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Research Article

Cytokine Filter Experience in Covid-19 Treatment; A Single Center Study

Covid-19 Tedavisinde Sitokin Filtresi Deneyimi;Tek Merkezli Bir Çalışma

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Abstract

Aim: Several studies state that the primary underlying mechanism of severe COVID-19 cases includes the hyperimmune response triggered following SARS-CoV-2 infections and the subsequent cytokine storm. The study aims to examine the effects of cytokine filters on patients with COVID-19 who developed cytokine storms.

Material and Methods: This is a retrospective, cross-sectional study. All the patients included in the study had tested positive for COVID-19 in their real-time polymerase chain reaction test. The study included patients with COVID-19 who developed cytokine storms and were treated in the ICU. The patients were divided into two groups those who applied cytokine filter or not. The demographic data and laboratory findings of the patients were recorded. The patient outcomes were categorized as discharged or deceased.

Results: The study included 149 patients. Patients' mean age was 56±29 years, and 125 (83.9%) patients were male. A significant decrease was detected in the levels of fibrinogen, ferritin, lymphocyte count, and CRP after cytokine filtration (p <0.001, <0.001, 0.031, and <0.001, respectively). Age, d-dimer, and lymphocyte count were found independent factors for discharge.

Conclusion: The blood filtration method has been found to be useful in the hyperimmune response when administered following early diagnosis in selected cases. When administered following early diagnosis in selected cases, the method can be beneficial in supplementing the effectiveness of primary therapies and preventing secondary cytokine release complications as it controls hyperinflammation.

Keywords: Cytokine storm, COVID-19, therapeutics, interleukin, blood

Öz

Amaç: Yapılan birçok çalışmada şiddetli COVID-19 vakalarının altında yatan ana mekanizmanın, enfeksiyonu takiben tetiklenen hiperimmün yanıt ve ardından gelişen sitokin fırtınası olduğu belirtilmektedir. Çalışmamız sitokin fırtınası gelişen COVID-19 hastalarında, sitokin filtrelerisinin tedavideki etkilerini incelemeyi amaçlamaktadır.

Materyal ve Metot: Çalışmamız retrospektif, kesitsel bir çalışmadır. Çalışmaya dahil edilen tüm hastaların gerçek zamanlı polimeraz zincir reaksiyonu ile COVID-19 testi pozitif olan hastalardan oluşmaktadır. Çalışma, sitokin fırtınaları geliştiren ve yoğun bakım ünitesinde tedavi edilen COVID-19 hastalarını içeriyordu. Hastalar sitokin filtresi uygulanan ve uygulanmayanlar olmak üzere iki gruba ayrıldı. Hastaların demografik verileri ve laboratuvar bulguları kaydedildi. Hasta sonuçları taburcu veya ölen olarak kategorize edildi.

Bulgular: Çalışmaya 149 hasta dahil edildi. Hastaların yaş ortalaması 56±29 yıl olup 125 (%83,9) hasta erkekti. Sitokin filtrasyonu sonrası fibrinojen, ferritin, lenfosit sayısı ve CRP düzeylerinde anlamlı düşüş tespit edildi (sırasıyla p <0,001, <0,001, 0,031 ve <0,001). Yaş, d-dimer ve lenfosit sayısının taburculuk için bağımsız faktörler olduğu tespit edildi.

Sonuç: Seçilmiş olgularda ve erken tanı sonrası kan filtrasyon yöntemlerinin uygulanması hiperimmün yanıt tedavisinde faydalı olduğu bulunmuştur. Seçilmiş vakalarda erken tanının ardından uygulandığında bu yöntem, hiperinflamasyonu kontrol altına aldığı için birincil tedavilerin etkinliğini desteklemede ve sitokin salınımına sekonder gelişen komplikasyonları önlemede faydalı olabilir.

Anahtar Kelimeler: Sitokin fırtınası, Covid-19, terapötik, interlökin, kan

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INTRODUCTION

After the detection of the initial cases of coronavirus disease 2019 (COVID-19) presenting with atypical pneumonia in Wuhan, China in late 2019, the infection was classified as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses on March 2, 2020 (1). Three months following the outbreak of the disease, it was declared a pandemic by the World Health Organization due to its high contagion (2). Since the disease rapidly spread due to its high virulence, it led to a swift increase in the number of cases, exceeding the capacities of health systems and resulting in serious losses of lives, as a specific antiviral treatment with proven efficacy was yet to be developed prior to the completion of vaccine generation (3). Although numerous hypotheses have been proposed concerning the pathogenesis of COVID-19, the certain mechanism of action and underlying causes of its varying clinical presentations are yet to be revealed (4).

