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Original Research Article

Phase-II RCT Convalescent Plasma Transfusion in Severe COVID-19 Patients -Evaluation of Efficacy and Tolerability

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Abstract

Background: The COVID-19 pandemic necessitated exploration of convalescent plasma (CP) therapy. This phase-II RCT evaluated CP's efficacy in 30 severe COVID-19 patients (June 2020–July 2021), comparing standard care (n=30) with CP-added therapy (n=30). Despite historical success in viral outbreaks, evidence remained conflicting. We assessed 28-day mortality, clinical improvement, and safety, addressing gaps in donor antibody variability and timing. ***Objective:*** To determine therapeutic Role of Convalescent Plasma (CP) therapy in the treatment of severe COVID-19. ***Methods and Procedure:*** It was a Randomized Controlled phase-II Trial which was carried out at COVID-19 unit and ICU Bangabandhu Sheikh Mujib Medical University, Dhaka from 01June 2020 to 31July 2021. Plasma was collected and supplied in the department of Transfusion Medicine of BSMMU and transfused in patient at ICU, BSMMU. After proper evaluation 30 healthy donors required amount of convalescent plasma of COVID-19 was collected by continuous flow cell separator. The collected convalescent plasma was transfused to; 30 (INTERVENTION ARM) severe ill patients receiving standard treatment protocol admitted in ICU, BSMMU, Dhaka. Then the improvement of these patients was observed and another 30(control) patients receiving standard treatment protocol only and comparison was made. Before administration of the plasma it was screened for RCT-PCR for covid-19. HBsAg, Anti-HCV, HIV and other infections. ***Results:*** The study included 60 COVID-19 patients (30 control, 30 intervention) with comparable baseline characteristics (mean age 51-53 years; 40% vs. 56.6% males). The intervention group showed significantly higher baseline D-dimer (4.3 vs. 0.5 µg/mL, $p<0.001$) and ferritin (1045 vs. 631 ng/mL, $p=0.049$). Both groups had similar 28-day mortality (26.6%, RR=1.00, $p=0.95$), hospitalization duration (10 vs. 9 days), and discharge rates (63.3%). Clinical parameters improved over time, with mortality declining from 7.1% (Week-I) to 4.5% (Week-IV). ***Conclusion:*** In conclusion, this phase-II randomized controlled trial demonstrated that convalescent plasma (CP) therapy did not significantly improve 28-day mortality or other clinical outcomes in severe COVID-19 patients compared to standard care alone.

Keywords: Covid-19, Convalescent plasma, transformation, Efficacy, Mortality.

INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19) was causing a public health emergency. There were a lots of literature had summarized its clinical and radiological features, whereas therapies for COVID-19 were rather limited. The use of convalescent plasma collected from previously infected individuals to passively transfer antibodies in order to protect or treat humans dates back almost 100 years, with some evidence for benefit against rabies, hepatitis B, polio, measles, influenza, Ebola and other pathogens [1]. Immune (i.e. "convalescent") plasma refers to plasma that was collected from individuals, following the resolution of infection and development of antibodies. Passive antibody therapy, through transfusion of convalescent plasma, might prevent clinical infection or blunt clinical severity in individuals with recent pathogen exposure. Antibody therapy could also be used to treat patients who were already manifesting symptoms of varying severity. However, passive antibody therapy was most effective when administered prophylactically or used early after the onset of symptoms [2]. Results from small case series during the prior MERS and SARS coronavirus outbreaks documented safety and faster viral clearance following convalescent plasma administration, particularly when given early in the disease course. Convalescent plasma could provide short-medium-term humoral immunity against the SARS-CoV-2 coronavirus. Convalescent plasma (CP) therapy, derived from recovered COVID-19 patients, has emerged as a potential treatment due to its passive immunization properties, providing neutralizing antibodies to combat viral replication and modulate immune responses [3]. The use of convalescent plasma has historical precedence in treating viral outbreaks, including SARS-CoV-1, MERS, and H1N1 influenza, with varying degrees of success [4]. Early observational studies during the COVID-19 pandemic suggested that CP transfusion could reduce viral load and improve clinical outcomes in severely ill patients [5]. However, randomized controlled trials (RCTs) have reported conflicting results, with some demonstrating mortality benefits [6] and others showing no significant improvement over standard care [7]. This discrepancy highlights the need for well-designed phase-II RCTs to evaluate the efficacy and safety of CP in severe COVID-19 patients, particularly in settings with limited access to monoclonal antibodies or novel antivirals [8]. This study aims to assess the efficacy and tolerability of CP therapy in severe COVID-19 patients through a randomized, open-label, parallel-group trial. The primary outcome is 28-day mortality, while secondary outcomes include duration of hospitalization, need for mechanical ventilation, and changes in inflammatory biomarkers [9]. Given the heterogeneity in donor antibody titers, transfusion timing, and patient comorbidities, a rigorous evaluation is essential to determine CP's role in modern COVID-19 management [10]. Previous studies have emphasized the importance of high-titer plasma [11], early administration [12], and patient selection [13] in optimizing CP efficacy. However, challenges such as logistical constraints [14] and variability in neutralizing antibody levels [15] persist.

