RESEARCH ARTICLE / ARAŞTIRMA

DOI: 10.4274/mjima.galenos.2022.2022.41
Mediterr J Infect Microb Antimicrob 2022;11:41
Erişim: http://dx.doi.org/10.4274/mjima.galenos.2022.2022.41

Comparison of the Effects of Continuous Renal Replacement Therapy and Hemodialysis on Complications, Vital Signs, and Laboratory Parameters in Patients with COVID-19

Sürekli Renal Replasman Tedavisi ve Hemodiyalizin COVID-19'lu Hastalardaki Komplikasyonlar, Yaşamsal Belirtiler ve Laboratuvar Parametreleri Üzerine Etkilerinin Karşılaştırılması

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Abstract

Introduction: Evidence shows that continuous renal replacement therapy (CRRT) and hemodialysis may be effective in the treatment of Coronavirus disease-2019 (COVID-19). This study aimed to compare the effects of CRRT and hemodialysis on complications, vital signs, and laboratory parameters in patients with COVID-19.

Materials and Methods: This cross-sectional study was performed on 113 patients with COVID-19 who underwent hemoperfusion in Kosar Hospital of Semnan city (Iran) between 2020 and 2021. The patients were divided into two groups, the CRRT hemoperfusion group (n=49) and the hemodialysis group (n=64). A checklist was used for collecting data, which included demographic variables, history of underlying diseases, vital signs, laboratory parameters, complications, and various outcomes, which were extracted through interviews with patients or companions and in medical records. IBM Statistical Package for the Social Sciences Statistics for Windows version 26 was used for data analysis.

Results: The time from hemoperfusion to hospital discharge (3.84±4.51 vs. 5.92±4.16 day), duration of intubation (0.33±0.94 vs. 1.84±3.42), death after hemoperfusion (64.06 vs. 26.5%), situational instability (21.9 vs. 8.2%), and death during hemoperfusion (14.1 vs. 0%) were significantly lower in the CRRT group than in the hemodialysis group ($p<0.05$). In the repeated-measures analysis of variance (ANOVA) test, the two groups demonstrated a statistically significant difference in lactate dehydrogenase, alkaline phosphatase, white blood cell count, and C-reactive protein at different time points; thus, the mean of these variables was significantly lower after hemoperfusion in the CRRT group than in the hemodialysis group ($p<0.05$).

Conclusion: Continuous renal replacement therapy hemoperfusion can be effective in the recovery process of patients with COVID-19 because the length of hospital stay, intubation period, situational instability, and mortality during and after hemoperfusion are less than those of hemodialysis.

Keywords: Continuous renal replacement therapy, CRRT, hemoperfusion, hemodialysis, COVID-19

Öz

Giriş: Kanıtlar, sürekli renal replasman tedavisi (SRRT) ve hemodiyalizin Koronavirüs hastalığı-2019'un (COVID-19) tedavisinde etkili olabileceğini göstermektedir. Bu çalışma, SRRT ve hemodiyalizin COVID-19'lu hastalardaki komplikasyonlar, yaşamsal belirtiler ve laboratuvar parametreleri üzerindeki etkilerini karşılaştırmayı amaçlamıştır.

Cite this article as: Izadi S, Memarian M, Khatib ZS, Lavaf S, Mansori K. Comparison of the Effects of Continuous Renal Replacement Therapy and Hemodialysis on Complications, Vital Signs, and Laboratory Parameters in Patients with COVID-19. Mediterr J Infect Microb Antimicrob. 2022;11:41.

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Received/Geliş Tarihi: 26.06.2022 **Accepted/Kabul Tarihi:** 14.11.2022
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Mediterranean Journal of Infection, Microbes and Antimicrobials published by Galenos Yayınevi.

