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Transfusion and Apheresis Science xxx (xxxx) xxx

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Effect of convalescent plasma therapy on mortality in moderate-to-severely Ill COVID-19 patients

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ARTICLE INFO

Keywords:
Convalescent plasma therapy
COVID-19
SARS Cov-2
Passive immunization
Mortality

ABSTRACT

Introduction: The role of plasma therapy in the management of the COVID-19, pandemic has been speculated. However, in view of the varied response regarding its effectiveness from various multicenter studies, there is a need to conduct more single center population-specific studies. We, thus, aimed to assess the role of convalescent plasma therapy in COVID-19 patient management in a single -center.

Methods: This retrospective study was conducted using records of all COVID-19 patients who received plasma therapy over a period of 6 months in a dedicated COVID-19 hospital in Delhi. Information pertaining to transfusion, disease severity, associated comorbidities, the treatment given and patient outcome were recorded. Data was analyzed using SPSSv23.

Results: Of the141 patients who received plasma therapy, 62% were discharged after treatment. Mortality was found to be significantly higher in patients > 60 years of age ($p < 0.001$), those with severe COVID-19 infection ($p < 0.05$) and pre-existing renal disease ($p < 0.05$). The admission-transfusion interval was significantly correlated to mortality and was a sensitive parameter for predicting outcome at cut off value of < 5 days ($p < 0.001$). There was no significant association of mortality with patient blood group, plasma antibody levels or donor hemoglobin levels.

Conclusions: We report improvement and recovery in a large number of patients who received convalescent plasma within the first 5 days of hospitalization with moderate to severe disease. Further research to compare dosage and administration protocols to delineate role of CCP in survival of COVID-19 patients is needed before it is
prematurely shelved.

1. Introduction

The COVID-19 pandemic has impacted health care globally at an unprecedented rate. It has affected millions of people across several countries, having recurring disastrous economic and health consequences globally and hence, is a major health threat [1,2]. Given its rapid spread and consequences, it has become necessary to look into possible treatment options that are both novel as well as other older practices with a possible unexplored role in this disease.

At present, there are no approved drugs and therapies for the treatment of human Coronaviruses (CoVs). However, several FDA-approved drugs that target key viral conserved elements have shown in vitro and in vivo antiviral activity, and therefore, were considered as potential drugs to use to fight CoVs infections. These included drugs such as Remdesivir, Ribavirin, Dasatinib, ivermectin, etc. Several other treatment methods, such as convalescent plasma therapy, were also considered [3].

Passive antibody transfer is a longstanding treatment strategy for infectious diseases that involve the respiratory system [4]. Transfer of blood products, particularly, plasma is one such well tolerated method

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https://doi.org/10.1016/j.transci.2022.103455
Received 3 January 2022; Received in revised form 3 May 2022; Accepted 6 May 2022
Available online 11 May 2022
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of passive antibody transfer, which has very few adverse effects. Convalescent plasma therapy (CP) is believed to contain receptor binding domain specific antibodies with strong antiviral activity [5]. It was observed that patients with Spanish influenza pneumonia who received influenza-convalescent human blood products experienced a clinically significant reduction in the risk for death [6]. Jenkins et. al also reported reduction in mortality with the use of plasma therapy in SARS coronavirus infection and severe influenza [7]. It also has an established role in Ebola Virus outbreak [8]. Therefore, convalescent human COVID-19 plasma (CCP) is an effective, timely, and widely available treatment option that has been explored as a possibility in the treatment of COVID-19 [6,8,9]. It was approved as a treatment option of COVID-19 by FDA and in India, by Indian Central Drugs Standard Control Organization during the first wave of COVID 19 for SAARS Co-V 2 variant. It was approved by the Ministry of Health and Family Welfare (MoHFW), Government of India, for "off label" use in patients with moderate and severe COVID-19, who were showing no improvement and had increasing oxygen requirement [10,11]. However, its efficacy has not been very widely explored [5].

CCP has been largely removed from COVID-19 treatment guidelines [12,13]. However, the evidence based on which this has been done may have been affected by several confounding factors including differing treatment protocols and reagents and anticoagulants used for storage of the convalescent plasma could may limit the validity of the results. Further, there is serious bias present in the design of these studies [4,5,12,13].

Recently the use of monoclonal antibody cocktails in reducing the COVID-19 viral load has gained popularity. These, like CCP, also target the ACE2 receptors and have been shown to have better results in patients where immune response has not yet been initiated [14]. However, in view of the difficulty in manufacturing, the high manufacturing and transportation costs as well as its poor availability, CCP appears to be a more cost-effective and feasible alternative. There is, thus, a need for a single center-based study done on the Indian population.

