

Potential benefits, mechanisms, and uncertainties of convalescent plasma therapy for COVID-19

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Abstract

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in China led to a public health emergency of international concern, putting all health organizations on high alert in the beginning of 2020. Corona virus disease 2019 (COVID-19) is highly infectious and has resulted in thousands of deaths which exceeded that of the SARS coronavirus (SARS-CoV) outbreak back in 2002 and 2003 in China. Besides, the number of diagnosed patients, patients who are suspected to have contracted the disease, and deaths are increasing worldwide. Unfortunately, effective drugs and vaccines to combat SARS-CoV-2 are still lacking. Convalescent plasma, a seemingly successful treatment for COVID-19 patients, proved to be of huge value in terms of saving severely ill patients. This review introduces the reported effects, potential mechanisms, and future uncertainties of convalescent plasma therapy in the treatment of COVID-19 patients, in the hopes that it will provide useful information for relevant physicians and researchers.

Keywords: SARS-CoV-2, COVID-19, convalescent plasma, mechanisms, adverse effects

1. INTRODUCTION

The current outbreak of novel coronavirus pneumonia took place in Wuhan, Hubei, China, since December 2019, which has been a catastrophe and attracted wide attention not only within China but around the world. Till now, there are more than 100,000 people who are diagnosed with COVID-19 pneumonia and more than 3000 deaths (until 7 March).¹ Chinese health authorities have taken urgent measures to control the spread of this disease and treat infected patients. However, compared with SARS or Middle East respiratory syndrome, this novel coronavirus infection has milder symptoms at the early stage and a longer incubation period, which make the diagnosis and prevention much more difficult. Besides, specific antiviral drugs and effective vaccines are still unavailable.

Nowadays, convalescent plasma therapy and stem cell therapy are the two main promising treatments for severely infected patients who cannot be treated using conventional supportive treatments. Many previous studies of varying sizes and qualities described the clinical experience of convalescent plasma in treating other viral infections, including those due to SARS-CoV,

Spanish influenza A(H1N1), avian influenza A(H5N1), and 2009 pandemic influenza A (H1N1).²⁻⁶ This review mainly introduces the benefits, mechanisms, and risks of convalescent plasma therapy in the hopes that it will provide some suggestions for clinical physicians to treat COVID-19.

2. DEFINITION, COMPONENTS, ACQUISITION, AND MECHANISMS OF CONVALESCENT PLASMA IN TREATMENT OF VIRAL INFECTION

Convalescent plasma therapy which belongs to passive immunotherapy originated in 1880 when patients suffering notably from diphtheria were successfully cured by serotherapy.⁷ Convalescent plasma is plasma collected from individuals who have survived a previous infection and developed humoral immunity against the pathogen responsible for the disease, and this plasma can be used to treat patients infected by the same pathogen.^{8,9} Convalescent plasma is usually obtained through donation from convalescent people. The components of convalescent plasma are similar to those of the common plasma in general, such as water, proteins, and inorganic salts, but it contains specific antibodies or immunoglobulins against the infectious pathogens which can specifically inhibit the virus and suppress viremia in the infected patients using several pathways. Those antibodies or immunoglobulins exhibit neutralization activity by

1. blocking special proteins such as glycoproteins on the surface of the virus to inhibit it from entering human cells;
2. inhibiting viral fusion with endosome;
3. preventing release of progeny virions from the infected cells;
4. inhibiting extracellular proteolytic cleavage of viral protein.¹⁰⁻¹²

An in vivo trial on HIV-1 infection showed that the effects of neutralizing antibody 3BNC117 are not only limited to free viral clearance and blocking new infection, but also include acceleration of infected cell clearance.¹³

