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Review Article

Role of Convalescent Plasma Therapy in Critically Ill Coronavirus Disease-19 (COVID-19) Patients

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Received: April 29, 2020; **Published:** May 21, 2020

Abstract

Coronavirus disease 2019 (COVID-19) is currently a big threat to global health. According to WHO management of COVID-19 has mainly focused on infection prevention, case detection, monitoring and supportive care. However, no specific treatment is recommended because of the absence of evidence. Several studies have started in many countries to test the effectiveness of convalescent plasma therapy for treating COVID-19 patients. The idea behind plasma therapy is that immunity can be transferred from a healthy individual to sick using convalescent plasma. Herein, discussed four case series with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection who received convalescent plasma. Results indicate convalescent plasma might be a potential therapy for critically ill patients infected with SARS-CoV-2. Also observed no serious adverse reactions associated with the transfusion of convalescent plasma. However, the relative contributions of supportive care, other antiviral therapies and patient's immune response on survival could not be determined. The safety and efficacy of convalescent plasma transfusion in SARS-CoV-2 infected patients should be studied in a well-designed clinical trial.

Keywords: *Coronavirus Disease 2019 (COVID-19); Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)*

Introduction

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) originating in Wuhan, China, has rapidly spread worldwide, which made World health organization (WHO) to declare it as a pandemic coronavirus disease 2019 (COVID-19) [1]. As of April 26, 2020, WHO had reported globally 2,810,325 confirmed cases of COVID-19, including 193,825 deaths.

SARS-CoV-2 belongs to the β-coronavirus family, a large family of single-stranded RNA viruses (+ssRNA) that can be isolated in different animal species. Its genome composed of about 30 kb nucleotides, which encodes four major structural proteins: spike protein (S), membrane protein (M), envelope protein (E), and nucleocapsid protein (N). Among these proteins, the S protein is of special interest because this club-shaped glycoprotein spikes give the virus a crown-like appearance under an electron microscope (coronam is the Latin term for crown) [2]. These viruses can infect humans and cause illness ranging from the common cold to more severe diseases such as SARS (severe acute respiratory syndrome), MERS (Middle East respiratory syndrome) and now Covid-19.

There are no specific treatments or vaccine has been proven to work for COVID-19 in humans. A lot is still unknown about SARS-CoV-2 infection. Multiple randomised control trials are ongoing; scientists and doctors are exploring various treatment options to fight covid19. One such treatment is convalescent plasma therapy several studies have already started in different parts of the world to test effectiveness of plasma therapy for treating COVID-19 patients.

Plasma therapy

Convalescent Plasma Therapy means, plasma from a COVID-19 patient who has recovered from the disease, is transfused into a critically ill patient.

History

Plasma therapy was discovered by German physiologist Emil von Behring, first used in 1890. This treatment was used during the Spanish flu pandemic of 1918, a diphtheria outbreak in the 1920s and during other outbreaks of infectious diseases. In 2014, WHO had recommended the plasma therapy to treat Ebola virus disease [3-5]. Immunotherapy with neutralizing antibodies present in convalescent plasma proved to be effective and safe for patients with SARS, MERS and the 2009 H1N1 influenza viruses [6].

Principle of passive antibody therapy [7]

Passive antibody therapy involves the administration of antibodies against a given agent to a susceptible individual for the purpose of preventing or treating an infectious disease due to that agent. Passive antibody administration is the only means of providing immediate immunity to susceptible persons. In contrast, active vaccination requires the induction of an immune response that takes time to develop and varies depending on the vaccine recipient [7].

In the case of SARS-CoV-2, the anticipated mechanism of action by which passive antibody therapy would mediate protection is viral neutralization [7]. However, other mechanisms may be possible, such as antibody-dependent cellular cytotoxicity and phagocytosis [8].

During plasma therapy, antibody is most effective when we administered shortly after the onset of symptoms. The reason for temporal variation in efficacy is not well understood but could reflect that passive antibody works by neutralizing the initial inoculum, which is likely to be much smaller than that of established disease [9]. Another explanation is that antibody works by modifying the inflammatory response, which is more easily achieved during the initial immune response [10]. As an example, passive antibody therapy for pneumococcal pneumonia was most effective when administered shortly after the onset of symptoms, and there was no benefit if antibody administration was delayed past the third day of disease [11].

A sufficient amount of antibody must be administered for an effective passive antibody therapy. When given to a person, this antibody will circulate in the blood, reach tissues, and provide protection against infection. Protection conferred by the transferred immunoglobulin can last from weeks to months, which depends on the antibody amount and composition.

The process for donating plasma is similar to donating blood and can collect it in different ways. Once the blood group, infection status and antibody concentration have been established, donors are connected to a apheresis machine via a needle in one arm. As the blood flows through it, the machine extracts antibody-rich plasma, while returning red and white blood cells back to the donor.

