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Convalescent plasma therapy in patients with COVID-19

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ABSTRACT

Introduction: Passive antibody therapy has been used to immunize vulnerable people against infectious agents. In this study, we aim to investigate the efficacy of convalescent plasma (CP) in the treatment of severe and critically ill patients diagnosed with COVID-19.

Method: The data of severe or critically ill COVID-19 patients who received anti-SARS-CoV-2 antibody-containing CP along with the antiviral treatment (n = 888) and an age-gender, comorbidity, and other COVID-19 treatments matched severe or critically ill COVID-19 patients at 1:1 ratio (n = 888) were analyzed retrospectively.

Results: Duration in the intensive care unit (ICU), the rate of mechanical ventilation (MV) support and vasopressor support were lower in CP group compared with the control group (p = 0.001, p = 0.02, p = 0.001, respectively). The case fatality rate (CFR) was 24.7 % in the CP group, and it was 27.7 % in the control group. Administration of CP 20 days after the COVID-19 diagnosis or COVID-19 related symptoms were associated with a higher rate of MV support compared with the first 3 interval groups (≤5 days, 6–10 days, 11–15 days) (p=0.001).

Conclusion: CP therapy seems to be effective for a better course of COVID-19 in severe and critically ill patients.

Abbreviations: CP, convalescent plasma; CFR, case fatality rate; ICU, intensive care unit; MV, mechanical ventilation.

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1. Introduction

At the end of 2019, a novel Coronavirus (CoV) started to cause similar clinical findings to Severe Acute Respiratory Syndrome (SARS) Cov-1 (SARS-CoV-1) and the Middle East Respiratory Syndrome (MERS) CoV (MERS-CoV) [1–3]. This novel CoV was named as SARS-CoV-2. SARS-CoV-2 has spread rapidly across the globe [4]. Researchers are investigating a variety of therapeutics including lopinavir/ritonavir, remdesivir, hydroxychloroquine or chloroquine and azithromycin [5–7]. However, as of 27 August 2020, globally, the disease has already caused more than 800.000 deaths, reported to World Health Organization (WHO) [8].

Passive antibody therapy and active vaccination are used to immunize vulnerable people against infectious agents. Vaccination needs initiation of an immune response that takes time to develop. On the other hand, in passive antibody therapy, antibodies against a particular agent are administered and it is the only way to immunize vulnerable people in a short time [9,10].

It has been suggested that the administration of convalescent plasma (CP) may be effective in COVID-19 [11]. There are also some clinical trials that are still ongoing about the use of CP in SARS-CoV-2 infected patients and also for the prophylactic purpose in order to prevent especially high risk people including health care providers and elderly people with comorbidities. However, there are some issues that need to be clearly determined to optimize the CP treatment, such as the efficacy and safety of the treatment, optimum volume of CP, the number of the transfusions, the interval between transfusions, the optimum titer of neutralizing antibody, efficacy of pathogen inactivation processes, optimal donation time and intervals etc [9]. In this regard, during the current pandemic, we need large scale, prospective, randomized studies about CP treatment as there have been no licensed therapeutics against SARS-COV-2. In this study, we aim to investigate the efficacy of CP in the treatment of severe and critically ill patients diagnosed with COVID-19 in Turkey.

2. Materials and methods

2.1. Patients

As of 22 May 2020, there have been 154.500 laboratory confirmed COVID-19 patients in Turkey. From the Republic of Turkey, Ministry of Health database, severe or critically ill COVID-19 patients who received anti-SARS-CoV-2 antibody-containing CP along with the antiviral treatment (n = 888) were selected and included in the study. An age-gender, comorbidity, and other COVID-19 treatments (favipravir, lopinavir + ritonavir, hydroxychloroquine, high dose vitamin C, azithromycin) matched severe or critically ill COVID-19 patients at 1:1 ratio (n = 888) were used for comparison. In total, the data of laboratory-confirmed 1776 COVID-19 patients were analyzed retrospectively.

