Efficacy and safety of convalescent plasma therapy for severe COVID-19 patients: a case series study and literature review

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Research Article

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is a new acute respiratory infectious disease that can lead to multiple organ dysfunction in severe patients. However, there is still a lack of effective antiviral drugs for COVID-19. Herein, we investigated the efficacy and safety of convalescent plasma (CP) in the treatment of severe COVID-19 in an attempt to explore new therapeutic methods.

Methods: Clinical data of three imported severe COVID-19 patients with CP treatment who were under quarantine and treated in a designated COVID-19 hospital from March 2020 to April 2020 were collected and analyzed.

Results: The three patients were clinically classified as severe type, including one male and two females, aged 57, 59 and 65 years old, respectively. The main underlying diseases included hypertension, diabetes, sequelae of cerebral infarction and postoperative thyroid adenoma. The common symptoms included cough, fever and shortness of breath. All patients received antiviral drugs and other supportive treatments. Additionally, CP treatment was also administered. Forty-eight to seventy-two hours after CP transfusion, all the patients improved with alleviated symptoms, elevated arterial oxygen saturation, and decreased C-reactive protein and interleukin-6 markers. Total lymphocytes, T lymphocytes (CD3+) and their subsets (CD4+, CD8+) were also obviously increased. Repeated chest CT also showed obvious absorption of lesions in the bilateral lungs. Only one patient had a mild allergic reaction during CP infusion, but no severe adverse reactions were found.

Conclusions: The early application of CP for severe COVID-19 patients can improve the condition rapidly, and the therapy is generally effective and safe.

Introduction

Coronavirus disease 2019 (COVID-19) induced by severe acute respiratory syndrome-associated coronavirus-2 (SARS-CoV-2) is a new acute respiratory infectious disease that can lead to multiple organ dysfunction in severe patients [1]. Worryingly, the infection remains worse in most countries and areas. As of January 2, 2022, the COVID-19 epidemic has caused more than 289 million cases and over 5.44 million deaths worldwide (<https://coronavirus.jhu.edu/map.html>). However, there is still a lack of effective antiviral drugs for COVID-19 [1, 2]. Convalescent plasma (CP) therapy has been used for treating influenza for more than a century. A meta-analysis of 32 studies showed that CP therapy could reduce mortality in influenza virus patients [3]. Currently, several clinical studies have shown that CP therapy can significantly improve the clinical symptoms and prognosis of severe and critically ill COVID-19 patients [4–6]. A randomized controlled trial in China further revealed that early infusion of CP had a better therapeutic effect in COVID-19 patients, and more benefits could be obtained in severe patients than in life-threatening patients [7–8]. This study retrospectively analyzed the clinical data of three severe COVID-19 patients who received CP therapy and obtained good curative effects to further improve the understanding of the application value of this therapy in severe COVID-19 patients.

1. Materials And Methods

Patients

Clinical data, including epidemiology, clinical manifestations, laboratory examinations, imaging results and treatment outcomes, were collected from three imported severe COVID-19 patients who were under quarantine and treated in a designated hospital in Fuzhou from March 2020 to April 2020. The last follow-up was completed on May 7, 2020. Respiratory tract specimens (throat swabs) of all enrolled cases were positive for SARS-CoV-2 RNA by reverse transcription-polymerase chain reaction (RT-PCR) qualitative detection. All patients met the diagnostic criteria according to the Diagnosis and Treatment Program for COVID-19 issued by the National Health and Family Planning Commission [9].

The disease severity in COVID-19 patients was classified as follows: Mild COVID-19 was defined as mild clinical symptoms without pneumonia on chest imaging; Moderate COVID-19 was defined as clinical symptoms (e.g., fever and respiratory symptoms) with limited pneumonia on chest imaging; Severe COVID-19 was defined as any of the following: respiratory distress and respiratory rate ≥ 30 breaths per minute, or in resting state, oxygen saturation $\leq 93\%$ on room air, or arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ≤ 300 , or significant lung lesion progression $\geq 50\%$ within 24 to 48 hours on chest imaging; Critically ill (Life-threatening) COVID-19 was defined as respiratory failure requiring mechanical ventilation, or shock, or other organ failure (apart from lung) requiring intensive care unit (ICU) monitoring [10]. All patients in our study were clinically classified as having severe COVID-19 according to the above criteria.

