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# Convalescent Plasma Therapy for Prophylaxis and Treatment of COVID-19: A Systematic Research of Facts and Files, A Narrative Review

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## Abstract

Humanity has witnessed a pandemic in late December or, early January. Novel corona virus nCov-19 is responsible for causing COVID-19. The first case was reported in Wuhan city, China in the month of December 2019. No specific drugs have been approved yet for its treatment, though, convalescent plasma (CP) therapy is expected to increase the survivable rate. The history of convalescent plasma therapy dates back to the early 20th century. A plethora of studies suggest that CP can be used to treat the emerging infectious diseases. We had a systematic search in PubMed and found numerous Chinese and Korean clinical trials of convalescent plasma transfusions. The present review gives an insight in to the same.

**Key words:** Convalescent plasma therapy, prophylaxis, treatment, COVID-19.

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## Introduction

Corona virus disease- 2019 is caused by severe acute respiratory syndrome- 2 (SARS-CoV-2), also, known as Novel corona virus (2019-nCoV). The disease, in its present state, emerged in Wuhan, Hubei province, China. On March 11th, 2020, World Health Organization (WHO) declared the Corona virus disease-2019 caused by Novel corona virus (2019-nCoV) as a pandemic. At the time of writing, it has spread to 213 countries so far and affected 2544791 people across the globe with 175694 reported deaths. In India, 681 deaths have been reported with the disease affecting 21393 people [1]. A phase-adjusted estimation of epidemic dynamic assumed that the effective reproduction number Ro was 3.1 and could gradually decrease which is comparably higher than the past COVID infection such as SARS and MERS [2]. To date, seven Human Corona viruses (HCoVes) have been identified of being capable of infecting human [3]. SARS-2 is the 7th and transmitted mainly via the respiratory droplets or, close contacts with the infected people [4]. In later stages, the virus has, also, been detected in the anal swabs of the affected patients suggesting the possibility of oral-faecal route of transmission [5]. As per date, no known efficient therapy including drugs or, vaccine has been approved for its treatment. Although anti-viral drugs such as Remdesivir, Ribavirin, Favipiravir along

with Chloroquine, Hydroxychloroquine have shown promising results based on anecdotal cases that have recovered in few of the cases, there is no defined treatment as such till date. In-vitro studies suggest Remdesivir and Chloroquine are highly effective against COVID-19 and might carefully be consider for future clinical trials to fight this global pandemic [6]. In absence of any defined treatment, though, a plethora of studies have suggested the possible use of immune plasma therapy, i.e., convalescent plasma (CP) therapy for the prophylaxis and treatment of COVID-19 [7-9].In India, the Indian Council of Medical Research (ICMR) is yet to approve the use of immune plasma therapy for all origination. The present review is based on a systemic search of the medical data base until April 16th, 2020 and the available evidence that have emerged so far in the efficiency of immune plasma therapy in the treatment of COVID -19 with or, without anti-viral drugs and Chloroquine and corticosteroids.

## Materials and Methods

We systemically searched the PubMed data base up till April 16th, 2020 with keyword 'covid-19 convalescent plasma' and retrieved a total of 22 articles. In addition, we, also, accessed and retrieved the cross references with significance. Articles written exclusively in the Chinese were excluded while all original articles published on COVID 19 convalescent plasma therapy were included for review.

## Discussion

Convalescent Plasma (CP) Therapy includes administration of immunoglobulins containing plasma of a recently recovered individual from a specific infection (SARS-2) to any individual who is susceptible or, infected (has manifested symptoms) for specific disease (such as COVID-19) for the purpose of prophylaxis and treatment [10]. Immunized plasma acts by binding to a given pathogen including virus (SARS-2) directly and causing its denaturisation, eventually, eradicating the latter from the peripheral blood stream while other antibody-mediated pathways including compliment system, antibody-dependent cell-mediated cytotoxicity and phagocytosis might, also, contribute towards the therapeutic effects achieved [11]. In the absence of any proven drugs or, therapy, convalescent plasma has been used previously in outbreaks of Machupo virus, Junin virus, Lassa fever and few others to name. In recent times, convalescent plasma therapy has been used effectively in treating SARS, MERS and Ebola virus outbreaks. Some studies, also, suggest convalescent plasma therapy to be effective in treating H5N1, Avian influenza, and H1N1 influenza. The use of pooled plasma or, extracted immunoglobulins from recovered patients of west Nile encephalitis has demonstrated a protective effect in infected mice and clinical benefit in patients as well [12-15].