2.2. Disease severity

Presence of dyspnea, hypoxemia ($SaO2 \leq 93$ %), $PaO2 / FiO2 < 300$ and > 50 % progression in lung infiltrates within 24–48 hours was defined as severe COVID-19. Presence of respiratory failure, septic shock and/or multiple organ dysfunctions was defined as critical COVID-19 [11].

2.3. Collection of convalescent plasma

Therapeutic apheresis centers licensed by the Republic of Turkey, Ministry of Health and Turkish Red Crescent carried out activities for obtaining CP from donors. Donor assessments were performed according to the Republic of Turkey, Ministry of Health, and Donor Eligibility Criteria for COVID-19 Convalescent Plasma [12]. The criteria were as the follows: (a) Evidence of COVID-19 documented by a laboratory test

Table 1
Demographic and clinical characteristics of the groups.

Demographic and clinical characteristics	CP group (n = 888)	Control group (n = 888)	p value
Gender			
Male	616 (69.4 %)	634 (71.4 %)	0.35
Female	272 (30.6 %)	254 (28.6 %)	
Age (median)	60 (19–96)	61 (21–91)	0.31
Comorbidity			
Diabetes Mellitus	302 (34 %)	297 (33.4 %)	0.84
Hypertension	490 (55.2 %)	512 (57.7 %)	0.25
Cardiovascular diseases	251 (28.3 %)	271 (31.5 %)	0.28
Respiratory system diseases	229 (25.8 %)	211 (23.8 %)	0.34
Chronic renal diseases	56 (6.3 %)	74 (8.4 %)	0.10
Chronic liver diseases	18 (%2)	21 (2.4 %)	0.62
Malignancy	35 (3.9 %)	27 (3.1 %)	0.31
Antiviral treatment			
Favipiravir	730 (82.2 %)	706 (79.5 %)	0.15
Lopinavir + ritonavir	66 (7.4 %)	86 (9.7 %)	0.90
Hydroxychloroquine	779 (87.7 %)	791 (89.1 %)	0.37
Azithromycin	643 (72.4 %)	622 (70 %)	0.27

CP, convalescent plasma; ICU, intensive care unit.

Table 2
Outcomes in CP group and control group.

	CP group (n = 888)	Control group (n = 888)	p-value
Duration in hospital	17 (0–74)	18 (0–77)	0.860
Duration in ICU	9 (0–68)	12 (0–74)	0.001
MV rate	438 (49.3 %)	488 (55 %)	0.02
Vasopressor Support			
Yes	219 (24.7 %)	305 (34.3 %)	0.001
No	669 (75.3 %)	583 (65.7 %)	
CFR	219 (24.7 %)	246 (27.7 %)	0.150

CFR, case fatality rate; CP, convalescent plasma; ICU, intensive care unit; MV, mechanical ventilation.

(b) Resolution of symptoms at least 14 days prior to donation and negative results for COVID-19. In addition to nucleic acid amplification tests, all donors were serologically screened for HBsAg, anti-HCV, anti HIV 1–2 and anti-Syphilis antibody. All CP donors were screened for the presence of anti-SARS-CoV-2 Ig G antibodies but the titer of neutralizing antibody was not routinely performed. 200–600 milliliter (mL) CP was collected by apheresis. Plasma components were labeled using the ISBT128 coding system and stored at or below −18/25 degrees in storage cabinets. Pathogen inactivation processes were not routinely performed. Anti-SARS-CoV-2 Ig G antibodies were not routinely screened in COVID-19 patients before CP treatment.

2.4. Statistical analysis

Data analysis was performed using IBM SPSS v26 software. Descriptive statistics were used to summarize data. Variables assessed for normal distribution with the Kolmogorov Smirnov test. Differences between categorical variables were analyzed with the Chi-Square test and post hoc Bonferroni correction was used when the group comparisons were higher than 2; and numeric variables were compared with the Mann-Whitney *U* test

3. Results

In total, there were 1776 severe and critically ill, laboratory confirmed COVID-19 patients in the study. The demographic and clinical characteristics of the groups are given in Table 1. The duration of hospital stay was similar between groups (p = 0.860). Duration in the intensive care unit (ICU), the rate of mechanical ventilation (MV) support and vasopressor support were lower in CP group compared with the control group (p = 0.001, p = 0.02, p = 0.001, respectively) (Table 2).

