

## The Role of Hemoperfusion in COVID-19 Infection: A Case Series

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### ABSTRACT

The rapid expansion of a novel human infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has evolved into a pandemic, affecting thousands of people world wide. Some patients with coronavirus disease 2019 (COVID-19) develop severe infection, which may progress to acute respiratory distress syndrome, multiple organ failure, and death. Increasing studies indicate that abnormal elevation of cytokine levels in response to SARS-CoV-2 may contribute to the pathological process that leads mortality of COVID-19. Thus, application of extracorporeal hemoperfusion (HP) for removal of excessive cytokines from the blood can potentially mitigate or reverse cytokine storm related complications of COVID-19.

Here, we presented series of COVID-19 patients, who were treated with HP (HA 380 cartridge, Jafron Biomedocal Co, China). The medical records were evaluated retrospectively to determine the effect of HP on patients' clinical outcome.

Our results showed that HP improve PO<sub>2</sub> and O<sub>2</sub> saturation in patients with severe COVID-19. After the last courses of HP, 5 out of 6 patients were extubated and transferred to the general ward with an acceptable medical condition.

The following case series demonstrate the promising role of HP in controlling the consequential effect of cytokine storm following a COVID-19 infection, which could facilitate patient survival.

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In December 2019, an outbreak crisis came into the World Health Organization's (WHO) attention that originated in Wuhan, Hubei; the alarming emerging disease had pneumonia manifestations secondary to infection with a new type of corona virus [1]. WHO named the new pandemic disease Coronavirus Disease (COVID-19). The causative virus, which is called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), genetically clustered within Betacoronavirus subgenus Sarbecovirus [2]. The genome structure, transmission mode, and pathogenesis of this zoonotic virus is similar to the other two beta-CoVs of medical importance, Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS).

Even though there is markedly higher mortality rate in elderly people and those with underlying preconditions, but young adults and children also experience severe COVID-19 related complications, facing hospitalizations and even deaths.

Though not definitive, the profile of cytokine and inflammation in later stages of SARS-CoV 2 infection suggests that cytokine storm syndrome (CSS) and secondary hemophagocytic lymphohistiocytosis (sHLH) are fundamental problems in some critically ill COVID-19 patients [3]. Thus, this SARS-CoV 2 related pattern of cytokine response seems to be prominent modulator for development of Multiple Organ Dysfunction Syndrome (MODS), Acute Respiratory Distress Syndrome (ARDS), multiple organ failure and following death within a short time.

Based on previous experience from SARS and MERS, reduction of viral load by antiretroviral therapy and attenuation of inflammatory responses via pharmacological or mechanical approaches appear to be favorable therapeutic options for the management of the serious complications in critically-ill COVID-19 infected patients [4-6].

Extracorporeal blood purification (EBP) methods using various membrane materials are proposed as promising adjunctive treatment modality, for elimination of toxins and inflammatory mediators. Hemoperfusion (HP) is one of the EBP methods based on removal of targeted molecules from blood via a specific sorbent. Here, we have presented clinical characteristics and laboratory results of six COVID-19 patients, who underwent HP

therapy in Noorafshar hospital, Tehran, Iran, during May 2020.

## Methods

This retrospective cohort study, has been performed on middle ages patients (aged  $\geq 50$  yrs), with severe COVID-19 disease admitted to Noorafshar hospital, Tehran, Iran, since 1st May 2020 to 31st May 2020. Six patients who had clinical symptoms of COVID-19 as well as positive radiographic (lung CT-scan) findings and confirmed real-time polymerase chain reaction oropharyngeal swab results were included, if they had one of the following criteria: partial pressure of oxygen in alveoli (PaO<sub>2</sub>) less than 60 mmHg, even after oxygen delivery via a face mask and reservoir bag; or peripheral capillary oxygen saturation less than 88% with no clinical improvement despite 48 h of non-invasive respiratory therapy. Direct HP was administered through jugular or femoral venous catheter at blood flow rate of 200 mL/min. The HP apparatus consisted of disposable cartridge (HA 380 cartridge, Jafron Biomedococ Co, China). All subjects received hydroxychloroquine and lopinavir/ritonavir according to Iranian national guideline [7]. Only one patient died due to cardiorespiratory arrest. Since the study has been performed on patients with severe COVID-19, there was neither a control group nor randomization in sampling. Age, gender, weight, symptoms onset (days), underlying diseases diagnosed before COVID-19, duration of ICU admission before HP, vasopressors and/or continuous renal replacement therapy (CRRT) requirement, duration of hemoperfusion as well as laboratory tests including serum creatinine, hemoglobin, plasma white blood cell count, plasma platelet count, concentrations of the enzymes aspartate transaminase (AST) and alanine transaminase (ALT), O<sub>2</sub> saturation, SpO<sub>2</sub>, HCO<sub>3</sub> and PO<sub>2</sub> have been recorded. Moreover, the mode of oxygen therapy (Reservoir bag or Intubation (SIMV) has been recorded during the sessions of the HP. Medical records and clinical outcome were documented at admission time, pre-hemoperfusion and last time of HP. Characteristics of patients are summarized in (Table 1). Improvement in outcomes was determined by improvement of respiratory function, higher level of PO<sub>2</sub> and improved O<sub>2</sub> saturation after completion of HP sections.

