Convalescent Plasma Therapy for Moderate COVID-19 Patients Real Cure Insight or Just a Mirage?

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ABSTRACT

Convalescent plasma, donated by COVID-19 recovered persons is a cellular component of blood that contains isotope specific antibodies such as IgA, IgG and IgM. Plasma therapy consists of transfusion of convalescent plasma to the COVID patients. The present investigation was a single center, non-randomized, comparative study to evaluate efficacy and safety of convalescent plasma therapy as an add on therapy to standard of care in moderate COVID-19 patients. A total of 135 patients received convalescent plasma and results showed no significant statistical difference in the outcome of the patients who received plasma therapy when compared with the patients who did not received plasma therapy. Therefore the study concludes that convalescent plasma therapy was not supportive to the standard of care in improving the health of COVID-19 patients with bronchopneumonia.

KEYWORDS
COVID - 19, Convalescent plasma, Bronchopneumonia, Antibodies, laparoscopy

HIGHLIGHTS

- Plasma therapy did not show statistically significant difference in outcome in COVID-19 patients.
- However, results of plasma therapy are best when administered to a moderate disease patient desaturates with exertion only, maintaining saturation at rest.
- Fresh plasma can yield better results. If first unit plasma has not helped then the second unit plasma will also be not helpful.

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How to Cite This Article:

Kaulgud R, Yevoor K, Maleyur V, et al. Convalescent Plasma Therapy for Moderate COVID-19 Patients-Real Cure Insight or Just a Mirage?. J Evid Based Med Healthc 2023;10(3):75.

Received: 13-Mar-2023;
Manuscript No: JEBMH-23-91493;
Editor assigned: 15-Mar-2023;
PreQC No. JEBMH-23-91493 (PQ);
Reviewed: 29-Mar-2023;
QC No. JEBMH-23-91493;
Revised: 18-May-2023;
Manuscript No. JEBMH-23-91493 (R);
Published: 26-May-2023;
DOI: 10.18410/jebmh/2023/10/03/75

INTRODUCTION

In 19th century immune system components were obtained from the laboratory for the treatment of patient's infection/disease such as diphtheria. The application of immune system components also known as passive serum immunotherapy to overcome infectious disease was of great success which was honored with Nobel Prize in 19011. In the year 2009, during influenza A H1N1 pandemic, a work carried out by Hung and co-workers observed, a significant reduction in relative risk of mortality of patients treated with convalescent plasma[2]. Further, during Ebola outbreak in 2014, WHO recommended, convalescent plasma obtained from the Ebola recovered patient as an empirical treatment to treat deadly Ebola virus infectious. Subsequently, a protocol was set in 2015, for the use of convalescent plasma in the treatment of Middle East respiratory syndrome corona virus (Middle East respiratory syndrome (MERS).[4] COVID-19 is a disease caused by SARS-CoV-2, a positive sense, single stranded RNA virus. It may manifest across a wide spectrum of clinical severity results into mild upper respiratory tract illness to a diffuse viral pneumonia, which leads to acute respiratory failure, with sequelae including acute lung injury, multiorgan dysfunction syndrome and death.[5] As per WHO guidelines, management of COVID-19 includes infection prevention, case detection, monitoring and supportive care. However, no specific anti-SARS-CoV-2 treatment is recommended due to lack of comprehensive evidence.[6] With previous history of passive immunotherapy, the use of Convalescent Plasma (CP) against SARS coronavirus 2 (SARS-CoV-2) is advocated for the treatment of coronavirus disease 2019.[7] Convalescent plasma, donated by a person who has recovered from COVID-19, is acellular component of blood including immunoglobulins that specifically recognize SARS-CoV-2. When these antibodies, transfused into patients with SARS-CoV-2, are thought to exert an antiviral effect in the human body, which further suppresses the viral replication before patients have mounted their own humoral immune responses. Indeed, virus specific immunoglobulins from the recovered person are often the first available therapy for emerging infectious disease, a stopgap treatment; while new antivirals and vaccines are being developed.-[10] Convalescent plasma therapy is a source of antiviral neutralizing antibodies. However, immune pathways, such as antibody dependent cellular cytotoxicity, complement activation and/or phagocytosis are putative mechanisms, through which convalescent plasma might exert its therapeutic effect in patients suffering with Covid-19.[11] On the contrary, other metabolic mechanisms such as, anti-inflammatory cytokines, defensins, pentraxins and other immunomodulatory proteins increase/decrease might have a role in developing systemic inflammatory response syndrome, which is the main pathophysiological basis for acute respiratory distress syndrome, which further leads to mortality from COVID-19 related pneumonia.[12,13] Convalescent Plasma (CP) therapy has been the subject of increasing expectation for the treatment of COVID-19. Indeed, preliminary reports on CP use have shown encouraging results without adverse events in patients. However, most of the studies of CP transfusion were focused on the severe COVID-19 patients, whereas only limited studies addressed CP benefits on less severe disease. Majority of the studies reporting COVID-19 infections and its treatment have come from the initially affected countries with their well-established health sector and research infrastructure, on the other side, very few studies reported from the low/middle income countries.[14] Indeed, CP therapy could make easily available option in low/middle income countries, and also it was observed that, the clinical trials conducted in middle income countries with high income countries differ significantly.[15.16] Previous reports published on CP treatment remain uncertain due to its safety and efficacy for COVID-19 virus. Also, some of the studies were not carried out in systematic manner and were non-randomized without control arm, these could be due to the concept that, administration of CP could save the life, before virus damage organs in the patient1. Despite of its limitation in some of the countries by Emergency Use Authorization (EUA) law or in the context of clinical trials, CP treatment has been increasingly adopted. CP clinical trial in the high income countries is centralized, with large scale procurement of required supplies, on the contrary, only one third of the CP trails were conducted in low middle income countries. The main objective of this study was to evaluate the efficacy and safety of CP in patients with moderate COVID-19.

