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MAIN TEXT

Hemadsorption in patients requiring V-A ECMO support: Comparison of Cytosorb versus Jafron HA330

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Abstract

Background: ECMO support is associated with the development of a systemic hyper-inflammatory response, which may become quite significant and extreme in some cases. We hypothesize that Cytosorb or Jafron therapy may benefit patients on V-A ECMO in terms of levels of inflammatory markers such as IL-6, complications, and overall outcomes.

Methods: We conducted a retrospective study of prospectively collected data in a single tertiary care center between January 2021 and April 2022. At the time of the analysis of this article, 20 patients on V-A ECMO had cytokine adsorption while on ECMO support: Cytosorb group ($n = 10$), Jafron group ($n = 10$). In 10 ECMO-supported patients cytokine adsorption was not used, this group served as a control group, which may be quite significant in some cases. Evaluation of the level of inflammatory markers (IL-1, 6, 8; CRP, Leukocyte, Lactate, PCT, NT-proBNP, TNF-α) was performed.

Results: There was statistically significant longer CPB time, aortic cross-clamp time and ICU stay in cytokine adsorption groups than in the control group, but there were no differences between subgroups with different types of haemoadsorption used. Moreover, in the control group mortality rate was higher than in the cytokine adsorption groups (60% vs. 20%, $p = 0.02$). All patients had an elevation of inflammatory markers in the perioperative and immediate postoperative periods. After 72 h of intensive care, blood inflammation markers had a tendency to decline.

Conclusion: At the time of writing, hemadsorption in patients requiring V-A ECMO support represents a good therapeutic effect. This effect is permanent for the whole period of extracorporeal cytokine hemadsorption application for both CytoSorb and Jafron HA330 devices.

KEYWORDS

blood purification, cytokine adsorption, extracorporeal membrane oxygenation

1 | BACKGROUND

Cytokine hemadsorption (CH) is being increasingly used in intensive care units for the management of severe inflammatory status and related complications in critically ill patients. Recently hemoadsorbtion of pro-inflammatory cytokines has been used in patients on veno-arterial extracorporeal membrane oxygenation (V-A ECMO) support. ECMO is associated with the development of a hyper-inflammatory response, which may become quite significant and extreme in some cases. This leads to an increased capillary permeability causing vasoplegia, shock, and multiorgan failure.[1,2] Therefore, cytokine adsorption has been suggested as a new approach to target systemic inflammation.[3]

In recent years, various extracorporeal blood purification cartridges have been proposed to eliminate cytokines and metabolites from the circulation, including CytoSorb, HA330, NKU-9, CYT-860- DHP, Lixelle, CTR-001, and MPCF-X.[4,5] CytoSorb CH device (CytoSorbents Europe, Berlin, Germany) contains porous polymer beads that adsorb molecules within the 5–55 kDa range including many cytokines and damage-associated molecular patterns (DAMPs) and eliminates them from the circulation.[6,7] HA330 (Jafron, China) includes a neutral microporous resin that efficiently eliminates 10–60-kDa molecules, including the cytokines interleukin-6 (IL-6) (6.5 kDa) and interleukin-8 (IL-8) (26 kDa). The use of both cytokine adsorbers may be associated with improved clinical outcomes when inserted into the cardiopulmonary bypass (CPB) circuit for the removal of inflammatory cytokines in the blood (Table 1). Promising results have been demonstrated in heart transplantation, surgical management of acute infective endocarditis, and in patients with severe post-CPB systemic inflammation response syndrome.[8–14]

At present, data regarding the use of CytoSorb or Jafron (HA330) hemoadsorbtion therapy in patients while on ECMO support and its efficacy in the realm of survival and morbidity is limited.[4,15–18] The latest published systematic review of randomized-controlled trials of therapy with CytoSorb in critically ill patients with inflammatory conditions showed no apparent benefits and at the same time risk of harm of hemoadsorption with CytoSorb.[19] We hypothesized that Cytosorb or Jafron therapy may benefit patients on V-A ECMO in terms of levels of inflammatory markers such as IL-6, complications, and overall outcomes. We report our experience in a single tertiary referral center in Kazakhstan with the use of blood purification in V-A ECMO-supported post-cardiotomy patients.

