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The effects of hemoperfusion on the recovery of COVID-19 patients: A pilot trial

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ABSTRACT

Background: As a treatment method, considerable amounts of patients' blood are transferred to absorbents to remove blood cytokines in hemoperfusion. The present research studies the contribution of hemoperfusion to the outcomes observed in patients with COVID-19. *Methods:* The present quasi-experimental pilot trial recruited 80 patients hospitalized in intensive care units (ICU) suffering from COVID-19 who received hemoperfusion. Hemoperfusion was conducted for the patients in the study group in two 3-hour sessions. The requirement of respiratory support and mortality were estimated. *Results:* The patients were 56.37±14.97 years old on average. 92.5% of patients were polymerase chain reaction (PCR) positive, while the others showed the radiographic characteristic of COVID-19. In total, 52.5% of the patients died. The most prevalent clinical presentations were fever and cough. The average saturation of oxygen after and before conducting the hemoperfusion was 81.41±10.92 and 77.84±13.33, respectively. Most of those who died had an involvement higher than 75%. The reductions observed in the platelet and hemoglobin levels following hemoperfusion were recorded. In addition, urea and alanine aminotransferase (ALT) levels increased following the hemoperfusion. *Conclusions:* Hemoperfusion can result in decreased levels of platelet and hemoglobin and increased levels of urea and ALT, indicating the adverse effects of hemoperfusion on the COVID-19 patients receiving this treatment. The most important predictive factor determining the mortality rate of the COVID-19 patients receiving hemoperfusion was intubation.

Keywords: Coronavirus Disease 2019, SARS-CoV-2, Hemoperfusion, COVID-19, Pilot Study, Recovery

1. INTRODUCTION

WHO (World Health Organization) declared the outbreak of the coronavirus disease 2019 (COVID-19) as an infectious pandemic with a great number of

adverse effects on human health on March 11th, 2020 (Mahdi, 2023). The adverse effects of COVID-19 on a variety of human organs, such as the liver, kidneys, and lungs, are fatal, and several factors may contribute to the severity and frequency of consequences. Despite administering a variety of drugs, such as antiviral drugs, no definitive treatment is still available for COVID-19 treatment (Lotfi et al., 2020; Rahimi et al., 2021). Given the lack of an approved and specific antiviral drug to treat COVID-19, novel therapeutic options, e.g., hemadsorption and hemoperfusion, are seriously needed to enhance the COVID-19 patients' prognosis (Sahrai et al., 2023).

In hemoperfusion, a large volume of the patient's blood is taken and transferred to an absorbent to remove the toxins (Sun et al., 2018). Hemoperfusion acts more effectively compared to other treatment methods used to remove specific blood toxins, particularly the toxins binding to the body proteins or the ones that are hardly dissolvable (Sahrai et al., 2023). One may use hemoperfusion to treat the overdoses caused by meprobamate, barbiturates, theophylline, glutathione, carbamazepine, digitalis, acetaminophen, and methotrexate and hemoperfusion treatments usually take three hours to complete (Sun et al., 2018; Amjadi et al., 2023). Theoretically, the patient's outcomes may be enhanced in the case of artificial neutralization or removal of inflammatory chemicals from the bloodstream (Vincent et al., 2019).

Nonetheless, hemoperfusion is believed to successfully remove infections and harmful drugs from the bloodstream and can greatly help COVID-19 patients developing critical health conditions (Vardanjani et al., 2020). One of the helpful techniques to treat COVID-19 patients is hemoperfusion by removing inflammatory factors, which is conducted by attaching a hemoperfusion filter to a dialysis device, bypassing the bloodstream through the same filter, and the removal of inflammatory factors (Dastan et al., 2020). Of the whole COVID-19 patients, about 67% may develop multi-organ failures (Ruan et al., 2020). According to a systemic review, no robust conclusion was reached with regard to the role played by hemoperfusion in COVID-19 patients' recovery (Sanfilippo et al., 2021).

Also, according to another case report, using hemoperfusion in the early stages for the treatment of acute respiratory distress syndrome (ARDS) in COVID-19 patients is capable of preventing acute kidney injury (AKI), the ARDS progression, long hospital stays, and mortality (Esmaeili-Vardanjani et al., 2021). Nonetheless, there was not much information regarding the clinical trials conducted to investigate the role of hemoperfusion in the recovery of COVID-19 patients. Given the use of hemoperfusion for infection treatment and the absence of sufficient investigations regarding COVID-19, this paper aims to study the contribution of hemoperfusion to the recovery of COVID-19 patients.

2. METHODS AND MATERIALS

Design and settings

The present quasi-experimental single-arm open-label pilot trial recruited 80 COVID-19 patients admitted to an ICU who received hemoperfusion in Imam Khomeini Hospital, Urmia, West Azerbaijan, Iran, during 2020- 2021.