Published: 15 November 2022

Öz

Gereç ve Yöntemler: Bu kesitsel çalışma, 2020-2021 yılları arasında Semnan şehrinin (İran) Kosar Hastanesi'nde hemoperfüzyon uygulanan 113 COVID-19'lu hasta üzerinde gerçekleştirildi. Hastalar, SRRT hemoperfüzyon grubu (n=49) ve hemodiyaliz grubu (n=64) olmak üzere iki gruba ayrıldı. Demografik değişkenler, altta yatan hastalık öyküsü, yaşamsal belirtiler, laboratuvar parametreleri, komplikasyonlar ve çeşitli sonlanımları içeren ve hastalarla veya refakatçilerle yapılan görüşmelerden ve tıbbi kayıtlardan elde edilen verilerin toplanmasında bir kontrol listesi kullanıldı. Veri analizi için IBM Statistical Package for the Social Sciences Statistics for Windows sürüm 26 kullanıldı.
Bulgular: Hemoperfüzyondan hastaneden taburcu olana kadar geçen süre (3,84±4,51 - 5,92±4,16 gün), entübasyon süresi (0,33±0,94 - 1,84±3,42), hemoperfüzyon sonrası ölüm (%64,06-26,5), durumsal istikrarsızlık (%21,9-8,2'ye) ve hemoperfüzyon sırasında ölüm (%14,1'e karşı %0); SRRT grubunda hemodiyaliz grubuna göre anlamlı derecede daha düşüktü (p<0,05). Tekrarlanan ölçümler varyans analizi (ANOVA) testinde, iki grup arasında farklı zamanlarda ölçülen laktat dehidrojenaz düzeyi, alkalen fosfataz düzeyi, beyaz küre sayısı ve C-reaktif protein düzeyi açısından istatistiksel olarak anlamlı bir fark vardı. SRRT grubunda hemoperfüzyondan sonra bu değişkenlerin ortalaması hemodiyaliz grubuna göre anlamlı derecede düşüktü (p<0,05).
Sonuç: SRRT hemoperfüzyon, hemoperfüzyon sırasında ve sonrasında hastanede kalış süresi, entübasyon süresi, durumsal instabilite ve mortalitenin hemodiyalizden daha az olması nedeniyle COVID-19'lu hastaların iyileşme sürecinde etkili olabilir.
Anahtar Kelimeler: Sürekli renal replasman tedavisi, SRRT, hemoperfüzyon, hemodiyaliz, COVID-19

Introduction

Coronavirus disease-2019 (COVID-19) is a pneumonic pandemic caused by Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2). This disease was first detected in December 2019 in Wuhan City, China[1-3].

In mild COVID-19, the immune response can eliminate the SARS-CoV-2, possibly with specific antiviral responses of a type 1 interferon and responses of Th1 CD4+ cells and CD8+ T cells. In severe cases, there may be an initial delay in antiviral responses, followed by an increase in the production of inflammatory cytokines and the movement of monocytes and neutrophils into the lungs, leading to a cytokine storm. These cytokines, including interleukins 1, 6, and 12 (IL-1, IL-6, and IL-12, respectively) and tumor necrosis factor-alpha, lead to increased vascular permeability and eventually respiratory failure. High levels of cytokines also indicate a poor prognosis of SARS-CoV-2. Various studies have suggested that "cytokine storms" may increase the risk of death from COVID-19. Laboratory findings include lymphocyte deficiency, increased inflammatory markers such as C-reactive protein (CRP) and increased D-dimer as activation of cascade coagulation[4-7]. In addition, hemoperfusion was found to be an effective procedure for killing cytokines and reducing their inflammatory effects on other diseases. Hemoperfusion, as a blood purification procedure, has many benefits compared with other nonselective forms of in vitro detoxification[8-10].

In respiratory infections, an increase in proinflammatory cytokines of the blood creates a cytokine storm that can cause severe sepsis, septic shock, and ultimately increase mortality. Some studies have reported that the use of hemoperfusion and clearance of cytokines and inflammatory mediators from the blood may improve the normal course of the disease by improving the patient's respiratory symptoms and peripheral oxygen saturation (SpO_2)[11-13]. However, to our knowledge, no comparative study has examined the effect of continuous renal replacement therapy (CRRT) and hemodialysis on COVID-19; therefore, this study aimed to compare the effect of CRRT hemoperfusion and hemodialysis on complications, vital signs, and laboratory parameters in patients with COVID-19.

Materials and Methods

Study Design and Subjects

This cross-sectional study enrolled patients with COVID-19 who were hospitalized in Kosar Hospital of Semnan (Iran) between 2020 and 2021. The study was conducted as a census; thus, all patients with COVID-19 who underwent hemoperfusion in this hospital from February 2020 to May 2021 were examined. Then, the patients were divided into two groups: the CRRT hemoperfusion group (n=49) and the hemodialysis group (n=64). The inclusion criteria were as follows: age 25-90 years, COVID-19 confirmed by a positive reverse-transcription polymerase chain reaction, lung involvement on computed tomography, and consent to undergo hemoperfusion. The exclusion criteria were as follows: incomplete medical record, pregnancy, and reluctance to participate in the study.

