Original Article

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TANAFFOS

Effect of Convalescent Plasma Therapy on Clinical Improvement of COVID-19 Patients: A Randomized Clinical Trial

Ebrahim Jalili [1], Salman Khazaei [2], Afshin Mohammadi [3], Fariba Keramat [4], Seyed Hamid Hashemi [4], Saeid Bashirian [5], Toos Kiani [6], Farid Azizi Jalilian [7], Samereh Ghelichkhani [6], Manoochehr Karami [8,9], Maryam Farrokhi [10], Rashid Heidarimoghadam [11], Tahereh Abbasi Garavand [12], Ebrahim Daneshyar [6], Mohammad Abbasi [12]

[1] Department of Emergency Medicine, School of Medicine, Besat Hospital, Hamadan University of Medical Sciences, Hamadan, Iran, [2] Research Center for Health Sciences, Hamadan University of Medical Sciences, Hamadan, Iran, [3] Blood Transfusion Organization, Hamadan, Iran, [4] Brucellosis Research Center, Sina Educational and Medical Center, Hamadan University of Medical Sciences, Hamadan, Iran, [5] Social Determinants of Health Research Center, Hamadan University of Medical Sciences, Hamadan, Iran, [6] Deputy of Treatment, Hamadan University of Medical Sciences, Hamadan, Iran, [7] Department of Virology, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran, [8] Modeling of Noncommunicable Diseases Research Center, Hamadan University of Medical Sciences, Hamadan, Iran, [9] Department of Epidemiology, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [10] Deputy of Research and Technology, Hamadan University of Medical Sciences, Hamadan, Iran, [11] Health Sciences Research Center, Hamadan University of Medical Sciences, Hamadan, Iran, [12] Department of Internal Medicine, School of Medicine, Shahid Beheshti Medical Educational Center, Hamadan University of Medical Sciences, Hamadan, Iran.

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Correspondence to: Abbasi M
Address: Department of Internal Medicine, School of Medicine, Shahid Beheshti Medical Educational Center, Hamadan University of Medical Sciences, Hamadan, Iran
Email address: mohammad.abbasi1967@gmali.com

Background: Due to the critical condition of COVID-19, it is necessary to evaluate the efficacy of administrating convalescent plasma to COVID-19 patients. Therefore, we decided to design a clinical trial to investigate the effect of convalescent plasma of patients recovered from COVID-19 on the treatment outcome of COVID-19-infected patients.

Materials and Methods: In this parallel randomized controlled clinical trial, patients in the intervention group received standard treatment plus convalescent plasma of patients recovered from COVID-19. We allocated 60 patients to each treatment group through balanced block randomization. Then, COVID-19 outcomes, vital signs, and biochemical parameters were compared between the two treatment groups by the independent *t* test and ANCOVA.

Results: The mean age (SD) of the patients in the intervention and standard treatment groups was 52.84 (15.77) and 55.15 (14.34) years, respectively. Although patients in the intervention group reported more hospitalization days (11.45±5.86 vs. 10.42±6.79), death rates (26.67% vs. 18.13%), ICU admission (45 vs. 41.67%), and ARDS (11.67% vs. 3.33%), these differences were not statistically significant (P>0.05). Moreover, the two groups were homogenous in vital signs and biochemical parameters before and after treatment (P>0.05).

Conclusion: The present study indicated that convalescent plasma therapy has no significant effect on the survival, hospitalization, and ICU admission of COVID-19 patients.

Key words: COVID-19; Convalescent Plasma Therapy; Randomized Clinical Trial

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) started in Wuhan, China, in late December 2019. Soon later, it spread worldwide and is now a global emergency. This pandemic quickly changed all aspects of people's lives and closed major business centers, universities, and schools, and created a severe crisis in health centers worldwide (1). Although this epidemic has been examined in many studies, there are still many ambiguities about the effectiveness of different treatment methods. Several therapies have been proposed for COVID-19, many of which are passing through clinical trials. One of the promising treatments is convalescent plasma therapy collected from a previous COVID-19-infected patient and transfused to infected patients.

