Short Communication

Treatment with convalescent plasma for COVID-19 with respect to experience from prior coronavirus epidemics

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ABSTRACT

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a major concern all over the world. There is currently no proven vaccine and specific treatment to be effective for SARS-CoV-2 infection. Convalescent plasma obtained from patients who have recently recovered from infection has been used as a therapeutic intervention in previous coronavirus-related pandemics including SARS-CoV, MERS-CoV, and now COVID-19. The presence of neutralizing antibodies which specifically recognize SARS-CoV-2 are thought to mediate antiviral effects before patient develop their own humoral immune responses leading to cytokine storm and disease severity. In this review, we have summarized existing literature on convalescent plasma for the treatment of MERS-CoV, SARS-CoV, and COVID-19. Data from studies using convalescent plasma in COVID-19 suggest clinical improvements such as reduced viral load, oxygen requirement, and radiographic resolution. Although randomized clinical trials describing the benefit of convalescent plasma in COVID-19 are limited but these studies point to better outcomes of convalescent plasma treatment when administered earlier in the course of the disease. However, more precise randomized trials are needed to investigate different indications such as time of plasma administration and/or combination with other antiviral treatments.

1. Introduction

From January 2020 an outbreak of pneumonia-related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), named COVID-19 has become a global concern. It first appeared in November 2019 in Wuhan, China, and spread rapidly worldwide in a couple of months and was specified as a pandemic by WHO on March 11, 2020 (Cui et al., 2019b). Coronaviruses belong to the *Coronavirinae* subfamily in the *Coronaviridae* family.

According to its genetic structure, the *Coronavirinae* subfamily includes four different types; Alpha, Beta, Gamma, and Delta. (Cui et al., 2019a) Before the appearance of SARS-CoV2, six coronaviruses had been identified which could affect humans. HCoV-NL63, HCoV-229E, HCoV-OC43, and HKU1 were the four viruses which usually showed mild respiratory symptoms, and the other two which have caused two pandemics in 2002-2003

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named Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) and in 2012 named Middle-East Respiratory Syndrome coronavirus (MERS-CoV), which revealed severe respiratory symptoms. SARS and MERS had respectively 10% and 37% mortality rate. (Cui et al., 2019a, Kin et al., 2015). SARS-Cov2 mortality is also high and a considerable percentage of the patients require ICU care. At the time of writing this article, more than 29 million confirmed cases and more than 926,000 deaths have been reported globally with no confirmed therapy which could improve disease course (Enzmann et al., 2020). Antiviral agents, corticosteroids, and supportive treatments have been proposed to reduce the severity of symptoms. Despite many clinical trials investigating the effect of antiviral treatments including remdesivir on COVID-19, no specific treatment has been approved by the FDA yet (Rosa and Santos, 2020, Wooding and Bach, 2020). Also, many companies are still working on their vaccines safety and efficacy, additional studies to find a specific treatment for severe COVID-19 is still needed (Rosa and Santos, 2020).

Passive immunization has been used from the past to treat infectious diseases with no specific treatment (Marano et al., 2016). Convalescent plasma therapy is based on using recently recovered patients serum for the treatment of infectious diseases relying on neutralizing capacities of developed antibodies by patients' humoral immune response (Bozzo and Jorquera, 2017). Convalescent plasma has shown beneficial effects for the treatment of viral infections such as measles, H1N1influenza, and Ebola as well as in past coronavirus epidemics such as MERS, SARS, (Marano et al., 2016).

Studies demonstrated that convalescent plasma therapy can significantly reduce the viral load and mortality rate of patients, due to the presence of neutralizing antibodies against virus particles in recovered patients' sera (Winkler and Koepsell, 2015, van Griensven et al., 2016, Mair-Jenkins et al., 2015).

Although numbers of randomized clinical trials (68 at the time of writing this article based on clinicaltrials.gov database) have been registered to investigate the effects of convalescent plasma as a therapy for COVID-19 there is a lack of related reports from these trials, however, observational studies were beneficial (Shen et al., 2020, Li et al., 2020). Therefore, the aim of this article is to review previous attempts on plasma therapy in SARS-CoV and MERS-CoV epidemics and also the efficacy, adverse effects, and benefits of convalescent plasma therapy for COVID-19 treatment.

