International Journal of Medical and Allied Health Sciences

ISSN: 2583-1879
Available at http://www.ijmahs.org/

*Original Research Article*

# Study on effect of COVID-19 convalescent plasma therapy on inflammatory parameters in COVID-19 patients

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**Article Information**: Received on 25-10-2021 Accepted on 27-12-2021 Available online 29/12 /2021

## Abstract

**Context:** The coronavirus has threatened mankind and has brought everything to a standstill. The treatment of Coronavirus Disease 2019 (COVID-19) remains elusive to the medical fraternity, trials are going on to search for an effective therapy. The CCP (COVID convalescent plasma) therapy is being tried in many institutes for reducing mortality.
**Aim:** To establish the clinical usage of CCP in hospitalized COVID-19 positive patients with decreased oxygen saturation levels.
**Settings and Design:** This is a retrospective study done at L. N. Medical College and Research Centre, Bhopal.
**Material and Methods:** Cases were selected from the COVID -19 facility ICU from September 2020 to March 2021. Patients with RT-PCR confirmed COVID-19 illness; PaO2/ FiO2: < 300 or Respiratory Rate > 24/min and SaO2 < 93% on room air; who were administered CCP therapy. Five inflammatory parameters were selected and were recorded before and 48 hours after administration of CCP therapy. Descriptive analysis and paired t-test were done to analyze the data with SPSS software.
**Result:** Of the five parameters studied four parameters were found to be statistically correlated, except TLC; while on paired sample test, no parameter had a valid significance.
**Conclusion:** CCP therapy in patients may not help in improving the clinical outcome. Howsoever, the different clinical morbidities and more so the dramatic behavior of SARS- CoV-2 poses a great difficulty in coming to a concrete conclusion.

**Keywords:** Coronavirus Disease 2019 (COVID-19), SARS- CoV-2, COVID Convalescent Plasma (CCP), Neutrophil Leukocyte Ratio (NLR), Total Leukocyte Count (TLC)

## 1. Introduction

The world is witnessing a catastrophic pandemic of Coronavirus Disease 2019 (COVID-19) devastating all spheres of the human health and economy of the world, and making human beings feel their incapability to bring out solutions to control and manage the COVID-19 pandemic. World Health Organization on 30th January 2020 declared COVID-19 as a public health emergency of international concern and on 11th March 2020, it was categorized as a pandemic [1].

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doi: http://doi.org/10.54618/IJMAHS.2021121


### *1.1 Pathophysiology*

The causative organism of COVID-19 is severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) also called Human coronavirus 2019 (HCoV-19). SARS CoV-2 is next in line with SARS CoV-1 that was the culprit of the SARS outburst in 2002-2004. SARS CoV-2 is a RNA virus with a positive sense single strand classified as Baltimore class IV that is contagious to humans. Its transmission primarily occurs by respiratory droplets [2].

After contracting with the virus, the invasion and infection of type II pulmonary epithelial cells via the Angiotensin-converting enzyme (ACE-II) occurs, leading to activation of the inflammatory markers and thus causing the cytokine storm, including a rise in

markers such as interleukin (IL) IL1, IL6, Tumor necrosis factor (TNF), Interferon (IFN)-gamma, etc. This is followed by the sequestration of these inflammatory markers in the lung along with the CD8 mediated cytotoxic lung injury, leading to diffuse alveolar damage and acute respiratory distress syndrome (ARDS) [3].

The cause of mortality in COVID-19 remains elusive; although some plausible pathophysiologic mechanisms have been hypothesized, the ARDS occurring in the disease is supposed to be due to the cytokine storm which in turn causes the hyper inflammation of the respiratory system and eventually leading to respiratory failure. Another school of thought says that COVID-19 causes micro thrombosis which is followed by occlusion of small pulmonary vessels leading to respiratory failure [4,5].

*1.2 Convalescent Plasma Therapy*

Blood, the circulating elixir of life, is composed of plasma and cellular components, of which the normal plasma forms the largest component making 55% of whole blood.

The normal plasma consists predominantly of water, dissolved proteins, clotting factors, glucose, electrolytes & hormones. It protects the body from infections and has other roles also as maintaining a balance of electrolyte concentration in the body.

On 14/4/2020 the Government of India approved the clinical trial proposed by the Indian Council of Medical Research (ICMR) to use COVID convalescent plasma (CCP) therapy on COVID-19 cases in collaboration with the Directorate General of Health Services Central Drugs and Standard Control Organization (Biological Division) [6].

