Efficacy of convalescent plasma therapy in severe COVID-19 patients

Hilal Akay Cizmecioglu [a],*, Mevlut Hakan Goktepe [a], Sinan Demircioglu [b], Atakan Tekinalp [b], Ahmet Cizmecioglu [c], Ali Kursat Tuna [a], Huseyin Ozer [d]

[a] Department of Internal Medicine, Meram Faculty of Medicine, Necmettin Erbakan University, Konya, Turkey
[b] Department of Hematology, Meram Faculty of Medicine, Necmettin Erbakan University, Konya, Turkey
[c] Department of Internal Medicine, Faculty of Medicine, Selcuk University, Konya, Turkey
[d] Department of Cardiology, Meram Faculty of Medicine, Necmettin Erbakan University, Konya, Turkey

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ABSTRACT

Introduction: The use of convalescent plasma (CP) transfusions is very valuable in the current COVID-19 outbreak, given that there are no specific preventive and therapeutic options.
Materials and methods: 50 patients with severe COVID-19 disease treated with convalescent plasma transfusion were included in the study. The efficacy of CP and in which situations it was effective were investigated.
Conclusion: 80 % of the patients recovered, and 20 % died in our study. The mean age of the patients who died was found to be higher than the patients who recovered. CRP, ferritin, D-dimer, neutrophil, MPV, and NLR counts were found to be higher, and lymphocyte and platelet counts were lower in the deceased group after CP. It was determined that patients who received CP within the first five days were hospitalized for a shorter period.
Discussion: Administration of CP transfusion within the first five days in severe COVID-19 patients has been shown to reduce hospital stay length.

1. Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the novel Coronavirus (SARS-CoV-2). It has an insidious onset and high contagion; severe cases can cause death [1]. The pandemic continues to spread rapidly worldwide, causing infection and more than 3 million deaths in more than 141 million people worldwide to date [2].

The spectrum of symptomatic infection varies from mild to critical; most infections are not severe [3,4]. The disease comes out as 81 % mild (none or mild pneumonia),14 % severe (e.g., shortness of breath, hypoxia, or >50 % lung involvement in imaging within 24–48 hours), 5% critical (e.g., respiratory failure, shock, or multiple organ dysfunction). The overall case mortality rate is 2.3 %; death has not been reported among non-critical cases [5].

Various treatments, including lopinavir/ritonavir, favipiravir, remdesivir, hydroxychloroquine or chloroquine, azithromycin, anakinra, tocilizumab and plasmapheresis are under investigation for the treatment of COVID-19 [6–8]. However, there are no specific antiviral agents approved for COVID-19 to date [9]. Although many vaccines types have been used, CP therapy is still used effectively in the acute treatment of the COVID-19 disease. It has become an urgent need to look for an alternative strategy for the treatment of COVID-19, especially among severe patients, since effective vaccines and specific antiviral drugs are not available.

To treat with convalescent plasma (CP), blood plasma is collected from a recovered patient and transfused to a symptomatic patient. CP therapy, which is classic adaptive immunotherapy, has been used to prevent and treat many infectious diseases for over a century [10]. The efficacy of CP was tested in the Spanish flu outbreak in 1915–1917 [11], severe acute respiratory syndrome (SARS) in 2003 [12], influenza A (H1N1) [13] in 2009, avian flu A (H5N1) [14], and Ebola [15].

Several small observational studies published during the COVID-19 outbreak suggest that CP is part of an effective treatment strategy for severe disease patients [16–19]. CP therapy was first applied to five patients with severe disease in the COVID-19 outbreak in Wuhan [17]. Four of the five patients had improved inflammatory biomarkers, and all patients had improved pulmonary lesions based on computed tomography (CT) scan.

It was observed in the study conducted by Duan et al. that clinical outcomes improved in 10 patients receiving a single CP transfusion, and no side effects were reported [16].

Subsequently, similar results were reported in two small case studies involving five and six patients [18,19]. Salazar et al. showed that CP therapy was a safe treatment option in their study, where they applied CP therapy to 25 patients [20]. The Food and Drug Administration of the United States (FDA) suggested that CP administration may have a clinical effect on the treatment of COVID-19 [21]. It has even been emphasized that CP administration is as protective as its therapeutic effect [22]. Here, plasma application containing high titer antibodies obtained from individuals recovered from COVID-19 disease is the easiest and most practical way to develop passive immunity [23]. The main definition for protection in CP treatment is virus neutralization provided by the obtained antibodies [24].