Treatment

Hemoperfusion: Hemoperfusion was performed through femoral vein catheters with a blood flow rate of 250-300 mL/min. Two types of hemoperfusion cartridges were used: Jafron© (HA330) or CytoSorb® 300 for 4 and 8-12 h, respectively.

Continuous renal replacement therapy: The CRRT dose volume was adjusted according to patient needs, although the CRRT dose was usually 20-25 mL/kg/h, and access was achieved through a central venous catheter placed in one of the large central veins. The cartridges used in CRRT were Jafron© (HA330) or CytoSorb® 300 for 8 or 12-24 h.

Data Collection

A checklist was used to collect data, including demographic variables (age, sex, BMI, and smoking), history of underlying diseases [diabetes, hypertension, hyperlipidemia, cardiovascular diseases, kidney transplant, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), asthma, and cancer], vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature, and SpO_2), clinical signs, laboratory parameters [lactate dehydrogenase (LDH), alkaline phosphatase (ALP), white blood count (WBC), CRP, fasting blood sugar (FBS), blood urea nitrogen (BUN), creatinine (Cr), erythrocyte sedimentation rate (ESR), ferritin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), partial thromboplastin time (PTT), prothrombin time (PT), international normalized ratio (INR), hemoglobin (HB), hematocrit (HCT), and platelet count (PLT)], complications, and various outcomes (duration of hospitalization, duration of intubation, death during and after hemoperfusion, hemoperfusion frequency, extubation frequency, fever and chills, gastrointestinal bleeding, coagulation disorders, and situational instability) that were partly extracted through interviews with patients or companions and partly extracted from medical records.

Ethical Considerations

Before data collection, the aims of the study were explained to the patients or their caregivers, and informed consent was obtained from them. In addition, this study was performed according to the principles expressed in the Declaration of Helsinki and was approved by the Deputy of the Research and Ethics Committee of Semnan University of Medical Sciences (Iran) (IR.SEMUMS.REC.1400.172, date: 26.10.2021).

Statistical Analysis

Data were analyzed using IBM Statistical Package for the Social Sciences Statistics for Windows version 26 (IBM Corp., Armonk, NY, USA). For descriptive analyses, the mean and standard deviation or number (%) was used. Then, independent samples t-test (quantitative variables) and chi-squared test (qualitative variables) were used to compare baseline data and complications in the two groups. Finally, repeated-measures analysis of variance (ANOVA) test was used to compare vital signs and laboratory parameters at different time points (two times before and after hemoperfusion) in the two groups, and p value <0.05 was considered a significant level.

Results

A total of 113 patients with COVID-19 underwent hemoperfusion. The mean ages of the patients in the CRRT and hemodialysis groups were 52.67±13.65 and 54.86±14.20 years, respectively. There were 30 (61.2%) and 40 (62.5) male patients, respectively. The mean body mass index (BMI) values were 27.77±4.17 and 27.96±3.97 kg/m^2, respectively. The mean rates of pulmonary involvement (%) in the two groups were 58.57±16.20% and 63.44±16.6%, respectively. No significant difference was found between the two groups in terms of age, sex, BMI, history of smoking, and underlying diseases, such as hyperlipidemia, cardiovascular diseases, CKD, COPD, asthma, and cancer (p>0.05). However, a statistically significant difference was found in the history of diabetes and hypertension; thus, the percentage of patients with diabetes (64.1 vs. 18.4%) and hypertension (53.1 vs. 26.5%) in the hemodialysis group was higher than that in the CRRT group (p<0.05) (Table 1).

Table 2 compares the duration of hospitalization, complications, and consequences of hemoperfusion in the two groups. The time from hemoperfusion to hospital discharge (3.84±4.51 vs. 5.92±4.16 day), time from hospitalization to intubation (2.24±4.85 vs. 4.81±5.50 day), and duration of intubation (0.33±0.94 vs. 1.84±3.42 day) were significantly lower in CRRT group than in the hemodialysis group (p<0.05). In addition, the rates (%) of death after hemoperfusion (64.06 vs. 26.5%), situational instability (21.9 vs. 8.2%), and death during hemoperfusion (14.1 vs. 0%) were significantly lower in the CRRT group than in the hemodialysis group (p<0.05). However, in terms of the length of hospitalization, time from hospitalization to the start of hemoperfusion, hemoperfusion frequency, extubation frequency, death 24 h after hemoperfusion, and complications (fever and chills, gastrointestinal bleeding, and coagulation disorders), no significant difference was observed between the two groups (p>0.05).

