



The effect of hemoperfusion on treatment outcomes in COVID-19 patients with respiratory failure: a prospective study

Effat Rafiee^{1#}, Samad Ghodrati^{1#}, Ayoub Pezeshgi^{2#}, Masumeh Hasanlu³, Fatemeh Salarpour⁴, Kamyar Mansori⁵, Negin Parsamanesh^{6*}

¹Department of Pulmonology, Vali-e-Asr Hospital, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran

²Department of Nephrology, Vali-e-Asr Hospital, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran

³Department of Internal Medicine, Vali-e-Asr Hospital, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran

⁴Department of Immune and Infection Diseases, CHU de Quebec Research Center, Laval University, Quebec City, Quebec, Canada

⁵Department of Epidemiology and Biostatistics, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran

⁶Zanjan Metabolic Diseases Research Center, Zanjan University of Medical Sciences, Zanjan, Iran

*Correspondence to

Negin Parsamanesh, Email:
parsamanesh@zums.com,
neginparsa.684@gmail.com

Received 31 Oct. 2022

Accepted 30 June 2023

Published online 29 July 2023

Keywords: Hemoperfusion,
COVID-19, Respiratory failure,
Intensive care unit

Abstract

Introduction: COVID-19 emerged as a global clinical threat following an outbreak in China in late 2019.

Objectives: The aim of the current study was to assess the effect of hemoperfusion in COVID-19 patients with respiratory failure.

Patients and Methods: In this prospective study, a total of 98 patients over the age of 18 with the positive COVID-19 polymerase chain reaction (PCR) test were investigated. The patients were divided into two groups; a control group consisting of 47 patients who did not receive hemoperfusion, and an exposed group consisting of 51 patients who met the criteria for hemoperfusion. Various parameters including complete blood cell counts, serum bilirubin, creatinine, C-reactive protein (CRP), and interleukin 6 (IL-6) levels were evaluated in all patients.

Results: The results of our study revealed a statistically significant difference in intensive care unit (ICU) admission between the two groups. Hospitalization time (19.941 ± 1.75 versus 14.615 ± 1.39 , $P=0.021$) and ICU time (14.98 ± 1.30 versus 9.62 ± 1.15 ; $P=0.003$) were significantly higher in patients who received hemoperfusion. Regarding the mortality rate, only 36.7% of the patients survived; however, there was no significant difference observed between the two groups ($P=0.34$).

Conclusion: In conclusion, the findings of our study indicate that hemoperfusion in COVID-19 patients with respiratory failure led to a significant increase in hospital stay and ICU stay compared to those without hemoperfusion. Further research is needed to determine the optimal timing and frequency of hemoperfusion to improve treatment outcomes in COVID-19 patients with respiratory failure.

Citation: Rafiee E, Ghodrati S, Pezeshgi A, Hasanlu M, Salarpour F, Mansori K, Parsamanesh N. The effect of hemoperfusion on treatment outcomes in COVID-19 patients with respiratory failure: a prospective study. Immunopathol Persa. 2023;x(x):e38457. DOI:10.34172/ipp.2023.38457.

Introduction

Coronavirus represents a significant pathogen affecting both humans and animals. Towards the end of 2019, a novel coronavirus was identified as the causative agent of a pneumonia outbreak in Wuhan, China. Subsequently, in February 2020, the World Health Organization (WHO) officially named the disease caused by this new virus as COVID-19. It is noteworthy that COVID-19 is the seventh known coronavirus to infect humans (1) and two other notable examples include acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) (2,3).

The most common clinical symptoms of COVID-19 are fever and cough, accompanied by nonspecific symptoms such as shortness

Key point

In a prospective study, on 98 positive COVID-19 patients, we found hemoperfusion in COVID-19 patients with respiratory failure led to a significant increase in hospital stay and ICU stay compared to those without hemoperfusion.

of breath, headache, muscle aches, fatigue, olfactory dysfunction, and earache. About 20% of patients have severe clinical symptoms and are associated with approximately 3% mortality (4,5). However, among patients with critical conditions, 67% develop other organ failure syndrome, and their mortality rate reaches 40% (6-8). The virus alone or superimposed bacterial infection probably leads to high levels of circulating



cytokines and this cytokine storm is a leading cause of several complications, such as acute heart damage, acute respiratory distress syndrome (ARDS), shock, and acute renal failure (6-10).

