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ORIGINAL RESEARCH

Efficacy of Convalescent Plasma Therapy in COVID-19 Patients at a Central India Tertiary Care Hospital

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ABSTRACT

Introduction: Coronaviruses, RNA viruses infecting various hosts, include severe strains like SARS-CoV and MERS-CoV, causing serious respiratory symptoms. Convalescent plasma therapy, using antibodies from recovered patients, has shown promise in reducing COVID-19 mortality and ICU needs.This study explores key aspects of convalescent plasma therapy and its potential effectiveness in treating COVID-19. **Material and methods:** The observational study at Netaji Subhash Chandra Bose Medical College, Jabalpur (Jan 2021 - Jun 2022), involved 40 COVID-19 patients. Inclusion criteria followed ICMR guidelines. Data on demographics, clinical parameters, and inflammatory markers were analyzed using SPSS/R. Ethical approval and informed consent were obtained. **Results:** The study involved 40 participants aged 20-80 years, 55% of whom were 40-60 years old. Males constituted 70%, and blood group 'B' positive was most common (35%). Comorbidities included diabetes (10%), mixed (5%), and hypertension (15%). Fever (62.5%), dyspnea (55%), and weakness (37.5%) were prevalent symptoms. Post-transfusion, D-dimer levels significantly increased. Among 36 on oxygen, 7 improved, 3 shifted to BIPAP, and 1 needed ventilation. No anaphylactic or febrile reactions occurred. Mortality was 83.33% among those with comorbidities. Overall, 52.5% were discharged, while 47.5% died. **Conclusion:** The study assessed convalescent plasma's impact on 40 COVID-19 patients, noting improvements primarily in those without comorbidities. It significantly raised D-dimer levels but showed minor changes in CRP levels. Mortality was notably higher among comorbid patients (83.33%). Of the total, 52.5% were discharged, and 47.5% succumbed, with no reported anaphylactic or febrile reactions. More research is warranted to refine convalescent plasma therapy, especially for complex cases.

Key Words-COVID-19, convalescent plasma (CP) therapy, Mortality

INTRODUCTION

The Coronaviridae family comprises viruses with positive-sense, single-stranded RNA genomes, ranging from 26 to 32 kilobases. These viruses have been identified in various avian and mammalian hosts, including bats, camels, mice, cats, dogs, and scaly anteaters.(1) While many coronaviruses cause mild or asymptomatic infections in humans, two particularly virulent strains have emerged in the last two decades: severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV).(2) These strains are associated with severe symptoms such as high fever, non-productive cough, myalgia, and dyspnea, often requiring ICU admission.There is concern that the similarity between viral and human proteins might provoke autoimmune responses due to molecular mimicry, especially in genetically predisposed individuals. This underscores the necessity of evaluating cross-reactivity between viral antigens and human proteins during vaccine development to mitigate potential autoimmune reactions.(3,4)

In December 2019, a new coronavirus emerged in Wuhan, now known as SARS-CoV-2, causing COVID-19. Its genetic similarity to bat coronaviruses suggests bats as the likely source. SARS-CoV-2 shares genetic links with SARS-CoV (79%) and MERS-CoV (50%).(5)

WHO named the disease COVID-19 on February 11, 2020, declaring it a pandemic on March 11, 2020. By April 17, 2020, there were 2,074,529 confirmed cases and 139,378 deaths globally, with a higher mortality

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rate than seasonal flu. Older adults and those with comorbidities face increased risk of severe outcomes.(6)

Passive antibody therapy, which administers preformed antibodies for immediate protection or treatment, has a history dating back to the 1890s. During epidemics, convalescent plasma (CP) therapy, using plasma from recovered patients containing antibodies, has been employed.(7,8)Multiple studies showed that collecting anti-SARS-CoV-2 antibody-rich plasma from recovered COVID-19 patients to reduce mortality rates and ICU needs.(9–11).This study explores key aspects of convalescent plasma therapy and its potential effectiveness in treating COVID-19.

