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Research Article

Evaluation of the Role of Hemoperfusion on Mortality and Morbidity in Patients with Severe Coronavirus Disease 2019 (COVID- 19)

Atabak Najafi[1], Arezoo Ahmadi[1], Mojtaba Mojtahed-Zadeh[1], Nasim Zarrin[2]*, Reza Shariat Moharari[1], Mohammad Reza Khajavi[1], Farhad Etezadi[1], Pejman Pourfakhr[1], Mohammad Reza Neishaboury[1]

[1]*Department of Anesthesiology and Critical Care Medicine, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran.*

[2]*Clinical Research Development Unit, Shahid Rajaee Hospital, Qazvin University of Medical Sciences, Qazvin, Iran.*

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ABSTRACT

Background: Cytokine storm in severe Covid-19 disease is one of the leading causes of death in these patients. Hemoperfusion is a method used to purify the blood from toxins and inflammatory factors. The aim of this study was to evaluate the effect of hemoperfusion on mortality and morbidity in patients with severe Covid - 19 disease.
Methods: This was a retrospective study which performed by reviewing the files of 30 patients with severe Covid-19 disease referred to Sina Hospital affiliated to Tehran University of Medical Sciences in 2020. Thirty patients with severe covid-19 disease and positive PCR participated in the study. All patients received routine treatment protocol for covid-19. Hemoperfusion was used for 15 patients in addition to receiving routine care. The remaining 15 patients were included in the control group. Patients in the hemoperfusion group underwent four sessions of hemoperfusion using continuous renal replacement therapy with continuous venovenous hemofiltration.
Results: the ICU length of stay in the control and hemoperfusion groups was 3.40 ± 11.40 and 9.65 ± 16.33 days, respectively (P= 0.075). 8 patients died and 7 patients were discharged in the control group, but 11 patients died and 4 patients were discharged in the hemoperfusion group (P= 0.256). The respiratory rate of patients in the control and hemoperfusion groups decreased from 7.43 ± 29.40 to 4.03 ± 24.60 and from 6.11 ± 31.60 to 5.04 ± 24.46, respectively (P < 0.001). The percentage of arterial blood oxygen saturation in the control and hemoperfusion groups increased from 90.86 ± 5.61 to 93.06 30 4.30 and from 92.33 26 3.26 to 92.06 31 5.31, respectively (P= 0.456).
Conclusion: Hemoperfusion could not prevent the mortality of patients and finally out of 15 patients, 11 patients died and 4 patients were discharged. Also, no significant difference was observed between the two groups in terms of arterial blood oxygen saturation.

The corona virus genome is 31kb and the largest single-stranded RNA virus [1]. Coronaviruses are hosted by human cells and several types of vertebrates that are associated with gastrointestinal and respiratory infections. Coronaviruses are endemic animal pathogens that infect the upper respiratory tract in humans [2]. Human coronaviruses, such as SARS-COV and MERS-COV, have been associated with severe respiratory disease [3-4], which is fatal in the elderly or with weakened immune systems [5-6].

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*Corresponding author.
E-mail address: n.zarin@qums.ac.ir

Pathological research in SARS patients has resulted in death and has been associated with acute pulmonary edema, severe inflammation and cellular infiltration, dysfunction of several vital organs, thromboembolic complication, and sepsis [7]. Severe pulmonary inflammation is thought to be due to disruption of cytokine regulation in SARS patients. Such as increased levels of TNFα, IPLO, IL-6 and IL-8 in the blood, which lead to unpleasant consequences [7]. This increase in cytokine is due to the activation of macrophages and other monocyte cell lines. In addition, there was an increase in the level of interferon type I (IFN) and a disturbance in the regulation of IFN gene stimuli [8-9]. MERS-COV infection has been associated with cold-like complications in patients with atypical pneumonia, including fever, dry cough, and severe shortness of breath [9].