**Table 1- Characteristics of patients with severe COVID-19, treated with hemoperfusion**

	P1	P2	P3	P4	P5	P6
<b>Demographics</b>						
Age (years)	73	75	66	50	82	68
Sex	Male	Female	Male	Male	Male	Male
Symptoms	Fever	Fever	Fever	Fever	Fever	Fever
	Cough	Cough	Cough	Cough	Cough	Cough
	Dyspnea	Dyspnea	Dyspnea	Dyspnea	Dyspnea	Dyspnea
		Myalgia	Myalgia		Myalgia	Myalgia

Symptoms onset (days)	5	Diarrhea 4	8	7	11	6
Underlying diseases diagnosed before COVID-19	HTN CABG	HTN DM	DM	HTN	No	DM Cancer
Weight (Kg)	80	78	85	100	75	73
<b>Pre-hemoperfusion clinical status</b>						
ICU length of stay pre-hemoperfusion (days)	1	2	1	1	1	1
Vasopressors required	No	No	No	No	Yes	No
CRRT required	No	No	No	Yes	No	No
Duration of hemoperfusion (days)	1	2	2	2	3	3
<b>Laboratory results</b>						
Creatinine, mg/dL (admission time/pre-hemoperfusion/last time)	1.3-1.3-1.5	1.2-1.5-1.3	1.2-1.1-1.1	3-3-6.4	1-1.1-1.6	1.1-1.4-1.5
Hemoglobin, g/L at admission time/pre-hemoperfusion/last time	13.1-13-13.5	11.1-9.6-9.4	15-14.6-10	13.5-11.4-10.4	12.3-13-8.3	9.5-9.8-8.2
WBC, ×10 <sup>9</sup> /L at admission time/pre-hemoperfusion/last time)	8.4-8.6-12.2	15.5-23.1-25.6	13.7-13.3-11	7.5-9.6-6.6	16.6-21-50	11.4-9.5-17
Platelet, 10 <sup>9</sup> /L at admission time/pre-hemoperfusion/last time	188-160-180	297-180-99	160-186-245	160-137-100	110-105-308	278-271-236
AST, U/L at admission time/pre-hemoperfusion/last time	38-38-36	342-342-342	38-42-41	79-67-75	12-12-23	21-21-23
ALT, U/L at admission time/pre-hemoperfusion/last time	24-25-24	88-88-88	21-20-21	64-55-56	38-40-42	41-40-45
O <sub>2</sub> required with reservoir bag or intubation	Reservoir bag	Intubation (SIMV)	Reservoir bag	Intubation (SIMV)	Intubation (SIMV)	Intubation (SIMV)
pH at admission time/pre-hemoperfusion/last time	7.33-7.29-7.28	7.46-7.34-7.45	7.31-7.4-7.36	7.34-7.35-7.33	7.32-7.36-7.35	7.23-7.36-7.35
PCO <sub>2</sub> at admission time/pre-hemoperfusion/last time	49-41-42	33-33.4-26.3	44.8-33.1-41.7	35.4-29.2-36.9	29.7-26.5-26.5	36-34.3-35.3
HCO <sub>3</sub> at admission time/pre-hemoperfusion/last time	21-20.06-18.5	24.01-18.4-18.5	22.8-24-24	19.5-19-39	15.7-15.1-21.2	17.2-17.9-18.9
PO <sub>2</sub> at admission time/pre-	56-47.2-47.6	52-61-36.7	55-50-53.3	74.2-50-36.5	46.6-36-55	50-65.3-78.1

hemoperfusion/last time	88-84-79	88-90-92	85-70-88	94-85-89	79-69-85	83-87-94
O2 saturation at admission time/pre-hemoperfusion/last time						
<b>Outcomes</b>						
Survival to hospital discharge	No	Yes	Yes	Yes	Yes	Yes

## Case Report

### Case 1

A 68-year-old man, a known case of severe COVID-19 pneumonia was referred to the hospital. His chief complaints were fever, cough, and dyspnea, which had started 5 days ago. He received oxygen supply with a reservoir bag due to low oxygen saturation (SpO<sub>2</sub> 85%) at admission time. Patient had past medical history (PMH) of hypertension (HTN) and underwent coronary artery bypass graft (CABG). Direct HP from femoral access was started for the patient on the admission day. Laboratory results such as WBC, platelet counts, and other parameters before, during, and at the end of the last HP session showed in table 1. Cardiorespiratory arrest occurred during the second HP session, and unfortunately, the patient died.

