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Case Report

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A Transient Effect of Convalescent Plasma Therapy in a Patient with Severe Covonavirus Disease 2019: A Case Report

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ABSTRACT

A 65-year-old male patient with an end-stage renal disease was diagnosed with coronavirus disease 2019 (COVID-19) by reverse transcription polymerase chain reaction. The patient complained of cough, sputum, and respiratory distress that worsened three days ago. The patient required mechanical ventilation and extracorporeal mentrane oxygenation. On day 9, convalescent plasma collected from a 34-year old man who recovered from COVID-19 45 days ago was administered. The patient showed immediate clinical improvement. However, on day 14, the patient's clinical course worsened again. On day 19 and day 24, vancomycin-resistant *Enterococcus faecium* bacteremia and methicillin-resistant *Staphylococcus aureus* pneumonia were found. After long-term supportive care, he slowly recovered. He was discharged on day 91 without any oxygen requirement. This case report suggests that convalescent plasma therapy might just provide a short-term relief and that persistent effort for critical care is necessary to save patients from severe COVID-19.

Keywords: Convalescent plasma; Coronavirus disease 2019; Therapy

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an acute respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). About 14% of patients with COVID-19 have severe pneumonia [1]. Old age and comorbidities such as diabetes mellitus, malignancy, cardiovascular disease, and chronic kidney disease are known as risk factors for

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Ethics statement
This study was approved by the Institutional Review Board (IRB) of Soonchunhyang University Bucheon Hospital (IRB 2020-04-016).Written informed consent was obtained from the patient for the publication of this case.

Conflict of Interest
No conflict of interest.

Author Contributions
Conceptualization: JHP, TK. Data curation: ARB, EJC, JYK, TSH, SWP, HBS, SKP, JHP, TK. Writing-original draft: ARB, TK. Review & editing: ARB, HBS, JHP.

fatality [2]. Although various therapeutic agents have been tried to treat patients with severe COVID-19, there have been no proven agents [3, 4]. Only remdesivir, a nucleoside analogue developed as a therapeutic agent for Ebola virus disease, has been reported to be able to shorten the illness duration of COVID-19 [5, 6].

Convalescent plasma of a patient recovering from COVID-19 is expected to include immunoglobulins such as neutralizing antibodies against SARS-CoV-2. This kind of convalescent plasma therapy has been tried to treat various viral infections such as severe acute respiratory virus syndrome [7], middle east respiratory virus syndrome [8], and influenza [9]. Based on these experiences, convalescent plasma therapy has also been tried to treat COVID-19 [10]. Case series have shown that convalescent plama therapy seems to be a successful therapeutic option [11, 12]. Recently, a case report published in Korea also shows that this therapy has a good outcome [13]. However, unlike previous reports, we experienced a transient effect of convalescent plasma therapy in a patient with severe COVID-19 who required extracorporeal membrane oxygenation (ECMO) therapy.

CASE REPORT

A 65-year-old male patient was diagnosed with COVID-19 by real-time reverse transcription polymerase chain reaction (PCR) (AllplexTM 2019-nCoV Assay, Seegene, Seoul, Korea) in another hospital's emergency room one day before he was transferred to the negative pressure isolation room of our hospital. The patient had cough, sputum, and respiratory distress that worsened three days ago. The patient was diagnosed with hypertension and end-stage renal disease 17 years ago. He had been maintaining hemodialysis three times a week in a local clinic, doing relatively well without any significant problem in daily life. After arriving at our hospital, he had blood pressure of 218/116 mmHg, pulse rate of 108 times/minute, respiratory rate of 26 times/minute, peripheral oxygen saturation of 81% (with non-rebreathing reservoir mask of 15 L/min applied). The patient spitted out bloody and frothy sputum with severe respiratory distress while using accessory muscles. However, his consciousness was alert. Even after applying an oxygen concentration of 100% and an oxygen flow rate of 60 L/min using a high-flow nasal cannula, the patient's oxygen saturation was still below 90%. His respiratory distress using accessory respiratory muscles was also sustained. Thus, intubation was immediately performed. Given the rapid worsening course of COVID-19, we immediately decided to apply venovenous ECMO to achieve ultra-protective ventilation with continuous renal replacement therapy.

