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Comparison of hematological and biochemical parameters in COVID-19 pneumonia patients before and after convalescent plasma (CP) treatment

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Ethics Committee Approval
The study was approved by the Health Science Ethics Committee of Muğla Sıtkı Koçman University (14.04.2021- 61) and the Ministry of Health (2021-02-01T_15-_26_43).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Convalescent plasma (CP) therapy, which includes processing and administering antibody-rich plasma from recovered patients to sick patients, is used for passive immunity in COVID-19 pneumonia patients in addition to antivirals and antibiotics. This study aimed to assess whether CP treatment significantly affects hyperviscosity and COVID-19 prognosis-related blood parameters.
Methods: This study was a single-center retrospective cohort study. Ninety-seven patients with COVID-19 polymerase chain reaction (PCR)-positive results and pneumonia observed on thoracic computed tomography (CT) were included. Patients' ferritin, d-dimer, C-reactive protein (CRP), and complete blood count levels before and after CP administration were compared.
Results: Ferritin, d-dimer, white blood cell (WBC), neutrophil, and plateletcrit (PCT) levels and the platelet distribution width (PDW) were significantly higher and there was a significant decrease in the CRP level after CP treatment compared to before CP ($P < 0.05$). Ferritin, d-dimer, and CRP values measured after CP were higher in deceased patients than in survivors ($P = 0.001$, $P = 0.007$, and $P < 0.001$, respectively)
Conclusion: Ferritin, d-dimer, WBC, and neutrophil levels, which we expected to decrease on the basis of the COVID-19 prognosis, unfortunately increased, and only CRP levels decreased. However, we found that these increases were more pronounced in patients who died. Considering these prognostic factors, the findings of our study suggest that CP treatment has no effect on the COVID-19 disease course and may lead to a worse prognosis.

Keywords: COVID-19, Convalescent plasma, CRP, d-dimer, WBC

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Introduction

The Coronavirus Disease 2019 (COVID-19), which first appeared in China, was declared a pandemic by the World Health Organization (WHO) in March 2020 [1]. As drug research continues for COVID-19, passive immunotherapies have come to the forefront in treatment. Convalescent plasma (CP) therapy, which was previously used for passive immunity in treating severe acute respiratory syndrome coronavirus (SARS-CoV), has also been used to treat COVID-19 [2]. It was first used in China in February 2020 for a patient with COVID-19 [3]. Shortly thereafter, the United States Food and Drug Administration (FDA) approved an emergency use recommendation in March 2020 [4].

CP is plasma collected from individuals who have recovered from a particular infection and have developed antibodies. In addition to neutralizing antibodies, other proteins such as anti-inflammatory cytokines, coagulation factors, natural antibodies, defensins, pentraxins, and other unidentified proteins are obtained from donors during apheresis [5].

In research on the use of CP in COVID-19, Shen et al. reported that the clinical condition in five critically ill patients improved after receiving CP and undergoing extracorporeal membrane oxygenation (ECMO) and mechanical ventilation [6]. However, a randomized controlled trial by Li et al. showed that CP in addition to the standard treatment did not make a significant difference in mortality [7]. Many studies on COVID-19 and CP have been published, but there are few studies on hyperviscosity associated with COVID-19 and CP. In the study conducted on six patients with COVID-19-related hyperviscosity, there was a decrease in the d-dimer, C-reactive protein (CRP), and fibrinogen levels [8].

This study aimed to observe whether CP treatment significantly affects hyperviscosity and COVID-19 prognosis-related blood parameters.

Materials and methods

Study design and settings

This retrospective cohort study was approved by the Health Science Ethics Committee of Muğla Sıtkı Koçman University (14.04.2021- 61) and the Ministry of Health (2021-02-01T_15-_26_43). The study was performed in the COVID-19 intensive care unit and COVID-19 services in a secondary care hospital in Muğla, Turkey. Between April 2020 and February 2021, patients with SARS-CoV-2 polymerase chain reaction (PCR)-positive results and pneumonia who received at least one unit of CP were included in the study. The following information was collected and examined: patients' demographic information, comorbidities, blood groups, the number of plasma units administered, ferritin, d-dimer, CRP, white blood cell (WBC) count, lymphocyte levels, neutrophil count, mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT) before and after plasma.