The U.S Food & Drug Administration on August 23, 2020, also issued an emergency use authorization (EUA) for the use of CCP therapy in COVID-19 cases [7]. The convalescent plasma is the plasma recovered from an already recovered person to treat a sick person. The convalescent plasma therapy has been used prior in the treatment of SARS, Middle East Respiratory Syndrome coronavirus (MERS-CoV), 2009 H1N1 pandemic with fair success [8,9,10]. These days the COVID-19 pandemic has threatened humans and has compelled all of us to revisit our inner self, making us feel helpless against the forces of nature. We only have supportive treatment available and are in search of an effective treatment to fight it. Because of the virological and clinical similarity to SARS, MERS-CoV, and H1N1 diseases with COVID-19; it is assumed that CCP may prove to be helpful and maybe a promising treatment to treat the COVID-19 pandemic [11].

The neutralizing antibodies (receptor binding domain-specific antibodies) present in the COVID convalescent plasma have potent antiviral activity; along with it antibody-dependent cellular cytotoxicity, phagocytosis, and complement system activation might exert their therapeutic effect in COVID-19 cases. The COVID convalescent plasma also contains anti-inflammatory cytokines, defensins, pentraxins, and other immunomodulatory proteins that might also help in subsiding the systemic inflammatory response syndrome [12].

The COVID convalescent plasma gained from a recovered covid positive person to treat a sick COVID-19 person undergoing treatment is being used in several states like UP, Delhi. Kerala, Maharashtra, Gujarat, Madhya Pradesh.

Aims and Objective:

To establish the clinical usage of covid convalescent plasma (CCP) in hospitalized COVID-19 positive patients with decreased oxygen saturation levels.

## 2. Material and Methods

This is a retrospective study done in L N Medical College and Research Center, Bhopal. Twenty cases of COVID-19 patients were administered CCP therapy from September 2020 to March 2021.

**Inclusion criteria.**

Patients with RT-PCR confirmed COVID-19 illness.
PaO2/ FiO2: < 300 or
Respiratory Rate > 24/min and
SaO2 < 93% on room air.
Patient administered CCP

**Exclusion Criteria**

COVID-19 Patients who were not administered CCP.

**Selection of Donors** [13,14]

Potential donors were selected by retrieving the list of recovered patients along with volunteered donors.

- Males or nulliparous female donors.
- Donors within an age group of 18 to 60 years and having weight >50 Kg.
- Donors who met all the routine blood donor criteria.
- Donor having a history of RT-PCR positive test for COVID-19.
- Donor recovered from COVID-19; with very high neutralizing antibody titer; five times the cut-off, asymptomatic for at least 28 days and have been declared cured or negative on a repeat test after treatment.
- Asymptomatic donors were also accepted, only if anti-SARS-CoV-2 IgG antibodies were present.
- Complete resolution of symptoms at least 14 days before the donation, with one negative RT-PCR test report, or complete resolution of symptoms 28 days prior/ post-discharge.
- COVID KAWACH Ig G Microlisa, kit by J. MITRA & Co. Pvt. Ltd. approved by ICMR was used and

donor's antibody titers five times the cut off were taken; reference range used was between .2 to .25.
- Donors were advised to donate not more than twice a month.

*2.1 Plasmapheresis*

Our blood bank possessed a license for plasmapheresis & has the facility to measure serum protein & anti-SARS-CoV-2 IgG antibodies. According to standard protocol and SOP'S being followed, ABO compatibility was screened for and screening of donors for HIV, hepatitis B, C & Syphilis, malaria was done and a proper record of the same was maintained. Serum proteins and the anti-SARS-CoV-2 IgG antibody titer were done by ELISA, specifically for CCP plasmapheresis donation. Total serum protein > 6gm/dl and presence of anti-SARS-CoV-2 IgG antibodies were seen.

A document from the DCGI document on 01/July/2020 mentioned a titer of 1:640, the working group recommends that in absence of quantitative test kits, at least the qualitative test (Yes/No) should be used for deciding upon donor eligibility. The donors with negative anti-SARS-CoV-2 IgG antibodies should be deferred, also it stated that a donor serum sample should be frozen at < -30° Celsius for a possible later date testing of titer, etc. [15]

*2.3 Procedure*

After the selection of the donor apheresis machine was used to separate the CCP. In a single dose 200-400 ml of CCP was transfused in two consecutive settings minimum 24 hours apart. Thereafter proper labeling was done along with the date of collection and date of expiry.

## 3. Results

All twenty cases selected for the study were those who were administered CCP, their records were meticulously scanned and the hematological and biochemical laboratory parameters were taken into the study.

