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ORIGINAL ARTICLE

Evaluation of Adsorption Therapy as an Extracorporeal Blood Purification Technique in Critically Ill Covid-19 Patients

Mehmet E. Yuksel[1], Nazan H. Selmi[2], Caglayan M. Ayaz[3], Seval Izdes[4]

[1] Ankara Etlik City Hospital, Surgical Intensive Care Unit, Ankara, Turkey; doctormehmeteren@yahoo.com
[2] Ankara City Hospital, Department of Intensive Care, Ankara, Turkey; nazanhasselmi3@gmail.com
[3] Ankara City Hospital, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey; merve.ayz@hotmail.com
[4] Ankara Yildirim Beyazit University School of Medicine, Department of Anesthesiology and Intensive Care, Ankara City Hospital, Ankara, Turkey; sevalizdes@yahoo.com

Correspondence: Mehmet Eren Yuksel, doctormehmeteren@yahoo.com

Abstract: *We aimed to evaluate the efficacy of adsorption therapy as an extracorporeal blood purification technique in critically ill patients with Coronavirus disease 2019 (COVID-19). A retrospective analysis was performed on 17 adult patients with severe COVID-19, who underwent adsorption therapy using an HA330 cartridge, at Ankara City Hospital. Each adsorption therapy was administered for three consecutive days, and each therapy session lasted three hours. Several parameters, including cytokine levels, blood count, biochemistry panel, clinical status, and mortality rate were assessed before and after each therapy session. The results obtained from this study revealed that adsorption therapy reduced IL-6 levels and improved oxygenation in the short term. However, heart rate, mean arterial pressure and SOFA score did not demonstrate significant changes. Notably, the dose of norepinephrine increased after the third session. Regrettably, only 4 out of 17 patients (23.5%) survived. Consequently, adsorption therapy appears to be effective in reducing IL-6 levels in severe COVID-19 patients. Nonetheless, further investigation is warranted to evaluate its impact on clinical outcomes.*

Keywords: *Adsorption therapy; coronavirus disease 2019; cytokine storm; extracorporeal blood purification*

INTRODUCTION

COVID-19 infects the airway epithelium, leading to widespread damage, severe inflammation, and pneumonia with a cytopathic effect. A cytokine storm, capillary leak syndrome, lung injury, and Acute Respiratory Distress Syndrome (ARDS) are all brought on by the local and circulating cytokines that are produced at this time [1-4]. In patients with severe COVID-19, several inflammatory mediators are involved, and the cytokine storm has a deleterious impact on the disease's progression [5].

Additionally, COVID-19 exhibits immunological dysfunction. Techniques for extracorporeal blood purification have previously been utilized as supportive therapy to manage immunological dysregulation in the treatment of sepsis [6]. Despite the use of a variety of treatments, critically ill COVID-19 patients have consistently significant mortality rates. As a result, the use of cytokine filters as a therapy option for these individuals is now being given further thought.

Patients with COVID-19 have considerably higher levels of proinflammatory cytokines and chemokines like tumor necrosis factor-α, interleukin 1 and 6, granulocyte-colony stimulating factor, monocyte chemoattractant protein-1, interferon gamma-induced protein-10, and macrophage inflammatory proteins 1-α [7]. In individuals with severe COVID-19, these proinflammatory cytokines and chemokines lead to a cytokine storm. The extracorporeal removal of these cytokines from COVID-19 patients' blood circulation using an adsorption therapy is hypothesized to minimize hyperinflammation and calm the cytokine storm. Extracorporeal blood purification systems do not only remove pathogenic toxins and proinflammatory mediators; they also remove regulating cytokines. As a result, their process is non-selective. These regulatory cytokines are also advantageous because they restrain the immune system from overreacting to inflammation [8]. Therefore, while the application of extracorporeal blood purification procedures may have short-term advantages, its possible adverse effects on long-term

outcomes have not yet been thoroughly assessed and understood.