Participant selection

Sample size calculations were performed using G*Power 3.0 (Franz Faul, University of Kiel, Germany) before starting the study. A study with 80% statistical power that allowed 5% Type I error required at least 78 participants.

Patients over 18 years of age who were hospitalized with COVID-19 pneumonia between April 2020 and February 2021 were included in the study. The COVID-19 pneumonia diagnosis was made based on COVID-19-positive results by PCR and the presence of ground-glass opacities on a thorax computed tomography (CT). Patients with incomplete file information were excluded from the study. Pediatric patients, pregnant people, and patients who were immunosuppressed or who had IgA deficiency were excluded from the study. The in-hospital treatment protocol was as follows: all patients received supportive treatment including oxygen and fluid therapy and, if necessary, vasopressor treatment. All patients received favipiravir (2×1600 mg loading and 1200 mg/day, orally), ciprofloxacin (400 mg/day parenterally), methylprednisolone (80 mg/day parenterally), and enoxaparin (4000–6000 IU twice a day).

Measurements and Outcomes

Patients with COVID-19 pneumonia, who received CP with a plasma therapy indication of at least one 200-mL unit at that time, and who were followed-up were included in the study. Only the first CP treatment was considered in patients who received more than one plasma unit, and at least 24-hours were required between two plasma treatments. Ferritin, d-dimer, CRP, WBC, lymphocyte, neutrophil, MPV, PDW, and PCT tests were analyzed before and after CP. The duration of hospitalization, the hospitalization day when the plasma was administered, and their discharge status were also examined.

Statistical analysis

Descriptive statistics were tabulated as the mean (standard deviation) or median, minimum, and maximum depending on the distribution of continuous variables in the data summaries obtained from the study. Categorical variables were summarized as the number and percentage. The normality test of numerical variables was assessed using the Shapiro–Wilk, Kolmogorov–Smirnov, and Anderson–Darling tests. On the basis of the patient's discharge, the Mann–Whitney U test was used for numerical variable comparisons when the variables were not normally distributed. To compare some blood parameters before and after CP, a paired *t*-test was used when numerical variables showed a normal distribution, and the Wilcoxon test was used when the data were not normally distributed. Statistical analyzes were performed using Jamovi Project (Version 1.6.13.0, Sydney, Australia) and JASP (Version 0.14.1.0, JASP Team, Amsterdam, the Netherlands). The level of significance in the statistical analysis was accepted as 0.05.

Results

Ninety-seven patients were included in the study, with a mean age of 53.9 (13.7) years. Fifty-seven patients were men and 40 patients were women. The most common blood group was A+ (37 patients, 38.1%). The most common comorbid disease was hypertension (32 patients; 33%). The mean length of the hospital stay was 13.1 (6.5) days. Thirty-eight (39.2%) patients were treated in the intensive care unit. The median number of plasma units administered to patients was 1. Twenty (20.6%) patients were discharged from the hospital (Table 1).

The ferritin level after CP treatment was higher than before CP treatment (367.6 vs. 266.5, $P < 0.001$). The d-dimer

level was higher after CP than before CP (0.4 vs. 0.3, $P = 0.043$). The CRP level was lower after CP than before CP (13.5 vs. 32.7, $P = 0.035$). The WBC count was higher after CP than before CP (10,300 vs. 5900, $P = 0.001$). The neutrophil level was higher after CP than before CP (8100 vs. 3600, $P < 0.001$). PDW was higher after CP than before CP (0.3 vs. 0.2, $P = 0.011$) (Table 2).

