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Predictors of Clinical Efficacy of Cytokine Hemoadsorption in COVID-19 (Clinical Trial)

Viacheslav A. Ratnikov[1], Alexej N. Sheglov[2], Stanislav V. Abramovskiy[1], Ionas S. Simutis[1,3]*, Mark S. Danilov[1,3], Galina G. Ivanova[1], Alexej A. Syrovatskii[1]

[1] Sokolov Northwestern District Research and Clinical Center, Federal Medico-Biological Agency of Russia, 4 Ave. Culture, 194291 Saint Petersburg, Russia
[2] Central Clinical Hospital with Outpatient, Russian Presidential Administration, Department 15 Marshala Timoshenko Str., 121359 Moscow, Russia
[3] I. I. Mechnikov North-Western State Medical University, Ministry of Health of Russia, 41 Kirochnaya Str., 191015 Str. Petersburg, Russia

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***Correspondence to:** Ionas S. Simutis, simutis@mail.ru

Summary

Aim of the study. To evaluate the value of predictors of hemoadsorption clinical efficacy in patients with COVID-19.

Materials and methods. This study analyzed the results of treatment of 62 patients with severe COVID-19 in the intensive care unit using selective hemoadsorption of cytokines. All patients with severe COVID-19 were admitted to the intensive care unit within 14 days from the disease onset were subdivided into two groups. Group 1 patients (n=32) received on a top of standard treatment the hemoperfusion (HP) procedure for 4 hours, for 2–3 days in a row, using a cytokine sorption column composed of mesoporous styrene-divinylbenzene copolymer matrix. Group 2 patients were not subjected to extracorporeal blood purification. All patients received IL-6 inhibitors at a baseline in accordance to the temporary guidelines. We evaluated factors of unfavorable outcomes by analyzing changes in biochemical markers of systemic inflammatory response and mortality rates in patients of both groups.

Results. Initiation of HP later than 10 days from NCI onset ($P < 0.001$), length of stay in the ICU, extent of lung damage ($P = 0.036$) and the SOFA (Sequential Organ Failure Assessment) score ($P = 0.009$) were the most powerful predictors of unfavorable outcome. Levels of systemic inflammatory response markers (interleukin-6, CRP, D-dimer) in both groups did not significantly affect the survival rates and length of hospital stay ($P > 0.05$). HP group demonstrated better survival ($P < 0.05$). Mean hospital stay was 31 and 27 days, ICU stay — 11 and 8 days for Groups 1 and 2, respectively ($P < 0.05$).

Conclusion. Treatment of severe COVID-19 patients with HP using novel hemoperfusion device composed of styrene-divinylbenzene copolymer resulted in decrease in CRP levels on the first day after application and, with early onset, contributed to a significant increase in survival and decreased hospital and ICU stay. Additional studies are warranted to clarify the optimal timing of the initiation of HP in severe COVID-19 patients.

Keywords: hemoadsorption, cytokines; COVID-19; styrene-divinylbenzene copolymer matrix; Efferon CT

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Recent experience with intensive therapy of severe novel coronavirus infection COVID-19 highlights the importance of pathogenetic treatment (including efferent therapy), which is particularly relevant given the lack of evidence for clinical efficacy of available etiologic treatments [1, 2]. High levels of circulating cytokines («cytokine storm») are important pathophysiological elements of COVID-19 progression, play a significant role in the development of multiple organ failure and poor outcome, and are associated with persistent post-COVID disease [2]. Cytokine adsorption and other methods of extracorporeal detoxification have been proposed in current version of temporary clinical guidelines to control cytokine storm when medical therapy is unsuccessful and respiratory failure progresses [3]. There are several reports in the literature on the successful use of cytokine adsorption alone and in combination with other efferent therapies in the treatment of severe COVID-19 [4, 5]. However, the actual use of these methods in infectious disease clinics is limited due to the lack of a clear understanding of the optimal timing, duration, and frequency of cytokine adsorption. In our study, we evaluated the changes in systemic inflammatory response and treatment outcomes in ICU patients with severe COVID-19 who underwent hemoperfusion to remove cytokines from the circulation in relation on the timing of the procedure.

Aim. To determine the significance of predictors of clinical efficacy of cytokine hemoperfusion in patients with COVID-19.

Material and Methods

A retrospective, single-center, case-control clinical study was conducted to evaluate the efficacy of extracorporeal anti-cytokine hemoperfusion (EACH) in combination with interleukin-6 receptor antibody therapy for severe COVID-19.