2 | METHODS

2.1 | Patient selection

We conducted a retrospective study of prospectively collected data in a single tertiary care center. The presented data were collected prospectively at the intensive care unit at the National Research Cardiac Surgery Center (NRCSC) between January 2021 and April 2022. All patients included were treated per protocol as part of standard care. The study was approved by the Local Bioethics Committee of the National Research Cardiac Surgery Center (№ 01-74/2021 from 10/06/20), and registered in ClinicalTrials.gov PRS, Protocol registration and results system (NCT05042622). At the time of writing, 20 patients on V-A ECMO had cytokine adsorption while on support: Cytosorb group ($n = 10$), Jafron group ($n = 10$). In 10 ECMO-supported patients, cytokine adsorption was not used, this group served as a control group. The initiation of ECMO and cytokine adsorption was the decision of the treating physician according to the patient's clinical condition. The main indication for cytokine adsorption was a suspected severe hyper-inflammatory reaction. According to our standard procedure, if procalcitonin (PCT) or interleukin-6 were markedly increased or failure to stabilize patient circulation despite volume resuscitation and catecholamine support, initiation of cytokine adsorption was discussed. However, the final decision for initiation of cytokine adsorption was at the discretion of the treating physician considering the individual patient's clinical course.

TABLE 1 Overview of cytokine adsorption devices

	Characteristics	Target	Application
CytoSorb (CytoSorbents Corporation, Monmouth Junction, NJ, USA)	Unselective adsorption of hydrophobic molecules within the 5–60 kDa range	Various cytokines (e.g., interleukins, TNF), bilirubin, myoglobin, toxins, and various therapeutic drugs	Septic shock and other severe inflammatory states, liver failure, rhabdomyolysis, intoxications
HA-330, HA-3804 (Jafron Biomedical, Zhuhai City, China)	Unselective adsorption of hydrophobic molecules within the 10–60 kDa range		

Note: Listed applications follow the manufacturers' recommendations. These recommendations are based largely on theoretical considerations and robust data suggesting a benefit from hemoadsorption in critically ill patients remain scarce. Therefore, the use of these devices in routine clinical practice cannot be recommended at this time.

In all patients included in our analyses, V-A ECMO was used due to post-cardiotomy shock non-responsive to conservative treatment. The size of the cannula was defined by body surface area and calculated ECMO flow necessary to achieve the metabolic requirements of the patient. For aortic cannulation, 22–24 Fr cannulas were used while venous cannulation was performed using a two-stage cannula ranging from 27–29 to 40–46 Fr. The cytokine adsorber was used according to the manufacturer's instructions and was inserted either within a continuous renal replacement therapy circuit or directly to the ECMO circuit. Blood flow rates through the cytokine adsorber were 300–700 ml/h, depending on the flow rate in the ECMO system when incorporated directly into the ECMO circuit. In this case, the cytokine hemadsorption (CH) cartridge was connected in a recirculating by-pass starting behind the oxygenator and going back into the system at a pre-pump-luerlock connection (Figure 1).

Three consecutive procedures of CH were applied for each patient. Anticoagulation was achieved with heparin (individual dosage, according to laboratory data and post-operation bleeding) with a goal ACT 180–210 s. The duration of the CH with CytoSorb cartridge was 24 h, Jafron HA330–6 h, this was done according to the manufacturer's recommendations.

2.2 | Data collection

All data were prospectively collected in our single-center ECMO registry. A prospectively maintained database contains data of all patients supported with ECMO following cardiac surgery. The severity of illness was assessed in all patients using APACHE II and operative risk using the EuroScore II risk calculator immediately before initiation of CH therapy. Evaluation of the level of the inflammatory markers (IL-1, 6, 8; CRP, Leukocyte, Lactate, PCT, NT-proBNP, TNF-α) was performed. Blood sampling was done according to the scheme (Table 2). Duration of mechanical lung ventilation, mean ICU length of stay, mean hospital length of stay, and hospital mortality were evaluated.

2.3 | Statistical analysis

Statistical analysis was performed using the SPSS system for statistics. Demographic and clinical data were summarized by mean and standard deviation, expressed through minimum and maximum, for metric variables or absolute frequencies for categorical variables. Differences between the groups were analyzed using the analysis of variance ANOVA test for comparing the means of two or more independent samples. Where possible, a two-sample independent *t*-test was used to compare the means. A significant difference was assumed for *p*-values <0.05. Results are presented as median within terquartile ranges.