AIMS & OBJECTIVES

1. To assess the clinical profile of COVID-19 patients who have received CP transfusions.
2. To evaluate changes in inflammatory markers (CRP and D-Dimer) in CP-transfused COVID-19 patients.
3. To analyze the oxygen requirement in CP-transfused COVID-19 patients.
4. To identify and document any adverse outcomes of CP transfusion in COVID-19 patients.
5. To evaluate the response to CP therapy in COVID-19 patients with comorbidities.

MATERIAL AND METHODS

Study Area and Target Population

Study was conducted in the Department of Medicine at Netaji Subhash Chandra Bose Medical College & Hospital, Jabalpur, Madhya Pradesh.

Study Period -The study period spans from January 1, 2021, to June 30, 2022.

Sample Size -The study includes 40 patients.

Study Design- This was an observational study.

Recipient Criteria for Transfusion of Plasma in COVID-19

Inclusion Criteria (As per ICMR Guidelines):

- Patients admitted with RT-PCR confirmed COVID-19 illness.
- Age >18 years.
- SpO2 <94% (range 90-94%) on room air.
- Respiratory rate ≥24/min.
- Availability of matched donor plasma.

Exclusion Criteria:

Relative Contraindications:

- Pregnant women.
- Breastfeeding women.
- Age <18 years.
- Dyspnea and/or hypoxia, fever, cough, including SpO2 <90% on room air.
- Respiratory rate >30/min.

Absolute Contraindications:

- Known hypersensitivity to blood products.

Donor Criteria for Plasma Donation in COVID-19

Eligibility of Donor Potential donors must meet the following criteria:

- **Age:**>18 years.
- **Weight:** Male or female donors with weight >55 kg.
- **Prior COVID-19 Diagnosis:** Documented by a laboratory test (RT-PCR) with symptomatic disease, including at least fever and cough.
- **Symptom Resolution:**
  - Complete resolution of symptoms at least 28 days prior to donation, **or**
  - Complete resolution of symptoms at least 14 days prior to donation with two negative real-time PCR tests for COVID-19 from nasopharyngeal swabs collected 24 hours apart.

The data collection for the study included the following methods: RT-PCR for COVID-19 was utilized to confirm the diagnosis, hematological investigations ,inflammatory markers were monitored to track CRP and D-Dimer levels, chest X-ray PA views were taken to evaluate lung conditions, and an apheresis system was used for plasma collection from donors.

Ethical Issues

Study was conducted after obtaining informed consent from the patients in their local language after obtaining approval from institutional ethic committee.

Funding Sources - No funding was received for this work.

Data Analysis Plan

All data will be documented using a structured schedule (case report form) and entered into a Microsoft Excel sheet. The data regularly checked for completeness and accuracy.

Statistical Analysis

The statistical analysis performed using statistical software such as SPSS (Statistical Package for the Social Sciences) or R software with p-value of <0.05 will be considered statistically significant.

1. **Descriptive Statistics:**
   - Continuous variables (e.g., age, SpO2 levels, respiratory rate, CRP, and D-Dimer levels) summarized using mean, median, standard deviation, and interquartile range.
   - Categorical variables (e.g., gender, presence of comorbidities, adverse outcomes) summarized using frequencies and percentages.
2. **Comparative Analysis:**
   - Paired t-tests or Wilcoxon signed-rank tests used to compare pre- and post-transfusion inflammatory markers and oxygen requirements

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Informed consent will be obtained from all participants, and the study will adhere to the ethical guidelines set forth by the institutional review board.