Owing to this critical situation, we admistered all possible therapeutic options such as hydroxychloroquine, lopinavir/liponavir, nafamostat, and methylprednisolone (**Fig. 1**). We also considered convalescent plasma therapy as another therapeutic option. A donor was recruited with the help of the Expert Committee of Gyeonggi COVID-19 Emergency Response Task Force. The donor was a 34 year-old man with Rh+ O blood type who was diagnosed as COVID-19 45 days ago. After allogeneic donor screening according to enforcement rules of the Blood Management Act in Korea, apheresis was performed with a Spectra Optia apheresis system (CMNC software; Spectra Optia ILD tubing set; Terumo BCT, Lakewood, CO, USA) and 500 mL of convalescent plasma was collected. Anti-SARS-CoV-2 IgG antibody in plasma was measured by enzyme-linked immunosorbent assay (EDI™ Novel Coronavirus COVID-19 IgG ELISA Kit; Eagle Biosciences, Nashua, NH, USA). It was detected as shown in **Table 1**.

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Table 1. Measurements of anti-SARS-CoV-2 IgG in donor and recipient plasma samples using enzyme-linked immunosorbent assay

Sample	Day of collection	Optical density ratio (540 nm)	Adjusted optical density ratio
Negative control 1	NA	0.112	0.105
Negative control 2	NA	0.077	0.070
Negative control 3	NA	0.133	0.126
Positive control	NA	0.600	0.593
Donor plasma 1[a]	Day 7	0.746	0.739
Donor plasma 2[a]	Day 7	0.797	0.790
Recipient plasma 1[a]	Day 7	0.245	0.238
Recipient plasma 2[a]	Day 7	0.272	0.265
Recipient plasma 1[a]	Day 10	0.609	0.602
Recipient plasma 2[a]	Day 10	0.659	0.652

Convalescent plasma was administered on day 9.
[a]Duplicated specimen.
SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; NA, not available.

