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Review Article

Convalescent Plasma Therapy in COVID-19Acute respiratory distress syndrome - Give It a Whirl!

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Abstract

Background

Convalescent plasma (CP)therapy has emerged as a promising therapy for COVID -19 disease on the background of non-availability of a vaccine or drugs of proven efficacy. We conducted this study to assess the safety and the potential efficacy of CP therapy in our study group.

Methodology

The patients hospitalized under the department of pulmonary medicine of our tertiary care hospital with laboratory confirmed COVID-19, receiving CP therapy on compassionate basis were included in the study. Clinical data of patients were obtained from the hospital medical record such as demographic data, presenting symptoms, comorbidities andtreatment details such as antivirals, steroids and immunomodulators. Outcomes were assessed by relief of dyspnea, improvement in oxygen saturation, laboratory values specifically Interleukin-6, requirement of steroids and oxygen at discharge.

Results

The 20 patients consisted of 14 (70%) men and 6 (30%) women. The mean age was 42.6(13.82). The cases were categorized as per severity of ARDS into 5 (25%) mild ARDS, 9 (45%) mod ARDS, and 6 (30%) severe ARDS. The mean day of hospitalization when patients received plasma therapy was 9.05(6.41). Post CP therapy there was clinicoradiological improvement and reduction in IL6 levels post CP therapy were statistically significant (paired t test, p-0.0013). All patients could be discharged successfully and there were no deaths.

Conclusion

CP therapy has a potential to reduce the mortality, hasten the clinicoradiological improvement and is safe.

Keywords: convalescent plasma therapy; safety; Interleukin 6 levels

Introduction

Coronavirus disease 2019 (COVID-19) has emerged as a highly infectious and morbid disease with global implications and hence declared as a pandemic and a global health emergency by the world health organization (WHO). The causative microbiological agent is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new positive-sense, single-stranded RNA virus belonging to the family Coronaviridae [1]. The myriad of its clinical manifestations encompasses a wide spectrum of severity ranging from a mild upper respiratory tract infection to a fulminant viral pneumonia culminating in acute respiratory failure. It may progress to develop multiorgan dysfunction syndrome and death [2]. Theinfection may rapidly transit from one stage to another with some overlap in the stages. These stages as per the timeline can be described as asymptomatic viral shredding(first five days), phase of escalating viremia coupled with inception of clinical manifestations (Day5 to 10), phase of cytokine storm (Day8 to 14) exhibiting clinically as acute respiratory distress syndrome (ARDS) and convalescent phase (Day14 to D28)[3].The therapeutic armamentarium against COVID-19 disease primarily involves supportive therapy, oxygenation, noninvasive ventilation, antiviral drugs like remdesivir and favipiravir or anti-inflammatory drugs like steroids and tocilizumab each having its own scientific rationale[4]. However none of the drugs have a robust evident for conclusively proven efficacy. Non-availability of a potent vaccine in the immediate future is another obstacle in our battle against this disease. Targetting and reducing the viremia forms the essence of any treatment modality. On this background, convalescent plasma (CP) therapy has emerged as a ray of hope admist the despair of ambiguity. It is based on the rationale of passive transfusion of neutralizing antibodies against the virus produced by the donor host recovered from the disease to a patient suffering from active infection[5]. The ultimate target is to arrest the viremia and thereby halt the progression of the disease into its further grave stages. We hereby conducted this study to assess the efficacy, safety and feasibility

of this therapy historically successfully used for many viral infections in this century like Influenza, argentine haemorrhagic fever and SARS [5]

Methodology

The patients hospitalized under the department of pulmonary medicine in the respiratory intensive care unit (RICU) of this tertiary care hospital receiving CP therapy from 15th July to 15th September 2020 were included in the study. Total 23 of our cases received plasma therapy. Three were excluded as they were included in the PLATINA study which was initiated in September at our center.