3 | RESULTS

We compared a group of 20 patients receiving V-A ECMO therapy with cytokine adsorption with a group of patients undergoing V-A ECMO support without cytokine removal. Subgroup analysis of different adsorbers used was also performed. In all groups, blood samples were collected according to a scheme in Table 2.

Baseline patient characteristics such as sex or age were similar in all three groups as shown in Table 3. The

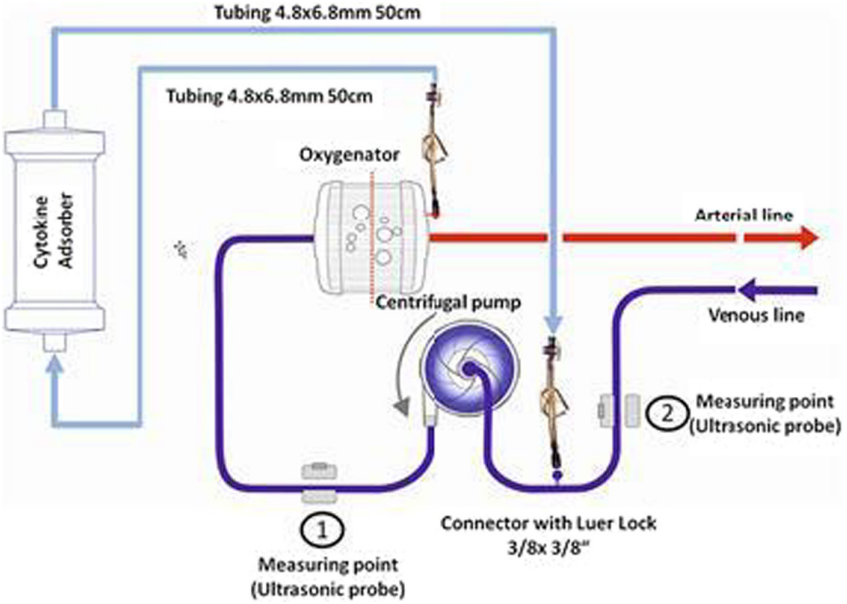


FIGURE 1 Technical implementation of the cytokine adsorber (Cytosorb or Jafron) into the veno-arterial ECMO circuit. The cytokine adsorber was connected in parallel, placed behind the oxygenator outlet, and returned to the preoxy line before the centrifugal pump. ECMO, extracorporeal membrane oxygenation.

TABLE 2 Blood sampling scheme

N of blood sample	#1	#2	#3	#4	#5	#6	#7
CH group	Before CH/ without CHprocedure	2 h after the beginning of the procedure	6 h after the beginning of the procedure	At the time of the 2nd CH procedure completion	At the time of the 3rd CH procedure completion	6 h after completion of the 3rd CH procedure	24 h after completion of the 3rd CH procedure

TABLE 3 Patient characteristics

	CytoSorb group ($n = 10$)	Jafron group ($n = 10$)	Control group ($n = 10$)	p
Patient characteristics				
Age	48.6 ± 17.6[b]	47.5 ± 13.1[b]	59.1 ± 13.7[b]	0.13
Male	30 (30%)[a]	6 (60%)[a]	2 (20%)[a]	0.18
BMI	25.4 ± 4.2[b]	29.2 ± 4.6[b]	27.5 ± 4.0[b]	0.12
Severity of disease				
APACHE II	12.2 ± 1.9[b]	12 ± 2.6[b]	8.46 ± 5.4[b]	0.05
EuroSCORE II	14.3 ± 3.9[b]	16.1 ± 2.1[b]	10.1 ± 2.3[b]	0.02

[a]Mean ± standard deviation.

[b]The number of patients (with percentage based on the number of patients with a non-missing value for that characteristic).