Conditions such as infections, malignancies, rheumatological diseases, and certain medications bring about the uncontrolled and excessive release of cytokines, known as a cytokine storm (5). Since proinflammatory cytokines are of critical significance to the inflammatory pathways, they are also important in the generation of cytokine storms (6). It is shown that the primary underlying mechanism of severe COVID-19 cases includes the hyperimmune response triggered following SARS-CoV-2 infections and the subsequent cytokine storm (7). In postmortem studies, patients with severe COVID-19 presented with pulmonary edema, widespread alveolar damage, reactive hyperplasia of type II pneumocytes, fibrinous exudate, and the inflammatory infiltrates of concentrated monocytes and macrophages (8). Following reports stating that one of the aggravating effects of the clinical picture of severe COVID-19 cases was the immune responses caused by uncontrolled cytokine release, the management, and treatment strategies of the disease began focusing on this issue (9,10). Blood purification is also among the methods employed to alleviate the effects of cytokine storm in COVID-19. With previous successful and promising outcomes in cases of sepsis where the method was attempted, blood purification is intended to eliminate the harmful effects of the systemic responses that develop due to the release of pro-inflammatory and anti-inflammatory agents (11,12).

The present study aims to examine the possible effects of blood purification on the outcomes and laboratory findings of patients in the intensive care unit (ICU) with severe COVID-19 who developed cytokine storms.

MATERIAL AND METHOD

Study Design

This is a retrospective, cross-sectional study conducted over a period of 5 months (May–September 2021). All data obtained from Mersin City Hospital. The study included patients with COVID-19 who developed cytokine storms and were treated in the ICU of a tertiary hospital and consequently followed up for COVID-19. The ethical approval for the study was obtained from the Mersin University local ethics committee (approval no. 2021/632; obtained on September 22, 2021), and the study was conducted in accordance with the Declaration of Helsinki.

Patient Selection

All the patients included in the study had tested positive for COVID-19 in their real-time polymerase chain reaction (RT-PCR) test. The criteria for ICU hospitalization were a respiratory rate of ≥30/min, severe respiratory distress (involving dyspnea and use of accessory respiratory muscles), and oxygen saturation at ambient temperature ≤90% (PaO_2/FiO_2 <300 in a patient receiving oxygen). The parameters indicating a hyperimmune response in the patients included prolonged and persistent fever despite treatment, elevated levels of C-reactive protein (CRP) (or CRP progression during treatment), ferritin, and D-dimer, existing lymphopenia and thrombocytopenia, and impaired liver function tests. The patients under the age of 18 years who were not diagnosed with cytokine storm during the hospitalization or follow-ups, those who tested negative in RT-PCR tests, and those whose data were completely or partially unavailable on the hospital information system were excluded from the study. Since interleukin (IL) inhibitors were not yet in supply, they were not among the treatments administered to the patients in the ICU for cytokine storms during the study period. Some of the patients received cytokine filtration treatment along with supportive treatment during the study period, whereas others only received the supportive treatment in the ICU because of disruptions in the supply of the cytokine filter.

CytoSorb (Cytosorbents Inc., New Jersey, USA) blood purification method was applied in the present study. CytoSorb is a blood purification method that removes inflammatory molecules from the blood using blood-coated beads that are highly absorbent and are coated with polyvinylpyrrolidone for biocompatibility (13). The criteria for the selection of the patients on whom cytokine filtration was to be applied were as follows: the presence of elevated levels of serum inflammatory molecules (ferritin >300 ug/L and an increased value during follow-up, lymphocyte <0.6×109/L, D-dimer >1mcg/mL, and CRP >5mg/dl or doubled after 48 hours), Sequential Organ Failure Assessment score >2, lactate levels >2mmol/L in blood gas measurement, vasopressor support in the absence of hypovolemia to keep the average arterial pressure at ≥65mmHg, shock, and appropriate antimicrobial therapy administration. After obtaining the consent of the patients selected for cytokine filtration, a double-lumen venous catheter for venovenous hemofiltration was put in place. The CytoSorb cartridge was used for hemofiltration. The

blood flow rate was planned as 150–200ml/min and the CytoSorb kit was replaced at intervals of 24 hours.