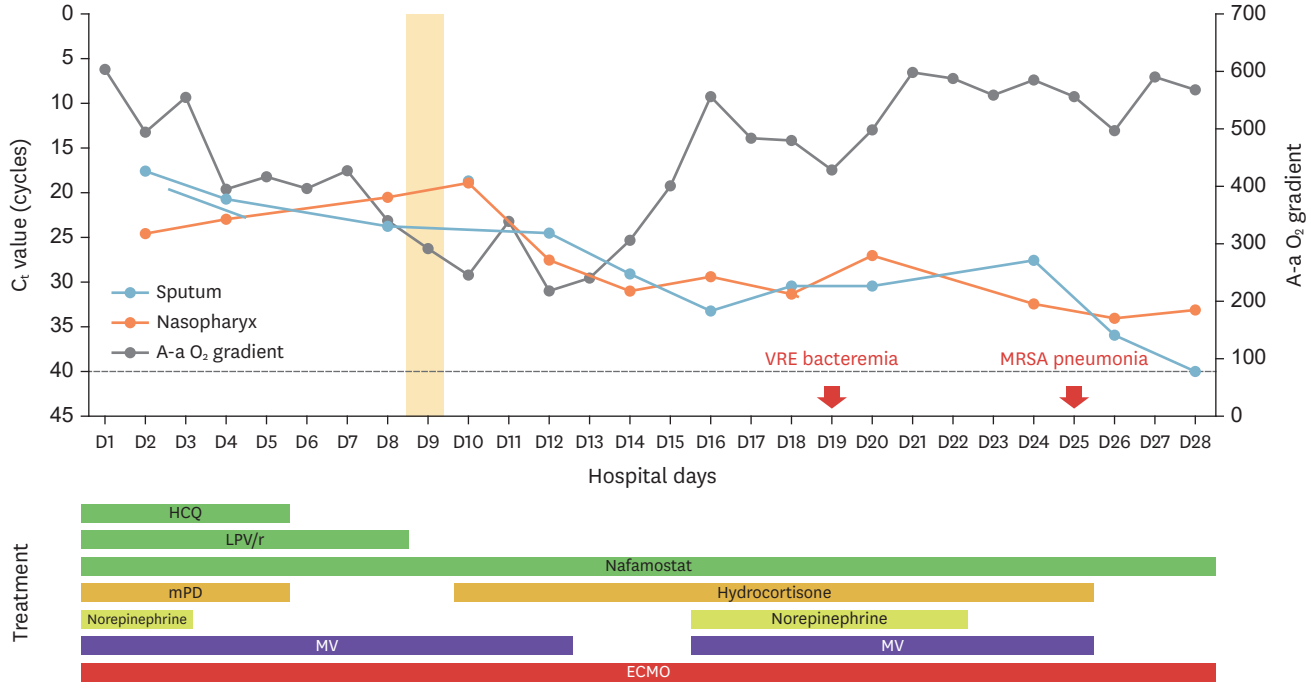

Figure 1. Treatment, viral titer, and oxygen requirement of a patient with COVID-19 who received convalescent plasma therapy.
Convalesent plasma was administered on day 9. VRE was isolated from blood on day 19. Orange and blue lines were values of cycle threshold of RNA-dependent RNA polymerase gene of SARS-CoV-2. Gray line was A-a O_2 gradient.
COVID-19, coronavirus disease 2019; VRE, vancomycin-resistant *Entercoccus feacium*; MRSA, methicillin-resistant *Staphylococcus aureus*; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; HCQ, hydroxychloroquine; LPV/r, lopinarir/ritonavir; mPD, methylprednisolone; MV, mechanical ventilation; ECMO, extracorporeal membrane oxygen.

On day 9, convalescent plasma was administered into the patient. Optical density for IgG in the patient's plasma increased to be as high as that in the donor plasma (**Table 1**). After administration of convalescent plasma, as shown in **Fig. 1** and **2**, immediate clinical improvement was shown. The setting of the fraction of inspired O_2 concentration (FiO_2) on ECMO was tuned from 0.7 to 0.5. However, on day 14, oxygen requirement was increased again until the setting of FiO_2 was increased up to 1.0. On day 18, bronchoscopy-guided tracheostomy was done. On day 19, vancomycin-resistant *Enterococcus faecium* (VRE) was isolated from blood culture. On day 25, methicillin-resistant *Staphylococcus aureus* was isolated from sputum culture. After two weeks of linezolid 600 mg iv q 12hr administration, the patient showed clinical improvement. He was weaned from ECMO on day 44. Negative results of

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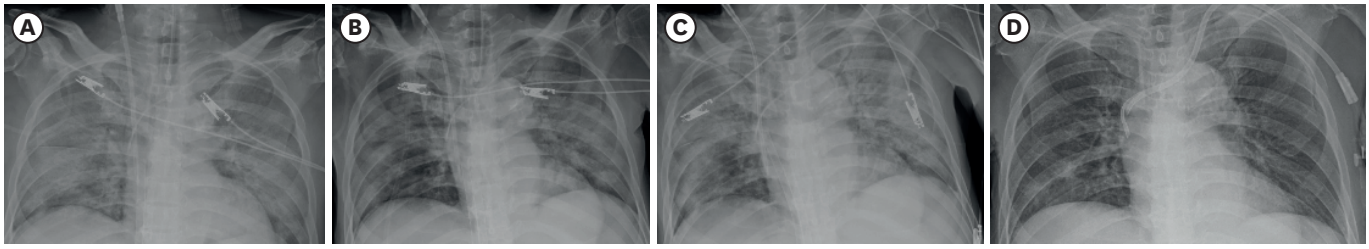

Figure 2. Changes of chest X-ray of a patient with COVID-19 who received convalescent plasma therapy.
Convalesent plasma was administered on day 9. Compared to that taken on day 7 (A) before convalescent plasma therapy, chest X-ray taken on day 12 (B) shows marked improvement of bilateral pulmonary infiltration. Aggravated pulmonary infiltration was found on day 14 (C). Pulmonary infiltration nearly disappeared at the time of discharge on day 91 (D).
COVID-19, coronavirus disease 2019.