Table 1: Demographic and clinical characteristics of the patients with COVID-19 patients given plasma

	Mean (SD) / n (%)	Median (Min- Max)
Age	53.9 (13.7)	52.0 (20.0- 83.0)
Gender		
Male	57 (58.8)	
Female	40 (41.2)	
Blood type		
0-	6 (6.2)	
0+	30 (30.9)	
A+	37 (38.1)	
AB+	7 (7.2)	
B+	17 (17.5)	
Diabetes Mellitus	21 (21.6)	
Hypertension	32 (33.0)	
Coronary Artery Disease	10 (10.3)	
Chronic Obstructive Pulmonary Disease	4 (4.1)	
Asthma	1 (1.0)	
Chronic Kidney Disease	2 (2.1)	
Cancer	2 (2.1)	
Stroke	1 (1.0)	
Length of hospital stay	13.1 (6.5)	11.0 (5.0- 34.0)
Intensive care unit admission	38 (39.2)	
Unit of plasma		1.0 (1.0- 4.0)
Day of plasma administration		4.0 (1.0- 24.0)
Exitus		
None	77 (79.4)	
Yes	20 (20.6)	

SD: Standard deviation

Table 2: Changes in laboratory parameters of patients before and after plasma treatment

Variable	Before	After	*P*-value
Ferritin (ng/ml)	266.5 (5.6- 2000.0)	367.6 (9.4- 4309.0)	<0.001**
D dimer (ng/ml)	0.3 (0.0- 10.2)	0.4 (0.1- 13.8)	0.043**
CRP (mg/l)	32.7 (0.8- 395.9)	13.5 (0.2- 222.8)	0.035**
WBC ($x10^3$)	5.9 (1.2- 56.7)	10.3 (4.5- 25.3)	<0.001**
Lymphocyte ($x10^3$)	1.3 (0.4- 8.4)	1.1 (0.2- 13.6)	0.952**
Neutrophil ($x10^3$)	3.6 (0.2- 18.9)	8.1 (0.6- 23.5)	<0.001**
MPV (fl)	10.6 (1.5)	10.8 (1.0)	0.075*
PDW (fl)	12.7 (2.4)	13.1 (2.5)	0.011*
PCT (%)	0.2 (0.1- 0.7)	0.3 (0.1- 0.6)	<0.001**

*: Independent Samples T-Test, **: Mann Whitney U Test, CRP: C-reactive protein, WBC: White blood cell, MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit

The ferritin level before and after CP in non-survivors was higher than in survivors ($P = 0.010$ and $P = 0.001$, respectively). In patients who died, the d-dimer level after CP was higher than in patients who survived (1.4 vs. 0.4, $P = 0.007$). The CRP level after CP in patients who died was higher than in patients who survived (76.1 vs. 9.1, $P < 0.001$). WBC counts were higher in patients who died before and after CP than in those who survived ($P = 0.002$ and $P < 0.001$, respectively). In patients who died, the lymphocyte count after CP was lower than in patients who survived (900 vs. 1200, $P = 0.019$). Neutrophil levels were higher in patients who died before CP and after CP than in patients who survived ($P = 0.004$ and $P < 0.001$, respectively). The MPV level in patients who died was higher in patients who survived (11.2 vs. 10.5, $P = 0.003$) (Table 3).

While the CRP level increased after CP (54.4% increase) in non-survivors, it decreased (69.6% decrease) in survivors ($P < 0.001$). The change in the MPV level was also different in patients who died and in those who survived ($P = 0.035$) (Table 4).

Table 3: Comparison of laboratory parameters between the patient who survivor and non-survivor after plasma administration

	Survivor (n = 77)	Non-survivor (n = 20)	*P*-value
Ferritin (ng/ml)			
Before plasma	214.0 (5.6- 2000.0)	483.0 (60.6- 2000.0)	0.010
After plasma	320.5 (9.4- 4309.0)	846.8 (134.2- 2000.0)	0.001
D dimer (ng/ml)			
Before plasma	0.3 (0.0- 7.9)	0.5 (0.1- 10.2)	0.154
After plasma	0.4 (0.1- 13.8)	1.4 (0.1- 10.0)	0.007
CRP (mg/l)			
Before plasma	27.7 (0.8- 186.9)	51.4 (3.6- 395.9)	0.09
After plasma	9.1 (0.2- 176.1)	76.1 (17.7- 222.8)	<0.001
WBC ($x10^3$)			
Before plasma	5.4 (1.2- 56.7)	7.7 (3.5- 20.1)	0.002
After plasma	9.4 (4.5- 24.4)	14.1 (6.8- 25.3)	<0.001
Lymphocyte ($x10^3$)			
Before plasma	1.4 (0.4- 3.4)	1.1 (0.5- 8.4)	0.397
After plasma	1.2 (0.2- 8.7)	0.9 (0.3- 13.6)	0.019
Neutrophil ($x10^3$)			
Before plasma	3.5 (0.2- 13.5)	5.0 (1.6- 18.9)	0.004
After plasma	7.9 (2.7- 20.7)	12.7 (0.6- 23.5)	<0.001
MPV (fl)			
Before plasma	10.4 (0.2- 12.4)	11.0 (9.3- 14.2)	0.101
After plasma	10.5 (8.7- 12.9)	11.2 (9.9- 13.3)	0.003
PDW (fl)			
Before plasma	12.3 (9.7- 18.4)	12.8 (10.3- 22.9)	0.081
After plasma	12.4 (8.9- 18.0)	13.8 (11.4- 22.2)	0.007
PCT (%)			
Before plasma	0.2 (0.1- 0.7)	0.2 (0.2- 0.5)	0.169
After plasma	0.3 (0.1- 0.6)	0.3 (0.2- 0.5)	0.895

