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The effect of convalescent plasma on the treatment of COVID-19 patients in Ardabil, Iran

Effat Iranijam[1], Hassan Ghobadi[1], Somaieh Matin[1], Shahram Habibzadeh[2], Hamed Zandian[3], Jafar Mohammadshahi[2], Shahnaz Fooladi[4], Abdollah Dargahi[3], Elham Safarzadeh[5], Mohammad Negaresh[1], Javad Hosseini[6], Ali Hossein Samadi[1], Saeed Hoseininia[1], Hossein salehzadeh[1], Sharareh Dezhkam[1]

[1]Department of Internal Medicine, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran, [2]Department of Infectious Disease and Tropical Medicine, Ardabil University of Medical Science, Ardabil, Iran, [3]Social Determinants of Health Research Center, Ardabil University of Medical Sciences, Ardabil, Iran, [4]Department of Anesthesiology, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran, [5]Department of Microbiology and Immunology, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran, [6]Department of Biostatistics, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran

Address for correspondence:
Dr. Somaieh Matin, Department of Internal Medicine, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran. E-mail: smh.matin@yahoo.com
Dr. Shahram Habibzadeh, Department of Infectious Disease and Tropical Medicine, Ardabil University of Medical Science, Ardabil, Iran. E-mail: s.habibzadeh@arums.ac.ir

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Abstract:

BACKGROUND: Infection with COVID-19 has resulted in considerable mortality all around the world. This study aimed to investigate the effect of convalescent plasma on the treatment of hospitalized patients with COVID-19 in Imam Khomeini Hospital at Ardabil, Iran.

MATERIALS AND METHODS: In this quasi-experimental clinical trial, patients over 18 years of age with polymerase chain reaction-positive COVID-19 were admitted based on the clinical criteria of respiratory distress with hypoxia (O_2 saturation <90) and tachypnea (R Relative Risk (RR) >24) with moderate-to-severe lung involvement and in the 1st week of respiratory disease who were not intubated were nonrandomly assigned to two groups: convalescent plasma therapy (CPT) group (197 cases) and control group (200 cases). We used the Chi-square, *t*-test, Fisher's exact test, and Pearson's correlation coefficient for statistical analysis.

RESULTS: Analyses revealed that length of stay in hospital was significantly lower in the CPT group as compared to the control group ($P = 0.001$). Twenty-four cases (22.0%) in the CPT group and 85 cases (78.0%) in the control group needed intubation. Furthermore, mortality was 17 cases (18.3%) in the CPT group and 76 cases (81.7%) in the control group, the difference of which was also found to be statistically significant ($P < 0.05$).

CONCLUSIONS: It seems that CPT can be used as an alternative treatment at the early stages of COVID-19 to prevent the progress of the disease, reduce the need for intubation and consequently the length of stay in hospital, and finally, decrease mortality.

Keywords:

Convalescent, COVID-19, mortality, treatment

Introduction

The outbreak of severe acute respiratory syndrome (SARS) coronavirus-2, which began in Wuhan, China, has become a big concern all over the world.[1-3] COVID-19 is mainly characterized by symptoms such as fever, dry cough, and shortness of breath. Some symptoms such as nausea, vomiting, abdominal discomfort, and diarrhea have also been reported, but they are not very typical for this disease.[4-7] There are only a few antiviral drugs that can be used for the treatment of COVID-19, and their effectiveness is unfortunately limited. Currently, there are no approved specific antiviral agents targeting the novel virus. However, there are some drugs which are still under investigation, including remdesivir and lopinavir/ritonavir.[8-10] In general, convalescent plasma therapy (CPT) has been used for improving the survival rate of patients afflicted with a variety of viral epidemics, including SARS, Middle East respiratory syndrome, influenza, and