In previous studies, plasma has been used to improve the survival of patients with SARS, shortening hospitalization and reducing mortality (2-4). In 2014, plasma therapy in patients recovered from Ebola was recommended by the WHO as an experimental method during disease outbreaks (5). In 2015, a protocol was developed for coronavirus respiratory syndrome plasma therapy in the Middle East region (6). In a prospective cohort study conducted in 2009 by Hung et al., the relative mortality risk was significantly reduced in H1N1 influenza patients treated with plasma compared to other patients (7).

Evidence has shown that receiving plasma antibodies from improved viral infection patients can be a low-complication treatment in COVID-19 patients (8-10). It seems that due to the critical condition of the disease, it is necessary to evaluate the efficacy of administrating convalescent plasma to COVID-19 patients.

Therefore, we decided to design a clinical trial to investigate the effect of convalescent plasma of patients recovered from COVID-19 on treatment outcomes.

MATERIALS AND METHODS

Trial Design

This is a randomized controlled clinical trial (RCT) with a parallel design. The study was performed in Sina hospital, Hamadan, Iran, between May and July 2020. By balanced block randomization (block size, 4), patients were randomly assigned to one of the two groups in an allocation ratio of 1:1, as follows: Standard treatment plus plasma of patients recovered from COVID-19 and standard treatment only. Both patients and clinicians were aware of the allocated treatment, and therefore the study was open-label.

Eligibility Criteria

The inclusion criteria for plasma recipients included patients with clinical manifestations of COVID-19 confirmed by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) aged 18-65 years. Exclusion criteria were disagreement of the patients or their relatives to participate in the project, pregnancy, lactation, immunoglobulin allergy, severe septic shock, blood group incompatibility, and participating in other RCTs. The inclusion criteria for plasma donors were recovery and discharge from the hospital after a COVID-19 infection, normal laboratory tests according to the Iran Blood Transfusion Organization guidelines, voluntary donation of plasma, and maximum plasma volume of 650 ml.

Intervention

Patients in the intervention group received standard treatment (hydroxyl-chloroquine sulfate tablet, 400 mg single dose, with two tablets Lupinavir 200 mg/Ritonavir 50 mg orally every 12 hours for 7 to 14 days) plus convalescent plasma of patients recovered from COVID-19, 250-500 U. Patients in the control group only received standard treatment. Also, depending on the patient's symptoms and physician's discretion, dexamethasone 8 mg every 12 hours for 5 to 10 days was prescribed.

Statistical Methods

The characteristics of the study participants according to the treatment group were presented as number (%) for categorized variables and mean (SD) for continuous variables. The Shapiro-Wilk test was used to check the

normal distribution of variables. The chi-square and Fisher's exact tests were used to compare background characteristics between the two groups. Comparison between the treatment groups was carried out by the independent t test and ANCOVA test, as appropriate. For the data analysis, Stata version 14 was used. A *p* value of ≤ 0.05 was considered statistically significant.

Ethics Statement

The Ethics Committee of Hamadan University of Medical Sciences approved this study (Research ID: 990216749, Ethics code: IR.UMSHA.REC.1399.037). Also, the protocol was registered in the Iranian Registry of Clinical Trials (IRCT registration number: IRCT20120215009014N353; date: 2020-04-27).

RESULTS

Figure 1 shows the CONSORT flow chart. There were 168 patients at enrollment. A total of 120 patients met the eligibility criteria and were randomized into standard treatment plus convalescent plasma group (n=60) and standard treatment group (n=60). No patients were dropped from the follow-up, and finally, 60 patients were analyzed in each treatment group.

Table 1 compares the characteristics of patients in the intervention and control groups. There were no statistically significant differences in age distribution between the intervention and control groups [52.84 (15.77) vs. 55.15 (14.34) years, P=0.41]. The sex distribution of patients was also similar between the two groups (P=0.71). The mean BMI (SD) for the intervention and control groups was 26.34 (4.32) and 26.51 (4.13), respectively (P=0.85). There was no significant difference between the two groups in background disease (P>0.05).

