Early Hemoperfusion for Cytokine Removal May Contribute to Prevention of Intubation in Patients Infected with COVID-19

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Keywords

Hemoperfusion · Cytokine · Continuous renal replacement therapy · COVID-19 · Acute respiratory distress syndrome

Abstract

Hemoperfusion (HP) was helpful to prevent the development and progression of acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), liver failure, and septic shock by removing cytokines and other inflammatory mediators and ultimately preventing progression toward multiple organ failure. A 54-year-old man diagnosed with COVID-19 was hospitalized in the intensive care unit. The patient's O₂ saturation was 80% using an oxygen mask, which was gradually declining. After 4 sessions of HP/continuous renal replacement therapies (CRRT), O₂ saturation reached to 95%, and the patient was transferred to the general ward. Performing HP/CRRT at the early stages of ARDS can obviate the need for intubating patients with COVID-19. Punctual and early use of HP and CRRT in the treatment of ARDS in

patients with COVID-19 prevented the progression of ARDS and patient intubation, reduced respiratory distress and the patient's dependence on oxygen, prevented other complications such as AKI and septic shock in the patient, and reduced mortality and hospital length of stay.

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Introduction

As with previous viral outbreaks, a percentage of patients with COVID-19 require intensive care and complex management [1, 2]. Current strategies for coronavirus disease 2019 (COVID-19) include extracorporeal membrane oxygenation (ECMO) in the most severe cases of acute respiratory distress syndrome (ARDS) [3], as well as high-flow nasal oxygen (HFNO) and mechanical ventilation for intubated patients [4]. Although these measures are effective in most cases, several COVID-19 patients may present a fatal outcome. Reports from around

Fig. 1. Patient's chest X-ray when admitted to the ICU.

Fig. 2. Patient's chest X-ray after session 2.

Fig. 3. Patient's chest X-ray in time of transfer from the ICU to the general ward.

the world differ due to the variable intensive care unit (ICU) policy for intubation, mechanical ventilation, and application of ECMO. Yang et al. [5] reported in their study in China that nearly 94% of patients with COVID-19 admitted to ICUs and undergoing mechanical ventilation die. Furthermore, besides such a low chance of recovery hospitals may also experience a shortage of ventilator devices, a problem that some countries are still facing to some extent. Given the high mortality rate of patients requiring mechanical ventilation, all efforts should be made to prevent disease progression and need for intubation. We hypothesize that early application of hemoperfusion (HP), either isolated or in combination with continuous renal replacement therapy (CRRT) or hemo-

dialysis (HD), may contribute to preventing the incidence and progression of ARDS, acute kidney injury (AKI), liver failure, and septic shock by removing cytokines, chemokines, interleukins, and other inflammatory mediators. This approach should allow a degree of immunomodulation, ultimately preventing or slowing down the progression to multiple organ failure [6] and the need for invasive ventilation.

Case Report and Presentation

A 54-year-old male with cough and dyspnea was referred to the emergency department 2 days ago. The patient received antiviral (chloroquine, coltra, and siltamivir), antibacterial (meropenem and vancomycin), and anticoagulant (heparin 10 U/kg/h) drugs. Due to the history of hypertension and diabetes mellitus, the patient also received antihypertensive and diabetes medications.

The patient treated in the present report was diagnosed with COVID-19 for shortness of breath, a decrease in O_2 saturation (80% with the reservoir bag mask), and transferred to the ICU. The patient had oliguria and a high level of BUN and creatinine before ICU admission (creatinine 2.7 and BUN 70). Our most important clinical parameters for patient monitoring were as follows: the clinical condition of the patient, respiratory rate, respiratory distress, O_2 Sat, FiO_2 , PaO_2 , Pf ratio, IL6 and chest X-ray. Figure 1 shows the patient's chest X-ray at ICU admission. The patient was heavily dependent on oxygen O_2 saturation, and it was rapidly decreasing to <70% upon mask removal. HP (HA280 cartridge, Jaftron Biomedical Co., Zhuhai, China) in combination with CRRT was initiated. Reasons for starting CRRT include kidney function: before the onset of HP-CRRT, the patient has oliguria (urine <400 cm^3 in 24 h). After HP-CRRT, the patient's urine output reached 1,100 cm^3 in 24 h. The patient had acute renal failure, and the patient had a history of diabetes and high blood pressure. Other rea-