In the present study, the results of repeated-measures ANOVA test showed no statistically significant difference between the two groups in terms of systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature, and SpO_2 at different time points (p>0.05) (Table 3).

Table 4 shows the comparison of the mean of laboratory parameters in the hemodialysis and CRRT groups at different time points before and after hemoperfusion by repeated-measures ANOVA test. A statistically significant difference in LDH, ALP, WBC, and CRP at different time points (p<0.05) was found between the groups; thus, the mean of these variables after hemoperfusion was significantly lower in the CRRT group than in the hemodialysis group. However, no statistically significant difference in FBS, BUN, Cr, ESR, ferritin, AST, ALT, PTT, PT, INR, HB, HCT, and PLT at different time points was found between the groups (p>0.05) (Table 4).

Discussion

Hemoperfusion is an extracorporeal blood purification procedure that involves the passage of whole anticoagulant blood through a device that contains absorbent particles. Similar to other extracorporeal methods, such as hemodialysis and hemofiltration, the patient's blood is filtered while passing through the device and then returns to the patient via an intravenous access. In some centers, this method was used to eliminate toxins in poisoning and remove cytokines in patients with sepsis[14]. The use of hemoperfusion to remove inflammatory cytokines produced by COVID-19 from the bloodstream and prevent the progression of the inflammatory process in the lungs and other organs may be effective.

Table 1. Baseline characteristics of the patients

Parameters	CRRT (n=49)	Hemodialysis (n=63)	p
Age (year)	52.67±13.65	54.86±14.20	*0.110
BMI (kg/m^2)	27.77±4.17	27.77±3.97	*0.801
Height (cm)	170.98±8.62	169.34±8.99	*0.331
Weight (kg)	81.33±12.70	80.22±12.50	*0.644
Pulmonary involvement (%)	58.57±16.20	63.44±16.15	*0.116
Sex (male/female)	30 (61.2)/19 (38.8)	40 (62.5)/24 (37.5)	**0.890
Smoking (yes/no)	6 (12.2)/43 (87.8)	6 (9.4)/58 (90.6)	**0.230
Diabetes (yes/no)	9 (18.4)/40 (81.6)	41 (64.1)/23 (35.9)	**0.041
Hypertension (yes/no)	13 (26.5)/36 (73.5)	43 (53.1)/30 (46.9)	**0.004
Hyperlipidemia (yes/no)	8 (16.3)/41 (83.7)	13 (20.3)/51 (79.7)	**0.589
Cardiovascular diseases (yes/no)	7 (14.3)/42 (85.7)	13 (20.3)/51 (79.7)	**0.405
CKD (yes/no)	1 (2)/48 (96)	2 (3.1)/62 (96.9)	**0.722
COPD (yes/no)	3 (6.1)/46 (93.9)	2 (3.1)/62 (96.9)	**0.651
Asthma (yes/no)	3 (6.1)/46 (93.9)	2 (3.1)/62 (96.9)	**0.651
Kidney transplant (yes/no)	1 (2)/48 (96)	4 (6.3)/60 (93.8)	**0.386
Cancer (yes/no)	1 (2)/48 (96)	2 (3.1)/62 (96.9)	**0.722

*Independent samples t-test, **chi-squared test.

BMI: Body mass index, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease

Table 2. Comparison of outcomes, complications, and duration of hospitalization

Parameters	CRRT (n=49)	Hemodialysis (n=63)	p
Duration of hospitalization (day)	11.04±4.97	9.98±5.92	*0.317
Hospitalization distance until the onset of hemoperfusion (day)	4.04±1.87	4.67±4.04	*0.272
Hemoperfusion distance to hospital l discharge (day)	5.92±4.51	3.84±4.16	*0.013
Hospitalization distance to intubation (day)	2.24±4.58	4.81±4.50	*0.010
Duration of intubation (day)	0.33±0.94	1.84±3.42	*0.001
Outcome (death/live)	13 (26.5)/36 (73.5)	41 (64.06)/23 (35.04)	<0.001
Hemoperfusion frequency (1/2/3)	21 (42.9)/24 (42)/4 (8.9)	19 (29.7)/37 (57.8)/8 (12.5)	**0.324
Extubation frequency (yes/no)	0 (0)/49 (100)	62 (96.9)/2 (3.1)	**0.504
Fever and shivering (yes/no)	3 (6.1)/46 (93.9)	7 (10.9)/57 (89.1)	**0.372
Gastrointestinal bleeding (yes/no)	0 (0)/49 (100)	1 (1.6)/63 (98.4)	**0.379
Coagulation disorder (yes/no)	24 (49)/25 (51)	23 (35.9)/41 (64.1)	**0.108
Situational instability (yes/no)	4 (8.2)/45 (91.8)	14 (21.9)/50 (78.1)	**0.048
Death during hemoperfusion (yes/no)	0 (0)/49 (100)	9 (14.1)/55 (85.9)	**0.006
Death 24 h after hemoperfusion (yes/no)	3 (6.1)/46 (93.9)	5 (7.8)/59 (92.2)	**0.728

