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Review Article

Life saving effect of early use of convalescent plasma in Covid-19 treatment

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Abstract

Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus, which is detected by the transmission from bat to person in Wuhan Province of China, has shown its effect all over the world in a very short time. There is no treatment method proven effective in Coronavirus disease 2019 (COVID-19) pandemics. The whole world is still working on it.

Convalescent Plasma (CP) treatment is a passive antibody treatment that has been shown to be effective during periods of epidemic disease in history. CP treatment is interesting in the treatment of virus infection without vaccine or specific treatment, such as SARS-CoV-2, which causes COVID-19.

The mechanisms of action of CP include neutralizing the virus by direct binding, initiating virus elimination by complement activation, antibody-dependent cellular cytotoxicity and / or phagocytosis. Neutralizing antibodies are the most important mechanisms of action. The most important point in recovery is the inactivation of the virus and the prevention of viral replication.

It was demonstrated for the first time that CP significantly reduced mortality in COVID-19 disease. Our results of CP treatment in COVID-19 patients have been published. We have shown that CP is effective and safe in COVID-19 disease. We aimed to gather CP experiences up to date in COVID-19.

Keywords: acute respiratory syndrome coronavirus 2 infection; Coronavirus disease 2019 (COVID-19); pandemic; plasma

INTRODUCTION

Passive antibody therapy is the process of giving antibodies to a particular person at risk or to a sick person in order to prevent or treat an infectious disease. Passive antibody administration is an important way of immediately immunizing sensitive individuals. Intravenöz immunoglobulins collected from a large number of healthy donors are used in the treatment and prevention of some viral infections. Passive antibody therapy has more than a hundred year of history. It has been one of the most important methods in the treatment of some infectious diseases until the development of an effective drug treatment (1).

The purpose of CP therapy is to collect the antibodies that provide immunity from the people who are thought to have acquired virus-specific immunity and give them to the patient. In this way, it is expected that the virus in the patient will be inactivated. When given to a sensitive person, this antibody is expected to circulate in the blood to reach tissues and protect against infection. Depending on the amount and composition of the antibody, the protection provided by the transferred immunoglobulin can last for weeks to months (2).

CP therapy is an effective and safe treatment that has been used in the treatment of infections for more than 100 years (3).

Donor selection

The titer of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) antibody can be determined on the donor or plasma unit using a biological or serological analysis. Plasma donors undergo ABO and RhD typing as well as standard infectious disease screening (4). Antibody titer is determined by serial dilution. The optimal antibody titer for the treatment of CP is unknown. FDA recommends a titer of 1: 160 (5).

Donor selection should be between 18-55 years old. All donor candidates must have a positive laboratory test result (with nasopharyngeal swab, molecular blood tests) diagnosed with COVID-19 disease. The donor candidate must have at least 14 days from clinical recovery after the negative test result.

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It is recommended to check Hepatitis B Surface Antigen, Hepatitis C antibody, The human immunodeficiency virus 1-2 and anti-syphilis antibody tests and Hepatitis B virus-DNA, Hepatitis C virus-RNA, Human immunodeficiency virus 1,2-RNA and nucleic acid amplification screening tests in donor candidates.

It is recommended that CP donors are preferably selected from men, women who are not pregnant, and people who have not received blood transfusions. It is recommended that women who have given birth or miscarriage and those who have had blood transfusions be screened for HLA antibodies and shown to be negative. CP should be collected by apheresis between 200 and 600 mL (6).

Plasma transfusions can result in transfusion-related adverse events such as febrile and allergic transfusion reactions, transfusion-related acute lung injury (TRALI), transfusion-related dyspnea, transfusion-related cardiac overload, hypotension, hemolytic transfusion reactions and septic transfusion reaction. Caution should be exercised in terms of fluid loading (TACO) in elderly patients with cardiac and renal dysfunction.

CP experience in COVID-19 disease

CP treatment has the potential to shorten the duration or severity of the disease to provide antibodies, prevent disease, or prevent life-threatening complications (7). It has been reported that CP treatment is more likely to be effective in the early stages of infectious diseases (8). CP treatment is thought to be more effective during the first 7-10 days of infection (9). It is unclear to what extent CP administration has benefited after the infectious process caused organ damage. The efficacy and success of CP in intensive care patients has increased significantly in recent publications.