OBJECTIVES

General Objective: To determine therapeutic Role of Convalescent Plasma (CCP) therapy in the treatment of severe COVID-19.

Specific Objectives:

- To compare 28-day mortality rates between patients receiving standard care plus convalescent plasma versus standard care alone.
- To assess differences in clinical improvement between the two treatment groups.

METHODS AND MATERIALS

Study Design: This study was conducted in the COVID-19 unit and ICU of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, where convalescent plasma was collected and supplied by the Department of Transfusion Medicine, BSMMU. The study population included 60 severely ill COVID-19 patients, with 30 receiving the standard treatment protocol (control arm) and another 30 receiving convalescent plasma alongside standard treatment (intervention arm). The research was carried out from 01 June 2020 to 31 July 2021 to evaluate the efficacy and safety of convalescent plasma therapy in severe COVID-19 cases.

Inclusion Criteria: Patients eligible for inclusion in the study were required to meet the following criteria: a respiratory rate greater than 30 breaths per minute, along with evidence of severe respiratory distress, a SpO2 level of 88% or lower on room air, or a PaO2/FiO2 ratio of 300 mmHg or less. In addition, radiological confirmation of bilateral lung infiltrates was necessary. Hemodynamic instability, indicated by a systolic blood pressure less than 90 mmHg or a diastolic blood pressure less than 60 mmHg, was also considered. Furthermore, patients who met criteria 1 through 4 and/or required ventilator support were included. Another criterion was the presence of lung infiltrates involving more than 50% of the lung fields within 24 to 48 hours.

Exclusion Criteria: Participants were excluded from the study if they were under 18 years of age, pregnant women, or breast feeding mothers. Additionally, individuals with a known history of allergic reactions to plasma products or those who had received pooled immunoglobulin therapy within the previous 30 days were not considered for inclusion. Patients who

declined to provide informed consent were also excluded from participation.

Study Procedure: 500-800 ml of convalescent plasma was collected after fulfilling inclusion criteria of a recovered COVID-19 donor. By Apheresis machine plasma was collected and antibody titer was performed then preserved as per plasma preservation guideline. After grouping, cross-matching and proper screening the convalescent plasma was transfused to severe or life threatening COVID-19 patients. Consecutive patients meeting the inclusion-exclusion criteria and providing informed consent was randomly assigned to the test. This randomized controlled trial (RCT) consisted of two arms: (a) standard care and (b) standard care plus 200 mL of convalescent plasma (CP), with 30 patients enrolled in each arm. Randomization was performed by an independent person using a random number table, with allocations concealed in sequentially numbered, opaque, sealed envelopes. Clinical parameters (fever, cough, dyspnea, respiratory rate, PaO_2 /FiO_2 ratio, pulse, blood pressure, oxygen requirement, etc.) and laboratory markers (CBC, CRP, chest X-ray, SGPT, SGOT, serum ferritin, and antibody titers) were recorded before and after CP transfusion. Adverse reactions, including allergic or serum sickness-like responses, were monitored. RT-PCR and other lab tests were conducted at BSMMU's microbiology and laboratory medicine departments, while apheresis plasma was collected at dept. of transfusion medicine, BSMMU. Antibody titers were assessed at BSMMU's microbiology department, and patients were enrolled from COVID-19 unit and ICU of BSMMU. The standard treatment arm included oxygen, enoxaparin, antibiotics, immune modulators (steroids), and/or antivirals (favipiravir, remdesivir, or lopinavir/ritonavir), while the experimental arm added 200 mL of CP. Donor eligibility required age 18–60 years, weight >55 kg, prior confirmed COVID-19 infection, symptom resolution for ≥28 days, two consecutive negative tests, and an antibody titer ≥1:80 (ELISA method). Female donors with no pregnancy history or negative HLA antibodies were prioritized, along with adequate venous access. Donor pool was prepared from recovered patients and campaign arranged by Central Shandhani. Convalescent plasma was transfused to severe or life-threatening COVID-19 patients admitted in the ICU, BSMMU. Transfusion of convalescent Plasma 30 COVID-19 patients of severe or life-threatening patients with standard treatment protocol was intervention group. Another 30 COVID-19 patients of severe or life-threatening condition who was receiving standard treatment alone and this group was the control group.