An effective laboratory model of SARS-COV-infected animals showed a baseline increase in cytokines TNFα-IL-6-IL-8-IP-10 and MCP-1 and chemokines CCL-3, CXCL-2 and CXCL-1 [10]. The onset of immune responses against the invasion of coronary pathogens (SASR-COV) is associated with the onset of direct infection of the airway epithelium. First, long resident respiratory dendritic cells (rDCs) inhibit antigens produced by virus-infected epithelial cells. Subsequently, activated DC cells and antigen processing migrate to the adjacent mediastinal cervical lymph nodes (DLN).

In DLNS and rDCs, it delivers processed antigen along with MHC to naïve circulating T cells. After TCR and MHC binding and induction of auxiliary signals, the activated T cell is formed and multiplies rapidly and migrates to the site of infection [11-12]. When infected, virus-specific T lymphocytes produce essential cytokines, including IL-2, TNF-α, and IFNγ, and the chemokines CXCL-9,10,11 and cytotoxic molecules (such as perforin and granzyme B) [13]. Executive cytokines such as IFNγ directly inhibit virus replication and enhance antigen delivery [14].

Chemokines produced by activated lymphocytes cause the migration of innate and acquired immune cells to the site of infection to control pathogens. Cytotoxic molecules such as granzyme B directly kill virus-infected epithelial cells and help reduce the amount of pathogens [15]. This mechanism is known for many human respiratory pathogens, but there is not much information about this mechanism for infections caused by respiratory coronaviruses. About 80% of patients with acute respiratory phase SARS from the family of coronaviruses are associated with severe leukopenia and lymphopenia, in which severe reduction of TCD4 and TCD8 is observed in 80 to 90% of patients [16-17]. In these patients, defects in TCD4 and TCD8 activity have been demonstrated by measuring CD25, CD28 and CD69 expression [18-19]. Severe SARS-COV infection in humans is associated with delayed development of acquired immune responses and prolonged infection time [20].

Coronavirus can easily alter host interspecific barriers between tissues and between cell types [21-22]. IL-6 production and signaling for complement activation and IFN response and processing and delivery of coronavirus antigen were associated with increased viral titers in the lungs and increased neutralizing antibody titers in the mouse model [20]. The production of specific antibodies against SARS-COV can be measured in a few days after viral infection, but IFNs resulting from the innate immune response of cells to acute respiratory infection due to SARS-COV have been observed in the model of date palms [20]. However, the role of increasing the production of complement components in this type of infection is not well understood, but C1INH and CR1 increase before recovery from the virus or disease progression [20].

The results of immunization studies in a mouse model (date) with rMVA vaccine expressing the S (Spike) protein of SARS coronavirus showed severe hepatitis and inflammation and the use of a complete virus vaccine inactivated with formalin and the use of adenovirus-based SARS vaccine in date palms has been promising to reduce coronavirus pneumonia [23]. rMVA, however, in the model of date-induced infection and re-infection with SARS coronavirus had a positive correlation with increasing the titer of specific neutralizing and protective antibodies, which indicates the usefulness of the antibody for protection [24].

In response to the SARS infection in 2003, several laboratories quickly began developing their proposed vaccines. The DNA vaccine consists of a single-stranded VRC-8318DNA single-stranded plasmid cyclic macromolecule grown in bacterial cell culture with specificity (VRC-SRSDNAO15-00-VP). As a result, Tcell CD4 +, Tcell CD8 + and antibodies neutralized in the serum and cell samples of healthy subjects were evaluated. The VRC-SARS-DNA vaccine was able to generate neutralizing antibodies against Spike glycoprotein as well as specific TCD4 + and TCD8 against Spike protein, but the specific response of TCD4 was higher than that of TCD8 [25].

Reports of COVID-19 patients from a sample of 41 patients in acute hospitalization indicate an increase in inflammatory cytokines IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, TNFα has been shown to be very similar to the pattern of cytokine storm and lymphopenia in SARS, MERS 20 [26]. Cytokine storms can trigger viral sepsis, inflammation, and lung damage, resulting in the consequences of pneumonia, acute respiratory distress syndrome (ARDS), shock, loss of respiratory function, and other organs, and ultimately death [27]. Preventing an overgrowth of these inflammatory mediators can stop the sepsis process and improve patient outcomes [28]. One treatment that can reduce the amount

