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Clinical efficacy of convalescent plasma for treatment of COVID-19 infections: Results of a multicenter clinical study

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ABSTRACT

Since Dec. 2019 the new coronavirus (SARS-CoV-2) has infected millions and claimed life of several hundred thousand worldwide. However, so far no approved vaccine or drug therapy is available for treatment of virus infection. Convalescent plasma has been considered a potential modality for COVID-19 infection. One hundred eighty-nine COVID-19 positive patients including 115 patients in plasma therapy group and 74 patients in control group, registered in the hospitals with confirmed COVID-19 infection, entered this multi-center clinical study. Comparison of outcomes including all-cause mortality, total hospitalization days and patients' need for intubation between the two patient groups shows that total of 98 (98.2 %) of patients who received convalescent plasma were discharged from hospital which is substantially higher compared to 56 (78.7 %) patients in control group. Length of hospitalization days was significantly lower (9.54 days) in convalescent plasma group compared with that of control group (12.88 days). Only 8 patients (7%) in convalescent plasma group required intubation while that was 20 % in control group. This clinical study provides strong evidence to support the efficacy of convalescent plasma therapy in COVID-19 patients and recommends this treatment for management of these patients. Clinical efficacy, immediate availability and potential cost effectiveness could be considered as main advantages of convalescent plasma therapy.

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1. Introduction

Shortly after WHO announcement of first signs of SARS-CoV-2, the virus that causes COVID-19 epidemic in the world on Dec. 31, 2019, the epidemic of new coronavirus quickly changed all aspects of the people's lives around the world. Countries' health care system soon became overwhelmed with exponentially growing number of patients referring to health care centers with severe acute respiratory syndrome (ARDS) symptoms. The mortality is high and considerable percentage of the patients contracted COVID-19, requires ICU admission and rapidly develops ARDS. There is no vaccine or specific anti-viral drug therapy yet to treat patients. Iran reported its first two cases of COVID-19 on Feb. 19, 2020 in the city of Qom and the disease rapidly spread to other cities and shortly to the whole country [1]. By the 4 July 2020, more than 237,000 cases tested positive and nearly 11,400 deaths were reported in Iran.

One of the hopeful treatment that has emerged is convalescent plasma therapy which is plasma that is collected from an infected individual by COVID-19 is then transfused into infected patients. Convalescent plasma has been used for SARS, 2009 influenza A (H1N1) pandemic, avian influenza A (H5N1), MERS, Ebola, and other viral infections to improve the survival rate of patients. Most of the published papers reported a significantly better patient's outcome with convalescent plasma [2–6].

A key advantage to convalescent plasma is that this treatment is provided by people who have been infected previously and is available immediately. It is also cost effective for resource limited medical centers. If it is infused at proper time, it may prevent patient getting into severe stage of the disease and reduce possibility of hospitalization in ICU.

Deploying passive antibody therapies against the rapidly increasing number of COVID-19 cases provides an opportunity to study the efficacy of this treatment against this new viral agent [7–12]. One possible explanation for the efficacy of convalescent plasma therapy is that the antibodies from convalescent plasma might suppress viraemia. Based on current data, viraemia peaks in the first week of infection in most viral illnesses. The patient usually develops a primary immune response by days 10–14. Therefore, probably, administration of convalescent plasma at the early stage of disease would create more benefit to the patients [13,14].

There are several published papers reporting use of convalescent plasma in COVID-19 patients [15]. In a case series study, 5 critically ill COVID-19 patients were treated with convalescent plasma. As assessed by computerized tomography (CT) Scan, viral load declined within days of treatment and the clinical conditions improved. Four patients who had been receiving mechanical ventilation and Extracorporeal membrane oxygenation (ECMO), no longer required respiratory support by 9 days after plasma transfusion [16].

In another case series study, 10 severe COVID-19 patients were received one dose of 200 mL of convalescent plasma with the neutralizing antibody titers above 1:640 in addition to maximal supportive care and antiviral agents. After convalescent plasma therapy, the clinical symptoms were significantly improved along with increase of oxyhemoglobin saturation within 3 days [17].

