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Effectiveness of Convalescent Plasma Therapy for COVID-19 Patients in Hunan, China

Xingsheng Hu[1], Chunhong Hu[1], Dixuan Jiang[2], Qian Zuo[3], Ya Li[4], Yang Wang[5], and Xiangyu Chen[4]

Abstract

Objective: To investigate clinical efficacy and safety of convalescent plasma (CP) therapy in coronavirus disease 2019 (COVID-19) patients.

Methods: We included 4 severe patients and 3 critical patients. The date of admission to hospital ranged from January 30 to February 19, 2020. We retrospectively collected clinical and outcome data. Relative parameters were compared.

Results: After CP therapy, the symptoms and respiratory functions were improved. Median PaO_2/FIO_2 increased from 254 (142-331) to 326 (163–364), and dependence of oxygen supply decreased. Median time to lesion's first absorption was 5 (2–7) days, undetectable viral RNA was 11 (3.5–15.7) days. Median lymphocyte count (0.77×10^9/L vs 0.85×10^9/L) and albumin level (31g/L vs 36 g/L) were elevated, C-reactive protein (44 mg/L vs 18 mg/L), D-dimer (5.9 mg/L vs 4 mg/L) and lactate dehydrogenase (263 U/L vs 245 U/L) decreased. No obvious adverse reactions were observed. At the follow-up on June 14, 2020, 6 patients had completely recovered and one died from terminal disease.

Conclusion: CP therapy for COVID-19 was effective and safe. Three patients who did not combine with antiviral therapy after CP also obtained viral clearance and clinical improvement. However, CP therapy failed to save the life of a terminally ill patient.

Keywords
COVID-19, SARS-CoV-2, convalescent plasma, PaO2/FIO2, clinical outcomes

Introduction

Coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1] that emerged in Wuhan, China in December 2019, and rapidly spread around the world. By Aug 6, 2020, COVID-19 had spread to >200 countries, caused >21 million infections, and 761 779 deaths,[2] and these figures are still increasing.

There were no new drugs or vaccines, and most of the antiviral therapies were derived from experience of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), and included interferon, lopinavir/ritonavir, arbidol, and chloroquine.[3] However, a recent clinical trial in Wuhan showed that addition of lopinavir/ritonavir to standard care did not significantly improve clinical prognosis or clearance of viral RNA.[4] A trial initiated on April 29, 2020 showed that remdesivir significantly shortened the recovery time from COVID-19, but it did not significantly reduce mortality rate

[1] Department of Oncology, The Second Xiangya Hospital of Central South University, Changsha, Hunan, People's Republic of China
[2] Department of Respiratory Medicine, The First Hospital of Changsha City, Changsha, Hunan, People's Republic of China
[3] Department of Radiology, The First Hospital of Changsha City, Changsha, Hunan, People's Republic of China
[4] Department of Radiology, The Second Xiangya Hospital, Central South University, Changsha, Hunan, People's Republic of China
[5] Department of Pathology, The Second Xiangya Hospital of Central South University, Changsha, Hunan, People's Republic of China

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Corresponding Authors:
Yang Wang, Department of Pathology, The Second Xiangya Hospital of Central South University, 410011 Changsha, Hunan, People's Republic of China.
Email: wangyang@csu.edu.cn

Xiangyu Chen, Department of Radiology, The Second Xiangya Hospital of Central South University, 410011 Changsha, Hunan, People's Republic of China.
Email: chenxiangyu@csu.edu.cn

compared with the placebo group.[5] Convalescent plasma (CP) therapy was approved by the Chinese Government[6] and US Food and Drug Administration (FDA),[7] owing to its success in the SARS, MERS and influenza A (H1N1) pandemics.[8-10] A meta-analysis, which included 2 studies of SARS, 5 of H1N1 and one of H5N1, showed that convalescent plasma or serum compared with placebo or no therapy significantly reduced mortality risk (odds ratio = 0.25; $P < 0.001$).[11] In nearly 2 months, between Mar. 2020 and Apr. 2020, 2 studies[12,13] and 3 case reports[14-16] of CP therapy of COVID-19 were published; all of which displayed clinical efficacy. Here, we describe our results of CP therapy of COVID-19.

Methods

Patients and Ethics

Patients came from Changsha Public Health Treatment Center of Hunan Province, which was one of the main treatment centers for COVID-19 in the local area. Inclusion criteria: (1) inpatients with laboratory-confirmed COVID-19, who received CP therapy; and (2) available clinical and outcomes data. This study was approved by the Institutional Review Board and Ethics Commission of The Second Xiangya Hospital (2020-017). Written informed consent was waived by the Ethics Commission of the designated hospital for retrospective analysis and emerging infectious diseases.

Data Collection

We retrospectively collected patient data from the above medical centers. The date of hospital admission ranged from January 30 to February 19, 2020. The date of discharge/transfer ranged from March 4 to 14, 2020. The data included the basic epidemiological and clinical features, especially the time of CP therapy, improvement of symptoms, oxygen supply, and radiological and laboratory parameters.

Diagnosis of COVID-19

COVID-19 was diagnosed according to the "Diagnosis and Treatment Protocol for Novel Coronavirus Infection-Induced Pneumonia, version 7."[17] Confirmation was based on the following: (1) real-time reverse transcription polymerase chain-reaction (RT-PCR), and nucleic acid test of respiratory or blood specimens were positive; and (2) high-throughput gene sequencing was highly homologous with SARS-CoV-2 in respiratory or blood specimens. RT-PCR assays were performed in accordance with the protocol established by the World Health Organization (WHO).[18]

Clinical Classification and Definitions

The clinical classification of patients was evaluated according to the "Diagnosis and Treatment Protocol for Novel Coronavirus Infection-Induced Pneumonia version 7."[17] Severe disease (one of the following conditions): I, respiratory rate $\geq$30 breaths/min; II, oxygen saturation $\leq$93% at rest; III, partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FIO_2) $\leq$300 mmHg; IV, developed rapidly on radiological findings within 24-48 hours. Critical criteria (one of the following conditions): I, respiratory failure and a requirement for mechanical ventilation; II, shock; III, combined failure of other organs and requirement for intensive care unit monitoring and treatment.