This study thus investigates the efficacy of CP in the treatment of severe and critical patients diagnosed with COVID-19, pneumonia, who were followed up in the internal medicine clinic of the university hospital.

2. Materials and methods

The patients diagnosed with COVID-19 between April 1, 2020, and September 1, 2020, in the university hospital's internal medicine clinic and received CP therapy were included in the study. The files of the patients suitable for the study were scanned, and their data were obtained. The effects of CP on length of hospital stay, need for intensive care, recovery, and mortality were examined. In addition, changes in laboratory values before and after CP administration and the effect of early and late CP administration on clinical practice were investigated. Permission was obtained from the local ethics committee for the study.

2.1. Patient selection

CP was administered to patients over 18 years of age, with the presence of SARS-CoV-2 by PCR at the time of diagnosis, with severe pneumonia, with the progression of the disease while using or after using hydroxychloroquine and favipiravir (CT findings consistent with COVID-19, >50 % increase in lung infiltration within 24−48 hours, respiratory rate >30/minute, PaO2/FiO2 < 300 mmHg, oxygen saturation <90 % despite nasal oxygen support of 5 L/minute and above, partial oxygen pressure <70 mmHg despite nasal oxygen support of <5 L/minute and above, development of mechanical ventilation requirement, need for vasopressor), and patients without IgA deficiency.

Severe pneumonia was defined as tachypnea (≥30/min), SpO2 level <90 % in room air, and bilateral diffuse pneumonia findings on chest radiography or tomography [25].

2.2. Donor selection

CP donors were selected according to the CP guide of the Ministry of Health of Turkey [26]. Men or women between the ages of 18–60 years were diagnosed with COVID-19 by PCR test, 28 days after recovery, who were positive for SARS-CoV-2 antibodies, who had not previously undergone blood product transfusion, or who did not have birth/-miscarriage were considered donors. Two units of 200 mL CP were collected by plasmapheresis from donors suitable for whole blood donation. Plasmas to be administered immediately were irradiated and transfused to the patient. Plasmas that were not used within 6 h after collection were frozen and stored at −18 to −25 °C.

2.3. Statistical analysis

Statistical analysis of our study was performed using IBM SPSS ver 22.0 software. The Kolmogorov-Smirnov test evaluated the distribution analysis of continuous numerical variables. The pre-and post-plasma

values of numerical variables were analyzed by Matched t-test and Wilcoxon test; intergroup comparisons were analyzed by Independent Sample t-test and Mann-Whitney U test Categorical variables were expressed as a percentage (%), and their comparisons were made by the chi-square test. The correlation coefficient (rho) was defined as the predictive values as weak between 0.00−0.24, moderate between 0.25−0.49, strong between 0.50−0.74, and very strong between 0.75−1.00. Multivariate analysis was performed according to Logistic regression modeling using the Backward selection method. Cases that were considered to be clinically significant and with p < 0.25 significance in univariate analysis were included in the model. In addition, one of the parameters with strong correlations between the cases was included. The results were evaluated as significant in a 95 % confidence interval (p < 0.05).

3. Results

Fifty patients with pneumonia and who were diagnosed with severe and critical COVID-19 were included in the study. 32 (64 %) of the patients were male, 18 (36 %) were female, and the mean age was 57.9±14.9 years. 25 (50 %) of the patients had type O blood, 20 (40 %) had type A blood, 1 (2%) had type B blood, and 4 (8%) had type AB blood. Forty patients (80 %) had at least one other disease or disorder. The mean time of CP administration was 4.5 days (2−12), the mean number of CP administered was 2 (1−3), and the mean duration of hospital stay was 14.7±6.8 days. 11 patients (22 %) needed intensive care, whereas 8 (16 %) patients were intubated. 40 (80 %) of the patients recovered, 10 (20 %) died, and no adverse effects were observed during and after CP administration.