TABLE 4 Patient outcomes

	CytoSorb group ($n = 10$)	Jafron group ($n = 10$)	Control group ($n = 10$)	p
CPB length (min)	200.8 ± 33.7[b]	175.75 ± 80.1[b]	111.4 ± 36.3[b]	0.03
Cross clamp time	138.2 ± 27.0[b]	125.3 ± 48.9[b]	60.1 ± 31.3[b]	0.01
ECMO days	8.1 ± 6.0[b]	5.2 ± 2.7[b]	7.4 ± 6.4[b]	0.45
ICU stay days	13.3 ± 8.6[b]	7.5 ± 3.6[b]	11.5 ± 8.0[b]	0.04
Hospital stay days	33.6 ± 19.5[b]	24.5 ± 7.9[b]	18.1 ± 10.5[b]	0.03
Mortality rate	2 (20%)[a]	2 (20%)[a]	6 (60%)[a]	0.02
Bleeding[a]	2 (20%)[a]	3 (30%)[a]	–	
Acute kidney injury	–	–	2 (20%)[a]	

Note: p values refer to the comparison between the V-A EMCO +CytoSorb group, V-A ECMO +Jafron group, and the patients with V-A ECMO without cytokine adsorption.

Abbreviations: APACHE II score, Acute Physiology, and Chronic Health Evaluation; EuroSCORE II, European system for cardiac operative risk evaluation; ICU, intensive care unit; V-A ECMO, venoarterial extracorporeal membrane oxygenation.

[a]Mean ± standard deviation.

[b]The number of patients (with percentage based on the number of patients with a non-missing value for that characteristic).

majority of the patients (60%) underwent valve repair or replacement. V-A ECMO implantation took place in the operating room in 90% of cases and the catheterization laboratory in 10% of cases. Table 4 shows patients' outcomes. There were no significant differences between groups except for higher APACHE II and EuroSCORE II in cytokine adsorption groups. There was statistically significant longer CPB time, aortic cross-clamp time and ICU stay in cytokine adsorption groups due to technical issues and time for blood return from the CH circuit, but there were no differences between subgroups with different types of haemoadsorption used. Moreover, the mortality rate in the control group was higher than in the cytokine adsorption groups (60% vs. 20%, $p = 0.02$). There was no difference in the rate of acute kidney injury or the need for renal replacement therapy between the groups. The most

common bleeding sources were ECMO cannula sites and haemothorax.

To evaluate the impact of cytokine adsorption on additional clinically relevant parameters, we evaluated interleukins (1α, 6, 8), procalcitonin (PCT), N-Terminal Pro-B-type Natriuretic Peptide (NT-proBNP), C-reactive protein (CRP), Leukocyte, Tumor necrosis factor alpha (TNF-α) levels, before and the start of cytokine adsorption as a measure of hemodynamic stabilization in all groups. Laboratory data of CytoSorb, Jafron HA300, and control groups in comparison are shown in Figures 2–4, respectively.

All patients had an elevation of inflammatory markers in the perioperative and immediate postoperative periods. After 72 h of intensive care, blood inflammation markers had a tendency to decline.

4 | DISCUSSION

The "Systemic Inflammatory Response Syndrome" (SIRS) definition has been formally borrowed from critical care medicine and applied to cardiac surgery.[20–22] The review by Butlerand et al. in 1993 described a consistent concept linking key pathophysiological components of the inflammatory response to cardiopulmonary bypass (CPB): triggered host response via complement, coagulation, fibrinolysis, kallikrein-kinin cascade, neutrophils activation with proteases, oxidative stress, hemolysis, and production of numerous cytokines leading to multiple organ dysfunction syndrome (MODS).

Post-cardiotomy ECMO support is often associated with severe generalized inflammation, which occurs due to the underlying disease, surgical trauma, CPB as well as the ECMO circuit itself.[23,24] All randomized trial data available to date indicate no significant difference in most inflammatory molecules in patients treated with CytoSorb versus conventional therapy. In these settings, in vivo cytokine adsorption capabilities of the devices are unclear.[19] The latter is more attributable to other devices such as Jafron. We are interested in the kinetics of the inflammatory factors as a trend given its more informative value considering that this aspect has not been addressed previously. It is valuable to analyze the systemic inflammatory burden and disease dynamics. Moreover, as we treat critically ill patients, clinical effects may not always be seen with or stable enough after usage of the first cartridge.

