Review Article

The application of COVID-19 convalescent plasma in clinical treatment

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Abstract: The severe acute respiratory syndrome (SARS) coronavirus disease known as coronavirus disease 2019 (COVID-19), which is caused by SARS-CoV-2 has caused a global pandemic since late 2019. As of 7 February 2020, more than 106 million people have been infected, and approximately 2,317 thousand people have died due to SARS-CoV-2 across 200 countries. Unfortunately, to date, many aspects of pathogenesis, infection, clinical manifestations and treatment methods remain unclear, no specific antiviral drugs or vaccines have been reported for patients with COVID-19 infection. Most patients with severe infections require supportive organ function therapies in the intensive care unit (ICU). Passive antibody therapies such as convalescent plasma (CP) therapy have been proved to be effective in the treatment of many infectious diseases such as SARS and Middle East respiratory syndrome (MERS), which are also assumed as a promising strategy in the treatment of critically ill COVID-19 patients. With the increasing investigation, the objective understanding of COVID-19 prevention, treatment and comorbid disease is beneficial for the application of the strategy applied in the clinical trials. Herein, we briefly discuss the current therapeutic approaches for patients with COVID-19, especially focuses on the application of therapeutic plasma exchange (TPE) for selected critically ill patients, aiming to provide some guidance for the treatment of severe COVID-19.

Keywords: Coronavirus disease 2019 (COVID-19); blood transfusion; convalescent plasma (CP)

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Introduction

Coronaviruses are typically single positive stranded RNA viruses that can be genetically classified into four major genera: beta-coronavirus, alpha-coronavirus, delta-coronavirus, and gamma-coronavirus (1-3). Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome (SARS)-CoV-2, is a novel enveloped virus belonging to the beta-coronavirus family (4,5). Since its outbreak, SARS-CoV-2 has resulted in more than 16 million infections and approximately 653 thousand deaths. Although there are still no specific drugs or vaccines reported against it, tremendous progress has been made in revealing the epidemiology, pathogenesis, diagnosis and treatment of COVID-19 in recent months (6-8). For example, many therapeutic approaches, including supportive intervention (9), immunomodulatory agents (10), antiviral therapy (11), and convalescent plasma (CP) transfusion (12), have been developed and applied in clinical practice. In our hospital (the Affiliated Hospital of Qingdao University), CP, the classic adaptive immunotherapy, has been applied to the treatment of severe patients infected with COVID-19.

Here, we mainly provide some insights into the disease, mainly about the treatment and management of the using CP in COVID-19 patients.

Pathogenic mechanism

Similar to the well-known coronaviruses SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV-2 with a diameter of 60–140 nm is a positive-strand RNA virus that encodes 27 proteins (13). Among these proteins, the spike protein plays a key role in receptor binding and helps the virus enter host cells. The pathogenic mechanism of SARS-CoV-2 is that the coronavirus spike (S) protein binds to the enzyme angiotensin converting enzyme 2 (ACE2) receptor and then invades alveolar epithelial cells, thereby promoting an excessive immune response and toxicity (14). As a result of systemic inflammation causing a cytokine storm as well as subsequent lung injury, patients develop respiratory failure and die if they have other serious diseases. SARS-CoV-2 not only affects lung function but also invades cells in kidney, heart, lung and intestinal tissues, then proliferates and destroys these organs, resulting in multiple organ dysfunction syndrome (MODS). In addition, the increase of IL-2, IL-6, IL-7, IL-10, MCP-1, IP-10, G-CSF, MIP-*1a*, and TNFα may be related to poor outcomes in severe COVID-19 patients (9). Regarding the effect on mild patients, the excessive activation of lymphocytes and the increase in proinflammatory $CCR4^+$ $CCR6^+$ Th17 cells cause immune-mediated damage, leading to an increased risk of the severity of mild diseases. Therefore, elderly people with weakened immunity and individuals with other comorbidities are more likely to be infected by COVID-19.

Transmission of COVID-19 Infection

Epidemiological investigation reveals that the transmission of SARS-CoV-2 is mainly caused by droplet transmission, such as talking, coughing or sneezing, when face-to-face contact occurs (15,16). In particular, long-term close contact with an infected person (at least 15 minutes within 6 feet) or short-term contact with patients with obvious symptoms results in an increased risk of transmission. For those who are asymptomatically infected, studies show that short-term exposure to infection is less likely. Beyond noncontact droplet transmission, contact transmission, such as touching surfaces with viruses in an unknown state, is another possible mode of transmission. Additionally, there are some reports that aerosols that droplets with viruses remain suspended in the air represent another method by which transmission might occur (17). However, this mode of transmission has not been confirmed outside the laboratory. Therefore, the detection of aerosols containing viral nucleic acids in the air does not mean that people will be infected in this environment.