During the period of hospitalization, respiratory tract specimens (throat swabs) of all patients were continuously monitored for viral shedding until the samples were negative for SARS-Cov-2 RNA for two consecutive days (at least 24 hours apart). This study was approved by the Ethics Committee of the People's Hospital Affiliated to Fujian University of Traditional Chinese Medicine, and the patients provided informed consent for paper publication.

2.2 Collection, Storage And Use Of Cp

According to the Clinical Treatment Scheme of COVID-19 Convalescent Plasma [11], CP was obtained from COVID-19 patients who had recently recovered and discharged from the hospital. Before venous blood sample collection, all donors had undergone strict medical screening and evaluation, including meeting the quarantine and discharge standards according to the Diagnosis and Treatment Program for COVID-19 [9], and at least 2 weeks after discharge. Respiratory specimens were negative for SARS-CoV-2 and other viral nucleic acids, and serum tests for hepatitis B virus, hepatitis C virus, human immunodeficiency virus (HIV) and syphilis were negative. Serum SARS-CoV-2 IgG antibody dilution titers of three donors were at least 1:80, and the total CP infusion dose of each patient was 200 to 400 ml (4 to 5 ml/kg) (Table 1). Early CP administration was defined as CP infusion initiated within one week after

admission and two weeks following symptom onset [12–14]. Adverse reactions to CP infusion were closely monitored during CP treatment, and the first efficacy assessment, including clinical symptoms, oxygenation function, inflammatory markers, lymphocyte counts, chest CT manifestations, etc., was performed 48 to 72 hours after transfusion.

Table 1
Characteristics of three patients with convalescent plasma therapy

Characteristics	Case 1	Case 2	Case 3
Importing nation	Brazil	America	France
Nationality	Chinese	Chinese	Chinese
Age (years)	57	65	59
Sex	Male	Female	Female
Body weight (kg)	82	50	58
BMI (kg/m ²)	27.7	22.2	20.3
Disease type	Severe	Severe	Severe
Underlying disease	Hypertension, Sequela of cerebral infarction	Hypertension, diabetes	Postoperative thyroid denoma
Symptom	Cough, expectoration, fever, breathlessness, headache	Cough, breathlessness, appetite, excessive fatigue	Cough, fever, breathlessness, dry thorat
Chest CT feature		Multiple lesions	Multiple lesions
Complication	Multiple lesions	None	Hypovolemia, pulmonary bacterial infection
Anti-viral treatment	None	Abidol, lopinavir/ritonavir	Human interferon α -2b spray
Antibiotic therapy	Abidol, hydroxychloroquine sulfate	None	Ceftriaxon
Anti-inflammatory agent	None	Xuebijing injection, ulinastatin	Xuebijing injection, ulinastatin
Immunostimulant	Xuebijing injection, ulinastatin	Thymalfasin	Thymalfasin
Chinese herbal medicine	Thymalfasin	Yes	Yes
Respiratory support	Yes	Ransnasal catheter oxygen therapy	Ransnasal catheter oxygen therapy
Blood type of CPR	Ransnasal catheter oxygen therapy	Type A, negative for RhD	Type B, positive for RhD
Blood type of CPD	Type B, positive for RhD	Type A, positive for RhD	Type B, positive for RhD
SARS-CoV-2 IgG titer of CPD	Type B, positive for RhD	Positive at 1: 80, Negative at 1:160	Type B, positive for RhD
Timing from onset to CP infusion (d)	Positive at 1: 160, Negative at 1:320	10	Weakly positive at 1: 80, Negative at 1:160
Timing from admission to CP infusion (d)	7	2	10
Total CP volume (ml)	400	200	7
Adverse reaction related CP infusion	None	Mild alergic reaction	200
			None

BMI: Body mass index; CP: Convalescent plasma; CPR: Convalescent plasma recipient; CPD:Convalescent plasma donor

2. Results

3.1 Plasma donors (Table 1)

Plasma was obtained from three COVID-19 patients who had recently recovered and were discharged from the COVID-19 designated hospital in Fuzhou. Among these donors, the anti-SARS-CoV-2 IgG titer in one case (Case 1) was $\geq 1:160$, and the antibody titers in the other two cases (Case 2 and Case 3) were $\geq 1:80$. One patient (Case 2) with blood type A who was negative for RhD received plasma from a donor with blood type A and positive for RhD, and the other two recipients were treated with complete blood type ABO and Rh-compatible CP.

