Convalescent Plasma Therapy for Pandemics, COVID-19 as example: A Mini Review

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Abstract

Pandemics are now becoming more frequently due to change due to human beings change of lifestyle. COVID-19 is a typical example of the global burden faced by humanity. During the pandemics, there is the urgent need of effective therapeutic intervention. In COVID-19, there is no specific drug, although remdesivir in combination with anti-inflammatory agents have been shown to shorten hospital stay. A novel approach is the use of convalescent plasma as therapy. This mini-review discusses the historical aspect of the use of CP as therapy, evidence from data on utilization of CP in COVID-19, acquiring CP and plasma composition, patients recruitments, risk of CP therapy, and potential mechanism of action. The review concludes that CP therapy would be a novel approach in managing pandemic when urgent therapeutic interventions are required. However, more clinical data is required to for definite conclusion on it use.

Keywords: SARS-CoV-2, COVID-19, convalescent therapy


Introduction

The SARS-CoV-2 pandemic ravaging through the world is one of the biggest global public health issues that has ever confronted the world. It has led to complete lockdown of global affairs which has affected all facet of human life. The pneumonia induced by SARS-CoV-2 is named coronavirus disease 19 (COVID-19). By 11th September 2020, 28,200,037 people had been infected with the virus globally with 909,927 mortality cases as reported by John Hopkins University & Medicine (https://coronavirus.jhu.edu/map.html). To date, there is no specific treatment proven to be specific for COVID-19 infection. Supporting care such as provision of oxygen in mild cases and extracorporeal membrane oxygenation for critically ill patients are the options. Lopinavir-ritonavir, ribavirin, and intravenous (IV) remdesivir have been reported to shorten hospital stay Other studies also suggested that Azithromycin in combination with Hydroxychloroquine resulted in reduced body temperature and cough remission however, due to small sample size and the short period of follow up, the clinical response was not conclusive. Due to the absence of specific treatment, there have been the
suggestions that use of convalescence plasma (CP) therapy could provide remedy to patients infected with COVID-19.

The principle of CP therapy was described in 1880 when it was reported that immunity against diphtheria or existing antibodies in the blood from animals that were intentionally immunized with non-lethal doses of toxins could be transferred to animals that were suffering from active infections\textsuperscript{4, 5}. It was then shown that immune plasma could neutralize pathogens and also provides passive immunomodulatory properties which allow the recipient animal to control excessive inflammatory response induced by several infectious pathogens or sepsis\textsuperscript{5, 6}. Early in the 1950s, it was also reported that purification and concentration of immunoglobulin from healthy donors or recovered patients could be option for treating serious infectious diseases and immune condition such as primary immunodeficiency, allergies, and autoimmune diseases\textsuperscript{4, 7, 8}.

A wide variety of convalescent blood products such as IV immunoglobulin (IVIg) and polyclonal or monoclonal antibodies have been produced that has been effective in the treatment of infectious diseases\textsuperscript{9}. However, in emergency situations such as global pandemic, these products are difficult and expensive to produce and in some cases may not even provide the necessary control. As such, the use of CP therapy has been utilized in different outbreaks as initial treatment options when there are no effective drugs or vaccines. CP therapy have also been used in some cases, as a last option or experimental option\textsuperscript{6}. The available data from the Spanish influenza to the current SARS-CoV-2 outbreaks show that the utilization of CP therapy was significantly associated with lower fatality rates and mild adverse events\textsuperscript{10, 11, 12, 13}. It has been claimed that there were some therapeutic benefits for measles, Argentine hemorrhagic fever, influenza, parvovirus B19 and Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory infections (SARIs) viruses when CP therapy was administered\textsuperscript{20, 23}. In some patients who were hospitalised with Lassa fever, the administration of CP therapy led to better clinical outcome\textsuperscript{24}. In eight (08) meta-analysis studies involving 1703 patients infected with Spanish influenza and the use of Convalescent Blood Products (CBP), the results showed significant reduction in risk of mortality in treated patients which predicted that CBP could be evaluated in influenza-associated diseases and other outbreaks\textsuperscript{25}. Another meta-analysis study by Mair-Jenkins et al, to evaluate the effectiveness of CP therapy and huperimmune immunoglobulin for treating viral-associated SARIs, reported a significant reduction in the risk of mortality among SARI-infected patients in comparison to patients who were given placebo\textsuperscript{26}. A study by Cheng et al, to evaluate the efficacy of CP therapy for SARS involving 80 SARS infected patients who were given CP therapy between 20 March and 26 May 2003 reported that there was higher day-22 discharge rate among patients who were given CP therapy before day 14 of illness and among those who were PCR positive and seronegative for coronavirus at the time of administering the plasma\textsuperscript{27}. In other cases of coronaviruses infections, the use of CP therapy was reported to be associated with reduction in hospital stay in patients who were critically ill\textsuperscript{14}. While others reported that using CP therapy in combination with mechanical ventilation resulted in reduced duration of invasive ventilation in patients with influenza A (H1N1) pdm09 and avian influenza A (H5N1)\textsuperscript{15, 16}. Furthermore, it has been reported that the use of CP in SARS-CoV and influenza infections resulted in the decrease in viral load in the respiratory tract\textsuperscript{17, 15}.