The study included 62 patients with severe and critical COVID-19 (7 or more points on the NEWS [National Early Warning Score] scale) admitted to the intensive care unit. In the first group, 32 patients each underwent a 4-hour hemoperfusion treatment using the Efferon® CT adsorber with styrene-divinylbenzene copolymer adsorbent beads. No other extracorporeal detoxification methods were used. Within this group, patients were divided into two subgroups: those who underwent hemoperfusion during the first 10 days after severe disease development and those with a longer duration of this period.

According to the temporary clinical guidelines, extracorporeal treatments are indicated for progressive respiratory or multiple organ failure due to cytokine storm that persists despite pharmacotherapy [3]. Vascular access was established with a dual lumen central venous dialysis catheter. The circuit was stabilized by microjet injection of sodium citrate (ACD-A). The procedure was repeated for 2–3 consecutive days (depending on patient condition, reduction of inflammatory mediator levels, oxygen and inotropic requirements).

In the second subgroup of 30 retrospectively selected patients («control»), no extracorporeal detoxification was performed.

At baseline and during intensive therapy, we evaluated changes in laboratory parameters such as ferritin, C-reactive protein, IL-6, D-dimer. All patients received anticytokine therapy (with recombinant humanized monoclonal antibodies against the human interleukin-6 receptor, such as tocilizumab 400–800 mg, sarilumab 400–800 mg, or levilimab 648–1296 mg) and anti-inflammatory therapy (dexamethasone up to 24 mg/day) according to current temporary clinical guidelines. Plasma cytokine levels were measured by enzyme-linked immunosorbent assay. Analysis of mortality, ICU and total hospital length of stay for patients was performed. The characteristics of the patients in the groups are shown in Table 1.

The clinical efficacy of EACH was evaluated statistically by intergroup differences. Parametric and non-parametric statistical methods were applied. Data collection, correction, primary processing, and presentation were performed using MS Office Excel 2010. Statistical analysis was conducted using Jamovi Desktop software (version 2.3.18) with assessment of distribution normality by the Shapiro-Wilk method, determination of mean values, mean square deviation, medians, lower and upper quartiles, maximum and minimum values. The values in the two independent groups were compared using the Mann–Whitney test. In addition, regression analysis with OR (odds ratio) estimation and survival analysis with competing risks curve plotting were used to assess the significance of the differences between the groups. The *P-value* < 0.05 was used as the threshold for significance.

Results and Discussion

Several patterns were observed when evaluating the impact of various predictors on the clinical efficacy of EACH therapy (Table 2). Significantly elevated

Table 1. Baseline patient characteristics.

Parameter	Values in groups		*P-value*
	Control, *N*=30	EACH, *N*=32	
Sex (male), %	57	58	1
Age, years	61 (56–69)	64 (54–68)	0.86
Body weight, kg	94 (82–00)	87 (78–93)	0.06
SOFA score, points	3 (3–4)	3 (2.5–4)	0.21
CRP, mg/l	41 (10–165)	122 (84–200)	0.09
IL-6, pg/ml	416 (280–600)	423 (230–820)	0.67
Ferritin, µg/l	1190 (660–1850)	800 (437–1770)	0.38
D-dimer, ng/ml	590 (330–970)	510 (330–1730)	0.75

Table 2. Ranking of predictors of clinical efficacy of EACH therapy in COVID-19 patients.

Parameter	OR	95% CI	*P-value* (LR)	50% survival		AUC
Age, years	1.007	(0.97–1.07)	0.33			
Body weight, kg	0.997	(0.99–1.02)	0.75			
CRP, mg/l	0.996	(0.98–1.01)	0.13			
D-dimer, ng/ml	1.000	(1.00–1.00)	0.25			
Ferritin, µg/l	1.000	(1.00–1.00)	0.35			
IL-6, pg/ml	1.001	(0.99–1.01)	0.086	⩽	522	0.62
Severity of lung involvement, %	1.14	(1.01–1.25)	0.036	⩽	77%	0.60
SOFA score, points	3.261	(1.39–7.61)	0.009	⩽	3	0.66
ICU stay, days	1.11	(1.07–1.16)	<0.001	⩽	16	0.75
Time to adsorption*, days	0.76**	(0.54–0.96)	0.016	⩽	7	0.58
Model based on both significant parameters						
Time to adsorption*	0.79**	(0.69–0.90)	<0.001			0.85
ICU stay, days	1.31	(1.28–1.34)	<0.001			