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Previous studies performed on influenza virus showed that antibody-dependent cellular phagocytosis may protect mice from infection^{14,15} and potentially contribute to the recovery from severe infections in humans.^{16,17} Antibodies from convalescent plasma can clear virus-infected cells and protect the body against the virus through antibody-dependent cell-mediated cytotoxicity by eliciting Fc-dependent effector functions which are determined by cross-talk among antibodies of varying specificities^{18–20} or inducing the activation of complement cascade to eliminate the virus either directly, by means of complement-dependent cytotoxicity, or indirectly through phagocytic clearance of complement-coated targets and the induction of an inflammatory response.²¹ Rapid viral clearance would halt further replication and the stimulus for the cytokine cascade which may result in cell injury or organ damage. The nutrients in the plasma would also strengthen the immune defense of body and accelerate the recovery.²²

3. BENEFITS OF CONVALESCENT PLASMA THERAPY

In the past, when several endemic/epidemic infectious diseases outbreaks took place, convalescent plasma played a vital role in saving infected patients, especially those who were severely ill.²³ Meta-analysis of reports from the H1N1 pandemic and studies on SARS-CoV infection demonstrated that patients who received influenza convalescent human blood components transfusion might have a clinically significant reduction in the risk of death of more than 50% and improvements in clinical signs and symptoms.^{22,24,25} Zhou et al and Wong et al indicated that convalescent plasma as an adjunctive treatment produced a favorable outcome in a patient in China with H5N1 and multiorgan failure despite using a high dose of oseltamivir.²⁶ One prospective cohort study about convalescent plasma treatment of pandemic influenza A(H1N1) 2009 virus (H1N1 2009) infection showed that 500 mL of convalescent plasma with neutralizing antibody titer of >1:160 was effective in decreasing mortality, respiratory tract viral load, and serum level of cytokines which can also offer a good balance between donor tolerability, volume overload, and sufficient antibody delivery in recipients.²⁷

On the contrary, a nonrandomized comparative study showed that convalescent plasma transfusion of up to 500 mL with unknown levels of neutralizing antibodies in patients with confirmed Ebola viral disease was not associated with a significant improvement in survival. This would possibly indicate that the titer of the neutralizing antibody in convalescent plasma was a pivotal factor to change of survival rate, and different viral varieties may make an impact on the therapeutic effect since the virulence and lethality of Ebola are more potent than other viral-related flu.^{28,29} As for the length of hospital stay, after excluding patients with comorbidities, convalescent plasma treatment increased the proportion of discharged SARS-CoV-infected patients and patients were discharged within 22 days of admission.²⁴ A further SARS-CoV infection case series reported that 47% of patients were discharged earlier upon the initiation of therapy.³⁰ An uncontrolled case series of 5 critically ill patients with COVID-19 and acute respiratory distress syndrome (ARDS) showed that administration of convalescent plasma containing neutralizing antibody (in which SARS-CoV-2-specific antibody [IgG] binding titer greater than 1:1000 (end point dilution titer) and a neutralization titer greater than 40), improved their clinical status: symptoms improved, viral load decreased, neutralizing

body titer increased, ARDS resolved and three patients discharged earlier.³¹ These successful applications of convalescent plasma in viral infection including COVID-19 indicated that convalescent plasma therapy could be a promising treatment for COVID-19, especially for those critically ill patients.

4. DEVELOPMENT OF COVID-19 IN CHINA AND APPLICATION OF CONVALESCENT PLASMA

In December 2019, an outbreak of unknown but highly infectious pneumonia occurred in Wuhan, China, and the pathogen was found to be a novel coronavirus that was a single positive-strand RNA virus and belonged to the family Coronaviridae. This novel coronaviral pneumonia was named as COVID-19 by WHO. From the first diagnosis of the COVID-19 until April 10, 2020, a total of 83,323 patients were diagnosed with this disease, and severely ill patients reached 13,000 and there were more than 3000 deaths around China; more than 1.5 million diagnoses and 90,000 deaths over the world. Furthermore, the number of confirmed diagnosis, suspected cases, and deaths are increasing and spreading worldwide right now. Controlling infection sources, cutting off routes of infection and protection of susceptible populations are critical steps to prevent the spread of this infectious disease.