Treatment outcomes in both groups are presented in Table 2. Although patients in the intervention group showed more hospitalization days (11.45±5.86 vs. 10.42±6.79), death rates (26.67% vs. 18.13%), ICU admission (45 VS. 41.67%), and ARDS (11.67% VS. 3.33%), these differences were not statistically significant (P>0.05).

Table 3 compares the vital signs and biochemical parameters between the two groups before and after the follow-up. Statistical analysis showed that the two groups were homogenous in these parameters before and after treatment (P>0.05). Concerning complications following plasma therapy, no sudden death and serious complications were observed following plasma treatment.

Table 1. Demographic Characteristics and underlying diseases of COVID-19 infected patients according to treatment groups

Variable	Standard treatment + Convalescent Plasma (N= 60)	Standard treatment only (N= 60)	P. Value
Age (year), mean (SD)	52.84 (15.77)	55.15 (14.34)	0.41*
BMI (kg/m^2), mean (SD)	26.34 (4.32)	26.51 (4.13)	0.85*
Male gender, n (%)	39 (65.00)	37 (61.67)	0.71**
Diabetes, n (%)	11 (18.13)	5 (8.33)	0.11**
Hypertension, n (%)	9 (15.00)	7 (11.67)	0.59**
Heart diseases, n (%)	3 (5.00)	4 (6.67)	1***
COPD*, n (%)	2 (3.33)	3 (5.00)	1***
Kidney diseases, n (%)	2 (3.33)	2 (3.33)	1***
Cancer, n (%)	2 (3.33)	1 (1.67)	1***
Smoking, n (%)	3 (5.00)	2 (3.33)	1***

*Student t.test, **Chi square test, *** Fisher exact test *COPD= Chronic obstructive pulmonary disease

Table 2. Outcome of COVID-19 patients following treatment in two groups

Variable	Standard treatment + Convalescent Plasma (N= 60)	Standard treatment only (N= 60)	P. Value
Duration of hospitalization (day), mean (SD)	11.45 (5.86)	10.42 (6.79)	0.39*
Death rate, n (%)	16 (26.67)	11 (18.13)	0.27**
Hospitalization in the ICU, n (%)	27 (45.00)	25 (41.67)	0.71**
ARDS*, n (%)	7 (11.67)	2 (3.33)	0.16**

*Student t.test, ** chi square test *ARDS= Acute Respiratory Distress Syndrome

Table 3. Comparing of vital signs and biochemical parameters at the first and last day of hospitalization among two groups

Variable		Before treatment			After treatment		
		Standard treatment + Plasma	Standard treatment only	P*	Standard treatment + Plasma	Standard treatment only	P*
Vital signs	Temperature (C)	37.36 (0.67)	37.4 (0.68)	0.74	37 (0.28)	36.9 (0.33)	0.89
	Pulse Rate	90.67 (13.58)	92.22 (17.51)	0.58	83.23 (17.6)	84.91 (13.8)	0.58
	Respiratory rate	21.07 (6.88)	22.34 (12.58)	0.50	19.75 (5.93)	18.11 (6.61)	0.18
	Systolic BP	117.6 (13.69)	121 (14.97)	0.20	115.4 (19.5)	115.3 (19.55)	0.98
	Diastolic BP	74.41 (8.81)	76.07 (9.78)	0.33	73.43 (8.44)	70.89 (9.74)	0.15
	SpO2+O2	85.41 (22.04)	91.04 (6.19)	0.22	94 (4.61)	93.6 (7.56)	0.8
	SpO2-O2	81.66 (15.56)	81.25 (10.50)	0.88	88.39 (10.48)	91.33 (5.64)	0.10
Biochemical markers	WBC (10^3/µl)	8.08 (12.7)	8.59 (10.18)	0.81	9.98 (5.67)	11.52 (12.76)	0.58
	Lymphocyte (%)	22.62 (11.81)	19.73 (9.62)	0.16	18.48 (17.24)	14.19 (10.17)	0.27
	Hemoglobin(g/dl)	14.14 (2)	13.58 (2.29)	0.18	12.9 (1.91)	12.81 (2.92)	0.89
	ALT (U/L)	43.37 (37.41)	47.75 (46.86)	0.62	59.4 (40.24)	57.4 (25.62)	0.90
	AST (U/L)	45.38 (25.33)	47.69 (37.89)	0.73	43.4 (28.05)	46.9 (22.99)	0.76
	Creatinine mg/dl	1.07 (0.51)	1.42 (1.94)	0.20	1.09 (0.71)	1.52 (2.05)	0.18
	BUN	15.65 (7.07)	19.1 (8.42)	0.03	19.4 (18.7)	29 (27.13)	0.11**
	ESR mm/h	43 (25.49)	48.89 (29.13)	0.31	2.05 (0.37)	2.02 (0.42)	0.77