Eligibility criteria

The inclusion criteria of the study included stable hemodynamic conditions (diastolic blood pressure (DBP)≥60 mmHg and systolic blood pressure (SBP)≥100 mmHg), or pulmonary involvements lower than 50% accompanied by respiratory distress, or oxygen saturation lower than 88% despite receiving oxygen using a reservoir mask or noninvasive ventilation, pulmonary involvements exceeding 50% in CT scans, ICU hospitalization, and informed consent to participate in the research. The study's exclusion criteria were a medical history of vasculitis, coagulopathy, sepsis, and systemic lupus erythematosus. A person's infection with COVID-19 was determined based on radiological findings favoring COVID-19 or the COVID-19 Polymerase chain reaction (PCR) positive results.

Interventions and outcomes

The hemoperfusion was carried out in two 3-hour sessions using a h330 cartridge once in two days. The investigated variables of the research included platelet and hemoglobin levels, white blood cell (WBC) count, urea and creatinine levels, liver profile, length of hospital stay, oxygen saturation, sex, age, PCR results, clinical symptoms, rate of mortality, and respiratory support.

Ethical approval

This research follows the guidelines of the Declaration of Helsinki (DoH) and is approved by the Ethics Committee of Urmia University of Medical Sciences (ethics code: IR.UMSU.REC.1399.259). As a result, all participants provided written informed consent before

conducting any intervention. The present trial has been registered in the Iranian Registry of Clinical Trials under IRCT20180625040232N7 (accessible via https://irct.behdasht.gov.ir/trial/52081).

Statistical analysis

The statistical analyses were carried out using the SPSS software (ver. 21). The results of descriptive objectives were provided us mean (± standard deviation (SD)) or percentage and frequency. Also, the chi-square test was utilized for categorical variables. To conduct before-after comparisons, a paired t-test was carried out. Univariate logistic regression was utilized to evaluate the predictive effects of several variables on the mortality rate. 95% confidence intervals (CIs) and the odds ratio (OR) were reported for the same purpose. The significance level was P-value < 0.05.

3. RESULTS

Baseline features

The participants were 56.37±14.97 years old on average. The number of female subjects was higher (n=41; 51.2%) in the sample population. Regarding comorbidities, 31.25% of patients had diabetes, 26.25% had hypertension, 5.00% suffered from chronic kidney disease (CKD), 6.25% had a background of cerebrovascular accident (CVA), 8.75% had chronic obstructive pulmonary disease (COPD), and 22.50% had ischemic heart disease. The average values of creatine phosphokinase (CPK), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), C-reactive protein (CRP), and the calcium and ferritin levels were 1.52 U/L, 47.13 mm/h, 753 U/L, 52.69 mg/L, 8.20 mg/dL, and 598 ng/mL, respectively. Among the subjects, 20 individuals received an intravenous daily dosage of 20 grams of immunoglobulin (IVIG) for three days, and 48 subjects received interferon once in two days for up to three doses before receiving the hemoperfusion treatment.

Clinical presentations

All in all, 19.00% of the patients experienced dyspnea, 23.33% reported fever, 14.33% reported chills, 23.33% had cough, 10.00% complained of asthenia, 3.33% developed anorexia, and 6.66% had vomiting.

Respiratory support modalities

While endotracheal intubation was the most frequent intervention (n=40; 50.0%), the other modalities were non-invasive ventilation (n=8; 10.0%), continuous positive airway pressure (n=2; 2.5%), pre-intubation optimization (n=22; 27.5%), and high-flow nasal cannula therapy (n=18; 22.5%).

Clinical and laboratory parameters

After conducting the hemoperfusion, the hemoglobin levels decreased significantly in comparison with the baseline (13.48 g/dL before hemoperfusion versus 11.91 g/dL after hemoperfusion; p<0.001). Also, a significant decrease was observed in the platelet level after conducting the hemoperfusion (212.95 ±109/L before hemoperfusion vs. 167.01 ±109/L after hemoperfusion; p=0.030). By contrast, the alanine aminotransferase (ALT) (43.50 U/L before hemoperfusion vs. 57.06 U/L after hemoperfusion; p<0.001) and urea (51.10 mg/dL before hemoperfusion vs. 94.40 mg/dL after hemoperfusion; p<0.001) levels showed a significant increase following the treatment in comparison with the baseline.

From another perspective, the alkaline phosphatase (ALP) levels (189.40 U/L before hemoperfusion versus 220.96 U/L following hemoperfusion; p=0.088), white blood cell count (10.32 ±109/L before hemoperfusion versus 23.83 ±109/L after hemoperfusion; p=0.191), oxygen saturation levels (77.84% before hemoperfusion vs. 81.69% following the hemoperfusion; p=0.117), and the aspartate aminotransferase (AST) levels (60.90 U/L before hemoperfusion vs. 71.94 U/L after hemoperfusion; p=0.499) did not present a significant change after conducting the hemoperfusion (Table 1).