A case series of two cases of COVID-19 treated with convalescent plasma infusion in Korea described that both patients presented severe pneumonia with ARDS and showed a favorable outcome after the use of convalescent plasma [18]

Despite low number of reported cases with COVID-19 convalescent plasma therapy, well known national regulatory agencies such as FDA on April 13, 2020 authorized use of convalescent plasma as a potentially effective treatment of the patients [19]. EU also issued its program for collection and use of convalescent plasma in COVID-19 pandemic as an immediately available experimental therapy with low risk, which should be considered as an urgent priority [20].

However, convalescent plasma is now being used in very large number of patients [21].

One obstacle in plasma therapy is providing convalescent plasma in large number to enable medical centers to use them routinely. Therefore, scalability to treat large numbers of patients may become an issue. In order to tackle logistical challenge of providing convalescent plasma it should be needed to encourage and regulate blood and plasma centers to collect COVID-19 convalescent plasma [22]. A stockpile of frozen convalescent plasma would be a precious asset in fight against COVID-19.

However, it was important to perform well controlled clinical trials to confirm efficacy of this modality to provide evidence for evidence-based decision making. Amidst the shortage of robust evidence regarding the use of this treatment in COVID-19 patients, the present study aims to explore the efficacy of administrating convalescent plasma to COVID-19 patients in a nonrandomized multi-center clinical trial. To the best of our knowledge, this is the only reported case control clinical study of use of convalescent plasma in COVID-19 patients

2. Materials and methods

Following approval of the ethical committee, this clinical study registered in Iran National Registry for Clinical Trails (IRCT20200325046860N1). The study was conducted between March to April 2020. Patients were recruited from confirmed COVID-19 infected patients. The presence of COVID-19 infection in patients was confirmed by quantitative real time polymerase chain reaction (qRT-PCR) on their admission to the hospital.

Demographic information of the enrolled patients is presented in Table 1. CT scan scoring was performed using a lung CT scan scoring system to evaluate the patient's lung involvement. CT scan was assessed for ground glass opacity, crazy paving, or consolidation in both lung fields. Each of the five lung lobes was scored from 0 to 5 based on the percentage of lobar involvement as follows: no involvement [0], 75 % [5]. Total CT scan score was calculated by adding five lobar scores and ranged from 0 (no involvement) to 25 (maximum involvement) [23].

2.1. Hospitals contribution

Enrolment of the patients (case and control) for this clinical trial were done in Baqiyatallah Hospital, MasihDaneshvari Hospital, Labbafinejad and RasoolAkram (Tehran), Beheshti Hospital (Qom), Qarazi Hospital (Isfahan) and Sadouqi Hospital (Yazd). However, most of the patients for this study have recruited from Baqiyatallah Hospital. This hospital from February 19, 2020 to April 15, 2020, received 12,870 patients of which 2,968 were hospitalized with COVID-19 diagnosis. The majority of cases were in the age group of 50–60 years of old. The male-to-female ratio was 1.93:1. A total of 239 deaths occurred among all cases for an overall Case Fatality Ratio (CFR) of 1.85 % based

Table 1
Demographic and basic clinical factors of patient groups on admission.

Variables		Patient groups		p-value
		Plasma (n = 115)	Control (n = 74)	
Age, year	Mean ± SD	54.41 ± 13.71	56.83 ± 14.98	0.250
	Range	23–93	19–90	
Gender, n (%)	Male	67 (58.3%)	37 (50.0%)	0.265
	Female	48 (41.7%)	37 (50.0%)	
Hypertension, n (%)	No	58 (72.5%)	31 (62.0%)	0.210
	Yes	22 (27.5%)	19 (38.0%)	
Diabetes, n (%)	No	53 (66.3%)	34 (68.0%)	0.837
	Yes	27 (33.8%)	16 (32.0%)	
On admission chest CT scan score	Mean ± SD	13.81 ± 4.87	13.36 ± 5.67	0.719
	Range	4–23	2–23	

on the total number of patients and 8.06 % among hospitalized patients [24].

