

**Review Article****Convalescent plasma therapy and COVID-19**

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**Abstract**

COVID-19 is a pandemic outbreak caused by a new coronavirus, SARS-COV-2. Corona infects almost all the countries of the World. Currently, the research on COVID -19 vaccination is still in the empirical stage. COVID is closely related to the original SARS-CoV outbreak in 2003 and convalescent plasma has a very long history of use in the treatment of infectious disease, so based on the previous study on other pandemics viral infectious disease, we try to find evidence to prove the effectiveness of convalescent plasma for the treatment of COVID-19. Treatment of COVID-19 using the convalescent plasma of recovered COVID-19 donors for the treatment of severe COVID-19 cases could be a better option. The convalescent plasma contains specific IgG and IgM anti-SARS-CoV-19 antibodies, which can neutralize the virus. However, the implementation of a convalescent plasma transfusion program might need comprehensive planning. Concluded that for patient safety, use convalescent plasma therapy along with other symptomatic and clinical treatment as possible as in the early stage of infection.

**Keywords:** Convalescent plasma (CP), Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

**Introduction**

The world regularly comes to light with uncontrolled infectious diseases. The most recent outbreak is COVID-19. Now it becomes pandemic. In December 2019, pneumonia associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It named coronavirus disease 2019 (COVID-19) by World Health Organization (WHO), which emerged in

Wuhan, China. The epidemic spread rapidly worldwide within three months and was characterized as a pandemic by WHO on March 11, 2020. As of 13 April 2020, there have been at least 1,314,458 Currently Infected Patients world wild from that 1,263,607 (96%) in Mild Condition and 50,851 (4%) Serious or Critical. The most common symptoms at disease are fever, cough, and shortness of breath, while less common

symptoms included sputum production, chest pain, diarrhea, nausea and vomiting, headache, and sore throat. Currently, the research on COVID-19 is still empirical stage. Based on the previous study on other pandemics viral infectious diseases and COVID-19, we try to find evidence to prove the effectiveness of convalescent plasma for the treatment of COVID-19. This review article aims to discuss the safety and efficacy of convalescent plasma for the treatment of COVID-19. Here we reassessed the usefulness of historic convalescent plasma trans fusion (CPT).

### Method

A literature search was conducted using a combination of free-text words and using the databases PubMed, EMBASE, and Web of Science. Relevant terms and appropriate filters were designed. The eligibility criteria were as follows: “convalescent plasma, outcomes, and infectious diseases.” To improve the report of this review, we used the preferred reporting items for systematic reviews and meta-analyses (PRISMA). In addition, we also searched the reference lists of selected studies.

The targets of COVID-19 treatment should divide into two categories. First, it aims at the virus itself. The first thing you can think of is destroying the body of the virus. However, destroying the virus itself is a concept of disinfection and is too dangerous for humans to apply. As a therapeutic agent, some drugs inhibit RNA-dependent RNA polymerase by inhibiting the replication of viruses (e.g., remdesivir), or drugs that impede protease (e.g., lopinavir/ritonavir).<sup>[4]</sup> Another target is an angiotensin-converting enzyme 2 (ACE2), a gatekeeper and receptor for viruses to enter human cells. By raising the intracellular pH and glycosylation of ACE2 can be prevented to block the entry of the virus (e.g., chloroquine).<sup>[5,6]</sup> It can be prevented from binding to ACE2 in advance by sticking to the spike protein of the virus.<sup>[7,8]</sup> currently, no approved specific antiviral agent is targeting the novel virus, while some drugs are still under investigation. The 2019-nCoV belongs

to *Betacoronavirus*, which also contains SARS-CoV and Middle East respiratory syndrome CoV (MERS-CoV). Several drugs, such as Lopinavir/Ritonavir, Interferon alpha-2b, oseltamivir, Ribavirin, corticosteroids, have been used in patients with SARS or MERS, although the efficacy of some drugs remains controversial. Treatment of COVID-19 it seems difficult with only one mechanism.

At the heels of the recent outbreak of coronavirus disease (COVID-19) in the world wild, the Indian Council of Medical Research prioritized the evaluation of treatment with convalescent plasma derived from patients who have recovered from the disease. We will review the safety and efficacy of convalescent plasma for the treatment of all pandemic and epidemic diseases.