Outcomes

The average length of stay in the intensive care unit (ICU) was 11.04±6.75 days, and the rate of mortality was 52.3%. The mean duration of intubation lasted seven days (ranging between four and nine), while the period from the onset of disease symptoms to admission to

the ICU lasted six days (ranging between 4 and 10) on average. Among the subjects receiving hemoperfusion (OR: 29.65; 95% CI: 1.55, 567.72), only intubation in the logistic regression model significantly decreased the chance of COVID-19 mortality. Nonetheless, the parameters of oxygen saturation, age, IVIG, interferon level, and creatinine level did not significantly affect the mortality rate of COVID-19 (Table 2).

Table 1 Comparison of laboratory and clinical findings before and after the hemoperfusion.

Variable		Mean	P value
Hemoglobin	Before hemoperfusion	13.48 g/dL	<0.001
	After hemoperfusion	11.91 g/dL	
WBC	Before hemoperfusion	10.32×109/L	0.191
	After hemoperfusion	23.83×109/L	
Platelet	Before hemoperfusion	212.95×109/L	0.030
	After hemoperfusion	167.01×109/L	
ALP	Before hemoperfusion	189.40	0.088
	After hemoperfusion	220.96	
Urea	Before hemoperfusion	51.10 mg/dL	<0.001
	After hemoperfusion	94.40 mg/dL	
Creatinine	Before hemoperfusion	1.57 mg/dl	0.937
	After hemoperfusion	1.59 mg/dl	
AST	Before hemoperfusion	60.90 U/L	0.499
	After hemoperfusion	71.94 U/L	
ALT	Before hemoperfusion	43.50 U/L	<0.001
	After hemoperfusion	57.06 U/L	
Oxygen saturation	Before hemoperfusion	77.84%	0.117
	After hemoperfusion	81.69%	

Abbreviations: WBC: White Blood Cell; ALP: Alkaline Phosphatase; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase.

Table 2 Predictive factor for mortality of COVID-19 patients undergoing hemoperfusion.

Variables	p-value	OR	95% CI	
			Lower	Upper
Intubation	0.024	29.654	1.549	567.720
Age	0.115	.938	.865	1.016
SpO2 after hemoperfusion	0.052	1.292	.997	1.673
Creatinine after perfusion	0.118	.041	.001	2.248
IVIG	0.670	.550	.035	8.633
Interferon	0.988	1.020	.078	13.378

Abbreviations: OR: Odds Ratio; CI: Confidence Interval; SpO2: Peripheral Oxygen Saturation; IVIG: Intravenous Immunoglobulin.

4. DISCUSSION

This investigation aimed at studying the contribution of hemoperfusion to the recovery of patients with COVID-19 demonstrated that hemoperfusion decreased platelet and hemoglobin levels while it increased ALT and urea levels. In addition, after conducting the hemoperfusion, only the intubation served as a COVID-19 mortality predictor, and receiving other medications or the demographic variables did not affect the outcomes significantly. The most prevalent clinical symptoms of COVID-19 in our sample were cough and fever (each with the same frequency of 23.33%), followed by dyspnea (19.00%) and chills (14.33%). According to our findings, the meta-

analysis and systematic review conducted by Chang et al., (2021) indicated that the most common clinical symptoms were cough, shortness of breath, and fever, with a prevalence of 76%, 75%, and 81%, respectively.

According to another systematic review, the mortality rate was 32.3%, the average length of stay in ICU was 9.0 (95% CI: 6.5–11.2) days, and 58% of the patients required mechanical ventilation. Also, they recorded a high rate of mortality (59%) among the intubated patients (Serafim et al., 2021). Their findings are almost consistent with our results because the mean length of stay in ICU was 11.04 days, the intubation was seven days long, and the mortality rate was 52.5%. Notably, the above-cited investigations were systematic reviews that pooled the findings of several primary investigations; however, the present paper only reported a sample of 80 patients with severe COVID-19. Dastan et al., (2020) employed the hemoperfusion technique to deal with a case of COVID-19. The patient who had a positive COVID-19 PCR showed severe acidosis. Hemoperfusion was carried out at a 35 ml/kg/hour rate.

