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ORIGINAL RESEARCH

Efficacy of Convalescent Plasma and Short-Course Corticosteroids in Patients with COVID-19

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Abstract

This study reported the efficacy of short-course corticosteroids and convalescent plasma (CP) transfusion in treating five patients with severe COVID-19 disease. Five adults (mean±standard deviation age: 70±9 years) with laboratory-confirmed COVID-19 and severe hypoxemia (PaO_2/FiO_2 [P/F]<100) requiring invasive mechanical ventilation received five days methylprednisolone (40 mg intravenously every 12 hours) and subsequent CP transfusion (250–400 ml). Compared with the baseline, P/F ratios increased by 46% and by 28% after short course corticosteroids and CP transfusion, respectively. Four patients survived. Short-course corticosteroids and CP transfusion may improve hypoxemia in patients with severe COVID-19 disease.

Introduction

COVID-19 is an enveloped single stranded RNA virus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that was first reported in Wuhan, China in December 2019. Since then COVID-19 disease has become a pandemic and spread to over 195 countries, with millions of cases and thousands of deaths worldwide.[1] Several therapeutic agents were proposed, including antiviral agents (e.g., lopinavir-ritonavir, remdesivir), chloroquine/hydroxychloroquine, and Interleukin-6 pathway inhibitors.[2] Currently, there is a lack of definitive evidence of clinical benefits from these therapeutic agents.

Corticosteroids were initially used in hospitalized patients with COVID-19 in China [3]; however, its use remains controversial as it may delay viral clearance and can cause complications.[4] Some experts advocate low-dose corticosteroid use in certain circumstances given the potential benefit of alleviating pulmonary fibrosis.[5] Convalescent plasma (CP) transfusion is another promising treatment for COVID-19 based on prior experiences treating Ebola, Middle East respiratory syndrome coronavirus, SARS-CoV1 and H5N1.[6, 7] CP transfusion has preliminary promising results against SARS-COV-2 in 2 case series.[8, 9] Clinical trials investigating the efficacy of CP are underway. This study aimed to share our clinical experience with corticosteroids and CP transfusion in five critically ill patients with COVID-19.

Methods

This study was conducted by the Infectious Diseases Department at Christus Spohn Hospital, Corpus Christi, Texas, USA, between March 23, 2020, and April 15, 2020. Food and Drug Administration (FDA) approval was obtained to use CP as an experimental therapy and as an emergency indication to treat severe COVID-19 infection. Following FDA approval, the Institutional review board (IRB) approved the study, and informed consent was obtained from the family to use CP.

Patients were eligible for CP transfusion if they met the following criteria: a) severe shortness of breath, respiratory rate > 30/mt, blood oxygen saturations <93%, Lung infiltrates >50%, multi-organ failure along with

confirmed COVID-19 diagnosis using the qualitative reverse transcriptase-polymerase chain reaction (qRT-PCR) (LabCorp Laboratory) on nasopharyngeal secretions; b) bilateral lung infiltrates requiring invasive mechanical ventilation; and c) PaO_2/FiO_2 (P/F) ratio less than 100.

Plasma donors were selected if they were previously diagnosed with laboratory-confirmed COVID-19 with complete resolution of the symptoms for fourteen days with negative result for COVID-19 on qRT-PCR. Appropriate type, screen, and cross-match were performed. Approximately 600 to 800 mL of convalescent plasma was retrieved from each donor. The neutralizing activity of plasma against SARS-CoV-2 was not evaluated in our laboratory. It is assumed that derived plasma has enough antibodies with neutralizing activity. Following the donation, 250 to 400 ml of CP was given to all patients at least once. In addition to CP transfusion, these five patients received 5 days short course of corticosteroids, defined as methylprednisolone 40 mg intravenously every 12 hours for five days. Short course corticosteroids and plasma transfusion were given at different points of the patient's disease course. Data are presented as actual values or mean (Standard deviations). Effect of short course corticosteroids and CP on P/F ratios and magnitude of change in P/F ratios after the treatment of short course corticosteroids and CP transfusion were summarized. Data were analyzed using SPSS v.24 (IBM, Armonk, NY).

