Convalescent Plasma as a Treatment for Severe Patients With SARS-CoV-2 Infection: A Case Report

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Case report

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Abstract

Background: Corona virus disease 2019 (COVID-19) has become a global pandemic, affecting the lives of millions of people around the world.Although research including hydroxychloroquine, antiviral drugs and vaccines is under way, there is still no effective therapy applied for COVID-19.

Case presentation: Here, we reported five cases of severe COVID-19 patients with respiratory failure treatment with supportable care and ABO-compatible convalescent plasma(CP).All the patients'clinical conditions, laboratory results, viral nucleic acid results, and chest CT images, were improved. Meanwhile, all the patients recovered and no severe adverse reactions were found. We also followed up the antibody levels of some patients within 2 months after onset, but our study did not show the inherent relationship between CP treatment and changes in antibody levels due to small samples.

Conclusions: Although short of evidence of randomized controlled trials, convalescent plasma therapy probably was a potentially safe and effective treatment for COVID-19.

Background

In late December 2019,A new type of highly infectious disease called COVID-19 (first named Novel Coronavirus 2019) broke out in Wuhan, Hubei Province,and rapidly became a public health emergency (1, 2). To date,it has caused more than 7.5 million confirmed cases and over 420,000 death.Although Remdesivir was hailed as the hope of the people, the latest reports showed that its clinical trials have achieved very different results in China and the United States(3). Besides, the development of vaccines has just entered the human experimental stage, so it will take time to be put into use. Therefore, we urgently need a reliable treatment to prevent disease outbreaks and reduce mortality. The CP has been used as a treatment for more than 100 years, which can give individuals short-term immediate immunity (4). Clinical benefits were observed in patients infected with severe acute respiratory syndrome (SARS),middle east respiratory syndrome (MERS),influenza treatment empirically with CP therapy(5–9). A recent study suggested that antibodies in convalescent COVID-19 patients did not cross-react with other human coronaviruses, indicating that it specifically targets SARS-CoV-2 (10).However, there are few studies on CP treatment of COVID-19. The efficacy and safety of CP treatment of COVID-19 are still unclear. Here, we demonstrated five cases of COVID-19 treated with supportable care and CP therapy.

Case Presentation

Case1

A 46-year-old female with fever, dry cough, shortness of breath after activity for 2 days, and no underlying disease in the past.On February 15 (the third day after onset, dpoi 3), the patient was diagnosed as COVID-19 due to RT-PCR test of throat swab. The patient's condition continued to worsen after treatment symptomatically with Arbidol and Lopinavir and Ritonavir and other supportive care. The blood gas analysis (no oxygen inhalation) suggested that the patient's partial pressure of oxygen (PO2) was 49 mmHg and the chest CT indicates ground-glass shadows in both lower lungs.Therefore,the patient was diagnosed with respiratory failure and initiated to receive non-invasive mechanical ventilation. She was transferred to the Chongqing Public Health Medical Center on February 16 (dpoi 4), and the antiviral drugs were changed to darunavir and Arbidol. After 3 days of treatment, the patient self-reported that there was no obvious relief of shortness of breath and poor sleep. We infused 200 ml ABO-compatible CP from convalescent patients with SARS-CoV-2 infection at 00:15 on February 19 (dpoi 7), and the second 200 ml ABO-compatible CP was given at 8: 00 a.m on February 20 (dpoi 8). No adverse reaction was observed. The symptoms were relieved and the ventilator was removed on February 22nd (dpoi 10). Twice repeated RT-PCR tests were performed on throat swabs (interval at least 24 hours) on February 23rd (dpoi 11) and February 25th (dpoi 13), and the results were all negative. The patient was rehabilitated and discharged on 28 February (dpoi 16). And she was advised to reexamine PCR and antibodies after 14 days of self-isolation after discharging.