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Ebola.[11] Preliminary investigations have indicated the effectiveness of CPT in the treatment of COVID-19, especially when the applied plasma has high titers of neutralizing antibodies (NABs) and is administered in the early stages of the disease.[12] Furthermore, it has been reported in a number of research articles that CPT seems to be one of the successful treatments for COVID-19.[13-15] From the outbreak of coronavirus, this treatment has been considered by many researchers in various countries around the world, as well as in Iran. In a hospital in India, for instance, plasma therapy was performed on 333 patients, of whom19 cases were admitted to intensive care unit (ICU). They observed that mortality reduced significantly in these patients.[16] In another study, Ye *et al*. investigated the effectiveness of convalescent plasma in the treatment of COVID-19 patients in Wuhan, China. Their results showed that this type of treatment reduced COVID-19 disease.[17] In this method of treatment, using an apheresis device, plasma is taken from recovered COVID-19 patients who have high levels of antibody in their blood and the result of their polymerase chain reaction (PCR) test is negative. Then, the obtained plasma is used for the treatment of afflicted patients. It seems that the use of convalescent plasma can reduce primary viremia and induce some level of passive immunity.[18-20] However, the effect of convalescent plasma on the treatment of COVID-19 patients has not been investigated in northwestern Iran, especially in Ardabil Province. Therefore, this study aimed to explore the effect of convalescent plasma on the treatment of COVID-19 patients hospitalized in Imam Khomeini Hospital in Ardabil, Iran, during 2020.

Materials and Methods

Study design and setting

In this quasi-experimental clinical trial, COVID-19 patients over 18 years of age were investigated after obtaining informed consent. The selected patients were hospitalized with positive PCR test results, respiratory distress, and moderate-to-severe pneumonia as revealed by computed tomography (CT) scan images and O_2 saturation of lower than 90% equal to the World Health Organization Progression Scale of 4, 5, and 6. The patients were in the 1st week of the disease and were not under mechanical ventilation. The day of entrance to the study for the patients in the CPT group was the day of receiving plasma. For patients in the control group, on the other hand, it was the day that the treating physician nominated them for receiving plasma, but they either were not in the randomization, were not consented to receive plasma, or there was no plasma compatible with their blood group.

Study participants and sampling

To obtain plasma, patients recovered from COVID-19 who met the following requirements were invited to the blood transfusion center: having a history of COVID-19 verified by real-time PCR test at the time of being afflicted with the disease, being in the age range of 20–60 years, being discharged from a hospital or convalescent home due to having recovered in terms of clinical symptoms (not having fever, coughing, shortness of breath, and other related symptoms) and the relevant blood tests (complete blood count, C-reactive protein, erythrocyte sedimentation rate, and lactate dehydrogenase), having arterial blood oxygenation of equal to or higher than 95% without oxygen supplementation, and showing complete or considerable recovery in the lung as indicated by CT scan images. The invited recovered patients were first interviewed by a physician. After that, they filled out a donation form and signed informed consent. Then, the test for specific antibodies against coronavirus was conducted on each of them. Based on the results, individuals with antibody titer of higher than 1.1 were picked out and 500 cc of blood was taken from each of them. The donated plasma was analyzed with virology tests as per the national standards of blood transfusion in Iran. After verification of the analyses, the plasma was transferred to the hospital where the study was being conducted.

Data collection tool and technique

Patients were randomly assigned to CPT (consisting of 197 cases) and control (consisting of 200 cases) groups by the treating doctor based on the criteria considered for entering the study. Patients in both groups received routine treatments. In this study, the patients were selected via the use of convenience sampling method from among the patients who were hospitalized in Imam Khomeini Hospital. Randomization means an equal number of participants in equal time intervals for both intervention and control groups. For example, one type of treatment is given to the first block and another type is given to the second block. The sample size was determined using the ratio difference test of two communities (Equation 1). In this equation, α is error of the first type, β is error of the second type, 1-β is test power, and P is the average ratio in the two groups.

