Original Article

Effects of Adding Convalescent Plasma Therapy for Treatment of COVID-19 Patients with Severe and Critical Symptoms: a Descriptive Study of 12 Cases

Shahnaz Sali[1], Shabnam Tehrani[1], Ensieh lotfali[2], Davood Yadegarynia[1], Sara Abolghasemi[1*]

[1]Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Medical Parasitology and Mycology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Received: 20 September, 2020; Accepted: 21 December, 2020

Abstract

Background: Severe symptoms of COVID-19 could be actually life-threatening and fatal. No effective treatment has been proposed yet. Plasma from COVID19 recovered patients may be effective according to past similar studies of some other viral infections.

Materials and Methods: This study was conducted at the infectious disease ward of Shahid Labbafi Nejad Hospital (Tehran, Iran) from 3rd of April 2020 up until 3rd of May 2020. Clinical information for the 12 patients, before and after receiving convalescent plasma transfusion was obtained from a review of the hospital computer medical system retrospectively and analyzed.

Results: Out of 12 patients with Covid-19 who received convalescent plasma**,** 7 patients were male (58.3%) and 5 were female (41.7%). The mean age of the patients was 52 years**.** Among them, 50% (n=6), improved and discharged and the rest of them died**.** Mean O_2 saturation of patients with final outcome of death and discharged before plasma therapy were 67 (33%) and 77 (83%), respectively, an improvement, defining partial resolution of lesions of chest CT scan or stop in progression of infiltrations was detected in all of 6 discharged patients.

Conclusion: Convalescent plasma may have effective role in improving O_2 saturation, lymphopenia and CT scan lesions and also decreasing inflammatory factors of cases with severe manifestations but could not change prognosis for critically ill patients. Therefore, an early administration of convalescent plasma may be helpful.

Keywords: Convalescent Plasma, COVID-19, treatment, severe

***Corresponding Author:** Sara Abolghasemi, Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: Saraabolghasemi1@gmail.com, Saraabolghasemi@sbmu.ac.ir, Orcid: https://orcid.org/0000-0001-7117-6079

Please cite this article as: Sali Sh, Tehrani Sh, Yadegarynia D, Abolghasemi S. Effects of Adding Convalescent Plasma Therapy for Treatment of COVID-19 Patients with Severe and Critical Symptoms: a Descriptive Study of 12 Cases. Novel Biomed. 2021;9(2):39-45.

Introduction

Treatment of COVID-19 patients with severe and critical symptoms has become a serious global challenge. Presently, no particular treatment has been effective for critically ill patients. Oxygenation, combination of antivirals and some drugs such as remdesivir, were somewhat hopeful for severe and critical patients. Current data are not sufficient and adequate, yet[1]. Plasma from COVID-19 recovered patients has antibodies to the virus and it may be used as an effective treatment[2].

About 15 years ago plasma or immunoglobulins of patients recovered from severe acute respiratory syndrome (SARS) was used as a salvage therapy for patients with critically ill presentations. This study together with several other studies has shown decrease in mortality and hospital stay of SARS patients after using convalescent plasma[3-5]. Moreover, using plasma of improved patients has been reported in the outbreak of other infections, such as H1N1 influenza, Ebola, and MERS (Middle East respiratory syndrome)[2, 6].

Theoretically prescribing convalescent plasma can be effective for treatment of COVID-19 patients[4]. Recently, the US Food and Drug Administration has approved the use of convalescent plasma for treatment of people who are critically ill with COVD-19[2]. However, the potential clinical advantages and disadvantages of convalescent plasma in COVID-19 remain unclear; accordingly, we evaluated response to therapy and outcome of 12 severe and critical COVD-19 patients who received convalescent plasma, as part of the treatment of their diseases.

Methods

This study was conducted at the infectious disease ward of Shahid Labbafi Nejad Hospital (Tehran, Iran), one of the educational hospitals of Shahid Beheshti University of Medical Sciences, during a period starting from 3rd of April 2020 up until 3rd of May 2020, when the follow up ended.

