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Original Article

The impact of convalescent (Immune) plasma treatment on the clinical course of COVID-19

Sude H Aktimur[1], Cagatay E Ozturk[2], Abdulcelil Kayabas[3], Selim Gorgun[4], Ahmet Sen[2]

[1]Department of Internal Medicine and Heamatology, University of Health Sciences, Samsun Training & Research Hospital, Samsun, Turkey; [2]Department of Anesthesiology and Reanimation, University of Health Sciences, Samsun Training & Research Hospital, Samsun, Turkey; [3]Department of Internal Medicine, University of Health Sciences, Samsun Training & Research Hospital, Samsun, Turkey; [4]Department of Microbiology, University of Health Sciences, Samsun Training & Research Hospital, Samsun, Turkey

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Abstract: COVID-19 is a major pandemic currently spreading worldwide. There is no specific method for its treatment. The aim of this study was to evaluate the effect of convalescent plasma in the treatment of COVID-19 and to compare it with patients not receiving plasma therapy. Between March-May 2020, 21 patients diagnosed with COVID-19 who received convalescent plasma therapy were investigated. For the control group, data of patients with similar clinical characteristics who did not receive plasma therapy were recorded. Plasma receivers received convalescent plasma treatment from donors infected and healed with the SARS-Cov-2 virus. Demographic data, laboratory parameters, oxygen saturations and SOFA scores were evaluated. In addition, the clinical outcomes on mortality and length of hospital stay were compared. The mean age of patients was 64.90±19.12. After convalescent plasma treatment, a significant decrease was detected in the respiratory rate, leukocyte count, ferritin, CRP, procalcitonin, lactate and sedimentation values. It was found that patients who received plasma demonstrated shorter length of hospital stay (P = 0.045), less worsened oxygen status/ex status (P = 0.043) compared to control patients. This study demonstrates that convalescent plasma therapy is well tolerated and can improve the clinical and laboratory results by neutralizing viremia in COVID-19 patients. Further larger prospective studies are needed to better assess the impact of convalescent plasma.

Keywords: COVID-19, SARS-CoV-2, convalescent plasma, mortality, oxygenation

Introduction

A serious illness that may lead to acute pneumonia associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) originating in Wuhan, China, has rapidly spread worldwide from December 2019 [1]. In March 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) as a pandemic. The first COVID-19 patient was seen in March 11, and as of May 1, a total of 122 392 confirmed cases and 3258 deaths had been reported in Turkey.

Many repurposed treatments with antiviral activities, such as remdesivir, favipiravir, lopinavir/ritonavir, tocilizumab, hydroxychloroquine, plasma exchange and intravenous immunoglobin were given, but currently, there is no specific treatment or vaccines for COVID-19 are available [2-7]. Immunotherapy with the use of convalescent plasma collected from recovered patients had been applied to improve survival of the patients with previous infectious outbreaks, such as SARS, Middle East respiratory syndrome coronavirus, Ebola virus, HIN1 influenza and H5N1 influenza [8-13]. Previous experience with the transfusion of convalescent plasma in these infectious diseases was effective [11, 14]. In diseases where specific vaccines or other pharmaceutical treatments are not available, immunization has been shown immediately by pathogen-specific antibodies contained in plasma obtained from clinically and serologically recovering patients [15, 16]. Thus, according to these findings the potential benefits of convalescent plasma transfusion in patients infected with SARS-CoV-2 was studied

and the beneficial effects had been showed in limited clinical studies [17-19]. U. S. Food and Drug Administration (FDA) has given approval for emergency use authorization of the use of convalescent plasma to treat critically ill patients with COVID-19 [20]. The safety of transfusion of convalescent plasma in hospitalized patients with COVID-19 has been demonstrated [21].

Although convalescent plasma is seen as a promising treatment method for COVID-19 disease, the lack of comprehensive large prospective studies yet does not provide sufficient information about the effectiveness of treatment. The aim of this study was to evaluate the effectiveness of convalescent plasma in the treatment of COVID-19 and to examine the factors affecting treatment efficacy.

Materials and methods

This study was conducted at the hematology department, Ministry of Health University, Samsun Training and Research Hospital, Samsun, Turkey, between March-May 2020. The data were analyzed in a retrospective manner. The study was approved by Turkish Ministry of Health (Approval number: GOKA/2020/6/11). This study was conducted in accordance with the Helsinki Declaration ethical principles and Good Clinical Practice quality standards. All patients or patients' relatives gave written informed consent.