Respiratory failure, acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS) was diagnosed according to the *Internal Medicine* version 7 of higher education issued by Chinese government.[19-21] Respiratory failure was defined as PaO2 < 60 mmHg included or not included PaCO2 >50 mmHg at rest.[19] ARDS was defined as PaO2/ FIO2 $\leq$200.[20] MODS was defined as combination of 2 or more than 2 organs' simultaneous failure.[21] Shock was defined according to the Third International Consensus Definitions for Sepsis and Septic Shock criterion.[22] Acute kidney injury was defined according to the KDIGO clinical practice guidelines.[23]

Donors

Seven donors who had previously been diagnosed with COVID-19 and then recovered were recruited and written informed consent was obtained. The recovery criteria were as follows: (1) no clinical symptoms for $\geq$7 days; (2) $\geq$3 weeks after onset of symptoms; (3) 2 occasions of continuous negative detection of SARS-CoV-2 by RT-PCR at an interval of 24 h; and (4) negative for other respiratory viruses, hepatitis B virus, hepatitis C virus, human immunodeficiency virus, and syphilis. CP (200 mL) was obtained from each donor. The titers of neutralizing antibody in our study ranged from 1:320 to 1:1280.

Outcomes

The first outcomes were recent improvement on symptoms, oxygen supply, and radiological and laboratory parameters. The second outcomes were discharge rate, death rate, and recurrence rate in the long term. The discharge criteria were[17]: (1) at least 2 occasions of continuous negative detection of SARS-CoV-2 by RT-PCR at an interval of 24 h; (2) no fever for $\geq$3 days; (3) obvious improvement of respiratory symptoms; and (4) obvious improvement of acute exudative lesion on computed tomography (CT)/X-ray.

Statistical Analysis

Continuous variables were expressed as median (interquartile range, IQR). Calculation of median and plotting of graphs were performed by SPSS 17.0.

Results

Clinical Characteristics

We enrolled 4 severe patients and 3 critical patients. The median age was 64 (57–70) years; median time from onset of

symptoms to hospital admission was 8 (4–20) days; median time from hospital admission to receiving CP transfusion was 23 (8–27) days; and median time from CP transfusion to discharge was 13 (10–16) days. Just before transfusion, 1 patient had low white cell count, 1 had high white cell count, 5 had high neutrophil proportion and low lymphocyte count, 2 had high aminotransferase levels, 1 had high creatinine, 6 had high D-dimer, 3 had high lactate dehydrogenase (LDH), and all of them had high C-reactive protein (CRP). Three patients were considered to combine with lung abscess. Except Patient 5 did not combine antibiotic therapy before (10 days)/after transfusion, all of other patients received antibiotic therapy before/after transfusion. Except Patients 3, 5 and 7, and Patient 2 (stopped just 1 day after transfusion), all other patients received antiviral therapy after CP transfusion. The clinical characteristics before transfusion are presented in Table 1, and parameters just before transfusion are presented in Tables 2 and 3.

Improvement of Clinical and Laboratory Parameters After CP Therapy

The improvement of several primary parameters within 1, 4, 7, 10 and 20 days (all of the patients discharged/transferred out) after transfusion are presented in Table 2 and Figure 1, and other laboratory parameters in Table 3. After transfusion, symptoms of all patients were improved. The median PaO_2/FIO_2 increased from 254 (142-331) to 326 (163–364), although the median SPO_2 level remained at 96%, 5 patients were tested with no oxygen supply after transfusion. Although Patient 3 received invasive mechanical ventilation after transfusion, she transferred to noninvasive mechanical ventilation and was weaned from extracorporeal membrane oxygenation before transferring out. Patient 2 was weaned from high-flow nasal cannula to discontinued low-flow nasal cannula oxygen supply, and other 4 patients were weaned from low-flow nasal cannula oxygenation to stopping oxygen supply. After CP therapy, improvement of CT/X-ray findings was observed at different periods (Figures 2 and 3). The median time of first absorption was 5 (2–7) days. Before transfusion, except Patient 7, all of other patients were positive for detection of SARS-CoV-2 RNA. After transfusion, SARS-CoV-2 RNA in all 6 patients became undetectable within 2–21 days [median 11 (3.5–15.7) days]. After CP therapy, 5 of 7 patients showed elevation of lymphocyte count (median: 0.77×10^9/L vs 0.85×10^9/L), and 5 of 6 patients showed elevation of albumin (median: 31 g/L vs 36 g/L). The inflammatory indicators CRP and erythrocyte sedimentation rate (ESR) decreased markedly (median: 44 mg/L vs 18 mg/L) and (median: 113 mm/h vs 66 mm/h), respectively. D-dimer (median: 5.9 mg/L vs 4 mg/L) and LDH (median: 263 U/L vs 245 U/L) also decreased. Elevated temperature and alanine aminotransferase decreased to normal in 2 patients, and procalcitonin level in 2 patients and lactic acid level in 3 patients also decreased. No obvious adverse effects were observed, such as fever, allergic reaction, elevation of liver and kidney function, or acute lung injury.