An adsorption therapy, which is an extracorporeal blood purification technique can be used as a cytokine filter in severe COVID-19 patients. For this aim, an extracorporeal filter which is a cartridge with a sorbent inside is used for blood purification by combining convection and diffusion for solute removal [9]. Additionally, through ionic attraction, hydrophobic interactions, hydrogen bonds, and van der Waals interactions, the sorbent in the cartridge comes into direct contact with blood to adsorb solutes [10,11]. The sorbent in the cartridge also targets TNF, IL-1, IL-6, IL-10, IL-18, and other cytokines [11]. Thus, cytokines and solutes in the bloodstream bind to the sorbent material. Therefore, adsorption therapy can also be used for patients with autoimmune diseases, chronic uremic symptoms, intoxications, and inflammatory conditions with cytokine storms such as sepsis and pancreatitis [9,12].

For adsorption therapy in COVID-19 patients, the Jafron HA330 cartridge can be used [13]. The neutro-macroporous resin-adsorbing beads in the HA330 cartridge are constructed of the styrene-divinylbenzene copolymer. The resin beads' average diameter ranges from 0.60 to 1.18 mm and is 0.8 mm. The resin's pore sizes range from 500 D to 60 kD, whereas the HA330 cartridge removes molecular weights from 10 to 60 kDa (kiloDalton; Dalton [9,12]. Multiple pore sizes of the sorbent material allow the removal of several molecules with different molecular weights such as free hemoglobin, cytokines, complements, drugs, uremic toxins, and protein-bound or hydrophobic substances. The recommended treatment duration with an HA330 cartridge is 2-2.5 hours, while the sorbent material can be saturated if it is used for a longer period which causes a decrease in clearance efficiency [9,12].

In this study, we wanted to assess the efficacy of adsorption therapy in patients with severe COVID-19. To understand the effects of adsorption therapy using HA330 cartridges in severe COVID-19 patients in the intensive care unit (ICU), we evaluated the changes in the clinical status of patients, cytokine levels, complete blood count, and biochemistry panel before and after the administration of the therapy

MATERIALS AND METHODS

A retrospective analysis was performed on 14 male (82.3%) and 3 female (17.6%) adult severe COVID-19 patients who received adsorption therapy (HA330 cartridge, Jafron) in the ICU at Ankara City Hospital between April 2020 and October 2021 (Table 1). Before and after adsorption therapy with HA330, the patients' laboratory results and clinical outcomes were assessed. Ankara City Hospital (E2-21-983) granted permission for this study with the approval of the local ethics committee.

Table 1: Characteristics of severe COVID-19 patients treated with HA330 adsorption cartridge

Characteristics of COVID-19 patients	
Demographics	
Age (years) (median, IQR)	53.5 (45-62.5)
Gender, male (n, %) female (n, %)	14 (82.3) 3 (17.6%)
Treatment	
Methylprednisolone 40 mg (n, %)	17 (100)
IVIG (n, %)	1 (5.8)
Anakinra (n, %)	9 (52.9)
Tocilizumab (n, %)	1 (5.8)
Outcomes	
Length of ICU stay (days) (median, IQR)	22 (34)
Mechanical ventilator duration (days) (median, IQR)	20 (30)
Survived (n, %)	4 (23.5)
Died (n, %)	13 (76.5)

1 IQR: interquartile range. IVIG: intravenous immunoglobulin. ICU: intensive care unit. Anakinra: An interleukin-1 receptor antagonist. Tocilizumab: A monoclonal antibody against the IL-6 receptor. In this study, 14 male (82.3%) and 3 female (17.6%) adult patients with severe COVID-19 were treated with adsorption therapy (HA330 cartridge, Jafron©) in the ICU. The median age of the patients was 53.5 (IQR: 45-62.5). All 17 patients received a ten-day course of iv methylprednisolone 40 mg once daily. Of the patients, nine were treated with anakinra, one with tocilizumab, and one received IVIG treatment without tocilizumab or anakinra. Four patients died after the first adsorption therapy session, and another four died after the second. Nine patients completed three sessions of adsorption therapy, but five of them died due to sepsis and ARDS-related complications in the ICU. Overall, 4 out of 17 critically ill COVID-19 patients survived after adsorption therapy with an HA330 cartridge (23.5%).

