Arch Clin Infect Dis. 2021 October; 16(5):e111405. doi: 10.5812/archcid.111405.

Published online 2022 January 10. **Case Report**

Plasmapheresis with Convalescent Plasma as a Rescue Therapy for COVID-19 Patients: A Case Series

Jamshid Vafaeemanesh [1,*], Seyed Hassan Adeli [1], Akram Asghari [1] and Fateme Sadat Razavinia [2]

[1] Clinical Research Development Center, Shahid Beheshti Hospital, Qom University of Medical Sciences, Qom, Iran
[2] Department of Student Research Committee, Qom University of Medical Sciences, Qom, Iran

[*] *Corresponding author*: Clinical Research Development Center, Shahid Beheshti Hospital, Qom University of Medical Sciences, Qom, Iran. Email: jvafaeemanesh@gmail.com

Received 2020 November 18; **Accepted** 2021 October 31.

Abstract

On December 29, 2019, an epidemic of an infectious disease caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) was declared in Wuhan, China. The first case of COVID-19 in Iran (Qom Province) was reported in February 2020, and within a short period, the number of infected cases increased rapidly around the country. Evidence suggests that the levels of pro-inflammatory cytokines are high in critically ill patients, and there is a correlation between the high level of cytokines and the pathogenesis of COVID-19; consequently, COVID-19 may have complications, such as acute respiratory distress syndrome (ARDS) and even death. These inflammatory factors can lead to a cytokine storm, while counteracting this storm seems to be an effective therapeutic approach. In this case series, we reported two critically ill patients with COVID-19, undergoing plasmapheresis with convalescent plasma, corticosteroid therapy, and interferon administration.

Keywords: Plasmapheresis with Convalescent Plasma, Rescue Therapy, COVID-19 Patients

1. Introduction

On December 29, 2019, an epidemic of an infectious disease caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China (1, 2). After extensive research and examination, on March 24, 2020, the World Health Organization (WHO) called this new RNA virus the novel coronavirus 2019 (2019-nCoV) (3-5). Evidence suggests that this virus originated from a local seafood market in Hubei Province, China (4). It seems reasonable to assume a relationship between early infected cases and a history of exposure to the original seafood market (3, 6, 7). Following exposure to the seafood market, humans were recognized as the secondary source of the virus.

Considering our limited knowledge of 2019-nCoV, besides the asymptomatic nature of this disease in some patients, this virus has spread rapidly around the world (8, 9). On March 18, 2020, infected cases were reported in almost 195 countries (10, 11). The first case of coronavirus disease 2019 (COVID-19) in Iran (Qom Province) was reported in February 2020, and within a short period, the number of infected cases increased rapidly around the country (12). According to the latest Chinese health guidelines, the incubation period of COVID-19 ranges from two to 14 days (4, 13). The clinical manifestations of COVID-19 are diverse, including cough, fever, cardiovascular, taste, and olfactory disorders, myalgia or fatigue, productive cough, runny nose, and headache (4, 14-16). However, symptoms and their severity are not completely identified yet, although the respiratory system is recognized as the main affected system (17).

Depending on the patient's critical condition, they can be classified into three groups: group 1 with respiratory failure requiring mechanical ventilation; group 2 with septic shock, receiving vasopressor therapy (lactate level > 2 mmol/L); and group 3 with a critical condition requiring admission to the intensive care unit (ICU) (17). According to a report by Shen, the most common age group of CVOID-19 patients is 35 - 55 years, while there are fewer reports in children and infants (17, 18). Therefore, a strong relationship has been proposed between the immune system and the risk of infection.

According to a study by Prompetchara et al., the levels of pro-inflammatory cytokines are high in critically ill patients (19), and there is a correlation between high levels of cytokines and the pathogenesis of COVID-19 (20). Therefore, complications, such as acute respiratory distress syndrome (ARDS) and even death, may occur in these patients (16). So far, no specific drug has been developed for this dis-

ease, and several therapies are under investigation. Therefore, one of the most important challenges in the management of COVID-19 is to introduce appropriate agents to control and treat the disease (4, 7).

In this case series, we reported two critically ill COVID-19 patients, undergoing plasmapheresis with convalescent plasma, corticosteroid therapy, and interferon administration.

2. Case Presentation

This study was performed at the internal medicine department of Shahid Beheshti Hospital, Qom, Iran, from January 20 to March 25, 2020. In this study, the ethical principles were observed. Informed consent was obtained from two conscious patients with COVID-19, confirmed by a quantitative reverse transcription-polymerase chain reaction (qRT-PCR) assay.

The treatment plan for the patients included a single dose of hydroxychloroquine sulfate (400 mg), lopinavir/ritonavir (100 mg/400 mg), and ribavirin (1200 mg), each for five days, as well as three doses of interferon-β (250 μg of IFN-β) every other day. The antiviral treatment protocol applied for other patients was also used for these two patients. After antiviral treatment, the severity of symptoms did not decrease in these patients; consequently, they were candidates for corticosteroid therapy (4 mg of dexamethasone TDS: Three times a day) to reduce the inflammatory response and improve the clinical status.