of cytokines in the blood is purification of blood outside the body or so-called hemoperfusion [29-32]. Homoperfusion is an extracorporeal technique that involves passing blood through a cartridge in which the salts are removed directly by binding to the absorbent material. Hemoperfusion works by the mechanism of absorption depending on the different cartridges provided in its structure. Hemoperfusion is different from hemodialysis because hemodialysis works by diffusion mechanism. In persistent intravenous hemofiltration (CVVH) the hemoperfusion mode, the convection mechanism is added, and no penetration occurs [33]. The effect of hemoperfusion on serum levels of IL-6, IL-8, IL-1β and tumor necrosis factor has been shown in some previous studies [34]. Four hemoperfusion therapies have been introduced to remove cytokines in patients with COVID-19: Continuous renal replacement therapy (CRRT) with hollow fiber filters with absorbent properties; direct hemoperfusion using neutromacroporus adsorbent; Adsorption of plasma on a resin after separation of plasma from whole blood; And high-dose CRRT by medium or high cut-off membranes [32]. Considering the relationship between increased secretion of cytokines and the severity of COVID-19 disease and the effect of hemoperfusion on the elimination of these cytokines [28, 34], this study was performed to evaluate the effectiveness of hemoperfusion on mortality and morbidity in patients with severe Covid disease 19.

Methods

The present retrospective study which was performed on patients with severe Covid-19 disease referred to Sina Hospital affiliated to Tehran University of Medical Sciences in 2020. Patients with clinical presentation of Covid-19 in addition to positive radiographic findings (lung CT scan) and laboratory confirmation by laryngeal specimen test using a real-time polymerase chain reaction, if one of these criteria is met; Patients who had arterial oxygen pressure less than 60 mm Hg recorded after various oxygen therapy procedures; patients who had to be treated with non-invasive ventilation to maintain blood oxygen saturation above 88% without receiving non-invasive ventilation, The percentage of blood oxygen saturation below 88% was recorded for them, they are included in the study. Only the records of patients for whom the hemoperfusion intervention method has been fully explained and informed consent written by the treatment team will be reviewed. Exclusion criteria for plasma platelet counts less than 30,000 per microliter are multi-organ dysfunction and patients who were intubated during the first 24 hours after the onset of noninvasive ventilation.

Patients in the hemoperfusion group underwent four sessions of hemoperfusion using continuous renal replacement therapy with continuous venovenous hemofiltration [10]. A temporary jugular catheter (Arrow trademark) was inserted by an ICU specialist assistant. Heparin was injected as an anticoagulant during CRRT depending on the patient's coagulation status [14]. Blood flow rate (QB) was 150 ml / min, fluid flow rate (QD) was 2 liters per hour and effluent volume was 2 liters at 150 cc per hour. During the CRRT procedure, the fluid output from the patient was adjusted to the same amount of fluid input.

Each session was performed for 12 to 14 hours a day. The first 2 to 4 hours were performed with CRRT plus hemoperfusion and the last hours with CRRT only. Resin-absorbing cartridges (Cytosorb-300) made by Braun Medical Company were used for patients in the group. The second period of hemoperfusion was performed less than 6 hours after the first session, the third session less than 6 hours after the second session and the fourth session less than 6 hours after the third session. The records of patients for whom routine treatment was performed will be in the control group and patients for whom hemoperfusion has been performed will be in the case group. Patients in both groups were treated with Remdesivir, ReciGen and oxygen therapy by non-invasive ventilation. The medication regimen in the patients studied in both groups was as follows: both Remdesivir and Resign were prescribed for patients for up to five days; Ramsedivir was 200 mg on the first day (intravenously) and from the second to the fifth day was 100 mg (intravenously), the resistance was 44 micrograms daily for up to five days (subcutaneously). The APACHE II score was measured and recorded at the time of admission to the ICU and the SOFA score during hospitalization in the ICU (one day after the end of treatment). So far, no specific classification is available in terms of the severity of Covid 19 pneumonia and there is a lot of scatter in this field, but in general, according to the CDC unit of the World Health Organization, patients with Covid-19 pneumonia are divided into four categories: mild, moderate, severe and Very severely divided according to the indicators given in the table below [35-36]. In the present study, a study was performed on patients with severe pneumonia.