Case 2

A 64-year-old female who was hospitalized in Jiangbei District people's Hospital of Chongqing because of dry cough and wheezing after activity for 2 days.Meanwhile, the patient was denied any previous comorbidity.The throat swabs for SARS-CoV-2 by RT-PCR were positive on Feb. 8 (dpoi 2). The chest CT revealed large ground glass shadow in both lungs and blood gas analysis (oxygen inhalation 2L/min) suggested PO2 was 61 mmHg. The patients were given symptomatic treatment with Lopinavir and Ritonavir, interferon and other supportive care. The patient was transferred to Chongqing Public Health Medical Center on February 9 (dpoi 3) for further centralized treatment, and was given symptomatic treatments, including darunavir, Arbidol, high-flow nasal catheter oxygen inhalation. The patient's symptoms of wheezing did not improve, and subsequent chest CT on February 14(dpoi 8) demonstrated that the lesions of both lungs continued to progress. In total, we infused 400 ml of ABO-compatible convalescent plasma into the patient.The first dose (200 ml) was given at 00:10 on February 18 (dpoi 12), and the second administration (200 ml) was at 12:50 on February 19 (dpoi 13). On February 21th (dpoi 15), she self-reported that the symptoms of wheezing were significantly improved, and the high-flow nasal catheter was changed to low-flow nasal catheter for oxygen inhalation. And the chest CT obtained on the same day (dpoi 15) suggested obvious absorption of bilateral lung lesions (Fig. 1).Two repeated RT-PCR tests results were negative on February 20 (dpoi 14) and February 22 (dpoi 16) (at least 24 hours apart).She was cured and discharged from the hospital on February 25 (dpoi 19). And, like other patients, we asked her to reexamine PCR and antibodies after 14 days of staying in isolation at home after discharge.

Case 3

A 70-year-old woman with cough and sputum for 4 days, shortness of breath for 1 day, and a past medical history of diabetes.She was diagnosed as COVID-19 in Zhongshan Hospital of Chongqing on January 25th (dpoi 4). Her chest CT showed multiple patchy high-density shadows and flocculent blurred shadows in both lungs and the blood gas analysis showed that the oxygenation index (OI) was 157 mmHg. Later, she was transferred to Chongqing Public Health Medical Center for centralized isolation treatment on January 26 (dpoi 5). Then,Lopinavir and Ritonavir, interferon and other supportive care were given at the beginning of the treatment. Later, it was changed to darunavir, Arbidol, methylprednisolone, and other supportive symptomatic treatment because of the condition did not improve. The chest CT on Feb.11 (dpoi 21) showed that there was no obvious absorption of bilateral lung lesions. The patient complained of obvious shortness of breath and the PO2 fluctuated from 45 to 80 mmHg. Multiple nucleic acid tests showed positive. Non-invasive ventilator was given oxygen therapy on February 16 (dpoi 26). We gave the patient a total of 400 ml ABO-compatible CP. The first dose was given at 8: 00 a.m (200 ml) on February 21 (dpoi 31), and the second administration time was at 08:30 a.m. (200 ml) on February 23rd (dpoi 33). After that, the patient's shortness of breath symptoms was relieved. She was withdrawn from the ventilator on Feb. 24 (dpoi 34), and the throat swab RT-PCR repeated test was negative on Feb. 25 (dpoi 35) and 26 (dpoi 36) (at least 24 hours interval). The chest CT showed partial absorption of both lung lesions on Feb. 27 (dpoi 37). The patient has met the discharge criteria and was discharged from hospital on Feb. 28 (dpoi 38). And she was advised to reexamine PCR and antibodies after 14 days of self-isolation after discharging.

Case 4

An 84-year-old male who was admitted to Yongchuan Hospital of Chongqing Medical University on February 3 (dpoi 4) with fever, cough, sputum and shortness of breath for 4 days. He has a previous medical history of chronic obstructive pulmonary diseases(COPD). On the same day, the nucleic acid amplification of material from a throat swab demonstrated the new coronavirus SARS-CoV-2. The chest CT showed diffuse parenchymal abnormalities in the periphery of the whole lungs and the PO2 was 60 mmHg (4L/ min of oxygen inhalation). Then, Arbidol, darunavir and non-invasive ventilation oxygen therapy were given. The patient complained of poor sleep quality and obvious shortness of breath after treatment. Considering that the patient was previously complicated with COPD, we treated the patient with methylprednisolone. The chest CT on February 15 (dpoi 16) showed that there was no significant change in both lung lesions. We gave the patient 3 times of total 800 ml ABO-compatible convalescent plasma from February20 (dpoi 21) to 23 (dpoi 24), and there was no obvious adverse reaction. The symptoms of wheezing were relieved on Feb. 24 (dpoi 25), and methylprednisolone was discontinued. The repeated RT-PCR tests of pharyngeal swabs were negative on February 25th and 26th (interval at least 24 hours). The chest CT on February 26th (dpoi 27) showed that the lesions of both lungs were partial absorbed. Now the patient was cured and discharged from hospital on February 28th. And he was advised to reexamine PCR and antibodies after 14 days of self-isolation after discharge from the hospital.