Results

Five patients with severe COVID-19 infection who had severe hypoxemia (PaO_2/FiO_2 [P/F]$<$100) requiring invasive mechanical ventilation were admitted to ICU. All were male and with a mean age of 70 ± 9 years. All the patients had one or more co-morbidities. Demographics, co-morbidities, and medical treatments administered during hospitalization are detailed in **Table 1.** All patients received short course methylprednisolone and CP transfusion. The volume of CP transfusion administered in our patients ranged from 250 ml to 400 ml. In the first two patients (patients A and B), CP transfusion was repeated three days after the initial transfusion. CP was started after short course corticosteroids, except in Patient E where short course corticosteroids and CP transfusion were given same day. These treatments and the starting day of the patient's illness are summarized in **Table 1.**

Methylprednisolone treatment preceded CP transfusion. The mean P/F ratio before short course corticosteroids was $82pm14$ and increased to $161pm53$, three days after the treatment. Following CP transfusion, the mean P/F ratio improved from $139pm54$ to $175pm65$. The P/F ratios have increased by 46% and by 28% from finishing the treatment of short course corticosteroids and CP transfusions (**Table 1**). Trends of P/F ratio changes of all patients are shown in **Figure 1.** There were no significant side effects from methylprednisolone and CP transfusion during the hospital stay.

The mean duration of invasive mechanical ventilation was 14 days (range: 4–22 days). Among these five patients, four survived and were successfully extubated within 7 days of starting short course corticosteroids and within five days after CP transfusion. One patient with significant co-morbidities died due to multi-organ failure from secondary infection.

Discussion

This case series delineated the clinical courses of five patients with severe COVID-19 on mechanical ventilation requiring treatment of CP transfusion and short course corticosteroid treatment. Improved oxygenation indicated by the P/F ratio may be correlated with the methylprednisolone and CP transfusion. In our study, we have seen improvement in P/F ratios soon after starting steroids. Patients that started on steroids and CP transfusion earlier had a shorter ventilation course.

Improved P/F ratios after CP treatment seen in this study was consistent with the results of two case-series studies. Shen *et al.* demonstrated that CP transfusion is associated with decreased viral loads and improvement in P/F ratios within 12 days in five patients. Unlike our study, they did not describe the timeline of steroids vs COVID-19 plasma administration, which could have skewed the results of oxygenation improvement, as the study did not differentiate between CP and steroids.[8] Similarly, Duan *et al.* also demonstrated clinical improvement and significant decrease in CRP level and viral loads and an increase in neutralizing antibody in ten patients.[9] The therapeutic effect from CP transfusion against COVID-19 is pathophysiologically plausible. The convalescent plasma collected from recovered patients from an infection contains antibodies that neutralizes the pathogen. Passive transfer of these antibodies from plasma transfusion is hypothesized to prevent infection or reduce the severity of current infection through several mechanisms, including neutralization of infectivity via direct binding with pathogens, antibody-medicated complement activation, and antibody-dependent cellular cytotoxicity.[6, 10]. These hypothetical effects were also observed in other infectious diseases (e.g. Ebola, SARS-CoV).[6, 7] However, one should also note the potentially harmful effects associated with CP transfusion, including transfusion-related infection (e.g. hepatitis C virus) and transfusion-related reactions. The definitive role of CP transfusion in the management of COVID-19 disease is evolving.