Age, sex, length of hospital stay and ICU due to COVID-19, comorbidities, medications received for recent illness; Vital signs include body temperature, heart rate, blood pressure and respiration rate; Laboratory tests including plasma white blood cell count, hemoglobin, plasma platelet count, serum creatinine, blood urea nitrogen, reactive protein c and lactate dehydrogenase, biliary liver function test (AST, ALT) and total and direct bilirubin; And SpO2 is recorded in the study data sheet. In addition, oxygen therapy is recorded before and after each hemoperfusion session based on the patient's record. The primary outcome of general condition improvement was based on patient evaluation one week after the third hemoperfusion session compared to the initial clinical condition before the first hemoperfusion session. Depending on the condition of the peripheral capillary oxygen saturation, the patient is considered to have

improved if intensive respiratory therapy is not required. In addition, patients' morbidity is measured based on the interpretation of liver, kidney and heart tests as a secondary outcome of the study.

Results

Out of 30 patients, 15 (6 males and 9 females) were in the control group and 15 (9 males and 6 females) were in the hemoperfusion group, there was no significant difference in terms of gender between the two groups (P=0.273). The age of patients in the control and hemoperfusion groups was 60.66±11.03 and 59.53±97.10 years, respectively, and there was no statistically significant difference (P=0.780). The length of stay in the ICU in patients in the control and hemoperfusion groups was 11.40±3.64 and 16.33±9.65 days, respectively, and there was no statistically significant difference (P=0.075) (Table 1).

APACHE-II score in the control and hemoperfusion groups was 10.42±3.42 and 11.26± 4.21, respectively, which did not show a statistically significant difference (P=0.742). SOFA scores in the control and hemoperfusion groups were 5.73±3.76 and 6.73±4.06, respectively, which did not show a statistically significant difference (P=0.490) (Table 1). The result of routine and hemoperfusion treatments were that 8 patients died and 7 patients were discharged in the control group, but 11 patients died and 4 patients were discharged in the hemoperfusion group, which was not statistically significant (P=0.256) (Table 1).

Comparison of vital signs of patients before and after hemoperfusion showed; Mean arterial blood pressure in the control and hemoperfusion groups decreased from 90.86±16.52 to 84.86±13.15 and from 90.93±15.87 to 81.26±13.76, respectively (Table 2). The decrease in mean arterial blood pressure between the two groups was significant (P= 0.009) (Table 2). Pulse of patients in control and hemoperfusion groups decreased from 94.60±17.07 to 83.26±21.93 and increased from 92.40±17.74 to 94.26±15.71, respectively, this difference was not significant (P=0.165) (Table 2).

Table 1- Baseline characteristic and clinical outcome of participants

Variable	Control	Hemoperfusion	P value
Age	60.66±11.03	59.53±97.10	0.780[a]
Gender			
Male	6 (40)	9 (60)	0.273[b]
Female	9 (60)	6 (40)	
Outcome			
Death	8 (53.3)	11 (73.3)	0.256[a]
Discharge	7 (46.7)	4 (26.7)	
ICU Length of stay, days	11.40±3.64	16.33±9.65	0.075[a]
APACHE-II Score	10.80±3.42	11.26±4.21	0.742[a]
SOFA Score	5.73±3.76	6.73±4.06	0.490[a]

Data are presented as mean ± SD and n (%).
A p-value less than 0.05 is statistically significant.
[a]Independent t-test.
[b]Pearson chi-square.

Table 2- Clinical findings of participants

Variable	Control	Hemoperfusion	P value
MAP, mmHg			
1st	16.52±90.86	90.93±15.87	0.009[a]
2nd	18.88±90.13	87.53±16.09	
3rd	13.15±84.86	81.26±13.76	
PR, breath per min			
1st	94.60±17.07	92.40±17.74	0.165[a]
2nd	92.60±13.14	94.33±17.49	
3rd	83.26±21.93	94.26±15.71	
RR, beat per min			
1st	29.40±7.43	31.60±6.11	<0.001[a]
2nd	28.80±5.97	28.33±5.42	
3rd	24.60±4.03	24.46±5.04	
SpO2, (%)			
1st	90.86±5.61	92.33±3.26	0.456[a]
2nd	91.00±6.42	91.80±4.93	
3rd	93.06±4.30	92.06±5.31	
Pa O2, mmHg			
1st	51.85±22.83	49.57±15.20	0.426[a]