Case 5

A 63-year-old male with fever, dry cough and shortness of breath after activity for 2 days. He had a medical history of hypertension. He was diagnosed with COVID-19 after performing real-time RT-PCR for COVID-19 by throat swab on February 3 (dpoi 2) and was admitted to Yongchuan Hospital affiliated to Chongqing Medical University. The chest CT suggested ground glass changes in both lungs and the PO2 was 70 mmHg. After treatment symptomatically with Arbidol, darunavir and high-flow nasal catheter oxygen inhalation, the symptoms of fever were significantly relieved, but the symptoms of shortness of breath were aggravated. The blood gas analysis (O2 4L/min) indicated that the PO2 was 60 mmHg on Feb.6 (dpoi 5), indicating that the patient had respiratory failure. Non-invasive mechanical ventilation was given. The patient had slight relief of shortness of breath and poor appetite after a few days of treatment. A total of 400 ml CP was given to the patient.The first time(200 ml) was at 8: 00 a.m. on February 13 (dpoi 12), and the second time(200 ml) was at 8: 00 p.m. on February 13 (dpoi 12). On February 15th (dpoi 14), the symptoms of the patients were significantly relieved and his spirits were improved. Chest CT obtained on the same day showed partial absorption of both lungs.The results of two continual RT-PC-reactive proteinCR tests of throat swabs were negative on February 16 (15) and 18 (dpoi 17) (at least 24 hours interval). The patient was rehabilitated and discharged on February 19 (dpoi 18). As usual, he was advised to reexamine PCR and antibodies after 14 days of self-isolation.

Discussion And Conclusions

Here, All patients survived and the virus turned negative within 7 days, accompanied by an increase in oxygen saturation(SaO2),IgG and lymphocyte count(LYM), as well as improvements in C-reactive protein (CRP) and chest imaging(Table 1).At the same time, the levels of serum IgM and IgG antibodies were measured by chemiluminescence immunoassay before and after infusion of CP. The results suggest that serum IgM and IgG can be detected within one week after onset,and IgM decreases quickly after the second week, but IgG can be maintained at a high level for a long time.In order to ensure safety,we closely observed that there was no severe adverse reaction 24 hours after the first dose of 200 ml CP, and the follow-up dose was administrated again. And all of our donors were meet the following criteria:negative for PCR test 3 times in a row;the pulmonary lesions absorbed completely or more than 90% in chest images;discharged from hospital for more than 2 weeks; the titers of antibodies in the plasma all more than 1: 160,and no other severe disease.

Table 1
Comparison of SaO2 and laboratory results before and after CP Transfusion

Clinical characteristic and Laboratory results	Patient				
	1	2	3	4	5
SaO2					
before CP treatment	95	93	90	86	91
after CP treatment	97	98	93	92	98
LYM,X10^9L^{-1}(normal range 1.10–3.20)					
before CP treatment	1.25	1.79	1.63	0.29	1.43
after CP treatment	1.36	1.74	1.33	0.86	1.84
NEU,X10^9L^{-1}(normal range 1.8–6.3)					
before CP treatment	4.14	5.58	3.84	4.09	2.1
after CP treatment	4.56	5.84	3.35	4.23	1.89
CRP,mg L^{-1}(normal range < 10)					
before CP treatment	3	3	7.5	22.6	13
after CP treatment	2.8	1.7	4.6	20.1	9.7
LDH,U L^{-1}(normal range 114–240)					
before CP treatment	171	168	263	275	379
after CP treatment	146	169	253	226	243
ALT,U L^{-1}(0–45)					
before CP treatment	14	22	17	12	27
after CP treatment	12	17	20	15	23
AST,U L^{-1}(normal range 0–45)					
before CP treatment	14	21	17	13	22
after CP treatment	11	18	16	12	21
IgM,g L^{-1}					
before CP treatment	1.91(+)	2.451(+)	1.45(+)	NA	NA

NA:not available;NEU:neutrophil;LDH:lactate dehydrogenase;ALT:alanine aminotransferase;AST:aspartate aminotransferase

Clinical characteristic and Laboratory results	Patient				
	1	2	3	4	5
after CP treatment	2.682(+)	1.13(+)	0.87(-)	NA	NA
IgG,g L^{-1}					
before CP treatment	3.467(+)	9.517(+)	13.79(+)	NA	NA
after CP treatment	11.91(+)	14.15(+)	20.311(+)	NA	NA
NA:not available;NEU:neutrophil;LDH:lactate dehydrogenase;ALT:alanine aminotransferase;AST:aspartate aminotransferase					

