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Coronavirus Pandemic

Evaluating convalescent plasma therapy in severe COVID-19: a retrospective cohort study

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Abstract

Introduction: Convalescent plasma (CP) therapy is a form of passive immunization which has been used as a treatment for coronavirus disease 2019 (COVID-19). This study aims to evaluate the efficacy and safety of CP therapy in patients with severe COVID-19.

Methodology: In this retrospective cohort study, 50 patients with severe COVID-19 treated with CP at Shahid Beheshti Hospital, Kashan, in 2019 were evaluated. Eligible plasma donors were COVID-19 survivors with high IgG levels and no comorbidities. Clinical and laboratory parameters, including vital signs, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and white blood cell (WBC) levels, were measured before and after CP therapy at specified intervals including 24 h and 48 h post-therapy.

Results: The average age of the patients was 55.96 years, and 46% had comorbidities. No adverse effects from CP therapy were reported. Significant associations were observed between baseline ESR levels and factors such as age, comorbidities, hypertension history, and intubation status. However, there was no significant correlation between the outcomes of WBC, ESR, and CRP levels and the IgG levels in recipients.

Conclusions: CP therapy appears to be a safe and potentially effective treatment for severe COVID-19, especially in patients with certain baseline characteristics. These findings add valuable insights into the management of severe COVID-19 cases, although further research is needed to fully understand the implications and optimize treatment protocols.

Key words: COVID-19; CP therapy; immunization.

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Introduction

The coronavirus disease (COVID-19) pandemic continues to affect every aspect of life. As of March 2023, COVID-19 had infected more than 670 million people and killed more than 6.8 million people [1]. COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which spread rapidly, and initially there was little understanding of the virus and its associated respiratory infection; and no confirmed treatment guideline was available [1]. Throughout the pandemic, researchers extensively investigated various strategies for managing COVID-19. Besides the development of novel drugs and vaccines, researchers also explored the potential of pre-existing interventions such as convalescent plasma (CP) therapy.

CP therapy is a passive immunization method with a long history and is used in the management of respiratory diseases [2]. The technique is supported by its theoretical background and studies on patients with severe acute respiratory syndrome (SARS) infection [3,4]. The Food and Drug Administration (FDA) of the US has granted an emergency use authorization (EUA) for the use of CP therapy in patients with COVID-19 [5]. CP therapy fortifies the immune system of critically ill patients passively, through transfusing antibody-rich plasma from recently recovered patients [6]. In the past, this method showed positive efficacy in the management of various infections caused by viruses including influenza viruses A, flaviviruses, respiratory beta-coronaviruses, and Ebola virus [7]. Although the exact mechanism of the therapeutic effects of CP therapy remains unclear, antibody-induced cellular cytotoxicity, complement activation, and viral neutralization have been suggested as its mechanism of action [8].

CP therapy has been extensively studied in COVID-19 with a particular focus on its effects on mortality. Reports on the effect of CP therapy on the mortality rate of patients with COVID-19 is inconsistent; and has been reported in various meta-analysis studies as effective, associated with a 13% reduced risk of mortality [9], or statistically ineffective [10]. This incoherency may arise from different follow-up duration, time of CP administration, and the types of studies included. However, researchers have focused less on the direct effects of CP therapy on the severity of infection with regard to clinical and laboratory characteristics.

We continue to observe severe COVID-19 cases, particularly in individuals with comorbidities. At the same time, there is lack of information on the exact influence of CP therapy on the severity of infection. In this study, we aimed to evaluate the efficacy of CP therapy in patients with severe COVID-19, focusing specifically on clinical and laboratory outcomes. This evaluation is particularly crucial given the ongoing challenges in managing severe cases of COVID-19, especially among patients with comorbidities. By assessing both clinical symptoms and laboratory findings, we hoped to provide a comprehensive analysis of the effectiveness of CP therapy. This could potentially contribute to the development of more effective treatment protocols for severely ill COVID-19 patients.

Methodology

In this retrospective cohort study, documented data of the patients with severe COVID-19, who were referred to Shahid Beheshti Hospital in Kashan in 2019, and were treated with CP, were analyzed. The severity of the condition was evaluated based on clinical and laboratory findings, and lung computed tomography (CT) scans.