MATERIALS AND METHODS

Study Design

The present investigation was carried out as a single center, non-randomized, comparative study to evaluate efficacy and safety of CP therapy as an add on therapy to standard of care therapy in moderate COVID-19 patients. Moderate COVID- 19 patients were categorized as defined by the clinical management protocol, released by ministry of health and family welfare, government of India. Patients who signed the informed consent and met the eligibility criteria were randomized to either of the following treatment arms:

Treatment arm 1(Investigational arm): CP administered 200 mL on day 1 and given again after 48 h depending on the clinical and laboratory response. Plasma was not administered after 48 h if there was clinical deterioration.

Treatment arm 2 (Comparator arm): Standard of Care treatment as per guidelines for management of COVID - 19 released by ministry of health and family welfare, government of India. Standard of care treatment such as corticosteroids/antiviral/antibiotics/vitamins etc. were administered as per investigator's discretion or institutional protocol or guideline released by ministry of health and family welfare, Government of India. Follow-up assessments were carried out at day 4, day 7 and day 14 (end of study visit).

Diagnosis and Main Criteria for Inclusion

- Men and women of >18 years of age.
- Admitted in hospital.
- Willing to provide informed consent, had confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection within 10 days as determined by RT-PCR.
- Availability of respective donor plasma at the point of enrolment.
- PaO_2/ FiO_2 <300.
- Respiratory rate >24/min and SpO_2 <93% on room air.

Exclusion Criteria

- Pregnancy.
- Breastfeeding women.
- Known hypersensitivity to blood products.
- Receipt of pooled immunoglobulin in last 30 days
- Critically ill patients.
- P/F ratio < 200 (moderate-severe ARDS).
- Shock (Requiring vasopressor to maintain a MAP ≥ 65 mmHg or MAP below 65).

Eligibility of Donor

The following criteria should be met for potential donors:

- Age >18 years.
- Males or nulliparous female donors of weight ≥ 55 Kg.
- Prior diagnosis of COVID-19 documented by a RT-PCR with symptomatic disease with at least fever and cough.
- Completely recovered patients without any symptoms (at least 28 days prior to donation) or complete resolution of symptoms at least 14 days prior to donation and two negative real time PCR test for COVID-19 from nasopharyngeal swab, collected 24 h apart.
- Donors who had transfusion of blood components in last 8 weeks were excluded.
- Donors who have had Covid diagnosis more than 4 months were excluded from donation.

Primary Endpoint

- Change in World Health Organization (WHO) ordinal scale from admission within 14 days.

Secondary Efficacy Endpoints

- Change in levels of biomarkers (D-dimer, C-reactive protein, and ferritin) during the course of stay in the hospital.
- Duration of hospitalization.
- Time to clinical improvement measured using ventilation; time frame: Day 14 WHO ordinal scale during hospital stay.
- Proportion of patients requiring mechanical.

Statistical analysis was carried out using SPSS 22 software. Data was analyzed using descriptive and inferential statistics. *Chi square*/Fischer exact test was used to compare the outcome between the plasma therapy and standard treatment groups.

RESULTS

In the present study a total of 81 unit of convalescent plasma was collected (each unit 500 ml), out of which 67 units were collected in 2020 and 14 units were collected in 2021. Further 108 COVID-19 patients were administered with CP during 2020 and similarly 27 patients received CP during 2021. All the patients included in the present study were above 18 years old, age wise distribution of patients is given in the Table 1. However, during CP therapy 22 deaths occurred and 8 patients lost to follow-up.