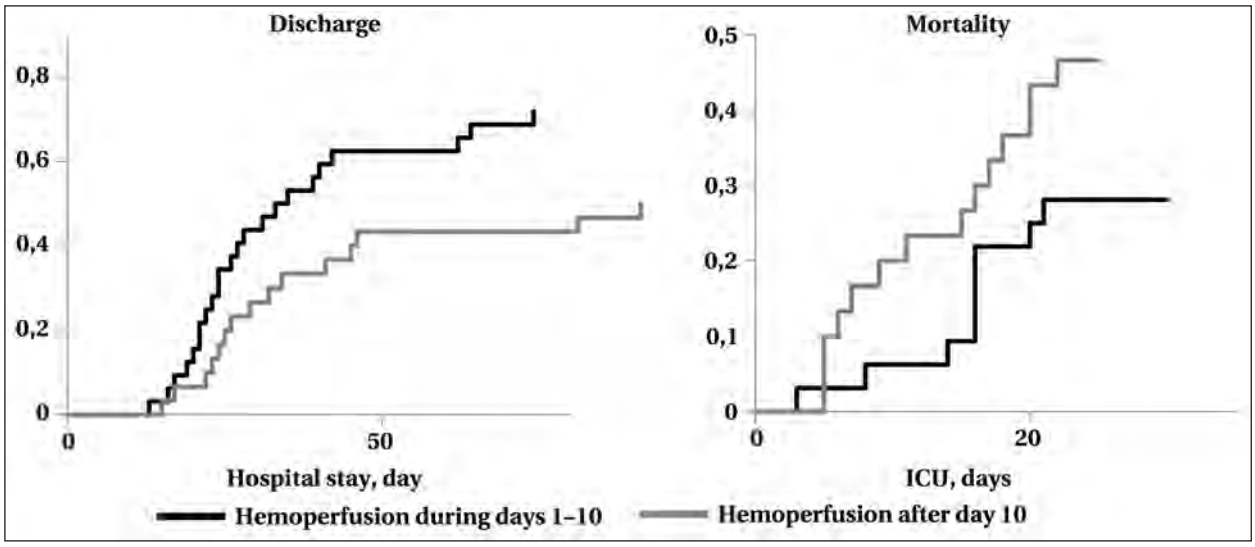

Fig. 1. Incidence curves of competing risks.

Table 3. Treatment results.

Parameter	Values in groups		*P-value*
	Control	Hemoperfusion	
Survival	53%	72%	0.19
ICU stay in survivors, days	8	11	0.45
Hospital stay, days	27	31	0.028

Table 4. Cox's competing risk model based on a length of hospital stay prior to the EACH treatment initiation

Event	SHR (day 10)	*P-value* (χ^2, df=1)	SHR (1/t)	95% CI	χ^2 (Wald)
Transfer	1.18	0.002	4.8	(1.8-12)	9.6
Discharge	1.17	0.002	5.2	(1.9-14.6)	9.8
Death	0.80	0.042	0.11	(0.013-0.92)	4

Note. SHR — sub-distributed hazard ratio.

levels of CRP, D-dimer, ferritin, and interleukin-6, traditionally used in the clinic to initiate adsorption therapy, had a less significant effect on the likelihood of discharge than did baseline disease severity as assessed by the SOFA scale (P = 0.009) and the severity of lung involvement (P = 0.036) (Table 2). However, there was a significant increase in adverse outcomes when the watchful waiting strategy was used and extracorporeal therapy was initiated at a later stage of the disease (P < 0.001), when inflammatory markers were significantly elevated and further deterioration of patients with progression of multiple organ failure was observed.

Notably, delaying extracorporeal detoxification until anti-inflammatory therapy has failed is not specified in the temporary clinical guidelines [3].

The results of treatment of patients are shown in Table 3. Analysis of the data characterizing the effect of extracorporeal procedures on mortality and duration of hospitalization in patients with COVID-19 allowed us to determine the most favorable period of EACH initiation from the onset of disease manifestations and hospitalization. Figure 1 shows mortality rates in relation to the time of initiation of EACH treatment and the onset of clinically significant signs and symptoms.

The interval of 1–10 days from the manifestation of the disease to the beginning of EACH treatment was optimal. The clinical outcome of EACH started within this period of hospitalization and the overall treatment efficacy are shown in Table 4.