Symptoms of COVID-19

Fever (70–90%), cough (60–86%), and shortness of breath (53–80%) are the three most common symptoms of patients with COVID-19. Additional symptoms, including weakness, fatigue, nausea, vomiting, diarrhoea, taste and smell changes, may also occur (18). Severe patients typically experience dyspnoea and/or hypoxemia within a week of onset. More seriously, these patients suffer from rapid progression to acute respiratory distress syndrome (ARDS), septic shock, difficulty correcting metabolic acidosis, disseminated intravascular coagulation (DIC) and MODS (19). The clinical manifestations of COVID-19 can also be summarized by the following indicators: (I) respiratory distress, requiring mechanical ventilation, respiratory rate ≥30 times/min; (II) oxygen synthetic index (PaO_2/FiO_2) ≤300 mmHg; (III) pulse blood oxygen saturation, oxygen saturation at rest ≤93%; (IV) lung imaging examination showing a significant lesion >50%; (V) neutrophil-lymphocyte ratio (NLR) ≥3.13 in some elderly patients (≥50 years old); and (VI) failure of other organs (20).

Treatment of COVID-19

To date, the treatment of COVID-19 remains a major challenge, there is still no specific and effective consensus regarding therapy (21). The current treatments for COVID-19 patients include protecting and supporting internal organs and reducing symptoms (22). In addition, oxygen therapy is required for patients with shortness of breath and hypoxemia. At the initial stage of the COVID-19 outbreak, corticosteroids were widely used by medical staff (21), but WHO advises against the wide use of corticosteroids for COVID-19 because some adverse outcomes occurred in the treatment of SARS-CoV and MERS-CoV with it. Therefore, according to the newest COVID-19 treatment guidelines, corticosteroids are only allowed in patients with severe conditions (23). Antibacterial drugs are approved to prevent secondary bacterial infections. However, the monitoring of immunocompromised and severe patients should be strengthened, which avoids the

blind and excessive use of antibacterial drugs. No specific drug for treating SARS-CoV-2 infection is available, and hormones and antibacterial drugs can cause serious adverse effects. Immunotherapy provides a new solution for the treatment of patients with new coronary pneumonia, which includes CP therapy and the administration of human monoclonal antibodies or polyclonal antibodies (24). In the following discussion, we will focus on the application of blood transfusion-related technologies in the field of COVID-19.

Blood transfusion-related technologies

The pathogenic mechanism of COVID-19 caused by SARS-CoV-2 is very complicated. Patients show stronger immunity after recovery due to adaptive humoral immunity and cellular immunity after infection. Antibodies have been detected in the serum of patients who have recovered from SARS-CoV-2 infection (25,26). Clinical results show that these isolated antibodies can be neutralized by the serum of COVID-19 patients (27). The history of collecting plasma from recovered patients for the treatment of human-related diseases can be traced back 100 years. During previous MERS and SARS coronavirus outbreaks, CP treatment exhibited faster virus clearance and high safety, especially in the early state of the disease process. Therefore, CP therapy should be effective in the treatment of severe COVID-19 patients (28-30).

The mechanism of CP therapy

CP therapy is a type of clinical treatment method that uses plasma obtained from a cured patient who suffered from the same disease and acquired specific immunity (31). CP collected from recovered patients contains specific antibodies that can protect against the coronavirus due to the immune response after their first infection. The mechanism of CP therapy in COVID-19 patients can be summarized as follows (32). First, the neutralizing antibody in the CP of recovered patients can effectively eliminate the virus and toxin given the specific binding reaction between the antigen and antibody (33). This process induces humoral immune response of the patient and prevents the invasion of pathogens. Second, specific antibodies for COVID-19 in CP can also induce antibody-mediated cytotoxicity, and some of the cytokines contained in CP can also induce adaptive immune responses in the body, further eliminate pathogens more effectively (34). Third, the therapeutic effectors in CP can also activate the complement system to dissolve and destroy the pathogen exhibiting a therapeutic effect on the rapid progression of COVID-19 patients (35).