$$\alpha = 0.05$$

$$\beta = 0.20$$

$$\bar{p} = \frac{p_1 + p_2}{2} = \frac{0.1 + 0.2}{2} = 0.15$$

$$n = \frac{2 \times \left(z_{1-\frac{\alpha}{2}} + z_{1-\beta} \right)^2 \times \bar{p}(1-\bar{p})}{(p_1 - p_2)^2}$$

$$n = \frac{2 * (1.96 + 0.84)^2 (0.15 \times 0.85)}{(0.2 - 0.1)^2} = 200$$

After obtaining informed consent and confirming the compatibility of the blood group of the donor and receiver of plasma, patients in the CPT group also received 500 cc of plasma in the course of 4 h. Based on the treating doctor's order, some patients who did not show any sign of improvement after the first round of plasma administration received a second dose 24 h after the first one. The vital signs of the patients were controlled and the possible side effects were checked carefully during the injection of plasma. The patients in the control group received only routine treatments and no plasma was used for them. The routine supportive cares were provided equally for both groups without interruption. The Consolidated Standards of Reporting Trials flowchart outlining participant flow from first contact to study completion is provided in Figure 1.

The patients' demographic information including their age, gender, height, weight, clinical symptoms, comorbidities, use of drugs, and smoking was recorded. Then, other related variables such as length of stay in hospital, response to treatment, intubation rate, and mortality were recorded in the related checklist. The validity of this checklist was tested and the obtained value was 0.8. The reliability of this tool was also checked using Cronbach's alpha and the obtained value was 0.86. The recovery criteria based on the treating doctor's opinion were cessation of fever and coughing, improvement of lungs as indicated by CT scan images, and arterial blood saturation of equal to or higher than 95% without oxygen supplementation. The clinical and paraclinical data in both groups of patients were collected using the same methods of data collection, and all of the patients were followed up until they were either discharged from, or died in, the hospital. The collected data were analyzed using various statistical techniques.

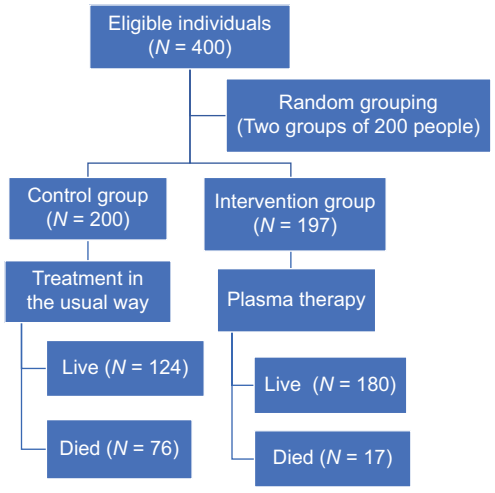

Figure 1: Consort flow diagram indicating sample sizes at each stage and each arm of the study

Ethical consideration

This research project has been approved by the Research Ethics Committee of Ardabil University of Medical Sciences with the code of IR.ARUMS.REC.1399.052 and the IRCT code of IRCT20150808023559N21.

Results

The patients' demographic and epidemiological characteristics were analyzed using descriptive statistics such as mean, standard deviation, and frequency percentage. From among inferential statistical techniques, *t*-test was used to compare two groups in terms of quantitative variables, one-way ANOVA as well as Chi-square or Fisher's exact test were employed to compare three or more groups in terms of quantitative variables, and linear regression was used to predict the value of variables. The obtained results are reported in two subparts below: descriptive statistics and inferential statistics [Table 1]. The relationship between disease outcome and intubation rate in the two groups of patients is presented in Table 1. The relationship between length of hospitalization (days) before receiving plasma and disease outcome in the patients of the CPT group based on Fisher's exact test is presented in Table 1.

Figure 2a and b show the relationship between disease outcome and intubation rate in the two groups of patients via the use of frequencies and percentages. Results of analysis with Chi-square indicated that the two groups of patients were significantly different in terms of mortality and discharge (P = 0.001). Results also revealed that a significant difference existed between the two groups as regards the intubation rate. In Figure 2c and d, the patients' mean length of stay in hospital and age are compared. As can be seen, the two groups were significantly different in terms of the patients' mean length of stay (P-0.001). However, as is evident in Figure 2c, the mean ages of the patients in the two groups were not significantly different. Based on the results obtained in this study, no significant difference was observed between disease outcome and the length of hospitalization before receiving plasma.