Clinical information for the 12 patients, before and after receiving 1 dose (650cc) convalescent plasma transfusion was obtained from a review of the hospital computer medical system retrospectively and they included the following: demographic data, days of admission from symptom onset, presenting symptoms, data about different treatments; including mechanical ventilation, antiviral therapies, laboratory data (White blood cell count, lymphocyte count, inflammatory factors C-reactive protein (CRP), Lactate Dehydrogenate (LDH), Blood type, medication administration, O_2 saturation rate and ventilator use data. The medical history of the patients was reviewed for any underlined diseases, as well.

All patients met such inclusion criterion as: (1) symptoms suggestive of COVID-19 pneumonia (fever, cough, dyspnea, myalgia); (2) chest computed tomography (CT) scan suggestive of COVID-19

Patients who were classified as critical or severe cases received plasma. Critical patient was defined as a patient with respiratory failure, shock or multiple organ dysfunction or failure and cases with dyspnea, respiratory rate ≥30 breaths per min, oxygen saturation≤ 93% with increase in lung infiltrate >50% in 24-48h were described as severe cases[7]. A total of 12 donors of convalescent plasma were between the ages of 35 to54years. The donors had been well for at least 10 days, with an average of anti-COVID 19 IgG 1161.5 mg/dl.

Results

Out of 12 patients with Covid-19 who received convalescent plasma between April 3rd and May 3rd, 2020, 7 patients were male (58.3%) and 5 were female (41.7%). The mean age of the patients was 52 years. The most common symptoms were dyspnea, myalgia and fatigue; noted amongst 91.7% (11/12), 75% (9/12) and 75% (9/12) (Table1); respectively. The mean length of hospital stay was 23.66 days for all 12 patients.

"A" group blood type had the highest percentage of blood types in patients. The most common underlined disease was diabetes (5/7) 41.7%.

The mean O_2 saturation of all 12 cases without O_2 supplement therapy was 84% at the admission and 72.5% just before transfusion of plasma. Only one of these patients was receiving mechanical ventilation at the time of transfusion. Although. intubation was occurred in average 8.57 days after admission for 7 of our study cases.

Table 2 shows details of laboratory results at admission time, before and after convalescent plasma transfusion. All of 12 patients had bilateral grand glass opacities in chest CT scan imaging before plasma transfusion and 2 patients had also consolidation. Moreover, 5 patients showed some degree of crazy paving pattern. An improvement, defining partial resolution of lesions of chest CT scan or stop in progression of infiltrations was

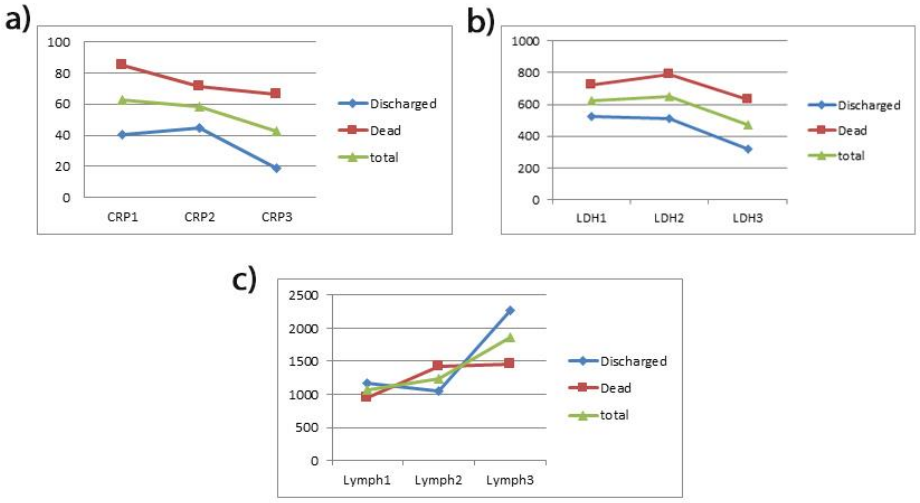

Figure 1. Changes of mean CRP level, mean Lymphocyte count and mean LDH level of Patients Receiving Convalescent Plasma Transfusion at admission time, before and after transfusion, considering the outcomes; a) Mean CRP Level, b) Mean LDH level, c) Mean Lymphocyte count.

detected in all of 6 discharged patients (Fig. 2).