Currently, supportive therapy is the main treatment for COVID-19 patients. However, the existing traditional antiviral drugs showed no effects, and there was no specific and effective therapeutic method, especially for critically ill patients who are infected with SARS-CoV-2. Many successful applications of convalescent plasma were reported in previous epidemic diseases. Reports on convalescent plasma therapy being used in SARS-CoV or Ebola infection showed that the condition of several patients improved or they were cured after transfusion of convalescent plasma.^{2,32} It is becoming urgent and vital to decrease mortality rates, improve symptoms of severely sick patients, and increase discharge numbers of patients; therefore, adopting the convalescent plasma as an optional treatment is considered. As a result, convalescent plasma therapy was included into the guidelines on diagnosis and treatment of COVID-19 in China in the sixth version. Theoretically, those convalescent patients would have high titer of anti-SARS-CoV-2 polyclonal antibodies in their plasma. Moreover, plasma collecting and transfusion are common in China, and it is feasible to apply convalescent plasma to clinical treatment. In terms of current treatment results, convalescent plasma has been proven to be effective. One pilot study on convalescent plasma treatment of 10 severe ill COVID-19 patients showed that a dose of 200 mL convalescent plasma transfusion with the neutralizing antibody titers above 1:640 could improve clinical symptoms, laboratory parameters, and pulmonary radiological results within 3 days, and the level of neutralizing antibody increased rapidly up to 1:640 and could be maintained at a high level (1:640), at the same time the viral load was undetectable in seven patients who had previous viremia after transfusion.³³ One case report on four critically ill patients with COVID-19 convalescent plasma also presented all of them were improved and there was no adverse events in both studies.³⁴

5. UNCERTAINTIES AND RISKS OF CONVALESCENT PLASMA THERAPY

In general, convalescent plasma therapy reduces the mortality and promotes the recovery of viral-infected patients, but in a few

cases, patients deteriorated due to usage of an inappropriate dosage of convalescent plasma or using the therapy at an improper stage of infection. Although convalescent plasma contains different neutralizing antibodies, not each one of them is useful in treating the virus. The other components in the plasma such as proteins and fibrinogen could cause allergy or thrombosis. Exotic plasma will induce the hyper-reaction of the virus which would activate macrophages or cellular factors. As a result, an inflammatory storm and multiorgan failure may occur. Meta-analysis of reports from the 1918 influenza A(H1N1) pandemic reported that there would be mild adverse events such as a transient elevation in body temperature by 1 to 2°F 30 to 120 min after the transfusion, and different blood products (serum, plasma, or whole blood) may produce different rates. The terminally ill patients or those who had underlying diseases were more likely to have moderate to severe adverse effects such as secondary bacterial pleuritis, empyemas, pneumonias caused by hemolytic streptococcus, septicemia, meningitis, and undifferentiated delirium and psychosis.²² Otherwise, Ivan et al reported that using convalescent plasma may increase the risk of acute renal failure but using the appropriate amount may not induce any adverse effects.²⁷ One evaluation of using convalescent plasma in treatment of Ebola virus disease demonstrated that transfusion of about 400 to 500 mL convalescent plasma did not cause any serious adverse effects and only a few patients had a slight or moderate adverse reactions which resolved spontaneously with symptomatic treatment or a reduced rate of transfusion.²⁹

Antibody-dependent enhancement (ADE) is one possible uncertainty following transfusion of anti-SARS-CoV-2 convalescent plasma. ADE means that neutralizing antibodies make the infection worse which is known to be exploited by a variety of viruses, such as dengue virus, HIV, and animal coronavirus. The possible mechanism of COVID-19 ADE phenomenon might be that antibodies produced by prior infection could not neutralize other serotypes of SARS-CoV-2 fully but contrarily bind to the virus and the IgG Fc receptors on immune cells and then mediate viral entry into cells and induce a severe inflammatory response.³⁵⁻³⁹ Vitro studies about coronavirus-ADE demonstrated that a neutralizing monoclonal antibody (MAb) binds to the surface spike protein of coronaviruses like a viral receptor, triggers a conformational change of the spike, and mediates viral entry into IgG Fc receptor-expressing cells canonical viral-receptor-dependent pathways.⁴⁰ Studies on SARS-CoV-2 infections demonstrated that severely ill patients usually had increased IgG response and higher titer of total antibodies, who were always associated with worse outcomes.^{41,42} This phenomenon indicated that ADE would occur during treatment of SARS-CoV-2 infections with convalescent plasma therapy.