### Criteria for Donor

The donor population will consist of adult (>18 years of age) who had a confirmed COVID-19 infection and were subsequently tested negative for the virus. The collection of plasma will be at least 28days from the onset of symptoms and at least two weeks of recovery from the disease. (Nucleic acid tests negative twice consecutively on respiratory tract samples such as sputum and nasopharyngeal swabs, sampling interval being at least 24 hours). Donors have to fulfill the criteria for eligibility for blood donation in this institution. Repeat sputum, and blood testing for COVID-19 PCR will be performed before plasma donation. Plasma will be discarded in case of positive PCR testing.

Plasma will be collected through the apheresis machine that is used routinely for apheresis donations in this institution. 600 ml of plasma will be collected in one setting. Collection may be repeated once, with the interval between the 2 donations being no less than 7 days.

### Criteria for Recipient

Recipient population will consist of an adult patient (>16 years of age) who has confirmed COVID-19 admitted to the hospital and requires treatment. Children and pregnant women will be

excluded. Both donors and recipients need to agree to participate and sign an Informed consent.

### Convalescent Plasma Dosage

The doses of CP used as described by the different studies is varied. In the study by Duan et al.<sup>[32]</sup>, 200 mL convalescent plasma with a neutralization titer above 640 was transfused, while 400 mL convalescent plasma with a neutralization titer above 1,000 was transfused in Shen et al.'s study.<sup>[30]</sup> Patients in both studies had positive clinical improvements. Another study by Bin Zhang et al.<sup>[31]</sup> reported a maximum of 2400 mL of convalescent plasma administered to a 73 years old male patient. Due to variability of CPT doses in reports, the optimal dose of CPT for COVID- 19 could not be determined.

### Discussion

List of infectious agents includes the West Nile virus (WNV), Dengue virus, chikungunya virus, severe acute respiratory syndrome (SARS) virus, Middle-East coronavirus, various avian flu viruses (H1N1, H5N1) some with pandemic potential, and Ebola virus (EBOV).<sup>[1], [2], [3]</sup>

Transfusing convalescent blood products has demonstrated some efficacy in fighting various viral or bacterial infectious diseases including influenza, measles, chickenpox, and, more recently, SARS and the H1N1 and H5N1 avian flu viruses, scarlet fever, mumps, measles, whooping cough and typhoid fever<sup>[9,10,11,12,13,14,15,16,17,18]</sup>. Convalescent serum was first used to treat EHF during the 1976 EBOV outbreak.

The virological and clinical characteristics share similarity among SARS, Middle East Respiratory Syndrome (MERS), and COVID-19<sup>[27]</sup>, CP therapy might be a promising treatment option for COVID-19 rescue<sup>[28]</sup>. Patients who have recovered recently from COVID-19 with a high neutralizing antibody titer may be a good source of CP donor.

Chenguang Shen et al studies found that CPT significantly reduces the viral load and increase the level of neutralizing antibody over time. Viral loads also decreased and became negative

between day 1 and 30 days after the CPT. He described that IgG titers of the treated patients increased up to 145 800 and the IgM titers also increased up to 145 800 after CPT.<sup>[30]</sup>

During the 1995 EBOV outbreak in Kiewit, the Democratic Republic of the Congo, CP was used in eight patients diagnosed with Ebola hemorrhagic fever [EHF], seven of which survived.<sup>[19]</sup>

Convalescent plasma treatment reduced mortality, and reduced respiratory tract viral load, serum cytokine response in patients with severe influenza A (H1N1) 2009 virus infection.<sup>[20]</sup>

Recently study published in New England Journal of Medicine it tracking the responses of 53 patients with severe cases of COVID-19 to remdesivir therapy given. According to the report, doctors observed clinical improvement in 36 of the 53 patients; eight got worse, and seven died. Blocking a virus with antibodies is not enough to win the battle. We must also suppress the replication of the virus, and prepare for a cytokine storm that occurs during treatment. Treatment of convalescent plasma to Ebola virus-infected patients prevents the transmission of viruses that may be best experienced by the use of virus-inactivated reconvalescent plasma.