In a Chinese study on 5 critically ill patients with confirmed COVID-19 infection as verified by laboratory diagnostics using reverse polymerise chain reaction (rPCR) including 1 male and 1 female patients in an age range of 50-70 years wherein the patients were kept on corticosteroid methylprednisolone and anti-viral drugs (Lopinavir/Ritonavir with Interferon alpha 2b; Lopinavir/Ritonavir with Arbidol and Darunavir; Lopinavir/Ritonavir with Interferon alpha 2b; Favipiravir with Interferon alpha 2b; and Lopinavir/Ritonavir with Interferon alpha 2b respectively), with the transfusion of immune plasma in the said COVID-19 patients (400 ml in two consecutive doses with ELISA Anti-SARS-CoV-2 antibody titre >1:1000), the neutralizing titres against SARS-CoV-2 were found to be in a range of 80-480 within 12 days. Furthermore, the clinical features disappeared with a significant decrease in the Sequential Organ Failure Assessment (SOFA) Score. The patients, also, presented with a resolved Acute respiratory distress syndrome (ARDS) and viral load was not delectable with a concomitant increase in PAO2/FIO2 (range, 172-276 before and 284-366-after) [16].

In another meta analysis study on 10 patients with 7 confirmed COVID-19 cases and 3 patients wherein viral load was not detectable but those who presented with the symptoms were treated with transfusion of 200 ml of immune plasma with neutralising antibody titres of 1:640 in addition to the anti-viral drugs and methylprednisolone, post-transfusion results showed complete resolution of symptoms in all the treated patients while 7 confirmed cases of COVID-19 tested negative after the plasma therapy who previously tested positive with a concomitant increase in their oxyhemoglobin saturation curve and absorption of lesion as seen on radiographic examination. Amongst these, 9 patients received Arbidol monotherapy or, combination therapy with Remdesivir, Ribavirin or, Peramivir while one patient received Ribavirin monotherapy. Six of them, also, received intravenous methylprednisolone. In the same study, a comparison data was recorded with 10 other patients who were not kept on plasma therapy in combination with corticosteroid methylprednisolone and anti-viral drugs wherein it was observed that 3 patients died while 6 others were in stable condition and one case in the control group revealed resolution of the symptoms, thus, revealing a higher mortality rate of around 30% in patients who did not receive plasma therapy [17].

In a similar study in Korea, 2 patients who presented clinical symptoms of COVID-19 infection confirmed by reverse polymerise chain reaction (rPCR) were treated in through convalescent plasma in combination with anti-viral drugs (Lopinavir/Ritonavir, 400 mg/BD) and Hydroxychloroquine, 400 mg OD. In the said study, neutralizing antibody titres were not determined and 250 ml of plasma was infused twice in a day along with intravenous methylprednisolone (1 mg/kg/day). In patient 1, the value of cycle threshold (Ct) changed from 24.98 on day 10 to 33.96 on day 20 after plasma infusion while SARS-CoV-2 was negative after day 26 and the patient was successfully weaned from mechanical ventilation while in patient 2, leucocytosis and lymphopenia were immediately recovered after convalescent plasma infusion while on day 9, the density of bilateral infiltration on chest X-ray showed resolution with increased PaO2/FiO2 up to the levels of 230. The level of C-reactive protein (CRP) and Interleukin 6 (IL-6), also, recovered to the normal range. SARS-CoV-2 was quantified by reverse polymerise chain reaction (rPCR) and was found to be negative after day 20 while the value of cycle threshold (Ct) changed from 20.51 on day 5 to 36.33 on day 9 after plasma infusion. The patient was successfully extubated and discharged from the hospital on day 24 [18].