2.2. Convalescent plasma donors

Convalescent plasma donors were selected from clinically and laboratory-confirmed recovered patients of COVID-19 who were between 18–60 years old. To prevent transfusion related acute lung injury (TRALI) female donors with a history of pregnancy were excluded. Selected donors had negative qRT-PCR for COVID-19 and other standard virology tests at the time of donation while their test results had been previously positive by qRT-PCR for COVID-19. Additionally, all donors should have no remaining symptoms of COVID-19 infection at least 14 days prior to donation. They were interviewed and examined by qualified physician and were asked to fill in related plasma donation and consent forms. Eligible donors were tested by the semi-quantitative enzyme-linked immunosorbent assay (ELISA) antibody identification test for COVID-19. Volume of donated plasmas was 500cc.

Donated plasma was tested by the semi-quantitative ELISA and Rapid Strip Test (IgG 98 % Pos, IgM 75 % Pos) antibody identification test for COVID-19. Based on laboratory testing, donated plasmas contained antibody titer cut off index higher than 1.1. Sampling from donated plasma was done in order to perform routine screening tests for transfusion transmitted infections (HIV, HBV, HCV, RPR). Donated plasma was stored in freezers till the release of screening tests' results. After meeting the eligibility criteria for transfusion, donated plasma was sent to hospital blood banks.

2.3. Convalescent plasma recipient

Recipients who met the inclusion criteria were selected by responsible physicians. Following signing the consent forms by recipient or authorized family members, the request for releasing convalescent plasma was sent to the hospital blood bank. Plasma transfusion to the recipient was performed according to standards for normal plasma including conformity of blood groups. The first 500 cc (one unit) plasma was infused within four hours and if the patient did not show any improvement after 24 h, based on the decision of responsible physician, another unit of plasma was administrated. All clinical and para clinical data was recorded and transferred to the researcher. Patients' follow up during hospitalization was performed by a monitoring chart every 12 h.

2.4. Patients

Criteria for inclusion and exclusion of the patients for this clinical study were as followings.

Inclusion Criteria - Patients who met all following criteria received convalescent plasma:

1 Age ≥ 18 years
2 Confirmed COVID-19 infection through laboratory (RT-qPCR) and/or lung involvement confirmed with chest imaging (CT scan)
3 Presence of some or all of disease clinical symptoms such as shortness of breath (dyspnea), respiratory frequency ≥ 20/min, fever and cough
4 Hospitalized with a blood oxygen saturation (SPO2) ≤93 % at rest on room air
5 ≤7 days since illness onset
6 Willingness to participate in the trail and sign the consent form

Exclusion Criteria - Patients with either of following criteria excluded from the trail:

1 Intubated patients or patients on mechanical ventilation.
2 Severe liver or kidney disease
3 Septic Shock
4 Physician decision that convalescent plasma therapy is not in patients' best interest
5 Patients with improving clinical conditions who meet hospital discharge criteria (defined as clinical recovery, i.e. return of body temperature, respiratory rate, oxygen saturation to normal and cough relief).
6 Known hypersensitivity to plasma

2.5. Outcome measures and definitions

The primary outcomes were the patient survival and length of hospital stay. Secondary outcomes included patients' needs for intubation, improvements in clinical symptoms such as tachypnea and para clinical measured of the patients and frequency of adverse effects resulting from plasma transfusion.

2.6. Statistical reporting

Categorical variables were expressed as counts (percentage), and continuous variable as Range and mean ± standard deviation (SD). The comparison demographic and clinical characteristics between two groups was assessed by *t*-test or Mann Whitney test for continuous variable and Chi-Square or Fisher's Exact test for categorical variables. All analyses were performed by using IBM® SPSS® 23.0. The P value less than 0.05 was considered significance level.

3. Results

3.1. Baseline features

Totally 189 patients (115 convalescent plasma treatment group and 74 control group) registered in this clinical study. Treatment and control groups, except for their number of patients, were matched based on gender, age and presence of two main comorbidities including hypertension and diabetes of mellitus (Table1). Their chest CT scan scores was also statistically matched indicating that both patient groups had similar clinical conditions on their entrance into the study. All patients in case and control groups received similar routine antiviral therapy including Lopinavir/Ritonavir, Hydroxychloroquine and an anti-inflammatory agent.