The plasma was taken from 100 voluntary patients with positive COVID-19 polymerase chain reaction (PCR, by nasal swab method) and without any comorbid diseases. These patients were free from SARS-CoV-2-related symptoms for a minimum period of four weeks. In order to confirm that the donors were free of COVID-19 at the time of blood donation, all the patients were tested with the COVID-19 antigen test. In addition, prior to plasma donation, all donors were tested for the IgG antibody level (IgG > 10 g/L), blood group, and other infection-related parameters. Those with IgM concentration of 1:10 and lower, and those with IgG concentration of 1:1000 and higher, were selected for plasma donation. The donated plasmas were categorized into 4 grades based on the level of IgG: 10–19, 20–29, 30–39, and > 40 g/L. Six-hundred mL plasma of each patient was taken at the dialysis center of Shahid Beheshti Hospital and sent to the blood bank. Multi-Component System Plus (MCS+) and Plasma Collection System 2 (PCS2) (Haemonetics®, Boston, Massachusetts, USA) plasmapheresis devices were used in this hospital. During plasmapheresis, the patients were monitored closely for any symptoms of hypotension and citrate-induced complications.

Inclusion and exclusion criteria

The patients with positive COVID-19 real time reverse transcriptase polymerase chain reaction (RT-PCR) test with loss of consciousness, COVID-19 related encephalitis, lung involvement over 50% shown on spiral chest CT scan, persistent fever for > 5 days, blood oxygen saturation less than 92%, or respiratory rate > 30, were selected for receiving CP therapy. A volume of 200 cc of the donated plasma was infused under sterile conditions through a microtube to the patients within 4 hours.

Patients with a history of prior allergic reaction to citrate were excluded. In addition, in case of any severe complication during plasma therapy, the intervention was ceased.

Patient assessment and data collection

Vitals signs, comprising blood pressure, respiratory rate, blood oxygen saturation, heart rate, and temperature of the patients were evaluated before CP therapy; and at 12 hours, 24 hours, and 48 hours after CP therapy. In addition, the levels of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and white blood cells (WBC) were measured at three distinct times: before CP therapy; and at 24 hours, and 48 hours after CP therapy.

Ethics statement

The study protocol was approved by the research ethics committee of Kashan University of Medical Sciences (approval date: March 10, 2021, ethics committee reference number: IR.KAUMS.REC.1399.053), and this study was performed in compliance with the Declaration of Helsinki and its later amendments.

Statistical analysis

The data were analyzed using IBM SPSS ver. 27 (IBM Corp., Armonk, NY, USA). The categorical variables were expressed as proportions and frequencies. Kolmogorov-Smirnov test was applied to

Table 1. Patients' characteristics.

Variable	Frequency/mean ± SD (minimum and maximum)
Gender	
Female	24 (48%)
Male	26 (52%)
Age (years)	55.96 ± 15.72 (23–87)
Comorbidity	
No	27 (54%)
Yes	
Diabetes	12 (52.2%)
CVDs	6 (26.1%)
HTN	20 (87%)
Pulmonary disease	3 (13%)
Renal diseases	2 (8.7%)
Intubation at admission	12 (24%)
Interval time from the onset of signs to receiving CP	13.82 ± 4.73 days
< 2 weeks	27 (54%)
> 2 weeks	23 (46%)
Plasma IgG antibody level	34.86 ± 17.42 (11–70.46)
1st grade (10–19 g/L)	17 (34%)
2nd grade (20–29 g/L)	5 (10%)
3rd grade (30–49 g/L)	10 (20%)
4th grade (> 40 g/L)	18 (36%)
LOS	18.90 ± 9.69 (6–42) days
Outcome	
Recovery	7 (14%)
Semi-recovery	26 (52%)
Death	17 (34%)

CP, Convalescent plasma; CVD, cardiovascular disease; HTN, hypertension; LOS, Length of stay in hospital.

test the normality distribution. The quantitative variables with normal distribution were summarized as mean ± standard deviation (SD). The Chi-square test was used to explore the impacts of categorical independent variables. The mean values were compared between two groups using the independent t-test, as well as non-parametric tests such as the Mann-Whitney U-test. Pearson or Spearman correlation coefficient was applied to determine the association between two variables. *p* values less than 0.05 were considered statistically significant.