CP therapy was allowed for off label use on compassionate grounds following completion of the PLACID trial at our center on 14th July 2020[6]. However. none of the subjects included in our study were a part of any other study/trial like the PLACID. Patients with laboratory confirmed COVID-19, diagnosed using reverse transcriptase–polymerase chain reaction(RT-PCR) were enrolled in this study.Clinical data of patients were obtainedfrom the hospitalmedical record such as demographic data, days of admission from symptom onset, presenting symptoms, comorbidities and various treatment data such as antivirals, steroids and immunomodulators.Basic laboratory data such as hemoglobin, complete blood count(CBC) , platelets, biochemistry panels assessing renal and liver function test(LFT, RFT), arterial blood gas(ABG), blood groups were documented. A chest radiograph (CXR) posteroanterior view, Electrocardiograph (ECG), High resolution Computer tomography (HRCT)of the chest if feasible wereobtained. If pneumonia was evident on radiological investigation, further biomarkers such as C- reactive protein (CRP), Procalcitonin (PCT), D-Dimer levels, Interleukin 6(IL-6) and Troponin I were performed.Patients were classified into Mild, Moderate and Severe Acute Respiratory Distress Syndrome(ARDS)as per severity by calculating partial pressure of oxygen in arterial blood/fraction of inspired oxygen (PaO2/FiO2) ratio as 200-300, 100-200 and <100 respectively. Patients were evaluated for their supplemental oxygen requirements. Four categories of supplemental oxygen use status were collected. These included, in order of increasing severity: low-flow oxygen delivery by standard nasal cannula; high-flow oxygen delivery, including non-rebreather mask (NRBM), high-flow nasal cannula (HFNC) or Non-invasive ventilationin form of bilevel positive airway pressure (BiPAP); and invasive mechanical ventilation. All our patients were treated as per the standard ICMR guidelines[7] in our RICU. Supportive care (oxygenation and ventilation) was the mainstay of our therapy. All patients received antivirals as per the hospital supply. The choice of oral antiviral in form of Favipiravir versus injectable drug in form of remdesivir was influenced by the severity of the ARDS and also on the availability of the drugs. Six cases additionally needed tocilizumab in view of COVID cytokine storm (CSS). The drug was irregularly availabledue to global short supply in the study period, hence we opted for plasma therapy initially over tocilizumab. CP therapy was given on compassionate grounds for patients with respiratory distress, respiratory rate (RR) ≥30 beats/min, lung infiltrates demonstrated by CXR or HRCT chest, oxygen saturation (SPO2) level less than 93% in resting state, partial pressure of oxygen (PaO_2)/fraction of inspired oxygen concentration (FiO_2) ≤ 300 mmHg. A written informed consent was obtained in all patients. A known hypersensitivity to blood products, pregnant and breastfeeding women, sepsis and severe organ dysfunction aregeneral exclusions which were absent in our patients before giving CP therapy.

Outcomes after transfusion were assessed by relief of dyspnea, improvement in oxygen saturation, laboratory values specifically IL-6, requirement of steroids and requirement oxygen at discharge.Post transfusion patients were closely monitored for any transfusion related adverse events. Descriptive statistics (Mean,Median, Standard deviation) were used appropriately by tabulation of the data.Categorical data as proportions was compared using Chi square and Fisher's exact while presentation of continuous variables was compared using paired t-test and ANOVA. Significance was set at $p<0.05$.

Results

The study enrolled 20 patients who received CP therapy on compassionate grounds for off label use. The 20 patients consisted of 14 (70%) men and 6 (30%) women. The mean age was 42.6(13.82). The mean age of men and women was 41.71(15.2) and 44.67(7.74) (t test, p=0.66). The cases were categorized as per severity of ARDS into 5 (25%) mild ARDS, 9 (45%) mod ARDS, and 6 (30%) severe ARDS. One of the mild ARDS patients had severe myocarditis. The male to female distribution to severity of ARDS is given in table 1.

	Male	Female
Mild ARDS	4	1
Moderate ARDS	4	5
Severe ARDS	6	0
	fisher test p=0.057	

There was no significant impact of gender on severity of disease (fisher test; p = 0.057). Ten had no comorbidities. Two had DM, 7 had HT. Presence of comorbidities impacted the severity of the disease significantly (table 2 fisher test; p= 0.04).