It is observed that CP treatment is used for post-contact prophylaxis in diseases such as hepatitis, measles, mumps, polio, and therapeutic purposes in diseases such as influenza, SARS-CoV, Middle East Respiratory Syndrome [MERS] and Ebola. CP treatment has been applied as a safe and effective therapy in SARS-CoV, MERS-CoV and 2009 H1N1 outbreaks in recent years. (10).

In December 2019, SARS-CoV-2 virus, which is detected by the transmission from bat to person in China, showed a rapid spread throughout the world in a very short time. There is still no effective and therapeutic agent against this virus in the past 7 months. (the time from beginning is more than 7 months) Many potential drug candidates have been proposed, including lopinavir/ritonavir, hydroxychloroquine, nucleoside analogues, favipiravir, remdesivir and umifenovir (11). It has also been approved by the American Food and Drug Administration (FDA) for experimental use of remdesivir and immune plasma treatment. After the FDA approval, the use of CP in the treatment of COVID-19 disease started in many countries of the world and some results have been published.

Considering the positive results obtained in the past years, the first experiences on CP administration in COVID-19 disease came from China, the center of the disease. It was reported that the first CP in COVID-19 was collected in Wuhan on 1 February 2020 and given to a patient on 9 February 2020 (12). It was reported that COVID-19 PCR (+) patients had decreased oxygen requirements in 3 days, decreased CRP levels, and improved chest x-ray in the first week (13,14).

In Korea, it has been reported that CP therapy was given to 2 severe patients (aged 37 and 71 years) on the 7th and 22nd days of patients' hospitalization. After CP treatment, viral load monitoring was performed. A decrease was observed in viral load follow-ups. It is thought that the decrease in the values of inflammatory markers and increased oxygen saturation are caused by the use of corticosteroids with CP treatment. However, the decrease in the viral load of SARS-CoV-2 has been evaluated as an indicator of the effectiveness of CP treatment. However, the combined use of antiviral agents, steroids and CP therapy prevents the effectiveness of CP therapy from being fully understood (15).

Duan et al. added CP to the treatment of 10 serious COVID-19 patients aged 34-78. After CP treatment, it was reported that the antibody titer and blood lymphocyte count increased, CRP and viral load decreased and lung lesions regressed in these critically ill patients. The patient group treated with CP was compared with a control group without CP treatment. The control group was formed by random selection of 10 patients treated in the same center. It was reported that the clinical outcomes of the CP group were even better than the other group (10).

Shen et al administered CP treatment for 5 serious COVID-19 patients aged 30 to 70 years. CP treatments were applied on the 10^{th} to 22^{nd} days of hospitalization of patients. Viral load monitoring and viral antibody titer were monitored in patients. Increased viral antibody titers and decreased viral loads were reported in 80% of patients. In addition, a decrease in fever was observed in the clinical follow-up (13).

Zhang et al administered CP to 4 serious patients aged 31-73. They informed that CP could be a potential therapy for severe patients infected with SARS-CoV-2. And they observed no serious adverse reactions associated with the transfusion of CP (16).

Erkurt et al administered CP therapy to the twenty-six patients with COVID-19. No side effects were reported after CP transfusion. It was reported that the patients who died were older and lymphopenias were more marked (17).

Ling Li et al. reported a study involving 103 COVID-19 patients in 7 open, multi-center random centers in China. Fifty-two patients received CP and standard therapy, and 51 patients received only standard therapy. Improvement was 51.9% in the patient group treated with CP, and 43.1% treated with standard therapy. However, this difference was not statistically significant (p=0.26). Mortality rates

of two groups were similar. The median time between symptom development and CP administration was 30 days. The target number of patients was 200, but the study was stopped prematurely due to the rapid decline in the region of China, the source of the epidemic disease (18).

In a non-randomized, controlled, multicenter study, 115 patients were given CP with standard therapy, and 74 patients were given only standard therapy. With this study, CP treatment has been shown to reduce the need for intubation (p = 0.006) and hospital stay (p = 0.002). Although there was no statistically significant difference in all-cause mortality between the two groups, those who received CP treatment had a lower mortality rate (14,8% vs 24,3% p = 0.09) (17).

Current data provide solid evidence that CP transfusion is safe in hospitalized patients with COVID-19. It supports the notion that in the clinical course of COVID-19, the earlier administration of CP is more likely to reduce mortality. A meta-analysis of 12 studies (3 studies included a control group), it was clearly demonstrated for the first time that CP significantly reduced mortality (18).