Among our patients, 50% (6), improved and discharged after receiving plasma and the rest of them died. The cause of death of 5 of 6 patients were classified as ARDS and 1 patient (number 5) died of septic shock and K*lebsiella pneumonia* was detected in two blood cultures, just before death.

In addition to hydroxychloroquine, which was prescribed to all of the study patients, half of the patients received Kaletra (Lopinavir- Ritonavir) 400/100 mg twice a day, and the other half received Favipiravir, 1200mg for loading 600mg every 8 hours (Table 3).

In the context of a research project, Interferon β1-a 12

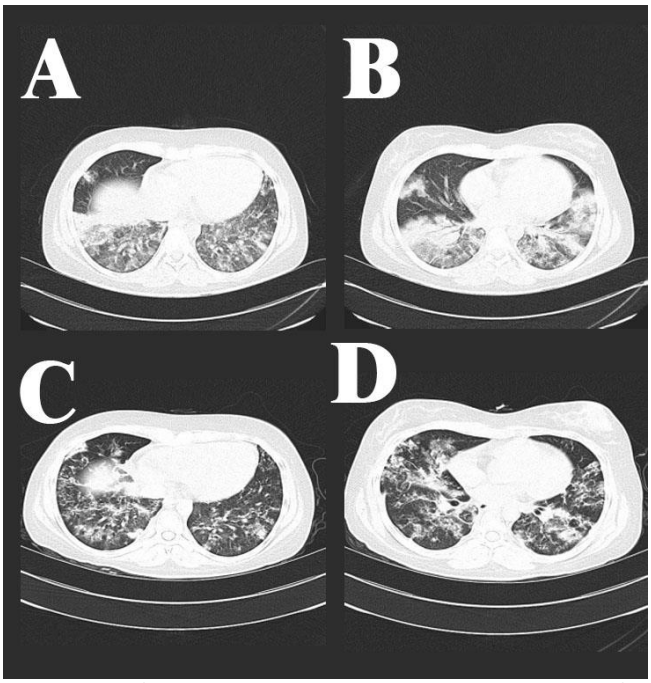

Figure 2. A 19 years old woman a known case of multiple sclerosis (case number 1), presented with fever, fatigue and myalgia. The first Chest CT scan showed bilateral grand glass opacities (GGO) and consolidation (A, B), she received hydoxychloroquine and Kaletra but fever was continued and O2 saturation was decreased, then interferon beta1-a was added but the general appearance of the patient became worse with the addition of shortness of breath and decreasing o2 saturation. Convalescent plasma was administrated 25 days after admission and after 7 days clinical and radiological manifestation were improved (C, D).

Table 1: Clinical Characteristic of SARS-CoV-2-Infected Patients Who Received Convalescent Plasma.