RESULTS

The study was conducted from January 1, 2021, to June 31, 2022, in the Department of Medicine, Netaji Subhash Chandra Bose Medical College, Jabalpur, Madhya Pradesh, India. A total of 101 COVID-positive patients were included for convalescent plasma transfusion, comprising 40 patients who fulfilled the ICMR criterion

Socio-demographic profile and baseline clinicalcharacteristics

The study included 40 participants aged between 20 and 80 years, with 55 % in the 40-60 age group. Among these participants, 70% were male and 30% were female. The most prevalent blood group was 'B' positive (35%), followed by 'A' positive (30%).(Table 1)

Socio demographic factors	Frequency (N=40) (%)
Age (in years)	
20-40	06 (15)
40-60	22 (55)
60-80	12 (30)
Sex	
Male	28(70)
Female	12 (30)
Blood group of recipients	
'A' positive	12(30)
'B' positive	14 (35)
'AB' positive	5 (12.5)
'O' positive	9 (22.5)
'AB' negative	--
'O' negative	--

Table1- Socio-demographic profile of Convalescent plasma recipients

In terms of comorbidities, 10% had diabetes mellitus, 5% had mixed comorbidities, 15% had hypertension, and 70% had none at all. The distribution of hemoglobin levels was as follows: 2.5% had levels below 8 gm/dl, 37.5% had levels over 12 gm/dl, and 60% had levels between 8 and 12 gm/dl. Furthermore, 97.5% had never received a blood transfusion before. Fever (62.5%), dyspnea (55%), and widespread weakness (37.5%) were the most common symptoms. Of the participants, 90% needed oxygen support, while 10% were on room air. According to laboratory results, 62.5% had increased D-dimer levels, 37.5% had moderate levels, and 62.5% had severe CRP levels.(Table 2)

Clinical Profile	Frequency (N=40) (%)
Co-morbidity	
Diabetes Mellitus	4(10)
Hypertension	6 (15)
Mixed	2 (5)
None	28 (70)
Hemoglobin (gm/dl)	
<8	1(2.5)
8-12	24 (60)
>12	15 (37.5)
Previous history of Blood transfusion	
Yes	1(2.5)
No	39 (97.5)
Symptoms	
Fever	25 (62.5)
Cough	9 (22.5)

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Shortness of breath	22 (55)
Generalized weakness	15 (37.5)
Sore throat	3 (7.5)
Asymptomatic	3 (7.5)
Oxygen requirement	
BiPAP	--
Mechanical ventilation	--
Oxygen support	36 (90)
Room air	4 (10)
CRP levels	
Mild (0.3mg/dl- 1.0mg/dl)	--
Moderate (1.0mg/dl- 10mg/dl)	15 (37.5)
Severe (>10mg/dl)	25 (62.5)
D- dimer levels	
<1000ng/ml	15 (37.5)
>1000ng/ml	25 (62.5)
Outcome	
Discharge	21 (52.5)
Death	19 (47.5)

Table 2- Baseline clinical profiles of Convalescent plasma recipients

Inflammatory markers pre and post CP therapy

Table 3 summarizes changes in CRP and D-dimer levels before and after plasma transfusion in 40 individuals. For CRP levels, there were moderate and severe groups. While moderate CRP levels showed a non-significant increase post-transfusion (11.45 to 15.73 mg/dl), severe CRP levels also increased non-significantly (23.12 to 36.30 mg/dl).. Regarding D-dimer levels, both <1000 ng/ml and >1000 ng/ml groups showed significant post-transfusion increases. D-dimer levels <1000 ng/ml rose from 465.13 to 614.20 ng/ml, and >1000 ng/ml rose from 2730.76 to 3402.44 ng/ml post-transfusion.