The hematological parameters (Total Leukocyte count, Platelet count, Neutrophil to lymphocyte ratio) & the Biochemical parameters (C reactive protein and D Dimer) values were taken into consideration. The values of these parameters were collected pre CCP therapy and post CCP therapy.

All the values were entered into the datasheet and were analyzed for descriptive statistics and paired t-Test was applied using SPSS version 25 software.

Lymphocytopenia is considered to be an important factor in the prognosis of COVID-19. Out of the twenty cases studied, seven cases had a decrease in total leukocyte count, while thirteen cases had an increase in total leukocyte count after CCP therapy.

In our study, we observed that before administration of CCP therapy minimum Total Leukocyte Count (TLC) observed was 3300 and a maximum of 34600 while it was found to be a minimum of 4200 and a maximum of 26900 post-CCP therapy. The TLC median count observed before administration of CCP therapy was 11,700 with a mean TLC of 12,575 while post CCP therapy the median TLC observed was 14,200 with a mean TLC of 14030 (Figure 1).

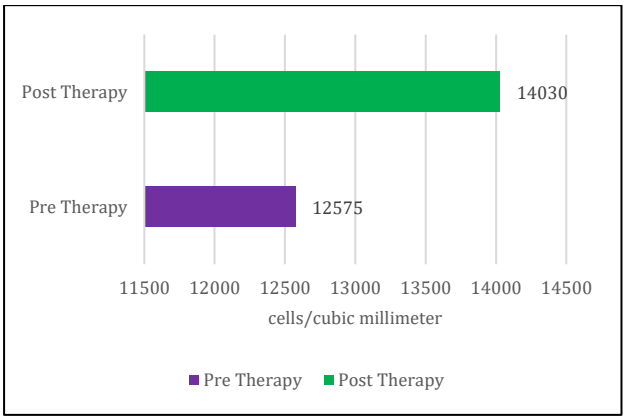


**Figure 2**. Mean Total Leukocyte Count (TLC) in cells/cubic mm Levels

In our study, we observed a minimum platelet count of 1.09 lakh and a maximum of 4.86 lakh in our cases before the CCP therapy in comparison to the minimum of 60,000 and maximum of 5 lakh post-CCP therapy. The platelet count before CCP therapy, had a median count of 1,95000 and a mean platelet count of 2,29100 while post-CCP therapy median platelet count was 2,81000 with a mean of 2,70000 (Figure 2).

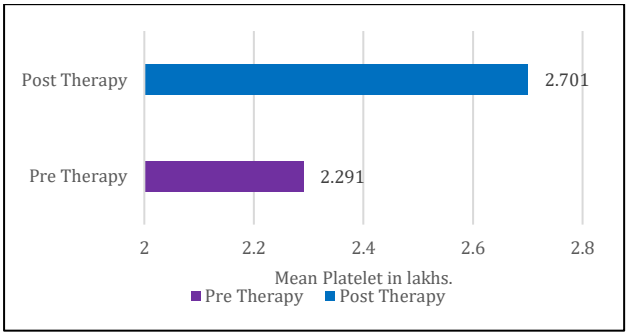


**Figure 2.** Mean Platelet count in lakhs

We observed that the C-Reactive Protein (CRP) value before the administration of CCP therapy had a minimum value of 5 and a maximum value of 192, while after the administration of CCP therapy minimum value observed was 3 and a maximum value of 48. The CRP value before the administration of CCP therapy had a median value of 27.5 and a mean value of 34.9. While post CCP therapy the CRP value observed had a median of 14 and a mean value of 22.7 (Figure 3).

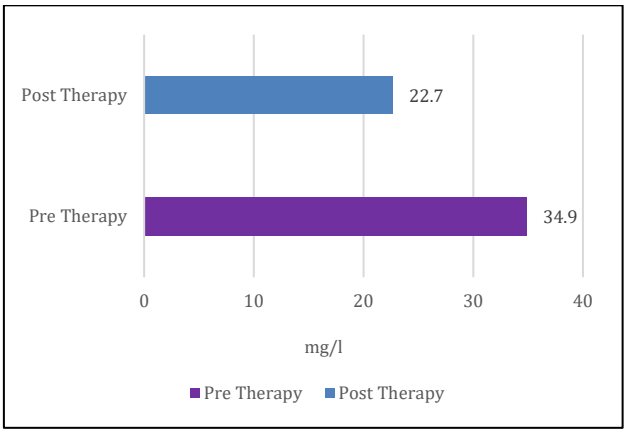


**Figure 3.** Showing mean CRP levels

The Neutrophil to Lymphocyte ratio (NLR) observed before the administration of CCP therapy was a minimum of 2.3 and a maximum of 23.5 while after administration of the CCP therapy it was found to be a minimum of 3.1 and a maximum of 23.1. The NLR, before administration of the CCP therapy, had a median of 8.60 and a mean of 9.62. While, after administration of CCP therapy median NLR was 8.90 with a mean of 9.67 (Figure 4).