Transfusion related acute lung injury (TRALI) is of particular concern of COVID-19 patients since they almost started with poor pulmonary performance. TRALI refers to a new onset of acute lung injury (ALI) within 6 h of transfusion, with evidence of hypoxia ($\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg or $\text{SpO}_2 < 90\%$ of room air) and radiological evidence.⁴³ Studies showed that antibodies or other factors in the blood products would activate a series of immune cells such as neutrophils, monocytes, or macrophages, to attack pulmonary endothelial cells.⁴⁴

Consequently, the collection, apheresis, and disposition of the human blood products have a great significance on the effectiveness of convalescent plasma therapy. In order to confirm and improve the outcome of convalescent plasma therapy, the following questions need to be answered. How is the efficacy of

convalescent plasma infusion in patients related to plasma quality, dose, antibody titer, and infusion timing? What is the best time to donate plasma after being discharged from the hospital? What is the appropriate amount of plasma for donation? How many times can a person donate? Should the viral load be tested before plasma donation? For patients receiving convalescent plasma, should the patient's viral load be measured before transfusion? For patients with low, moderate, and severe levels of infection, at which level could convalescent plasma therapy be used? What laboratory indicators can guide the clinical selection of patients for infusion of convalescent plasma? What tactical indicators are observed to evaluate the effect of convalescent plasma after its infusion?

According to Chinese guidelines on convalescent plasma therapy in COVID-19 treatment (2nd edition),⁴⁵ first, people who can donate their plasma should meet strict requirements:

1. at least more than 3 weeks should pass since the onset of initial symptoms;
2. they should be adult COVID-19 survivors between 18 and 55 years old;
3. they should have two consecutive sputum, nasopharyngeal swabs, and other respiratory tract samples tested negative for viral nucleic acid (at least 24 h apart) and are qualified for other criteria of discharge and are cured before discharge;
4. males should be of more than 50 kg and females more than 45 kg;
5. they should have no infectious disease transmitted via blood.

Secondly, laboratory tests for HIV-1 and HIV-2, hepatitis B, hepatitis C, syphilis, and other common pathogens for respiratory, and digestive and urinary systems should be negative, and the donors should be tested for the blood type, hemoglobin level and ALT. Thirdly, in the donors, 2019-nCoV nucleic acid in convalescent plasma should test negative and reaction type of IgG with dilution of 1:160 or total antibody level with dilution of 1:320 should test positive.

As is known IgM is the first line of defense during viral infections, and high affinity IgG responses are responsible for long term immunity and immunological memory.⁴⁶ Enzyme linked immunosorbent assay (ELISA) kits are commonly used to test total antibodies (Ab), IgM, IgG, and other antibodies. The ELISA for total antibodies detection was developed based on double-antigens sandwich immunoassay (Ab-ELISA), using mammalian cell expressed recombinant antigens contained the receptor binding domain (RBD) of the spike protein of SARS-CoV-2 as the immobilized and HRP-conjugated antigen. The IgG antibodies were tested using indirect ELISA kit (IgG-ELISA) based on a recombinant nucleoprotein. The specificity of the assays for Ab and IgG was determined as 99.1% and 99.0%.⁴² The titer of Ab and IgG could also be tested by chemiluminescence immunoassay analysis (CLIA) with two antigens of SARS-CoV-2 coated on the magnetic beads of these CLIA assays (Nucleocapsid protein and Spike Protein).⁴⁷