Effectiveness of convalescent plasma treatment in SARS-CoV infection

In 2003, an outbreak of severe acute respiratory syndrome affected 26 countries and emerged in more than 8000 cases. Fever, nonproductive cough, myalgia, and dyspnea were the common clinical presentations that were observed in most cases (Hsueh and Yang, 2003). Ribavirin, methylprednisolone, levofloxacin, clarithromycin were the mostly used drugs as supportive care for SARS infection (Nie et al., 2003). Also, convalescent plasma therapy was among therapeutic interventions. Five studies that conducted convalescent plasma for treatment of SARS patients are listed in Table 1. Most of these studies believed in the effectiveness of convalescent plasma therapy in line with reduced mortality rate, prolonged survival time, length of staying in the hospital, decreased viral load, and overall improved clinical symptoms (Wooding and Bach, 2020).

In a non-randomized study held in Hong Kong by Y. Cheng and colleagues, receiving convalescent plasma before day 14th from SARS disease onset resulted in earlier discharge from hospital (Cheng et al., 2005). Another retrospective nonrandomized study by Soo et al. indicated that plasma therapy of SARS patients along with methylprednisolone results in a higher discharge rate on the 22nd day of the disease. According to this study, all of the patients in the treatment group survived (Soo et al., 2004).

Another study was conducted on a 57-years-old SARS patient. Treatment started with antivirals, antibiotics, and corticosteroids, followed by 200 mL of convalescent plasma due to the persistence of lymphopenia on day 15 from disease onset. Therapy strategy resulted in lesions improvement as shown by lung x-ray (Wong et al., 2003). In another study in Taipei, 8 confirmed SARS cases among healthcare workers were assigned in a trial. Treatment in the test group (n=3) consisted of corticosteroid, IVIG, antivirals, and convalescent plasma. Lab

results revealed a decreased viral load after 24h of injection and survival of all patients (Yeh et al., 2005).

Effectiveness of convalescent plasma treatment in MERS-CoV infection

MERS is a viral respiratory disease caused by Middle East respiratory syndrome coronavirus that was initially identified in Saudi Arabia in 2012 in a 60 years old man who developed a severe acute respiratory infection and subsequent acute renal failure leading to his death. So far more than 2500 MERS cases have been identified, nonetheless, no specific treatment for MERS-CoV infection exists (Chafekar and Fielding, 2018, Enzmann et al., 2020). Antivirals were the most common agents used to lessen disease symptoms, also convalescent plasma treatment was proposed. In a case report, 3 male patients diagnosed with MERS-CoV infection received four convalescent plasma injections. Among these patients only one who received donor plasma with a plaque reduction neutralization test (PRNT) titer of 1:80 showed a meaningful serologic response after convalescent plasma infusion, emphasizing on the importance of neutralizing antibody titer when selecting donor plasma for treatment (Ko et al., 2018). In another study in Korea, 7 confirmed MERS cases were undergone onvalescent plasma treatment. Employment of convalescent serum in this study resulted in the survival of >85% of patients(Choi et al., 2016). There are two more studies reporting the use of convalescent plasma therapy for the treatment of one or two MERS patients. One of these studies reported the possible transfusion-related acute lung injury following Convalescent Plasma Transfusion (Hong et al., 2018, Chun et al., 2016).

Results of convalescent plasma therapy for the treatment of COVID-19

Providing the overall promising results of SARS and MERS treatment using convalescent plasma and since no specific drug has been approved for COVID-19 yet, some studies employed clinical trials to investigate the effects of plasma therapy in COVID-19.

In a study in China, 10 COVID-19 patients with severe symptoms underwent treatment using convalescent plasma of recently survived COVID-19 patients. Fever, cough, and shortness of breath were the most complaining symptoms. Early treatment protocols consist of corticosteroids, antivirals including arbidol, remdesivir, peramivir, oseltamivir, and ribavirin in line with antibacterials and/or antifungals in patients with coinfection. 200 mL inactivated convalescent plasma with neutralization activity titer of >1:640 was injected into the patients. Results showed that symptoms such as fever, nonproductive cough, dyspnea, and chest pain began to disappear within 1 to 3 days after plasma injection, and the requirement for ventilator support was generally reduced.

Also, lung CT showed improved pulmonary lesions and the total number of lymphocytes increased in most patients. All patients' COVID-19 PCR test turned negative within a maximum of 6 days. Overall all patients in the test group were discharged and had much-improved status in comparison with the control group with no specific adverse effects following convalescent plasma injection (Duan et al., 2020). Zeng et al. also recruited six COVID-19 patients for convalescent plasma treatment about 21 days after disease onset. In this study although plasma therapy resulted in reduced viral load, but could not improve the clinical symptoms of critical patients, indicating that convalescent plasma would be a benefit when applied in earlier stages of infection (Zeng et al., 2020). In another descriptive study by Ye et al. six COVID-19 patients showed improvement of symptoms, radiologic lesions, and laboratory tests after receiving convalescent plasma (Ye et al., 2020).