*T.test, ** Ancova test

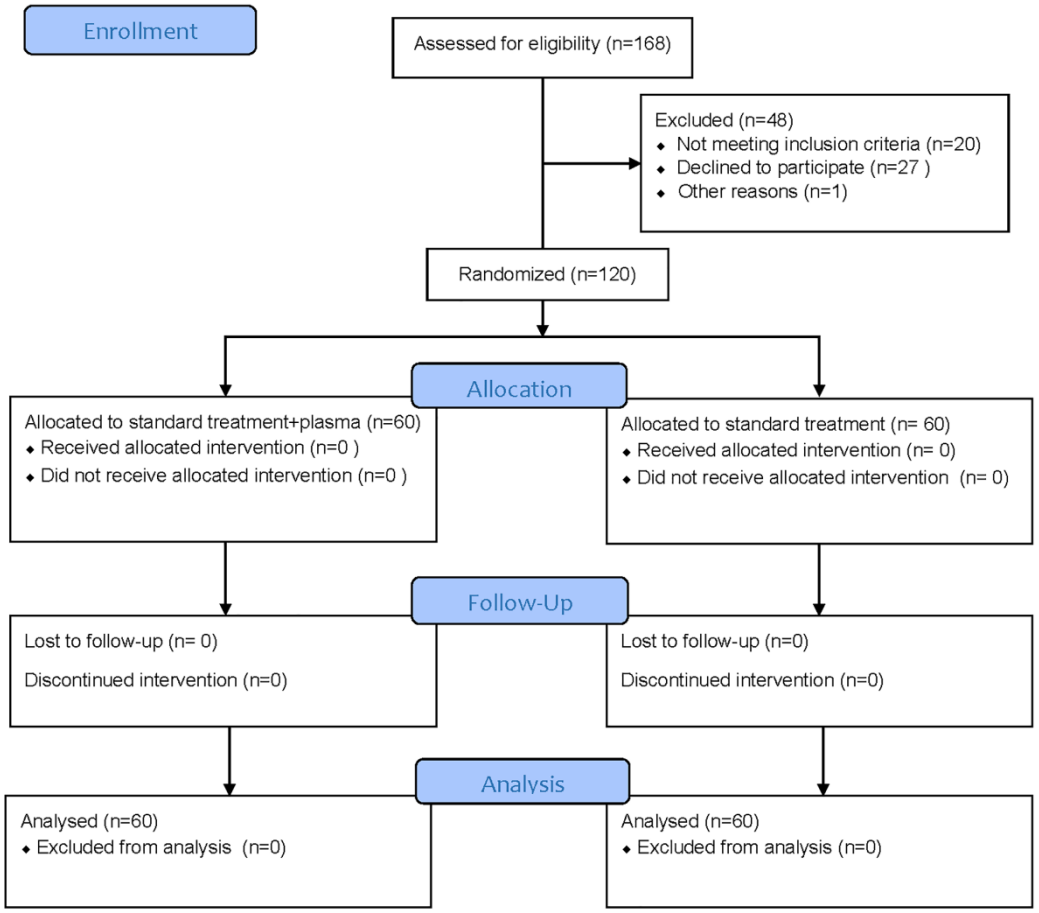

Figure 1. CONSORT flow chart

DISCUSSION

In the present study, we evaluated the effect of convalescent plasma therapy on the clinical improvement of COVID-19 patients. Our study showed no significant difference in the survival, length of hospital stay, and the need for ICU admission between patients who received convalescent plasma transfusion therapy plus standard treatment compared to those who received standard treatment only.