Potential Risk: Human plasma transfusion was a routine, daily event in modern hospitals. Human Anti-SARS-CoV-2 plasma differs from standard plasma only by virtue of the presence of antibodies against SARS-CoV-2. Donors satisfying all criteria for blood donation based upon WHO and national safe blood polices for volunteer donor eligibility and was collected. Therefore, the risks to transfusion recipients were likely to be no different from those of standard plasma. Risk of transfusion-transmissible infection was same as standard plasma. There were also noninfectious hazards of transfusion such as allergic transfusion reactions, Transfusion Associated Circulatory Overload (TACO), and Transfusion Related Acute Lung Injury (TRALI) was take special attention and care. Specific tasks pertaining to Human Anti-SARS-CoV-2 plasma include transfusion-transmitted SARS-CoV-2. This was largely theoretical since the recipient was already infected and there had never been a report of transmission of a respiratory virus by blood transfusion. SARS-CoV-2 was not considered to be a relevant transfusion-transmitted infection and only 1% of symptomatic patients had been reported to had detectable SARS-CoV-2 RNA in their blood (FDA. Electronic Code of Federal Regulations, Updated March17, 2020 Accessed March 19, 2020, Wang W, *et al.*, Al JAMA 2020)

Statistical Analyses: One way ANOVA test, a non-parametric Mann-Whitney test, and a Kruskal-Wall test were performed to compare the arms. For parametric outcomes, the investigators compared the odds ratios across the pairs. All the data were rechecked, coded, and analysis was performed by standard statistical software (SPSS-version: 22)

Ethical aspect: Ethical clearance for the study was taken from the Institutional Review Board (IRB) of BSMMU. Permission for the study was taken from the concerned department from where we collected our study subjects. The entire study subject was thoroughly appraised about the nature, purpose and implications of the study, as well as entire spectrum of benefits and risks of the study. Interest of the study subjects was not be compromised to safeguard their rights and health. All study subjects were assured of adequate treatment of any complications developed in relation to the study purpose. Subjects were assured about their confidentiality and freedom to withdrawn them from the study anytime.

RESULTS

Table 1: Demographics, Clinical and laboratory characteristics at baseline

Factor	Level	Control group	Intervention group	p Value
n	-	30	30	-
Age, mean (SD)	-	50.7	52.6	0.66

Sex	Men	12 (40%)	17 (56.6%)	0.43
	Women	18 (60%)	13 (43.33%)	-
Smoker	-	-	-	-
Diabetes	-	12 (40%)	15 (50%)	-
Hypertension	-	9 (30%)	11 (36.6%)	-
Cardiac disease	-	3 (10%)	5 (16.6%)	-
Chronic Kidney disease	-	4 (13.3%)	6 (20%)	-
Chronic lung disease	-	1 (3.3%)	7 (23.3%)	-
Chronic liver disease	-	2 (6.6%)	1 (3.3%)	-
Oxygenation device required on admission	Nasal canula or face mask	30 (100%)	30 (100%)	-
	Nonrebreather mask or high flow nasal canula	2 (6.6%)	5 (16.6%)	-
PaO2:Fio2, mean (SD)	-	232 (56.9)	220 (60.9)	0.52
Labs on admission	-	-	-	-
WBC, mean (SD)	-	7.0 (4.0)	5.9 (2.0)	0.27
LDH (N=25), mean (SD)	-	345 (91.1)	420 (172.2)	0.11
CRP, mean (SD)	-	91 (52)	110 (63)	0.31
D-Dimer (N=25), mean (SD)	-	0.5 (0.2)	4.3 (1.3)	<0.001
Ferritin (N=39), mean (SD)	-	631 (460)	1045 (935)	0.049
Steroids	-	3 (10%)	2 (6.66%)	016
Blood Group	O	14 (46.6%)	15 (50%)	-
	A	8 (26.6%)	7 (23.3%)	-
	B	4 (13.3%)	5 (16.6%)	-
	AB	2 (6.6%)	1 (3.3%)	-
	Not Available	2 (6.6%)	2 (6.6%)	-

Table 1 presents the baseline characteristics of 60 severe COVID-19 patients, evenly divided into control (standard care) and intervention (standard care + convalescent plasma) groups. The two arms were well-balanced in terms of age (mean ~51–53 years, p=0.66) and sex distribution (40% vs. 56.6% men, p=0.43). Comorbidities such as diabetes (40% vs. 50%) and hypertension (30% vs. 36.6%) were comparable, though chronic lung disease was more frequent in the intervention group (3.3% vs. 23.3%). All patients required oxygen at admission, with a similar PaO_2 : FiO_2 ratio (p=0.52). Laboratory markers showed no significant differences in WBC, LDH, or CRP, but the intervention group had higher D-dimer (4.3 vs. 0.5, p<0.001) and ferritin (1045 vs. 631, p=0.049).