The patients' response to treatment with corticosteroids was poor, and they still showed significant hypoxia. Based on our previous successful experience of treatment for severe COVID-19 using plasmapheresis, this procedure was performed to suppress the cytokine storm. The plasmapheresis (plasma exchange) procedure included daily filtration (2 L), compensated for with four units of fresh frozen plasma (FFP), two vials of calcium gluconate (20%) depending on the patient's serum calcium level and 5 vials of albumin. According to the sample size estimation status, the remaining volume was replaced with normal saline.

Since plasmapheresis has potential side effects, we would terminate the plasma exchange process if any change occurred in the patient's condition. Every 10 to 15 minutes during apheresis, the patient's vital signs were monitored. Although the patients did not experience any side effects of plasmapheresis, after three sessions, no improvement was observed in their status. In the next session, the plasma of patients, who were previously diagnosed with COVID-19 and had recovered, was used. The donated plasma, examined twice by PCR, was negative for COVID-19. It was also examined using an ELISA assay, which showed high levels of immunoglobulins (IgG and IgM) against COVID-19.

Following stage 4 (plasmapheresis), the patients' conditions improved. Based on the findings, their oxygenation and respiratory status improved, and both of them were extubated. Finally, both male and female patients were discharged from the hospital in a better general condition after 35 and 45 days, respectively. Besides respiratory distress symptoms, one of the two patients (a 48-year-old woman) had symptoms of quadriplegia that persisted after endotracheal extubation. In this case, Guillain-Barré syndrome was ruled out based on neurological and rheumatological guidance by performing electromyography (EMG) and nerve conduction velocity (NCV). After plasmapheresis, myopathy improved, and the patient's status improved.

3. Discussion

We reported two critically ill COVID-19 patients, undergoing convalescent plasma therapy, which could successfully improve their clinical status. After treatment, parameters, such as the oxygenation index (PAO2/FIO2), body temperature, and quadriplegia, improved, and CT scans indicated a significant reduction in the pulmonary involvement and viral load. In this study, the treatment protocol consisted of three essential stages for critically ill patients: (1) reduction of virulence; (2) reduction of cytokine production; and (3) elimination of cytokines produced. In the first stage, different antiviral agents were used; IFN is a recommended agent. In the second stage, based on the satisfactory early data on corticosteroid use, they were considered to be suitable. To achieve the goal of the third stage, we had performed plasmapheresis for patients in a previous study (16). However, in the present case series, plasmapheresis with convalescent plasma from a donor, who had been tested positive for COVID-19, was performed, which could successfully improve the patients' clinical condition.

In this case series, plasmapheresis was performed based on a method proposed in recent studies. However, in the final stage (fourth stage), since the patients' conditions had deteriorated, plasmapheresis was performed with the plasma of patients who had been previously infected with the virus and had recovered. By using this lifesaving method, besides improving their clinical condition, laboratory markers, such as cytokine level and inflammatory markers, were also suppressed. Overall, it was found to be an ideal method for treating and controlling COVID-19.

According to previous research, including a study by De Jong on the level of cytokines and viral load, a strong link was found between the viral load, disease progression, and disease severity (21). In addition to antiviral treatment, specific neutralizing antibodies play an important role in restriction and clearance of viruses by preventing viral entry (targeting cells) and accelerating viral clearance (17, 21). Also, the correlation of cytokines and inflammatory markers with plasma exchange has been highlighted in recent studies. In this regard, a previous study reported treatment of a severe influenza infection (H1N1) using an effective method that could reduce mortality (22).

In our method, inflammatory cytokines, such as interleukin-6, reduced in patients treated with corticosteroid therapy (methylprednisolone) and plasmapheresis, and they recovered completely. The therapeutic effects of convalescent plasma in the treatment of COVID-19 patients have been reported in the literature (23). Evidence suggests that convalescent plasma antibodies are correlated with viral clearance and improvement of patient's symptoms.

In a previous study, we had a promising experience in the treatment of critically ill patients with COVID-19 using plasmapheresis (16). Therefore, we applied plasmapheresis for our critically ill patients in this case series. The use of this treatment in the third session usually improved the patient's general condition. In our two patients, because no improvement was detected, convalescent plasma was used in the final session of plasmapheresis. To the best of our knowledge, this report is the first to use this treatment method successfully. Besides, in the first session of plasmapheresis, by removing the patient's plasma, the risk of cytokine storm was eliminated, and in the final session, the patient's plasma was replaced with convalescent plasma rich in antiviral antibodies.

Footnotes

Authors' Contribution: J.V. developed the original idea and protocol of the study, abstracted and analyzed the data, and wrote the manuscript (guarantor). S.H.A., A.A.A., and F.S.R. contributed to the development of the study protocol, abstraction of data, and preparation of the manuscript.

Conflict of Interests: The authors declare no conflicts of interest.

Funding/Support: The authors declared no funding/support.

Informed Consent: Informed consent was obtained from the patients.