In popular press, it has been stated that China puts 245 COVID-19 patients on convalescent plasma therapy wherein 91 of them were benefitted from plasma therapy while it was said to be safe and effective, although, till date, there has been no mention about the remaining 154 patients. Furthermore, no further information about the amount of plasma infused and neutralizing antibody titres was provided [19].

In yet another study, different amount of plasma were transfused in 4 different critically ill patients with other systematic disease such as Hypertension (HT), Chronic Obstructive Pulmonary Disease (COPD), Hypertension (HT) with Chronic Renal Failure (CRF) and in a pregnant female with a mean age of 57 years (range 31-73 years). The drugs included were Arbidol (200 mg/TDS), Lopinavir/Ritonavir (400 mg/BD), Interferon alpha inhalation (50 ug/BD) with additional drugs including Human albumin, Zadixin, Immunoglobulins in patient 1 while Arbidol (200 mg/TDS), Lopinavir/Ritonavir(500 mg/BD), Interferon alpha 2b (5 milion units/BD) in patient 2 and Arbidol (200 mg/TDS), Lopinavir/Ritonavir (400 mg/BD), Interferon alpha 2b (5 milion units/BD), Oseltamivir (75 mg/BD), Ribavirin (500 mg/BD) in patient 3 while Lopinavir/Ritonavir (400 mg/BD), Ribavirin (500 mg/BD) in patient 4. Furthermore, 900 ml of immune plasma was infused in three consecutive doses in patient 1, 200 ml of plasma was infused in patient 2, 2400 ml of plasma was infused in 8 consecutive doses in patient 3 and 300 ml of plasma was infused in patient 4 respectively. A notable feature observed in this case was that all the four patients included suffered from different critical illnesses along with COVID-19 while inspite of continuous use of anti-viral drugs and Interferon alpha 2b, their health deteriorated and they developed secondary complications in the form of septic shock, co-infection with bacteria and aspergillus and multiple organ failure syndrome which got resolved once the plasma therapy was initiated. In addition to this, with the initiation of plasma therapy, all the patients showed significant absorption of the lungs lesions while the reverse polymerise chain reaction (rPCR) revealed the viral load to be negative. The clinical condition, also, improved significantly with the progress of treatment and the patients got stabilised. Three of the patients were discharged from the hospital in few days while one was admitted in intensive care unit (ICU) for the treatment of other secondary complications [20].

Likewise, an analysis of the use of convalescent plasma therapy in Corona virus outbreaks including MERS and SARS in Shenzhen, China, one female patient suffering from SARS was transfused with 500 ml of plasma in two consecutive rounds in 12 hours durations while the patient showed improvement in clinical condition [21].Another study in Hongkong, China showed significant improvement in clinical status with 200 ml of convalescent plasma transfusion while in yet another study, 3 severely ill patients infected with SARS were given 500 ml of plasma in Taipei, Taiwan with serum antibody IgG titres greater than 640 while a marked improvement in the clinical condition of all the patients was observed [22,23]. Similarly, numerous other studies conducted revealed marked improvement in the cases treated with convalescent plasma therapy, though, these studies highlighted the significance of further trials to be conducted in this regard to come to valid conclusions [24-26]