Table 2
Changes of serum IgM and IgG levels after onset of disease

Laboratory result	Patient				
	1	2	3	4	5
IgM,g L^{-1}					
1weeks	1.91(+)	1.67(+)	1.23(+)	NA	NA
2weeks	2.682(+)	2.451(+)	1.573(+)	NA	NA
3weeks	NA	1.13(+)	1.45(+)	NA	NA
4weeks	0.409(+)	NA	0.87(-)	NA	NA
5weeks	0.27(-)	0.62(-)	0.63(-)	NA	NA
6weeks	0.306(-)	0.289(-)	NA	NA	NA
7weeks	0.092(-)	0.124(-)	0.21(-)	NA	NA
8weeks	0.11(-)	0.098(-)	0.12(-)	NA	NA
IgG,g L^{-1}					
1weeks	3.467(+)	3.44(+)	7.89(+)	NA	NA
2weeks	11.91(+)	9.517(+)	11.2(+)	NA	NA
3weeks	NA	14.15(+)	13.79(+)	NA	NA
4weeks	14.68(+)	NA	20.311(+)	NA	NA
5weeks	16.78(+)	11.367(+)	22.614(+)	NA	NA
6weeks	14.842(+)	8.882(+)	NA	NA	NA
7weeks	13.763(+)	8.907(+)	18.982(+)	NA	NA
8weeks	15.872(+)	6.354(+)	17.19(+)	NA	NA
NA:not available					

Several studies have showed clinical benefits were observed in patients infected with various infections(4–9). In a prospective cohort study on severe cases of influenza A(H1N1) infection,the case-fatality rate of patients treated with CP decreased by 35% compared with the control group(6). And a systematic review and meta-analysis showed that patients with Spanish influenza A(H1N1) infection receiving CP treatment had a significant reduction of 21% (95% CI,15–27%) in the case-mortality rate (4).

Previous studies have demonstrated that the time point of treatment is closely associated with the prognosis of the patients.In a study of SARS, patients who were treated with CP before dpoi 14 had a

higher discharge rate by dpoi 22(58.3% vs 15.6%) and lower mortality(6.3% vs 21.9%) than those in the control group(8).This is consistent with the conclusion of another systematic review and meta analysis(11).The possible mechanism is related to the time when the body is immune to viremia.It is worth noting that our third patient is unlike previous studies because CP is used for a relatively late course of disease (about a month). We found that this case was still clinically beneficial. The patient did not improve after about a month of active support care, but 2 days after CP treatment, the viral nucleic acid turned negative and the clinical symptoms gradually improved. The mechanism of action in this case was still unclear. Therefore more studies should be performed to further explore its value.

Although several clinical studies have suggested the feasibility and clinical benefits of CP treatment for COVID-19 patients (12, 13), and no severe side effects have been reported until now, there are still some limitations in the treatment of CP. First of all, the optimal dose and safety is not clear due to lack of large-scale RCT trials. Second, all studies have used antiviral drugs before and after CP therapy until now, so its individual therapeutic effects were still unknown. Then,although our study followed up the changes of serum IgM and IgG, our study can not explain the relationship between the changes of serum IgM and IgG and CP treatment due to the small sample size. Finally, as with ordinary plasma transfusions, there are still some potential risks, such as transfusion-transmitted infections, transfusion-related circulatory load (TACO), and transfusion-related acute lung injury (TRALI)(14, 15).

In conclusion, although our cases and several previous studies have shown the feasibility of CP treatment in COVID-19, its safety and optimal treatment dose still need to be further explored. As more and more patients have recovered from SARS-CoV-2 infection, the number of potential donors of CP has also increased. Moreover, despite the sample size are very small in our study, it still shows the feasibility of CP treatment for COVID-19 patients, especially when the current standard treatment cann’t improve the clinical conditions of patients.

List Of Abbreviations

COVID-19：coronavirus disease 2019

CP：convalescent plasma

OI:oxygenation index

SARS:severe acute respiratory syndrome

MERS:middle eastrespiratory syndrome

PO2:partial pressure of oxygen

Dpoi:the day after onset

COPD:chronic obstructive pulmonary diseases

CRP:C-reactive protein

TACO:transfusion-related circulatory load

TRALI:transfusion-related acute lung injury

SaO2:oxygen saturation

LYM:lymphocyte

NEU:neutrophil

ALT:alanine aminotransferase;

AST:aspartate aminotransferase

Declarations

Ethics approval and consent to participate

Written informed consent from all the patients was obtained.