Level	**CRP (mg/dl) (N=40)**			
	Pre transfusion		**Post transfusion**	**p-value**
	Frequency	Mean±SD	Mean±SD	
Mild (0.3-1 mg/dl)	None	-	-	-
Moderate (1-10 mg/dl)	15	11.45± 16.99	15.73± 21.55	0.242
Severe (>10 mg/dl)	25	23.12± 13.06	36.30± 21.55	0.246
	D-dimer (ng/ml) (N=40)			
<1000	15	465.13± 245.62	614.2± 841.40	0.041
>1000	25	2730.76± 2211.52	3402.44± 2135.67	0.02

Table 3- Inflammatory markers pre and post Convalescent plasma therapy

Oxygen requirements among patients pre and post CP therapy

Oxygen req. before transfusion (N=40)	**Oxygen req. after transfusion (N=40)**				**Outcome**	
	Room air	**O2 support**	**Bipap**	**Mechanical ventilation**	**Death**	**Discharge**
O2 support (n=36)	7	25	3	1	18	18
Room air (n=4)	2	2	--	--	**1**	**3**
Total	**9**	**27**	**3**	**1**	**19**	**21**

Table 4 Oxygen therapy profiling before and after Convalescent Plasma transfusion in Recipients

Initially, 4 patients didn't need oxygen, but 2 did post-Convalescent plasma transfusion. Among 36 on oxygen, 7 improved, 25 continued, 3 shifted to BIPAP, and 1 needed mechanical ventilation after transfusion.

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Adverse events associated with CP therapy

There were 04 (10%) individuals in first group while 06(9.83%) individual in another group of study who led to Transfusion reaction associated with circulatory overload. None of the individual in the study reported with Anaphylactic or Febrile transfusion reaction.

Response to plasma therapy in COVID-19 patients with comorbidities

Among 40 patients 12 patients in the study had preexisting co morbidity amongst whom 10 patients (83.33%) were succumbed to death while only 2 patients were discharged (16.6%).(p value 0.005).

Outcome of patients

During the study period, 52.5% of patients were discharged, while 47.5% succumbed to the disease. The interval between a positive COVID-19 diagnosis and the administration of convalescent plasma transfusion ranged from 1 to 10 days, with a mean duration of 3.95 ± 2.459 days. Among the patients who died, 78.94% survived for more than 72 hours post-transfusion, 15.78% survived for 24 to 72 hours, and 5.26% survived for less than 24 hours.

CONCLUSION

This study on severe 40 COVID-19 patients evaluated the effects of convalescent plasma transfusion, revealing that it stabilizes or improves conditions in some patients, particularly those without comorbidities. However, it is associated with significant increases in D-dimer levels and non-significant changes in CRP levels. The mortality rate was high among patients with comorbidities (83.33%). Overall, 52.5% were discharged, and 47.5% succumbed to the disease. No anaphylactic or febrile transfusion reactions were reported. Further research is needed to optimize convalescent plasma use, especially for patients with underlying health conditions.

DISCUSSION

The study was conducted by the Department of Medicine at Netaji Subhash Chandra Bose Medical College, Madhya Pradesh, following ethical clearance from the Institutional Ethics Committee. The study period concluded on June 31, 2022. This research focused on Covid-19 patients who received Convalescent Plasma therapy, analyzing the effects and outcomes of the treatment on these patients.

The age distribution of Convalescent Plasma recipients in our study ranged from a minimum of 23 years to a maximum of 79 years. The largest proportion of recipients, approximately 55%, belonged to the 40-60 years age group. Budhiraja et al. reported that the majority of recipients were in the 60-74 years age group .(12) Simonovich indicated that 55% of patients were below 65 years of age . (13)Additionally, most studies, including ours, observed a male predominance among recipients, with males constituting 70-80% of the study population .(9,12,13)

Most common symptoms amongst patients transfused with Convalescent plasma was Fever (62.5%), followed by shortness of breath (55%), generalized weakness (37.40%), cough (22.5%) and sore throat (7.5%) respectively, Rest 7.5% of the subject were asymptomatic. Similarly, studies by Agarwal et al. (9) and Duan et al.(11) also identified fever, cough, and shortness of breath as the most prevalent symptoms in patients.