Huang et al reported that hospitalized patients in intensive care unit (ICU) and non-ICU have higher level of serum inflammatory cytokines compare to healthy people. According to their results and other similar studies, it has been shown that the higher level of cytokines such as interleukin (IL)-2, IL-10, IL-7 and tumor necrosis factor alpha result in the inflammation process more in ICU patients (9,10). On the other hand, some studies have used hemoperfusion to remove cytokines from the blood of patients with influenza a virus subtype H1N1 (A/H1N1) flu. As given that H1N1-induced ARDS has been treated with hemoperfusion, this method may also be useful reducing the mortality of critically COVID-19 patients (11,12).

Hemoperfusion consists of passing whole blood along with an anticoagulant through a filter containing adsorbent particles to blood purification. This method is conducted for poisoning and to remove cytokines in septic patients. Substances with a molecular weight of 100 to 40000 Da attach to the adsorbent particles and are separated from the blood, thus preventing disease progression and reducing mortality (6,13-16).

COVID-19, in addition to its extraordinary contagiousness within communities, can lead to severe and uncontrollable exacerbation of inflammatory mediators (cytokine storm) either autonomously or through the induction of secondary infections. Consequently, it can cause severe tissue damage, organ failure, and ultimately, death of patients. Currently no effective antiviral drug for COVID-19 is existed. Therefore, new therapeutic interventions such as adjunctive treatments like hemoperfusion and hemoabsorption to improve the prognosis of this patient group are necessary. Apart from using antiviral and antibiotic therapies and controlling the primary source of the disease, symptomatic treatments are often employed. By modulating the patient's immune system through extracorporeal techniques such as hemoperfusion and non-specific removal of inflammatory mediators, precise and targeted therapeutic interventions can greatly prevent tissue damage, organ failure, and mortality in patients.

Objectives

In this study, our objective was to evaluate the effect of hemoperfusion on improvement of biochemical and clinical parameters in critically ill COVID-19 patients.

Patients and Methods

Study design

Ninety-eight patients over 18 years old with the positive polymerase chain reaction (PCR) test for COVID-19 were included to the study. Among them, 51 patients met

the criteria for hemoperfusion (at least one respiratory criterion, one clinical criterion, and four laboratory criteria) (Table 1).

Other 47 patients were considered as control (without hemoperfusion). In fact, control group was those met the hemoperfusion criteria but did not receive that due to different reasons such as temporary lack of special hemoperfusion filters or no consent of the patient's companions.

In the present study inclusion criteria were patients with a definite diagnosis of COVID-19 by PCR test, patients with severe cytokine storms and respiratory symptoms (ARDS) and age over 18 years. Occurrence of coagulation disorder confirmed by the attending physician after performing hemoperfusion once, lack of satisfaction created in the patient to continue the intervention during its implementation, unwanted errors of the medical staff affecting the results of the research and complications due to hemoperfusion were considered as exclusion criteria.

Experimental

Patients underwent hemoperfusion using HA330 cartridge with a blood flow rate of 200 to 250 cc/min for 4 hours daily, preferably three days (depending on the patient's clinical condition for up to five days). Afterwards, the patients were compared in terms of the SOFA score (sequential organ failure assessment) (17), vital organ dysfunction and oxygenation status improvement, PaO₂/FiO₂ ratio, decreased fever and C-reactive protein (CRP), lymphocyte percentage improvement as well as length of hospital stay, ICU stay and mortality. Complications associated with hemoperfusion were also evaluated in the exposed group.

Prior to initiating of hemoperfusion treatment, blood samples were collected from the patients to measure the following parameters; complete blood count, bilirubin levels, creatinine levels, CRP, and IL-6. Following the treatment and in a specific period of time, the same tests were repeated for both groups to assess the impact of the treatment on these values. Furthermore, all patients were evaluated based on clinical criteria, including pulse rate, respiratory rate, fever, mean arterial pressure (MAP), and Glasgow Coma Scale (GCS). Throughout the treatment,