Follow-Up and Prognosis

On the follow-up of March 15, 2020, all patients were discharged/transferred out because of negative detection of viral RNA on continuous 2 or 3 occasions. Patients 1 and 5 were discharged with complete recovery. Patients 2, 4 and 6 were transferred to the general hospital for comorbidity. All of them recovered, Patient 4 was discharged on April 3, 2020, patient 6 on March 19, 2020, but the date for Patient 2 is unclear. Patient 3 and Patient 7 was transferred out for integrated treatment on March 14, 2020 and March 10, 2020 respectively, Patient 7 died at March 10, 2020 because of MODS. At June 14, 2020 patient 3 was discharged for complete recovery. All of patients had at least 3 occasions of continuous negative detection of SARS-CoV-2 by RT-PCR after discharge.

Discussion

Nearly 2 decades ago, CP was successfully used to treat SARS and H1N1. Soo et al. reported patients with SARS who deteriorated after ribavirin and methylprednisolone therapy.[8] The CP therapy group ($n = 19$) compared with the steroid therapy group ($n = 21$) had a higher discharge rate by 22 days (74% vs 19%, $P = 0.001$) and lower mortality rate (0% vs 23.8%, $P = 0.049$). Another study showed that CP therapy reduced mortality of SARS compared with the statistical data in the same period (12.5% vs 17%) in Hong Kong.[24] Similar results were found for H1N1.[10,25] One study showed that mortality in the CP group was 20.0% compared with 54.8% in the non-CP group ($P = 0.011$).[10] Two of 3 patients with MERS showed neutralizing activity after receiving CP therapy.[9] However, in Ebola virus disease, CP therapy did not significantly reduce mortality rate (31% vs 38%, $P > 0.05$).[26] The reason was unknown, and may have been due to absence of detection of antibody titer, or using a historical control group, or other confounding factors. Nevertheless, the use of CP therapy in Ebola is recommend by WHO.[27]

In this study, we evaluated the efficacy and safety of CP therapy in 7 patients with COVID-19. After CP therapy, clinical manifestations of all patients were improved, and respiratory function was elevated, as assessed by improved PaO_2/FIO_2 and SPO_2. The dependence of oxygen supply was decreased. One patient was weaned from invasive to noninvasive mechanical ventilation; another was transferred from high-flow nasal cannula oxygenation to discontinued low-flow nasal cannula oxygenation; and 4 patients no longer needed oxygen therapy. After CP therapy, lesions detected by CT/X-ray were gradually absorbed and viral RNA gradually became undetectable. Most interestingly, 3 patients did not receive antiviral drugs after CP therapy (1 patient stopped antiviral drugs just 1 day after CP therapy), and all of them achieved viral clearance and clinical improvement.

Several primary laboratory parameters were also improved after CP therapy. Previous studies showed lower lymphocyte count and albumin level, and increased CRP, D-dimer and LDH, and all patients were associated with poor prognosis of

Table 1. Clinical Characteristics of Patients.

Variables	Patient 1	Patient 2	Patient 3	Patient 4
Sex	Female	Male	Female	Male
Ages	64	64	66	57
Smoking	No	No	No	No
Days from symptoms onset to admission	5	20	2	30
Days from admission to transfusion	8	1	24	14
Date of transfusion	Feb. 19	Feb. 20	Feb. 27	Feb. 27
Days from transfusion to discharge	20	12	15	14
Coexisting disease	CHD, cirrhosis, gastric varices, diabetes, pancytopenia	CHD, heart failure	No	No
Clinical classification	Severe	Critical	Critical	Severe
Complications				
Pre-transfusion	Bacterial pneumonia	Hydrothorax, hydropericardium, liver injury, PTE, multiple vein thrombus	Bacterial pneumonia, ARDS, fungal infection?	Bacterial pneumonia, ARDS, fungal infection?
Posttransfusion	Ditto	Ditto+bacterial pneumonia	Ditto+PTE, class III atrioventricular block, shock, septicopyemia	Ditto(no ARDS)
Drugs therapy				
Antiviral drugs	LPV/r Feb.11-Feb.18, interferon-α Feb.11-Feb.25, arbidol Mar.5-Mar.13, chloroquine Feb. 20-Feb.27	Arbidol Feb.19-Feb.21	Arbidol Feb.3-Feb.11, LPV Feb.11-Feb.18	LPV/r Feb.13-Feb.19, arbidol Feb.16-Feb.26, interferon-α Feb.13-Mar.6
Antibiotic[a]	Moxifloxacin Feb.11-Feb.18 PIP/TAZ Feb.22-Mar.2	PIP/TAZ Feb.22-Mar.4	Meropenem Feb.27-Mar.2, voriconazole+ Tigecycline Mar.2-Mar.7 daptomycin Mar.4-Mar.7, linezolid+PIP/TAZ Mar.7-Mar.14	Voriconazole Feb.23-Feb.27, meropenem Feb.25-Mar.2, mer- openem Mar.5-Mar.13, Cefperazone-Sulbactam Mar.2-Mar.5, voriconazole Feb.27-Mar.13
Steroid				
Pre-transfusion	Intermittent	No	Intermittent	Intermittent
Posttransfusion	No	No	Intermittent	No
Other main therapies	No	No	CRRT Mar.3-Mar.13	No

Variables	Patient 5	Patient 6	Patient 7
Sex	Female	Male	Male
Ages	72	25	No
Smoking	No	No	No
Days from symptoms onset to admission	8	10	4
Days from admission to transfusion	23	27	28

(continued)

Table 1. (continued)