Data Collection

The demographic data (age, gender) and laboratory findings (creatinine, alanine transaminase, fibrinogen, D-dimer, ferritin, white blood cell (WBC), neutrophil, lymphocyte, platelet, CRP, procalcitonin) of the patients were recorded. The patient outcomes were categorized as discharged or deceased. Finally, the total number of cytokine filters applied to each patient was recorded. During the study, no complications related to the device or method were encountered in the treatment group.

Outcome

The primary outcome of the investigation was the effect of cytokine filter application on the laboratory findings of the patients who developed a cytokine storm due to COVID-19. The secondary outcome was to determine the effect of this treatment following patient discharge.

Statistical Analysis

To statistically analyze the findings obtained in the present study, IBM SPSS Statistics 22 (IBM SPSS, Turkey) software was used. Shapiro Wilks test was used to confirm the normal distribution of the parameters. Along with the descriptive statistical methods (mean, standard deviation, median and interquartile range, frequency), Wilcoxon signed-rank test was also used to compare the dependent quantitative variables. Logistic regression analysis was employed to examine the effects of the variables on discharge. The statistical significance was set at $p<0.05$.

RESULTS

The study included 149 patients. Patients' mean age was 56±29 years, and 125 (83.9%) patients were male.

According to the comparison of the laboratory parameters measured before and after cytokine filtration, a significant decrease was detected in the levels of fibrinogen, ferritin, lymphocyte count, and CRP ($p<0.001$, <0.001, 0.031, and <0.001, respectively). In contrary, WBC, neutrophil, and platelet counts were significantly elevated ($p<0.001$, <0.001, and 0.031, respectively). The other values are shown in Table 1.

Cytokine filtration was performed at least once and a maximum of six times on each patient. In 115 (77.2%) patients, a total of three cytokine filtrations were performed. The number of applied cytokine filter median was 3 [3-3].

The logistic regression analysis of the parameters that might affect the discharge outcome revealed that age, D-dimer, and lymphocyte count influenced the discharge. Increased age and D-dimer levels significantly reduce the rate of discharge (odds ratio [OR] = .948, 95% confidence interval [CI; .909–.989] and OR = .749, 95% CI [.604–.928], respectively). Increased lymphocyte levels had a positive effect on discharge. The logistic regression analysis and parameter data are summarized in Table 2.

Table 1. Changes in laboratory parameters before and after cytokine filter application

	Before Treatment	After Treatment	p*
Creatinine	0.78 (0.38 IQR)	0.82 (0.92 IQR)	.079
ALT	50.00 (61.50 IQR)	63.00 (80.00 IQR)	.007
Fibrinogen	560.00 (218.50 IQR)	429.00 (260.00 IQR)	<.001
D-dimer	1.52 (2.78 IQR)	2.96 (7.18 IQR)	<.001
Ferritin	1441.00 (509.50 IQR)	938.00 (855.00 IQR)	<.001
WBC	11000 (7395 IQR)	13410 (6966 IQR)	<.001
Neutrophil	9750 (6730 IQR)	12000 (7000 IQR)	<.001
Lymphocyte	585 (415 IQR)	500 (550 IQR)	.031
Platelet	207000 (109000 IQR)	216000 (124000 IQR)	.031
CRP	10.91 (12.07 IQR)	5.36 (12.64 IQR)	<.001
Procalcitonin	0.20 (0.50 IQR)	0.20 (0.92 IQR)	.270

* Wilcoxon Signed Rank Test was used, IQR: Interquartile Range

Table 2. Logistic regression analysis of patients' parameters in terms of discharge

	Wald	Odds Ratio	95% C.I.	
Age	6.168**	.948	.909	.989
ALT	1.803	1.005	.998	1.012
Fibrinogen	.257	1.001	.997	1.004
D-dimer	6.979**	.749	.604	.928
Ferritin	1.944	1.000	.999	1.000
WBC	2.247	1.000	1.000	1.001
Neutrophil	2.573	.999	.999	1.000
PLT	.893	1.003	.997	1.008
Lymphocyte	6.026**	1.002	1.000	1.003
CRP	.802	.964	.889	1.045
Procalcitonin	3.724	.287	.081	1.020
Number of filter applications	.337	1.205	.642	2.265

