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Case Series

Compassionate use of convalescent plasma for the management of severe pneumonia in critically ill COVID-19 patients-a single center experience, Kerala, India

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ABSTRACT

We assessed treatment effectiveness with convalescent plasma in critically ill COVID-19 pneumonia patients and their association with reduction in C reactive protein level as a sensitive inflammatory marker to the ongoing cytokine storm. Retrospective cohort study based on the detailed electronic medical chart review. The primary outcome was a clinical improvement on day 14, defined as the reduction in cytokine storm as demonstrated by a drop in acute phase reactant C reactive protein; de-escalation from the prior mode of oxygen delivery or not on mechanical ventilation in critically ill COVID-19 patients. C reactive protein was measured by using immunoturbidimetry. IgG antibody against spike protein S1 was measured by chemiluminescent immunoassay. Of 14 patients, all had severe COVID-19 pneumonia [category C], and 9 (64%) were mechanically ventilated soon after the admission into the medical intensive care unit. De-escalation of the oxygenation strategy mode was noted in 11 (79%) patients after convalescent plasma infusion. All patients showed a significant drop in C reactive protein when compared to pre-infusion and post-infusion day 5. Early compassionate use of convalescent plasma with higher titters of IgG antibodies against S1may positively benefit the overall outcome in critically ill COVID-19 patients with severe pneumonia.

Keywords: Convalescent plasma therapy, Severe COVID-19, C reactive protein

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has developed into a pandemic with global severe public health and economic sequelae. The WHO declared coronavirus disease a pandemic by March 2020.[1] The threatening pandemic spread rapidly worldwide and resulted in the infection of 107 million, and caused the death of 2.34 million people worldwide. COVID-19 resulted in an infection of 9, 97,000 and caused the death of 3902 patients in Kerala, India.[2] There are no specific therapeutic agents against the virus. In the absence of effective, established treatment, COVID-19 is managed mainly using antiviral agents with a low dose of steroids in addition to supportive care. Addressing a rapidly emerging pandemic can become an urgent, local, regional, or global public priority.

Serum therapies were successfully used to treat infectious diseases (anthrax, plague, scarlet fever, measles, tularaemia, diphtheria, dysentery, meningococcal meningitis, rabies, pneumococcal pneumonia) for half a century after Emil Van Boehring first demonstrated their effective use in diphtheria.[3] Convalescent plasma use declined rapidly after the invention of antibiotics. However, human and animal-derived immunoglobulin remain important therapies for a variety of viral infections (parvovirus, CMV, hepatitis B, hepatitis A, rabies).[4] Additionally, there is a precedent in the usage of convalescent plasma in the modern era for empirical treatment of the Ebola virus in 2014 and the middle East respiratory syndrome in 2015.[5]

The potential efficacy of convalescent plasma or serum will depend on the extent to which antibodies generated during recovery of the donor would directly neutralize a virus or otherwise mediate an effective immune response. Additionally, questions arise regarding the effective therapeutic dose and whether it can be derived from conventional units of plasma or serum. There is an ample number of studies in patients with COVID-19 which established independent association of biomarkers of inflammation (such as C -reactive protein, interleukin [IL-6], and ferritin) with poor overall outcome in severe disease.[6-9] Similarly, multiple research works demonstrated prognostic significance of C-reactive protein in hospitalized patients with COVID-19 disease.[10-12] Observations from previous studies stated that convalescent plasma therapy might be considered for critically sick COVID-19 patients.[13] There is a bias owing to a combination of non-randomized evaluations such as participant selection, timing, and dosage of plasma. The purpose of this study was to describe the clinical experience of convalescent plasma and its effect in critically ill COVID-19 patients.

CASE SERIES

This case series includes patients who were critically ill with laboratory-confirmed COVID-19, diagnosed by detecting SARS-CoV-2RNA by CBNAT technology [GeneXpert, Cepheid, CA, USA] and received convalescent plasma transfusion. Inclusion criteria for compassionate convalescent plasma therapy were all the following-Age>18 years, Laboratory confirmed diagnosis of infection with SARS CoV-2, Severe life threatening COVID-19, informed consent provided by patient or relative and emergency approval from institutional ethics committee.