Respiratory distress with peripheral capillary oxygen saturation (SpO_2) 93% in room air, dyspnea with a respiratory rate of at least 30 breaths per minute, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2) less than 300 mmHg, and more than 50% infiltration of the lung fields are all considered to be severe COVID-19 in adult patients [14]. Moreover, cytokine release syndrome was defined as having one or more of C-reactive protein >100 (or >50 mg/L but doubled in the past 48 hours), lymphocyte count <0.6 × 109/L, serum interleukin-6 (IL-6) level higher than 3 times of the upper normal limit, ferritin >300 ug/L with doubling within 24 hours, ferritin >600 ug/L at presentation and LDH >250 U/L, and elevated D-dimer (>1 mcg/mL) [15]. These 17 patients had confirmed COVID-19 diagnoses based on real-time reverse transcription polymerase chain reaction (RT-PCR) test results and ground glass appearance with pneumonia on thorax computed tomography before admission to the ICU. They also had previously defined severe COVID-19 disease and cytokine release syndrome features. The exclusion criteria for this study included being under the age of 18, having severe heart failure with a left ventricular ejection fraction of less than 35%, having coagulation issues, and being pregnant.

All 17 patients received methylprednisolone 40 mg iv once daily for ten days. 9 patients were treated with anakinra, whereas 1 patient was treated with tocilizumab. 1 patient received immunoglobulin (IVIG) treatment without tocilizumab or anakinra.

Adsorption therapy was initially planned for 3 hours daily with an HA330 cartridge for 3 consecutive days. However, adsorption therapy could be applied to 17 patients once, 13 patients twice, and 9 patients three times. Thus, creatinine, glomerular filtration rate, urea, albumin, alanine transaminase (ALT), aspartate transferase (AST), total bilirubin, lactate dehydrogenase (LDH), troponin, fibrinogen, D-dimer, lactate, ferritin, erythrocyte sedimentation rate, C-reactive protein (CRP), procalcitonin, interleukin-6 (IL-6), hemoglobin, neutrophil/lymphocyte ratio (NLR), number of leukocytes, neutrophils, lymphocytes, and platelets were noted before and after adsorption therapy sessions. Additionally, the patients' vital signs, requirements for vasopressor medications, partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2), and Sequential Organ Failure Assessment (SOFA) scores were recorded from their medical records before and after adsorption therapy sessions.

Statistical evaluation was performed using the Statistical Packages for the Social Sciences (v17.0, SPSS 24 Inc., Chicago, IL) software. Categorical data were presented as numbers and percentages, while quantitative data were presented as mean standard deviation or median and interquartile range (IQR), as appropriate. The differences between the two groups were evaluated with the Mann-Whitney U test and the Wilcoxon test. The statistical significance level was accepted as $p<0.05$.

RESULTS

Adsorption therapy with a Jafron HA330 cartridge was applied once to 17 patients, twice to 13 patients, and three times to 9 patients. The median age of the patients was 53.5 (IQR: 45-62.5). The median ICU length of stay was 22 (IQR:34) days. The median mechanical ventilator duration was 20 days (IQR:30). The median APACHE II score was 18 (IQR:10). The median length of stay in the ICU before the initiation of adsorption therapy was 4 days (IQR:2-6) (Table 1).

