Original Article

Convalescent Plasma Therapy in Late-State, Severe COVID-19 Infection

Neil R. Kumar, MD[1]; Veena C. Karanam, MD[2]; Shari Kumar, BS[3]; and Sunil D. Kumar, MD[4]

Objectives: Current evidence favors plasma to be effective against coronavirus disease 2019 (COVID-19) in critically ill patients in the early stages of infection. We investigated the safety and efficacy of convalescent plasma in specifically late-stage (designated as after 2 weeks of hospital admission) severe COVID-19 infection. We also conducted a literature review on the late-stage use of plasma in COVID-19.

Methods: This case series examined eight COVID-19 patients admitted to the intensive care unit (ICU) who met criteria for severe or life-threatening complications. Each patient received one dose (200 mL) of plasma. Clinical information was gathered in intervals of 1 day pretransfusion and 1 hour, 3 days, and 7 days posttransfusion. The primary outcome was effectiveness of plasma transfusion, measured by clinical improvement, laboratory parameters, and all-cause mortality.

Results: Eight ICU patients received plasma late in the course of COVID-19 infection, on average at 16.13 days postadmission. On the day before transfusion, the averaged initial Sequential Organ Failure Assessment (SOFA) score, PaO_2:FiO_2 ratio, Glasgow Coma Scale (GCS), and lymphocyte count were 6.5, 228.03, 8.63, and 1.19, respectively. Three days after plasma treatment, the group averages for the SOFA score (4.86), PaO_2:FiO_2 ratio (302.73), GCS (9.29), and lymphocyte count (1.75) improved. Although the mean GCS improved to 10.14 by posttransfusion day 7, the other means marginally worsened with an SOFA score of 5.43, a PaO_2:FiO_2 ratio of 280.44, and a lymphocyte count of 1.71. Clinical improvement was noted in six patients who were discharged from the ICU.

Conclusions: This case series provides evidence that convalescent plasma may be safe and effective in late-stage, severe COVID-19 infection. Results showed clinical improvement posttransfusion as well as decreased all-cause mortality in comparison to pretransfusion predicted mortality. Randomized controlled trials are needed to conclusively determine benefits, dosage, and timing of treatment.

Key Words: convalescent plasma, COVID-19, severe, late stage, life threatening

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), has spread quickly across the globe, with the numbers as of mid-January 2023 showing more than 668 million cases.[1] Given the speed of the outbreak and sheer volume of those infected, there was initially a sparsity of effective treatments for this virus, with many agents undergoing trials; just as the virus spread, the approach to management of the infection also evolved quickly, with four agents leading the way. Clinical data suggest dexamethasone use in patients with severe COVID-19 who need oxygenation or ventilatory support because it reduces 28-day mortality when compared with placebo.[2] Baricitinib has a mortality benefit in patients receiving high-flow oxygen therapy and noninvasive ventilation as well as in certain patients on low-flow oxygen therapy but with escalating oxygen requirements while on dexamethasone.[3]

Key Points

- In this case series, plasma was administered on average across 2 weeks after hospital admission to the intensive care unit for patients with severe or life-threatening coronavirus disease 2019 (COVID-19) infection.
- Plasma use in late-stage COVID-19 infection led to clinical improvement, decreased mean Sequential Organ Failure Assessment scores, increased mean PaO_2:FiO_2 ratios, and increased mean Glasgow Coma Scale scores.
- There were no significant adverse events caused by plasma transfusion.
- Convalescent plasma may be a safe and effective therapy for critically ill COVID-19 patients in the late stages of infection; however, randomized controlled trials are necessary to determine benefits, dosage, and timing of treatment.

From [1]Internal Medicine, University of Miami/Jackson Memorial Hospital, Miami, Florida, the [2]University of Miami Miller School of Medicine, Miami, Florida, [3]Columbia University College of Dental Medicine, New York, New York and the [4]Pulmonary/Critical Care, Broward Health Medical Center, Ft Lauderdale, Florida.

Correspondence to Dr Sunil Kumar, Broward Health Medical Center, 1600 S Andrews Ave, Ft Lauderdale, FL 33316. E-mail: dhanvanintensivist@gmail.com.