Table 1. Criteria for starting hemoperfusion in COVID-19 patients

Criteria	Results
Laboratory measures	PaO ₂ <60 mm Hg
	PaO ₂ /Fio ₂ <200
	++ < CRP or CRP >80 mg/dL
	Ferritin > 1000 ng/mL
	D-Dimmer > 1000 ng/mL
	Lactate > 4 mg/L
Respiratory criteria and chest CT scan	IL6 > 12 pg/mL
	Spo ₂ less than 85% despite all non-invasive or invasive measures for oxygenation

Note: Patients must have both respiratory criteria + at least 4 abnormal laboratory criteria.

patients were regularly monitored for blood pressure, pulse rate, and oxygen saturation on an hourly basis. It should be noted that patients included in this study were at the severe stage of COVID-19 disease and had received supportive treatments such as corticosteroids, interferon, and remdesivir too.

Statistical analysis

Data were analyzed by SPSS version 26. For descriptive analyses, the mean, standard deviation (SD), and number (%) were reported. Then, independent samples *t* test and chi-square test were conducted to compare demographic and clinical variables in the exposed (with hemoperfusion) and control (without hemoperfusion) groups. *P* values <0.05 were considered as statistically significant.

Results

In the current prospective study, the number of 47 patients as a control who did not receive hemoperfusion, and 51 patients who met the criteria for hemoperfusion were compared. In Table 2, the demographic characteristics of patients are presented and as shown there were no significant differences between two groups in regards of gender distribution ($P>0.05$). However, the mean age of the patients in control group was significantly higher ($P=0.005$).

In Table 3, we compared clinical and biochemical characteristics of the patients in both groups. As shown, two groups were homogenous in regards of temperature, pulse rate, respiratory rate, MAP, GCS score, PAO_2 , PaO_2 /

FiO_2 , SOFA, and CRP ($P>0.05$). However, hospitalization time (19.941 ± 1.75 versus 14.615 ± 1.39 , $P=0.021$) and ICU admission time (14.98 ± 1.30 versus 9.62 ± 1.15 , $P=0.003$) were significantly higher in patients who received hemoperfusion.

Regarding the complications of hemoperfusion, no serious or life-threatening complications were observed among the patients who underwent the procedure. Hypotension occurred in only 9.8% of the patients, which was managed by temporarily discontinuing hemoperfusion or adjusting fluid therapy. Pneumothorax, catheter thrombosis, and hypotension were assessed in the hemoperfusion group. In terms of the mortality rate, only 36.7% of the patients survived; however, there was no significant difference observed between the groups ($P=0.34$).

Discussion

In current study, we assessed the effect of hemoperfusion on improvement of biochemical and clinical parameters in critically ill COVID-19 patients with respiratory failure. Our results showed that hemoperfusion was unable to make remarkable improvement in the situation of patients with COVID-19 disease.

A study on the effect of hemoperfusion on COVID-19 recovery in hospitalized individuals; case assessment and review study, was conducted by Hajian and Rastgoo in Qazvin. The study focuses on the analysis of four cases who underwent treatment with hemoperfusion along with conventional therapies. Overall, the results obtained

Table 2. The baseline characteristics of the patients in the investigated groups

Variable	Total (n= 98)	Groups		P value
		Control (n=47)	Hemoperfusion (n=51)	
Age (y), mean \pm SD	60.63 \pm 14.67	64.91 \pm 13.703	56.35 \pm 15.65	0.005
Gender (male), No. (%)	40 (41.2)	22 (47.8)	18 (33.3)	0.570

Table 3. Comparison of the biochemical and clinical variables between the investigated groups

Variables	With hemoperfusion (exposed group)	Without hemoperfusion (control group)	P value
Temperature, °C	36.86 \pm 0.47	36.85 \pm 0.55	0.286
Hospitalization Time (days)	19.941 \pm 1.75	14.615 1.39 \pm	0.021
ICU time (days)	14.98 \pm 1.30	9.62 \pm 1.15	0.003
Pulse rate /min	85.17 \pm 14.47	85.65 \pm 45.29	0.446
Respiratory rate/min	22.90 \pm 9.83	21.63 \pm 5.78	0.066
MAP, mm Hg	649.30 \pm 83.75	626.97 \pm 2.49	0.874
PaO_2 mm Hg	54.23 \pm 14.37	51.57 \pm 30.88	0.735
PaO_2 / FiO_2 ratio	258.24 \pm 69.11	245.61 \pm 73.55	0.735
SOFA	4.58 \pm 1.41	6.27 \pm 3.02	0.815
C-reactive protein, 80 mg/L	76.14 \pm 69.11	174.45 \pm 15.44	0.208
Interleukin-6, pg/mL	37.22	47.23	
GCS	13.96 \pm 1.80	14.44 \pm 1.35	0.168