Comparative study Published in New England Journal of Medicine, Jan 2016, showing 99 patients of various ages (including pregnant women) with confirmed Ebola virus disease [EVD] received convalescent plasma, and the control group was 418 patients who received symptomatic treatment. The risk of death was 31% and 38% simultaneously in the convalescent-plasma group and control group. No serious adverse reactions integrated with the use of convalescent plasma were observed.<sup>[21]</sup>

One drawback regarding treatment with CP during this human trial was the inability to quantify the amount of EBOV-specific antibodies contained in each transfusion. Those transfusions with fewer antibodies may have been less effective as a therapeutic intervention for EHF patients. In addition, the timing at which the CP transfusions were harvested may have influenced antibody

levels in each transfusion. Blood for transfusion is typically collected from convalescent patients as soon as they are asymptomatic, and two consecutive blood samples, collected a minimum of 48 h apart, are negative for EBOV RNA<sup>[22]</sup>

Meta-analysis for treatment of H5N1 suggest that Patients with Spanish influenza pneumonia who received influenza-convalescent human blood products may have experienced a clinically important reduction in the risk for death<sup>[23]</sup>

A recent Case study was done by The Catholic University of Korea in April 2020 it describes two cases of COVID-19 treated with convalescent plasma infusion. Both patients presented severe pneumonia with acute respiratory distress syndrome showed a favorable outcome after the use of convalescent plasma in addition to systemic corticosteroid.<sup>[24]</sup>

Chloroquine was often administered to patients because of its broad-spectrum activity against a range of bacterial, fungal, and viral infections. In addition, four of seven (57%) transfusion recipients tested positive for EBOV-specific IgG or IgM antibodies prior to receiving CP treatment, which may have developed during their course of the disease and contributed to their increased chance of survival<sup>[25]</sup>.

A researcher in the UK analyzing samples from the 1976 outbreak fell ill with symptoms of hemorrhagic fever and was subsequently administered 450 ml of heat-inactivated serum harvested from a recovered patient from Zaire, followed, three days later, by 330 ml of heat-inactivated serum from a recovered Sudan patient. The researcher recovered from illness after 15 days, but the efficacy of the transfusions remains questionable due to the interferon and supportive care also provided throughout his course of disease<sup>[26]</sup>

Another research in National Engineering Technology Research Center for Combined Vaccines, Wuhan, China, ten severe patients confirmed with COVID-19. One dose of 200 mL convalescent plasma (CP) transfused to the patients as an addition to maximal supportive care and antiviral agents. The results from 10 severe

adult cases showed that one dose (200 mL) of CP was well tolerated and could significantly increase or maintain the neutralizing antibodies at a high level, leading to disappearance of viremia in 7 days. Meanwhile, clinical symptoms and paraclinical criteria rapidly improved within 3 days.<sup>[29]</sup>

Shen et al report findings from a preliminary study of 5 severely ill patients with coronavirus disease 2019 (COVID-19). Four patients without coexisting diseases received convalescent plasma around hospital day 20, and a patient with hypertension and mitral valve insufficiency received the plasma transfusion at day 10. Although these patients continued to receive antiviral treatment primarily with lopinavir/ritonavir and interferon, the use of convalescent plasma may have contributed to their recovery because the clinical status of all patients had improvement approximately 1 week after transfusion, the patients' neutralizing antibody titers increased and respiratory samples tested negative for SARS-CoV-2 between 1 and 12 days after transfusion.<sup>[30]</sup>

The safety of the use of CP is another issue that has been historically relevant in epidemics. Currently, evidence exists of the safety of CP in situations of emergency. In epidemics of Influenza a (H1N1), SARS-CoV and MERS-CoV, studies did not find any adverse event associated to CP administration.<sup>[9, 20, 24, 28]</sup> In the case of Ebola, CP administration was associated with mild adverse reactions such as nausea, skin erythema, and fever<sup>[21]</sup>. In COVID-19, reports have shown that administration of CP is safe, and it was not associated with major adverse events.<sup>[29, 30,31, 32]</sup>

### Conclusion

Convalescent plasma therapy improves mortality rate and very fast recovery from symptoms. Whole blood and plasma are the first options to consider before other approaches, provided they are prepared under ethical and controlled conditions. Production of safe convalescent blood products should rely, whenever possible, on a well-structured and well-coordinated national

blood-collection organization. Theoretically, viremia peaks during the first week of most viral infections, and it should be more effective to give recovery plasma early in the disease. It concluded that for patient safety, use convalescent plasma therapy along with other symptomatic and clinical treatment as possible as in the early stage of infection.

### Conflict of Interest

All the contributing authors declare that they have no disclosures and no conflict of interest.

### Author's Contribution

Dr Mital Patani and Dr Nitin Patani performed the literature search and wrote the first draft of the manuscript, which was critically reviewed by Dr. Angel Espinosa.

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