This study aimed to assess the role of CCP in COVID-19 patient treatment in our center, which could help identify possible treatment protocols for the near future.

2. Materials and methods

This was a retrospective study done in a Regional Blood Transfusion Center of a tertiary care hospital in Delhi for a period of 6 months from July to December 2020. CCP became available at our center in July, 2020.

CCP was given according to moderate-to-severely ill COVID-19 patients not responding to other treatment modalities. CCP unit administered had serum IgG values of > 1 IU/dl and were collected from donors recovered from COVID-19 infections after atleast 28 days of recovery. Relevant clinical details regarding disease severity, associated comorbidities, the treatment given and patient outcome of moderate-to-severely ill patients of COVID-19 and information pertaining to transfusion was collected from Blood Center archives as well as from the hospital case records as per the study format. Moderately ill patients showed clinical features of dyspnea and or hypoxia, fever, cough, including SpO2 $< 94\%$ and respiratory rate of more than or equal to 24/min. Severely ill patients had features of Pneumonia and one of the following; respiratory rate > 30 breaths/min, severe respiratory distress, SpO2 $< 90\%$ on room air [11]. Both these categories of patients also had one or more co-morbidities.

Identity of both patients and donor was not revealed at any point in the study. Confidentiality and anonymity of both patients and donors was maintained. The data was tabulated and analyzed using SPSSv23 software. Normally distributed variables were expressed as mean (SD) and non-normally distributed ones as intervals. Chi-square test, Fisher's Exact test, Wilcoxon-Mann-Whitney U Test and t-test were used to assess statistical significance. P values < 0.05 were considered significant. Survival analysis was performed using Cox Proportional Hazards Regression Analysis to assess survival in COVID-19 patients on CCP.

3. Results

The mean (SD) age of the patients in the study was 56.11 (13.74) years. Of the 141 patients, majority, 72 (51.1%) belonged to age group 40–60 years and 107 (75.9%) were males. Male to female ratio was found to be 3.1:1. Associated comorbidities were found in 120 patients and 91 out of 141(64.5%) were severely ill. CCP was administered to all the patients in the study after cross-matching and testing. The antibody titers were done for all the CCP units and the levels ranged from 1.1 to 85.5 IU/ml with a mean of 15.64 IU/ml. It was found that majority patients (44%) had blood group B+ followed by O+ (26.2%), A+ (22%), AB+ (7.1%) and finally O- (0.7%).

The Admission Transfusion Interval ranged from 1 to 21 days. Twenty-two (15.6%) patients received two transfusions, 210 ml each. The Inter-Transfusion Interval was ranged from 0 to 16 days.

The mean Transfusion-Outcome Interval was 10.45 ± 9.17 days (range: 0–75 days). Fifty-four (38.3%) died while 87 (61.7%) were discharged after recovery.

It was found that age group, grade of illness, presence of any co-morbidity, renal injury and Admission Transfusion Interval (days) were significantly ($p < 0.05$) associated with patient outcome (Table 1).

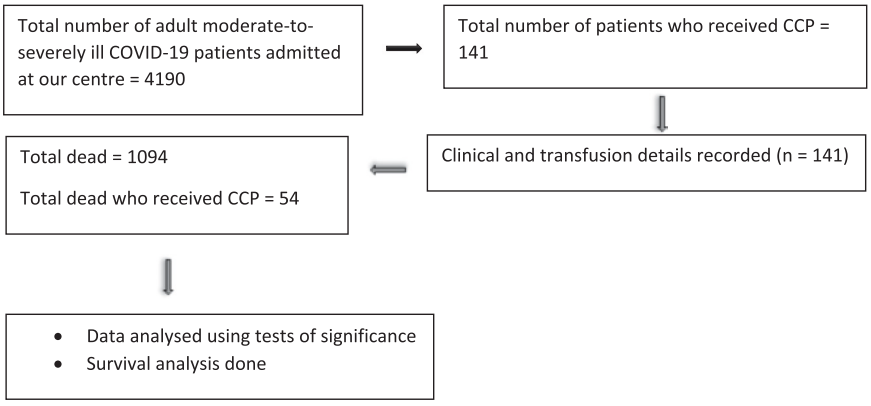

Table 1
Association of demographic and clinical parameters of patients with treatment outcome after CCP therapy.