Data demonstrate that patients who started EACH during the first 10 days were:

- 18% more likely to be discharged from the ICU to the ward (P = 0.002)
- 17% more likely to be discharged from the ICU to home (P = 0.002)
- 20% less likely to die (P = 0.042)

Literature data exist on the importance of timely initiation of efferent therapy. For example, Amir Ahmad Nassiri et al. (2021) observed the relationship between mortality and the timing of hemoadsorption initiation [6], while Ali Esmaeili Vardanjani et al. (2021) evaluated the efficacy of the procedure during the early period of ICU stay [7] (not based on specific time limits, but rather on the course of the disease, i.e. before clinical deterioration or need for mechanical ventilation). In the study

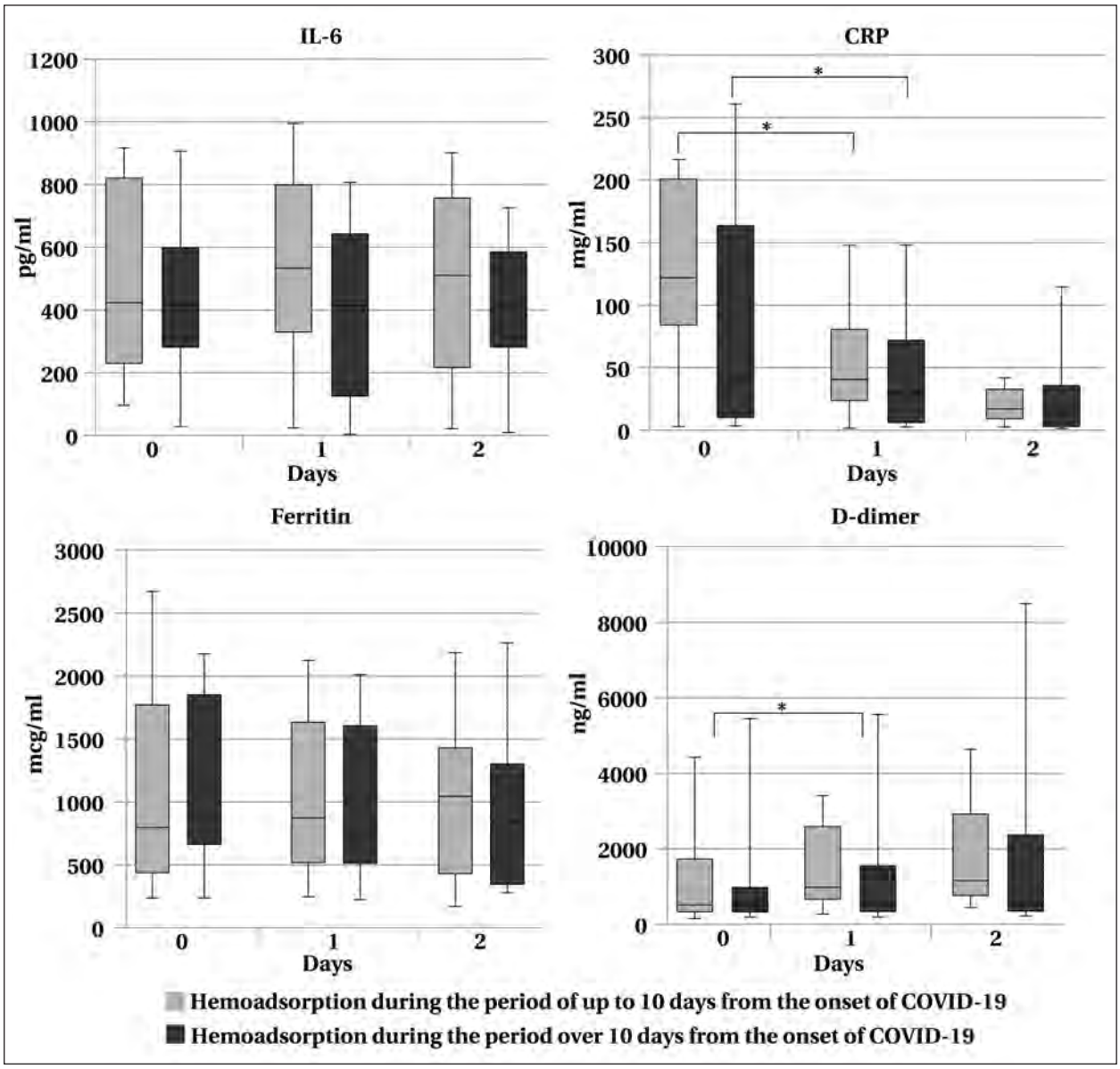

Fig. 2. Changes in systemic inflammatory response and coagulation parameters during ECH.

by Haleh Mikaeili et al. (20–21), evaluating the efficacy of cytokine adsorption in comparison with a control group of patients without efferent therapy, the average time of treatment initiation was 7 days after the onset of signs and symptoms [8], which confirms our findings.