Altuntas et al. compared the efficacy of CP treatment in serious or critical COVID-19 patients with a control group. 888 patients receiving CP treatment were compared with 888 patients in the control group matched for age, gender and comorbidities. As a result, it was shown that CP treatment shortened the length of stay in the intensive care unit and reduced the need for mechanical ventilation and vasopressor (all p <0.05). While the fatality rate was lower in the group receiving CP treatment compared to the other group, this difference was not statistically significant (24.7% vs 27.7%, p = 0.15) (19).

Mazhar M et al reported that CP in immunocompromised patients represents the situation in which exogenous antibody is provided in an immunocompromised environment (20). Similarly, Senefeld, J et al reported the benefits of using CP in the early period in COVID-19 infection, especially in immunocompetent patients (21). CP has also been found to be safe and effective in COVID-19 patients with heart rhythm abnormalities and COVID-19 patients with common variable immunodeficiency, myasthenia gravis and Sjögren syndrome (20,21).

Jamir I et al presented the clinical course of a 49-year-old male recipient who underwent live donor liver transplantation due to recurrent gastrointestinal bleeding and developed severe COVID-19 pneumonia in the third postoperative week. They reported on the successful management of severe COVID-19 pneumonia with CP treatment and remdesivir. It has been reported that CP treatment with Remdesivir may be an ideal combination in the treatment of severe COVID-19 pneumonia in solid organ transplant recipients (22).

London J et al reported their experience with CP in patients diagnosed with hypogammaglobulinemia and B cell alymphocytosis. Successful results of both patients with CP treatment were reported. It has been reported that CP may be effective in prolonged or uncontrolled Sars-Cov2 infection in patients with persistent B cell alymphocytosis (23).

Hueso T et al examined 17 consecutive COVID-19 with deep B-cell lymphopenia and long-term COVID-19 symptoms, treated with 4 units of CP. Among the first 48 hours after transfusion, all but 1 patient had an improvement in clinical symptoms. The inflammatory response gradually abated within a week. The study, in which no adverse events were reported, predicted that CP with anti-SARS-CoV-2 antibodies could be a very promising progress in the situation of long-term symptoms in patients who failed a specific humoral response to SARS-CoV-2 (24).

In their study, where Libster R et al reported 160 randomized COVID-19 patients, they accepted the median IgG titer = 1: 3,200. Early administration of high titer CP against SARS-CoV2 to mildly ill elderly has been reported to reduce the progression of COVID-19 disease. The use of CP within the first 72 hours of hospitalization for the treatment of serious COVID-19 patients has been reported. It was reported that under 65 years of age, there was a 4-fold reduction in mortality (25,26). In 3 studies, it was reported that using CP at an average of 44-72 hours reduces mortality, including the elderly (25-27).

Ah Yoon H et al reported no difference in mortality between the groups that received and did not receive CP. However, when classified by age, it was reported that CP recipients under 65 years of age showed a 4-fold reduction in mortality and a 4-fold reduction in oxygenation impairment or mortality(p = 0.04) (28). It was reported that there was no significant difference in the mortality rate for CP recipients aged 65 and over. Mortality before day 28 was associated with the time from symptom onset to CP transfusion (P = 0.04) and early admission week (p = 0.05).

Alsharidah S et al. included 135 CP and 233 control groups in their study, median age 54 [range 15-82] years. CP therapy was reported to be significantly associated with a higher rate of clinical improvement in patients with moderate or severe COVID-19 disease. The time to clinical recovery among those with moderate COVID-19 disease was 7 days in the CP group and 8 days in the control group (p = 0.006). In patients with severe COVID-19 disease, the time to clinical recovery was 7 days in the CP group and 15.5 days in the control group (p = 0.003). Patients treated with moderate disease CP were reported to have significantly lower 30-day mortality. No significant side effects were reported in patients undergoing CP (29).

Ahmad A et al. reported the meta-analysis results of 3 randomized studies, two pseudo-randomized observations, and 12 matched cohort studies using CP. There were 2,378 CP treated and 5,188 control groups in the study, which examined 17 studies in total. Only 2 studies have shown that CP treatment reduces 30-day mortality. The overall reduction in death was shown to be significant for all series (p = 0.00001), all matched cohort series (p = 0.001), and two pseudo-randomized series (p = 0.005), but not for the three technically inadequate randomized

studies (p=0.397). In two of the randomized studies, it was reported that viral DNA had a faster clearance 72 hours after CP compared to placebo (30).