Currently, the Federal Drug Administration (FDA) is allowing the use of convalescent plasma from recovered COVID-19 patients as an treatment trial for COVID-19. The eligibility requirements for who can donate blood is restricted to people who had laboratory confirmed cases and severe or life-threatening COVID-19. They must give informed consent and also have to have recovered from all symptoms at least 28 days prior to donating, or 14 days prior with a laboratory confirmed negative result for a COVID-19 test. The ratio of antibodies in the plasma should be at least 1:160 in order for a detectable reaction, according to the FDA.

Indian Council of Medical Research (ICMR) has recently allowed states to start clinical trials of plasma therapy. More than 100 institutes have shown interest to study how safe and efficient plasma therapy is in treating COVID-19. Several states like Kerala, Gujarat and Punjab have already started to use plasma therapy trail for COVID-19 patients.

Convalescent plasma for managing COVID-19 - Case series

Shen C., *et al*. [12]: This study evaluated the administration of convalescent plasma to five critically ill patients, was conducted at the infectious disease department, Shenzhen Third People's Hospital in Shenzhen, China, from January 20, 2020, to March 25, 2020. Results showing all 5 patients (age range, 36 - 65 years; 2 women) were receiving mechanical ventilation at the time of treatment and all had received antiviral agents and methylprednisolone. After plasma transfusion, body temperature normalized within 3 days in 4 of 5 patients, the SOFA score decreased, and Pao_2/Fio_2 increased within 12 days (range, 172 - 276 before and 284 - 366 after). Viral loads also decreased and became negative within 12 days after the transfusion, and SARS-CoV-2–specific ELISA and neutralizing antibody titers increased following the transfusion (range, 40 - 60 before and 80 - 320 on day 7). ARDS resolved in 4 patients at 12 days after transfusion, and 3 patients were weaned from mechanical ventilation within 2 weeks of treatment. Of the 5 patients, 3 have been discharged from the hospital (length of stay: 53, 51 and 55 days) and 2 are in stable condition at 37 days after transfusion.

Mingxiang Ye, Tangfeng Lv., *et al*. [13]; this descriptive study done in Wuhan, 6 laboratory confirmed COVID-19 patients were enrolled and received the transfusion of ABO-compatible convalescent plasma. The efficacy of this intervention was determined by the symptomatic improvement, changes in radiologic abnormalities and laboratory tests. No obvious adverse effect observed during the treatment. Convalescent plasma transfusion led to a resolution of ground glass opacities (GGOs) and consolidation in 5 patients. In 2 patients who presented with SARS-CoV-2 in throat swab, convalescent plasma therapy elicited an elimination of virus. Serologic analysis indicated an immediate increase in anti-SARS-CoV-2 antibody titers in all patients.

Duan K., *et al*. [14]; Researchers in Wuhan, China, performed this study in 10 severely ill COVID-19 patients who also received many different antivirals. Median age of the patients was 53, 4 had chronic illnesses, and 3 were on ventilators. Within 3 days of convalescent plasma therapy, most patients exhibited improved clinical symptoms, higher levels of blood oxygen, lower C-reactive protein levels, undetectable viral loads, and improved chest computed tomography scans; two patients were weaned from ventilators. Treatment was particularly successful if convalescent plasma was given within 14 days of symptom onset; no adverse effects were noted. The investigators assembled a historical control group of 10 COVID-19 patients in the same hospitals and of the same age, sex, and disease severity. Of the 10 convalescent plasma -treated patients, 3 were discharged and 7 were much improved, whereas in the control group, 3 patients died, 6 were stable, and 1 improved.

Zhang B., *et al*. [15]; they presented four critically ill patients with SARS-CoV-2 infection who received supportive care and convalescent plasma. Results showed all four patients (including a pregnant woman) recovered from SARS-CoV-2 infection. They observed no serious adverse reactions associated with the transfusion of convalescent plasma. In this study, three patients were tested for either virus load or antibodies IgM and IgG. In the first case, SARS-CoV-2 virus load after convalescent plasma transfusion significantly dropped. Among the four patients, the time from transfusion to negative RT-PCR test results ranged from 3 to 22 days. The third and fourth cases produced anti-SARS-CoV-2 IgG approximately 14 days after convalescent plasma transfusion.

Previous experience with the use of convalescent sera

The use of convalescent plasma is not new; it was used for severe acute respiratory syndrome (SARS), pandemic 2009 influenza A (H1N1), avian influenza A (H5N1), several hemorrhagic fevers such as Ebola, and other viral infections.

During the 2003 SARS outbreak in Hong-Kong, a non-randomized study in hospitalized SARS patients (n = 50) showed that treatment with convalescent plasma (convP) from SARS-recovered donors significantly higher discharge rate by day 22 following onset of illness (73.4% vs 19.0%; P < .001) and lower case-fatality rate (0% vs 23.8%; P = .049) in the convalescent plasma treatment group (n = 19 patients) when compared with steroid treatment group (n = 21) [16].