Fig. 4. Hemoglobin saturation of the patient during the treatment period from admission to the intensive care unit until discharge.

sons for using CRRT with HP were as follows: continuous venovenous hemofiltration (CVVH) mode with a convection mechanism has the ability to remove middle-molecule toxins and helps to remove cytokines in the interval between HP sessions. Numerous articles have been shown to increase the performance of HP and CRRT when combined. In addition to kidney damage, septic shock and multiple organs failure can be mentioned as possible complications of patients with corona disease. CRRT prevents septic shock and multiple organ failure by removing toxins and middle-molecule cytokines. CRRT mode used was as follows: CVVH predilution and postdilution every 2 h, blood flow: 200–250 mL/min, substitution flow: 25 cm³/kg/h, UF rate: 20 cm³/h, heparin: 10 U/kg/h, patient weight: 70 kg. The HP cartridge was added to the CRRT circuit simultaneously with the start of CRRT, and HP and CRRT were started simultaneously. After 6 h (saturation time), the HP cartridge was removed from the CRRT circuit, and CRRT was continued. After 20 h, the second HP cartridge was added to the CRRT circuit, and it was used for 6 h and then removed. The fluid balance was maintained neutral. The O₂ saturation of the patient gradually increased after the first hour of HP/CRRT, reaching 95 and 100% after several hours. Figure 2 shows the patient's chest X-ray after the second HP cartridge application. After 24 h, the patient's clinical condition was significantly improved. CRRT was then stopped. After about 10 h from discontinuation, O₂ saturation gradually declined and after 20 h reached about 90%, and CRRT/HP was started again. Two HP sessions were performed within the following 24 h in conjunction with CRRT, and the O₂ saturation climbed above 95% again. CRRT continued for another 12 h, and the O₂ saturation was still above 95% using a mask with a reservoir bag. The patient's creatinine and BUN levels also decreased significantly (creatinine 0.7 and BUN 30). The patient's dependence on oxygen decreased, and he could remove the mask for a few minutes. The patient was monitored for loss of O₂ saturation, but O₂ saturation had stabilized, and there was no decrease in the following 24 h. After 5 days, the patient was finally discharged from the ICU. Figure 3 shows the patient's chest

Table 1. Inflammatory and biochemical parameters before and after HP-CRRT

Test	Before HP	After 4 sessions of HP-CRRT	Reference range
CRP, mg/mL	103	12	0–3
ESR, mm/h	52	15	1–13
Fibrinogen, mg/dL	450	260	200–400
PCT, ng/mL	0.22	0.12	<0.05
D-dimer, ng/mL	750	120	<250
LDH, U/L	500	112	140–280
IL6, pg/mL	265	10	0–7
WBC, 10 ³ /mm ³	8,300	6,700	4.5–11
RBC, 10 ⁶ /mm ³	5,500	4,300	4.3–5.9
Hemoglobin, g/dL	14.5	12.8	13.5–17.5
Platelets, 10 ³ μ L	257	19	150–450
Neutrophil, 1.70–7.00 $\times 10^9$ /L	85	73	40–60%
Lymphocyte, 0.90–2.90 $\times 10^9$ /L	6%	17%	20–40%
Monocyte, 0.30–0.90 $\times 10^9$ /L	10	16	2–8%
Cr, mg/dL	2.7	0.8	0.5–1.5
BUN, mg/dL	70	35	10–20

HP, hemoperfusion; CRRT, continuous renal replacement therapy.

X-ray at that time. Figure 4 shows the trend of the patient's hemoglobin O₂ saturation during the treatment period from admission to ICU until discharge. Table 1 shows the comparison of inflammatory parameters and biochemical parameters before and after HP-CRRT.