Severe COVID-19 is defined as one or more of the following: Respiratory rate ≥30/min, blood oxygen saturation ≤90% on room air, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen ratio of >300 and lung infiltrates>50% within 24-48 hrs.

Life threatening COVID-19 infection can see following symptoms-Respiratory failure, septic shock and multiorgan failure.

Exclusion criteria for the study excluded patients having age<18 years and no hypersensitivity to blood products.

The patients were transfused with 400 ml convalescent plasma in 200 ml divided doses 24 hours apart. They also received antiviral treatments and other supportive treatments till they become COVID 19 negative. Patients could get a low dose of steroids, anticoagulation, and antivirals as per the discretion of treating physicians. The donors who are recovered from moderate to severe SARSCOV-2 infection were motivated to donate convalescent plasma. They were screened according to national AIDS control organization [NACO] guidelines. Donor eligibility criteria for convalescent plasma donation are mentioned in supplementary Table 1.

Donors were screened by using an apheresis donor screening questionnaire followed by a brief physical examination. Donors who had COVID-19 infection for more than four months were excluded from donation. Blood grouping (ABO and Rh typing) was done along with complete blood count, including haemoglobin, haematocrit, platelet count, total and differential leukocyte count. Donors with haemoglobin>12.5 g/dl, platelet count more than 150000 per microliter, and total leukocyte count within normal limits accepted.

Screening for HIV, HBV, HCV, syphilis, and malaria was performed on the donors and was accepted if negative. Total serum protein, if measured more than 6 gm/dl, was taken. Plasmapheresis of the donors were performed using TRIMA ACCEL apheresis machine (TERUMO BCT, CO, USA). Pre-donation counselling and informed consent are taken before each donation. The levels of serum IgG antibody titer against S protein to SARS-CoV-2 was measured by chemiluminescent immunoassay (CLIA) using a validated commercial kit (VITROS® anti-SARS-COV-2IgG assay, ortho clinical diagnostics, NJ, USA) following manufacturer's instructions. The assay is interpreted as low titer positive when the assay value is ≥1 . The positive titers were reclassified as low titer [1.0-9] and high titer [≥9].[14-16] The antibody titer of convalescent plasma donors has been detailed in supplementary Table 1.

Frozen convalescent plasma units were transfused after thawing according to standard procedure. The initial dose of 200 ml convalescent plasma was transfused on the day of approval from the medical board (day 1), and if it was well tolerated second dose of 200 ml. The second convalescent plasma unit was from the same donor. Patients also received various treatment regimens [low dose steroids, repurposed antiviral agents (Remdesivir, favipiravir), anticoagulation along with broad-spectrum antibiotics] as per the discretion of the medical board under national guidelines for the management of COVID-19 by the government of India from time to time.

The primary outcome was overall (clinical and laboratory) improvement at day 14 after the administration of convalescent plasma. Clinical improvements were defined as being alive, de-escalation from existing oxygenation mode, or recovered. Laboratory parameter improvement was defined as the rate of reduction in systemic inflammatory response due to COVID-19 infection following transfusion of convalescent plasma and measured by serial monitoring of acute inflammatory marker (C reactive protein) in critically ill severe COVID-19 patients from a day before convalescent plasma transfusion till post-infusion-day 5. Non-improvement was defined as death, being continued or escalated from the prior mode of oxygen therapy, or worsening overall clinical status. Serious events, including allergic reactions, transfusion-associated circulatory overload, and transfusion-associated lung injury and anaphylaxis monitored. Statistical analysis was done using graph pad prism version 9. An unpaired t-test was used, and a value of 0.05 or less was considered statistically significant.

Of 17 requests for compassionate use of convalescent plasma therapy, 14 (82%) were approved by the medical board according to the inclusion and exclusion criteria. Characteristics of patients and donors are detailed in Table 1.