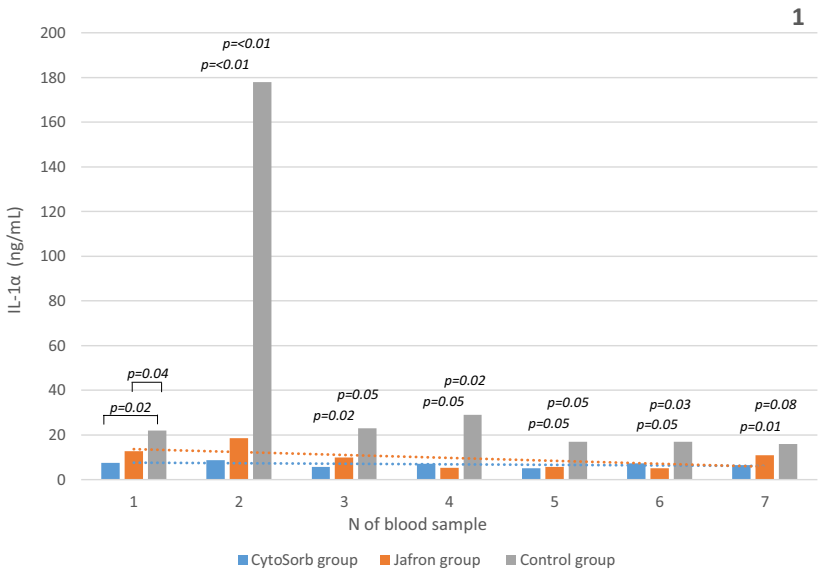
The majority of trials studied the CytoSorb regimen by incorporating the cartridge in the CPB circuit for a couple of hours.[19] In other studies, CytoSorb is either used alone in hemoperfusion mode or incorporated in the RRT circuit. Conventional therapy, i.e., CPB without CytoSorb or sham hemoadsorption was the only comparison intervention. There are no trials aimed to compare two devices for CH and standard therapy for better understanding and differentiating the effects of CH in critically ill patients. Knowing that inflammation is sometimes multifaceted and unpredictable, we studied the clearance of inflammatory markers in the control group also as in all published studies.[19,25] The choice of IL 6 and the panel of other studied parameters was done to achieve full coverage with this potentially beneficial adjunctive treatment.

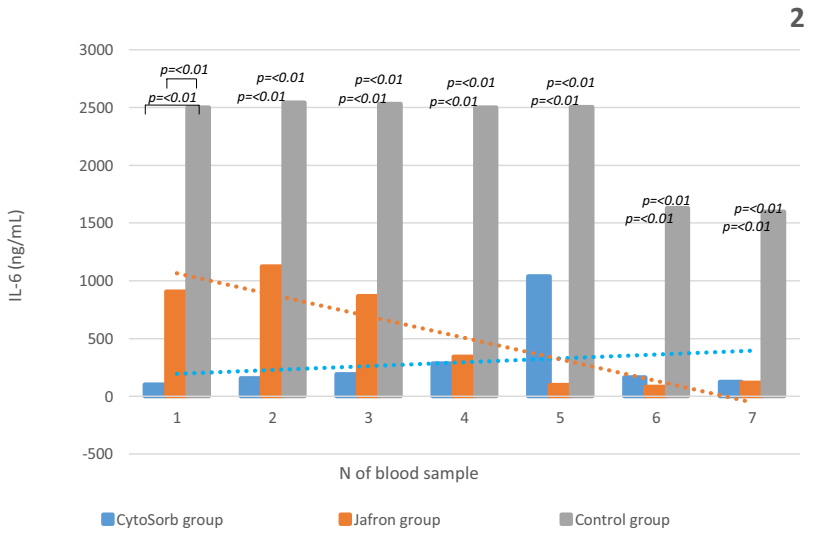
In rapidly evolving post-cardiotomy cardiogenic shock, the early use of CH may be justified even though the levels of inflammatory markers such as IL-6 may still be low at this point in time. It warrants additional parameters to be studied as markers of inflammation, disease progression, and treatment goals such as TNF-α, IL-1α, IL-8, etc. The laboratory values should further be interpreted in the context of the underlying pathologic condition leading to ECMO support: the IL-6 level of 500 ng/L in patients after a circulatory arrest has a high degree,[26] but the same index for example, in patients with sepsis (active infective endocarditis or abdominal catastrophes) may be rather low. It is known that the persistence of IL-6 in the blood rather than the exact peak levels indicates and predicts negative outcomes in patients.[27,28]

Lactate is another commonly used parameter in ICU practice. The use of this marker in patients receiving ECMO and CRRT is limited.[29] On the one hand, CRRT potentially results in a high lactate removal. On the other hand, increasing lactate levels while on ECMO may trigger inadequate flow conditions. In our series lactate level was consistently low in both CH groups. We believe these figures should be trusted as they were obtained at the earliest period of ECMO support and patients did not receive CRRT at that time.