After conducting three sessions of hemoperfusion, the chest involvement declined, resulting in the transfer of the subject to the ward, who was then discharged (Dastan et al., 2020). Another retrospective research on 48 patients with severe COVID-19 indicated that hemoperfusion resulted in a noticeable increase in oxygen saturation levels and reduced CRP levels among the subjects receiving hemoperfusion compared to the typical treatments (p=0.009) (Soleimani et al., 2021). Also, we observed an increased oxygen saturation level from 77.8% to 81.7%. However, it was not noticeable. A case series on ten subjects suffering from severe COVID-19 indicated insignificant changes in platelet (p=0.07) and hemoglobin (p=0.77) levels and the white blood cell count (p=0.09) (Peng et al., 2022).

Our investigation found significant decreases in the platelet and hemoglobin levels, while a nonsignificant elevation was observed in the count of the white blood cells (p=0.191). The difference between the results is explainable given that the investigations were conducted in different settings, inclusion criteria, and statistical populations characterized by different risk factors or comorbidities besides applying interventions featuring various durations and techniques. In general, a scoping review indicated that employing plasma exchange and hemoperfusion during the cytokine storm phase could provide significant advantages for treating patients with severe COVID-19 (Mousavi-Roknabadi et al., 2021).

A systematic review conducted by Borthwick et al., (2017) on the contribution of high-volume hemofiltration (HVHF) to the outcomes in adults suffering from infectious shock or severe infection admitted to the intensive care unit indicated that the combined risk of mortality at 28 days and high-volume hemofiltration had preventive effects; however, only a few studies were conducted regarding this issue (Borthwick et al., 2017). An investigation conducted on 30 patients with COVID-19 in Iran revealed that their mean length of stay in the ICU was 9.65 days (Najafi et al., 2023). This is higher than that of our study (six days). Mikaeili et al., (2022) conducted a clinical trial on 68 subjects with COVID-19 receiving standard or hemoperfusion standard treatment. Their study indicated a noticeably lower mortality among the subjects receiving hemoperfusion (37.1% versus 63.6%, p=0.02) (Mikaeili et al., 2022).

According to a systematic review, invasive mechanical ventilation (70.3%), followed by high-flow nasal cannula (13.7%), and non-invasive ventilation (11.3%) served as the governing respiratory support for ICU patients suffering from COVID-19 (Quah et al., 2020). In the same way, endotracheal intubation, employed in nearly half of our subjects, served as the most frequently used respiratory support. According to the results obtained by a multicenter observational investigation on 62848 hospitalized subjects with COVID-19 in the United States, intubation led to an increased risk of in-hospital mortality by 31 times approximately (adjusted OR: 31.28; 95% CI: 28.22, 34.67) (Nolan et al., 2023). In line with this finding, our results indicated that intubation led to an increased probability of mortality by 29.65 among patients with COVID-19.

An investigation conducted in China by Yang et al., (2021) indicated that higher ages, increased levels of IL2 receptor, interleukin (IL)-1b, and N-terminal pro-B-type natriuretic peptide showed a significant correlation with increased risk of mortality among COVID-19 patients using ventilators. Even though we analyzed the contribution of other variables, such as creatinine level, age, IVIG, oxygen saturation, and interferon levels, to the mortality outcomes, their effects were insignificant. Although this is a pilot trial for a comparatively new treatment technique against severe COVID-19 in a developing country like Iran, it faces some limitations that should be retold:

The present trial was a pilot investigation lacking control groups. As a result, it was impossible to compare the findings related to a standard of care.

Notably, the present investigation was carried out as an open-label trial that could introduce potential biases in outcome evaluations and treatment administration.

The interventions did not measure several inflammatory cytokine levels, such as IL-6.

The present study had a comparatively small sample size, and COVID-19 was determined based on radiologic findings and PCR tests.

Thus, the results may have limited generalizability because of the potential variations in diagnosis criteria and disease symptoms.

5. CONCLUSIONS

The use of hemoperfusion to treat patients with COVID-19 led to decreased levels of platelet and hemoglobin and elevated levels of urea and ALT. Intubation served as a significant mortality predictive factor. Further large-scale randomized controlled trials are necessary to estimate the contribution of hemoperfusion to treating patients with severe COVID-19 and analyze its indications for efficiency and safety.

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Ethical approval

The research followed the Declaration of Helsinki. The Ethics Committee of Urmia University of Medical Sciences approved this study (ethics code: IR.UMSU.REC.1399.259). Accordingly, written informed consent was taken from all participants before any intervention. This trial was registered in the Iranian Registry of Clinical Trials under the code IRCT20180625040232N7, which is available at https://irct.behdasht.gov.ir/trial/52081.

Informed consent

Written informed consent was obtained from individual participants included in the study.

Authors' Contributions

Conceptualization and study design: MH and SF; data acquisition: MH and RD; data analysis/interpretation: MH and KM; statistical analysis: MH and BB; supervision/mentorship: SF; drafting of the manuscript: MH; responsibility of submitting for publication: MH. All authors were critical in revising the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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