3.2. Safety, Clinical and para Clinical measures of the patients

Although there are some concerns regarding possibility of antibody dependent enhancement (ADE) in convalescent plasma therapy [25], except in one case (transient mild fever and chill following infusion of the plasma) no adverse effect was observed resulting from convalescent plasma transfusion during the study. Clinical parameters and laboratory measures of patient groups are shown in Tables 2 and no significant difference was found between treatment and control groups on their admission into the hospital. Table 3 shows comparison of outcomes including all-cause mortality, total hospitalization days and needs for intubation between the two patients' groups. Total of 98 (98.2 %) of patients who received convalescent plasma were discharged from hospital which is substantially higher compared to 56 (78.7 %) patients in control group. Length of hospital stay was significantly lower (9.54 days) in convalescent plasma group compared with that of control group (12.88 days). Only 8 patients (7%) in convalescent plasma group required intubation while this value was 20 % in control group.

4. Discussion

Based on results of this multicenter clinical study administration of convalescent plasms to COVID-19 infected patients resulted in

Table 2
Clinical parameters and laboratory measures of patient groups on admission.

Factor		Patient groups		p-value
		Plasma (n = 115) Mean ± SD	Control (n = 74) Mean ± SD	
Vital signs	SpO2 (%)	85.95 ± 6.42	84.00 ± 8.57	0.100
	sBP	124.68 ± 16.70	125.86 ± 17.16	0.872
	dBP	75.56 ± 10.71	79.74 ± 13.21	0.088
Laboratory Parameter	WBC	7.53 ± 5.07	7.89 ± 4.74	0.464
	Lymph	1346 ± 2822	1189 ± 722	0.542
	Hb	13.77 ± 1.93	14.49 ± 8.82	0.709
	PLT	196.50 ± 77.60	207.82 ± 86.97	0.289
	CRP	26.27 ± 28.66	33.65 ± 29.90	0.116
	LDH	676.09 ± 289.77	654.33 ± 317.68	0.520
	Albumin	3.58 ± 0.54	3.49 ± 0.54	0.397
	Cr	1.17 ± 0.89	1.37 ± 1.48	0.205
	BUN	20.26 ± 13.72	20.56 ± 15.93	0.957
	Ferritin	472.11 ± 426.29	454.95 ± 318.98	0.461
	CPK	264.44 ± 232.98	311.33 ± 389.74	0.241
	ESR	49.25 ± 29.17	58.39 ± 30.15	0.104

significant improvements of their clinical outcomes including all-cause mortality, hospital length of stay and needs to mechanical ventilation. Similar to the most viral illnesses the primary immune response develops by days 10–14, which is followed by virus clearance. Therefore, transfusion of convalescent plasma at the early stage of disease theoretically should be more effective. Early administration of convalescent plasma in COVID-19 patients is a critical measure for its clinical efficacy. Therefore, all patients in treatment group received convalescent plasma in less than 3 days of their hospital admission. However, availability of blood group match plasma was a determinant factor to define time of convalescent plasma administration.

Convalescent plasma substantially reduced all-cause mortality in treatment group compared with control group (14.8 % vs 24.3 %). However, this was not statistically different. Smaller number of patients in control group (74) compared to plasma group (115) might contribute to this phenomenon.

Convalescent plasma therapy significantly reduced patients' hospitalization period from 12.88 days to 9.54 days (Table 3). This obviously increases availability of hospital beds in this virus pandemic. This effect also will considerably reduce treatment costs of COVID-19 infected patients. It should be mentioned that for this comparison we consider date of admission as start day of hospitalization for both treatment and control groups. However, based on calculation of length of hospital stay since administration of convalescent plasma, reduction in length of hospitalization will be more prominent and hospitalization period of treatment group will further reduce to 6.25 days (Table 3). Additionally, 28.1 % of patients who received convalescent plasma discharged from hospital in less than 5 days after transfusion compared to 8.9 % in control group.

Convalescent plasma also significantly reduced needs to mechanical ventilation in treatment group compared to control group (7% vs 20.3 %). Since it was previously reported that patients who require intubation have poor prognosis [26] this reduction likely contributed to better final outcomes in convalescent plasma group.