The relationship between length of stay in hospital and neutrophil-to-lymphocyte ratio has been investigated via the use of Pearson's correlation coefficient. As can be seen, no significant correlation was observed between the two variables neither in the CPT group nor in the control group. In the CPT group, the correlation between these two variables was negative and decreasing, while in the control group, it was positive and increasing.

The analysis of the results indicated no significant correlation between the relationship between the two variables of length of stay in hospital and

Table 1: Distribution of demographic characteristics, relationship between disease outcome and intubation rate, and relationship between length of hospitalization (days) before receiving plasma and disease outcome in the two groups of patients

Demographic variables	Case (*n*=197; 49.6%), *n* (%)	Control (*n*=200; 50.4%), *n* (%)	Total (*n*=397; 100.0%), *n* (%)
Age group			
>40	18 (9.12)	20 (10)	38 (9.57)
40-50	36 (18.2)	34 (17)	70 (17.6)
51-60	50 (25.4)	52 (26)	102 (25.6)
61-70	70 (35.5)	69 (34.5)	139 (35)
71-80	16 (8.12)	20 (10)	36 (9)
<80	7 (3.5)	5 (2.5)	12 (3)
Sum	197 (100)	200 (100)	397 (100)
Gender			
Male	97 (49.2)	98 (49)	195 (49.1)
Female	100 (50.8)	102 (51)	202 (50.9)
Sum	197 (100)	200 (100)	397 (100)
Occupation			
Self employed	73 (37.1)	76 (38)	149 (37.5)
Employee	36 (18.3)	34 (17)	70 (17.6)
Housewife	62 (31.5)	57 (28.5)	119 (30)
Retired	26 (13.2)	33 (16.5)	59 (14.9)
Sum	197 (100)	200 (100)	397 (100)
Education			
Under diploma	101 (51.3)	97 (48.5)	198 (49.9)
Diploma	29 (14.7)	41 (20.5)	70 (17.6)
University degree	67 (34)	62 (31)	129 (32.5)
Sum	197 (100)	200 (100)	397 (100)
Residence			
Urban	158 (80.2)	167 (83.5)	325 (81.9)
Rural	39 (19.8)	33 (16.5)	72 (18.1)
Sum	197 (100)	200 (100)	397 (100)
Smoke			
No	181 (91.9)	181 (90.5)	362 (91.2)
Yes	16 (8.1)	19 (9.5)	35 (8.9)
Sum	197 (100)	200 (100)	397 (100)
Underlying disease			
No	64 (44)	132 (66.3)	196 (48.8)
Yes	133 (66)	68 (39.7)	201 (51.2)
Sum	197 (100)	200 (100)	397 (100)
Blood group			
A	80 (40.6)	53 (26.5)	133 (33.5)
B	28 (14.2)	21 (10.5)	49 (12.3)
AB	7 (3.6)	2 (1)	9 (2.3)
O	82 (41.6)	60 (30)	142 (35.8)
Sum	197 (100)	136 (68)	333 (83.9)

Variable	Groups		Total, *n* (%)	Significance	Test type
	CP, *n* (%)	Control, *n* (%)			
Disease outcome					
Death	17 (18.3)	76 (81.7)	93 (100.0)	0.001	χ^2
Release	180 (59.2)	124 (40.8)	304 (100.0)		
Total	197 (49.6)	200 (50.4)	397 (100.0)		
Intubation rate					
Yes	24 (22.0)	85 (78.0)	109 (100.0)	0.001	χ^2
No	173 (60.1)	115 (39.9)	288 (100.0)		
Total	197 (49.6)	200 (50.4)	397 (100.0)		
Duration of hospitalization	8.72 (2.58)	13.21 (8.15)	9.98 (6.87)	0.001	*t*-test
Age	57.15 (12.14)	58.02 (12.82)	5.57 (47.12)	0.487	*t*-test

Contd...

Table 1: Contd...