Consent for publication

Written informed consent for publication was obtained from the patients.

Availability of data and materials

The datasets used or analyzed in our cases are available from the corresponding author.

Competing interests

All authors declare that they have no conflicts of interest to report, financial or otherwise.

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Authors' contributions

Daoxin Wang, Xinyu Deng designed the study;Yuyan Song and Wenguang Tian performed experiments;Chaoying Yong and Daoxin Wang analyzed the data;Chaoying Yong wrote the manuscript;

Daoxin Wang, Di Qi and Xinyu Deng revised the manuscript.All authors have read and approved the present submitted version.

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Figures

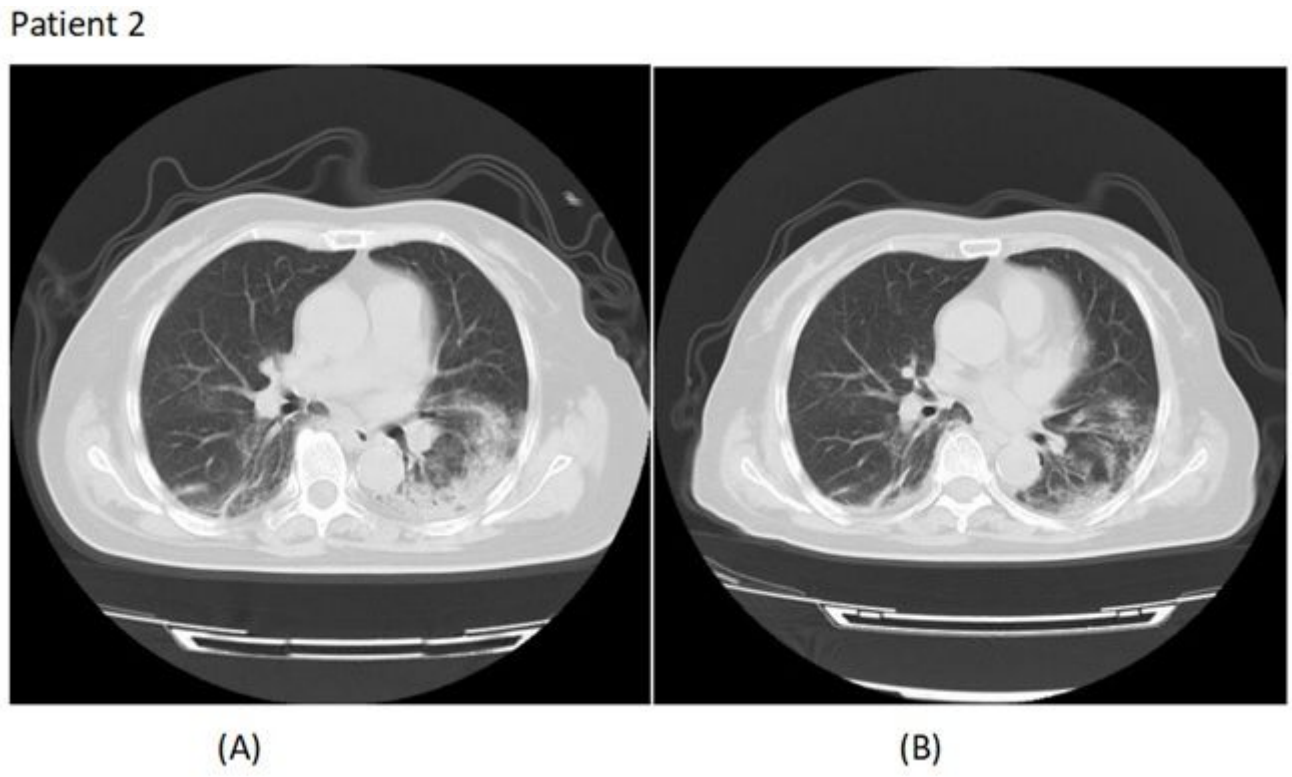

Figure 1

Chest CT images of the second patient. (A) Chest CT images on February 14 (dpoi 8) before CP transfusion showed large ground glass shadow in both lungs. (B) Chest CT images on February 21 (dpoi 15) showed the absorption of bilateral ground-glass shadow after CP transfusion.