Table 2: Clinical status of patients before and after 1st, 2nd and 3rd sessions of adsorption therapy with HA330 cartridge

Clinical parameters	Before adsorption therapy (IQR)	After 1st session (IQR)	*P**	After 2nd session (IQR)	*P**	After 3rd session (IQR)	*P**
PaO_2/FiO_2 (mmHg) (n=12)	0.59 (0.46-0.92)	0.69 (0.47-0.95)	*0.12*	0.54 (0.46-0.69)	*0.44*	0.62 (0.51-0.71)	*1.0*
HR (bpm/min) (n=13)	87.0 (66.5-100.0)	80.0 (69.5-102.5)	*0.72*	77.0 (67.5-120.0)	*0.86*	90.0 (72.8-113.8)	*0.74*
MAP (mmHg) (n=14)	80.0 (73.8-102.5)	80.0 (68.8-97.5)	*0.44*	75.0 (65.0-92.5)	*0.23*	71.5 (61.2-96.0)	*0.53*
Dose of NE (μg/kg/min) (n=9)	0.12 (0.04-0.43)	0.15 (0.03-0.67)	*0.46*	0.04 (0.12-0.17)	*0.89*	0.25 (0.07-0.19)	*0.11*

*[2] Numerical data were given as a median and interquartile range (IQR). PaO_2/FiO_2: partial pressure of arterial oxygen/the fraction of inspired oxygen. HR: Heart rate. MAP: Mean arterial pressure. NE: norepinephrine. SOFA: Sequential Organ Failure Assessment. *Wilcoxon test was used.*

The first, second, and third sessions of adsorption therapy using the HA330 cartridge are shown in Table 2 along with the patients' clinical status before and after each session. For each clinical parameter, including PaO_2/FiO_2, heart rate (HR), mean arterial pressure (MAP), norepinephrine dose (NE), and Sequential Organ Failure Assessment (SOFA) score, the median and interquartile range (IQR) are shown in the table. According to these findings, the first adsorption therapy session led to a statistically significant increase in PaO_2/FiO_2 levels ($p=0.03$), whereas the second and third sessions did not. None of the three sessions of adsorption therapy resulted in statistically significant changes in heart rate, mean arterial pressure, or SOFA score.

The dose of NE showed a statistically significant increase after

the third session of adsorption therapy (p<0.11). Overall, these data imply that the use of an HA330 cartridge in adsorption therapy may improve oxygenation in patients with severe COVID-19, but larger sample sizes and additional research are required to confirm these results.

Table 3 shows the variations in cytokine levels, complete blood counts, and biochemistry panels in severely ill COVID-19 patients receiving first, second, and third adsorption therapy sessions using HA330 cartridges. A statistically significant decrease in IL-6 levels was observed after the first, second, and third adsorption therapy sessions (361, 86.5, 28, 20.3, p<0.03, p<0.03, p<0.007, respectively). There was a statistically significant increase in leukocyte count after the first adsorption therapy compared to the leukocyte count before adsorption therapy (12.2 to 14.6, p=0.02). However, the leukocyte count decreased from 14.6 to 12.9 after the 2nd session and increased to 13.5 after the 3rd therapy session, neither of which was statistically significant (p=0.42, p=0.12, respectively). When compared to the neutrophil count prior to the first adsorption therapy (10.9 to 13.6, p=0.03), there was a statistically significant rise in neutrophil count.

However, the neutrophil count climbed to 12.1 after the third therapy session but declined to 11.6 after the second (p=0.46 p=0.19). Neither change was statistically significant (Table 3).

Table 3: Statistical analysis of laboratory parameters of severe COVID-19 patients before and after first, second, and third sessions of adsorption therapy with HA330 cartridge