*Independent samples t-test, **chi-squared test.

CRRT: Continuous renal replacement therapy

The results of our study were in line with the findings of some related studies. For example, Asgharpour et al.[15] evaluated the effect of hemoperfusion on patients with severe COVID-19 and found that 6 of 11 patients recovered after hemoperfusion. The mean SpO_2 increased significantly after three sessions of the intervention (89.60±3.94% to 92.13±3.28% after the intervention). Serum levels of CRP (136.25±84.39 to 78.25±38.67 mg/L, p=0.016) and IL-6 (139.70±105.62 to 72.06±65.87 pg/mL, p=0.073) also decreased. Finally, the authors concluded that hemoperfusion may be effective in improving patients with COVID-19. In addition, Dastan et al.[16] evaluated the effectiveness of CRRT using a disposable hemoperfusion cartridge in a 54-year-old man with COVID-19; after 4 days of hospitalization, the patient's clinical condition worsened, and he underwent intubation for invasive mechanical ventilation. SpO_2 decreased to 82%. Therefore, the patient underwent hemoperfusion by CRRT because of cytokine storm and hypoxemia. After three CRRT sessions, the SpO_2 increased to 95%, and no specific laboratory abnormalities were observed during CRRT. Finally, the researchers suggested that CRRT with a disposable hemoperfusion cartridge may be a promising option for reducing inflammatory cytokines in patients with COVID-19. In Iran, Haleh Mikaeili et al.[17] and Alavi Darazam et al.[18] have also shown that hemoperfusion may be effective in reducing the mortality of patients with severe COVID-19.

In a case report study, a 73-year-old man developed myocardial infarction about a month before the onset of COVID-19 symptoms. Owing to episodic conditions and worsening symptoms, cytokine storm was considered the main cause of postural instability, and the patient became a candidate for hemoperfusion. During hemoperfusion, the symptoms improved, and the Sequential Organ Failure Assessment scores that peaked during hospitalization following hemoperfusion decreased significantly. Finally, the study indicated that cytokine storm could be a good indicator for predicting COVID-19 severity and mortality and that hemoperfusion may be an appropriate treatment to reduce COVID-19 complications[8].

Table 3. Comparison of vital signs at different time points by repeated-measures ANOVA test

Variables	Time	Group	N	Mean	SD	p*
Systolic blood pressure	Before	CRRT	49	120.41	13.53	**0.726**
		Hemodialysis	64	119.33	13.54	
	After	CRRT	49	120.61	14.20	
		Hemodialysis	64	120.58	15.00	
Diastolic blood pressure	Before	CRRT	49	75.71	9.41	**0.285**
		Hemodialysis	64	73.85	9.32	
	After	CRRT	49	74.90	9.65	
		Hemodialysis	64	75.48	10.30	
Heart rate	Before	CRRT	49	88.59	14.64	**0.067**
		Hemodialysis	64	88.87	18.85	
	After	CRRT	49	88.20	13.66	
		Hemodialysis	64	9.37	13.25	
Respiratory rate	Before	CRRT	49	23.22	3.35	**0.189**
		Hemodialysis	64	23.38	4.05	
	After	CRRT	49	22.49	4.87	
		Hemodialysis	64	23.69	5.60	
Body temperature	Before	CRRT	49	43.68	47.88	**0.289**
		Hemodialysis	64	36.76	0.40	
	After	CRRT	49	36.95	0.58	
		Hemodialysis	64	37.11	0.67	
SpO_2	Before	CRRT	49	79.98	7.97	**0.113**
		Hemodialysis	64	76.38	9.50	
	After	CRRT	49	83.29	11.63	
		Hemodialysis	64	76.90	13.24	

*Time, *group (interaction).