Table 3
The effect of interval between COVID-19 symptoms and CP transfusion on the outcome.

	Group 1 ≤5 days [n = 69-(11.3 %)]	Group 2 6–10 days [n = 159- (25.9 %)]	Group 3 11–15 days [n = 171-(27.9 %)]	Group 4 16–20 days [n = 87- (14.2 %)]	Group 5 >20 days [n = 127- (20.7 %)]	p-value
CFR (n) (%)	23 (33.3 %)	36 (22.6 %)	46 (26.9 %)	24 (27.6 %)	41 (32.3 %)	0.340
MV rate* (n) (%)	35 (50.7 %)	85 (53.5 %)	100 (58.5 %)	60 (69 %)	103 (81.1 %)	0.001
VP Support (n) (%)	18 (26.1 %)	47 (29.6 %)	47 (27.5 %)	26 (29.9 %)	40 (31.5 %)	0.920

CFR, case fatality rate; CP, convalescent plasma; MV, mechanical ventilation; VP, vasopressor. Data is not available in 275 patients.

Table 4
The effect of interval between COVID-19 diagnosis and CP transfusion on the outcome.

	Group 1 ≤5 days [n = 138–21.7%)]	Group 2 6–10 days [n = 219 (34.5 %)]	Group 3 11–15 days [n = 145 (22.8 %)]	Group 4 16–20 days [n = 73 (11.5 %)]	Group 5 >20 days [n = 60 (9.5 %)]	p-value
CFR (n)(%)	48 (34.8 %)	55 (25.1 %)	37 (25.5 %)	18 (24.7 %)	19 (31.7 %)	0.26
MV rate* (n) (%)	81 (58.7 %)	117 (53.4 %)	88 (60.7 %)	56 (76.7 %)	53 (88.3 %)	0.001
VP Support (n) (%)	48 (34.8 %)	57 (26 %)	37 (25.5 %)	27 (37 %)	19 (31.7 %)	0.18

CFR, case fatality rate; CP, convalescent plasma; MV, mechanical ventilation; VP, vasopressor. Data is not available in 253 patients.

The case fatality rate (CFR) was 24.7 % in the CP group, and it was 27.7 % in the control group. Although the CFR was lower in CP group, this difference did not achieve a statistical significance ($p = 0.150$). Administration of CP 20 days after the COVID-19 diagnosis or COVID-19 related symptoms were associated with a higher rate of MV support compared with the first 3 interval groups (≤5 days, 6–10 days, 11–15 days) ($p = 0.001$) (Tables 3 and 4).

CP treatment was applied to severe and critically ill COVID-19 patients. Therefore, patients who received CP treatment in the first 5 days of their COVID-19 diagnosis may represent a rapidly worsening clinical course as they became severely or critically ill in the first 5 days of the disease. The slightly higher CFR in patients who received CP treatment in the first 5 days of their diagnosis compared with other groups (6–10 days, 11–15 days, >20 days) may be attributed to rapidly worsening clinical course of COVID-19 in this group.

4. Discussion

SARS-CoV-2 is the third CoV that caused infection in humans. Therefore, experience in the use of CP against a human CoV was first obtained during SARS COV-1 and MERS-CoV outbreaks. In a previous study conducted during SARS COV-1 outbreak, 19 patients with SARS COV-1 infection who were refractory to ribavirin and 1.5 g of pulsed methylprednisolone, received 200–400 mL CP. At the same study, 21 patients who were refractory to ribavirin and 1.5 g of pulsed methylprednisolone, were administered additional dose of pulsed methylprednisolone. They observed that discharge rate up to 22 days from the hospital was 77.8 % in patients who received CP, while it was 23 % in patients who were administered additional dose of pulsed methylprednisolone. In their study, none of the patients who received CP died, on the other hand, 23.8 % of the patients who received steroids died [13]. In a study from Taiwan, 3 patients with SARS-COV-1 infection who were refractory to steroids, ribavirin, intravenous immunoglobulin, and protease inhibitors received 500 mL CP. All of them recovered after CP treatment [14]. Cheng et al. demonstrated a higher day-22 discharge rate among patients with SARS-COV-1 infection who received CP before day 14 of illness [15]. Treatment with CP was also reported in three patients with MERS. In this study, 3 patients received CP, and only two of them had neutralizing activity. Donor plasma with a neutralizing activity titer of 1:80 demonstrated meaningful serological response, while that with a neutralizing activity titer of 1:40 did not [16].