Laboratory parameters	Before adsorption therapy (n=17) (IQR)	After 1st session (n=17) (IQR)	*P**	After 2nd session (n=13) (IQR)	*P**	After 3rd session (n=9) (IQR)	*P**
Hemoglobin (g/dL)	11.6 (9.1-12.7)	11.0 (9.4-12.9)	0.64	11.0 (10.1-12.4)	0.48	11.0 (9.1-11.6)	0.22
Leukocyte Count x10^9/L	12.2 (9.1-14.3)	14.6 (9.7-21.0)	**0.02**	12.9 (8.8-20.2)	0.42	13.5 (8.9-14.6)	0.12
Neutrophil Count x10^9/L	10.9 (7.8-13.4)	13.6 (8.2-19.3)	**0.03**	11.6 (7.1-19.2)	0.46	12.1 (7.7-13.0)	0.19
Lymphocyte Count x10^9/L	0.64 (0.39-0.77)	0.62 (0.42-0.80)	0.96	0.55 (0.43-0.70)	0.92	0.48 (0.38-0.78)	0.82
Platelet count x10^9/L	262.0 (200.0-303.0)	274.0 (162.0-328.0)	0.47	266.0 (195.0-350.0)	0.75	213.0 (175.0-307.0)	0.60
NLR	20.2 (15.9-32.8)	28.8 (17.9-42.1)	**0.03**	24.3 (22.1-49.7)	0.20	23.4 (18.7-29.3)	0.80
Glucose mg/dL	189.5 (114.3-236.8)	211.0 (146.5-224.0)	0.51	153.0 (128.0-205.5)	0.38	151.0 (118.5-210.5)	0.53
Creatinine mg/dL	0.93 (0.56-1.93)	0.86 (0.64-2.0)	0.64	1.0 (0.73-2.40)	0.03	1.09 (0.62-1.30)	0.26
Estimated GFR ml/min/m^2	88.0 (41.0-118.0)	94.0 (43.5-112.5)	0.60	78.0 (30.0-99.5)	0.11	83.5 (59.0-108.0)	0.25
Urea mg/dL	62.0 (42.8-98.0)	65.5 (50.3-132.8)	0.06	84.5 (52.3-161.3)	0.07	73.0 (64.0-105.0)	0.24
Albumin g/L	29.0 (26.0-32.0)	28.0 (22.5-31.5)	**0.04**	30.0 (28.3-31.8)	0.20	28.0 (26.3-30.8)	0.49
ALT U/L	46.5 (27.8-126.8)	59.0 (30.0-200.0)	0.55	51.0 (30.0-225.5)	0.64	66.0 (26.0-100.5)	0.99
AST U/L	37.0 (27.3-81.0)	59.0 (32.5-228.0)	0.84	58.0 (22.5-180.5)	0.51	45.0 (21.0-63.0)	0.30
Total bilirubin mg/dL	0.9 (0.5-1.2)	0.8 (0.5-1.2)	0.84	0.6 (0.5-0.8)	0.18	0.75 (0.4-1.3)	0.21
Troponin Ng/L	49.0 (8.8-423.1)	114.4 (24.0-647.0)	0.74	186.0 (22.8-360.7)	0.07	-	-
INR	1.4 (1.2-1.7)	-	-	1.3 (1.2-1.48)	0.60	-	-
Fibrinogen g/L	6.4 (3.7-7.2)	6.5 (3.8-7.3)	0.51	5.7 (3.4-7.8)	0.65	5.0 (1.6-7.0)	0.64
D-dimer mg/L	5.8 (1.9-13.6)	4.9 (2.4-7.3)	0.35	8.6 (1.8-17.7)	0.44	7.90 (4.4-22.0)	0.98
Lactate	2.3 (1.6-3.2)	1.9 (1.3-2.9)	0.07	1.8 (1.4-2.4)	0.21	-	-
LDH U/L	600.5 (516.8-766.5)	659.0 (543.0-963.5)	0.65	671.0 (468.5-889.0)	0.97	578.5 (488.8-674.5)	0.39
Ferritin ml/ng	961.0 (393.5-1540.0)	1500.5 (880.3-5546.0)	0.06	1461.0 (1025.5-3667.0)	0.58	1236.5 (377.5-1611.5)	0.12
ESR mm/h	56.0 (21.8-108.3)	78.0 (15.0-125.0)	0.07	65.0 (22.5-103.0)	0.72	-	-
CRP mg/L	0.16 (0.13-0.218)	0.15 (0.13-0.25)	0.51	0.15 (0.09-0.17)	0.10	0.10 (0.06-0.14)	0.09
Procalcitonin µg/L	1.01 (0.17-11.3)	4.2 (0.28-11.6)	0.44	0.53 (0.22-8.84)	0.35	0.19 (0.11-0.58)	0.06
IL-6 pg/mL	361.0 (68.2-739.8)	86.5 (10.9-167.7)	**0.03**	28.0 (20.8-76.9)	**0.03**	20.3 (7.6-32.4)	**0.007**