Table 2: Medication given in control & intervention group

Medication	Control	Intervention	P. value
Hydroxychloroquine	23	19	0.08
Ribavirin	6	4	0.50
Azithromycin	19	18	0.64
Methylprednisolone	5	2	0.16
Anticoagulant (LMWH/Heparin)	21	23	0.33
PPI	11	8	0.12
ACEI/ARB	5	4	0.69
Calcium channel blocker	5	7	0.47
Beta blocker	4	5	0.69
Aspirin	5	4	0.26
Diuretics	7	5	0.49
Statin	2	1	0.6
Insulin	7	9	0.53
Metformin	7	4	0.25
Carbimazole	2	-	0.30
Thyroxine	1	1	-
Allopurinol	2	1	0.32

Table 2 compares medication use between the control (standard care) and intervention (standard care + convalescent plasma) groups. Hydroxychloroquine was the most commonly prescribed drug in both arms

(76.7% vs. 63.3%, p=0.08), followed by azithromycin (63.3% vs. 60%, p=0.64) and anticoagulants (70% vs. 76.7%, p=0.33). Methylprednisolone use was higher in the control group (16.7% vs. 6.7%, p=0.16), while other medications, including cardiovascular drugs (ACEI/ARBs, beta-blockers, calcium channel blockers) and diabetes treatments (insulin, metformin), showed no significant differences. Minor variations were noted in less frequently used drugs (e.g., carbimazole, allopurinol), but none reached statistical significance.

Table 3: Comparison of clinical characteristics & laboratory parameters of patients receiving convalescent plasma transfusion

	Baseline n=30	**Week-I n=30**	**Week-II n=**	**Week-III n=**	**Week-IV n=**
Haemoglobin (g/dL)	11.5	11.2	10.5	10.5	10.2
Leucocyte (x10^8/mL)	8.7	8.6	11.0	11.5	11.5
Neutrophil (x10^8/mL)	80	81	82	88	86
Thrombocyte ((x10^8/mL)	270	282	310	325	280
Prothrombin time (second)	10.5	10.9	10.4	10.6	10.7
INR	1.0	1.0	1.0	0.8	1.0
CRP (mg/L)					
≥6					
D-Dimer (µg/mL)	0.8	0.4	0.5	0.3	0.5
≥0.5					
Aspartate aminotransferase (IU/L)	27.5	25.0	28.5	35.0	21.0
Alanine aminotransferase (IU/L)	35	37	46	77	54
Total Bilirubin (mg/dL)	0.5	0.7	0.4	0.6	0.7
Creatinine	0.7	0.7	0.8	0.7	0.6
PaO2/FiO2 ration	275	256	203	276	352
SOFA Score	4 (40%)	3 (30%)	3 (30%)	2 (20%)	2 (20%)
Discharged			3 (12%)	2 (8.6%)	5 (22.7%)
Hospitalization, no supplemental oxygen					3 (13.6%)
Hospitalization. requiring low-flow supplemental oxygen	10 (33.3%)	8 (28.5%)	5 (20%)	5 (21.7%)	3 (13.6%)
Hospitalization. requiring HFNC/non-invasive ventilation		2 (7.1%)	4 (16%)		
Hospitalization. requiring ECMO/invasive ventilation	5 (16.6%)	4 (14.2%)	3 (12%)	2 (8.6%)	
Death		2 (7.1%)	2 (8%)	2 (8.6%)	1 (4.5%)

Table 3 tracks clinical, laboratory, and outcome measures in COVID-19 patients over four weeks. Key trends include a gradual decline in hemoglobin (11.5 to 10.2 g/dL) and a rise in leukocytes (8.7 to 11.5 ×10³/µL) and neutrophils (80% to 86%), suggesting persistent inflammation. The PaO_2 /FiO_2 ratio initially worsened (Week-II: 203) but improved by Week-IV (352). Thrombocytosis (270 to 325 ×10³/µL) and elevated liver enzymes (ALT peak: 77 IU/L) were observed, while D-dimer levels normalized (0.8 to 0.5 µg/mL). Clinical outcomes improved over time, with fewer patients requiring oxygen (33.3% to 13.6%) or invasive support (16.6% to 0%), and increasing discharges (12% to 22.7%). Mortality was highest in early weeks (7.1–8.6%) but declined to 4.5% by Week-IV.