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Recommendations regarding tocilizumab vary among different groups. The National Institutes of Health recommends the use of tocilizumab in patients already taking dexamethasone, on high-flow oxygen or higher oxygenation support, and either admitted to the intensive care unit (ICU) within 24 hours or with increasing inflammatory markers.[3] Meanwhile, the Infectious Diseases Society of America suggests the use of tocilizumab in patients with severe or critical COVID-19 and elevated inflammatory markers.[4] Nevertheless, the clinical evidence from a meta-analysis indicates an all-cause mortality benefit with tocilizumab in comparison with placebo or standard of care.[5] Lastly, both the National Institutes of Health and Infectious Diseases Society of America recommend remdesivir in hospitalized COVID-19 patients who are receiving any form of oxygenation support aside from mechanical ventilation or extracorporeal membrane oxygenation.[3,4] In several randomized controlled trials, however, remdesivir has not clearly shown mortality or major clinical benefits.[6]

Another avenue for therapy has been convalescent plasma (CP), which contains antibodies from patients who have recovered from the virus. The current recommendation is to use high-titer CP as early as possible in the disease process[7]; however, most of the literature on CP in COVID-19 studied patient populations of noncritically ill patients or critically ill patients in the early stages of COVID-19 infection. In our study, we differentiate early stages (within the first 2 weeks of hospital admission) from late stages (after 2 weeks of hospital admission) to identify patients with a prolonged course of severe COVID-19 infection. The research on CP in late-stage COVID-19 infection is sparse. Some studies have not shown a significant benefit when plasma treatment was given late in the disease course[4] (M.J. Joyner, unpublished data, August 2020). Salazar et al[4] and Joyner et al (unpublished data, August 2020) showed that transfusion before 72 hours of admission and diagnosis, respectively, is clinically more efficacious than afterward. Although Salazar et al recognized that COVID-19 patients who received transfusions after 72 hours of admission had an improved mortality of 7.8% versus a control group of 14.3%, the difference was not significant.[5] Furthermore, it is important to note that Joyner et al (unpublished data, August 2020) created subgroups based on transfusion within or after 3 days postdiagnosis, rather than postadmission. This raises the question of whether the variable time from onset of symptoms to diagnosis creates a source of variation within subgroups. Lastly, Klassen et al completed a 16-study subgroup analysis on the effects of time between hospital admission and transfusion, showing a mortality reduction in patients transfused within 3 days of hospital admission compared with those receiving CP greater than 3 days of admission.[6] Interestingly, however, they noted that their results were heavily influenced (relative weight of 73%) by a single study, and upon removing it, there was no longer an association between mortality reduction and duration from hospital admission to transfusion.

Other studies showed a benefit of late-stage transfusion. A randomized controlled trial used weight-based dosing to transfuse individuals with severe or life-threatening COVID-19 after a median interval of 30 days from symptom onset.[7] Their subgroup analysis showed a statistically significant faster time to clinical improvement for those with severe but not life-threatening disease who were transfused in comparison to the control group. Furthermore, Xia et al analyzed the effect of CP at different time points, stratifying patients into groups based on elapsed time between symptom onset and transfusion: 1 to 4, 5 to 6, 7, and 8 weeks.[8] Overall, 200 to 1200 mL CP were transfused based on the clinical status and weight of the patient. The results showed that CP was effective in improving respiratory symptoms of patients with severe disease. Those transfused in the first 7 weeks had a median time to clinical improvement of 10 days, whereas those transfused after 7 weeks had a significantly prolonged time to clinical improvement. Xia et al therefore postulated that CP transfused after 2 weeks of symptom onset could improve the symptoms and mortality of patients with severe or critical cases of COVID-19. Although the interval of this study from symptom onset to transfusion does not directly correlate with our late-stage definition of a minimum 2-week interval from admission to transfusion, Xia et al conducted their study at transfusion schedules that are later in the disease course than most other studies, yielding promising results.[8] Lastly, two small randomized controlled trials administered plasma at a mean of 15 days after onset of symptoms and a median of 17 days after onset of symptoms, respectively; the first study demonstrated a significant reduction in mortality and the second trial showed a decrease in illness severity.[8,9]

We seek to add to the growing body of evidence concerning CP treatment in the late stages of the COVID-19 disease by examining eight ICU patients treated at a large teaching hospital in Broward County, Florida. Because most studies have examined patients with severe COVID-19 in the early stages of infection, there is limited clinical evidence on the use of CP in late-stage, severe COVID-19 infection. By examining disease course, timing of treatment, and adverse reactions, we hope to evaluate the efficacy and safety of CP as a treatment for COVID-19 in the late stages of infection.