*[3] Numerical data are given as a median and interquartile range (IQR). NLR: neutrophil-lymphocyte ratio, GFR: glomerular filtration rate, ALT: Alanine transaminase, AST: Aspartate transferase LDH: lactate dehydrogenase, INR: international normalized ratio, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, IL-6: interleukin-6. (-): data could not be retrieved. There was a statistically significant decrease in IL-6 levels after the first, second, and third adsorption therapy sessions (361, 86.5, 28, 20.3, p <0.03, p<0.03, p<0.007, respectively). *Wilcoxon test was used*

There was a statistically significant increase in the neutrophil-lymphocyte ratio (NLR) after the first adsorption therapy compared to the NLR before adsorption therapy (20.2 to 28.8, p=0.03). Although the NLR dropped from 28.8 to 24.3 after the second session and then further to 23.4 after the third (p=0.20 and p=0.80, respectively), neither of these decreases was statistically significant. When compared to the albumin level before the initial adsorption therapy, there was a statistically significant drop in albumin (29.0 to 28.0, p=0.04). However, albumin increased from 28.0 to 30.0 after the second session and reduced to 28.0 after the third (p=0.20 and p=0.49, respectively), neither of which was statistically significant.

No statistically significant changes were observed in creatinine, glomerular filtration rate, urea, alanine transaminase (ALT), aspartate transferase (AST), total bilirubin, lactate dehydrogenase (LDH), troponin, fibrinogen, D-dimer, lactate, ferritin, erythrocyte sedimentation rate, CRP, procalcitonin, hemoglobin, glucose, lymphocyte, or platelet count after the first, second, and third sessions of adsorption therapy with HA330 cartridges. Four patients died after the first, and another four patients died after the second adsorption therapy session. Nine patients completed three sessions of adsorption therapy. However, five of these nine patients died due to sepsis and ARDS-related complications in the ICU. Only 4 out of 17 critically ill COVID-19 patients survived after adsorption therapy with an HA330 cartridge (23.5%).

DISCUSSION

There are a limited number of publications in the English medical literature related to the use of extracorporeal blood purification techniques with the United States Food and Drug Administration (FDA) approved filters such as oXiris filter (Baxter, Deerfield, IL), CytoSorb filter (CytoSorbents, Monmouth Junction, NJ), Seraph 100 Microbind blood affinity filter (ExThera Medical, Martinez, CA) and the Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge (Terumo BCT, Lakewood, CO) for the treatment of COVID-19 patients [8]. According to Padala et al., using an oXiris filter improved clinical outcomes in two out of three patients and reduced levels of interleukin-6, erythrocyte sedimentation rate, and CRP [16]. According to Zhang et al., CRP, IL-6, IL-8, IL-10, APACHE II, and Sequential Organ Failure Assessment (SOFA) scores all significantly decreased after oXiris filter treatment, while IL-4, IL-8, and procalcitonin showed a nonstatistically significant downward trend. Unfortunately, two of five patients passed away despite treatment [2]. Ugurov et al. reported using oXiris in ten patients with COVID-19. Two of the ten patients passed away related to complications of ARDS. According to Ugurov et al., the number of white blood cells and thrombocytes increased to the normal range whereas IL-6, CRP, and fibrinogen levels decreased [17]. According to Villa et al., treatment with oXiris resulted in a significant drop in IL-6 levels as well as improvements in hemodynamic stability, multiorgan dysfunction, and oxygenation index in 37 patients [18].