Moore JL et al reported that the symptoms of COVID-19 disease in a 63-year-old female patient with a history of non-Hodgkin lymphoma in remission during maintenance treatment with the anti-CD20 monoclonal antibody obinutuzumab regressed after CP administration. The patient was reported to experience symptoms after a close contact exposure that was positive for SARS-CoV-2 and 37 days after the last dose of obinutuzumab. After CP application, the symptoms of the patient improved and it was found to be asymptomatic in the follow-up 1 week later (31).

Baang JH et al. shared their CP experience in a 60-year-old patient with lymphoma and B-cell immunodeficiency. Antibody therapy to a second B cell in combination with a CD20 bispecific antibody and cyclophosphamide, doxorubicin, and prednisone for refractory mantle cell lymphoma treatment was ongoing. Two doses of CP and remdesivir treatment were given on the 31st and 122nd days of his illness. The patient, whose need for oxygen gradually decreased, was discharged on the 131st day of his illness (32).

Luetkens T et al reported their CP experience in the treatment of COVID-19 in a 72-year-old patient with a diagnosis of MM for 10 years. The patient, who was in partial remission after eight cycles of carfilzomib/pomalidomide/dexamethasone treatment, received her last chemotherapy 3 weeks before her hospital admission. The patient whose humoral immune system was evaluated was found to have very low absolute normal IgG and IgM levels and severe hypogammaglobinemia. Based on FDA clinical criteria and severe immunosuppression due to lack of clinical improvement, a 1200 mL unit of CP was transfused from a COVID-19 survivor donor. The patient had not received any other treatment that could potentially have an impact on the course of COVID-19, such as steroids or antivirals. After the transfusion of CP, the patient became asymptomatic and was discharged home after just 2 days. Asymptomatic patient's +19. on day one, the SARS-CoV-2 PCR test in the nasopharyngeal sample was negative and showed complete viral clearance (33).

Van Damme KF et al. reported their experience with CP treatment in a 37-year-old patient with common variable immunodeficiency and COVID-19. CP was performed in the patient, who needed intensive care, was followed intubated and underwent ECMO, due to persistence of viral RNA, persistent fever and underlying B cell defect. On the 20th day of his hospitalization, the patient received 460 ml CP transfusion. Transfusion was well tolerated and no adverse reactions were observed. After CP, the patient became independent of ECMO within one day and was successfully weaned from the mechanical ventilator within two days. The patient, who was transferred from the ICU to the service on the 26th day of his hospitalization, was discharged 7 days later (34).

Agarwal A et al reported an open-label, parallel arm, phase II, multicenter, randomized controlled trial (PLACID trial). In the study, which included 464 COVID-19 patients over the age of 18, 235 patients were applied CP in addition to supportive therapies, and only supportive treatments were applied to 229 patients. Two doses of 200 mL CP were given by transfusion every 24 hours. The presence and levels of neutralizing antibodies were not previously measured. CP was not associated with a reduction in progression to severe COVID-19 or death for all causes (35).

In the study conducted in India, which included 1079 COVID-19 patients, 694 patients needed intensive care. While 333 of these patients were given CP, 361 were not. There was no statistically significant difference in mortality between the groups with and without CP. However, mortality was statistically significantly lower in the group that received CP between the patients followed in the intensive care unit and the group that was not given CP (p=0.026). They reported that CP decreased mortality in patients followed up in the intensive care unit (36).

It has been stated that the virus can mutate in order to escape from the antibodies in CP. Since antibodies in plasma are polyclonal, they are not easy to escape. CP may be able to speed up the process by forcing the virus to mutate (37).

Considering the past uses of CP therapy, it is aimed to review its use in COVID-19 disease, which has recently developed and has no effective treatment, in the light of the data in the literature.

CONCLUSIONS

CP treatment is a proven treatment modality that has been applied for many years. It has always been an urgent and hopeful therapy option before vaccines and new drugs have been improved against these newly identified infections. In COVID-19 patients, the clinical utility of CP treatment, especially in the early stages, has been demonstrated in many studies and case series. CP will still be a light of hope of treatment if the vaccine does not get satisfactory results.

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