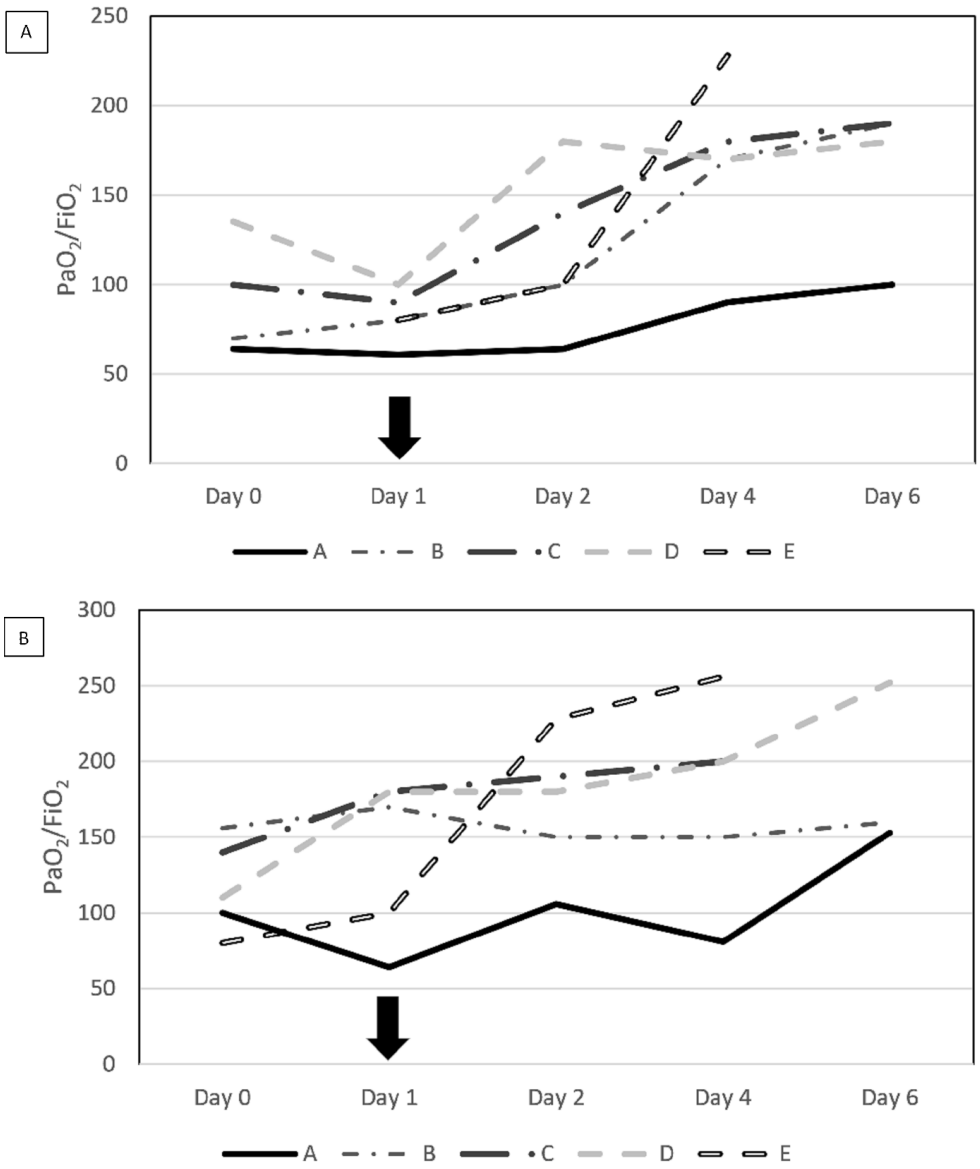

Figure 1. The trend of changes of PaO_2/FiO_2 ratio after initiation of treatment of steroids and convalescent plasma transfusion.
A) Temporal changes in the P/F ratio of patients receiving steroids. Arrow represents the start date of treatment steroids. Patient A expired on day 10 post the initiation of steroids; patient C was extubated on day 8 post the initiation of steroids; patient E was extubated on day 6 post the initiation of steroids. Patient E does not have a baseline PaO_2/FiO_2 ratio before the initiation of treatment of steroids.
B) Temporal changes in the P/F ratio of patients receiving convalescent plasma transfusion. Arrow represents the start date of the convalescent plasma (CP) transfusion. Patient A expired on day 10 post CP transfusion; patient B was extubated on day 8 post CP transfusion; patient C was extubated on day 6 post CP transfusion; patient D was extubated on day 8 post CP transfusion; patient E was extubated on day 6 post CP transfusion.