Case studies of COVID-19 patients who received treatment with a CytoSorb filter were described by Rizvi et al., Melegari et al., and Berlot et al. [1, 19, 20]. All three patients survived with an improvement in CRP, IL-6, and oxygenation. Rieder et al. treated 4 patients under venovenous extracorporeal membrane oxygenation (vv-ECMO) support with cytokine adsorption with CytoSorb filter, which decreased IL-6 in COVID-19 patients [21]. According to Alharthy et al., continuous renal replacement therapy (CRRT) sessions using a CytoSorb cartridge were administered to 50 patients. Thirty-five patients who survived after CytoSorb therapy had decreased ferritin, lactate dehydrogenase, CRP, IL-6, and D-dimer levels [15].

According to Olson et al., the Seraph-100 filter was utilized in two COVID-19 patients, and as a result, post-treatment vasopressor dose, IL-6, and CRP levels decreased [22]. The use of a Seraph-100 filter on a patient with COVID-19 significantly decreased D-dimer level, according to Pape et al. [23]. Four hemodialysis patients with severe COVID-19 were treated using a Seraph-100 haemoperfusion device, according to Sandoval et al. Despite findings from other research, Sandoval et al. failed to find any appreciable drop in IL-6, D-dimer, or ferritin levels following the treatment [24]. According to Schmidt et al., 78 COVID-19 patients who received treatment with a Seraph-100 microbind affinity blood filter were evaluated. According to Schmidt et al, patients who received Seraph-100 treatment within 60 hours of ICU admission had a reduced mortality rate [25].

Reverse Takotsubo cardiomyopathy associated with COVID-19 was treated with therapeutic plasma exchange utilizing a Spectra Optia apheresis system outfitted with a Depuro D2000 adsorption cartridge, according to Faqihi et al. Following treatment, both lactate levels and left ventricular function returned to normal [26].

Koc et al. published a review of hemadsorption therapy in severe COVID-19 patients [13]. 86 patients with severe COVID-19 were included in 16 trials that were examined by Koc et al. CytoSorb®, oXiris®, Biosky filter, SeaStar® CLR filter, HA280, HA330 Jafron, and resin-directed hemadsorption cartridges were used in hemoperfusion therapy. According to Koc et al., the mortality rate, mean intubation time, and length of stay in the ICU and hospital were, respectively, 29%, 14.93 days, 17.21 days, and 31.7 days. Following hemoperfusion sessions, the

mean levels of CRP and interleukin-6 reduced (131.7 to 66.0 and 527.5 to 334.7, respectively). According to Koc et al., hemoperfusion and cytokine adsorption reduced cytokine levels, CPR, and IL-6 relative to pre-therapy, decreased mortality to 29%, and improved clinical conditions. However, these outcomes lacked statistical significance. Hemadsorption therapy was described by Koc et al. as an alternate salvage therapy for COVID-19 patients who were critically unwell. Moradi et. al reported a 73-year-old male patient was treated with hemoperfusion (HA230 cartridge, Jafron) due to a cytokine storm for 4.5 hours [27]. Moradi et al. claimed that the symptoms and need for oxygen support were alleviated during hemoperfusion treatment.

Theoretically, blocking the formation of proinflammatory cytokines can reduce hyperinflammation. The clinical outcome of severely ill COVID-19 patients can be improved by reducing hyperinflammation. Thus, anti-interleukin-6R monoclonal antibodies and corticosteroids were recommended to reduce the inflammatory response. However, IL-6 promotes neutrophil-mediated viral clearance by initiating a preliminary response against viral infections [7]. Moreover, Dienz et al. reported that IL-6 or IL-6 receptor-deficient mice could not resist Influenza A infection, which caused pulmonary damage leading to death [28]. Despite its theoretical benefit, Clark et al. reported that hemoperfusion was an experimental treatment because of its limited evidence of efficacy [29]. However, Kang et al. reported that in patients with severe COVID-19 and non-acute kidney injury, continuous renal replacement therapy using an oXiris filter might not be able to successfully reduce cytokine release syndrome [30].