Results

Clinical features

The medical records of the 50 patients with COVID-19 who were treated with CP therapy in Shahid Beheshti Hospital in 2019 were analyzed. The mean age of the patients was 55.96 ± 15.72 years, ranging from 23 to 87 years (Table 1). Twenty-three patients (46%) had comorbidities, including diabetes, cardiovascular diseases (CVDs), hypertension (HTN), respiratory disorders, and renal issues. At the time of CP therapy, 12 patients were intubated. During the treatment, none of the patients experienced adverse effects of CP therapy including allergic and immune-mediated reactions, fluid overload, and transfusion-related acute lung injury.

Associations between baseline characteristics and biomarker levels

The overall mean of ESR levels in the three evaluated time points were significantly associated with age ($r = 0.301$, $p < 0.05$), comorbidity ($p < 0.05$), history of hypertension ($p < 0.05$), and intubation at the time of admission ($p < 0.01$). On the other hand, the mean levels of CRP were significantly higher in patients who were intubated at the time of CP therapy ($p < 0.05$).

Clinical and laboratory findings

Among the vital signs, only peripheral oxygen saturation (SPO_2) was significantly enhanced 48 hours after CP therapy compared to the pre-CP therapy conditions ($p < 0.05$; Table 2). Regarding the inflammatory biomarkers, WBC significantly increased, and ESR and CRP significantly decreased after CP therapy (Table 3 and Figure 1). In addition, the WBC, ESR, and CRP mean outcomes were not significantly associated with the different IgG grade donors (WBC $p > 0.05$, ESR $p > 0.05$, and CRP $p < 0.05$).

Table 2. Vital signs of the patients before and after CP therapy.

Variable	Before CP therapy	After CP therapy			*p* value
		12 hours	24 hours	48 hours	
SBP (mmHg)	120.28 ± 16.55	124.30 ± 16.84	125.48 ± 14.95	119.60 ± 14.79	0.106
Heart rate (bpm)	85.98 ± 16.55	88.19 ± 76.95	86.64 ± 15.80	83.44 ± 14.36	0.074
Respiratory rate (/min)	21.80 ± 6.80	21.18 ± 4.06	20.24 ± 2.76	20.68 ± 3.88	0.219
Temperature (°C)	36.81 ± 0.53	36.55 ± 2.04	36.87 ± 0.41	36.78 ± 0.39	0.383
SpO_2 (%)	84.98 ± 9.44	86.35 ± 8.10	86.75 ± 8.04	87.69 ± 8.70	0.030*

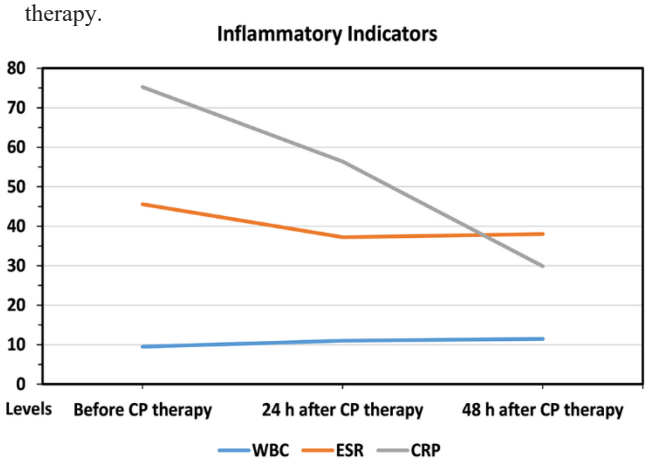
Independent t test was used to compare the values of before CP therapy and after 48 hours of CP therapy; *, significant at 0.05 level. CP, Convalescent plasma; SBP, systolic blood pressure, SpO_2, oxygen saturation.

Table 3. Comparison of laboratory findings before and after CP therapy.