CRP; C-reactive protein, ICU; Intensive care units, SOFA; Sequential Organ Failure Assessment; GCS, Glasgow Coma Scale; MAP, Mean arterial pressure.

from the evaluation of these four patients consistent with our findings indicate that hemoperfusion does not have a significant impact on the improvement of COVID-19 patients. However, in the discussion section of the article, positive therapeutic effects of hemoperfusion in COVID-19 patients were observed by reviewing some case reports from other studies (17). A recent literature review conducted by Koc and Uysal on 16 studies including 86 patients with severe COVID-19, treated by hemoperfusion, showed that the mean concentration of CRP and IL-6 diminished following hemoperfusion. In this narrative review, Koc and Uysal highlighted that treatment by hemadsorption would be an alternative salvage modality in critically ill COVID-19 cases (18).

Recently Tibubos et al in a retrospective cohort study compared the clinical consequences of hemoperfusion between severe and critical COVID-19 individuals who admitted in a COVID-19 center. Severe cases are due to overwhelming hyper-inflammatory reaction named cytokine release syndrome. About 435 patients enrolled in the study, where 155 were cases without hemoperfusion, since 280 individuals with hemoperfusion. This study showed a meaningful diminution of inflammatory biomarkers post-hemoperfusion for both severe and critical groups. They also showed a higher likelihood of survival among severe COVID-19 cases with hemoperfusion. At this study, the main conclusion was a correlation between hemoperfusion and improved survival in severe COVID individuals, however not among critical COVID cases. They also concluded that, hemoperfusion was also accompanied by improved survival in severe cases who were intubated during admission (19). More recently, Uysal et al in a study on 55 patients showed a significant decrease of fibrinogen, lactate dehydrogenase, CRP, and platelet with the hemadsorption therapy. However, at this study, WBC, lymphocyte, procalcitonin, ferritin and D-dimer levels were not changed by hemadsorption. They showed all cases tolerated hemadsorption therapy well, and 16.4 % of the individuals with life-threatening COVID-19 survived. They suggested that treatment could be favorable even if selected as a salvage therapy (12).

Evidence suggested that hemoperfusion and kidney replacement therapies if conducted promptly and early in the ARDS treatment of COVID-19 patients, may prevent the progression of ARDS and patient intubation, across with prevention of other complications in the patient including septic shock and acute kidney disease, decreased mortality and also hospital length of stay. Extracorporeal organ support therapies, such as hemoperfusion, could be considered in essentially ill patients using effective sorbent cartridges for removal of cytokines and other inflammatory circulating mediator's patients with COVID-19. When large volumes of the patient's blood are passed through its absorbent substance, the main mechanism of hemoperfusion is the removal of circulating inflammatory mediators and

endotoxins. Through hydrophobic, ionic, and Vander Waals interactions, circulating endotoxin or inflammatory mediators bind to the extremely adsorptive membrane and are thereby removed from circulation. Besides, other reports showed that hemoperfusion can reduce inflammation and organ failure in COVID-19 patients who are critically ill.

Conclusion

This study revealed that both groups were comparable in terms of various clinical parameters, including temperature, respiratory rate, pulse rate, MAP, oxygenation status, organ dysfunction score, CRP, and GCS. However, patients who received hemoperfusion had significantly longer hospitalization and ICU stay compared to the other group. This suggests that hemoperfusion may not have a substantial impact on the overall improvement of COVID-19 patients, as indicated by the lack of significant differences in the evaluated clinical parameters. Further research and larger-scale studies are needed to better understand the potential benefits and limitations of hemoperfusion and to assess the ideal timing to start the hemoperfusion and the number of sessions needed to improve patient outcomes in the treatment of COVID-19.