Discussion and Conclusion

ARDS is the most common cause of intubation in patients with COVID-19 and admission in the ICUs. Subsequently, septic shock, elevated liver enzymes and renal markers, acute hepatic and renal failure, and multiple organ failure occurred and resulted in death for the patient. Cytokine storm is addressed as one of the contributing factors to ARDS. Applying HP/CRRT with a mechanism of adsorption appears to capture and harvest cytokines from the blood, prevents them from lying on the wall of the alveoli and pulmonary arteries, and ultimately prevents the incidence of ARDS and/or its progress [7–10]. Thus, we consider that there is a rationale for early application of HP/CRRT before the patient's clinical condition becomes so severe to require invasive mechanical ventilation. This is especially true in the absence of pharmacological remedies for the COVID-19 infection. Indications and duration of HP/CRRT should respond to specific criteria in order to be consistent in the application of this rescue treatment. High level of inflammatory markers and cytokines, the severe tendency to hypoxia, clinical signs of hemodynamic instability, and need for vasopressor support may represent a trigger for early application of HP/CRRT. Further studies are needed to confirm this hypothesis, but recent data are promising. In conclusion, with clinical experiences we have shown that the application of CRRT/HP in the early stages of ARDS, when the O₂ saturation of the patient's blood with a reservoir oxygen mask is <90%, prevented the progression of the disease to moderate-to-severe ARDS, stabilized the O₂ saturation, and gradually led to increased O₂ saturation, prevention of intubation, improved clinical conditions, reduced dependence on oxygen, discharge from ICUs, and ultimately discharge from the hospital.

References

- 1 Murthy S, Gomersall CD, Fowler RA. Care for critically ill patients with COVID-19. *JAMA*. 2020;323(15):1499.
- 2 Ronco C, Ricci Z, Husain-Syed F. From multiple organ support therapy to extracorporeal organ support in critically ill patients. *Blood Purif*. 2019;48(2):99–105.
- 3 Ramanathan K, Antognini D, Combes A, Paden M, Zakhary B, Ogino M, et al. Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic and other outbreaks of emerging infectious diseases. *Lancet Respir Med*. 2020;8(5):518–26.
- 4 Matthay MA, Aldrich JM, Gotts JE. Treatment for severe acute respiratory distress syndrome from COVID-19. *Lancet Respir Med*. 2020;8(5):433–34.
- 5 Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y, 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(5):475–81.
- 6 Monard C, Rimmele T, Ronco C. Extracorporeal blood purification therapies for sepsis. *Blood Purif*. 2019;47:2–15.
- 7 Ronco C, Reis T, De Rosa S. Coronavirus epidemic and extracorporeal therapies in intensive care: si vis pacem para bellum. *Blood Purif*. 2020;49(3):255–8.
- 8 Zuccari S, Damiani E, Domizi R, Scorcella C, D'Arezzo M, Carsetti A, et al. Changes in cytokines, haemodynamics and microcirculation in patients with sepsis/septic shock undergoing continuous renal replacement therapy and blood purification with CytoSorb. *Blood Purif*. 2020;49(1–2):107–13.
- 9 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. 10.18502/ijaa.v19i(s1.r1).2848.
- 10 Ma J, Xia P, Zhou Y, Liu Z, Zhou X, Wang J, et al. Potential effect of blood purification therapy in reducing cytokine storm as a late complication of severe COVID-19. *Clin Immunol*. 2020;214:108408.

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Statement of Ethics

The authors have no ethical conflicts to disclose. The study was conducted in accordance with policies and procedures approved by the local institution review board. The patient, described in this case report, has given his written consent to publish data and images.

Conflict of Interest Statement

CR consulted or advised in the last 3 years for ASAHI, Astute, Baxter, Biomerieux, B. Braun, Cytosorbents, ESTOR, FMC, GE, Jafron, Medtronic, and Toray. The other authors have no conflicts of interest.

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Author Contributions

A.E.V. and M.H.P. performed HP/CRRT for the patient and were involved in data collection and writing and editing of the manuscript. C.R. was involved in writing and editing of the manuscript and gave final approval for publishing. M.G. performed literature search and was involved in data collection and writing and editing of the manuscript. M.M. and H.R. were involved in writing and editing of the manuscript.