From the above pooled data, one thing in common which comes forth is that viral load was not detectable after few days of plasma infusion and the patients were found to be stable and recovering [16-18] It is not clear, though, whether it was because of plasma infusion or, due to the combined effect of anti-viral drug regimes or, Chloroquine/Hydroxychloroquine treatment and corticosteroids. The anti-viral drugs that were included in all the three SARS-CoV-2 cases were Lopinavir/Ritonavir with corticosteroid, methylprednisolone, though, as per the current status and a trial of Lopinavir/Ritonavir in adults hospitalized with severe Covid-19 infection, no benefit was observed with the Lopinavir/Ritonavir anti-viral treatment in COVID-19 patients while methylprednisolone has not been advisable to be used due to a lack of evidence in reducing mortality in COVID-19 patients [27,28]. Corticosteroids have an inherent tendency to suppress the immune system and are used only in case of severe respiratory distress or, symptoms for a short duration of time in severe cases. Corticosteroids inhibit immune response by preventing antibody formation and thus, theoretically, can delay the viral clearance [29]. There has been evidence, though, that Remdesivir and Hydroxychloroquine have been found to be effective against the COVID-19 viral genome as has been suggested by an in-vitro study, though, it is not clear that whether the use of these drugs was taken into consideration in a controlled clinical trial or, not [6] Also, in cases where plasma transfusions have shown promising results, in one case, the amount of plasma transfused was 400 ml while in yet another case, it was 200 ml, though, with higher neutralizing antibody titres (80-480 ; 1:640), the efficiency of convalescent plasma therapy increased as neutralizing increases, though, it, also, has not been substantiated what exactly decreased the viral load since this might be due to the other anti-viral drug regimens along with Hydroxychloroquine and methylprednisolone [16,17].

Despite this uncertainty, the efficiency of plasma transfusion cannot be denied since there are reports wherein it has been shown to considerably reduce the mortality rate as well as length of hospitalisation. The mortality rate for Covid-19 infection in the age group of 50-59 as estimated by researchers at Imperial College, London has been kept at 0.6 while the same rate as per WHO reports in this age range can be as high as 21% looking globally [30]. In an analysis study with COVID-19 patients, the mortality rate was found to be as high as 30% without plasma therapy [13]. It can, thus, be concluded that the use of convalescent plasma therapy in COVID-19 patients is safe and effective, if transfusion guidelines are strictly followed [16]. Plasma therapy has been proven to be effective in several outbreaks in corona infections and even, has shown good results in COVID-19 cases in the Chinese and Korean studies, though, to increase its acceptability and to prove its efficacy, further controlled clinical trials are highly recommended. Even 69 and 73 year old critically ill patients have shown promising recovery with marked improvement in their clinical status leading to RT-PCR test negativity for SARS-COV-19 once the plasma therapy was initiated [30]. The findings of the various trials done so far, thus, signify that convalescent plasma therapy has an ability to decrease the mortality rate and improve clinical condition in cases of SARS-CoV-19 infections and can be used as a promising therapy in future [20].

Convalescent plasma contains neutralising antibodies which have the ability to suppress the virus. In animal research, it has been found that passively transferred antibodies, i.e., immune plasma into an individual shows maintenance of high level of antibody titres until the host immune response is increased for the clearance of the existing infection. In-vitro study suggests neutralizing antibodies add in the acceleration of virus clearance [31]. Despite limitations of the current research work in this aspect and no well-established clinical trials, the present data that is available in the literature suggests that the convalescent plasma recovered from patients who have survived COVID-19 infection might be beneficial in the treatment of active COVID-19 patients and that, it might add benefit in the prophylactic treatment of the same. In the early onset of disease, if convalescent plasma containing high antibody titres is provided, it might be more beneficial. The other modes of treatment including the well-known anti-viral drugs, Chloroquine/Hydroxychloroquine and systemic corticosteroids can be used simultaneously without any noted adverse effects.

**Table 1** COVID-19- Recent trials and locations with key findings.

| Table 1 COVID-19. | No. of Patients in Trial/ Location | Dose of CP | Titres | Key Findings |
|---|---|---|---|---|
| COVID-19 | 5, Shenzhen, China | 400ml in two consecutive doses of 200 ml each | •ELISA anti-SARS CoV-2 antibody titre less than 1:1000<br>•Neutralising antibody titres > 40 | Clinical status improved, SOFA score decreased, ARDS resolved, viral antibodies not detectable, increase in PAO2/FIO2 (range 172-276 before and 284-366 after), all were on other medications including steroids and antiviral, no significant adverse effects reported. |
| COVID-19 | 10, Wuhan, China | 200ml | • Neutralising anti-SARS CoV-2 antibody titres > 1:640 | Clinical status improved, increased oxyhemoglobin saturation, absorption of lung lesions in radiographic examination noted, no significant adverse effects, other therapy included steroids, antimicrobials and antiviral. |
| COVID-19 | 2, Korea | 500 ml in total; infused 250ml twice in 24 hrs | Not stated | - |
| COVID-19 | 245 | Not stated | Not stated | 91 patients benefitted, plasma therapy said to be safe and effective. |
| COVID-19 | 4 | Different amount of plasma were infused in each patients (900ml, 200ml, 2400ml, 300ml) | Not stated | See Table 2. |