Mann Whitney U test. The variable that does not show normal distribution is shown as [min-max]. CRP: C-reactive protein, WBC: White blood cell, MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit

Table 4: Comparison of percentages of change before and after plasma administration in survivor and non-survivor patients

	Survivor (n = 77)	Non-survivor (n = 20)	*P*-value
Δ Ferritin	-26.7 (-1101.4- 62.7)	-54.4 (-498.7- 4.8)	0.126
Δ D dimer	-30.8 (-3629.7- 84.6)	-72.7 (-7584.6- 74.2)	0.355
Δ CRP	69.6 (-1283.5- 99.1)	-54.4 (-1104.1- 56.4)	<0.001
Δ WBC	-70.7 (-1740.3- 73.0)	-64.5 (-210.7- 30.2)	0.880
Δ Lymphocyte	-2.1 (-328.6- 80.8)	24.5 (-78.5- 80.2)	0.130
Δ Neutrophil	-113.7 (-8525.0- 66.0)	-92.5 (-323.5- 63.0)	0.950
Δ MPV	0.0 (-5300.0- 15.9)	-5,9 (-18.8- 7.1)	0.035
Δ PDW	-3.6 (-34.1- 22.0)	-7,7 (-72.1- 8.1)	0.143
Δ PCT	-38.4 (-176.5- 73.1)	-29,4 (-200.0- 43.4)	0.275

Mann Whitney U test. The variable that does not show normal distribution is shown as [min-max]. CRP: C-reactive protein, WBC: White blood cell, MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit

Discussion

When laboratory differences before and after CP were examined in patients who received CP due to COVID-19 pneumonia, ferritin, WBC, neutrophil, PDW, and PCT values increased statistically after CP. Considering the differences in blood parameters according to the survival and death status of the patients who received plasma, the ferritin level in patients who died was higher. After CP, d-dimer and CRP were more elevated in patients who died than in those who survived.

Although the efficacy of CP in COVID-19 pathogenesis is controversial, its rapid availability has allowed its emergency use in epidemics such as Spanish flu, SARS-CoV, West Nile virus, and recently Ebola [9-11].

In this study, we wanted to investigate the effect of CP on blood parameters. A recent study showed that platelet indices were not useful parameters to determine the prognosis of COVID-19 patients [12]. In our research, we found that blood parameters did not improve after CP treatment.

In a study by Abolghasemi et al. [13] that included 115 COVID-19 pneumonia patients who received CP, the most common comorbidities were hypertension and diabetes mellitus, which is consistent with the results of our study.

A study conducted in our country evaluated patients who received CP, and it showed that patients with blood group A received CP most often and had a high follow-up rate in the

intensive care unit [14]. Similarly, in our study, blood group A was the most common blood group among patients who received CP [14]. This may be because COVID-19 patients with blood group A have a high risk and a poor prognosis [15, 16] and plasma is given to patients with a poor prognosis.