Variables	Patient 5	Patient 6	Patient 7
Date of transfusion	Feb. 27	Feb. 27	Mar. 7
Days from transfusion to discharge	12	12	3
Coexisting disease	No	No	Hypertension, diabetes
Clinical classification	Severe	Severe	Critical
Complications			
Pre-transfusion	Bacterial pneumonia, ARDS	Bacterial pneumonia, lung abscess, ARDS, fungal infection?	Bacterial pneumonia, septicemia, GIB, anemia, renal failure, shock, ARDS, MODS, fungal infection?
Posttransfusion	Ditto(no ARDS)	Ditto(no ARDS)	Ditto
Drugs therapy			
Antiviral drugs	LPV/r Feb.5-Feb.17, arbidol1 Feb.7-Feb.23, interferon-α Feb.17-Feb.25	LPV/r Jan.30-Feb.13, arbidol Mar.6-Mar.11, interferon-α Feb.19-Mar.11, chloroquine Feb.19-Feb.27	LPV/r Feb.4-Feb.18, interferon-α Feb.4-Feb.18, arbidol Feb.25-Mar.1
Antibiotic[d]	Moxifloxacin Feb.5-Feb.15, PIP/TAZ Feb.17-Feb.18	PIP/TAZ Feb.24-Feb.28 meropenem Feb.28-Mar.5, linezolid+voriconazole Mar.2-Mar.11	Meropenem Mar.7-Mar.9, daptomycin Mar.7-Mar.9, voriconazole Feb.25-Mar.9, caspofungin Feb.25-Mar.9
Steroid			
Pre-transfusion	Intermittent	Intermittent	Intermittent
Posttransfusion	No	No	
Other main therapies	No	No	CRRT Feb.26-Mar.9

[a]The latest time or posttransfusion.
CHD: Coronary heart disease; PTE: Pulmonary Thromboembolism; ARDS: Acute respiratory distress syndrome; GIB: Gastrointestinal Bleeding; MODS: Multiple organ dysfunction syndrome; LPV/r: Lopinavir/ritonavir; PIP/TAZ: Piperacillin-tazobactam; CRRT: Continuous renal replacement therapy.

COVID-19.[28] In our study, after CP therapy, lymphocyte count increased (0.77×10^9/L to 0.85×10^9/L), although this increase seems mild (Patient 1 had combined chronic pancytopenia). Most of severe/critical patients have combined serious lymphocytopenia owing to immune injury by the virus.[28] Our result was consistent with the study of Duan et al. (lymphocyte count: 0.65×10^9/L to 0.76×10^9/L).[13] COVID-19 is associated with a serious inflammation reaction, but after CP therapy, CRP and ESR decreased markedly, which demonstrates that CP may reduce the cytokine storm.[10] We also want to display the change of these inflammation markers, but they were not the routine examinations in our hospital.

The mechanism of CP therapy was main supply neutralizing antibody, which displayed the function of viral clearance. The titers of neutralizing antibody in our study ranged from 1:320 to 1:1280, which exceeded the level of previous study ($\geq$1:160).[10,24] In the previous study in COVID-19,[12,13] after CP transfusion, the elevation of antibody titers in receivers were also observed. Owing to this study was a retrospective study, we did not obtain the record of antibody titer in receivers, as far as our best endeavor.

There are several key challenges and problems that needed to be addressed. (1) Owing to the shortage of CP and emergency nature of COVID-19, it is difficult to carry out randomized controlled trials. (2) Time of collection of CP. Previous study of SARS showed that neutralizing antibody titers reached a peak at 4 months,[29] IgG titers increased to an average of 1:256 at week 3 and reached a peak at 3–4 months.[29,30] So the time of collection of CP is important. (3) Therapeutic antibody titers. In previous studies of SARS and H1N1,[9,10] the range of neutralizing antibody titers was above 1:160. Whether antibodies display a therapeutic effect at titers below 1:160 is still unknown. (4) Time of transfusion. A previous study showed that the efficacy of CP therapy was better before than after day 14 in SARS patients.[24] However, in COVID-19, Shen et al.[12] and Duan et al.[13] showed that a transfusion time >14 days was effective. In a previous study, the median viral shedding time was 20 days (the longest was 37 days) after onset of symptoms

Table 2. Improvement of Clinical Features and Primary Laboratory Parameters After CP Therapy.