**Table 2** COVID-19- Case files.

| Case | Drugs | Past Medical History | Secondary Infection | Amount of plasma diffused | Key Findings |
|---|---|---|---|---|---|
| 1) Age 69/ Female | Arbidol (200mg/TDS), Lopinavir/Ritonavir (400mg/BD), Interferon alpha inhalation (50ug/ BD); Additional drugs: Human albumin, Zadixin, Immunoglobulins (Dose not stated) | Hypertension (HT) | Co-infection with bacteria and aspergillus (For this, patient was treated with Caspofungin and Voriconazole) | 900ml in three consecutive doses | •Radiographic examination revealed absorption of consolidation.<br>•RT-PCR test results negative. |
| 2) Age 55/Male | Arbidol (200mg/TDS), Lopinavir/Ritonavir(500mg/ BD), Interferon alpha 2b (5milion units/BD) | Chronic Obstructive Pulmonary Disease (COPD) | - | 200ml | •Chest images showed absorption of interstitial pneumonia.<br>•RT-PCR test results negative. |
| 3) Age 73/Male | Arbidol (200mg/TDS), Lopinavir/Ritonavir (400mg/BD), Interferon alpha 2b (5milion units/BD), Oseltamivir (75mg/BD), Ribavirin (500mg/BD) | Hypertension (HT) with Chronic Renal Failure (CRF) | Septic Shock, Co-infection with bacteria and aspergillus (For this, patient was treated with Caspofungin and Voriconazole) | 2400ml in 8 consecutive doses | •Reduced viral load.<br>•Radiographic examination showed absorbed infiltrative lesions.<br>•RT-PCR test results negative. |
| 4) Age 31/ Female | Lopinavir/Ritonavir (400mg/BD), Ribavirin (500mg/BD) | Pregnancy | Multiple Organ Failure Syndrome, Septic Shock | 300ml | •RT-PCR test results negative. |

As initial in-vitro trials of Remdesivir and Chloroquine show potential benefit in COVID-19 patients, the combination use of these drugs along with plasma therapy is a matter of research to determine its efficiency. Plasma therapy adds in decreasing the mortality rate and improving the clinical status in the affected individuals. Although evidence is limited, we believe that it would be wise to conduct a quick interim analysis in large numbers of patients in controlled clinical trials following all standard protocols of Indian Council of Medical Research (ICMR) and Food and Drug Administration (FDA) regarding donations of plasma to reduce the risk of any blood products transfusion disease including the HIV, Hepatitis A, B and V infections. It should, also, be kept in mind that donor is clear of the viral load and is negative. While the final drafting of this review, we can come across article in press that the use of 200 ml of plasma shows progressive improvement in the clinical condition of a patient who has been weaned-off from the support of ventilator in New Delhi by Max Hospital [32]. From the above discussion and considering the facts and recovery rates and response to therapy, it can be concluded, thus, that in absence of any proven drugs or, therapy, convalescent plasma (CP) therapy can be efficiently used for the prophylaxis and treatment of COVID-19 patients, though, the search for anti-viral targeting the Novel corona virus (2019-nCoV) and its vaccine continues.

## Conclusion

In case of critically ill patients, plasma transfusions improve clinical condition and decrease mortality rates, though, further studies and controlled clinical trials are always mandated to determine its efficiency and exact role in treatment of Novel corona virus (2019-nCoV) Table 1 and 2.

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