.09]	198.49 [23.04; 66159.66]			0.219
			71.43 [2.93; 155.10]	65.48 [2.36; 928.36]	0.838
IL-10#	5.12 [0.96; 238.67]	4.65 [0.61; 120.57]			0.455
			15.38 [1.21; 76.23]	17.00 [1.19; 102.29]	0.603
IL-12	7.48±4.42	7.00±4.94			0.273
			25.83# [6.87; 389.82]	25.83# [7.85; 473.97]	0.889

CF_{12} – concentration in dialysis fluid after 12 hrs of HCO-CVVHD; CF_{24} – concentration in dialysis fluid after 24 hrs of HCO-CVVHD; CL_{12} – clearance after 12 hrs of HCO-CVVHD; CL_{24} – clearance after 24 hrs of HCO-CVVHD; n/a – non-available; # median [range];
* concentrations below or on the level of the detection limit.

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Table 4. The differences in IL-6 concentrations during HCO-CVVHD.

Group	C_0 [pg/ml]	C_{24} [pg/ml]	CF_{12} [pg/ml]	CF_{24} [pg/ml]	CL_{12} [ml/min]	CL_{24} [ml/min]	p - value
IL-6# risers (n=10)	39.87 [14.28; 2088.89]	165.97 [40.19; 2177.41]					0.005
			322.58 [59.29; 4154.04]	348.42 [130.40;3600.60]			0.284
					75.20 [16.22; 241.73]	59.68 [15.21; 219.36]	0.028
IL-6# deepers (n=18)	214.98 [1.66; 2634.98]	102.52 [1.66; 1841.01]					<0.001
			258.13 [19.33;37375.09]	173.01 [23.04;66159.66]			0.011
					65.53 [2.93; 515.18]	71.55 [2.36; 928.36]	0.170
p-value	0.187	0.260	0.904	0.221	0.904	0.517	–

C_0 – concentration before HCO-CVVHD; C_{24} – concentration and after 24hrs of HCO-CVVHD; CF_{12} –concentration in dialysis fluid after 12 hrs of HCO-CVVHD; CF_{24} – concentration in dialysis fluid after 24 hrs of HCO-CVVHD; CL_{12} – clearance after 12 hrs of HCO-CVVHD; CL_{24} – clearance after 24 hrs of HCO-CVVHD; # median.

Table 5. Spearman coefficient in significant correlations of cytokines, SOFA score and outcomes.

	SOFA	Period to discharge or death	Death due to sepsis	Death of all causes
IL-4 (C24)	–	–	0.426	–
IL-6 risers	–	–	0.400	–
IL-10 (C0)	–	–0.404	–	–
IL-10 (C24)	–	–0.680	–	0.516
IL-10 (CF12)	–	–0.591	–	0.475
IL-10 (CF24)	–	–0.568	–	0.449
IL-1β (CF12)	–	–	–0.560	–0.494
IL-1β (CL12)	–	–	–0.560	–0.494
INF-γ (CF12)	0.511	–	0.378	–
INF-γ (CF24)	0.521	–	0.407	–
INF-γ (CL12)	0.525	–	0.435	–
INF-γ (CL24)	0.483	–	0.493	–
TNF-α (CL12)	–0.547	–	–0.416	–
TNF-α (CL24)	–0.547	–	–0.416	–

C_0 – concentration before HCO-CVVHD; C_{24} – concentration and after 24hrs of HCO-CVVHD; CF_{12} – concentration in dialysis fluid after 12 hrs of HCO-CVVHD; CF_{24} – concentration in dialysis fluid after 24 hrs of HCO-CVVHD; CL_{12} – clearance after 12 hrs of HCO-CVVHD; CL_{24} – clearance after 24 hrs of HCO-CVVHD; IL-6 risers – patients with the rise of IL-6 during HCO-CVVHD.

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parallel elevation of related clearances (Table 3). Concentrations of INF-γ and TNF-α were below or equal to the detection limit.

Mean 24-hour clearance of IL-6 was approximately 4-fold higher than IL-10 clearance. To find out the reason of discrepancies between IL-6 concentrations in serum and its clearance during HCO-CVVHD, we divided patients into two groups: those with an increase of IL-6 concentrations after 24 hours of intervention (IL-6 risers) and those with decreasing IL-6 (IL-6 deepers) (Table 4). In both groups, the change of IL-6 during dialysis (decrease or increase) was significant. Moreover, clearances of IL-6 in both groups were similar.

The initial concentration of IL-6 (C_0IL-6) negatively correlated with the rise of IL-6 during the dialysis (r=–0.696). In univariate regression analysis C_0IL-6 was the independent factor influencing the IL-6 elevation during HCO-CVVHD (b=–0.62, r^2=0.52, p<0.001). The ROC analysis showed that C_0IL-6 equal 77.36 pg/mL allowed us to predict further increase of of 74.1% (AUC 0.716). The rise of IL-6 during HCO-CVVHD significantly correlated with deaths due to sepsis (r=0.40). In the IL-6 risers group, 9 out of 10 patients died, whereas in the group of IL-6 deepers 9 out of 18 patients died (p<0.05).

Significant correlations of considered cytokines, SOFA scale and outcomes are presented in Table 5.