Patients

Laboratory confirmed critically ill COVID-19 patients, who had severe pneumonia with rapid progression to acute respiratory distress syndrome (ARDS) despite antiviral and supportive treatment, PaO_2 (mmHg)/FIO_2 < 300, and currently or had been supported with mechanical ventilation. COVID-19 diagnosis was confirmed using quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) (Bioeksen Co, Ltd) [22], and rapid antibody test. The neutralizing antibody titers of recipients were not tested due to the absence of test kits.

All patients (with and without plasma treatment) received a standard treatment regimen (hydroxycloroquine 2 * 200 mg/day, Azithromycin 1 * 500 mg/day, Oseltamivir 2 * 75 mg/day and Favipiravir 2 * 600 mg/day). The clinical practice of convalescent plasma was applied according to the guidance set forth by the Turkish Health Ministry and Food and Drug Administration [20]. All convalescent plasma transfusion was applied with ABO compatibility for safety. Patients received 1, 2 or 3 consecutive transfusion (per 48 hours) in addition to the antiviral and supportive treatment algorithm of National Treatment Guide of Turkish Ministry of Health for patients with COVID-19 [23].

Eligible patients

According to the Turkish Ministry of Health guide of convalescent plasma application, the patients who had following clinical conditions were accepted as eligible to receive convalescent plasma [24].

- Laboratory confirmed COVID-19.

- COVID-19 compatible computerized tomography findings and bilateral infiltrates (lung infiltrates > 50%).

- > 30/min respiratory rate.

- PaO_2 (mmHg)/FiO_2 < 300.

- < 90% oxygen saturation or < 70 mmHg PaO_2 despite ≥ 5 liter/min nasal oxygen support.

- Need for mechanical ventilation.

- Increased Sequential Organ Failure Assessment (SOFA) score.

- Need for vasopressor to maintain sufficient blood pressure.

- The patients, who were expected to rapidly deteriorate, or who had poor prognostic parameters (who had decreased lymphocyte count; increased CRP, erythrocyte sedimentation rate (ESR), ferritin, lactate dehydrogenase (LDH) and D-dimer).

- Informed consent provided by the patient or healthcare proxy.

Donors

According to the Turkish Ministry of Health guide of convalescent plasma application, all convalescent plasma donations were managed and collected by Turkish Red Crescent Association with written informed consents obtained [24].

Donors were 18 years or older who recovered from COVID-19 disease. All donors had been previously diagnosed with laboratory confirmed COVID-19 and their hospital record about the COVID-19 treatment must be complete, followed and documented. Donors were extensively evaluated clinically by the local doctor to evaluate absolute contraindications to the apheresis procedure. Also, at the time of blood donation, routine tests for hepatitis B virus, hepatitis C virus, HIV, and syphilis must be negative.

- For hospitalized patients, two negative consecutive tests for SARS-CoV-2 must be obtained, and at least 14 days clinically follow-up is mandatory.

- For non-hospitalized patients, a negative test must be obtained before donation and they must be followed minimum 28 days after full clinical recovery.

A 400 mL of convalescent plasma was obtained from each donor by apheresis and the plasma was transfused to appropriate recipients as defined by the national guideline [24]. With appropriate clinical and instrumental monitoring available, 200 ml of plasma was infused over 1 to 2 hours to the patient. Patients were checked every 15 minutes for signs of transfusion-related adverse events/reactions and were monitored after transfusion. When there was no clinical response (O_2 saturation) within 48 hours (day 3), a second dose was administered. A third unit could be administered within 48 hours according to the clinical response (O_2 saturation) status.

Clinical follow-up

In order to evaluate the effectiveness of convalescent plasma treatment, we have performed a propensity-score-matched analysis using the pool of patients diagnosed with COVID-19 between 11 March and 2 May in the same hospital.

Before and after convalescent plasma transfusion following information was recorded for 21 patients: demographic data, days of admission from symptom onset and clinical progress, PaO_2/FiO_2, SOFA score, progress to ARDS, bacterial pneumonia and multiple organ dysfunction syndrome; laboratory data, including white blood cell count (WBC), lymphocyte count, liver and kidney function, C-reactive protein (CRP), Procalcitonin, lactate, chest imaging studies; ongoing treatments, including antiviral or other supportive treatments and mechanical ventilation.

In order to evaluate the length of hospital stay of control patients and plasma recipients, "0 day" was defined as the day of transfusion for plasma recipients and the corresponding day of hospitalization of control patients.