Variables	Patient 1	Patient 2	Patient 3	Patient 4
Respiratory symptoms				
Just pre-transfusion	Cough, dyspnea	Cough, expectoration, dyspnea	Cough, expectoration, dyspnea	Cough, expectoration, dyspnea, hemoptysis
Day 1 posttransfusion	Dyspnea alleviation	Above symptoms alleviation	Ditto	Ditto
Day 4 posttransfusion	Ditto	Continuous alleviation	Lack record (owing to mechanical ventilation)	Cough, expectoration and dyspnea alleviation, no hemoptysis
Day 7 posttransfusion	Cough alleviation	Continuous alleviation	Lack record	Ditto
Day 10 posttransfusion	No symptoms	Continuous alleviation	Lack record	No symptoms
Day20[a] posttransfusion	No symptoms	No symptoms	No respiratory distress after tube drawing	No symptoms
Oxygen supply				
Just pre-transfusion	Low-flow nasal cannula	High-flow nasal cannula	High-flow nasal cannula[b]	Low-flow nasal cannula
Day 1 posttransfusion	Low-flow nasal cannula	High-flow nasal cannula	High-flow nasal cannula[b]	Ditto
Day 4 posttransfusion	Intermittent oxygenation	Low-flow nasal cannula	Invasive ventilation	Ditto
Day 7 posttransfusion	Ditto	Ditto	Invasive ventilation +ECMO(day 5)	Ditto
Day 10 posttransfusion	Ditto	Ditto	ditto	Ditto
Day 20 posttransfusion	Stop oxygenation	Intermittent oxygenation	Non-invasive ventilation, stop ECMO (day 11)	Stop oxygenation
PaO2/FIO2				
Just pre-transfusion	309	207	152	397
Day 1 posttransfusion	300	293	144	528
Day 4 posttransfusion	373	336	80	437
Day 7 posttransfusion	315	489	220	–
Day 10 posttransfusion	315	240	300	–
Day 20 posttransfusion	330	323	183	–
SPO2				
Just pre-transfusion	94% (oxygen 2L/min)	96% (FIO2 45%)	95% (FIO2 45%)	96% (oxygen 2L/min)
Day 1 posttransfusion	96% (oxygen 2L/min)	99% (FIO2 45%)	98% (FIO2 50%)	98% (oxygen 2L/min)
Day 4 posttransfusion	95% (no oxygenation)	96% (oxygen 2L/min)	91-94% (FIO2 60%)	98% (oxygen 2L/min)
Day 7 posttransfusion	98% (no oxygenation)	99% (oxygen 2L/min)	97-99% (FIO2 35%)	98% (oxygen 2L/min)
Day 10 posttransfusion	98% (no oxygenation)	99% (oxygen 2L/min)	97-99% (FIO2 35%)	98% (oxygen 2L/min)
Day 20 posttransfusion	98% (no oxygenation)	95% (no oxygenation)	95% (FIO2 45)	98% (no oxygenation)
CT changes				
Just pre-transfusion	Bilateral GGO	Bilateral GGO, bilateral hydrothorax, hydropericardium	Bilateral GGO, consolidation, Interstitial abnormalities	Bilateral GGO, left cavity
Lesion absorption date posttransfusion	Day 5, 20	Day 2	Day 7, 11	Day 4, 9
SARS-CoV-2 RNA				
Just pre-transfusion	Positive	Positive	Positive	Positive
Undetectable date posttransfusion	Day21, Day22, Day23	Day2, Day3, Day5	Day13, Day14, Day15	Day14, Day15
Lymphocyte (*10^9/L)				
Just pre-transfusion	0.16	0.37	0.74	0.80
Day 1 posttransfusion	0.29	0.68	–	0.90
Day 4 posttransfusion	0.14	0.50	0.94	1.10
Day 7 posttransfusion	0.17	0.55	1.46	–
Day 10 posttransfusion	0.20	0.65	0.92	1.50
Day 20 posttransfusion	0.28	0.68	0.6	2.00

(continued)

Table 2. (continued)

Variables	Patient 1	Patient 2	Patient 3	Patient 4
D-dimer (mg/L)				
Just pre-transfusion	5.9	13	9.18	2.2
Day 1 posttransfusion	–	–	–	–
Day 4 posttransfusion	–	6.8	10	2.3
Day 7 posttransfusion	6.5	–	10	–
Day 10 posttransfusion	7.2	–	10	1.1
Day 20 posttransfusion	5.0	–	4	1.3
LDH (U/L)				
Just pre-transfusion	211	N	327	232
Day 1 posttransfusion	209	N	–	255
Day 4 posttransfusion	230	N	270	206
Day 7 posttransfusion	–	N	277	–
Day 10 posttransfusion	190	N	250	237
Day 20 posttransfusion	–	N	308	245
CRP (mg/L)				
Just pre-transfusion	3.4	44	76.4	>80
Day 1 posttransfusion	2.9	–	–	54
Day 4 posttransfusion	3.9	46	>80	49
Day 7 posttransfusion	1.7	75	>80	–
Day 10 posttransfusion	1.6	51	>80	19
Day 20 posttransfusion	1.1	53	18	–
Albumin (g/L)				
Just pre-transfusion	26	34	33	31
Day 1 posttransfusion	–			34
Day 4 posttransfusion	27	29	35	41
Day 7 posttransfusion	31	30	30	–
Day 10 posttransfusion	33	31	44	36
Day 20 posttransfusion	36	–	36	–

Variables	Patient 5	Patient 6	Patient 7	Median[c]
Respiratory symptoms				–
Just pre-transfusion	Cough, expectoration, dyspnea	Cough, expectoration	Dyspnea	–
Day 1 posttransfusion	Above symptoms alleviation	No symptoms	Alleviation	–
Day 4 posttransfusion	No symptoms	No symptoms		–
Day 7 posttransfusion	No symptoms	No symptoms		–
Day 10 posttransfusion	No symptoms	No symptoms		–
Day20 posttransfusion	No symptoms	No symptoms		–
Oxygen supply				–
Just pre-transfusion	Low-flow nasal cannula	Low-flow nasal cannula	Invasive ventilation	–
Day 1 posttransfusion	Ditto	Intermittent nasal cannula	Invasive ventilation	–
Day 4 posttransfusion	Ditto	Ditto	Invasive ventilation	–
Day 7 posttransfusion	Ditto	Ditto	–	–
Day 10 posttransfusion	Ditto	Ditto	–	–
Day 20 posttransfusion	Stop oxygenation	Stop oxygenation	–	–
PaO2/FIO2				–
Just pre-transfusion	300	359	111	254 (142-331)[d]
Day 1 posttransfusion	–	–	85	–
Day 4 posttransfusion	583	–	104	–
Day 7 posttransfusion	355	–	–	–
Day 10 posttransfusion	340	–	–	–
Day 20 posttransfusion	–	–	–	326 (163-364)
SPO2				–
Just pre-transfusion	97% (oxygen 2L/min)	96% (no oxygen supply)	97% (FIO2 60%)	96 (95-97)
Day 1 posttransfusion	97% (oxygen 2L/min)	96% (no oxygenation)	97% (FIO2 60%)	–