	Comorbids Yes	Comorbids No
Mild ARDS	0	5
Moderate ARDS	6	3
Severe ARDS	4	2
	fisher test p=0.04	

Table 2

All our patients were treated as per the standard Indian council of medical research (ICMR) guidelines in a respiratory intensive care unit. Supportive care (oxygenation and ventilation) was the mainstay of our therapy.Eight needed only oxygen therapy with NRBM, 6were treated with HFNC, 6 with NIV and 0 needed invasive mechanical ventilation. All received antivirals as per the hospital supply and six cases additionally needed tocilizumab. The drug was also irregularlyavailabledue to global short supply in the study period, hence we opted for plasma therapy initially over tocilizumab. Mean hospital stay was for 21.65 (10.36). The severe the disease, the greater was the hospital stay (ANOVA test, p= 0.0018). All patients were discharged home. There were no deaths. Three needed home oxygen at discharge, which was weaned off at one month follow up. Discharge therapy included steroids for more than 15 days in eight patients in view of exercise desaturation below 90%. The mean day of hospitalization when patients received plasma therapy was 9.05(6.41). The pts blood groups included A+, B+, AB+, O+, B-, and O-. The distribution of blood group as per severity is given in table 3.

Blood group	O	A	B	AB

mild	1	1	2	1
mod	2	4	2	1
severe	1	1	3	1
	4	6	7	3
	Chi Square; p value 0.9			

Table 3

It's impact on severity of disease statistically insignificant (chi square test, p=0.9). Mean pre plasma therapy IL6 levels was 167.84(170.76). Meanpostplasma therapy IL6 level was32.32 (36.54). The reduction in IL6 levels were statistically significant (paired t test, p-0.0013). We used IL6 levels for monitoring as they were easily and consistently available for all cases.

Discussion

Convalescent Plasma (CP) Therapy basically implies the passive transfusion of plasma rich in immunoglobulins derived from a patient recently recovered from a particular infection to any individualwho has been infected with the disease acutely [8]. The COVID-19 pandemic has led to the upscaling of the role of CP therapy to manifold levels on background of lack of an effective antiviral therapy which is feasible available and cost effective[9]. However, as the pandemic is relatively recent there is still lack of definitive evidence pertaining to the efficacy and safety of this therapy in this disease. Hence, we conducted this study on a selected study group to obtain a better understanding of this potential life saver therapy. Our study group comprised of 20 patients harbouring varied severities of COVID-19 diseasewho received plasma on compassionate grounds for off label use. The mean age was 42.6(13.82). This is slightly lower than the mean age reported in other studies like a study carried out by Liu STH et al on 39 patients where the mean age reported was 55 years [10]. However, this study was conducted exclusively on patients with severe COVID -19 disease. Also, as per various Indian studies it has been observed that the pattern of age distribution of COVID-19 infection in India shows a predilection for younger adults as compared to that acrossthe world [11]. The gender distribution showed a trend of 70% being men and 30% being women. This distribution was similar to the other similar studies[2].There was no significant impact of gender on severity of disease in our study (fisher test; p = 0.057). However, studies done prior have reported that the severity of the disease amongst women is lesser as compared to men [11].