References

1. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *Radiology*. 2020;**296**(2). doi: 10.1148/radiol.2020200642. [PubMed: 32101510]. [PubMed Central: PMC7233399].
2. Riou J, Althaus CL. Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020. *Euro Surveill*. 2020;**25**(4). doi: 10.2807/1560-7917.ES.2020.25.4.2000058. [PubMed: 32019669]. [PubMed Central: PMC7001239].
3. Bai Y, Yao L, Wei T, Tian F, Jin DY, Chen L, et al. Presumed Asymptomatic Carrier Transmission of COVID-19. *JAMA*. 2020;**323**(14):1406–7. doi: 10.1001/jama.2020.2565. [PubMed: 32083643]. [PubMed Central: PMC7042844].
4. Adhikari SP, Meng S, Wu YJ, Mao YP, Ye RX, Wang QZ, et al. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. *Infect Dis Poverty*. 2020;**9**(1):1–12. doi: 10.1186/s40249-020-00646-x. [PubMed: 32183901]. [PubMed Central: PMC7079521].
5. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020;**579**(7798):270–3. doi: 10.1038/s41586-020-2012-7. [PubMed: 32015507]. [PubMed Central: PMC7095418].
6. Zhou P, Yang X, Wang X, Hu B, Zhang L, Zhang W, et al. Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin. *bioRxiv*. 2020. doi: 10.1101/2020.01.22.914952.
7. 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. doi: 10.1016/s0140-6736(20)30183-5.
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**(5). doi: 10.1016/s2213-2600(20)30079-5.
9. Gralinski LE, Menachery VD. Return of the Coronavirus: 2019-nCoV. *Viruses*. 2020;**12**(2):135. doi: 10.3390/v12020135. [PubMed: 31991541]. [PubMed Central: PMC7077245].
10. World Health Organization. *Coronavirus disease 2019 (COVID-19): situation report, 80*. World Health Organization; 2020.
11. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*. 2020;**14**(1). doi: 10.5582/bst.2020.01047. [PubMed: 32074550].
12. Arab-Mazar Z, Sah R, Rabaan AA, Dhama K, Rodriguez-Morales AJ. Mapping the incidence of the COVID-19 hotspot in Iran - Implications for Travellers. *Travel Med Infect Dis*. 2020;**34**:101630. doi: 10.1016/j.tmaid.2020.101630. [PubMed: 32184130]. [PubMed Central: PMC7118655].
13. Hamid S, Mir MY, Rohela GK. Novel coronavirus disease (COVID-19): A pandemic (epidemiology, pathogenesis and potential therapeutics). *New Microbes New Infect*. 2020;**35**:100679. doi: 10.1016/j.nmni.2020.100679. [PubMed: 32322401]. [PubMed Central: PMC7171518].
14. Akpoveta OA, Joy O, Joy O. COVID-19 Pandemic: Nigeria's economic and business disruptions. *Int J Arts Soc Sci Res*. 2020;**2**(4):14–31.
15. Kraemer MUG, Yang CH, Gutierrez B, Wu CH, Klein B, Pigott DM, et al. The effect of human mobility and control measures on the COVID-19 epidemic in China. *Science*. 2020;**368**(6490):493–7. doi: 10.1126/science.abb4218. [PubMed: 32213647]. [PubMed Central: PMC7146642].
16. Adeli SH, Asghari A, Tabarraii R, Shajari R, Afshari S, Kalhor N, et al. Therapeutic plasma exchange as a rescue therapy in patients with coronavirus disease 2019: a case series. *Pol Arch Intern Med*. 2020;**130**(5):455–8. doi: 10.20452/pamw.15340. [PubMed: 32380821].

17. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 Critically Ill Patients with COVID-19 with Convalescent Plasma. *JAMA*. 2020;**323**(16):1582–9. doi: 10.1001/jama.2020.4783. [PubMed: 32219428]. [PubMed Central: PMC7101507].
18. Wang C, Wang X. Prevalence, nosocomial infection and psychological prevention of novel coronavirus infection. *Chin General Pract Nurs*. 2020;**18**:2–3.
19. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. *Asian Pac J Allergy Immunol*. 2020;**38**(1):1–9.
20. 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**(10223):507–13. doi: 10.1016/s0140-6736(20)30211-7.
21. De Jong MD, Uehara T, Hayden FG, Kawaguchi K, Omoto S, Hurt AC, et al. Treatment-Emergent Influenza Variant Viruses with Reduced Baloxavir Susceptibility: Impact on Clinical and Virologic Outcomes in Uncomplicated Influenza. *J Infect Dis*. 2020;**221**(3):346–55. doi: 10.1093/infdis/jiz244. [PubMed: 31309975].
22. Wang C, Li W, Drabek D, Okba NMA, van Haperen R, Osterhaus A, et al. A human monoclonal antibody blocking SARS-CoV-2 infection. *Nat Commun*. 2020;**11**(1):1–6. doi: 10.1038/s41467-020-16256-y. [PubMed: 32366817]. [PubMed Central: PMC7198537].
23. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. *Lancet Infect Dis*. 2020;**20**(4):398–400. doi: 10.1016/s1473-3099(20)30141-9.