Consistent with the present study results, a study conducted from April 22 to July 14, 2020, in 39 medical centers in India found no significant difference in disease progression and mortality during a 28-day follow-up. In that study, 14.5% of the patients in the plasma therapy group and 13.6% in the standard treatment group died (11). In contrast to the present study results, Mair-Jenkins et al. acknowledged reduced mortality and complications in hospitalized patients after receiving different doses of plasma from recovered COVID-19 patients (12).

Abolghasemi et al. in Iran also showed the effectiveness of plasma in reducing mortality and length of hospital stay (13). The researchers also acknowledged that the need for intubation was 7% in the plasma receiving groups and 20% in the standard treatment group (13, 14). In the present study, 11.7% of the patients receiving plasma from non-intubated groups developed ARDS symptoms, and only 3.33% of the patients in the control group developed respiratory distress.

A study also showed that clinical symptoms, especially fever, cough, and chest pain, improved within 1 to 3 days of plasma injection, and plasma recipients showed improved usual laboratory parameters such as increased number of lymphocytes and improved pulmonary function. These results contradict the findings of the present study (14). Other studies have shown that only 13% of non-intubated plasma recipients with a 1:320 antibody titer who had plasma injections in the first 72 hours and concomitant use of corticosteroids died compared with 24% of patients with standard treatment. Therefore, this study showed the advantage of using plasma (15).

Some studies have shown that non-intubated patients receiving higher plasma antibody titers had better clinical outcomes than those receiving lower antibody titers, especially when given within 72 hours of COVID-19 diagnosis (16). These results demonstrated the importance of assessing donor plasma levels before plasma injection and within the first 72 hours of injection. However, other researchers acknowledged that hospitalized COVID-19 patients might already have a COVID-19 neutralizing antibody titer, which is comparable to plasma donors and potentially limits the benefit of receiving plasma in these patients. Therefore, because no test for the measurement of neutralizing antibodies is widely available and agreed upon and the antibody titer in the plasma of patients recovered from COVID-19 is highly variable, it is not yet possible to accept plasma as a treatment for COVID-19 (11, 17).

No sudden death and serious complications were observed following plasma treatment in the present study. In a similar study, clinical results indicated that serious side effects or complications following plasma therapy are rare (16).

In the present study, the antibody titers of plasma donors were not measured. Although, according to the evidence, the efficacy of convalescent plasma therapy depends on strong antibody responses in convalescent plasma donors (18, 19), the results of a study showed that despite variability in donor titer, 80% of convalescent plasma recipients showed a significant increase in antibody levels post-transfusion (20).

It is necessary to pay attention to Antibody-dependent Enhancement (ADE) in antibody-based drugs against COVID-19. Evidence suggests that anti-SARS-CoV-2 antibodies could exacerbate COVID-19 through ADE.(21). Although its mechanism is not completely clear, the role of antibodies in the pathogenesis of highly pathogenic coronaviruses has been shown previously (22).

This study had some limitations. First, the study's sample size was relatively small and may not have provided enough power to show some statistical differences between the two groups. Second, the patient allocation to treatment groups began a few days after the onset of symptoms until the results of the PCR test were determined, and it is unclear whether earlier treatment would have resulted in greater benefit. Third, this open-label study may be prone to surveillance bias. Finally, at the time of the study, according to the national guidelines, it was not necessary to check the antibody titers of plasma donors, which could affect the study results.

CONCLUSION

We found that convalescent plasma therapy has no significant effect on the survival, hospitalization length, and ICU admission of COVID-19 patients.

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