Demographic variables	Case (*n*=197; 49.6%), *n* (%)		Control (*n*=200; 50.4%), *n* (%)	Total (*n*=397; 100.0%), *n* (%)	
Variable	Groups		Total, *n* (%)	Significance	Test type
	CP, *n* (%)	Control, *n* (%)			
Disease outcome					
Death	17 (18.3)	76 (81.7)	93 (100.0)	0.001	χ^2
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Total	197 (49.6)	200 (50.4)	397 (100.0)		
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Yes	24 (22.0)	85 (78.0)	109 (100.0)	0.001	χ^2
No	173 (60.1)	115 (39.9)	288 (100.0)		
Total	197 (49.6)	200 (50.4)	397 (100.0)		
Duration of hospitalization	8.72 (2.58)	13.21 (8.15)	9.98 (6.87)	0.001	*t*-test
Age	57.15 (12.14)	58.02 (12.82)	5.57 (47.12)	0.487	*t*-test

CP: Convalescent plasma

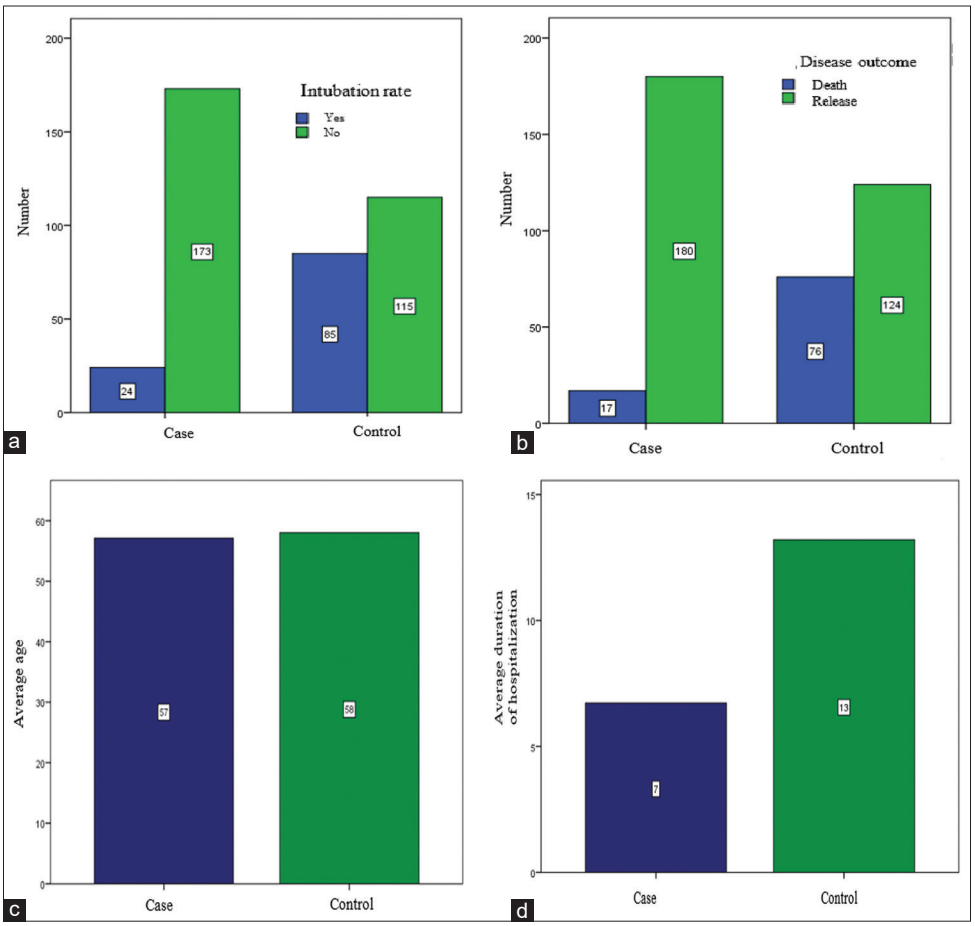

Figure 2: (a) The relationship between intubation variable in the two groups; (b) Investigating the relationship between mortality variable in two groups; (c) Evaluation of the mean age variable in the two groups; (d) Evaluation of the mean variable of duration of hospitalization in the two groups

neutrophil-to-lymphocyte ratio neither in the CPT group nor in the control group. In the CPT group, the linear trend was decreasing, while in the control group, it was increasing.