Age	Number of patients plasma therapy arm	Number of patients control arm
<40	24	26
40-50	12	14
50-60	45	41
60-70	29	33
70-80	21	21
80	4	2

Table 1: Age Wise Distribution of the Patients.

Primary Efficacy Endpoint

The primary efficacy endpoint of the present study showed that the proportion of patients with clinical improvement (defined as ≥ 2 points reduction on WHO ordinal scale) up to day 14.

Secondary Efficacy End Points

Resolution of symptoms on day 7 fever, shortness of breath, fatigue, cough.

The distribution of co-morbidities among the study (intervention arm) and the control arm. Indeed, there was no significant difference noticed with regards to the clinical features or the other treatments received between the plasma therapy and the control groups. Both groups received standard treatment as per ICMR guidelines. Further in the present study no significant differences were observed with the outcome of patients between those who received plasma therapy and those who did not receive plasma therapy. The statistical analysis was carried out using different possible scenarios, like considering missing people as all recovered, as all dead. But still there was no significant difference between the two groups with regards to outcome. Though a series of patients showed really good response following administration of plasma therapy, the final analysis was not significantly different between the groups. The distribution of age was not significantly different between the groups. Various biomarkers studied were not found to be significantly different in distribution between the two groups. However, to study the impact of timing of plasma therapy on outcome, we compared the outcomes between groups receiving early plasma therapy those receiving plasma within 48 hrs of onset of symptoms with those receiving plasma more than 48 hrs after onset of symptoms. The death was significantly less in patients receiving early plasma therapy. Further, we also compared the impact of exact timing of plasma therapy in patients who died versus patients who recovered. There was very significant difference. The patients who died after receiving plasma therapy had received plasma therapy significantly late compared to those subjects who recovered. None of the patients who required invasive mechanical ventilation recovered and there was 100 percent mortality.

DISCUSSION

COVID-19 is a new disease, and there is lot of research is going on to understand it, however, there is lack of evidence on its treatment. It is know from the previous studies that the, passive antibody transfer is a promising tool in patients suffering from respiratory infections. It has been generally recognized that the, COVID-19 disease course is operated by two mechanisms; one is through damage caused by virus pathogenicity and second disturbance of host immune

system. Usually pathogenicity is marked by common clinical symptoms such as, fever, cold, cough and elevated biological markers and reduced $CD4^+$ and $CD8^+$ T-cells in the blood. While the second mechanism of COVID-19 infections is caused by the downstream upregulation of transcription factors which further elevate the pro-inflammatory and coagulation parameters. Thus, applying a detail investigation in a comprehensive manner is required. During the time of COVID-19 outbreaks, CP therapy emerged as a potential lifesaving hope in viral infections; however, there is need to gather more evidences with CP therapy. Plasma therapy has been tried as a therapeutic option in numerous studies. The results have been less than satisfactory in majority of the studies. But the experience at our center has been different. The results of this therapy in moderate COVID-19 patients have been encouraging in our study site. Some principles which we used while using this therapy may be reason for this observed results in moderate COVID-19. First of all we used this therapy within a week of onset of symptoms. Logically this therapy, being anti-viral, should be used within first week, which is the phase of viremia. By applying these principles, we got some good results. On the contrary, in some patients, therapy was slightly delayed and results observed were unsatisfactory. Also, freshly collected plasma response on patients was different compared to plasma collected days or week back. This may be because of possibility of availability of more active antibodies. We also observed in our study that, patients with high d dimer values on admission had poor outcome with plasma therapy compared to the patients who had normal d dimer values; this could be due to pro coagulant action of plasma. Though encouraging results were noted in numerous patients, but still there was no significant difference in overall outcome between the study and the control groups and also the mortality was not statistically significantly between the groups.

CONCLUSION

Convalescent plasma therapy was not helpful in improving outcome in COVID-19 patients with bronchopneumonia, but a series of cases showed really good response. Timing of plasma therapy plays a pivotal role in determining the outcome of subjects receiving plasma therapy. Subgroup of patients who received plasma therapy early had significantly better outcome compared to patients receiving plasma therapy late. Some modifications in inclusion criteria based on our and similar studies can give valuable inputs in refining plasma therapy protocol and make therapy uniformly successful in COVID-19 patients.

LIMITATIONS OF THE STUDY

The study is non-randomized trial. Randomization could not be performed because of limited availability of plasma, some of the blood group plasma was difficult to get.

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