SD: Standard deviation, CRRT: Continuous renal replacement therapy, SD: Standard deviation

Table 4. Comparison of laboratory parameters at different time points by repeated-measures ANOVA test

Variable	Time	Group	N	Mean	SD	p*
FBS	Before	CRRT	49	166.61	45.82	**0.105**
		Hemodialysis	64	164.92	59.07	
	After	CRRT	49	227.65	76.68	
		Hemodialysis	64	202.48	89.44	
BUN	Before	CRRT	49	23.29	11.29	**0.185**
		Hemodialysis	64	40.90	28.71	
	After	CRRT	49	24.12	13.62	
		Hemodialysis	64	37.60	26.90	
Cr	Before	CRRT	49	1.20	0.50	**0.422**
		Hemodialysis	64	1.93	1.59	
	After	CRRT	49	1.19	0.52	
		Hemodialysis	64	1.83	1.49	
ESR	Before	CRRT	49	37.20	25.52	**0.234**
		Hemodialysis	64	45.44	26.18	
	After	CRRT	49	18.67	22.02	
		Hemodialysis	64	34.54	34.40	
LDH	Before	CRRT	49	1056.57	368.67	**0.019**
		Hemodialysis	64	1018.60	436.41	
	After	CRRT	49	918.37	527.55	
		Hemodialysis	64	1106.00	553.84	
Ferritin	Before	CRRT	49	472.80	292.67	**0.939**
		Hemodialysis	64	554.98	309.35	
	After	CRRT	49	509.57	296.53	
		Hemodialysis	64	586.81	303.84	
AST	Before	CRRT	49	49.82	28.30	**0.380**
		Hemodialysis	64	52.65	31.72	
	After	CRRT	49	81.45	109.78	
		Hemodialysis	64	101.31	121.22	
ALT	Before	CRRT	49	43.02	40.83	**0.222**
		Hemodialysis	64	41.49	32.53	
	After	CRRT	49	64.96	56.11	
		Hemodialysis	64	82.80	135.90	
ALP	Before	CRRT	49	159.90	52.47	**0.022**
		Hemodialysis	64	155.71	47.86	
	After	CRRT	49	198.08	80.38	
		Hemodialysis	64	221.35	88.62	
PTT	Before	CRRT	49	35.92	7.28	**0.305**
		Hemodialysis	64	34.58	6.08	
	After	CRRT	49	64.76	29.49	
		Hemodialysis	64	69.33	28.81	
PT	Before	CRRT	49	13.15	0.46	**0.548**
		Hemodialysis	64	13.74	3.47	
	After	CRRT	49	16.00	6.69	
		Hemodialysis	64	17.31	5.73	

Table 4. Continued

Variable	Time	Group	N	Mean	SD	p*
INR	Before	CRRT	49	1.03	0.07	**0.176**
		Hemodialysis	64	1.14	0.61	
	After	CRRT	49	1.45	0.72	
		Hemodialysis	64	1.77	0.94	
WBC	Before	CRRT	49	13.92	4.70	**0.029**
		Hemodialysis	64	12.42	6.90	
	After	CRRT	49	12.77	6.71	
		Hemodialysis	64	14.25	10.56	
HB	Before	CRRT	49	13.06	1.96	**0.436**
		Hemodialysis	64	12.25	1.82	
	After	CRRT	49	12.30	1.74	
		Hemodialysis	64	11.64	1.97	
HCT	Before	CRRT	49	38.05	5.90	**0.116**
		Hemodialysis	64	37.42	5.35	
	After	CRRT	49	36.81	5.38	
		Hemodialysis	64	35.36	5.71	
PLT	Before	CRRT	49	233.43	92.50	**0.147**
		Hemodialysis	64	198.08	78.54	
	After	CRRT	49	240.06	84.24	
		Hemodialysis	64	187.27	87.86	
CRP	Before	CRRT	49	62.69	33.47	**0.006**
		Hemodialysis	64	65.33	35.37	
	After	CRRT	49	23.33	28.62	
		Hemodialysis	64	50.10	41.25	

*Time, *group (interaction).