3.2 Clinical manifestations, treatment and prognosis of plasma receptors (Tables 1, 2)

Table 2
Dynamics of indicators during plasma therapy

Characteristics	Case 1	Case 2	Case 3
Pre-treatment of CP	94	94	93
SaO ₂ (%)	63.9	17.6	45.9
CRP (mg/L, normal range 0-10)	59.9	29.3	44.3
IL-6 (pg/ml, normal range <7.0)	550	966	541
CD3+ (cells/μL, normal range 955-2860)	355	421	305
CD3+CD4+ (cells/μL, normal range 550-1440)	186	528	228
CD3+CD8+ (cells/μL, normal range 320-1250)	952	1331	755
Total lymphocyte (cells/μL, normal range 1530-3700)	Improvement	Improvement	Improvement
48-72 hours after CP treatment	Partially absorption	Partially absorption	Partially absorption
Symptom	97	96	96
Lung lesion	25.8	5.7	9.1
SaO ₂ (%)	8.1	10.3	7.2
CRP (mg/L)	818	1087	872
IL-6 (pg/ml)	550	537	583
CD3+ (cells/μL)	250	508	282
CD3+CD4+ (cells/μL)	1298	1450	1239
CD3+CD8+ (cells/μL)	Sustained absorption	Sustained bsorption	Sustained absorption
Total lymphocyte (cells/μL)	98	96	98
Nine days after CP treatment	2.5	0.62	0.92
Lung lesion	< 1.5	< 1.5	< 1.5
SaO ₂ (%)	707	1282	958
CRP (mg/L)	468	713	562
IL-6 (pg/ml)	235	561	358
CD3+ (cells/μL)	984	1651	1239
CD3+CD4+ (cells/μL)	1122	2466	813
CD3+CD8+ (cells/μL)	707	1041	545
Total lymphocyte (cells/μL)	382	1345	259
30 days after CP treatment	1878	3203	1074
CD3+ (cells/μL)	17	16	33
CD3+CD4+ (cells/μL)	17	13	33
CD3+CD8+ (cells/μL)			
Total lymphocyte (cells/μL)			
Timing from onset to a negative viral test result (d)			
Hospital stay (d)			
CD3+: T-lymphocyte, CD3+CD4+: CD4+ T-lymphocyte subset, CD3+CD8+: CD8+ T-lymphocyte subset, CP: Convalescent plasma, CRP: C-reactive protein, IL-6: interleukin-6, SaO ₂ : arterial oxygen saturation.			

During the study, three severe COVID-19 patients, one male and two females, were enrolled and received CP transfusion. These patients were 57, 59 and 65 years old, respectively. The main underlying diseases included hypertension, diabetes, cerebral infarction and postoperative thyroid adenoma. The common symptoms included cough, fever and shortness of breath. Blood laboratory examinations showed a decrease in arterial oxygen saturation (SaO₂), an increase in C-reactive protein (CRP) and interleukin-6 (IL-6), and a decrease in total lymphocytes (CD45+), T lymphocytes (CD3+) and their subsets (CD4+, CD8+) (Figure 1). Chest CT showed multiple patchy and nodular ground glass opacities, consolidation and linear opacities in both lungs (Fig. 2A, 2B, Fig. 3A, 3B, Fig. 4A, 4B). After admission, all the patients received transnasal catheter oxygen therapy and were given antiviral treatment with arbidol, hydroxychloroquine, sulfatopinavir/ritonavir or recombinant human interferon α-2b spray, and one patient was treated with a combination of antibiotics.

Other medicines, including immunostimulants (thymalfasin), anti-inflammatory agents (Xuebijing injection and ulinastatin) and Chinese herbal medicine, were also administered.