In the study largest number of Convalescent Plasma recipient belonged to Blood group 'B' positive 35% followed by 'A' positive (30%) followed by 'O' positive and 'AB' positive (22.5% and 12.5% respectively) . Agarwal et al. indicated that among patients receiving Convalescent Plasma therapy, 37% had blood group B, followed by 34% with blood group O, and 23% with blood group A.(9)

In our study, 15% suffering of patients from hypertension and 10% from diabetes mellitus, while 70% of the subjects had no comorbidities. The presence of comorbidities was associated with significant mortality even after receiving Convalescent Plasma therapy (p=0.005) compared to those without comorbidities. Similarly, Agarwal et al. reported diabetes mellitus in 48% and hypertension in 39% of patients.(9) In the study by Simonovich et al, hypertension was found in 48.7% and diabetes mellitus in 17.5% of patients(13). Budhiraja et al. reported diabetes mellitus in 18.3% and hypertension in 54.7% of their study population(12).

Requirement of Oxygen in plasma transfused Covid 19 patients

Prior to Convalescent Plasma (CP) therapy, approximately 90% of cases required oxygen support, while 10% were on room air. After CP therapy, the need for oxygen support decreased to 77.5%, with 22.5% of patients improving to room air. Although this reduction in oxygen requirement post-CP therapy was not statistically significant, similar findings were noted in other studies.(9,14)

Changes in Inflammatory markers

The results indicated that before Convalescent Plasma (CP) transfusion, 62.5% of patients exhibited severe levels of C-reactive protein (CRP), and 37.5% had moderate levels, with values ranging from 4 mg/dL to 73 mg/dL. Three days post-transfusion, 67.5% of patients still had severe CRP levels, and 32.5% had moderate levels, with CRP values ranging from 3 mg/dL to 78 mg/dL. This indicates no significant change in CRP levels following CP therapy. In contrast, the study by Duan et al. reported a significant decrease in CRP levels pre- and post-CP therapy.(11).

In our study, 25 patients presented with elevated D-dimer levels before Convalescent Plasma (CP) transfusion, of whom 19 patients (76%, $p < 0.001$)

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succumbed to death. After CP transfusion, 24 patients had elevated D-dimer levels, and among these, 22 patients (91.6%, $p < 0.001$) succumbed to death.

To evaluate the mortality ratio before and after administering Convalescent Plasma (CP) therapy to Covid-19 patients, various studies have reported distinct outcomes. One study demonstrated that CP therapy was beneficial, as all patients recovered after receiving the treatment.(11) Conversely, another study found no significant difference in mortality between patients treated with CP and those who were not (19% vs. 18%; Adjusted OR = 1.07, 95% CI: 0.73 - 1.58)(9). Budhiraja et al.reported that CP therapy was associated with reduced mortality in severe Covid-19 patients over 60 years of age, particularly among females, those with comorbidities, and those requiring ventilation.(12) Our study found that patients with comorbidities benefited significantly from CP therapy compared to those without comorbidities.

Adverse effect of CP therapy

When discussing the adverse effects of Convalescent Plasma (CP) therapy, Shen et al. did not identify any adverse impacts on Covid-19 patients (15). Similarly, Mahapatra et al. reported no adverse effects associated with plasma transfusion (14). In contrast, our study showed that 10% of patients experienced circulatory overload. Notably, none of the cases reported anaphylactic or febrile transfusion reactions.

CONCLUSION

This study on 40 COVID-19 patients evaluated the effects of convalescent plasma transfusion, revealing that it stabilizes or improves conditions in some patients, particularly those without comorbidities. However, it is associated with significant increases in D-dimer levels and non-significant changes in CRP levels. The mortality rate was high among patients with comorbidities (83.33%). Overall, 52.5% were discharged, and 47.5% succumbed to the disease. No anaphylactic or febrile transfusion reactions were reported. Further research is needed to optimize convalescent plasma use, especially for patients with underlying health conditions.

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