Sepsis related Organ Failure Assessment Score (SOFA) was developed by the European Society of Intensive Care Medicine in 1996 to identify the degree of organ failure associated with sepsis [25]. However, since its validity was determined in patients with organ dysfunction not related to sepsis, it was renamed as "sequential organ failure assessment". Six organ systems (respiratory, cardiovascular, central nervous system, renal, coagulation and liver) were evaluated between 1 and 4 points, with a total score of 6-24 (**Table 3**). The score is given based on the worst value in the previous 24 hours. If there is no measured value, it is scored according to the closest measured value. Having SOFA score ≥ 3 is defined as organ failure for that system.

Statistical analysis

SPSS 21.0 (IBM, NY, USA) program was used for statistical analysis. The normality of the distribution was evaluated by the Kolmogorov-Smirnov test. Mean and standard deviation values, median and interquartile range and percentages were specified. Evaluation of parameters before and after plasma treatment was done with Wilcoxon test and paired sample t test. ANOVA test was used for evaluation daily changed parameters. Comparison of the data with the matched group was examined with Mann Whitney U test and Chi Square test. Significant p value was < 0.05.

Results

Demographics

In addition to antiviral and supportive treatments, 21 critically ill patients were treated with convalescent plasma. The mean age of patients was 64.90±19.12 years. Convales-

Table 1. Patient characteristics

Characteristics		Patients (n = 21)
Mean Age ± SD		64.90±19.12
Gender (Male/Female)		13/8
Comorbidities	Diabetes Mellitus	5 (23.8%)
	Hypertension	13 (62%)
	COPD	9 (42.8%)
	Cerebrovascular Disease	3 (14.2%)
	Cancer	2 (9.6%)
Comorbidities	0-1	10 (47.6%)
	> 1	11 (52.4%)
Smoking		5 (23.8%)
ACE Inhibitory use		11 (52.4%)
NSAID Use		2 (9.6%)
Mechanical Ventilation (Yes)		10 (47.6%)
Vasopressor Use (Yes)		20 (95.2%)
Multiple Organ Dysfunction Syndrome		9 (42.8%)

ACE: Angiotensin Converting Enzyme, COPD: Chronic Obstructive Pulmonary Disease, NSAID: Non-Steroid Anti-inflammatory Drug.

Table 2. Comparison of parameters before and after plasma treatment

	Before Convalescent Plasma Treatment	After Convalescent Plasma Treatment	*p* Value
Respiratory Rate/min (Median [Range])	40 (35-45)	20 (10-22)	0.001[w]
Hb (Median [Range]) (g/dl)	11.8 (10.3-12.9)	11.5 (11.1-13.5)	0.553[w]
WBC (Median [Range]) (10^9/L)	10 800 (7 250-15 150)	4 650 (4 400-6 125)	0.013[w]
Lymphocyte (Median [Range]) (10^9/L)	600 (450-800)	1 300 (1 200-1 400)	0.074[w]
PLT (Median [Range]) (10^3/µl)	187 (156.5-313.5)	254 (149.75-345.5)	0.093[w]
Ferritin (Mean ± SD) (ng/ml)	1276.76±824.66	29.5±13.98	< 0.001[p]
D-Dimer (Mean ± SD) (µg/ml)	6.69±16.86	0.15±0.23	0.045[p]
Fibrinogen (Median [Range]) (mg/dl)	553 (441-588.5)	249.5 (227.5-376.25)	0.022[w]
CRP (Median [Range]) (mg/lt)	140 (60-165.45)	5 (3.5-11.75)	0.005[w]
Procalcitonin (Mean ± SD) (ng/ml)	1.77±3.15	0.045±0.061	0.003[p]
Lactate (Mean ± SD) (mEq/L)	3.71±0.55	0.78±0.58	< 0.001[p]
Sedimentation (Median [Range]) (mm/hour)	67 (55.5-86.5)	6 (4-25.5)	0.005[w]
SOFA Score (Median [Range])	7 (5-9)	2 (1-3)	0.003[w]
PaO_2 (Median [Range]) (mmHg)	55 (49.5-65.6)	95 (88.5-97)	0.005[w]
sO_2 (Median [Range]) (mmHg)	75.5 (66.3-86.15)	98 (95-98.25)	0.005[w]
PaO_2/FiO_2 (Median [Range]) (mmHg)	150 (125.5-208)	380 (328-402)	0.003[w]

Hb: Hemoglobin, WBC: White Blood Cell, PLT: Platelet, CRP: C-Reactive Protein, SOFA: Sepsis related Organ Failure Assessment. w: wilcoxon test; p: paired sample t-test.

cent plasma up to three times (one, two and three administrations; n = 5, 4, 12, respectively) was administered between 7 to 22 days after admission. More than one comorbidity was present in 52.4% of the patients. About 62% (13/21) of the patients were male. Demographic features are shown in (**Table 1**).