Table 1

Variables	Patients, (n=14); Median (%/ Range)
Number of patients	
Males	9 (64)
Females	5 (36)
Age (years)-median (IQR)	56.5 (24-76)
Blood group types	
O	5 (35)
A	3 (21)
B	6 (43)
AB	0
Time from positive SARS-CoV-2 PCR to receive convalescent plasma (days)	5.7 (2-11)
Co-morbidity	
Diabetes	5 (36)
Hypertension	5 (36)
Ischemic Heart disease	4 (29)
Chronic kidney disease	2 (14)
Chronic liver disease	2 (14)
Rheumatological disease	1 (7)
Malignancy	1 (7)
Oxygen delivery method prior to convalescent plasma transfusion	
Mechanical ventilation	9 (64)
Non-invasive ventilation	4 (29)
High flow nasal canula	1 (7)
Oxygenation through face mask	0 (0)
COVID-19 pneumonia status at convalescence plasma transfusion	
Mild	0
Moderate	0
Severe	0
Critical	14 (100)
De-escalation of oxygen delivery method post convalescent plasma infusion	11 (79)
Time from positive SARS-CoV-2 PCR to COVID-19 PCR negativity in patients got discharged (days)	27 (18-37)
Number of patients who succumbed to illness	5 (36)
Other treatments received	
Repurposed antiviral agents	14 (100)
Low dose steroids (Dexamethasone)	14 (100)
Anticoagulation	13 (92)
Broad spectrum antibiotics	14 (100)

Nine (64%) were males. The median age was 56.5 years (IQR 24-76). About a third had hypertension and diabetes. In all patients with the critical disease, 9 (64%) were on mechanical ventilation before convalescence plasma therapy. The median time from PCR diagnosis to convalescent plasma infusion was 5.7 days (IQR 2-11). Inflammatory response burden due to critical COVID-19 infections was assessed with the rate of reduction in C reactive protein levels following infusion of convalescent plasma. It was measured serially from a day before the transfusion of convalescent plasma to post-infusion day 5. The rate of drop-in C reactive protein levels is depicted in Figure 1.

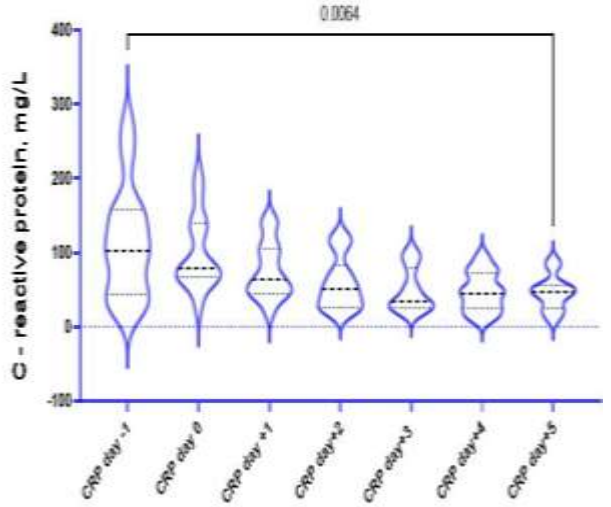

Figure 1

Characteristics of donors are presented in the Table 2. Ten donors (71%) were males. The median age was 32 years (IQR 24-44). The median IgG antibody titer was 12.6 (IQR4.1-25.9), and 10 (71%) donors were in the high titer group. The median levels of IgG antibody per donated unit were 12.6 (IQR 4.1-25.9). 71% of the donated convalescent plasma was in the high titer group. The ten donors of convalescent plasma were between 18-60 years of age.

The clinical outcome of improvement (clinical improvement defined as being alive, de-escalation from existing oxygenation mode and laboratory parameter improvement was defined as the rate of drop in C reactive protein following convalescent plasma transfusion) was attained as follows, 11 (79%) had de-escalation in the oxygenation mode, five (36%) patients died. There was a significant drop in acute phase reactant C reactive protein following convalescence plasma therapy prior to the day of transfusion when compared to day 5 (p=0.0064). In the study cohort who received convalescent plasma, 9 (64%) patients showed clinical improvement, and out of this, 7 (78%) were received a high titer of IgG antibodies. No serious adverse events were noted in this group.