One issue that has been raised is the safety of CP therapy. The available evidence show that CP therapy is safe in emergency situations as found in the epidemics of Influenza A (H1N1), SARS-CoV, and MERS-CoV. However, with Ebola virus epidemic, it was reported that administration of CP therapy led to mild adverse
events such as nausea, skin erythema, and fever\textsuperscript{18}. This means that CP therapy can be utilized as good candidate for evaluation during a pandemic as a therapeutic option to control such pandemic. However, during the EVD outbreaks in 2015, the WHO did adopt the evaluation of CP therapy derived from patients as a priority. The Ebola-Tx Consortium undertook a non-randomized study which involved 99 patients with confirmed EVD and given two consecutive transfusions. The control group were 418 patients. They concluded that transfusion of up to 500 ml \(\text{CP}\) with unknown levels of neutralizing antibodies were not linked with significant improvement in survival\textsuperscript{28}.

**Use of CP in COVID-19: Evidence from Data**

In view of the urgency to provide therapeutic solution for SARS-CoV-2 infection, a number of studies have been undertaken to assess the effectiveness of \(\text{CP}\) therapy in COVID-19 patients. In a review study Valk et al\textsuperscript{19}, conducted eight studies involving 32 subjects. The aim of the studies was to assess whether convalescent plasma or hyperimmune immunoglobulin infusion is effective and safe in the treatment of COVID-19 patients. The studies concluded that there were some uncertainties involving the effectiveness of \(\text{CP}\) therapy for patients admitted to hospitals with COVID-19. The synthesised studies, reported of inconsistent results which made it difficult for comparison of results and draw conclusions. The studies identified very low-certainty evidence on the effectiveness and safety of \(\text{CP}\) therapy for people with COVID-19. However it was observed that all the studies were at high risk of biasness and the quality of reporting was low.

Shen et al\textsuperscript{29}, conducted a study involving 5 critically ill patients with laboratory confirmed SARS-CoV-2 infection and acute respiratory distress syndrome (ARDS). The aim of the study was to evaluate whether \(\text{CP}\) transfusion could be beneficial for the treatment of critically ill patients with SARS-CoV-2 infection. The following markers were used: severe pneumonia with rapid progression and continuous high viral load even when antiviral drugs were administered, \(\text{PAO}_2/\text{F}_1\text{O}_2< 300\), and on mechanical ventilation. The effect of \(\text{CP}\) therapy was compared before and after administration of \(\text{CP}\) transfusion. All patients were on mechanical ventilators, received antiviral drugs and methylprednisolone. After transfusion of the plasma, the body temperature of 4 of 5 patients became normal within 3 days. Sequential organ failure assessment score decreased while \(\text{PAO}_2/\text{F}_1\text{O}_2\) went up within 12 days. Inflammatory parameters such as C-reactive protein (CRP), procalcitonin, interleukin-6 (IL-6) improved within 12 days. Viral loads decreased and became negative within 12 days post-transfusion while SARS-CoV-2-specific ELISA and neutralizing antibody (nAb) became high after the transfusion. ARDS also resolved 12 days after transfusion among 4 of the 5 patients. 3 patients were taken off mechanical ventilators within 2 weeks post-transfusion. At day 37, post-transfusion, 3 of the patients were discharged while 2 became stable. The authors therefore concluded that the base on their case study of 5 critically ill patients with COVID-19 and ARDS, the administration of \(\text{CP}\) consisting of nAb was associated with improvement in their clinical status.