PCR (AllplexTM 2019-nCoV Assay, Seegene, Korea) from both nasopharyngeal and sputum specimen were found on day 49. On day 61, pneumothorax occurred. It was resolved after chest tube thoracostomy. The patient's lung function was slowly recovered. He was finally transferred to a long-term care facility for supportive care on day 91. Chest X-ray at the time of discharge is shown in **Figure 2**. The patient no longer needed supplemental oxygen therapy.

DISCUSSION

This case report showed that the effect of convalescent plasma therapy might last for only a few days in patients with severe COVID-19. A smiliar transient effect following by worsening of clinical course has also been shown in a recent case report [14]. In that previous report, definite clinical improvement was maintained only for three days and the patient needed ECMO at five days after the convalescent plasma therapy [14]. Several reasons for this short-term effect of convalescent plasma therapy can be assumed. Firstly, passive antibody may rapidly wane and offer only short-term immunity. However, this hypothesis cannot explain the previous result about passive antibody therapy and immune formation in patients with COVID-19. It seems to take weeks to a few months for passive antibodies to wane, not a few days [15]. Also, two weeks of illness was enough to get the patient's own neutralization antibody [16]. In our case, we were unable to evaluate this hypothesis, because we only checked the antibody titer just on a day after convalescent plasma therapy (10 days from hospitalization). Further studies on the humoral dynamics after convalescent plasma therapy should be followed. Secondly, bacterial infection such as bacteremia and ventilator-associated pneumonia as complications of severe COVID-19 might have made the clinical course worse again. Indeed, VRE bacteremia occurred after a few days from clinical worsening and the patient suffered from ventilator-associated pneumonia. It is well-established that seasonal viral respiratory infection is linked to increased risk of bacterial infection [17]. This is also possible in patients with COVID-19 [18]. A recent systemic analysis showed that 14% (95% confidence interval: 5 – 26%) of patients with COVID-19 in intensive care unit had bacterial co-infection [19]. In a recent report on critically ill patients with COVID-19, bacterial pneumonia was complicated at two to three weeks after the time of diagnosis [20], similar to our case report.

This case report on a transient effect of convalescent plasma therapy for COVID-19 has therapeutic implications. Therapeutic approach using passive immunity such as convalescent plasma or monoclonal antibody might need to be repeated during the illness of COVID-19. Whether a similar phenomenon will occur using convalescent plasma and

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monoclonal antibody should be observed in clinical trials. This case report also suggests that convalescent plasma therapy alone might be insufficient for treating COVID-19. Further studies on a combination therapy using antiviral agents and/or anti-inflammatory drug with convalescent plasma therapy should be performed. Finally, this case report demonstrates that a persistent effort of competent experts in preventing and treating bacterial co-infection and complication in critical care can save patients from severe COVID-19.

This case report has limitations that make it difficult to interpret the efficacy of a convalescent plasma therapy. Effects of co-administered antiviral agents and corticosteroid on transient improvement could be biased for interpreting the effect of convalescent plasma therapy. Also, lowered viral titer and IgG formation after convalescent plasma therapy might be a natural prognosis, not due to the effect of the convalescent plasma therapy itself.

In conclusion, this case report suggests that convalescent plasma therapy might be just a booster shot rather than a Messiah who can save severe patients from COVID-19. Further well-controlled trials should be performed to prove the role of convalescent plasma therapy in treating COVID-19.

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