Table 1. Demographics, clinical characteristics and administered treatment of the patients.

	Patients				
	A	B	C	D	E
Demographics					
Age (years)	58	64	77	80	72
Gender	Male	Male	Male	Male	Male
Weight (kg)	119	105	80	109	102
BMI	37	31	29	33	30
Smoker	No	No	Ex-smoker	No	No
Co-Morbidities	HTN, DM, HIV	HTN	ESRD, DM, CHF	HTN, CAD, CHF	HTN, DM
Treatment					
Mechanical Ventilation	Day 2	Day 5	Day 1	Day 2	Day 1
Tocilizumab	Day 7	Day 6	None	Day 8	Day 1
Methylprednisolone	Day 9	Day 13	Day 1	Day 6	Day 1
Plasma transfusion	Day 12	Day 15	Day 3	Day 13	Day 1
Hydroxychloroquine with azithromycin	Day 2	Day 2	Day 1	Day 5	Day 1
Vitamin C and Zinc	Day 2	Day 2	Day 1	Day 5	Day 1
PaO_2/FiO_2					
Before steroids	61	80	90	100	80
After steroids	90	130	180	180	228
Percentage change after steroids (%)	32	38	50	44	65
Before CP	64	170	180	180	100
After CP	81	150	190	200	256
Percentage change after CP (%)	21	-13	5	10	61
Survival	No	Yes	Yes	Yes	Yes

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; HTN, hypertension.

Corticosteroid use in COVID-19 infection remains controversial. Concerns for delayed viral clearance and increased risk for complications from high-dose corticosteroids have led to WHO and CDC recommendations against its routine use in COVID-19. However, these suggestions were based on observational studies with potential selection bias and uncontrolled confounding that might obscure the clinical benefits of corticosteroids for a subset of patients with advanced acute respiratory distress syndrome (ARDS), such as attenuation of pulmonary fibrosis.[5] The expert panel from China recognized the potential benefits of short course corticosteroids and advocates for its use in COVID-19 infections in certain settings.[7] The claimed benefits of short course corticosteroids were observed in our study. We observed a good response to short course corticosteroids, with improved oxygenation and close to 50% improvement in P/F ratio and a good survival rate of 80% (4/5) among elderly patients with various co-morbidities.

There were several limitations of this study. First, since this was a small case series without controls, it prevented us from accurately ascertaining the definitive therapeutic benefits of short course corticosteroids and CP transfusion independently. Second, it was difficult to differentiate the therapeutic effect of CP transfusion from the remaining effects of short course corticosteroids given prior. Furthermore, it was not feasible to administer both a single agent and observe patients' response before changing therapy in a critical setting. Third, the lack of evidence in both decreasing viral loads and increasing neutralizing antibody titers after the short course corticosteroids and CP transfusion prevented us from confirming their efficacy. An additional limitation was lead-time bias, as the observed therapeutic effects could have resulted from patients' self-recovery, as we have no controls for comparison. Furthermore, the time points of administered treatment differ across patients, which could be another source of heterogeneity. To understand better the timing for CP transfusion and its benefits in COVID-19 patients, we are planning a larger multicenter study with coordination of various centers in the USA.

In summary, short course corticosteroids and convalescent plasma transfusion may improve oxygenation in patients with severe COVID-19 infections. Well-designed studies with adequate statistical power will shed more light on the benefits of short course corticosteroids and CP in patients with COVID-19 infections.

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