Parameters	Outcome		Total	p value
	Death (n = 54)	Discharge (n = 87)		
Age (Years)* **	61.67 ± 12.48	52.66 ± 13.41		< 0.001[1]
Age Group* **				< 0.001[2]
< 40 Years	1 (1.9%)	16 (18.4%)	17	
40–60 Years	24 (44.4%)	48 (55.2%)	72	
> 60 Years	29 (53.7%)	23 (26.4%)	52	
Gender				0.993[2]
Male	41 (75.9%)	66 (75.9%)	107	
Female	13 (24.1%)	21 (24.1%)	34	
Grade Of Illness* **				< 0.001[2]
Moderate	1 (1.9%)	49 (56.3%)	50	
Severe	53 (98.1%)	38 (43.7%)	91	
Comorbidity: Any (Yes)* **	50 (92.6%)	70 (80.5%)	120	0.049[2]
Comorbidity: HTN (Yes)	28 (51.9%)	42 (48.3%)	70	0.680[2]
Comorbidity: T2DM (Yes)	31 (57.4%)	44 (50.6%)	75	0.429[2]
Comorbidity: TB (Yes)	2 (3.7%)	2 (2.3%)	4	0.637[3]
Comorbidity: Renal Injury (Yes)* **	19 (35.2%)	17 (19.5%)	36	0.038[2]
Comorbidity: COPD (Yes)	7 (13.0%)	11 (12.6%)	18	0.956[2]
Patient Blood Group				0.611[3]
A+	11 (20.4%)	20 (23.0%)	31	
AB+	6 (11.1%)	4 (4.6%)	10	
B+	24 (44.4%)	38 (43.7%)	62	
O-	0 (0.0%)	1 (1.1%)	1	
O+	13 (24.1%)	24 (27.6%)	37	
Patient Rh Blood Group (Positive)	54 (100.0%)	86 (98.9%)	140	1.000[3]
Donor: Blood Group				0.626[3]
A+	11 (20.4%)	21 (24.1%)	32	
AB+	6 (11.1%)	4 (4.6%)	10	
B+	24 (44.4%)	36 (41.4%)	60	
O-	1 (1.9%)	3 (3.4%)	4	
O+	12 (22.2%)	23 (26.4%)	35	
Donor: Rh Blood Group (Positive)	53 (98.1%)	84 (96.6%)	137	1.000[3]
Donor: IgG Levels (s/co)	14.23 ± 16.92	16.52 ± 17.44		0.557[4]
Donor: Hemoglobin (g/dl)	14.30 ± 0.98	14.24 ± 0.86		0.760[4]
Admission Transfusion Interval (days)* **	6.37 ± 4.61	3.83 ± 2.98		< 0.001[4]
Number of Transfusions				0.452[2]
One	44 (81.5%)	75 (86.2%)	119	
Two	10 (18.5%)	12 (13.8%)	22	
Inter-Transfusion Interval (Days)	2.33 ± 3.43	3.25 ± 4.20		0.224[4]

***Significant at p < 0.05, 1: t-test, 2: Chi-Squared Test, 3: Fisher's Exact Test, 4: Wilcoxon-Mann-Whitney U Test

The mean age of patients who died was 61.6 years while those discharged was 52.6 years. There was a significant difference between the age groups (t = 4.049, p = <0.001).

Out of all the patients in the study, 120 (85.1%) patients had associated comorbidities. Proportion of patients with associated comorbidities was larger, 50/54 (92.6%), among those who died. The mortality was significantly higher in patients with pre-existing renal disease (Table 1).

There was no significant association of mortality with patient blood group, plasma antibody levels or donor hemoglobin levels. The admission transfusion interval revealed significant correlation with mortality (Table 1). Though only a few patients received more than one CCP transfusion, no significant correlation between inter-transfusion interval and number of transfusions with mortality in those who were transfused twice was noted.

The Admission Transfusion Interval was found to be a sensitive parameter for predicting outcome at cut off value of < 5 days as we found that death was more likely if patient was transfused CCP 5 days after admission in contrast to more likelihood of discharge if patient was transfused within 5 days of admission (Fig. 1). Admission Transfusion Interval (days) significantly predicted outcome as death (p < 0.001).

The odds ratio (95% CI) for death when Admission Transfusion Interval (days) was ≥ 5 was 3.84 (1.77–8.32). The inter transfusion interval was found to be a sensitive parameter for treatment outcome if patient was transfused at a gap of at least one day. Table 2.