Table 2 represents the results of applying independent *t*-test on variations of vital signs after plasma therapy. The two variables of mean respiratory rate and mean body temperature were found to be significantly lower in the CPT group as compared to the control group. Moreover, the mean heart rate, systolic blood pressure, and diastolic blood pressure turned out to be significantly higher in the control group as compared to the CPT group ($P < 0.001$). The relationship between the two variables of vital signs upon admission and mortality was investigated using linear regression, the results of which are given in Table 2. As can be observed, the results did not show any significant relationship between the two variables.

Table 2: Comparison of vital signs in the two groups after convalescent plasma therapy via the use of independent *t*-test and comparison of patients' vital signs upon admission with mortality

Variable	Group	*n*	Mean (SD)	Test statistics	Significance
Respiratory rate	CPT	197	19.35 (2.89)	−18.044	<0.001
	Control	200	24.24 (2.48)		
Pulse rate	CPT	197	88.59 (11.09)	10.56	<0.001
	Control	200	78.13 (8.44)		
Body temperature	CPT	197	37.074 (0.56)	−13.34	<0.001
	Control	200	37.69 (0.99)		
Systolic blood pressure	CPT	197	128.68 (15.23)	5.61	<0.001
	Control	200	111.0 (11.87)		
Diastolic blood pressure	CPT	197	72.84 (9.58)	6.90	<0.001
	Control	200	66.40 (8.99)		

Variable	Coefficient B	SE	Significance	Exp (B)
Constant	4.464	1302	0001	86.852
Fever	−0.686	0663	0301	0.504
Cough	−0.636	0883	0471	0.529
Dyspnea	−0.731	0964	0449	0.482
Body pain	1.029	0.951	0.279	2.799
Anorexia	−0.430	0.740	0.562	0.651
Weakness	−0.448	0.873	0.608	0.639
Diarrhea	−1.406	0.941	0.135	0.245

SD=Standard deviation, SE=Standard error, CPT=Convalescent plasma therapy

Discussion

Currently, there is no effective clinical treatment for COVID-19. The use of convalescent plasma seems to be one of the possible treatments.[21] The results of the present study indicated that length of stay in hospital, need for intubation, and mortality resulting from COVID-19 were significantly lower in the CPT group as compared to the control group. In a separate study, Abolghasemi *et al*. conducted a multicenter clinical trial on 189 patients afflicted with COVID-19 (115 patients in plasma therapy group and 74 patients in control group) with the aim of investigating the clinical effects of CPT on the infections induced by COVID-19. They found that mortality, length of stay in hospital, and the need for intubation were significantly lower in patients receiving plasma.[22] Therefore, their findings are all consistent with the findings of the current study. In another study, Agarwal *et al*. explored the effectiveness of convalescent plasma on the treatment of the moderate forms of COVID-19 in adolescent patients in India. In their study, the use of plasma obtained from recovered patients did not prevent the progression of the disease to its severe forms. Furthermore, they did not observe any decrease in mortality. The reason for the inconsistency of their findings with ours might be the difference in the methods of conducting the study.[23]

In another study in Kuwait, Alsharidah *et al*. explored the effectiveness of CPT in the treatment of moderate and severe forms of COVID-19. To this end, they investigated 135 patients and found that CPT was associated with higher levels of clinical recovery. They also observed that in patients with moderate forms of COVID-19, 30-day mortality was significantly lower in patients receiving CPT. Therefore, they concluded that CPT was a safe method for the treatment of COVID-19 since it positively affected the level and duration of clinical recovery.[24] As can be seen, their findings are in line with the findings of the current study.