The mean age of the patients who died was higher and statistically significant in our study. The number of lymphocytes examined before CP administration was significantly lower in the recovering group than the deceased group (p = 0.026). On the other hand, CRP, ferritin, D-dimer, neutrophil, and neutrophil-lymphocyte (NLR) counts were significantly higher in the deceased group after CP (p = 0.001, p = 0.033, p = 0.008, and p < 0.001, respectively). In addition, significantly deeper lymphopenia, lower platelet count, and MPV increase were detected in patients

Table 1
Comparison of recovered and deceased patients before and after CP.

	Patients recovering n = 40 (%80)	Exitus n = 10 (%20)	P value
Age	57,9 ± 14,9	75,8 ± 7,9	<0,001[a]
Fibrinogen (CPB)	567,1 ± 153,4	483,5 ± 174	0,188
Fibrinogen (CPA)	508,9 ± 153,6	388,8 ± 183,7	0,080
CRP (CPB)	82,4 (6,2−302,7)	71 (15−302,7)	0,396
CRP(CPA)	30,6 (3,0−158,5)	96,7 (50,6−343,7)	0,001[b]
Ferritin (CPB)	546,4 (34,8−11210)	948,7 (196,7−5631)	0,104
Ferritin (CPA)	575,2 (51−8470)	1218 (273−5609)	0,033[b]
D-dimer (CPB)	285 (45−4056)	275(254−4879)	0,221
D-dimer (CPA)	417,5 (63−4579)	2115,5 (222−16000)	0,008[b]
Neutrophil (CPB)	5650 ± 3260	5850 ± 2110	0,054
Neutrophil (CPA)	5740 ± 2850	10020 ± 4080	<0,001[a]
Lymphocyte (CPB)	130(110−2640)	430(260−2060)	0,026[b]
Lymphocyte (CPA)	1140 ± 680	610 ± 330	<0,001[a]
NLR (CPB)	3,9 (1,3−53)	13,2 (2,3−23,3)	0,051
NLR (CPA)	3,5 (0,8−147,3)	18,6 (7,4−42,3)	<0,001[b]
PLT (CPB) (x10³/mm³)	240 ± 89	190 ± 98	0,182
PLT (CPA) (x10³/mm³)	340 ± 122	208 ± 113	0,003[a]
MPV (CPB)	10,3 ± 1,2	10,8 ± 0,9	0,210
MPV (CPA)	9,9 ± 1,0	11,0 ± 0,9	0,003[b]
Hospitalization day	14,7 ± 6,5	14,7 ± 8,1	0,984

CP; Convalescent plasma, CPB; Convalescent plasma before, CPA; Convalescent plasma after, CRP; C-reactive protein, PLT; Platelet count, NLR; Neutrophil to lymphocyte ratio, MPV; Mean platelet volume.

[a] Independent samples T-test.
[b] MannWhitney U test.

who died after the administration of CP (p < 0.001, p = 00.3, p = 0.003, respectively) (Table 1).

In comparing the parameters in terms of gender, neutrophils results (μL) before plasma treatment were found to be significantly higher in males (6400 ± 3390 vs 4420 ± 1760, p = 0.009). There was no significant difference between the remaining laboratory parameters and the length of hospitalization (p > 0.05). Although death rates were higher in males than in females, it was not statistically significant (25 % vs 118% p = 0.3).

In blood group evaluations, pre-plasma fibrinogen was significantly higher in patients with 0 blood groups than other groups (602 ± 151 vs 498 ± 153, p = 0.019). When the O blood group was compared with the blood type A (n = 20), which was the second in the frequency, both pre-treatment and post-treatment fibrinogen levels were higher in the O groups (602 ± 151 vs 492 ± 155, p:0.022 and 533 ± 152 vs 410 ± 137, p:0.008). No differences were ascertained in other parameters. The mortality rates were 12 % in the O groups only and 28 % in the other group patients; however, no significant statistical result was obtained.

According to logistic regression models, there was no statistically significant effect of the amount of CP used for the recovery of the patients, the day of CP administration, the presence of other diseases, age, gender, blood type, and intubation status. However, a moderate positive correlation was found between the number of comorbidities and length of hospitalization (rho:0,34, p:0.014).