(continued)

Table 2. (continued)

Variables	Patient 5	Patient 6	Patient 7	Median[c]
Day 4 posttransfusion	97% (oxygen 2L/min)	96% (no oxygenation)	95% (FIO2 70%)	–
Day 7 posttransfusion	97% (oxygen 2L/min)	96% (no oxygenation)	–	–
Day 10 posttransfusion	97% (oxygen 2L/min)	96% (no oxygenation)	–	–
Day 20 posttransfusion	97% (no oxygenation)	96% (no oxygenation)	–	96 (95-98)
CT changes				
Just pre-transfusion	Bilateral GGO	Bilateral GGO, left cavity	Bilateral GGO, Interstitial abnormalities	–
Lesion absorption date posttransfusion	Day 6, 10	Day 9	Day 2	5 (2-7) days[e]
SARS-CoV-2 RNA				–
Just pre-transfusion	Positive	Positive	Negative	–
Undetectable date posttransfusion	Day4, Day7, Day9	Day9, Day11, Day12	Day1, Day2, Day3	11 (3.5-15.7)[f]
Lymphocyte (*10^9/L)				–
Just pre-transfusion	0.60	1.16	1.37	0.77 (0.6-1.16)
Day 1 posttransfusion	–	1.22	1.00	–
Day 4 posttransfusion	0.80	–	0.85	–
Day 7 posttransfusion	–	2.00	–	–
Day 10 posttransfusion	1.20	–	–	–
Day 20 posttransfusion	–	–	–	0.85 (0.6-2.0)
D-dimer (mg/L)				–
Just pre-transfusion	0.87	0.21	7.9	5.9 (0.87-9.18)
Day 1 posttransfusion	–	0.61	5.8	–
Day 4 posttransfusion	Normal	–	10.8	–
Day 7 posttransfusion	Normal	0.75	–	–
Day 10 posttransfusion	0.42	–	–	–
Day 20 posttransfusion	Normal	–	–	4 (0.75-6.8)
LDH (U/L)				–
Just pre-transfusion	263	Normal	337	263 (222-332)
Day 1 posttransfusion	–	–	250	–
Day 4 posttransfusion	<245	–	420	–
Day 7 posttransfusion	–	–	–	–
Day 10 posttransfusion	<245	–	–	–
Day 20 posttransfusion	–	–	–	245 (210-364)
CRP (mg/L)				–
Just pre-transfusion	35	3.3	>80	44 (3.4-80)
Day 1 posttransfusion	–	55	>80	–
Day 4 posttransfusion	32	–	>80	–
Day 7 posttransfusion	13	8.9	–	–
Day 10 posttransfusion	7.1	–	–	–
Day 20 posttransfusion	–	–	–	18 (7.1-53)
Albumin (g/L)				–
Just pre-transfusion	30	32	24	31 (26-33)
Day 1 posttransfusion	–	–	35	–
Day 4 posttransfusion	33	–	40	–
Day 7 posttransfusion	34	–	–	–
Day 10 posttransfusion	–	–	–	–
Day 20 posttransfusion	35	–	–	36 (34-37)

[a]The last day within 20 days.
[b]Using High flow humidification instrument (40-50L/min).
[c]As for patient 1 to patient 7.
[d]Excluding case 6.
[e]The median of first absorption.
f The median of first negative detection RNA, and excluding patient 7.
LDH: Lactate dehydrogenase CRP: C-responsive protein; CT: Computed tomography ECMO: Extracorporeal Membrane Oxygenation; GGO: ground-glass opacity.

Table 3. Improvement of Other Laboratory Parameters After CP Therapy.

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Temperature (°C)							
Just pre-transfusion	N	N	N	37.4	N	N	38.2
Posttransfusion	N	N	N	N	N	N	N
White cell (*10^9/L)							
Just pre-transfusion	3.4	N	N	N	N	N	12.4
Posttransfusion	0.94	3.8	N	N	N	N	17.7
Neutrophil (%)							
Just pre-transfusion	88%	N	81	77%	N	71	83
Posttransfusion	N	76%	91	N	N	N	92
ESR (mm/h)							
Just pre-transfusion	129	–	125	115	90	53	112
Posttransfusion	71	–	60	95	118	58	10
ALT (U/L)							
Just pre-transfusion	N	69	N	N	N	55	N
Posttransfusion	N	N	N	N	N	N	N
AST (U/L)							
Just pre-transfusion	N	80	N	N	N	N	57
Posttransfusion	N	N	N	N	N	N	100
Total bilirubin (umol/L)							
Just pre-transfusion	N	162	N	N	N	N	48
Posttransfusion	N	110	N	N	N	N	82
Creatinine (umol/L)							
Just pre-transfusion	N	N	N	N	N	N	224
Posttransfusion	N	N	N	N	N	N	N
PT (s)							
Just pre-transfusion	N	26	N	N	N	N	19
Posttransfusion	N	22	N	N	N	N	N
APTT (s)							
Just pre-transfusion	N	58	N	N	N	N	N
Posttransfusion	N	55	N	N	N	N	N
Procalcitonin (ug/L)							
Just pre-transfusion	<0.05	<0.05	0.07	0.1	<0.05	<0.05	5.3
Posttransfusion	<0.05	0.2	<0.05	0.1	<0.05	<0.05	1.2
Lactic acid (mmol/L)							
Just pre-transfusion	1.9	–	2.4	2	1	1.3	1.4
Posttransfusion	1.4	–	1.2	–	1.3	–	0.9

N: Normal; ESR: Erythrocyte sedimentation rate; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PT: Prothrombin time; APTT: Activated partial thromboplastin time.