4. Discussion

Our retrospective analysis found significantly higher mortality in older patients with severe COVID-19 infection and associated renal comorbidities even when treated with CCP. Majority of the patients who received CCP recovered. We also found that admission-transfusion interval at a cut-off of 5 was a significant predictor of patient outcome.

Out of the141 patients who received CCP, 38.3% died. Mortality was significantly higher in patients > 60 years of age (p < 0.001), those with severe COVID-19 infection (p < 0.05) and pre-existing renal disease (p < 0.05) compared to younger, moderately-ill patients with no comorbidities. The early institution of CCP reduced mortality in moderate-to-severe cases of COVID-19 and is associated with improved ICU survival rates in patients with COVID-19 related acute respiratory failure. [15,16] Older age, patients with higher respiratory rate, greater disease severity and pre-existing renal disease have been shown to have a greater risk of mortality [17–20].

Klassen et al. in 2021, in their systematic review and meta-analysis involving 10 randomized clinical trials, 20 matched control studies, 2 dose-response studies, and 96 case reports and case series, concluded that COVID-19 patients transfused with CCP had a comparatively lower mortality rate than patients under standard treatment regimens. They also concluded that transfusion within 3 days of hospital admission was associated with lower mortality [15]. Briggs et al. in their cohort study conducted on 3368 patients admitted in the Yale New Haven Health system (YNHHS) from March 8, 2020 to July 25, 2020, observed that though the early administration of CCP led to improvement in patients with moderate-to-severe COVID-19, they did not see this with late CCP administration [21]. Our study results agree with these studies as the admission-transfusion interval was revealed to have a significant correlation with mortality and was found to be a sensitive parameter for predicting outcome at a cut-off value of < 5 days (p < 0.001).

We found no significant association between the patient's ABO or Rh blood type and disease severity and mortality. However, the majority of the hospitalized patients with moderate to severe COVID-19 infection had blood group B+ . Latz et al. also reported no significant association between patient blood group and hospitalization, intubation, or death in COVID-19 patients. They also reported that patients with blood types B, AB and Rh + were more likely to test positive if tested than blood type O [22]. However, we could not find such an association in our study.

There was no significant association of mortality with plasma antibody levels or donor hemoglobin values. The units administered to our patients had serum IgG levels > 1 IU/ml. Contrary to this, Yu et al. proposed that donor plasma antibody titer and patient weight might be key factors in treatment outcome after administration of CCP [23]. Joyner et al. concluded that amongst hospitalized COVID-19 patients not on mechanical ventilation, plasma transfusion with higher anti-SARS-CoV-2 IgG antibody levels was associated with a lower risk of death [24]. The fact that the majority of the patients who received plasma therapy in our study were severely ill and had received mechanical ventilation at some point during their hospital stay can explain the discrepancy in findings.

Though only a few patients received more than one CCP transfusion, amongst those who did, there was no significant correlation between inter-transfusion interval and the number of transfusions with mortality. However, we found that inter-transfusion interval was a sensitive parameter for predicting survival if the patient received transfusion at a gap of at least one day.

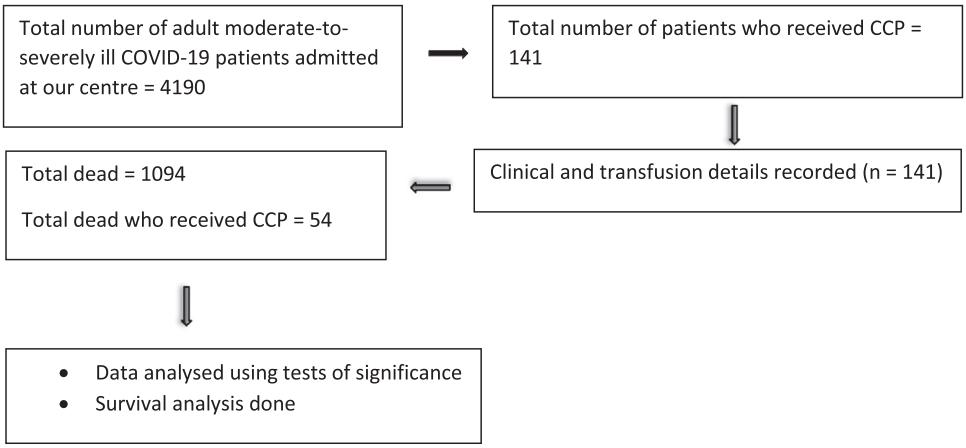

Fig. 1. ROC curve analysis showing diagnostic performance of Admission Transfusion Interval (days) in predicting outcome in patients who received CCP.