There are also several reports about the use of CP in SARS-CoV-2 pandemic. In a study, 400 mL CP was given to 5 critically ill COVID-19 patients who were refractory to steroid and antiviral therapy. All the donors had anti-SARS-CoV-2–antibody titer higher than 1:1000; and neutralizing antibody titer greater than 40. Two weeks after CP transfusion, 3 patients extubated; 3 of the 5 patients (60 %) were discharged from the hospital, and the other two patients were stable after 37 days [17]. In another study, 10 critically ill COVID-19 patients were treated with 200 mL CP that had a neutralized antibody titer of at least 1:640, in addition to antiviral therapy and steroid. After CP transfusion, clinical symptoms improved rapidly in 3 days and on radiological examination lung lesions regressed within 7 days [18]. Also Zheng et al. reported 6 critically ill COVID-19 patients who received CP; researchers compared the CFR in patients who received CP with a control group of 11 critically ill COVID-19 patients who did not receive CP; they did not find any statistically significant difference [19]. Additionally, Zhang et al. reported 4 critically ill patients who received CP ranging from day 11 to day 18 of admission, and all patients recovered [20].

There are only a limited number of large-scale studies that evaluated the effect of CP in COVID-19 patients. In the study conducted by Joyner et al., 5000 hospitalized severe or critically ill COVID-19 patients received CP. The overall 7 day mortality rate was 14.9 % [21]. In a multicenter randomized study from China, 52 severe and life-threatening COVID-19 patients who received CP in addition to standard treatment were compared with a control group including 51 severe and critically ill COVID-19 patients who received standard treatment alone. They observed clinical improvement within 28 days in 51.9 % of the CP group and in 43.1 % of the control group. They did not find any significant difference between groups regarding the 28-day mortality [22].

Our study was conducted to demonstrate the outcome of severe and critically ill COVID-19 patients who received CP. The main findings of the current study were : (i) hospital stay was similar between groups; (ii) duration in ICU was shorter in CP group compared with the control group; (iii) the rate of MV support was significantly lower in CP group compared with the control group; (iv) the rate of vasopressor support was significantly lower in CP group compared with the control group; (v) the CFR was 24.7 % in CP group, and it was 27.7 % in the control group; (vi) >20 days interval between CP transfusion and COVID-19 diagnosis or COVID-19 related symptoms were associated with a higher rate of MV support.

There are some limitations of our study. First, the patients received some therapeutics such as antiviral agents before CP transfusion. As a result, the possibility that these agents contributed to the recovery of patients could not be ruled out. Second, patients in the study received CP transfusion up to 600 mL, optimal dose for the disease could not be scheduled. Third, the study had a retrospective design. The superior side of our study is that we used an age-gender, comorbidity, and other

COVID-19 treatments (favipravir, lopinavir + ritonavir, hydroxychloroquine, high dose vitamin C, azithromycin) matched group for comparison because in most of the previous studies, control groups used for comparison were not composed of age-gender, comorbidity, and other COVID-19 treatments matched patients.

In conclusion, SARS-CoV-2 has spread rapidly across the globe. During the current pandemic, thousands of patients need ICU support; therefore, until the active vaccination against SARS-CoV-2, approaches that reduce the need for ICU support have great importance. Therefore, CP therapy seems to be effective for a better course of COVID-19 in severe and critically ill patients. CP transfusion can reduce the ICU stay, and the rate of MV support, and also can ease the workload of healthcare professionals, especially when transfused within the first 20 days of COVID-19. Finally, the optimal dose and transfusion time, as well as the safety and efficacy of CP transfusion, need to be investigated in detail with well-designed randomized clinical studies.

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Declaration of Competing Interest

All authors declare that they do not have any conflict of interest that could inappropriately influence the present study.

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