### Case 2

A 75-year-old woman with a known case of severe COVID-19 pneumonia was referred to the hospital. She was complaining of fever, cough, dyspnea, myalgia, and diarrhea, which she was experiencing for the last 4 days. On admission, SpO<sub>2</sub> was 89%, and she received supplementary oxygen with a reservoir bag. Before the initiation of the HP session, the patient was intubated and underwent invasive mechanical ventilation due to severe hypoxemia. She had PMH of HTN and diabetes mellitus (DM). Direct HP from jugular vein was initiated for her on the second day of ICU admission. She received two courses of HP and after 7 days, she was extubated. The patient was transferred to the general ward with an acceptable medical condition. The patient was discharged after 10 days.

### Case 3

A 66-year-old man, a known case of severe COVID-19 pneumonia was referred to the hospital. His chief complaints were fever, cough, dyspnea, and myalgia for the last 8 days. He received oxygen supplementation with a reservoir bag due to SpO<sub>2</sub> of 91% at admission time. His PMH was positive for DM. Direct HP from femoral vein access was started for the patient on the first day of ICU admission. He received two courses of HP, and after 2 days, he was transferred to the general ward with an

acceptable medical condition. The patient was discharged after 15 days.

### Case 4

A 50-year-old man, a known case of severe COVID-19 pneumonia was referred to the hospital. He was complaining of fever, cough, and dyspnea for the last 7 days. He received oxygen supply with a reservoir bag due to SpO<sub>2</sub> of 75% on admission. The patient was later intubated and underwent invasive mechanical ventilation due to severe hypoxemia before initiation of the first course of the HP. He had a positive medical history for HTN. Direct HP from the femoral vein access was initiated for the patient on the first day of ICU admission. He received two courses of HP and CRRT. After 8 days, he was transferred to the general ward with an acceptable medical condition. The patient was discharged after 10 days.

### Case 5

An 82-year-old man, a known case of severe COVID-19 pneumonia was referred to the hospital. He was complaining of fever, cough, dyspnea, and myalgia for the last 11 days. He was intubated and received invasive mechanical ventilation due to severe hypoxemia on the first day of hospital admission. He had no underlying diseases. Direct HP from femoral vein access was initiated on the first day of ICU admission. He received three courses of HP and norepinephrine infusion. The patient was extubated and discharged after 3 days.

### Case 6

A 68-year-old man, a known case of severe COVID-19 pneumonia, was referred to the hospital. His chief complaints were fever, cough, dyspnea, and myalgia for the last 6 days. He received oxygen supply with a reservoir bag due to SpO<sub>2</sub> of 90% on admission. He was later intubated and received invasive mechanical ventilation due to severe hypoxemia before initiation of the first course of HP. He had a positive history for cancer and DM. Direct HP from jugular vein access was started for him on the first day of ICU admission. Three courses of HP were performed and after 4 days the patient was transferred to the general ward with an acceptable medical condition. The patient was discharged after 6 days.

## Discussion

In our study, among 6 participated COVID-19 patients, two completed three courses of HP. Our results showed that three sessions of HP could improve PO<sub>2</sub> and O<sub>2</sub> saturation in patients with severe COVID-19. After the last courses of HP, 5 patients were extubated and transferred to the general ward with an acceptable medical condition.

COVID-19 is highly infectious disease and can lead to serious comorbidities. Currently, no confirmed specific anti-COVID-19 treatment is available; therefore, supportive treatment has been adopted as the main therapeutic strategy [15]. Cytokine storm, which is characterized by severe systemic elevation of several inflammatory cytokines, is suggested to be a potential underlying mechanism of ARDS and septic shock, multi organ failure and disease severity in COVID-19 patients [8-10]. Application of HP has been reported to have favorable results for treatment of influenza (especially H1N1 and H5N1 subtypes). Thus, a number of studies have investigated the therapeutic impact of this technique in severe cases of COVID-19 [11-14] (Safari, Salimi et al. 2020). Available findings suggest that the application of HP technique seems to have beneficial effects by elimination of circulating cytokines and preserve hemodynamic as well as organ functions. HP cartridges adsorb cytokines and impede their binding to alveoli and blood vessel endothelium. Consequently, this may prevent the development and progression of ARDS and reduce the disease's mortality rate [16]. The treatment of severe COVID-19 with HP remains a challenge and controversial.

## Conclusion

In conclusion, early treatment with HP may improve oxygenation, mainly in ARDS due to COVID-19 infection, resulting in a successful outcome. Only through well-conducted randomized controlled studies with appropriate patient selection criteria and endpoints of physiological relevance we will know whether the HP technique is a future therapy for COVID-19.

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## Author Contribution

All the authors met the standard criteria of authorship based on recommendations of the international committee of medical journals editors.

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