Hemadsorption therapy has several additional drawbacks. Arrhythmia, coagulation issues, thrombocytopenia, and bleeding were listed as the most typical short-term hemoperfusion consequences in patients with COVID-19 by Darban et al. [31]. However, the majority of the difficulties emerged on the second and third days following hemoperfusion, not during hemoperfusion itself.

A highly biocompatible sorbent covered with a surface that inhibits platelet adherence and clotting activation is necessary for hemoperfusion. The various sorbent types utilized determine how hemoperfusion removes substances, with the effective surface area being a key factor. The sorbent material within the hemoperfusion cartridge can both absorb and lead to the loss of antibiotics and nutrients from the bloodstream [9, 10, 32].

The Jafron HA330 cartridge was the only available single-use hemoperfusion cartridge at Ankara City Hospital. Thus, we performed adsorption therapy on severe COVID-19 patients in the ICU with single-use Jafron HA330 cartridges. We used adsorption therapy as a salvage therapy when the patients did not respond to other treatment options such as antibiotics, corticosteroids, hydroxychloroquine, immunoglobulin, convalescent plasma, tocilizumab or anakinra [33].

There is still no single laboratory parameter with a cut-off value identified to initiate adsorption therapy. Moreover, the duration of therapy and the parameters to monitor the patient's response to the treatment are still under investigation [6]. Unfortunately, there is no universally accepted standardized adsorption therapy protocol. We preferentially used adsorption therapy to treat severely ill COVID-19 patients with low procalcitonin but high CRP and IL-6 levels.

Except for a decline in IL-6, we were unable to find a statistically significant link between the quantity of adsorption therapy sessions and laboratory values. The majority of the research previously cited showed that adsorption treatment reduced IL-6 levels. However, anakinra and tocilizumab might be responsible for the IL-6 decline in COVID-19 patients [34].

Moreover, our study has certain drawbacks. First of all, the sample size was quite small. Secondly, during the pandemic, we mostly served severe COVID-19 patients in our intensive care unit, which restricts the applicability of our findings to other patient populations. Finally, because a control group was not included in our investigation, additional variables, such as medication modifications and illness progression, might have an impact on the observed changes in laboratory values. Hopefully, our study contributes to the growing body of research on the use of adsorption therapy in COVID-19 patients despite these limitations.

CONCLUSION

After examining this study's data, it can be concluded that in patients with severe COVID-19, the use of an HA330 cartridge during adsorption therapy was connected to a statistically significant drop in IL-6 levels after the first, second, and third therapy sessions. Except for a rise in the leukocyte and neutrophil counts following the first session, there were no statistically significant associations between the quantity of adsorption therapy sessions and other laboratory findings.

To draw a definitive conclusion about the effect of adsorption therapy with HA330 cartridges on COVID-19 patients, further studies with larger and more diverse patient populations are needed. These studies should also consider other potential confounding factors, such as the administration of other treatments and underlying medical conditions. Nevertheless, the findings of this study point to the possibility that adsorption therapy could be a potential supplementary treatment option for individuals with severe COVID-19.

Conflicts of interest and sources of funding

The authors declare no conflict of interest. This research received no external funding.

Authors' contribution

Conceptualization, M.E.Y, N.H.S., C.M.A., S.I.; methodology, M.E.Y., S.I.; software, M.E.Y.; validation, N.H.S., C.M.A., M.E.Y., S.I.; formal analysis, M.E.Y.; investigation, M.E.Y.; resources, N.H.S., C.M.A., M.E.Y., S.I.; data curation, N.H.S, C.M.A, M.E.Y., S.I.; writing-original draft preparation, M.E.Y.; writing-review and editing, N.H.S., C.M.A., M.E.Y., S.I.; visualiza-tion, M.E.Y.; supervision, S.I.; project administration, S.I. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

The study was conducted under the Declaration of Helsinki, and local ethics committee approval for this study was obtained from Ankara City Hospital (E2-21-983).

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