WBC: White blood count, ALP: Alkaline phosphatase, FBS: Fasting blood sugar, BUN: Blood urea nitrogen, Cr: Creatinine, ESR: Erythrocyte sedimentation rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, PTT: Partial thromboplastin time, PT: Prothrombin time, INR: International normalized ratio, HB: Hemoglobin, HCT: Hematocrit, PLT: Platelet count, SD: Standard deviation, LDH: Lactate dehydrogenase, SD: Standard deviation

Generally, various mechanisms have been proposed for severe COVID-19 and related complications. Cytokine storm is one of the mechanisms of interest. IL-6 is the most important cause of cytokine storm. When a cytokine storm occurs, the immune response intensifies, and subsequently, COVID-19 progresses rapidly[19-22]. One of the treatment strategies to reduce and stop the production of inflammatory cytokines is hemoperfusion, which can be effective in patients with severe COVID-19. Studies have shown that improving SpO_2 during blood purification is more associated with a cytokine reduction than volume load reduction because in the CRRT method, the same amount of fluid is removed from the patient and the same amount of fluid is replaced. In addition, reducing cytokines prevent damage to various organs, especially in patients who are in the early stages of cytokine storms[23-25].

Study Limitations

C-reactive protein is another biomarker that is elevated in the early stages of COVID-19, and a higher level is associated with severe lung damage. A study showed that this marker also decreases after hemoperfusion[26]. These studies have several strengths and weaknesses. The most important weakness of the present study is the lack of random allocation of patients to intervention groups; thus, the two groups were incomparable in terms of many known and unknown confounding variables. Therefore, clinical trial studies with random allocation are necessary. One of the study's strengths is the nearly appropriate sample size in the two groups, and the comparative nature of the study because most of the studies conducted in this field were case reports or case series and did not have a control group.

Conclusion

This study suggests that CRRT hemoperfusion can be effective in the recovery process of patients with COVID-19 because the length of hospital stay, intubation period, situational instability, and mortality during and after hemoperfusion are less than those of hemodialysis. However, multicenter clinical trial studies with appropriate sample sizes are recommended.

Acknowledgments

This article is extracted from Zahra Shaabani Khatib's thesis of general medicine in Semnan University of Medical Sciences, Iran. We would like to express our sincere gratitude to the staff of Kosar Hospital of Semnan city (Iran) for their cooperation in this research.

Ethics

Ethics Committee Approval: This study was performed according to the principles expressed in the Declaration of Helsinki and was approved by the Deputy of the Research and Ethics Committee of Semnan University of Medical Sciences (Iran) (IR.SEMUMS.REC.1400.172, date: 26.10.2021).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.I., M.M., S.L., Concept: M.M., Z.S.K., Design: S.I., M.M., K.M., Data Collection or Processing: Z.S.K., S.L., K.M., Analysis or Interpretation: S.L., K.M., Literature Search: S.I., M.M., Z.S.K., S.L., Writing: S.I., M.M., Z.S.K., S.L., K.M.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The study was supported by Deputy of Research of Semnan University of Medical Sciences, Semnan, Iran.