In a randomized study, no improvement was observed in the clinical condition after 28 days in patients with COVID-19 who received CP, but there was a decrease in mortality [17]. In the PlasmAR Study, which is a double-blind study comparing CP and placebo that compared 228 CP patients and 105 placebo patients with COVID-19 pneumonia, there was no significant difference in the clinical status and mortality between the CP group and the placebo group [18]. Similarly, the CONCOR-1 study was a multi-center, open-label, randomized trial that showed no decrease in 30-day mortality in hospitalized CP patients with COVID-19 [19]. In a randomized study by Li et al. [7], 103 patients with severe or life-threatening COVID-19 received CP in addition to standard treatment, but CP treatment did not show a clinical improvement within 28 days. In our study, 77 of the patients treated with CP recovered, while 20 died. However, it is not possible to draw a firm conclusion on the effect of CP treatment on mortality because no comparison was made with a control group.

While other studies showed that CP does not have a significant positive contribution to mortality and clinical status, its effects on hematological and biochemical parameters show that lymphocyte counts increased and CRP level decreased after ten patients with severe COVID-19 received CP [20]. In a clinical study conducted by Huang et al. [3], a decrease in WBC and CRP values and an increase in lymphocyte values were reported after CP. In contrast to their study, we observed an increase in WBC levels after CP, and we did not observe a significant increase in the lymphocyte count. Similarly, a significant decrease in the CRP level was observed. These differences may be because they evaluated the results of 14 patients who benefited from CP, and we evaluated patients who died and who did not benefit from CP treatment.

Truong et al. [8] investigated six patients with COVID-19-associated hyperviscosity and showed a decrease in the d-dimer level after CP, but we found an increase in d-dimer after CP in our study. This difference may be because the six patients studied had a disease associated with hyperviscosity, and this was not the case in our patients.

Another study conducted with 26 intensive care unit patients in our country showed no difference in CRP levels between patients who died and those who survived, whereas, in our study, the CRP level was initially high and then increased in patients who died [21]. The reason for this difference may be the high number of patients and because only patients in the intensive care unit were included in the other study while patients in both the intensive care unit and the pandemic clinic were included in our study.

When the patients who died and survived in our study were compared, d-dimer, CRP, MPV, and PDW values were similar in both groups before CP, but they showed a significant increase in patients who died after CP. Additionally, ferritin, WBC, and neutrophil values were significantly higher in deceased patients compared to survivors before CP, but increased more after CP. In our study, only the lymphocyte value was found to be significantly lower in patients who died after CP. Although these data were not calculated for every patient, they suggest that the neutrophil-to-lymphocyte ratio increased in patients who died. Atlas et al. investigated COVID-19 patients who were followed-up in the intensive care unit, and they showed that an increase in the neutrophil-to-lymphocyte ratio, d-dimer, and CRP levels was associated with an adverse outcome [22]. In our study, an increase in neutrophils, d-dimer, and CRP and a decrease in lymphocyte levels were observed after CP in patients who died, which is consistent with Atlas et al.'s results. Thus, CP treatment may not have a positive effect on patient prognosis. Although CP treatment was initially recommended in the COVID-19 treatment guideline from the Ministry of Health of the Republic of Turkey, the recommendation for use was later removed from the guideline [23]. This is consistent with the results of our study.

Limitation

There are some limitations to our study. First, at the time of the study, there were no clearly defined CP indications. Second, the time elapsed between the disease diagnosis and CP administration was not similar. Additionally, including patients who did not receive CP treatment in studies of patients who received CP would have provided more explanatory results. The inability to measure the anti-SARS-CoV-2 antibody levels in our patients is a critical limitation of our study. Furthermore, the retrospective nature of the study is a limitation of our research.

Conclusion

In patients with COVID-19 pneumonia who received CP and were followed-up, values such as ferritin, d-dimer, WBC, neutrophil, PDW, and PCT values, which were expected to decrease based on the COVID-19 prognosis, unfortunately increased after CP. Only the CRP level decreased, which reflected positively on the prognosis. When patients who died were compared with the survivors, increased ferritin, d-dimer, CRP, WBC, neutrophil, MPV, and PDW values and a decreased lymphocyte count were evident in those who died. Because the neutrophil-to-lymphocyte ratio, d-dimer, and CRP values were associated with a negative outcome, administering CP was suggested to have no effect on the COVID-19 prognosis, and it may lead to worsening of the prognosis. However, additional studies are needed to clearly evaluate the effect of CP therapy on the prognostic factors for COVID-19.

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