Table 2
The univariate and multivariate regression results for all the significant predictors of survival in patients who received CCP therapy identified using Cox Proportional Hazards Regression analysis.

Dependent: Surv (Time, Event)		all	HR (univariable)	HR (multivariable)
Age (Years)	Mean (SD)	56.1 (13.7)	1.05 (1.02–1.07, p < 0.001)	1.04 (0.99–1.10, p = 0.098)
Age Group	< 40 Years	17 (100.0)	–	–
	40–60 Years	72 (100.0)	7.65 (1.03–56.72, p = 0.046)	2.13 (0.22–20.69, p = 0.515)
	> 60 Years	52 (100.0)	14.41 (1.96–106.01, p = 0.009)	1.48 (0.09–24.39, p = 0.784)
Grade of Illness	Moderate	50 (100.0)	–	–
	Severe	91 (100.0)	30.01 (4.15–217.19, p = 0.001)	24.37 (3.33–178.26, p = 0.002)
Comorbidity: Renal Injury	Yes	36 (100.0)	–	–
	No	105 (100.0)	0.53 (0.30–0.93, p = 0.028)	0.85 (0.47–1.52, p = 0.573)

Several factors could explain the high mortality of patients who received plasma therapy in our study. The majority of these patients had severe COVID-19 infection and had associated comorbidities. Further, 36.9% were > 60 years old. We know that higher mortality is present in older age group patients, those with pre-existing comorbidities, and a severe grade of illness. Also, many patients received CCP late during their hospital stay as the Admission-Transfusion Interval ranged from 1 to 21 days. This delay in the institution of transfusion may have severely impacted its efficacy.

Korper et al. in their randomized control trial on 105 patients concluded that CCP added to standard treatment did not significantly impact the primary and secondary outcomes. However, they found a significant benefit among those who received CCP with greater amount of neutralizing antibodies. The poor general condition of these patients, cross-over of 7 patients in poor condition, late administration of CCP, however, are serious limitations of this study [24]. According to our study results, early institution of CCP in younger, moderately-ill COVID-19 patients with no comorbidities, has a vital role in the treatment and even prediction of survival.

Our study was limited by factors such as the shortage of availability of CCP during the early pandemic, inability to perform a randomized control trial and the protocol being used that utilized CCP only on patients who were unresponsive to other treatment modalities. Furthermore, However, further research is necessary in the age-matched, severely-ill population for its role. there is also a need for standardization of the time frame for the administration of CCP and the gap between two transfusions when needed.

Although the use of CCP in the treatment of COVID-19 has been discontinued as per the recent ICMR guidelines [13], recent use of antibody cocktails that work along the same principle but are more expensive and inaccessible has prompted the re-evaluation of the role of CCP in COVID-19. It has been shown to have an essential role as an adjuvant therapeutic agent. Also it has been already stated that convalescent plasma use led to significant reduction in mortality in Spanish flu, ebola virus and SARS coronavirus infection [6–8]. Historical data on mortality reduction seen in infectious viral diseases with the use of convalescent plasma has been tabulated below (Table 3) [6,15,25–30]. Thus, it is crucial to utilize CCP while ensuring the appropriate drafting of guidelines for administration and effective implementation.

Table 3
Historical data of mortality reduction in infectious diseases with the use of Convalescent Plasma.

S. No.	Disease	Year	Mortality reduction due to Convalescent Plasma
1.	Meningitis (Bacterial and Viral) [25,26]	1912	55%
2.	Influenza pandemic (influenza A H1N1 virus) [6,25]	1918	21%
3.	SAARS Co-V 1 [25,27]	2003	24%
4.	Argentine hemorrhagic fever [25,28]		16%
5.	influenza pandemic (influenza A H1N1 virus) [25,29]	2009–2010	80%
6.	Ebola Virus [25,30]	2013	16%
7.	COVID-19 pandemic (SARS-CoV-2) [15,25]	2019	51%

5. Conclusion

While plasma therapy has been written off by several researchers, we report improvement and recovery in a large number of patients who received convalescent plasma within the first five days of hospitalization with moderate to severe disease. We believe that this therapy merits slightly more than premature dismissal, specifically in the light of newer emerging strains and more expensive alternatives targeting similar pathophysiological pathways of action. Further research to compare dosage and administration protocols is needed to delineate role of CCP in evaluating survival in COVID-19 patients is needed before it is hastily written off.

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