Methods

This case series analyzed eight critically ill patients with laboratory-confirmed COVID-19 and acute respiratory failure. These patients were part of the data collection process approved by the Broward Health Medical Center institutional review board. Patient written informed consent was waived. All of the patients were admitted to the ICU of a major teaching hospital in Broward County, Florida from March 29 to April 30, 2020.

Donors must have had SARS-CoV-2 neutralizing antibody titers of at least 1:160. The patient eligibility criteria for CP transfusion included laboratory confirmed COVID-19 and severe or immediately life-threatening COVID-19. Severe disease was

Table 1. Clinical characteristics

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Sex	Male	Male	Male	Male	Male	Male	Male	Male
Age, y	83	46	69	43	72	53	53	78
BMI ≥30	No	No	Yes	No	Yes	No	No	Yes
Hypertension	Yes	Yes	Yes	No	Yes	No	Yes	Yes
Diabetes mellitus	No	Yes	Yes	No	Yes	Yes	Yes	No
Chronic lung disease	No	No	No	No	No	No	No	Yes
Cardiovascular disease	Yes	No	No	No	No	No	No	No
Hydrocortisone 100 mg IV q8h, d						Yes (4)		
Hydrocortisone 50 mg IV q6h, d	Yes (2)	Yes (8)		Yes (5)	Yes (4)	Yes (4)	Yes (5)	Yes (2)
Hydrocortisone 50 mg IV q8h, d	Yes (1)		Yes (1)	Yes (1)	Yes (1)	Yes (5)	Yes (2)	
Hydrocortisone 50 mg IV q12h, d	Yes (3)	Yes (1)	Yes (1)	Yes (4)	Yes (1)	Yes (6)	Yes (4)	Yes (8)
Hydrocortisone 50 mg IV q24h, d	Yes (1)			Yes (2)			Yes (3)	Yes (1)
Hydrocortisone 25 mg IV q8h, d						Yes (4)		
Hydrocortisone 25 mg IV q12h, d						Yes (14)		
Hydrocortisone 25 mg IV q24h, d						Yes (4)		
Methylprednisolone 40 mg IV q12h		Yes (12)			Yes (17)			
Methylprednisolone 40 mg IV q24h				Yes (4)	Yes (3)			
Methylprednisolone 20 mg IV q24h					Yes (5)			
Prednisone 20 mg po q24h							Yes (3)	
Prednisone 10 mg po q24h							Yes (3)	

The number of days that patient received treatment is shown in parentheses. BMI, body mass index; IV, intravenous; po, per os; q6h, every 6 h; q8h, every 8 h; q12h, every 12 h; q24h, every 24 h.

defined as one or more of the following: shortness of breath, respiratory frequency ≥ 30/min, blood oxygen saturation ≤ 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and lung infiltrates >50% within 24 to 48 hours of admission. Life-threatening disease was defined as one or more of the following: respiratory failure, septic shock, and multiple organ dysfunction or failure. If eligible, patients were transfused with one dose of CP (200 mL) at an infusion rate of 100 to 200 mL/h.

Clinical information from the plasma recipients was obtained from the hospital's electronic medical record system in the intervals of 1 day pretransfusion and 1 hour, 3 days, and 7 days posttransfusion. The data collected during the hospital stay involved the following variables: demographic data; baseline comorbidities; treatment, including medications and oxygen delivery methods; radiographic findings; laboratory data, including leukocyte counts, chemistry panels, coagulation factors, and blood gas analysis; and clinical