5. Study limitation

Due to clinical features of the patients it was not possible for the investigators to design the study as a randomized clinical trial. Therefore, the main limitation of this study was related to assigning patients into control group. Due to ethical consideration, responsible physicians were reluctant to deprive COVID-19 patients from convalescent plasma therapy. Therefore, patients in control group were mainly comprises of patients with mild clinical presentation who did not have blood group convalescent plasma match on their hospital admission or in the next 3 days. That is why number of patients in control group is substantially smaller than treatment group. The other limitation is the use of other treatment regimens including antiviral medications along with convalescent plasma transfusion, which was inevitable.

In this study convalescent plasma administered in less than 3 days of hospital admission, it is unclear whether this timing is optimal or if earlier administration might have been associated with different clinical outcomes. Although we have administrated 500 mL of convalescent plasma, optimal volume of plasma should also be determined.

6. Conclusion

The nonrandomized clinical trial presented here demonstrates the clinical efficacy of convalescent plasma in COVID-19 infected patients and indicates that convalescent plasma treatment should be considered as a safe and effective therapy for COVID-19 patients. Convalescent plasma therapy substantially improved patients' survival, significantly reduced hospitalization period and needs for intubation in COVID-19 patients in comparison with control group. Despite some limitations, this clinical study provides strong evidence to support the efficacy of convalescent plasma therapy in COVID-19 patients and therefore this therapy is recommended for better management of these patients.

Table 3
Comparison of primary and secondary outcomes between the two groups.

Outcome		Patient groups		p-value
		Plasma (n = 115)	Control (n = 74)	
All-cause mortality	Died, (n; %)	17 (14.8 %)	18 (24.3 %)	0.09
	Alive, (n; %)	98 (85.2 %)	56 (75.7 %)	
Length of stay, day[1]	Mean ± SD	9.54 ± 5.07	12.88 ± 7.19	0.002
	Range	2 – 24	2 – 32	
Length of stay, day[2]	Mean ± SD	6.25 ± 4.33	12.88 ± 7.19	0.000
	Range	0 – 20	2 – 32	
Patients discharged from hospital ≤5 days post admission	n (%)	27 (28.1 %)	5 (8.9 %)	0.010
Intubation	No, (n; %)	107 (93 %)	59 (79.7 %)	0.006
	Yes, (n; %)	8 (7.0 %)	15 (20.3 %)	

[1]Total hospital stay based on 1st day of hospital admission.
[2]Total hospital stay based on 1st day of convalescent plasma transfusion.

Declaration of Competing Interest

The authors declare that there are no competing interests

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CRediT authorship contribution statement

Hassan Abolghasemi: Conceptualization, Methodology, Project administration, Supervision, Writing - review & editing. **Peyman Eshghi:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing - review & editing. **Abdol Majid Cheraghali:** Conceptualization, Methodology, Supervision, Writing - review & editing. **Abbas Ali Imani Fooladi:** Conceptualization, Methodology, Project administration, Supervision. **Farzaneh Bolouki Moghaddam:** Investigation. **Sina Imanizadeh:** Investigation. **Matin Moeini Maleki:** Investigation. **Mohammad Ranjkesh:** Investigation. **Mohammad Rezapour:** Investigation. **Ali Bahramifar:** Investigation. **Behzad Einollahi:** Investigation. **Mohammad Javad Hosseini:** Investigation. **Nematollah Joneidi Jafari:** Investigation. **Mohamad Nikpouraghdam:** Investigation. **Nariman Sadri:** Conceptualization, Funding acquisition, Methodology. **Mokhtar Tazik:** Data curation, Project administration. **Shanaz Sali:** Investigation. **Shamsi Okati:** Data curation. **Elham Askari:** Investigation. **Payam Tabarsi:** Investigation. **Jafar Aslani:** Investigation. **Ehsan Sharifipour:** Investigation. **Mohammad Hossein Jarahzadeh:** Investigation. **Nastaran Khodakarim:** Investigation. **Mahmood Salesi:** Data curation. **Ramezan Jafari:** Investigation. **Samira Shahverdi:** Investigation.

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