Table 2

Variables	Donors, (n=14); Median (%/Range)
Number of patients	
Males	10 (71)
Females	4 (29)
Age (years)	32(24-44)
Blood group types	
O	5 (35)
A	3 (21)
B	6 (43)
AB	0
Time from negative SARS-CoV-2 PCR to donate convalescent plasma (weeks)	5.3 (4.5-8)
IgG antibodies titer in each donated unit of convalescent plasma	12.6 (4.1- 25.9)
Convalescent plasma group (Based on the titre)	
Low titer	4 (29)
High titer	10 (71)

DISCUSSION

This case series suggests that early compassionate administration of convalescence plasma with high titer IgG levels of antibodies against S1of SARS-CoV-2 may improve overall outcome in patients with critical COVID-19 infection. This series demonstrated the efficacy of convalescence plasma in rapidly reducing the systemic inflammatory response triggered by the COVID-19 infection when administered early in the course of illness. It also demonstrated improvement in oxygenation in the majority of the patient following convalescence plasma administration.

At present, there are no validated data from randomized clinical trials to evaluate the safety and efficacy of convalescent plasma for the treatment of severe COVID-19 infection. Convalescent plasma was used extensively in the United States of America through Mayo clinic's expanded access program (EAP). Based on the retrospective analysis of the EAP data by the Food and Drug Administration (FDA) and Mayo clinic, it was evident that patients who received convalescent plasma with high titers of SARS-CoV-2 neutralizing antibodies had better outcome.[17] Their analyses showed that convalescent plasma with higher antibody titer might be more effective in non-intubated patients when administered within 72 hours of COVID-19 diagnosis. These data, along with small randomized and non-randomized studies, observational cohorts, and few animals experiment works, lead to emergency use issuance.

The data regarding the possible development of any adverse events are infrequent and consistent with regular plasma transfusions for other therapy. The safety and

efficacy of convalescent plasma are not established in pregnancy and pediatric age groups. There are much available literature showing the positivity of administering convalescent plasma in critically ill patients from the onset of this pandemic. The first case series was published by Shen et al. at the end of March 2020.[18] The authors reported the case series of five critically ill patients with ARDS under mechanical ventilation. This study compared the clinical outcomes before and after transfusion. The study found out that four patients' ARDS resolved after 12 days after transfusion, and three patients were discharged while two patients were in stable conditions after the plasma therapy.

Similarly, Hu et al, demonstrated the effectiveness of early compassionate use of convalescent plasma in reducing the systemic inflammatory response through serial drop in serial C reactive protein levels like in our study.[19] Maor et al showed that use of convalescent plasma with a high titer of antibodies against S1 may improve the clinical outcome in patients with critically COVID-19 infection, and it was reciprocated in our study.[20] As per much available literature in the recent past, our study demonstrated the efficacy of early use of convalescent plasma.[21-24] In our study, almost all patients who succumbed to COVID-19 infections were older patients with multiple co-existing diseases.

CONCLUSION

Early compassionate use of convalescent plasma with a high titer of IgG antibody against S protein of SARS-CoV-2 may improve the overall clinical outcome in critical COVID-19 infections.

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SUPPLEMENTARY TABLES

Table 1: Donor eligibility criteria.

S. no.	Donor eligibility criteria
1	>18 years of age.
2	Males or female donors' weight >55 kg
3	Prior diagnosis of COVID-19 documented by laboratory test RT-PCR with symptomatic disease with fever and cough and complete resolution of symptoms at least 28 days prior to donation. Or Complete resolution of symptoms at least 14 days prior to donation and 2 negative real time PCR test for COVID-19 from nasopharyngeal swab collected 24 hrs apart.

Table 2: Demographic details and antibody titre of convalescent plasma donors.

S. No.	Age (Years)	Sex	Blood type	Donated plasma volume (ml)	Interval between COVID negativity and plasma donation (Weeks)	IgG antibody titer by CLIA method
1	38	M	B+	400	6	17.3
2	24	M	B+	400	8	25.9
3	29	M	O+	400	8	10
4	44	M	O+	400	4.5	6.67
5	33	M	B+	400	4.5	10.6
6	32	M	B+	400	6	6.81
7	35	M	A+	400	6	20.7
8	37	M	O+	400	7	9.26
9	31	M	B+	400	6	8.99
10	27	F	A+	400	6	9.81
11	32	F	A+	400	6	4.11
12	34	F	O+	400	6	18.7
13	29	F	B-	400	6	18.9
14	29	M	O+	400	6	8.29