Table 2. Clinical timeline from hospital admission day 1

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Mean
Day of ICU admission	2	1	3	1	1	3	2	1	1.75
Day of intubation	2	2	4	3	1	3	2	1	2.25
Day of plasma	22	15	22	21	7	14	15	21	17.13
Day of extubation	Trach (day 22)	Trach (day 18)	22	16	Trach (day 22)	Trach (day 27)	12	Died (day 23)	16.67
Day of ICU discharge	24	Died (day 27)	32	21	27	57	16	Died (day 23)	29.50
Day of hospital discharge	45	Died (day 27)	72	27	59	66	21	Died (day 23)	48.33
Interval between symptom onset and hospital admission (day 1)	5	1	3	10	7	8	7	9	6.25
Interval between hospital admission (day 1) and plasma transfusion	21	14	21	20	6	13	14	20	16.13
Interval between intubation and plasma transfusion	20	13	18	18	6	11	13	20	14.88
Interval between plasma transfusion and ICU discharge	2	Died (day 27)	10	0	20	43	1	Died (day 23)	12.67

ICU, intensive care unit; trach, tracheostomy.

data, including vital signs, respiratory requirements, neurologic status, length of stay, and mortality.

The primary outcome was the effectiveness of plasma transfusions for patients with COVID-19. This was measured by clinical improvement, laboratory parameters, and all-cause mortality. Clinical improvement was assessed by respiratory requirements, Sequential Organ Failure Assessment (SOFA) score,[10] PaO_2:FiO_2 ratio, and Glasgow Coma Score (GCS). The secondary outcome was the safety of plasma transfusion for these patients, determined by adverse events.

Results

From April 19 to April 22, 2020, eight patients (all men with an age range of 43–83 years), were treated with CP (Table 1). At the time, there were no Food and Drug Administration–approved treatments for COVID-19, and therefore options such as tocilizumab and remdesivir were not used. Steroids were administered in varying doses and duration as found in Table 1. The mean time from onset of symptoms to hospital admission was 6.25 days (Table 2). The most common preexisting conditions were hypertension (six patients), followed by diabetes mellitus (five patients), and obesity (three patients) (Table 1). All eight patients were found to have radiographic findings of bilateral pulmonary infiltrates. Plasma was administered to the eight patients on an average of 16.13 days postadmission (Table 2). Patient 8, however, died before information from posttransfusion days 3 and 7 could be collected.

The SOFA score ranged from 3 to 13 a day before transfusion and decreased to a range of 0 to 10 by 7 days after transfusion (Table 3; Supplemental Digital Content Appendix 1A, see http://links.lww.com/SMJ/A334). The mean SOFA score for the group was calculated based on the average of the individual patients' scores on each day, which decreased overall through time; it averaged 6.5 a day pretransfusion and decreased to 4.86 by posttransfusion day 3, but it was noted to increase to 5.43 by posttransfusion day 7 (Supplemental Digital Content Appendix 1B, see http://links.lww.com/SMJ/A335). The PaO_2:

Table 3. Comparative analysis of clinical findings and laboratory markers in relation to timing of transfusion

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Mean
SOFA score									
1 d pretransfusion	5	10	5	3	13	6	3	7	6.50
3 d posttransfusion	5	7	7	0	7	8	0	N/A	4.86
7 d posttransfusion	7	8	6	0	10	7	0	N/A	5.43
PaO_2/FiO_2 ratio									
1 d pretransfusion	200.00	84.29	606.67	108.00	120.00	168.00	279.31	258.00	228.03
3 d posttransfusion	247.50	330.00	242.34	479.37	132.86	219.00	468.03	N/A	302.73
7 d posttransfusion	221.43	227.14	211.43	473.70	95.71	260.00	473.70	N/A	280.44
GCS									
1 d pretransfusion	6	3	11	14	3	8	14	10	8.63
3 d posttransfusion	9	3	13	15	3	7	15	N/A	9.29
7 d posttransfusion	9	6	13	15	3	10	15	N/A	10.14
WBC									
1 d pretransfusion	3.56	8.21	18.37	7.26	18.51	7.27	11.29	11.25	10.72
3 d posttransfusion	5.08	5.14	14.21	7.59	15.18	9.62	11.36	N/A	9.74
7 d posttransfusion	5.17	5.80	28.16	6.93	11.96	11.63	13.73	N/A	11.91
Absolute lymphocyte									
1 d pretransfusion	0.61	0.68	1.19	1.45	1.48	0.86	2.31	0.97	1.19
3 d posttransfusion	0.98	0.88	1.40	2.62	0.61	1.71	4.07	N/A	1.75
7 d posttransfusion	0.41	0.99	1.09	2.22	0.94	0.67	5.63	N/A	1.71
D-Dimer									
1 d pretransfusion	5.84	3.47	10.31	3.48	10.31	1.75	1.67	3.10	4.99
3 d posttransfusion	N/A	1.37	11.51	N/A	3.48	1.21	N/A	N/A	4.39
7 d posttransfusion	N/A	3.73	5.70	N/A	2.84	2.02	N/A	N/A	3.57
CRP									
1 d pretransfusion	2.50	2.75	15.92	6.40	13.53	10.37	0.89	2.37	6.84
3 d posttransfusion	N/A	12.07	12.84	N/A	5.45	9.37	N/A	N/A	9.93
7 d posttransfusion	N/A	31.75	9.02	N/A	10.67	4.29	N/A	N/A	13.93