Parameters of patients

After using the convalescent plasma treatment, a significant decrease in the respiratory rate, leukocyte value (count), ferritin, CRP, procalcitonin and sedimentation values was detected. In addition, there was a significant improve-

Table 3. Daily change of PaO_2, sO_2, PAO_2/FiO_2 and SOFA scores

	PaO_2 (mmHg)	sO_2 (mmHg)	PaO_2/FiO_2 (mmHg)	SOFA
1st Day (Median (Range))	66 (61.45-72.55)	75.1 (71.55-81.6)	165 (142.5-213)	8 (5-10.5)
3rd Day (Median (Range))	83.4 (78.3-84.4)	89.3 (85-89.9)	210 (202-260)	5 (4-7)
5th Day (Median (Range))	98.8 (85-110.4)	92.6 (87-96.1)	280 (220-326)	4 (2-7)
7th Day (Median (Range))	113 (91.95-147.3)	96.3 (91.9-98)	350 (269-377)	3 (1-4)
14th Day (Median (Range))	145.5 (124-162.6)	97.8 (96.2-98.6)	380 (328-402)	2 (1-2)
p value	< 0.001	< 0.001	< 0.001	< 0.001

ANOVA was used.

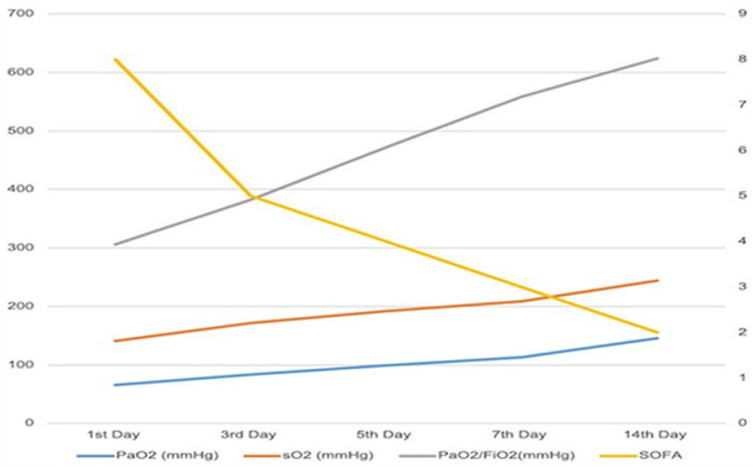

Figure 1. Daily change graph of oxygen parameters of patients. Significant improvements were observed on daily PaO_2, sO_2, PaO_2/FiO_2 and SOFA scores.

ment in PaO_2, sO_2, PaO_2/FiO_2 parameters. A significant decrease in SOFA scores was observed in patients compared to pretreatment (**Table 2**). Significant improvements were observed, after day 3 of convalescent plasma treatment on the examination of the patients' daily PaO_2, sO_2, PaO_2/FiO_2 and SOFA scores (**Table 3**; **Figure 1**).

Mortality

It was demonstrated that the convalescent plasma use shortened the length of hospital stay (P = 0.045), improved the oxygenation status and mortality rate (P = 0.043) when compared to the control patients (**Table 4**; **Figure 2**).

The mean IgG level after treatment was 5.03±2.86 (0.77-8.22). No adverse events were detected in the patients receiving convalescent plasma therapy.

Discussion

As a result of our study, significant improvements were observed in the clinical and laboratory parameters with convalescent plasma transfusion therapy in addition to the treatments used as per the Turkish Health Ministry guidelines in the severe COVID-19 patient. In addition, when compared with the standard treatment group, there was an improvement in the oxygenation and mortality, and convalescent plasma treatment has been shown to shorten the hospitalization process.

The main purpose in the use of convalescent plasma is to provide passive immunity containing viral neutralizing antibodies. Due to the lack of reliable drugs or vaccines yet, the convalescent plasma option seems promising for the treatment of critically ill SARS-COV2 infected patients. Although the use of convalescent plasma in a number of diseases has been researched and used many times in the past, it has not reached the sufficient level of evidence [26]. In most studies, problems arise due to the lack of standardization and the procedure not being fully disclosed. Therefore, different effects can be seen in different studies [27].