In another study by Duan et al involving 10 severe patients with confirmed real-time viral RNA test for SARS-CoV-2 who were enrolled prospectively were administered with a dose of 200mL \(\text{CP}\) obtained from donor with nAb titre above 1:640 was transfused to patients as an additional supportive care plus antiviral agents. The primary endpoint was the safety of the intervention while the second endpoint was improvement of clinical symptoms and laboratory parameters within 3 days post-CP transfusion. They found that after \(\text{CP}\) transfusion,
the nAb level increased up to 1: 640 in 5 cases while in other cases, the level was maintained relatively high. Clinical symptoms improved with high level of oxyhemoglobin saturation post-transfusion within 3 days. There was improvement in some parameters in comparison before transfusion, including high lymphocyte count. Viral load became undetectable after post-transfusion in 7 patients who earlier had viremia. No adverse events were reported. The study therefore concluded that CP therapy was well tolerated and could help improve the clinical outcome by neutralizing viremia in severe COVID-19 cases. Other studies have also reported of the safety and potential effectiveness of CP therapy. However, a systematic and meta-analysis study by Devasenapathy et al concluded that CP therapy has minimal or no benefit in the treatment of COVID-19 and there is low-quality evidence to show that it does not possesses serious adverse events. However, from the data available, it cannot be definitely concluded that CP therapy would be effective for COVID-19. This is due to the limited sample size. Therefore, more clinical studies are needed to ascertain the definite conclusion of the potential benefit of this therapy for COVID-19. In addition, we need to evaluate the optimal dose and the clinical benefits of this intervention in larger controlled clinical studies.

**Acquiring CP and plasma Composition**

The convalescent donors must first undergo standard pre-donation evaluation to be certain that the procedure follows due regulation with regard to plasma donation. Currently the accepted parameter is donors between 18 and 65, with negative result for COVID-19 14 days post-recovery and without any symptoms of infection. The tests should be repeated 48 hours and at the time of donation. Donors from areas associated with tropical diseases such malaria and dengue fever should be excluded. Furthermore, apart from molecular tests, donors should be evaluated for emotional status so as to exclude the exploitation of donors.

The acceptable form of obtaining plasma is apheresis which is base on the continuous centrifugation of blood from a donor so that plasma can be collected. The efficiency of this technique is around 400-800 mL from one apheresis procedure. This amount of plasma can then be stored in units of 200 or 250 mL then frozen within 24 hours of collection for subsequent transfusion. Because CP products require high quality of standard, samples must be infection-free, therefore test for human immunodeficiency virus (HIV), hepatitis viruses, human T-cell lymphotropic virus 1 and 2 as well as Trypanosoma cruzi should be performed. Based on this, tests for HIV and hepatitis viruses are a must so that the safety of the recipients is not compromised. It is suggested that potential pathogens should be inactivated with riboflavin or psoralen with exposure to ultraviolet light so that the safety of CP is increased. There are no standard transfusion dosages for CP. However, some studies involving other coronaviruses have administered CP ranging between 200 and 500 mL in a single or double round of dosages.