	1	2	3	4	5	6	7	8	9	10	11	12
Gender	F	M	M	F	M	M	M	F	F	M	M	F
Age	19	56	52	71	38	41	26	83	81	45	58	54
Blood Type	B	AB	A	A	B	O	A	AB	O	O	B	A
Fever	+	-	+	-	-	-	+	-	+	+	+	+
Cough	-	+	-	-	+	+	+	+	+	+	+	+
Myalgia	+	+	+	-	-	+	+	+	+	+	-	+
Dyspnea	-	+	+	+	+	+	-	+	+	+	+	+
Fatigue	+	+	+	+	+	-	+	-	+	+	-	+
Length of hospital stayed	30	19	14	18	24	8	23	30	35	7	35	41
SO2% (Admission to hospital)	89	85	78	75	91	89	96	90	62	85	82	88
SO2% (Just before transfusion)	82	60	78	73	78	68	84	87	65	60	68	68
SO2% (Posttransfusion)	94	65	89	68	73	60	94	95	60	65	88	95
Intubation	No	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes
Length of hospitalized till intubation	-	10	-	5	9	7	-	-	19	5	-	9
Length of hospitalized till transfusion	25	16	7	6	8	5	8	16	20	3	21	7
Past diagnosis												
Diabetes	-	+	-	-	-	+	-	+	+	+	-	-
Hypertension	-	-	-	-	-	-	-	+	-	-	-	-
Chronic kidney disease	-	-	-	-	-	+	-	+	-	-	-	-
Wegner	-	-	-	+	-	-	-	-	-	--		+
Ischemic heart disease	-	-	-	-	-	-	-	-	+	-	-	-
Multiple sclerosis	+	-	-	-	-	-	-	-	-	-	-	-
Psoriasis	-	-	+	-	-	-	-	-	-	-	-	-
Outcome	Discharged	Dead	Discharged	Dead	Dead	Dead	Discharged	Discharged	Dead	Dead	Discharged	Discharged

million unit in 3 subcutaneous doses were administrated for 6 patients, in addition to other regimens.

Discussion

In this study, 12 patients who were severely or critically ill with COVID-19 were treated with convalescent plasma. Previous studies have reported the use of convalescent plasma transfusion in the treatment of various infections. In addition to antiviral treatment, virus specific neutralizing antibody, may improve viral clearance and interfere the entrance of virus into target cells, remain the main mechanism for the combating the diseases by the host[8].

Among 12 patients in the study, 6 patients showed improved clinical manifestations, so they were discharged with good general condition. The mean O_2 saturation of the discharged patients was about 10% higher than the dead group (77.83% vs.67.33%) at the admission time, Therefore, it raises the possibility that severe cases had better response to plasma therapy in comparison to the critical patients.

Without considering the outcome, our results indicate that the average of CRP, as an inflammatory biomarker was decreased in Posttransfusion time compared to the admission time. It seems convalescent plasma has been

Table 2: Comparison of laboratory results at admission time, before and after convalescent plasma transfusion.

	1	2	3	4	5	6	7	8	9	10	11	12	Mean
C-reactive protein													
Admission to hospital	41	36	20	160	50	150	22	41	28	87	40	77	62.66
Just before transfusion	69	42	32	160	77	60	25	38	49	41	45	60	58.16
Posttransfusion	22	50	16	56	56	45	5	35	140	50	25	8	42.33
WBC count /ml													
Admission to hospital	3900	5900	9200	22100	8500	6800	7300	6600	3500	5700	7800	2300	7442
Just before transfusion	3500	7500	13100	16200	14500	5800	10000	7000	9100	6400	16800	4100	9500
Posttransfusion	5200	4100	8200	8600	6800	8400	7000	7500	2100	5350	6800	19000	7420
Lymphocyte \ml													
Admission to hospital	390	1298	1380	105	1700	340	2409	1660	1400	855	780	437	1062.83
Just before transfusion	350	1875	1310	810	1450	1450	1400	1050	2275	640	2016	145	1110
Posttransfusion	936	820	1804	2150	1904	2100	1750	1875	420	1337	1496	5700	1857.66
Platelets $*10^3$ /ml													
Admission to hospital	130	167	345	183	210	381	190	284	166	250	160	135	216
Just before transfusion	145	135	400	207	219	210	125	220	151	146	190	216	197
Posttransfusion	168	124	225	90	85	184	165	280	100	90	155	195	155.08
LDH													
Admission to hospital	471	621	420	980	710	887	695	372	880	280	661	548	627.08
Just before transfusion	601	500	400	990	590	890	690	300	875	913	601	460	650.83
Posttransfusion	224	480	320	685	520	760	420	250	435	895	442	250	473.41
Albumin													
Admission to hospital	2.2	2.8	2.9	2.5	2.4	3.5	3.8	3.4	3.5	3.4	2.9	3.9	3.1
Just before transfusion	2.1	2.6	2.2	2.4	2.3	3.4	2.9	3.0	3.2	4.2	2.6	3.5	2.86
Posttransfusion	3.2	2.0	3.2	2.8	3.1	1.7	3.2	3.2	3.1	3.8	2.2	2.2	2.8