CRP, C-reactive protein; GCS, Glasgow Coma Scale; N/A, not applicable; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell count.

FiO_2 ratio increased for six patients by posttransfusion day 3 but then decreased for four of those patients by posttransfusion day 7 (Supplemental Digital Content Appendix 1C, see http://links.lww.com/SMJ/A336). The mean PaO_2:FiO_2 ratio increased overall; the mean ratio started at 228.03 a day pretransfusion and increased to 302.73 by posttransfusion day 3, but then decreased to 280.44 by posttransfusion day 7 (Supplemental Digital Content Appendix 1D, see http://links.lww.com/SMJ/A337). GCS scores for all of the patients improved after plasma treatment, except for one patient who remained stable (Supplemental Digital Content Appendix 1E, see http://links.lww.com/SMJ/A338). The initial GCS mean was 8.63 a day pretransfusion, which improved to 9.29 by posttransfusion day 3 and then 10.14 by posttransfusion day 7 (Supplemental Digital Content Appendix 1F, see http://links.lww.com/SMJ/A339).

Six patients experienced an increase in the absolute lymphocyte counts by posttransfusion day 3 (Table 3; Supplemental Digital Content Appendix 2A, see http://links.lww.com/SMJ/A340). The mean absolute lymphocyte count marginally increased from 1.19 a day pretransfusion to 1.75 by posttransfusion day 3 and remained relatively stable (1.71) by posttransfusion day 7 (Supplemental Digital Content Appendix 2B, see http://links.lww.com/SMJ/A341). The mean white blood cell count decreased by posttransfusion day 3, but was noted to increase by posttransfusion day 7. D-Dimer and C-reactive protein were recorded as well; however, these patients were receiving anticoagulation treatment throughout their hospital stay and only five patients had full data. Although the mean D-dimer decreased from 4.99 a day pretransfusion to 3.57 by posttransfusion day 7, no trend was identified for D-dimer among individual patients (Table 3). Posttransfusion, C-reactive protein decreased in three of the five patients observed.

All eight patients in this study were intubated and admitted to the ICU within 3 days of admission and received plasma on average at 14.88 days postintubation (Table 2). Of the eight patients enrolled in this study, six clinically improved and were safely discharged from the hospital, and two patients died. These six patients had an average length of stay in the ICU postplasma transfusion of 12.7 days.

In this study, we monitored for tachycardia, hypotension, and fever (Table 4), with four patients developing tachycardia, one patient developing hypotension, and one patient developing a fever posttransfusion. Plasma transfusion was completed in all of the patients without any serious adverse events.

Discussion

This study examined eight critically ill patients at a large teaching hospital in Broward County, Florida who were treated for the COVID-19 infection with CP therapy. In this study, plasma was administered on average 23 days after onset of symptoms, during 16 days after hospital admission and 14 days postintubation. By the end of this study, six patients were discharged from the ICU, having had an average posttransfusion ICU length of stay of 12.7 days. Given the improvement of clinical status and laboratory findings, high discharge rate from the ICU, and lack of serious adverse effects, this study strengthens the evidence indicating the effectiveness and safety of CP treatment in the late stages (after 2 weeks of hospital admission) of the COVID-19 infection.