Selection of recovered patients and screening of CP

Fully recovered patients with COVID-19 developed neutralizing antibodies represent potential donors for CP. Given that the length of the recovery period of the recovered patients varies, the selection criteria for the recovery donors are different. Generally, Donors should meet specific criteria for donation of CP, such as blood type, haemoglobin, major transfusion transmitted infectious, indicators of the clearance of SARS-CoV-2 virus should be assessed. If possible, the corresponding antibodies and neutralizing antibody titre (NAT) in potential plasma donors should be measured before donating to ensure the therapeutic effect and avoid ineffective collection. The American AABB recommends that the NAT in the CP should be at least 1:160 (36). If no alternative treatment can be adopted, CP collection can be conducted when the NAT indicator is 1:80 in an emergency. Similarly, the European Union recommends that the NAT in CP should be greater than 1:320, but CP with lower NAT may also exhibit effectiveness (31). In short, the final plasma donor should meet the general legal blood donor selection criteria. SARS-CoV-2 virus testing should be negative, TTIDs should be negative, and therapeutic effectors should exist in the collected CP (33,37).

Clinical treatment application of CP

Under the severe situation of the current global pandemic of COVID-19, it is recommended that one dose of 200 mL of inactivated CP with neutralization activity of >1:640 transfused for the COVID-19 patients within 4 h following the WHO blood transfusion protocol. Many countries have begun to reconsider the use of CP therapy for severe patients with COVID-19 as there are no specific therapeutic drugs or vaccines that can be used currently. For example, Duan *et al.* reported that 10 patients with severe COVID-19 were infused with 200 mL of CP with an antibody titre of 1:640 (34). After CP transfusion, the clinical symptoms of these patients significantly improved, and the virus load in their plasma decreased to undetectable levels. Moreover, no obvious adverse reactions were observed in these patients after infusion of CP. This finding suggests that CP therapy can be used as

a potential therapy for COVID-19. Salazar reported that early treatment of COVID-19 patients with CP containing high-titer anti-spike protein receptor binding domain (RBD) IgG significantly decreases mortality. And they used a propensity score-matched analysis of a large patient cohort confirmed and extended their findings which suggested that transfusion of CP containing high-titer anti-RBD IgG early in hospitalization reduces mortality in COVID-19 patients (38). The potential benefit of CP therapy and risk of convalescent blood products in COVID-19 needs further investigation, but with the continuous increase in plasma donations from cured patients, more CP will be available. AABB recommends that early treatment with high titer CP for COVID-19 patients is an effective therapeutic modalities for critically ill COVID-19 patients. We believe that CP therapy might be a promising treatment option for COVID-19 rescue in the future.

COVID-19-associated coagulopathy

Critically ill COVID-19 patients may experience COVID-19-mediated cytokine storm, a series of inflammatory reactions, endothelial dysfunction, and increased inflammatory factors (39), all these can also lead to abnormal coagulation and increased D-dimer levels, causing multiple organ failure and DIC, venous thrombosis and further leading to longer hospital stays, increased mortality (40) and threaten the life of patients (41). Therefore, timely and effectively reduction of the risk factors of coagulopathy can greatly help patients recover. Therapeutic plasma exchange (TPE) is an effective method at removing humoral components from the plasma fraction. TPE merits consideration in the treatment of critically ill COVID-19 patients.

Plasma exchange during recovery of new coronavirus

TPE is relatively safe to separate the whole blood into plasma and cell components from the body. In this process, the plasma that contains harmful components to the patient is discarded, and fresh plasma or albumin, balance liquid or other plasma substitutes are substituted back into the body to reduce pathological damage and remove pathogenic substances. TPE has become a common cardiopulmonary bypass to purify harmful components from the blood. People infected with COVID-19 will experience a series of inflammatory reactions, the resulting D-dimer, inflammatory factors, lactate dehydrogenase and other harmful components can be removed in a timely manner effectively by plasma exchange. But albumin and other plasma substitutes may result in depletion of procoagulant factors and increased bleeding risk in practice, we recommend 1.0–1.5 plasma volume using fresh plasma if necessary. As of 7, July 2020, more than 10,000 patients with COVID-19 all over the world have already received TPE and achieved positive results (31).

Outlook

In COVID-19 epidemics, an understanding of the underlying pathogenesis, rapid diagnosis and effective therapeutic modalities are essential to overcome the epidemic. Although tremendous progress of public health measures to limit viral spread has been made, this RNA virus is constantly evolving, which may pose new challenges to the diagnosis and treatment of COVID-19. CP was used for SARS, pandemic 2009 influenza A (H1N1), avian influenza A (H5N1), Ebola and other viral infections. The specific antiviral agents in the plasma in recovered COVID-19 patients could potentially improve the clinical outcomes through neutralizing viremia in critically ill COVID-19 cases. The development and promotion of novel treatment options to reduce mortality is currently the top priority in the fight against COVID-19. TPE as an adjunctive treatment strategy in the management of severe COVID-19 patients should be further explored.

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Footnote

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