The current recommendation for CP administration is 3mL/kg per dose over 2 days. The reason is this will aid the distribution of the plasma units and provide a standard delivery option. Though the composition of CP varies, it has been found to consist of a number of blood derived substances. Plasma consists of mixture of inorganic salts, organic compounds, water, and more than 1000 proteins such as albumin, immunoglobulin, complement, coagulation and antithrombotic factors. Based on the links of cytokine storm with COVID-19 outcome, it is of interest to note that plasma from donor can provide immunomodulatory effect through the infusion of anti-inflammatory cytokines and antibodies that can inhibit complement, inflammatory cytokines,
and autoantibodies\textsuperscript{41}. This would potentially have an impact on the immunomodulatory effect of CP in patients with SARS-CoV-2 infection.

**Patients Recruitment**

A number of clinical studies are ongoing around the globe with each having its eligibility criteria\textsuperscript{(42)}. This means recruitment of patients differs across research groups. However, the Food & Drug Administration (FDA) USA gives the following recommendation\textsuperscript{(43)}:

- Laboratory confirmed COVID-19.
- Severe or immediately life-threatening COVID-19.
- Severe disease is defined by one or more of the following:
  - Dyspnoea.
  - Tachypnoea \(\geq 30/\text{min}\).
  - Blood oxygen saturation \(\leq 93\%\).
  - \(\text{PaO}_2/\text{FiO}_2<300\).
  - Lung infiltration \(>50\%\) within 24-48 hours.
- Life threatening disease is defined as having one or more of the following:
  - Respiratory failure.
  - Septic shock
  - Multiple organ dysfunctions.

**Risk of CP therapy**

Generally, the risks associated with administration of CP therapy are similar to those associated with standard plasma infusion. Infections with others pathogenic agents such as viral transmission, bacterial contamination, and immunological reactions such as urticaria, transfusion-related circulatory overload or TRALI have been described in CP-related study\textsuperscript{(44)}. During the SARS-CoV-1 outbreaks, two observational studies reported of complication associated with CP\textsuperscript{(45)}. Data from developed countries showed that risk of transfusion-transmissible infection is less than an infection per 2 million donations\textsuperscript{(46)}. The risk of TRALI is mostly less than a case in every 5000 transfused units. However, in COVID-19, the risk of TRALI should be of interest as majority of critically ill patients have ARD and disseminated intravascular coagulation which are both risk factors for the development of TRALI\textsuperscript{(47)}. A major concern is the potential risk is transfusion-transmission of SARS-CoV-2 from anti-SARS-CoV-2 CP. This
is however hypothetical since there has not been any reported case of blood transfusion of SARS-CoV-2. This risk should be regarded as highly essential as critically ill patients are already infected. Another hypothetical risk of CP is an antibody-dependent enhancement (ADE). Antibodies developed from previous infections caused by different viral serotype may worsen clinical conditions. Furthermore, previous infections with other types of coronaviruses should be concern about the possibility of ADE in COVID-19. Currently, there is no data to show that there has been worsened clinical condition that could be linked to ADE after CP transfusion. In addition, there has been no report that ADE occurred after CP use for SARS and MERS. Another possible risk of use of CP is effect of the development of natural immune response, especially after the administration of CP as prophylaxis treatment. It is therefore recommended that CP treatment is administered in academic or well prepared centres that would manage the potential complications associated with CP treatment. Some adverse reactions such as transfusion-associated events like chills, fever, anaphylactic reactions; transfusion-associated acute lung injury and haemolysis should be considered. All these should be source of vigilance when utilizing CP as therapy.

**CP: Mechanism of Action**

There is no data which outlined the exact mechanism of action of CP therapy in COVID-19. However, past studies involving other viruses such as Ebola virus has shown the mechanism of action of CP which showed it was mainly via viral neutralization. Another described mechanism is antibody-activation and phagocytosis. When neutralizing antibodies are delivered through CP, it can lead to control of viral load. In addition, non-neutralizing antibodies can also help in prophylaxis as well as improved recovery.

To conclude, the risks of global pandemics continue to increase. Taking COVID-19 as a model, CP therapy is a novel treatment for such outbreaks. However, there are still some challenges to be surmounted. One important issue is lack of data therefore international multicenter randomized controlled trials are required. Till that data is available, we should cautiously consider the use of CP as treatment option for COVID-19 and other pandemics.

**References**

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