Posttransfusion, an overall positive trend was seen in clinical and laboratory factors noted by the mean improvement in SOFA score, PaO_2:FiO_2 ratio, GCS, and lymphocyte count. The results of this case series are in line with prior case studies that showed clinical status improvement following plasma transfusion in patients with COVID-19. Notably, however, mean SOFA scores, PaO_2:FiO_2 ratio, and lymphocyte count improved by posttransfusion day 3, but then marginally worsened by day 7. This trend warrants further investigation into whether a higher dose or repeated treatments of plasma may be beneficial in late-stage COVID-19 infection, given the initial improvement then deterioration of these values.

In this study, each patient was treated with one dose of 200 mL plasma. Likewise, many COVID-19 plasma case studies have used one to two treatments of plasma with dosing of 200 to 300 mL plasma. Interestingly, however, the two studies that showed significant benefit for CP administration late in the COVID-19 disease course also were the only studies that used varying dosages of up to 1200 mL plasma in one study, based on the weight and disease severity of patients.[7,8] In fact, Tegenge et al claimed that plasma dosing should be based on initial viral load and involve pharmacokinetic monitoring; for severe infection especially, they recommended a weight-based, relatively high initial dose following by repeat dosing based on viral load.[9] Another variable in transfusion practices is antibody titers, with most of the literature[6,10] indicating that high-titer CP transfusions correlated with reduced mortality when compared with low-titer plasma (M.J. Joyner, unpublished data, August 2020).

Table 4. Adverse effects

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Tachycardia (HR >100)	N	Y	Y	N	N	N	Y	Y
Hypotension (systolic <90, diastolic <60)	N	N	N	N	N	N	N	Y
Fever (axillary temperature ≥ 37.2 °C)	N	Y	N	N	N	N	N	N
Termination of transfusion	N	N	N	N	N	N	N	N

HR, heart rate; N, no; Y, yes.

Because there is no standard therapeutic dosage of plasma in patients with COVID-19, it is possible that higher initial doses (>200 mL), higher titer levels, and/or multiple doses of CP are necessary to provide sustained therapeutic effects in late-stage, critically ill patients with COVID-19.

Optimal timing of transfusion is the cornerstone of CP therapy in COVID-19 infections. Evidence from the 2003 SARS outbreak showcased that plasma given in the early stages of viremia resulted in higher efficacy; Cheng et al described longer hospital stays and higher rates of death among SARS patients who received CP after day 14 of symptom onset in comparison to those transfused before day 14.[11] They, as well as Soo et al, postulated that because the viral load in SARS peaks in the first week of infection, whereas the primary immune reaction develops by the end of week 2, plasma theoretically is most effective early in disease progression.[12] In COVID-19 infection, however, the detectable humoral immune response takes longer to set in. In a Cochrane systematic review of 38 studies, Deeks et al noted that since the start of symptoms in patients with COVID-19, the combination of immunoglobulin M (IgM) and IgG was detected in 30% of patients by week 1, 72% by week 2 and 91% by week 3.[13] Although there are fewer studies on antibody sensitivity from 3 to 5 weeks, pooled results estimate detection of the IgM and IgG combination in 96% of patients. As a result, early plasma therapy provides the antibody response that the human body fails to generate quickly, which is in conjunction with the beneficial results from early CP therapy in prominent COVID-19 plasma studies,[4] (M.J. Joyner, unpublished data, August 2020). Plasma transfusion in the late stages of COVID-19, however, could still provide substantial benefit because the endogenous humoral response is still developing up to 5 weeks in most patients.[13]

In late stages of the disease, the immune system suffers from severe dysregulation with a high state of inflammation, especially in patients with severe and life-threatening COVID-19 infection.[14,15] In a randomized controlled trial, Ray et al compared 40 patients who received two 200-mL doses of CP on consecutive days with 40 patients receiving standard of care therapy to identify the factors influencing the immunologic and clinical benefits of CP in patients with severe COVID-19. They concluded that plasma contributed not only neutralizing antibodies but also prominent anti-inflammatory effects through the possible attenuation of systemic cytokines.[15] This is yet another reason why late-stage transfusion has potential benefits, especially in patients with severe COVID-19 with hyperinflammatory manifestations.

The only adverse event in this study was a transient fever in one patient that did not cause cessation of transfusion. Adverse events associated with CP therapy in COVID-19 are rare at this time.[4,16,17] An analysis of more than 20,000 patients transfused with CP showed that <1% of all transfusions were associated with serious adverse events.[18] The low frequency of these adverse reactions points toward the safety of plasma treatment in COVID-19.