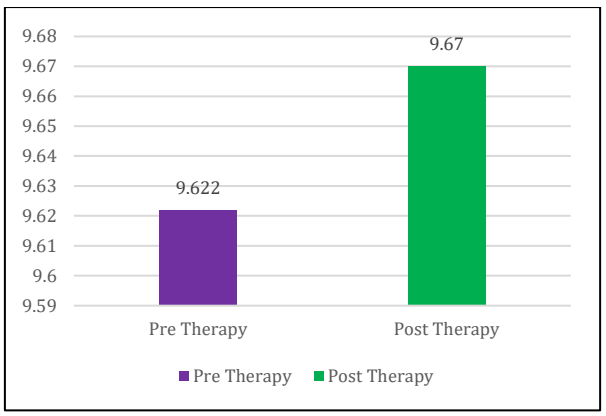


**Figure 4.** Mean Neutrophil to leukocyte Ratio

The D-dimer values observed were 324 as minimum and maximum were 10,000 before the administration of CCP therapy, which after administration of CCP therapy, the minimum and maximum values observed were 243 and 10,000 respectively. The D-Dimer levels observed before the administration of CCP therapy, had a median level of 1000 & a mean level of 1883. While, after the administration, CCP therapy observed median D-Dimer level was 819 with a mean level of 1401 (Figure 5).

On comparing the study parameters by application four parameters were found to be statistically correlated, except TLC which did not correlate. The paired sample t-test, none of the parameters showed a valid significance value thereby accepting the null hypothesis that CCP does not help improve the above-said parameters.

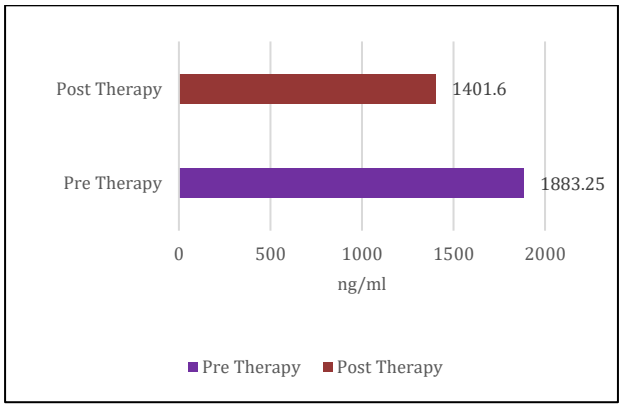


**Figure 5.** Mean D-Dimer Values

## 4. Conclusions

Since the outbreak of covid 19 pandemic, various agencies have published guidelines to standardize the patient management; Indian council of medical research **(**ICMR) and Ministry of health and family welfare (MOHFW) Govt. of India published guidelines for the covid 19 patients; according to ICMR guidelines patients admitted with RT-PCR confirmed COVID-19 illness and had either PaO2/ FiO2: 200-300 or Respiratory Rate > 24/min and SaO2 < 93% on room air and according to the MOHFW guidelines, an adult with clinical features of dyspnoea, hypoxia, fever, cough, SpO2 <94% on room air, Respiratory Rate more than or equal to 24/minute and moderate disease with increasing oxygen requirements not responding to steroids, should receive CCP therapy prior the patient goes into organ failure.

In our study, we didn't find any significant change in the five parameters (TLC, Platelet, CRP, NLR, Dimer) studied after the administration of CCP therapy at our institute.

A similar study was done by Simonovich VA et al; also showed no significant change in the D-dimer and the ferritin levels in the cases studied [16]. A similar study was done by AlQahtani M, et al also showed that there was no significant improvement in the parameters of the patients who were administered CCP therapy rather there was an increase in ferritin and D-dimer levels and a higher systemic inflammatory response in the patients who received CCP therapy [17]. To conclude the CCP therapy doesn't appear to improve the biochemical and pathological parameters studied and hence might not be helpful as these parameters reflect the inflammatory state in the body. Howsoever because of the limitations in our study, more studies in due course of time and a better understanding of the nature and pathogenesis of SARS COV 2 in the future would open new dimensions.

### Limitations of the Study

- Sample size taken was small.
- Antibody titer of CCP (quantitative) given was not known.

- The comorbid conditions of the patients, receiving CCP were not taken into account.
- The role of concomitant treatments cannot be ruled out.

## Competing interest

The authors declare that there are no conflicts of interest.

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