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 worldwide. 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 to 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 Biomedical Co, China). The medical records were evaluated retrospectively to determine the effect of HP on patients’ clinical outcome.

Our results showed that HP improve PO2 and O2 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.

The authors declare no conflicts of interest.
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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).

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 ≥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 (PaO2) 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, Jafroon Biomedocal 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), O2 saturation, SpO2, HCO3 and PO2 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 PO2 and improved O2 saturation after completion of HP sections.

| Table 1- Characteristics of patients with severe COVID-19, treated with hemoperfusion |
|----------------------------------------|--------|--------|--------|--------|--------|--------|
| **Demographics**             | **P1** | **P2** | **P3** | **P4** | **P5** | **P6** |
| 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  | Cough  |
| Dyspnea                     | Dyspnea| Dyspnea| Dyspnea| Dyspnea| Dyspnea| Dyspnea|
| Myalgia                     | Myalgia| Myalgia| Myalgia| Myalgia| Myalgia| Myalgia|
| Symptoms onset (days) | Diarrhea | 5 | 4 | 8 | 7 | 11 | 6 |
|----------------------|----------|---|---|---|---|----|---|
| Underlying diseases diagnosed before COVID-19 | HTN, DM | 100 | 75 | 73 |
| Weight (Kg) | 80 | 78 | 85 | 100 | 75 | 73 |
| Pre-hemoperfusion clinical status | ICU length of stay pre-hemoperfusion (days) | 1 | 2 | 1 | 1 | 1 | 1 |
| Vasopressors required | No | No | No | No | Yes | No | No |
| CRRT required | No | No | No | Yes | No | No | No |
| Duration of hemoperfusion (days) | 1 | 2 | 2 | 2 | 3 | 3 |
| Laboratory results | 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 | 1-1.4-1.5 |
| Hemoglobin, g/L (admission time/pre-hemoperfusion/last time) | 13.1-13.1-13.5 | 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, x10^9/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, 10^9/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 |
| O2 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 |
| PCO2 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 |
| HCO3 at admission time/pre-hemoperfusion/last time | 21-20.06-18.5 | 24.01-18.2-18.5 | 22.8-24-24 | 19.5-19-24 | 15.7-15.1-21.2 | 17.2-17.9-18.9 |
| PO2 at admission time/pre- | 56-47.2-47.6 | 52-61-36.7 | 55-50-36.5 | 74.2-50-36.5 | 46.6-36-55 | 50-65.3-78.1 |
**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 (SpO2 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, SpO2 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 SpO2 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 SpO2 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 SpO2 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.

| 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 | No       | Yes      | Yes      | Yes      | Yes      | Yes      |

**Outcomes**
Survival to hospital discharge
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 PO2 and O2 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.

Acknowledgment

The authors express their sincere thanks to the staff of Noorafshar hospital, Tehran, Iran, for their assistance.

Author Contribution

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

Funding

The authors declare there is no funding support was included in the study.

References

[1] Abedini A, Mirtajani SB, Karimzadeh M, Jahangirifard A, Kiani A. Can Hesperidin be the Key to the Treatment of Severe Acute Respiratory Syndrome COV-2? Biomedical and Biotechnology Research Journal (BBRJ). 2020; 4(5):108.
[2] McCreary EK, Pogue JM. Coronavirus disease 2019 treatment: a review of early and emerging options. Open Forum Infect Dis. 2020; 7(4):ofaa105.
[3] 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(10223):497-506.
[4] Frimmel S, Schipper J, Henschel J, Yu TT, Mitzner SR, Koball S. First description of single-pass albumin dialysis combined with cytokine adsorption in fulminant liver failure and hemophagocytic syndrome resulting from generalized herpes simplex virus 1 infection. Liver Transpl. 2014; 20(12):1523-4.
[5] Greil C, Roether F, La Rosée P, Grimbacher B, Duerschmied D, Warnatz K. Rescue of cytokine storm due to HLH by hemoadsorption in a CTLA4-deficient patient. J Clin Immunol. 2017; 37(3):273-6.
[6] Bottari G, Guzzo I, Marano M, Stoppa F, Ravà L, Di Nardo M, et al. Hemoperfusion with Cytosorb in pediatric patients with septic shock: A retrospective observational study. Int J Artif Organs. 2020; 43(9):587-93.
[7] Jamaati H, Dastan F, Tabarsi P, Marjani M, Saffaei A, Hashemian SM. A Fourteen-day Experience with Coronavirus Disease 2019 (COVID-19) Induced Acute Respiratory Distress Syndrome (ARDS): An Iranian Treatment Protocol. Iran J Pharm Res. 2020; 19(1):31-6.
[8] Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Autoimmune hemophagocytic syndrome. Lancet. 2014; 383(9927):1503-1516.
[9] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. HLH Across Speciality Collaboration. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020; 395(10229):1033-4.
[10] Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents. 2020; 55(5):105954.
[11] 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(5):906-7.

[12] Safari S, Salimi A, Zali A, Jahangirifard A, Bastanagh E, Aminnejad R, et al. Extracorporeal Hemoperfusion as a Potential Therapeutic Option for Severe COVID-19 patients; a Narrative Review. Arch Acad Emerg Med. 2020; 8(1):e67.

[13] Binh NG, Manabe T, Co DX, Tuan ND, Thach PT, Kudo K. Polymyxin-B-immobilized-fiber column hemoperfusion with oseltamivir treatment for ARDS due to influenza H1N1/09. Respirol Case Rep. 2015; 3(2):57-60.

[14] Dastan F, Saffaei A, Mortazavi SM, Jamaati H, Adnani N, Samiee Roudi S, et al, Continues renal replacement therapy (CRRT) with disposable hemoperfusion cartridge: a promising option for severe COVID-19. J Glob Antimicrob Resist. 2020; 21:340-1.

[15] Li X, Ma X. Acute respiratory failure in COVID-19: is it “typical” ARDS? Crit Care. 2020; 24(1):198.

[16] Esmaeili Vardanjani A, Moayedi S, Golitaleb M. COVID-19 Pandemic Hemoperfusion Therapy Versus Plasma Exchange Therapy in Intensive Care. Iran J Allergy Asthma Immunol. 2020;19(S1):7-9.