The mortality rate in the CH groups was three times less than in the control one. This was despite to primordial higher degree of APACHE II and EuroSCORE II scores. Patients in both CH groups had a stable low value of inflammatory markers throughout the first 3 days of ECMO support (Figure 2). Therefore, this impact on cytokines removal may explain the favorable effect on mortality. Only one randomized trial evaluated the combination of CytoSorb with ECMO.[30] CytoSorb failed to reduce IL-6 levels in this study and was associated with increased mortality. Yet, these findings cannot be extrapolated to other conditions beyond V-V ECMO support in COVID-19 patients.

The bleeding rate was higher in HA patients: 20% in the CytoSorb group, and 30% in the Jafron group. This was due to the need of heparinization in the early postoperative period. Importantly, according to our institutional





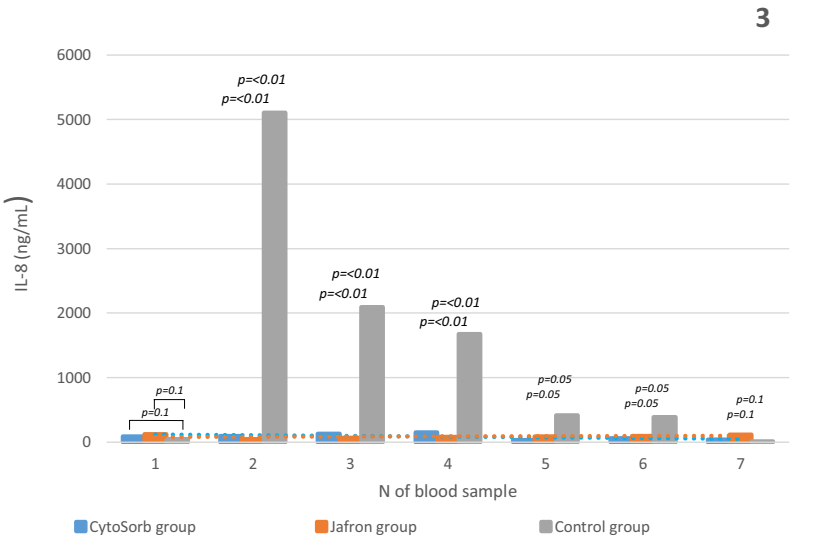


FIGURE 2 Outcome parameters of interleukins 1-IL-1α, 2–6, 3–8 in patients with V-A ECMO+Cytosorb adsorption, V-A ECMO+Jafron cartridge, and a cohort with VA ECMO alone. According to Table 2 blood sampling scheme.

protocol for the first days we use heparin not for ECMO reasons, but to prevent HA cartridge or CRRT circuit thrombosis upon application.

A reduction in ECMO support as well as in ICU and hospital stay was observed in the Jafron HA330 group, although without correlation with the levels of all studied