There are, however, some factors affecting the internal and external validity of this study. First, this study was limited in large part because of the small sample size and all-male patient population, which limited generalizability, as well as the varying comorbidities of each patient, which would affect clinical response. Second, we were unable to delineate the anti-inflammatory response of CP because inflammatory markers were not consistently obtained for all of the patients. Lastly, because this was not a randomized controlled trial, there was no control group and we were unable to clearly attribute the recovery of these patients to CP use.

This case series shows that CP may be an effective therapy for patients in the late stages of COVID-19 infection. Randomized controlled trials are required to definitively show the risks and benefits of CP as well as to determine the optimal amount, titer, and frequency of dosing in late-stage COVID-19 infection, however.

Conclusions

This retrospective study provides preliminary evidence that treatment with CP can be an effective and safe treatment modality for critically ill patients with COVID-19 in the late stages (after 2 weeks of hospital admission) of infection. Plasma transfusion in this study was largely followed by the improvement of clinical status with no serious adverse events. Furthermore, the findings presented in this study warrant investigation into the optimal dosing and timing of treatment. Randomized controlled trials are necessary, however, to make a definitive statement concerning CP transfusion in patients with late-stage COVID-19.

References

1. Johns Hopkins University & Medicine, Coronavirus Resource Center. COVID-19 dashboard. https://coronavirus.jhu.edu/map.html. Accessed January 19, 2023.
2. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group; Sterne JAC, Murthy S, et al.. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA* 2020;324:1330–1341.
3. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Respir Med* 2021;9:1407–1418.
4. Salazar E, Christensen PA, Graviss EA, et al. Treatment of coronavirus disease 2019 patients with convalescent plasma reveals a signal of significantly decreased mortality. *Am J Pathol* 2020;190:2290–2303.
5. Salazar E, Christensen PA, Graviss EA, et al. Significantly decreased mortality in a large cohort of coronavirus disease 2019 (COVID-19) patients transfused early with convalescent plasma containing high-titer anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein IgG. *Am J Pathol* 2020;191:90–107.
6. Klassen SA, Senefeld JW, Johnson PW, et al. The effect of convalescent plasma therapy on mortality among patients with COVID-19: systematic review and meta-analysis. *Mayo Clin Proc* 2021;96:1262–1275.
7. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. *JAMA* 2020;324:460–470.
8. Xia X, Li K, Wu L, et al. Improved clinical symptoms and mortality among patients with severe or critical COVID-19 after convalescent plasma transfusion. *Blood* 2020;136:755–759.
9. Tegenge MA, Mahmood I, Struble E, et al. Dosing considerations for antibodies against COVID-19. *Drugs R D* 2021;21:1–8.

10. Joyner MJ, Carter RE, Senefeld JW, et al. Convalescent plasma antibody levels and the risk of death from Covid-19. *N Engl J Med* 2021;384: 1015–1027.
11. Cheng Y, Wong R, Soo YO, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis* 2005;24:44–46.
12. Soo YOY, Cheng Y, Wong R, et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. *Clin Microbiol Infect* 2004;10:676–678.
13. Deeks JJ, Dinnes J, Takwoingi Y, et al. Antibody tests for identification of current and past infection with SARS-CoV-2. *Cochrane Database Syst Rev* 2020;6:CD013652.
14. Paces J, Strizova Z, Smrz D, et al. COVID-19 and the immune system. *Physiol Res* 2020;69:379–388.
15. Ray Y, Paul SR, Bandopadhyay P, et al. A phase 2 single center open label randomised control trial for convalescent plasma therapy in patients with severe COVID-19. *Nat Commun* 2022;13:383.
16. Agarwal A, Mukherjee A, Kumar G, et al. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID trial). *BMJ* 2020;371: m3939.
17. Salazar E, Perez KK, Ashraf M, et al. Treatment of coronavirus disease 2019 (COVID-19) patients with convalescent plasma. *Am J Pathol* 2020;190: 1680–1690.
18. Joyner MJ, Bruno KA, Klassen SA, et al. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. *Mayo Clin Proc* 2020; 95:1888–1897.