Authors' contribution

Conceptualization: ER.
Methodology: ER, SG.
Validation: AP.
Formal analysis: KM.
Investigation: NP.
Resources: ER, SG.
Data curation: MH, FS.
Visualization: AP
Supervision: ER, SG
Project administration: NP.
Writing—original draft: MH, FS.
Writing—review and editing: NP.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the declaration of Helsinki. The institutional ethical committee at Zanjan University of Medical Sciences approved all study protocols (Ethical code #IR.ZUMS.REC.1400.344). Accordingly, written informed consent was taken from all participants before any intervention. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/support

Nil.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Eng J Med*. 2020.
2. 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. doi:10.1016/j.ijantimicag.2020.105954
3. McIntosh K, Perlman S. Coronaviruses, Including Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 2015;1928-1936.e2. doi: 10.1016/B978-1-4557-4801-3.00157-0
 4. Stoichițoiu RD, Petrica M, Rebedea T, Popescu I, Leordeanu M. A self-supervised neural-analytic method to predict the evolution of COVID-19 in Romania [preprint]. <https://arxiv.org/abs/2006.12926>.
 5. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet*. 2020;395:470-473. doi: 10.1016/S0140-6736(20)30185-9.
 6. Ronco C, Reis T, De Rosa S. Coronavirus Epidemic and Extracorporeal Therapies in Intensive Care: si vis pacem para bellum. *Blood Purif*. 2020;49:255-258. doi: 10.1159/000507039.
 7. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020;46:846-8. doi: 10.1007/s00134-020-05991-x.
 8. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8:475-81. doi: 10.1016/S2213-2600(20)30079-5.
 9. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497-506. doi: 10.1016/S0140-6736(20)30183-5.
 10. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395:507-513. doi: 10.1016/S0140-6736(20)30211-7.
 11. Nihei Y, Nagasawa H, Fukao Y, Kihara M, Ueda S, Gohda T, et al. Continuous extracorporeal treatments in a dialysis patient with COVID-19. *CEN Case Rep*. 2021;10:172-177. doi: 10.1007/s13730-020-00538-x.
 12. Uysal S, Merter M, Uysal A, Akbulut A. Effects of cytokine hemadsorption as salvage therapy on common laboratory parameters in patients with life-threatening COVID-19. *Transfus Apher Sci*. 2023;62:103701. doi: 10.1016/j.transci.2023.103701.
 13. Takeda S, Munakata R, Abe S, Mii S, Suzuki M, Kashiwada T, et al. Hypercytokinemia with 2009 pandemic H1N1 (pH1N1) influenza successfully treated with polymyxin B-immobilized fiber column hemoperfusion. *Intensive Care Med*. 2010;36:906-7. doi: 10.1007/s00134-010-1830-8.
 14. Shimizu T, Hanasawa K, Sato K, Umeki M, Koga N, Naganuma T, et al; PMX Treatment Study Group. Direct hemoperfusion with polymyxin-B-immobilized fiber columns improves septic hypotension and reduces inflammatory mediators in septic patients with colorectal perforation. *Langenbecks Arch Surg*. 2009;394:303-11. doi: 10.1007/s00423-008-0395-2.
 15. Poli EC, Rimmelé T, Schneider AG. Hemoadsorption with CytoSorb®. *Intensive Care Med*. 2019;45:236-239. doi: 10.1007/s00134-018-5464-6.
 16. Lin JH, Chen YC, Lu CL, Hsu YN, Wang WJ. Application of plasma exchange in association with higher dose CVVH in Cytokine Storm Complicating COVID-19. *J Formos Med Assoc*. 2020;119:1116-1118. doi: 10.1016/j.jfma.2020.04.023.
 17. Hajian S, Rastgoo N. The effect of hemoperfusion on the recovery of COVID-19 in hospitalized patients; case series and review study. *Immunopathol Persa*. 2021;7:e13. doi: 10.34172/ipp.2021.13.
 18. Koc S, Uysal H. Literature Review of Hemadsorption Therapy in Severe COVID-19 Cases: a Narrative Review. *Clin Lab*. 2022;68(2). doi: 10.7754/Clin.Lab.2021.210839.
 19. Tibubos M, Royeca R, Ong-Cabrera G, Evangelista P, Orden M, Estabillo A, et al. Comparative study of clinical outcomes of severe and critical COVID-19 patients who underwent and did not undergo hemoperfusion admitted in a referral hospital. *Am J Respir Crit Care Med* 2023;207:A5143.