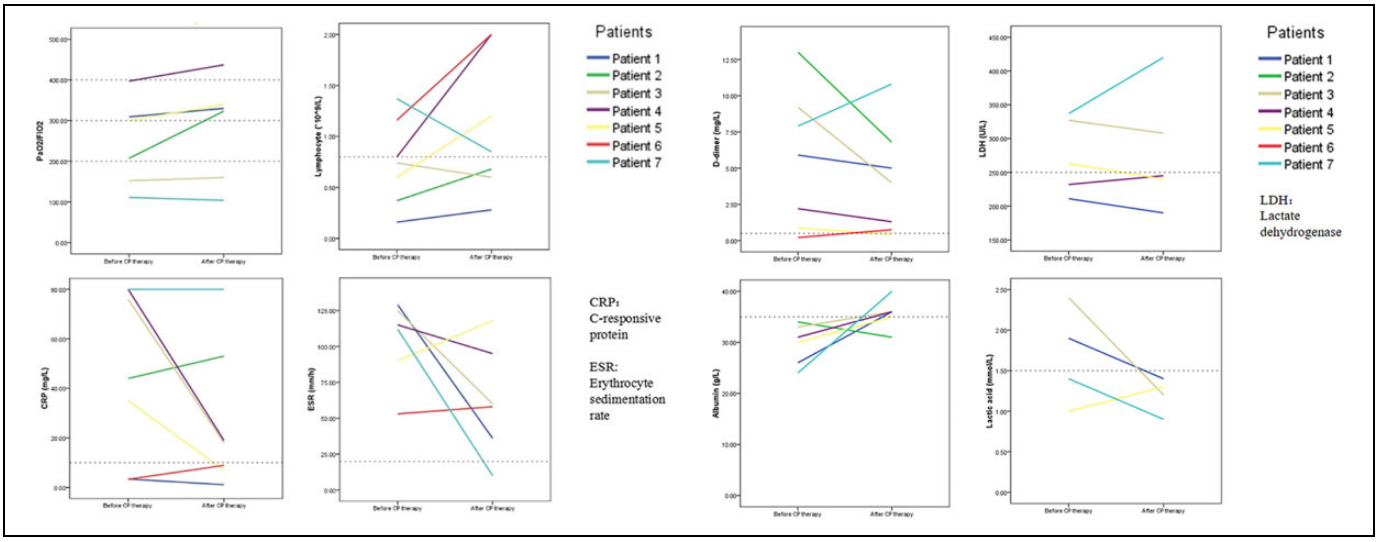

Figure 1. Laboratory parameters changes before and after CP therapy.

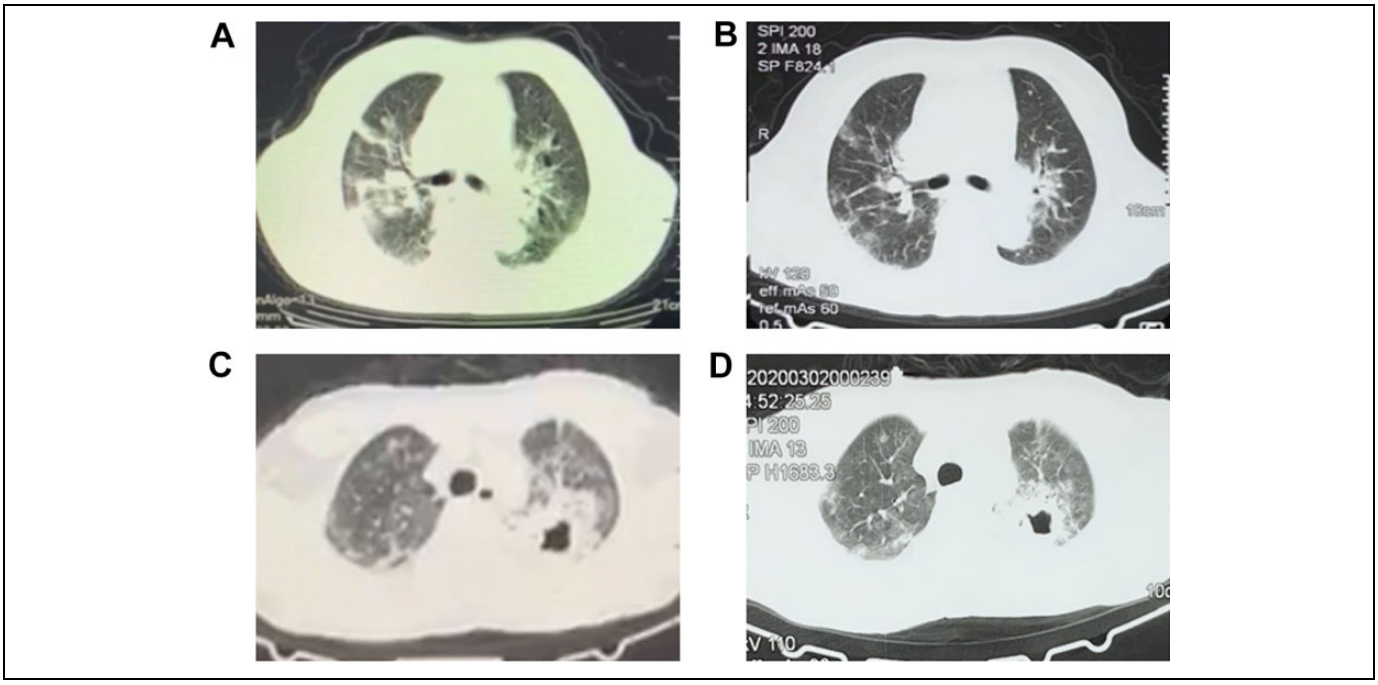

Figure 2. CT changes of patient 1 and patient 4 before and after CP therapy. A, CT of patient 1 obtained on February 16 before CP therapy with local patchy shadowing in right lung and slight ground-glass opacity in bilateral lung. B,CT of patient 1 obtained on February 24 after CP therapy showed the absorption of above lesions after CP therapy. C,CT of patient 4 obtained on February 22 before CP therapy with cavity and exudative lesions. D, CT of patient 4 obtained on March 2 after CP therapy showed the shrunken cavity and exudative lesions.