Factors affecting survival were evaluated according to Cox Regression modeling. Those thought to be clinically significant and with p < 0.25 significance were included in the single analysis among the model variables. In addition, one of the parameters with a strong correlation was included. No significant effect on survival was detected.

The median was calculated to be 4.5 on the day convalescent plasma therapy was initiated after hospitalization. Accordingly, it was determined that the duration of hospital stay of the patients who received plasma within the first five days was significantly shorter (average 12.6 ± 4.9 days to 18.4 ± 8.2 days, p = 0.013) when the patients who received CP within the first five days and the patients who received CP after five days were compared (Table 2). In addition, in patients given plasma for the first five days, although there was no statistical significance, the recovery rate was higher, and the need for intubation was lower (Table 3).

Table 2
Comparison via CP application day.

	Within the first 5 days n = 32 (%64)	After the 5th day n = 18 (%36)	P value
Fibrinogen (CPB)	529,2 ± 149,4	588,1 ± 173,8	0,213
Fibrinogen (CPA)	490,8 ± 181,6	474,5 ± 135,9	0,741
CRP (CPB)	100 (6,1−271)	71 (15−302,7)	0,968
CRP (CPA)	43 (3,1−343,7)	46,4 (3−296)	0,952
Ferritin (CPB)	546,4 (78,7−6293)	726 (34,8−11210)	0,952
Ferritin (CPA)	585,9 (64,5−5609)	607,4 (51−8470)	0,716
D-dimer (CPB)	275,5 (45−4056)	493 (105−4579)	0,206
D-dimer (CPA)	421 (63−15430)	637,5 (89−16000)	0,479
Neutrophil (CPB)	6050 ± 3020	5160 ± 3550	0,835
Neutrophil (CPA)	6290 ± 1960	5070 ± 3560	0,795
Lymphocyte (CPB)	920 (260−2300)	865 (110−2640)	0,992
Lymphocyte (CPA)	1170 ± 700	1230 ± 700	0,780
NLR (CPB)	3,9 (1,6−27,6)	7,3 (1,3−53)	0,671
NLR (CPA)	4,2 (0,8−42,3)	6,6 (2−147,3)	0,571
PLT (CPB) (x10^3/mm^3)	221 ± 87	248 ± 99	0,334
PLT (CPA) (x10^3/mm^3)	295 ± 134	347 ± 120	0,183
MPV (CPB)	10,3 ± 1,2	10,6 ± 1,0	0,351
MPV (CPA)	10,1 ± 1,1	10,2 ± 1,1	0,753
Hospitalization day	12,6 ± 4,9	18,4 ± 8,2	0,013*

CP; Convalescent plasma, CPB; Convalescent plasma before, CPA; Convalescent plasma after, CRP; C-reactive protein, PLT; Platelet count, NLR; Neutrophil to lymphocyte ratio, MPV; Mean platelet volume.
* Independent samples T-test.

Table 3
Clinical comparison via CP application day.

	Within the first 5 days	After the 5th day	P value
Intensive Care Need			
Positive, n (%)	8 (25)	3 (16,7)	0,724*
Negative, n (%)	24 (75)	15 (83,3)	
Entubation (n)			
Positive, n (%)	6 (8,8)	2 (11,1)	0,694*
Negative, n (%)	26 (81,2)	16 (88,9)	
After treatment			
Recovery, n (%)	26 (81,2)	14 (77,8)	1,0*
Dead, n (%)	6 (18,8)	4 (22,2)	

CP; Convalescent plasma.
* Fisher's Exact chi-square test.

4. Discussion

Eighty percentage of the patients recovered, and 20 % died in our study. The mean age of the patients who died was found to be higher than the patients who recovered. CRP, ferritin, D-dimer, neutrophil, MPV, and NLR counts were found to be higher and lymphocyte, and platelet counts were found to be lower in the deceased group after CP. It was determined that patients who received CP within the first five days were hospitalized for a shorter period.

Moreover, in our study, a moderate positive correlation was found between the number of comorbidities and the length of hospitalization (rho:0,34, p:0.014). A meta-analysis conducted in China also points out that mortality increases significantly with the presence of comorbidity [27]. However, the low sample size in our study limited our chance to interpret comorbidities one by one.