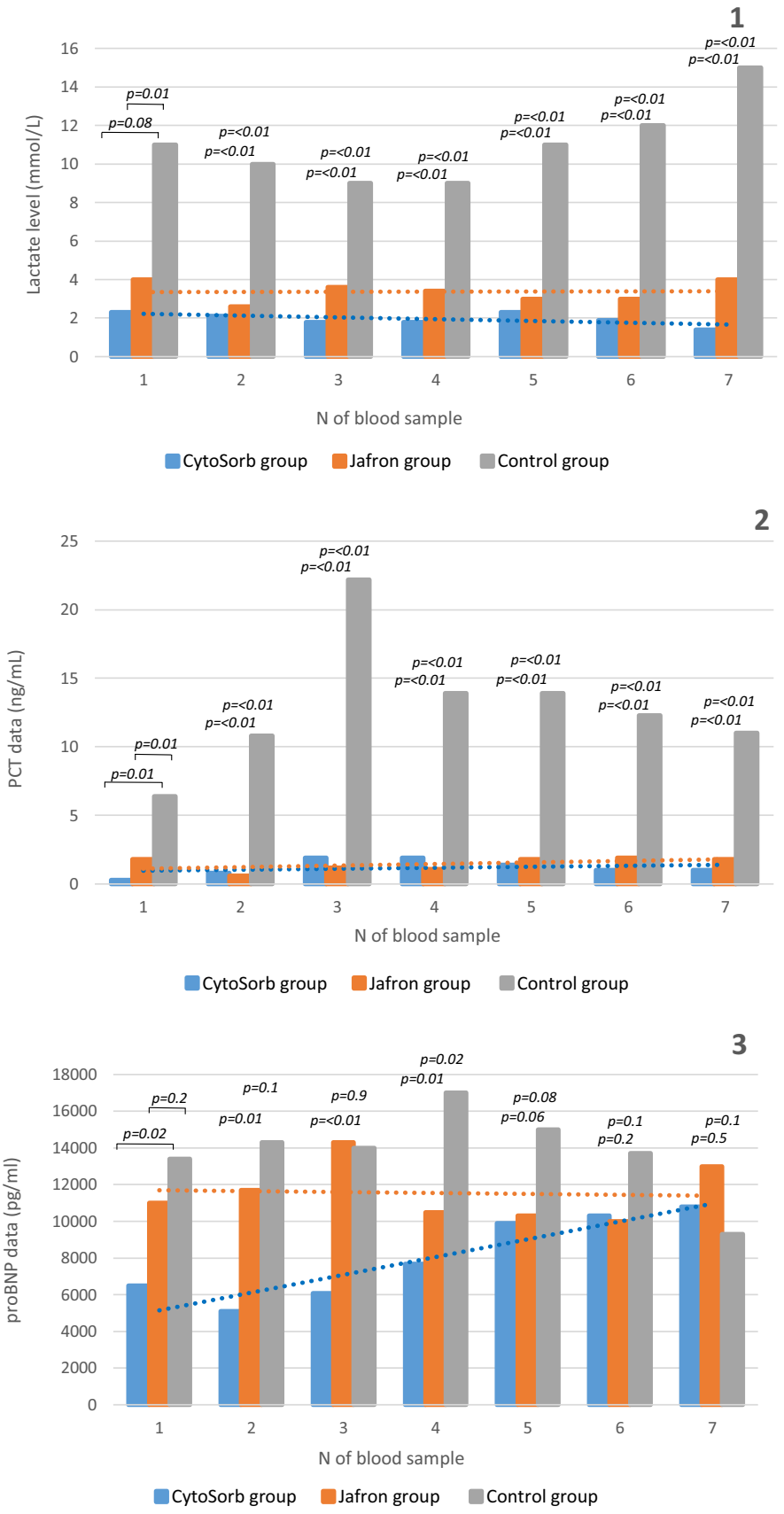


FIGURE 3 Outcome parameters: 1-lactate, 2-PCT, 3-proBNP in patients with V-A ECMO+Cytosorb adsorption, V-A ECMO+Jafron cartridge, and a cohort with VA ECMO alone. According to Table 2 blood sampling scheme.