Omnibus $\chi 2$ (12) = 63.001 $p<0.001$ R2 = 0.478 (Negelkerke)
**$p<0.05$ C.I.: Confidence Interval

DISCUSSION

Kogelmann et al. used the CytoSorb blood filtration method in sepsis and septic shock patients who were followed up in the ICU. In the study, the patients who had an Acute Physiology and Chronic Health Evaluation II score of >25 and developed two or more organ failures presented with accelerated hemodynamic stabilization and significant decline in blood lactate levels and lower mortality rates. Hence, it was accepted that applying the filtration within the first 24 hours following sepsis diagnosis resulted in significant improvements in the clinical outcomes of the patients, and the benefits reduce especially if the filtration is applied ≥48 hours later (13). Rimmelé et al. reported that

hemoadsorbtion treatments are well tolerated by patients and effective in removing inflammatory molecules and endotoxins from the blood and in increasing hemodynamic stabilization and oxygenation (14). In another study, the researchers found a significant decrease in the IL-6 levels and vasopressor requirements of a patient with septic shock after 4 days of treatment using the CytoSorb method, with no side effects associated with the device or method (15). In a study where Taniguchi et al. examined the efficacy of hemoperfusion therapy in endotoxemia management, the researchers found the method to be successful in removing small and medium protein molecules such as cytokines, enterotoxins, and toxic shock syndrome toxin 1 and reducing mortality by controlling the inflammatory response and recommended the use of the method in selected cases with sepsis clinic (16).

According to a few studies on cytokine filtration conducted in patients with COVID-19, one study examining the efficacy of blood filtration methods in the management of the disease reported that factors such as increased vascular permeability caused by the uncontrolled release of IL-6 in plasma and cardiac dysfunction predominantly affected the mortality rates of COVID-19. Furthermore, the study reported that along with the existing treatment protocols, the early use of blood filtration methods in individuals presenting with cytokine storms may reduce the need for intensive care support (17). In a study by Ruiz-Rodríguez et al., an underlying state of uncontrolled immune response and hyper inflammation in patients with severe COVID-19 was reported and the researchers argued that extracorporeal cytokine adsorption methods were clinically useful in ensuring oxygenation and hemodynamic stability in the patients whose clinical state could not be managed with the standard treatments and who developed cytokine storm (18). In several case reports and series, similar observations have been made, highlighting the positive effects of the method on oxygenation and hemodynamic stability; however, all such studies emphasize that the method is to be considered a supplementary to the primary treatment option for managing the hyperimmune response and the consequent cytokine storm that may occur during the disease (19,20).

On comparison of the laboratory data of the patients before and after blood filtration in the group of patients who were administered with this method, the levels of the clinical markers of a cytokine storm i.e., ferritin, CRP, fibrinogen, and D-dimer, were found to be significantly decreased, whereas the WBC, platelet, and neutrophil counts were significantly elevated in the post-filtration period. It was determined that increased age and D-dimer levels negatively impacted discharge while lymphocyte levels had a positive effect on it. The literature states that this method should be applied following early diagnosis only in selected cases rather than being considered a standard treatment (21). Previous studies have shown that cytokine filtration is associated with hemodynamic stabilization, reduction in vasopressor requirements, a significant reduction in serum lactate levels, and improvement in lung functions, with no serious side effects associated with the device and method being reported (22).

Limitations

This study was a single-center study. More efficient results can be obtained with studies to be carried out with the participation of more than one center. In this study, the effects of the cytokine filter method on mortality were not examined. More comprehensive studies are needed to examine the effects of cytokine filters on mortality.

CONCLUSION

The blood filtration method has been found to be useful in the hyperimmune response that develops during the inflammatory process and reduces inflammatory cytokine release. When administered following early diagnosis in selected cases, the method can be beneficial in supplementing the effectiveness of primary therapies and preventing secondary cytokine release complications as it controls hyperinflammation. However, further studies with a better study design including extensive clinical trials are needed.

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