A retrospective study of 39 patients showed that CP was potentially effective against COVID-19 and increased survival [28]. Clinical improvement was investigated up to 28 days after CP transfusion, and 52 % of plasma recipients and 43.1 % of the control group were shown to improve in a randomized controlled clinical trial. However, no significant difference was observed in 28-day mortality [29]. Two hundred thirty-five patients received two units of CP and best standard care at 24 -h intervals, whereas 229 patients in the control group received the best standard care in a randomized controlled trial consisting of 464 COVID-19 patients in India. CP therapy was not associated with a decrease in progression to severe COVID-19 or all-cause deaths due to of this study [30, Placid trial]. Chai et al. evaluated 19 studies, 2 of which were randomized controlled trials. In this systemic review, they reported that they could not reach a definitive conclusion about whether CP was beneficial for patients hospitalized due to COVID-19 [31]. No significant difference was found between CP and control groups in terms of mortality risk or discharge rate in a study conducted with 64 patients receiving CP and 177 patients receiving standard treatment [32]. Definitive results on CP's efficacy have still not been obtained in the literature as in these studies. It seems ineffective in some studies, whereas it seems useful in some studies. The main reasons for this are that the patients' clinical characteristics, their disease status, the drugs they used, the time of CP administration, and the neutralizing antibody levels contained in CP were different.

Treatment timing is considered an essential factor associated with CP therapy's effectiveness [33]. Viremia peaks in the first week of infection in most viral diseases. Patients usually develop a primary immune response on days 10–14, followed by viral clearance [34,35]. Better clinical outcomes were observed in PCR positive and seronegative patients for Coronavirus during plasma infusion and who received CP before the 14th day in a study consisting of eighty patients [35]. The 7-day mortality rate was 8.7 % in patients who received CP within the first three days, and 11.9 % on the 4th day and later in a study with a very high number of cases. Similar results were found in 30-day

mortality rates (21.6 % and 26.7 %) [36]. There was a need for more mechanical ventilators in the CP group after 20 days in a study conducted in Turkey [37]. Our study showed that administering CP within the first five days in support of these data shortened hospitalization.

Our study found the mortality rate as 12 % in the O blood group and 28 % in the other blood groups. The lack of statistical significance of these values was attributed to the number of patients. In the literature, mortality and intubation rates were higher in individuals with AB and O blood groups [38]. In this context, our results are inconsistent with the literature. In addition, we concluded that the mortality rate in male patients is higher than in the female. The results were not statistically significant; however, they were consistent with the literature [39,40]. Our study revealed that the mortality rates in elderly patients were statistically significantly higher than the young patients. This result is compatible with many studies and meta-analyses in the literature [40].

Unexpectedly, lymphocytosis was found in both the deceased and surviving patient groups before and after CP treatment. We interpreted this situation as relative lymphocytosis. We concluded that the decrease in neutrophil counts displayed a relatively high lymphocyte count. Relative lymphocytosis and similar data have been reported in COVID-19 patients in the literature [41].

Our study had some limitations. The first is that the number of patients is low. Our number of patients was low because patients with similar clinical conditions with pneumonia and who received the same treatment were included in the study. The second is that our study was conducted retrospectively. The third is that there was no control group. CP is given to all severe cases in our hospital. Therefore, a control group was not included in the study. The fourth is that neutralizing antibody levels in CPs could not be measured. Antibodies against SARS-CoV-2 were demonstrated prior to all CPs. The level of neutralizing antibodies could not be studied due to technical impossibilities.

As a result, uncertainties continue in the treatment of COVID-19. The effectiveness of CP therapy is controversial in the literature. Early administration of CP seems to be beneficial at least on the hospitalization length, as presented in our study. There is a need for randomized controlled trials on this subject.

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CRediT authorship contribution statement

Hilal Akay Cizmecioglu: Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing. **Mevlut Hakan Goktepe:** Conceptualization, Methodology, Writing - original draft. **Sinan Demircioglu:** Conceptualization, Investigation, Writing - original draft. **Atakan Tekinalp:** Software, Formal analysis. **Ahmet Cizmecioglu:** Software, Investigation, Writing - review & editing. **Ali Kursat Tuna:** Data curation, Resources. **Huseyin Ozer:** Resources.

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