Table 4: Comparative Analysis of 28-Day Mortality and Clinical Outcomes between Standard Care and Convalescent Plasma Therapy Groups

	Control group (n=30)	**Intervention group (n=30)**	**RR**	**p value**
Primary outcome				
Mortality at 28 days	8 (26.6%)	8 (26.6%)	1.00	0.95
Secondary outcomes				
Median duration of hospital, days	10 (6 ot >28	9 (6 to>28)		
Discharged from hospital ventilation or death*	19 (63.3%)	19 (63.3%)	0.99	0.57
Invasive mechanical ventilation or death*	8 (26.6%)	8 (26.6%)	0.99	0.78
Death	7 (23.3%)	7 (23.3%)	0.96	0.45

Table 4 compares primary and secondary outcomes between the control (standard care) and intervention (standard care + convalescent plasma) groups. Both groups had identical 28-day mortality rates (26.6%, RR=1.00, p=0.95), with no significant differences in secondary outcomes, including median hospitalization duration (10 vs. 9 days), discharge/ventilation-free survival (63.3% in both), invasive ventilation/death (26.6% in both), and overall death (23.3% in both).

DISCUSSION

The present phase-II randomized controlled trial evaluated the efficacy and tolerability of convalescent plasma (CP) therapy in severe COVID-19 patients. Our results demonstrated no significant difference in 28-day mortality between the intervention (standard care + CP) and control (standard care alone) groups (26.6% vs. 26.6%, RR=1.00, p=0.95). Similarly, secondary outcomes, including duration of hospitalization, need for mechanical ventilation, and discharge rates, were comparable between the two arms. These findings align with several recent RCTs that failed to demonstrate a mortality benefit with CP therapy in severe COVID-19 patients [16]. For instance, the RECOVERY trial found no significant reduction in mortality with high-titer CP (RR=0.95, p=0.57) in hospitalized COVID-19 patients [17]. Similarly, the CONCOR-1 trial reported no improvement in clinical outcomes with CP, even when administered early in the disease course [18]. Our study also observed that baseline inflammatory markers (D-dimer, ferritin) were significantly higher in the CP group, suggesting a potentially sicker cohort at enrollment. Despite this, CP did not confer additional clinical benefits, reinforcing the hypothesis that CP may have limited efficacy in advanced disease stages where immune-mediated organ damage predominates over viral replication [19]. This is consistent with findings from Salazar *et al.,* (2020), who reported that CP was most effective when administered early (within 72 hours of symptom onset) but had minimal impact in critically ill patients [20]. The lack of benefit in our study may also be attributed to variable neutralizing antibody titers in donor plasma, as suboptimal antibody levels have been associated with reduced therapeutic efficacy [21]. A meta-analysis by Janiaud *et al.,* (2021) found that while some studies reported benefits with high-titer CP, most RCTs showed no significant advantage over standard care [22]. Additionally, the heterogenous immune responses in severe COVID-19 patients may limit the effectiveness of passive antibody therapy, particularly in those with excessive cytokine activation [23]. Interestingly, our findings contrast with early observational studies that suggested CP could reduce mortality in severe COVID-19 [24]. However, these studies were limited by selection bias and lack of randomization. Our rigorously controlled trial adds to the growing body of evidence that CP, while safe, does not significantly alter clinical outcomes in severe COVID-19 when added to standard care [25].

CONCLUSION

In conclusion, this phase-II randomized controlled trial demonstrated that convalescent plasma (CP) therapy did not significantly improve 28-day mortality or other clinical outcomes in severe COVID-19 patients compared to standard care alone. Despite theoretical benefits, the lack of efficacy may be attributed to late administration, variable antibody titers in donor plasma, and the predominance of immune-mediated pathology in advanced disease.

Limitations of the study: This study has several limitations, including a relatively small sample size (n=60), which may limit statistical power to detect subtle differences between groups. Additionally, the open-label design could introduce bias, and the heterogeneity in donor antibody levels may have influenced therapeutic efficacy. The standard treatment protocol might have decreased study's overall power to assess convalescent plasma.

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Conflict of interest: None declared

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