Discussion

No visible progress in the treatment of sepsis, and septic shock in particular, has become the reason for the search of new treatment options. Hemodialysis therapy using a high cut-off membrane has been a proposed option in recent years. To date, these membranes have been made from polyarylethersulfone/polyvinylpyrrolidone, polysulfone, and cellulose triacetate. Although a definition for a HCO membrane remains to be confirmed, pore sizes are typically around 0.008 to 0.01 µm, 2- to 3 fold bigger than in high-flux membranes [5]. This allows for a removal of substances with a molecular weight up to 65 kDa.

Reports about the effectiveness of dialysis methods using HCO membranes come from very few centers and generally small groups of patients. In 1995 Bellomo et al. were the first to demonstrate the effectiveness of CVVHD treatment in the removal of IL-6 and IL-8 in 10 patients with severe sepsis [6]. These observations were confirmed by experimental study by Mariano et al. conducted in 2005 on a group of 15 voluntary patients [7]. The blood collected from the volunteers was incubated with bacterial lipopolysaccharide and then the patients subjected to dialysis methods (hemofiltration, hemodialysis, hemodiafiltration) using HCO membranes. The authors demonstrated a high efficiency of membranes in removing IL-6 and TNF-α. In 2003 Morgera et al. compared the ability to remove IL-6 and TNF-α with hemofiltration using a conventional hemofilter as well as hemofiltration using a HCO hemofilter with a cut-off point for molecules having a mass of up to 60 kDa in a group of 29 patients with AKI and sepsis [8]. They showed a better ability to remove IL-6 and TNF-α in the case of HCO membranes., but in contrast to the results of Mariano et al. [7], weaker elimination of TNF-α. In another study published in 2004 Morgera et al. attempted to answer the question whether continuous hemofiltration using HCO hemofilters with a cut-off point of up to 60 kDa removes selected cytokines from blood more effectively than continuous hemodialysis [9]. Hemofiltration treatment was more efficient in removing a soluble receptor for IL-1 (IL-1ra) compared to continuous hemodialysis treatment. However, there was no difference between treatments as far as removal of IL-6 was concerned. The clearances for TNF-α achieved by both methods were very low. Haase et al. compared the removal of IL-6, IL-8 and IL-10 in a group of 10 patients with AKI during sepsis using high flux or HCO dialyzers [10]. When using HCO the authors observed a decrease in concentration of the examined cytokines in serum, and the highest reduction of approximately 30% was observed for IL-6.

In our study TNF-α concentrations in serum also did not change during the CVVHD treatment and were similar to stable concentrations in the dialysis liquid. However, unlike other reports, we initially observed an increase of IL-6 concentrations in the serum after dialysis treatment, which suggested low efficiency of removal of this cytokine as well. This thesis was negated by almost 4-fold higher IL-6 clearance than IL-10, which final concentration was significantly lower than initial level. The division of patients into two groups: IL-6 risers and IL-6 deepers demonstrated that change of IL-6 during HCO-CVVHD depends in 62% of cases on the initial level of this cytokine, and the value C_0IL-6 equal 77.36 pg/mL identified cases of growth in IL-6 with an accuracy of 74%. In both groups, the clearance of IL-6 was similar, so the lack of decrease in IL-6 during dialysis does not prove the lack of efficiency of the dialysis method, but indicates that cytokine production excesses elimination mechanisms. Moreover, the occurrence of IL-6 rise was significantly correlated with death due to sepsis. This suggests that rise of IL-6 during HCO-CVVHD could be a marker of bad prognosis in septic shock patients. This is the first study reporting prognostic possibility of IL-6 change during HCO-CVVHD, but for the reason of a rather small group, this hypothesis required further studies.

In majority of published studies, the ability of HCO membranes to remove IL-6, IL-8 and TNF-α was observed. These cytokines corresponds with 8, 17 and 26 kDa respectively [11]. In our study, we significantly increased a number of the studied cytokines, both in blood and in the dialysis fluid compared with

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other studies. Our study group consisted of 28 patients, which is a considerable number of patients in comparison with other studies.

In the available publication databases there are few reports concerning the effects of continuous hemodialysis treatments using HCO on concentrations of cytokines in serum [9,12–14]. Most of the previous studies relate to continuous hemodiafiltration and hemofiltration treatments with the use of HCO membranes on concentrations of cytokines. The studies of CVVHD treatments and their effect on concentration of cytokines relate to membranes other than HCO. One of the first reports on the use of HCO membranes in CVVHD treatment and the impact of this treatment on selected cytokines in the serum comes from our center [12]. The treatment was performed in 2009 in a 62-year old woman with acute solitary kidney damage during septic shock caused by *Staphylococcus aureus*. Within several hours after the end of a 20-hour treatment, the clinical condition of the patient and the standard markers of inflammation had improved. At the same time a significant decrease of IL-1β, IL-6, IL-10 and TNF-α in serum was achieved.

In summary, the use of HCO membrane during CVVHD caused significant reductions of IL-10 and IL-12 in serum, accompanying high INF-α, IL-1β, IL-2 and IL-6 clearances in the course of the procedure. The rise of IL-6 during HCO-CVVHD is significantly correlated with mortality related to sepsis.

Conclusions

The use of a high cut-off membrane during continuous veno-venous hemodialysis is an effective way to eliminate INF-α, IL-1β, IL-2 and IL-6, IL-10 and IL-12. The clinical significance of IL-6 rise during HCO-CVVHD as a marker of bad prognosis in septic shock patients and should be the subject of further research.

Conflict of interest

The authors declare that they have no conflict of interest.

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