	2nd	54.07±29.44	105.60±208.22	
	3rd	62.16±30.06	60.29±35.37	
T, °C				
	1st	36.98±0.43	36.79±0.48	0.181[a]
	2nd	37.14±0.56	36.89±0.50	
	3rd	37.27±0.64	36.90±0.67	

Data are presented as mean ± SD and n (%).
A p-value less than 0.05 is statistically significant.
[a]GLM repeated measures.

Discussion

Our study showed hemoperfusion could not prevent the mortality of patients and finally out of 15 patients, 11 patients died and 4 patients were discharged. Also, no significant difference was observed between the two groups in terms of arterial blood oxygen saturation.

As our results, Soleimani et al. (2021) showed there was no significant difference between the two groups in terms of length of stay in the ICU (P= 0.330) [37]. In the study of Soleimani et al. (2021) there was no significant difference between the two groups in terms of mortality (P= 0.330) [37]. In the study of Chadler et al. (2013) with the aim of investigating the effect of hemoperfusion on patient mortalityARDS, they did not report a decrease in the number of deaths of patients [38], Which was consistent with our study. In the study of Soleimani et al. (2021), the heart rate decreased from 92.04 to 85.46, which was statistically significant (P= 0.028) but did not match our study [37]. The respiratory rate of patients in the control and hemoperfusion groups decreased from 7.43 ± 29.40 to 4.03 ± 24.60 and from 6.11 ± 31.60 to 5.04 ± 24.46, respectively, this difference between the two groups was significant (= 0.000P). Also in the study of Soleimani et al. (2021) the number of breaths had decreased from 39.50 to 23.94 (P= 0.001), which was statistically significant [37]. The percentage of arterial blood oxygen saturation in patients in the control and hemoperfusion groups increased from 90.86 61 5.61 to 93.06 30 4.30 and from 92.33 26 3.26 to 92.06 31 5.31, respectively, no significant difference was observed between the two groups (= 0.456P). In the study of Soleimani et al. (2021), the percentage of arterial blood oxygen saturation increased significantly (P= 0.009), which was not consistent with our study [37]. In the study of Dastan et al. (2020), the percentage of oxygen saturation of arterial blood was significantly increased [39]. In the study of Asgharpour et al., This rate increased and was consistent with our study [40]. The urinary output of patients in the control and hemoperfusion groups increased from 565.32 23 2523.33 to 1028.95 ± 2636.66 and from 845.92 ± 2466.66 to 899.57 ± 2626.66, respectively, this difference was not significant between the two groups (= 0.121=P). The temperature of patients in the control and hemoperfusion groups was from 36.98 43 0.43 to 37.27 64 0.64 and from 36.79 ± 0.48 to 36.90 67 0.67, there was no significant difference between the two groups (P= 0.181).