In another study, Ahmad *et al*. investigated the effect of CPT on the treatment of patients afflicted with severe forms of COVID-19 and found that length of stay in ICU, mechanical ventilation support, vasopressor support, and mortality were lower in the CPT group as compared to the control group. Based on the results obtained, they concluded that CPT could be effective in the treatment of patients afflicted with severe forms of COVID-19.[25]

In the study conducted by Duan *et al*., 10 patients afflicted with severe forms of COVID-19 were investigated. The patients in their study received one dose of convalescent plasma (200 mL) with NAB titer of higher than 1.640 that was donated by people newly recovered from COVID-19. They observed that CPT was a bearable method of treatment for these patients. They also observed that it could improve clinical symptoms in patients afflicted with severe forms of COVID-19 via neutralizing viremia.[26] Their findings are also consistent with the findings of the present study.

In a randomized clinical trial, Gharbharan *et al*. compared the effects of CPT and standard medical care on patients hospitalized for COVID-19 in the Netherlands. In their study, no significant differences were observed between

the two types of treatment as regards mortality, length of stay in hospital, and severity of the disease on the 15th day after the onset of symptoms. Since NAB titer in most of the COVID-19 patients participating in this study was higher upon their hospitalization, the study was terminated ahead of schedule, and antibody screening was determined to be one of the key steps to be taken in recognizing the patients that might benefit from CPT.[27]

A systematic and meta-analytic investigation was also conducted on the findings related to the clinical effects of CPT on COVID-19. The results of global meta-analysis as well as the analysis of the data obtained from 28-day or 30-day standard follow-up of patients revealed that CPT was associated with lower mortality among COVID-19 patients. However, in two randomized controlled trials mentioned in this meta-analysis, CPT did not bring about any difference in mortality.[23,28] The findings of this meta-analysis suggest that CPT can be effective in the treatment of patients with COVID-19. Nonetheless, the mixed results of different studies regarding mortality make it impossible to arrive at a definitive conclusion on the improvement of survival rate as the result of CPT.[28]

In another study, Simonovich *et al*. investigated patients treated with CPT and those treated with placebo. Their results also did not show any significant differences between patients of the two groups as regards their clinical condition or mortality.[29] Bikdeli *et al*. investigated the effects of intermediate-dose versus standard-dose prophylactic anticoagulation on the treatment of COVID-19 patients admitted to the ICU. Their results showed that intermediate-dose compared with standard-dose prophylactic anticoagulation did not reduce a composite of death, treatment with ECMO, or venous or arterial thrombosis at 90-day follow-up.[30]

In the present study, the mean respiratory rate and body temperature of the patients in the CPT group were reported to be lower than those of the control group, the reason for which might be the decrease of COVID-19 viremia in the blood and the improvement of symptoms.

The mean heart rate, systolic blood pressure, and diastolic blood pressure were significantly higher in patients of the control group as compared to those in the CPT group, which might be due to fluid overload. In patients of the CPT group, there was a negative and decreasing correlation between length of stay in hospital and neutrophil-to-lymphocyte ratio, while in those of the control group, a positive and increasing correlation was observed between these two variables. These differences were not statistically significant.[31,32] Therefore, it can be assumed that CPT has improved this ratio and that improvement, in turn, has led to an improvement in the patients' prognosis. The strengths of this study included the following: (1) relatively big sample size and comparison of patients with a control group, (2) studying patients in a certain phase of the disease (first week), and (3) using plasma therapy when antiviral therapies were not being used yet.

Limitation and recommendation

The limitations of the study include the impossibility of randomization and the lack of donated plasma compatible with blood group.

Conclusions

The findings of this clinical trial indicated the effectiveness of CPT in the treatment of COVID-19 patients suffering from severe respiratory symptoms at the early stages of the disease. According to the findings of the current study, CPT can decrease intubation rate, length of stay in hospital, and mortality via preventing the progress of the disease and improving the related symptoms, especially body temperature and respiratory rate. Therefore, the result of this study shows that CPT can be used in severe COVID-19 patients without significant adverse events. One of the limitations of this study was the impossibility randomization due to the possible unwillingness of some patients to enter the study. Another limitation was lack of plasma compatible with some patients' blood type to be administered at the time of need.

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Conflicts of interest

There are no conflicts of interest.

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