References

1. Cau R, Falaschi Z, Paschè A, Danna P, Arioli R, Arru CD, Zagaria D, Tricca S, Suri JS, Karla MK, Carriero A, Saba L. Computed tomography findings of COVID-19 pneumonia in Intensive Care Unit-patients. J Public Health Res. 2021;10:2270.
2. Liu P, Niu R, Chen J, Tang Y, Tang W, Xu L, Feng J. Epidemiological and clinical features in patients with coronavirus disease 2019 outside of Wuhan, China: Special focus in asymptomatic patients. PLoS Negl Trop Dis. 2021;15:e0009248.
3. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. J Med Virol. 2020;92:401-2.
4. Toor SM, Saleh R, Sasidharan Nair V, Taha RZ, Elkord E. T-cell responses and therapies against SARS-CoV-2 infection. Immunology. 2021;162:30-43.
5. Pasrija R, Naime M. The deregulated immune reaction and cytokines release storm (CRS) in COVID-19 disease. Int Immunopharmacol. 2021;90:107225.
6. King C, Sprent J. Dual nature of type I interferons in SARS-CoV-2-Induced Inflammation. Trends Immunol. 2021;42:312-22.
7. Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine storm in COVID-19: the current evidence and treatment strategies. Front Immunol. 2020;11:1708.
8. Moradi H, Abbasi S. Hemoperfusion as a supportive treatment in a COVID-19 patient with late pulmonary thromboembolism: a case report. Int Med Case Rep J. 2020;13:341-5.
9. Safari S, Salimi A, Zali A, Jahangirifard A, Bastanhagh E, Aminnejad R, Dabbagh A, Lotfi AH, Saeidi M. Extracorporeal Hemoperfusion as a Potential Therapeutic Option for Severe COVID-19 patients; a Narrative Review. Arch Acad Emerg Med. 2020;8:e67.
10. Shokouhi S, Barati S, Kazeminia N, Jamali F, Roshan B, Sahraei Z. Evaluating the elimination status of medications used for COVID-19 during hemoperfusion and therapeutic plasma exchange: A review. Int Immunopharmacol. 2021;97:107707.
11. Amınnejad R, Ghazi FFS, Behseresht A, Saeıdı M, Shafıee H, Bastanhagh E. Is Hemoperfusion A Beneficial Treatment Option In Covid-19? 2020.
12. Esmaeili Vardanjani A, Ronco C, Rafiei H, Golitaleb M, Pishvaei MH, Mohammadi M. Early Hemoperfusion for Cytokine Removal May Contribute to Prevention of Intubation in Patients Infected with COVID-19. Blood Purif. 2021;50:257-60.
13. Mousavi-Roknabadi RS, Haddad F, Fazlzadeh A, Kheirabadi D, Dehghan H, Rezaeisadrabadi M. Investigation of plasma exchange and hemoperfusion effects and complications for the treatment of patients with severe COVID-19 (SARS-CoV-2) disease: A systematic scoping review. J Med Virol. 2021;93:5742-55.
14. Ghannoum M, Bouchard J, Nolin TD, Ouellet G, Roberts DM. Hemoperfusion for the treatment of poisoning: technology, determinants of poison clearance, and application in clinical practice. Semin Dial. 2014;27:350-61.
15. Asgharpour M, Mehdinezhad H, Bayani M, Zavareh MSH, Hamidi SH, Akbari R, Ghadimi R, Bijani A, Mouodi S. Effectiveness of extracorporeal blood purification (hemoadsorption) in patients with severe coronavirus disease 2019 (COVID-19). BMC Nephrol. 2020;21:356.
16. Dastan F, Saffaei A, Mortazavi SM, Jamaati H, Adnani N, Samiee Roudi S, Kiani A, Abedini A, Hashemian SM. Continues renal replacement therapy (CRRT) with disposable hemoperfusion cartridge: A promising option for severe COVID-19. J Glob Antimicrob Resist. 2020;21:340-1.
17. Mikaeili H, Taghizadieh A, Nazemiyeh M, Rezaeifar P, Zununi Vahed S, Safiri S, Ardalan M, Ansarin K. The early start of hemoperfusion decreases the mortality rate among severe COVID-19 patients: A preliminary study. Hemodial Int. 2022;26:176-82.
18. Alavi Darazam I, Kazempour M, Pourhoseingholi MA, Hatami F, Rabiei MM, Javandoust Gharehbagh F, Amirdosara M, Hajiesmaeili M, Shabani M, Shokouhi S, Lotfollahi L, Mardani M, Haghighi-Morad M, Nassiri AA, Rangraz D, Falahaty H, Syami H, Irannejad Y, Fallah M, Zangi M, Shafigh N. Efficacy of Hemoperfusion in Severe and Critical Cases of COVID-19. Blood Purif. 2022:1-9.
19. Ronco C, Reis T. Kidney involvement in COVID-19 and rationale for extracorporeal therapies. Nat Rev Nephrol. 2020;16:308-10.
20. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. J Infect. 2020;80:607-13.
21. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395:1033-4.
22. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents. 2020;55:105954.
23. Schädler D, Pausch C, Heise D, Meier-Hellmann A, Brederlau J, Weiler N, Marx G, Putensen C, Spies C, Jörres A, Quintel M, Engel C, Kellum JA, Kuhlmann MK. The effect of a novel extracorporeal cytokine hemoadsorption device on IL-6 elimination in septic patients: A randomized controlled trial. PLoS One. 2017;12:e0187015.
24. Monard C, Rimmelé T, Ronco C. Extracorporeal Blood Purification Therapies for Sepsis. Blood Purif. 2019;47 Suppl 3:1-14.
25. Ma J, Xia P, Zhou Y, Liu Z, Zhou X, Wang J, Li T, Yan X, Chen L, Zhang S, Qin Y, Li X. Potential effect of blood purification therapy in reducing cytokine storm as a late complication of critically ill COVID-19. Clin Immunol. 2020;214:108408.
26. Wang L. C-reactive protein levels in the early stage of COVID-19. Med Mal Infect. 2020;50:332-4.