Variable	Before CP therapy	After CP therapy		*p* value
		24 hours	48 hours	
WBC	9.50 ± 4.20[a]	11.00 ± 3.96	11.48 ± 5.38	0.016*
ESR	45.58 ± 26.83[b]	37.20 ± 26.01	38.00 ± 33.10	0.078
CRP	75.26 ± 70.86	56.40 ± 80.78	29.86 ± 54.29[c]	0.000*

*, significant at 0.05 level; [a], significant difference between before and 24 hours ($p = 0.002$) and 48 hours ($p = 0.011$) after CP; [b], significant difference between before and 24 hours after CP ($p = 0.017$); [c], significant difference between 48 hours after CP and before and 24 hours after CP ($p < 0.001$). CP, Convalescent plasma; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell.

Figure 1. Trend of inflammatory factors before and after CP therapy.



ESR and CRP significantly decreased within the first 24 hours, but only CRP continued its significant reduction for another 24 hours. WBC had a steady significant reduction 48 hours after CP therapy. CP, Convalescent plasma; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell.

Discussion

We investigated the effect of CP therapy on the clinical and laboratory findings of COVID-19, using the medical records of 50 patients with severe COVID-19. Since the level of plasma CRP is positively correlated with the severity of COVID-19 pneumonia [11], CRP level can be a suitable indicator for evaluating the response to the treatment. In this regard, we evaluated the level of CRP, along with WBC and ESR levels, and revealed a significant effect of CP therapy on these parameters. In contrast to the lowering influence of CP therapy on CRP which lasted for 48 hours, the major influences of CP therapy on ESR and WBC levels were limited to mostly the first 24 hours.

Although it has been demonstrated that in non-survivor patients WBC levels significantly increased [12], we have shown a significant increase in WBCs within 24 hours after CP therapy, followed by a plateau condition. In addition, SpO_2 levels significantly increased within 48 hours after CP therapy and patients' need for oxygen supply was reduced, which is in line with the findings of Ghadami *et al*. in severe cases of COVID-19 [13]. Another study revealed that CP therapy can improve SpO_2 levels within three days in patients with moderate COVID-19, while in severe cases it was not effective [14]. In 2021, Kurtz *et al*. compared the laboratory and clinical findings of 41 COVID-19 patients who received CP therapy with a group of 72 patients in standard care. They demonstrated a significant decrease in CRP and a significant increase in the number of lymphocytes in the CP therapy group [15]. While our findings showed a significant increase in SpO_2 levels following CP therapy, this study reported no significant difference in fraction of inspired oxygen to partial pressure of oxygen level (PaO_2) — an indicator of pulmonary shunt fraction compared to standard care [15]. Consistent with our findings, Ghadami *et al.* reported a significant decrease in ESR and CRP levels, but an insignificant increase in WBCs after CP therapy [13]. Similarly, in a study by Malinowska-Moniuszko *et al*., CP therapy significantly decreased CRP and significantly increased blood oxygen saturation, but it had no significant effect on WBC [16].

There are conflicting results on the effect of CP therapy on the prognosis of COVID-19 patients [17, 18], which can be affected by duration of the disease, the level of antibody in the donor plasma, and the severity of the disease. In a recent meta-analysis study by Filippatos *et al*. [19], although patients who received CP therapy had a statistically significantly decreased probability of needing inpatient care than those who received placebo or the standard treatment, it was shown to be not related to increased survival or clinical outcomes. Nonetheless, they demonstrated that CP therapy was strongly associated with better ICU-related outcomes, particularly if administered early.

CP therapy is not devoid of side effects, including allergic reactions, antibody-dependent enhancement, transfusion-associated circulatory overload, and infection transmissions [20]. However, none of the patients in this study experienced any side effects.

This study has some potential limitations. Since this study is reporting nonrandomized and uncontrolled investigation, generalization of the findings has a high risk of biases. Further controlled and randomized studies can overcome this limitation. In addition, the

patients were treated with antiviral drugs and corticosteroid treatments along with the CP therapy, which may have a potential confounding effect on the outcomes.

Conclusions

In this study, we demonstrated a significant effect of CP therapy on inflammatory parameters including CRP, ESR, and WBC. CP therapy significantly decreased the levels of ESR and CRP, and increased WBC levels, indicating its potential to alleviate the severity of the disease, particularly in severe cases.

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Authors' contributions

Study design, RE, MMT, and MS; data collection, MZT and MS; data analysis, MS; manuscript preparation, RE and MZT; supervision, MMT and HRB. All the authors agree with the authorship rules and the final version of this submission.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and are available from the corresponding author upon reasonable request.

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