Comparison of laboratory findings of patients before and after hemoperfusion showed; Arterial blood oxygen partial pressure increased in patients in control and hemoperfusion groups from 22.83 ± 51.85 to 30.06 ± 62.16 and from 15.20 ± 49.57 to 35.37 ± 60.29, respectively, this difference was not significant between the two groups (0.426=P). The number of white blood cells in the control and hemoperfusion groups increased from 4.36 ± 8.99 to 4.12 ± 10.78 and from 7.30. 10.61 to 13.24 ± 16.62, respectively. This difference was significant between the two groups (P= 0.000) (Table 3). The hemoglobin level of patients in the two groups of control and hemoperfusion decreased from 13.48 ± 1.13 to 1.41± 12.64 and from 1.94 ± 13.01 to 1.96 ± 11.86, respectively, this difference between the two groups was significant (P= 0.013). The platelet counts of patients in the control and hemoperfusion groups increased from 209.06 80 80 to 241.06 99 99.28 and decreased from 264.80 15 268.22 to 181.33 104 104.11, respectively. This difference was significant between the two groups (P= 0.007). The creatinine level of patients in the control and hemoperfusion groups decreased from 0.19 ± 1.02 to 26.28 ± 0.87 and increased from 0.31 ± 0.98 to 0.97 ± 1.05, respectively, this difference was not significant between the two groups (P= 0.523). The urea levels of patients in the control and hemoperfusion groups were from 17.78 ± 39.80 to 23.89 ± 56.06 and from 14.77 ± 39.00 to 42.51 ± 54, respectively. 26 increased, this difference was not significant between the two groups (P= 0.765). The amount of C-reactive protein in patients in the control and hemoperfusion groups increased from 67.58 ± 88.20 to 63.42 ± 113.06 and decreased from 100.37 ± 120.91 to 63.09 ± 113.72, respectively. This difference between the two groups was not significant (P= 0.211) (Table 3). In the study of Soleimani et al. (2021), the amount of C-reactive protein was slightly reduced, which was consistent with our study [37]. In the study of Asgharpour et al., This rate decreased and was consistent with our study [40]. Also in the study of Shador et al., A small amount of reactive proteinC was decreased in the hemoperfusion group [41], Which was consistent with our study. The levels of aspartate aminotransferase in the control and hemoperfusion groups decreased from 77.6 ± 93.11 to 53.15 ± 78.46 and from 23.78 ± 71.93 to 35.70± 68.86, respectively. This difference between the two groups was not significant

(0.599=P). The level of bilirubin T in the control and hemoperfusion groups decreased from 9.58 ± 3.42 to 0.75 ± 0.95 and increased from 0.44 ± 0.82 to 0.71 ± 0.97, respectively. This difference was not significant between the two groups (P= 0.345). The level of bilirubin D in the control and hemoperfusion groups decreased from 0.30 ± 0.41 to 0.22± 0.38 and increased from 0.16 ± 0.33 to 0.66 ± 0.50, respectively, this difference between the two groups was not significant (P= 0.283). The level of troponin in the control and hemoperfusion groups increased from 41.05± 24.73 to 53.04 ± 33.59 and from 6.95 ± 7.09 to 23.17 ± 12.38, respectively. This difference was not significant between the two groups (P= 0.949). The level of alkaline phosphatase in patients in the control and hemoperfusion groups decreased from 106.13 ± 192.21 to 89.38 ± 191.28 and increased from 109.61 ± 221.60 to 99.77 ± 224.40, respectively, this difference between the two groups was not significant (P= 0.827). The rate of erythrocyte sedimentation rate in patients in the control and hemoperfusion groups was 56.66 27 27.70 to 62.31 31 31, respectively. 66 increased from 55.93 34 34.39 to 55.93 .2 29.22, this difference between the two groups was not significant (P= 0.371) (Table 3). Very few clinical trial studies have been performed to date on the efficacy of hemoperfusion on morbidity and mortality in patients with Covid-19.

Table 3- Labratory findings of participants

Variable	Control	Hemoperfusion	P value
WBC, (×ng/L)			
1st	8.99±4.36	10.61±7.30	<0.001[a]
2nd	10.15±3.60	15.74±11.20	
3rd	10.78±4.12	16.62±13.24	
CRP, mg/dL			
1st	88.20±67.58	120.91±100.37	0.211[a]
2nd	102.05±59.25	120.02±70.70	
3rd	113.06±63.42	113.72±63.09	
ESR, mm/hours			
1st	56.66±27.70	55.93±34.39	0.371[a]
2nd	62.06±30.14	50.60±31.63	
3rd	62.66±31.62	55.93±29.22	

Data are presented as mean ± SD and n (%).
A p-value less than 0.05 is statistically significant.
[a]GLM repeated measures.

Conclusion

The present study showed that hemoperfusion significantly reduced the number of breaths in patients. On the other hand, the length of stay in the ICU was longer in patients in the hemoperfusion group. Hemoperfusion could not prevent patient mortality and finally 15 patients, 11 patients died and 4 patients were discharged. Also, no significant difference was observed between the two groups in terms of arterial blood oxygen saturation.

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