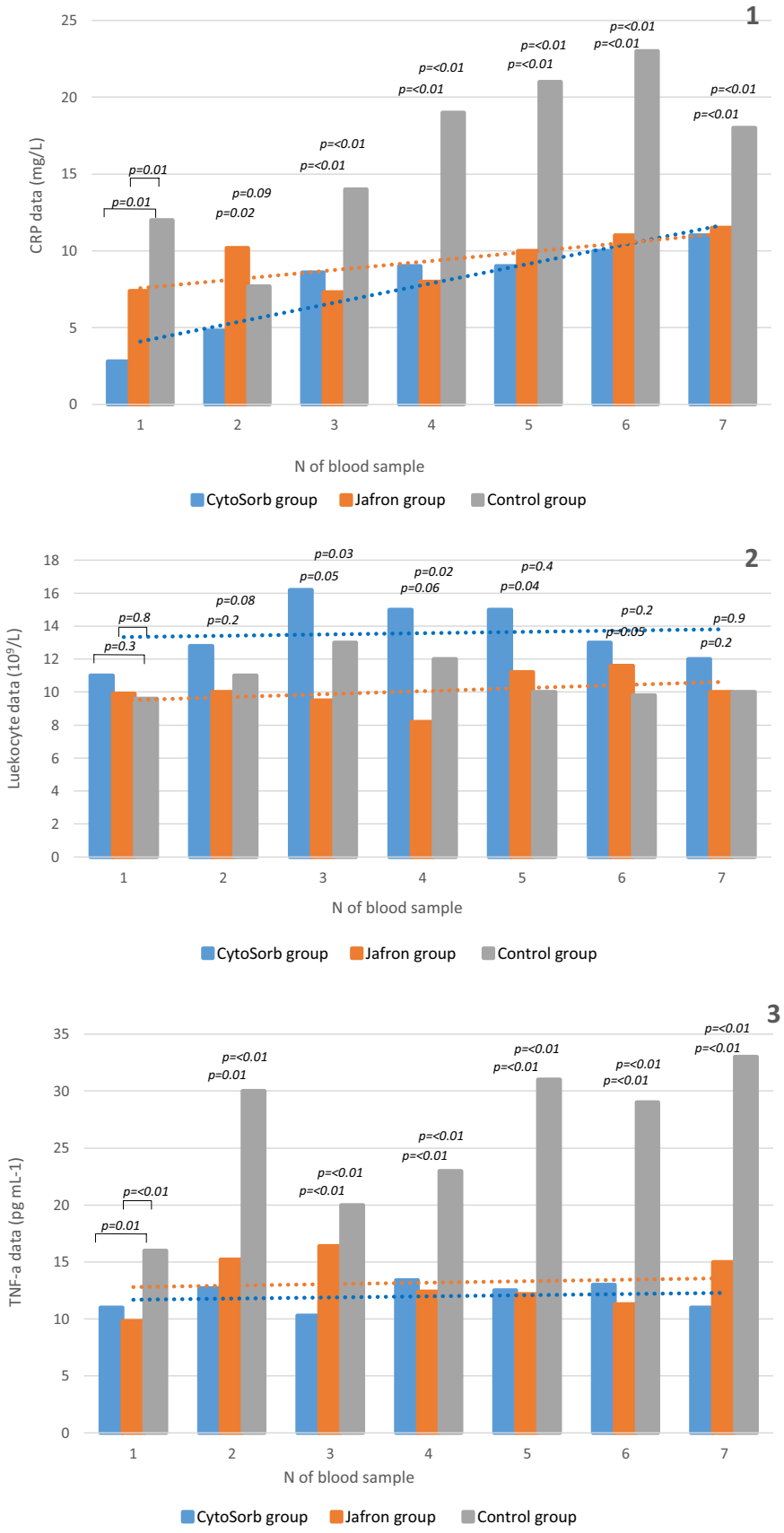


FIGURE 4 Outcome parameters: 1-CRP, 2-. Leukocyte, 3- TNF-a in patients with V-A ECMO+Cytosorb adsorption, V-A ECMO+Jafron cartridge, and a cohort with V-A ECMO alone. According to Table 2 blood sampling scheme.

inflammatory markers. The value of all laboratory parameters was sustained and did not differ in CytoSorb and Jafron HA330 groups. If so, this strategy is also likely to be cost-effective in settings with similar clinical effectiveness.

Our study has some limitations. First, the three groups were not randomly selected. Second, this study includes its single-institution nature. Third, the number of patients included is small, which limits the interpretation and generalization of our results.

5 | CONCLUSION

Hemadsorption in patients requiring postcardiotomy ECMO support represents a good therapeutic effect. This effect is permanent for the whole period of extracorporeal HA application for both CytoSorb and Jafron HA330 devices. Jafron HA330 seemed to be correlated to more favorable clinical outcomes, although not substantiated by laboratory findings. Just like ECMO, HA is also an adjunct tool and the timing for its application should follow the criteria for ECMO. The panel of parameters comprising both pro-inflammatory and anti-inflammatory markers should be validated under certain clinical condition as a postcardiotomy shock. The latter is always stated as a profound shock justifying indication for CH therapy.

AUTHOR CONTRIBUTIONS

Timur Lesbekov: data analysis/interpretation, critical revision of the article; Zhuldyz Nurmykhametova: data analysis/interpretation, critical revision of the article, data collection; Rymbay Kaliyev: concept/design, approval of article; Aidyn Kuanyshbek: approval of article; Linar Faizov: concept/design; Bolat Bekishev: data collection; Nilufar Jabayeva: data collection; Robertas Samalavicius: statistics, data interpretation; Yuriy Pya: approval of the article.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

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