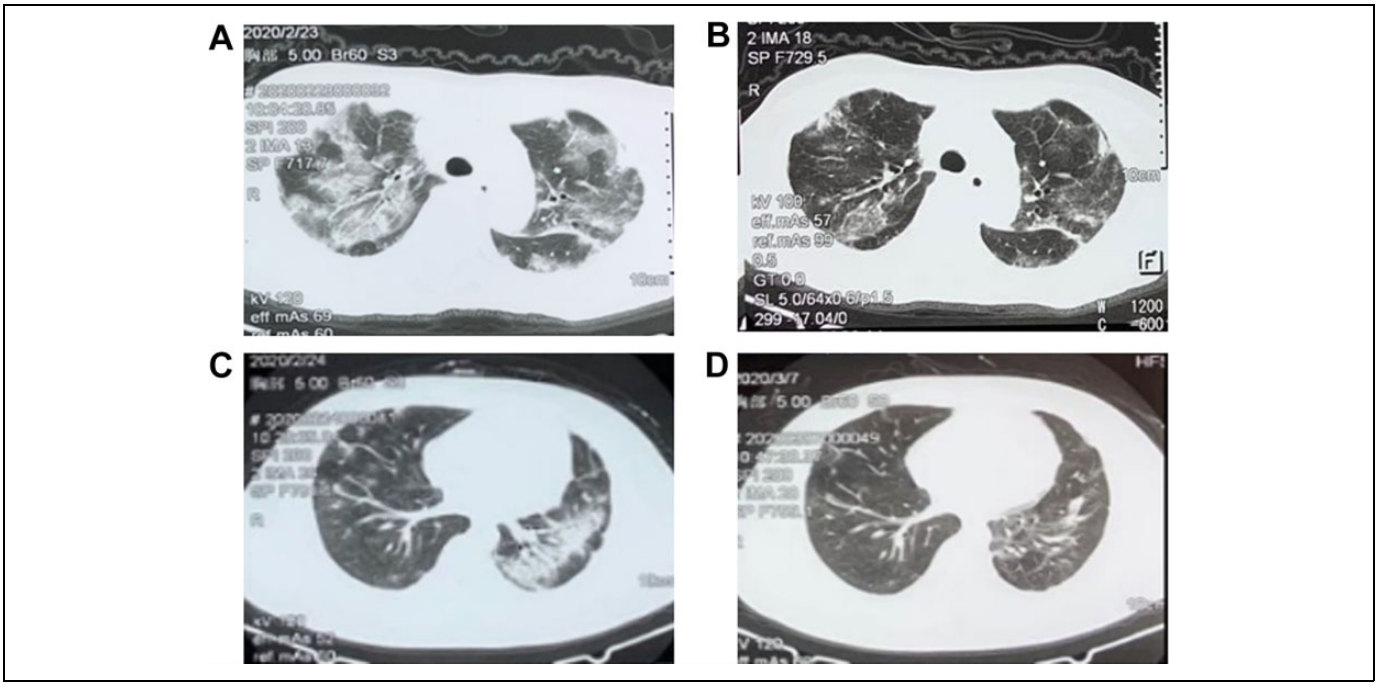

Figure 3. CT changes of patient 5 and patient 6 before and after CP therapy. A,CT of patient 5 obtained on February 23 before CP therapy with ground-glass opacity in bilateral lung. B, CT of patient 5 obtained on March 4 after CP therapy showed the absorption of above lesions after CP therapy. C, CT of patient 6 obtained on February 24 before CP therapy with ground-glass opacity and consolidative opacities. D, CT of patient 6 obtained on March 7 after CP therapy showed the absorption of above lesions after CP therapy.

in COVID-19,[28] and we also detected viral RNA after 3 weeks of admission.

There were some limitations to our study. (1) Due to the retrospective nature of the study, we did not obtain antibody titers from the recipients of CP. (2) Three patients received combined antiviral therapy after CP, which may have contributed to viral clearance. (3) Six patients received combined antibiotics, which may have contributed to the absorption of CT/X-ray-detected lesions. (4) Because of the shortage of CP sources, the number of patients was small and we did not establish a control group. We used patients self-matching as controls before and after CP transfusion. (5) A small number of patients received CP therapy, therefore, we included all patients who received CP therapy to assess the efficacies in all types of disease status.

In conclusion, this pilot study showed the potential effectiveness and safety of CP therapy in COVID-19, as assessed by improvement of clinical manifestations, respiratory function, viral clearance, other laboratory parameters and long-term follow-up. However, we showed that CP therapy failed to save the life of a terminally ill patient. The limited number of patients and uncontrolled patients preclude definitive conclusions about CP therapy for COVID-19; therefore, clinical trials are needed to determine antibody titers and optimal time of transfusion.

Authors' Note

The primary data of this article are available from the corresponding author upon reasonable request.

Declaration of Conflicting Interests

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ORCID iD

Xiangyu Chen https://orcid.org/0000-0002-4233-8822

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