effective in reducing inflammatory factors. Study of Shen and colleagues showed similar results[8]. But the dead cases of our research had higher CRP level in comparison of discharged patients at both admission and post-transfusion time (Table 4 & Fig. 1). As it is mentioned in many articles, high level of CRP of COVID-19 patients may indicate severity of the disease [10,11].

The number of leukocytes did not show any difference before and after the plasma transfusion. But lymphocyte count of all of 12 cases was increased after receiving plasma. The dead group had lower mean lymphocyte count at the admission time (Table 4). It could be a predictor worse prognosis for them. The relation between lymphopenia and prognosis has been discussed in some articles[11-13]. There was an increase in the median of lymphocyte count and a decrease of LDH level for all patients after plasma transfusion which was consistent with the pervious and similar study[8]. LDH level could be an indicator of lung injury for critically ill COVID-19 patients[11]. In our study, the median level of LDH among dead patients which showed critical manifestations and lower O_2 saturation at the admission time was higher than patients with improved outcome (Table 4 and Fig. 1).

The present study indicates that there is an association between diabetes and death of patients (Table 1) comorbidities and underlying diseases have been

Table 3: COVID-19 treatment drugs and other medication of patient receiving convalescent plasma.

Patients / Drug	1	2	3	4	5	6	7	8	9	10	11	12
Medication before COVID-19	**Interferon**	**Metformin**	**Methotrexate**	**Steroid**	**-**	**Insulin Captopril Metoral**	**-**	**Insulin**	**Captapril Metoral**	**Insulin**	**-**	***Prednisolon***
COVID-19 treatment drugs	Hydroxychloroquine Kaletra Interferon-beta	Hydroxychloroquine Favipiravir	Hydroxychloroquine Interferon-beta Favipiravir	Hydroxychloroquine Kaletra	Hydroxychloroquine Interferon-beta Favipiravir	Hydroxychloroquine Kaletra	Hydroxychloroquine Interferon-beta Favipiravir	Hydroxychloroquine Kaletra	Hydroxychloroquine Interferon-beta Favipiravir	Hydroxychloroquine Favipiravir	Hydroxychloroquine Kaletra Interferon-beta	Hydroxychloroquine Kaletra

Table 4: Changes of CRP level, Mean Lymphocyte count and LDH level of Patients Receiving Convalescent Plasma Transfusion at admission time, before and after transfusion, considering the outcomes.

	CRP1	CRP2	CRP3	Lymph1	Lymph2	Lymph3	LDH1	LDH2	LDH3
Discharged	40/16	44/83	18/5	1176	1045/16	2260	527/83	508/66	317/66
Dead	85/16	71/5	66/16	949/66	1416/66	1455	726/33	793	629/16
Total	62/66	58/165	42/33	1062/83	1230/91	1857/5	627/08	650/83	473/41

suggested as predictors of poor prognosis in many articles[14-16]. Regardless the treatments achieved for patients, diabetes should be considered as an important risk factor for mortality, diseases progression and lung injury. So, diabetic Covid 19 patients may need serious attention and care[16, 17].

In our study, convalescent plasma was used as a salvage therapy. Thus, before plasma therapy, patients received different types of treatment (Table 3). 6 patients received Interferon β1-a in which 4 of them were among patients with discharged or improved outcome. Currently, some studies show encouraging findings with Interferon β1 therapy at the early stages of COVID-19 diseases[18,19].