The strongest evidence, especially in respiratory tract infections, suggests that the benefit of passive antibody transfer can best occur in patients treated immediately after the symptom begins [28, 29]. In a meta-analysis involving 32 studies on SARS infection and severe influenza, a statistically significant reduction in the mortality rates of plasma treatment com-

Table 4. Comparison with the matched control group

	Matched Control Group	Convalescent Plasma Group	*p* value
Age	66.60±17.49	64.90±19.12	0.824[m]
Gender (Male/Female)	12/8	13/8	0.577[c]
PaO_2	54.8 (51.73-58.78)	55 (49.5-65.6)	0.250[m]
sO_2	58 (56.08-75.98)	75.5 (66.3-86.15)	0.158[m]
PaO_2/FiO_2	163.8 (143.18-236)	150 (125.5-208)	0.159[m]
SOFA Score	7 (6-7.75)	7 (5-9)	0.185[m]
Hospital Stay	9 (6.25-13.75)	7 (4.50-10.50)	0.035[m]
Mortality	7/21	13/20	0.043[c]

m: Mann Whitney U test, c: Chi Square.

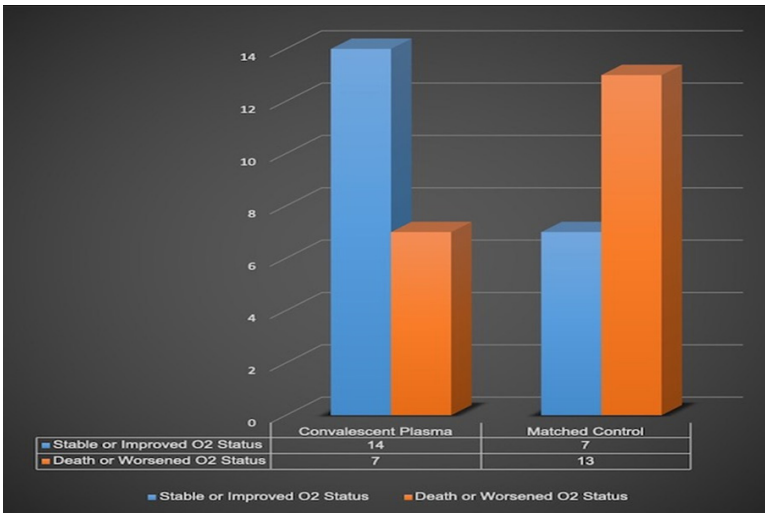

Figure 2. Comparison of O_2 requirements or exitus status between the groups. The convalescent plasma use shortened the hospitalization time (P = 0.045), improved the oxygenation status and mortality rate (P = 0.043) when compared to the controls.

pared to placebo was observed (OR: 0.25%; 95 CI: 0.14-0.45) [29]. In a small case series previously evaluating convalescent plasma in COVID-19 disease, generally a beneficial effect has been found [17, 18, 30]. Although positive effects have been seen in the treatment of patients, it has been reported that convalescent plasma treatment does not significantly affect the clinical outcomes in a 28-day treatment period, while demonstrating a significant anti-viral effect according to a recent randomized controlled trial [31]. However, the completion of the study before the planned time and the heterogeneity in the patients were the limitations of the study.

In the present study, quite effective improvements in the oxygen requirement of patients who received convalescent plasma treatment have been demonstrated. A decrease in the SOFA scores of the patients was observed since the first plasma administration and a significant de-crease was observed in the 14-day follow-up. In addition, there was an improvement in infection parameters and a significant increase in PaO_2, sO_2 and PaO_2/FiO_2 ratios after the first plasma treatment. Another important factor is the timing of the plasma therapy infusion. Since viremia is expected to be maximum in the first week, it is likely that it will give the best clinical response if infused early. Convalescent plasma therapy appears to be a promising method in the treatment of COVID-19, although data is limited.

The study has some limitations. First, the sample size was small. However, the findings are important, even in this single center experience; it demonstrates somewhat promising clinical outcomes in critically ill COVID-19 patients. Another limitation is that the control group was not admitted on the same dates as the treatment group, and somewhat heterogeneous, as well. This was due to the fact that the convalescent plasma treatment was approved by the Ministry of Health, 1 month after March 11th, when the COVID-19 cases began to appear in Turkey. The absence of antibody titers was related to the absence of this test across the country.

In conclusion, the convalescent plasma therapy may be considered as a promising treatment, showing some improvement in a few

days in the clinical and laboratory parameters in COVID-19 patients infected with the SARS-Cov-2 virus. Further larger and powered prospective studies are needed in order to elucidate the role of convalescent plasma therapy use in the critically ill COVID-19 patients, to evaluate its long-term efficacy and the side effects of treatment.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Sude Hatun Aktimur, University of Health Sciences, Samsun Training & Research Hospital, Kışla, Barış Blv, No: 199, Ilkadim 55090, Samsun, Turkey. Tel: +90 532 668 56 46; E-mail: sudehatun@yahoo.com

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