The cases were categorized as per severity of ARDS into 5 (25%) mild ARDS, 9 (45%) mod ARDS, and 6 (30%) severe ARDS. This is very similar to a prospective multicenter study done on 742 patients where they observed 17.1%with mild, 44.6% with moderate and 38.1% with severe ARDS [12]. In our study,10 patients had no comorbidities,2 had DM, 7 had hypertension.In a study done on 25 patients with severe COVID 19 disease, comorbids observed were DM in 10 patients, hypertension in 9 patients, and hyperlipidemia in 5 patients. The lower proportion of comorbids in our study could be attributed to the relatively younger age group [13]. Presence of comorbidities impacted the severity of the disease significantly in our study. This is in concordance with many studies conducted worldwide where patients with associated comorbidities have demonstrated a worse outcome [14]. The distribution of blood group as per disease severity was statistically insignificant in our study.However as per data from a Swedish cohort, blood type A or AB demonstrated a heightened risk of requiring intensive careor succumbing to the disease[15].All our patients were treated as per the standard ICMR guidelines[7] in our RICU. Supportive care (oxygenation and ventilation) was the mainstay of our therapy. As per the severity of ARDS the oxygenation and ventilation requirement of our patients varied. However, no patient needed invasive mechanical ventilation. All patients received antivirals as per the hospital supply. The choice of oral antiviral in form of Favipiravir versus injectable drug in form of remdesivir was influenced by the severity of the ARDS and also on the availability of the drugs. Six cases additionally needed tocilizumab in view of cytokine storm. The drug irregularlyavailabledue to global short supply in the study period, hence we opted for plasma therapy initially over tocilizumab.

We observed a favorable outcome in our study group in terms of all patients demonstrating a clinicoradiological improvement post therapy and could be successfully discharged home without any mortality. However, our study did not have a control arm. As per a study done by Li L et al, on 103 patients where they had a control arm too, there was no significant differencein the primary outcomeof time to clinical improvement or the secondary clinical outcome of 28day mortality within 28 days inboth the groups. However, among patients with severe disease, the rateof negative viral PCR at 72 hours was statistically significantly higher in CP therapy group the convalescent plasma group compared with the control group [16]. Also, as per the PLACID study[6] conducted across 39 hospitals across India, CP therapy was not associated with a reduction in mortality or the rate of progression to severe disease. CP therapy was however associated with a better improvement in the clinical parameters subjectively and objectively in form of reduction in FiO2 requirement and also a heightened negative conversion of viral RNA on day 7 post enrolment in intervention arm[6]. Mean hospital stay in our study population was for 21.65 (10.36).This is in concordance to other prospective multicenter study done on 742 patients[12].The reduction in IL6 levels post CP therapy was statistically significant .We used IL6 levels for monitoring as they were easily and consistently available for all cases.Il6 is a marker that has been reliably used as a marker of the disease severity and also heralds the onset of the cytokine storm syndrome (CSS)[17], Even after an extensive literature search we could not gather substantial data pertaining to the effect of CP therapy on IL6 levels, however in a case series of from Korea, 2 patients of severe COVID 19 disease treated with CP therapy showed a reduction in their ferritin and IL6 levels post CP transfusion along with clinicoradiological improvement[19].Thus in our study the association of reduction of IL6 levels after CP therapy can be said to be a surrogate marker of reduction of the viremia and hence an indicator of reduction of the disease severity after CP therapy. CP therapy has been associated with a range of adverse events of varying severity and nature. This may include transfusion related volume overload and pulmonary edema,transfusion related acute lung injury(TRALI), allergic reactions, febrile reactionsand hemolytic reactions[16] .None of the patients in our study group had any adverse reactions post CP therapy.In a study done by Ling Li on 103 patients, they observed CP therapy related adverse events in only 2 cases and both were non severe in nature[16].

These evidences definitely hint that CP therapy has an optimistic impact on the reduction of the viremia and a potential to hasten the clinical recovery though the effect on mortality is yet to be proven conclusively. We thus conclude that CP therapy in COVID-19 disease plays an opportune role by virtue of its safety and has a potential to reduce the mortality, hasten the clinicoradiological improvement and halt or flatten the severity of the cytokine storm. It can also be safely used in combination with other treatment modalities like antiviral and anti-inflammatory drugs [20,21].

Limitations

Our study had various limitations. The referral bias was a major challenge. Our RICU dealt with patients who were referred promptly and early after diagnosis as per the intra-institute policy for covid-19 screening. There was negligible time lag in identification of progression/criticality of disease and

shift to ICU care. The good outcomes could be partly attributed to this efficient intra-institute strategy and policy. We did not have a control arm.

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