In the present study, patients with better outcome and response to plasma had generally better condition in O_2 saturation and laboratory tests at the admission time and before plasma transfusion (Table 4).

The present study has some limitations; the number of study cases was small and limited and the control group was not defined for them. All patients received different types of antiviral agents before and concurrent with plasma therapy. Different time of transfusion of plasma from the admission time may affect different outcomes. Finally, we had limitation for measuring of viral load before and after plasma therapy. Correlation of viral loads with disease severity has been reported in some studies and neutralizing antibodies of plasma may improve viral clearance[8].

Conclusion

Convalescent plasma may have effective role in improving O_2 saturation, lymphopenia and CT scan lesions and also decreasing inflammatory factors of cases with severe manifestations but could not change prognosis for critically ill patients. So, an early administration of convalescent plasma may be helpful.

Acknowledgment

None.

References

1. Cunningham AC,Guh HP, Koh D . Treatment of COVID-19: old tricks for new challenges Critical Care

(2020)24:91,https://doi.org/10.1186/s13054-020-2818-6
2.Janice Hopkins Tanne , Covid-19: FDA approves use of convalescent plasma
to treat critically ill patients BMJ 2020;368:m1256
3. Lai ST. Treatment of severe acute respiratory syndrome. Eur J Clin Microbiol Infect Dis 2005;24:583–91.
4. Soo YO, Cheng Y, Wong R, et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. Clin Microbiol Infect 2004;10:676–78.
5. Cheng Y, Wong R, Soo YO, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis 2005;24:44–6.
6. WHO. Use of convalescent whole blood or plasma collected from patients recovered from Ebola virus disease for transfusion, as an empirical treatment during outbreaks. 2014. http://apps.who.int/iris/rest/ bitstreams/604045/retrieve (accessed Feb 20, 2020).
7. https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf
8. Shen Ch, Wang Zh, Zhao F, Yang Y, et al; Treatment of 5 Critically ill patients with COVID-19 with convalescent plasma, JAMA. 2020;323(16):1582-9.
10. Wang l, C-reactive protein levels in the early stage of COVID-19; Médecine et maladies infectiousness. 2020;50:332-4.
11. Yan li, Zhang HT, Goncolves J and et al; An interpretable mortality prediction model for COVID-19 patients. Nature Machin e Intelligence. 2020;2:283–8.
12. Haung G, Kovali AJ, Garber CJ, Prognostic Value of Leukocytosis and Lymphopenia for Coronavirus Disease Severity; https://wwwnc.cdc.gov/eid/article/26/8/20-1160_article
13. Tan l, Wang Q, Zhang D and et al; Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study:https://doi.org/10.1038/s41392-020-0148-4
14. Ruan Q, Yang K, Wang W, Jiang L and et al; Clinical predictors of mortality due
to COVID‑19 based on an analysis of data of 150 patients from Wuhan, China; Intensive Care
Med (2020) 46:846–848https://doi.org/10.1007/s00134-020-05991-x
15.Haybar H, Kazemnia K, Rahim F, underling chronic disease and COCID-19 infection: a state of the art review, Jundishapour J Chronic Dis Care, Online ahead print; 9(2): e103452. Doi: 10.5812/ggcdc. 103452.
16. Huang L, Rim MA, Pranata R; Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia e A systematic review, metaanalysis, and meta-regression; Diabetes & Metabolic Syndrome: Clinical Research & Reviews 14 (2020) 395e403.
17. Roncon L, Zuin M, Rigatelli G, Zuliani G; Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome; Journal of Clinical Virology 127 (2020) 104354.
18. Hung IF, Lung K-C, Yuk Kand et al; Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial; Lancet 2020; 395: 1695–704 Published Online May 8, 2020 https://doi.org/10.1016/ S0140-6736(20)31042-4.
19. Sallard E, Lescure F-X,Yazdanpanah Y and et al; Type 1 interferons as a potential treatment against COVID-19; https://doi.org/10.1016/j.antiviral.2020.104791.