Notably, several authors report the efficacy of early hemoperfusion to remove cytokines from the circulation [6–10], but the available data do not provide sufficient information on the timing of treatment initiation. Only one of these papers reports that patients were in the ICU for 9 days, without specifying the time from admission to hemoperfusion [6].

In order to exclude the influence of other factors on the described effect of the time of initiation of EACH, which reduce the effectiveness of the procedure when performed later, a comparative analysis of the changes in SIR (systemic inflammatory response) markers was made in the subgroups of timely and late extracorporeal blood purification (Fig. 2).

In both subgroups, there was a rapid and significant decrease in IL-6 and C-reactive protein after each EACH procedure, which is consistent with the literature [4, 5], but no significant differences were found between patients who received hemoperfusion within 10 days of disease onset and those who received it later. As expected, CRP levels decreased significantly after the first session and correlated strongly with interleukin-6 levels (K=0.89). These results reflect a significant contribution of adsorption to the control of SIR and provide a rationale for its use, including in combination with biological therapy.

Since coagulopathy in patients with COVID-19 is a predictor of disease severity, whereas coagulation

parameters are traditionally associated with the evolution of SIR syndrome, we examined the changes in D-dimer and fibrinogen levels in both groups [11, 12]. Evaluating the temporal changes in D-dimer (Fig. 2), we observed an increase in this parameter in the subgroup of patients with early EACH initiation.

Such a trend has been described in the literature and is probably associated with severe disease and progressive coagulopathy [13], as well as with an imbalance of factors controlling systemic fibrinolysis, which could also be due to their removal with adsorption.

In addition, the mean fibrinogen level decreased with treatment in both subgroups (from 6.4 g/l to 4.25 g/l), which can be considered an additional indicator of effective correction of systemic inflammation [14].

The significant increase in the probability of death in the subgroup of patients who started treatment at a later stage of the disease is also noteworthy. The subgroup differences in the likelihood of discharge from the ICU to the ward (18% higher, $P = 0.002$), the likelihood of discharge to home (17% higher, $P = 0.002$) and the likelihood of death (20% lower, $P = 0.042$) start to emerge after day 10 of disease onset, suggesting that this period can be considered critical for the decision to start cytokine adsorption.

Hypercytokinemia is a potentially detrimental factor leading to the onset and progression of multiple organ failure (MOF) [15–19]. According to the available data, cytokines directly or indirectly stimulate coagulopathy, endothelial destruction and increased catabolism. Their levels correlate with the severity of COVID-19 and prognosis and influence the efficacy of medical therapy [20–24]. Biologic therapy only partially solves this problem because it selectively targets a specific group of cytokines and their receptors without affecting other equally important inflammatory factors, does not prevent further production of cytokines and their new receptors, and has a long-term immunosuppressive effect, especially with repeated use, as well as significantly increases the cost of treatment.

Cytokine adsorption alone and in combination with immunobiologic therapy can be an important adjunct in the treatment of patients with both COVID-associated sepsis and infection-related organ dysfunction of other etiologies, but as shown by our and similar studies, should be initiated in a timely manner [7, 25, 26]. In particular, we did not differentiate the contribution of adsorption and biological drugs in the regression of systemic inflammation, because we believe that these methods should be used together.

Our study has several limitations. We conducted a single-center, nonrandomized study. The delay in EACH initiation may have been influenced by exacerbating factors (e. g., hematoma development, thrombocytopenia, etc.), which may have worsened the treatment outcome. Further studies are needed to better understand the indications for optimal initiation of EACH procedure in COVID-19 patients.

Conclusion

Cytokine adsorption with the Efferon® CT extracorporeal adsorber has shown its clinical efficacy in patients with severe COVID-19 when performed earlier (up to 10 days) after the onset of the disease, reducing mortality and shortening the duration of hospitalization.

The most important predictors of adverse outcome are the later initiation of EACH treatment (10 days and later after the onset of coronavirus infection) and the severity of multiple organ failure.

The level of CRP decreased significantly after the first hemoperfusion session and correlated strongly with the level of interleukin-6.

In the follow-up period, the levels of IL-6, CRP, ferritin, D-dimer did not change significantly in the course of anti-inflammatory medical therapy after the EACH.

Initiation of EACH therapy should be considered in combination with conservative anti-inflammatory treatment, but not as an alternative or «last resort» method.

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