In another study Ann et al. treated two COVID-19 patients with convalescent plasma on day 22 or 7 after disease onset respectively. Both patients' clinical symptoms, radiographic and laboratory results were alleviated subsequent plasma therapy (Ye et al., 2020). In a case report, Figlerowicz et al. successfully used convalescent plasma for treatment of a six-year-old girl with severe COVID-19 along with aplastic anemia which resulted in the removal of the virus from her nasopharyngeal swab (Figlerowicz et al., 2020).

In another study in China, all five COVID-19 patients who were treated with convalescent plasma between day 10 and 22 of admission showed clinical improvement (Shen et al., 2020). All patients had severe, progressive

pneumonia (PAO2/FIO2 <300) with a high level of viral load. Treatment started firstly with antivirals, corticosteroids, and support of mechanical ventilation. In this study, each patient received totally about 400 ml of ABO-compatible convalescent plasma in two consecutive transfusions on the same day taken from the donors. Sequential Organ Failure Assessment (SOFA) score, decreased continuously following transfusion and overall clinical and laboratory findings showed improvement in all five cases. However, due to the lack of a control group in this study, it is difficult to conclude whether the observed clinical improvements are due to convalescent plasma effects or other therapeutic agents used to treat patients (Shen et al., 2020).

There are also studies investigating the effect of convalescent plasma for treatment of COVID-19 with a small number of patients. In a study in China, four critically ill patients aged 31 to 73 were assigned for plasma therapy. Patients were treated earlier in their disease course with antivirals such as arbidol, lopinavir-ritonavir, ribavirin, oseltamivir, and interferon alfa-2b with no improvement of chest radiographs. In this study between 200 ml to 2400 ml of convalescent plasma was transfused to patients. The patients' condition started to improve slowly along with the absorption of opacities in lung CT with no significant adverse effect on recruited patients (Zhang et al., 2020).

In a propensity score-matched, case-control study in the USA, convalescent plasma therapy was used to treat 39 patients with severe COVID-19. Plasma recipients showed improved survival and ventilatory oxygen requirement in comparison to retrospectively matched controls (Liu et al., 2020). In another cohort study by Enzemann et al. 138 COVID-19 patients treated with convalescent plasma resulted in increased survival and improved dyspnea in comparison with patients receiving other standard treatments(Enzmann et al., 2020).

In the first randomized clinical trial by Li et. al. 103 COVID-19 patients were registered for convalescent plasma therapy. In this study, patients were divided into two groups of severe and critical COVID-19. Final results showed that there was no significant difference in the primary outcome of time to clinical improvement within 28 days between the convalescent plasma group vs. the control group

(which only received standard treatment) (Li et al., 2020). However, it should be noted that because of the containment of the outbreak in China, approximately half of the intended sample size (N=200) were recruited in this trial (Casadevall et al., 2020). Moreover, there was a significant effect of plasma therapy in those with severe disease compared to controls showing significantly shorter time (5 days) to clinical improvement with convalescent plasma, pointing to the fact that convalescent plasma is more effective when administered early in patients(Casadevall and Scharff, 1995). Notably, the editorial implies an important signal of benefit in the severely ill COVID-19 patients treated with plasma containing high titer anti-SARS-CoV-2 antibody and also suggest that using convalescent plasma in combination with antiviral therapies such as remdesivir may exert synergistic effects (Casadevall et al., 2020). In another randomized trial, Eckhardt et. al. plan to enroll 129 participants for treatment with convalescent plasma. Although receive of anti-virals are among study exclusion criteria, the use of remdesivir as a treatment for COVID-19 is permitted in this study. So results from this and other randomized trials would demonstrate the efficacy and safety of human anti-SARS-CoV-2 convalescent plasma alone or along with Remdesivir for treatment of COVID-19 (Eckhardt et al., 2020).

Conclusion:

Overall, results from studies that used convalescent plasma from recovered patients for treatment of SARS-CoV, MERS-CoV, and SARS-CoV-2 are promising. However more empowered randomized control trials are needed to consider different aspects of convalescent plasma therapy and possible beneficial combination therapies for treatment COVID-19.

Refereces

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