On the basis of conventional treatment after admission, the condition of these patients continued to worsen. Then they all received additional CP therapy. All patients provided informed consent for CP treatment before transfusion. The CP transfusion volume was 400 ml (two consecutive days, 200 ml per day), 200 ml and 200 ml. Forty-eight to seventy-two hours after CP transfusion, all the patients improved with alleviated symptoms, elevated SaO₂, decreased CRP and IL-6, and increased lymphocyte counts (Figure 1). Repeated chest CTs also showed obvious absorption of lesions in the bilateral lungs (Fig. 2C, 2D, Fig. 3C, 3D, Fig. 4C, 4D). On days 9 and 30 after CP transfusion, the above indicators continued to improve, and the patients improved until they were discharged stably. The latest outpatient follow-up was performed on May 7th, 2020, when the patients remained well without signs of recurrence.

3.3 Adverse reactions related to CP transfusion (Table 2)

One patient (Case 2) developed a red rash with pruritus around the infusion site of the right upper extremity 17 hours after CP transfusion, and the rash extended to the whole body with pruritus 22 hours after transfusion. Considering the CP transfusion-related allergic reaction, the patient received antianaphylactic treatment with 10% calcium gluconate infusion and oral ebastines. Then, the symptoms were gradually relieved after treatment, and the rash completely disappeared 5 days after CP transfusion. No severe adverse reactions were found in any of the patients.

3. Discussion

To date, COVID-19 influenza is still rapidly spreading worldwide. Clinical data from China have shown that the severe COVID-19 rate can be as high as 41.1%~48.3% in the early stage of the epidemic [15, 16]. Due to the rapid progression with high mortality in severe COVID-19 patients, effective treatment is urgently needed to control the deterioration of the disease. However, there are no current proven antiviral drugs that could effectively treat the novel virus [17, 18]. A multicenter trial showed that plasma therapy could accelerate the rate of viral negative conversion and clinical recovery in COVID-19 patients, shorten the length of hospital stay, and reduce the risk of death by 35% [7]. Ibrahim et al. reported that early application of plasma therapy was helpful to accelerate clinical recovery and reduce mortality [12]. In a large retrospective case-control study, Xia et al. also showed that CP therapy improved clinical symptoms, reduced ICU admission risk, and reduced mortality (the death risk was reduced by 50%) [19]. Previous studies have also shown that early application of plasma to severe patients was more effective, while the overall benefit of CP in extremely critical patients, such as tracheal intubation or life-threatening conditions, was not significant [7, 12, 19, 20]. The three cases in our study were severely elderly patients with basic diseases such as diabetes and high blood pressure but without endotracheal intubation. After admission, the condition of these patients progressed rapidly, and there was a high risk of developing critical illness. Then, CP was administered based on conventional treatment. After the combined therapy, the symptoms were alleviated rapidly, the lung lesions were significantly absorbed, the inflammatory indexes were decreased, and the oxygenation function and cellular immune function were improved. The remarkable improvement of these patients suggests that plasma treatment is an effective remedy for severe COVID-19 patients. Hegerova et al. reported that patients who received CP within one week after admission had a significantly reduced risk of death within 14 days (mortality was 0) [13]. The CP treatment time of all patients in our study was within one week after admission (within 10 days after onset), which was significantly earlier than the time reported by Xia et al. (the median time from onset to CP was 45 days) [19]. Significant improvement was achieved within 72 hours of CP treatment in our research, suggesting that early active CP therapy in severe COVID-19 patients becomes even more effective.

Notably, although the three patients improved significantly after CP, one of them (Case 3) remained positive for SARS-CoV-2 RNA for more than one month (33 days). At the beginning of the disease, the lymphocyte counts in the three patients all decreased, and the number of lymphocytes gradually increased after CP, which was consistent with a previous report [5]. However, the lymphocyte counts in one patient (Case 3) were still lower than the normal standards 30 days after CP, whereas the other two patients (Case 1, Case 2) all returned to normal. The prolonged viral removal in Case 3 was considered to be associated with a prolonged period of immunodeficiency. Additionally, the donor plasma antibody titer results showed that the titer in Case 1 was the highest ($\geq 1:160$), and the titers in the other two patients (Case 2, Case 3) were $\geq 1:80$, but the antibody titer in Case 3 was only weakly positive at 1:80. This suggested that this patient (Case 3) received the lowest antibody level of CP in these three patients, which may reduce the plasma efficacy [19].