Another study involved the treatment of 80 patients with SARS in Hong Kong; patients treated before day 14 had improved prognosis defined by discharge from hospital before day 22, consistent with the notion that earlier administration is more likely to be effective. Although this investigation was not a randomized trial, of 1775 patients, the 80 who received convalescent plasma had a lower mortality rate (12.5%) compared with the overall SARS-related mortality for admitted patients (n = 299 [17%]). The antibody titers and plasma transfusion volumes varied and did not appear to correlate with clinical response; however, patients receiving transfusion within 14 days of symptom onset (n = 33) had better outcomes and no adverse events were reported [17]. In Taiwan, three patients with SARS were treated with 500 mL convalescent serum, resulting in a reduction in serum virus titer, and each survived [18].

An analysis of 99 samples of convalescent sera from patients with SARS showed that 87 had neutralizing antibody, with a geometric mean titer of 1:61 [19]. This suggests that antibody declines with time and that few patients make high-titer responses. It is possible that non-neutralizing antibodies are produced that contribute to protection and recovery, as described for other viral diseases [20].

In South Korea, three patients with MERS were treated with convalescent serum, but only two of the recipients had neutralizing antibody in their serum [21]. In another study of 93 patients with influenza A(H1N1), patients who received convalescent plasma treatment (n = 20) compared with those in the control group (n = 73) had significantly fewer deaths (20% vs 54.8%; P = .01) and a lower median lymphocyte count on ICU admission [22]. In a study involving patients with pandemic influenza A(H1N1) 2009 virus infection, treatment of severe infection with convalescent plasma (n = 20 patients) was associated with reduced respiratory tract viral load, serum cytokine response, and mortality [12].

Risks and benefits

COVID-19 convalescent sera can be used for either treatment of disease or prophylaxis of infection. In a prophylactic mode, the benefit of convalescent serum therapy is that it can prevent infection and subsequent disease in those who are at high risk for disease, such as vulnerable individuals with underlying medical conditions, health care providers, and those with exposure to confirmed cases of COVID-19. Passive antibody administration to prevent disease is already used in clinical practice, like hepatitis B and rabies. In addition, passive antibody is used for the prevention of severe respiratory syncytial virus (RSV) disease in high-risk infants. Convalescent serum would be administered therapeutically to those with clinical disease in an effort to reduce their symptoms and mortality. The efficacy of these approaches cannot be inferred without carrying out a controlled clinical trial. Based on the historical experience with antibody administration, it can be anticipated that antibody administration would be more effective in preventing disease than in the treatment of established disease [23].

Risks of passive administration of convalescent sera fall into two categories, known and theoretical.

Known risks are those associated with transfer of blood substances, which include inadvertent infection with another infectious disease agent and reactions to serum constituents, including immunological reactions such as serum sickness. Convalescent sera used in a therapeutic mode would likely be administered to individuals with pulmonary disease, in whom plasma infusion carries some risk for transfusion-related acute lung injury (TRALI), and this should be a consideration in the risk-benefit assessment [24].

The theoretical risk involves the phenomenon of antibody-dependent enhancement of infection (ADE). ADE can occur in several viral diseases and involves an enhancement of disease in the presence of certain antibodies. For coronaviruses, several mechanisms for ADE have been described, and there is the theoretical concern that antibodies to one type of coronavirus could enhance infection to another viral strain. It may be possible to predict the risk of ADE of SARS-CoV-2 experimentally, as proposed for MERS [25]. The available evidence from the use of convalescent sera in patients with SARS1 and MERS [16] and anecdotal evidence from its use in 245 patients with COVID-19 [26], suggest it is safe. Nevertheless, in convalescent serum trials, caution and vigilance to identify any evidence of enhanced infection will be required.

Another theoretical risk is that antibody administration to those exposed to SARS-CoV-2 may prevent disease in a manner that attenuates the immune response, leaving such individuals vulnerable to subsequent reinfection. In this regard, passive antibody administration before vaccination with respiratory syncytial virus was reported to attenuate humoral but not cellular immunity [27]. This concern could be investigated as part of a clinical trial by measuring immune responses in those exposed and treated with convalescent sera to prevent disease. If the risk proved real, these individuals could be vaccinated against COVID-19 when a vaccine becomes available.

Limitations of the Study

Administration of convalescent plasma was not evaluated in a randomized clinical trial, and the outcomes in the treatment group were not compared with outcomes in a control group of patients who did not receive the intervention. Therefore, it is not possible to determine the true clinical effect of this intervention or whether patients might have recovered without this therapy. In addition, patients received other therapies (including antiviral agents and steroids), making it impossible to disentangle the specific contribution of convalescent plasma to the clinical course or outcomes. Moreover, convalescent plasma was administered up to 3 weeks after hospital admission, and it is unclear whether this timing is optimal or if earlier administration might have been associated with different clinical outcomes.

Conclusion

The preliminary uncontrolled studies of convalescent plasma therapy containing neutralizing antibody showing significant clinical response in critically ill patients with COVID-19 and is believed to be a promising state of art therapy during this pandemic crisis. However, the relative contributions of investigational therapies, supportive care, and patient's immune response on survival could not be determined. The safety and efficacy of convalescent plasma transfusion in patients infected with SARS-CoV-2 should be studied in a well-designed clinical trial.

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Volume 9 Issue 6 June 2020