Additionally, only one patient (Case 2) had a mild allergic reaction with erythema and pruritus at the early period of transfusion, but no other serious adverse reactions were found in the follow-up. As previously described in our paper, the blood type of this patient (Case 2) was type A and negative RhD, which is a rare Rh blood type. She later received CP with blood type A and positive RhD, suggesting that the allergic reaction in this patient might be related to treatment with incomplete Rh-compatible plasma, but other serious adverse reactions, such as acute hemolytic transfusion reaction and shock response, were not found. Generally, plasma treatment in our study was safe and reliable, consistent with the literature reports [19, 21].

Notably, there are some limitations in our research. First, this study was only performed with 3 patients without solid controls (directly compared to patients with CP and without CP treatment). Second, the patients were also given other medications (including antiviral drugs, antibiotics, anti-inflammatory agents, immunostimulants and Chinese herbal medicine)/treatment. Hence, this does serve as one of the confounding factors. It could be that these factors might play an important role in recovery as well in synergy with CP treatment. However, there were no proven effective antiviral drugs or other traditional therapies in our study for controlling the novel virus. Combined CP therapy was initiated after the condition worsened with conventional treatment. Additionally, as mentioned previously, patients who received CP earlier can have more favorable clinical outcomes [12]. The CP remedy in our study was utilized in the early disease course. Moreover, the first curative effect evaluation was assessed in a short time after CP transfusion (within 48 to 72 hours), and the findings that showed obvious improvement with clinical symptoms, radiological images and laboratory tests were encouraging. As a result, we think the marked efficiency should be mainly attributed to additional CP treatment.

In summary, the early application of CP for severe COVID-19 patients can improve the condition rapidly, and the therapy is generally effective and safe. This therapy can reduce the COVID-19 progression risk from severe to critical, lower the mortality rate [22], and is helpful to raise the rescue success rate of severe patients. Due to the absence of effective anti-SARS-CoV-2 drugs, CP therapy is an alternative adjuvant method to treat severe COVID-19 patients [22].

Declarations

Ethics approval and consent to participate

This study was in line with the Declaration of Helsinki and approved by the Ethics Committee of the People's Hospital Affiliated to Fujian University of Traditional Chinese Medicine, and the patients provided informed consent to participate.

Consent for publication

The patients provided informed consent for paper publication.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no conflicts of interest for this work.

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Authors' Contributions

JH conceived of the study, drafted the manuscript, and reviewed all drafts of the manuscript. CL managed the data collection, data analysis, prepared figures 1-4 and tables 1-2 and help trafted the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

Dynamics of laboratory indicators after plasma therapy. Dynamics of laboratory indicators after plasma therapy. After plasma therapy, the results showed an increase in arterial oxygen saturation (SaO₂), a decrease in C-reactive protein (CRP) and interleukin-6 (IL-6), and an increase in total lymphocytes, T lymphocytes (CD3+) and their subsets (CD4+, CD8+).

Figure 2

Case 1. On the second day of admission (the 7th day of onset), chest CT showed patchy and nodular ground glass opacities, consolidation and linear opacities in the bilateral lungs, mainly in both lower lungs (A, B). Seventy hours after plasma treatment, the lung lesions were significantly absorbed (C, D).

Figure 3

Case 2. On the second day of admission (the 10th day of onset), chest CT showed patchy consolidation and linear opacities in the bilateral lungs, mainly in both lower lungs (A, B). Seventy hours after plasma treatment, the lung lesions were significantly absorbed (C, D).

Figure 4

Case 3. On the 7th day of admission (the 10th day of onset), chest CT showed multiple patchy and nodular ground glass opacities, consolidation and linear opacities in the bilateral lungs, mainly in the subpleural area (A, B). Forty hours after plasma treatment, the lung lesions were significantly absorbed (C, D).