High-throughput platforms, such as the large-scale single-cell RNA sequencing of B cells from convalescent people, have also provided the identification of SARS-CoV-2-specific neutralizing antibodies.³⁹ Human angiotensin converting enzyme 2 (hACE2) is confirmed to be the receptor for SARS-CoV-2 and the spike glycoproteins on the surface of SARS-CoV-2 use ACE2 to enter human cells to induce infection.^{48,49} While those coronavirus spike glycoproteins are the main target of antibodies.⁵⁰

Lastly, HNA and HLA antibody should be screened if the donor had a history of pregnancy or blood transfusion. Last but

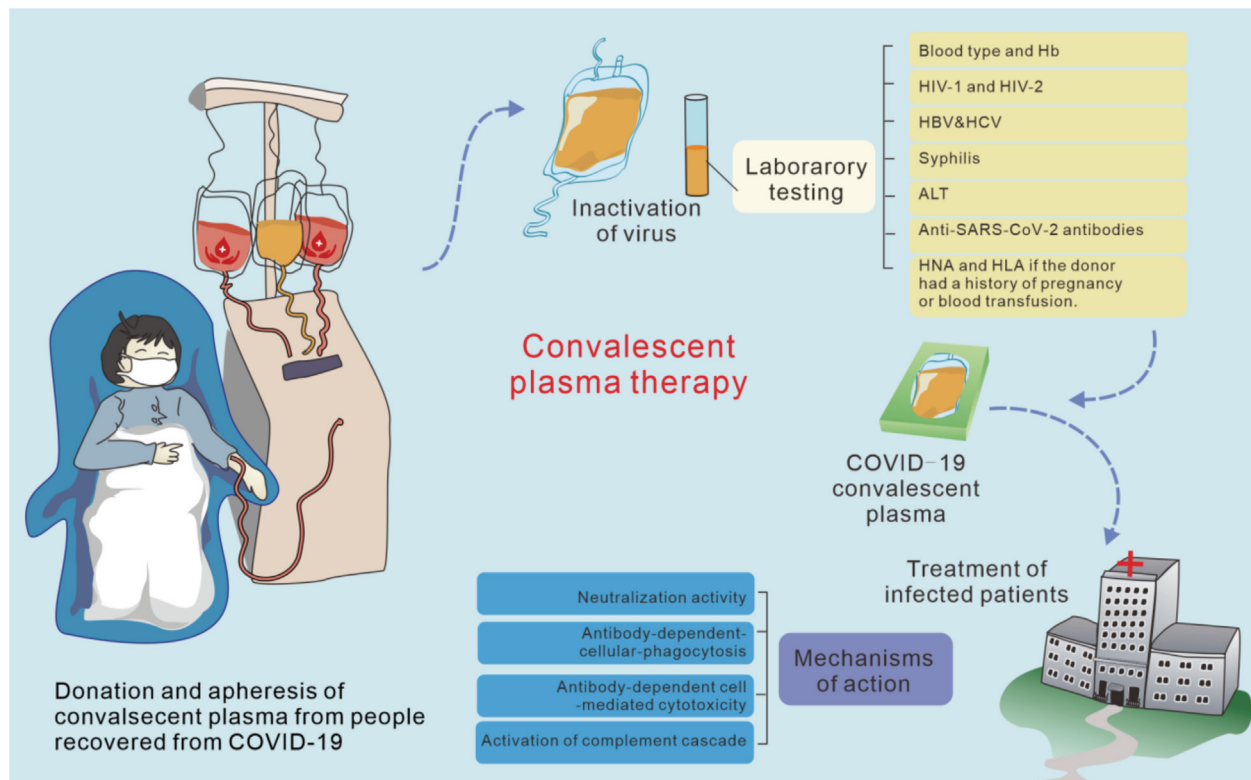


Figure 1. Schematic diagram of the convalescent plasma therapy: the whole process of convalescent plasma therapy includes donation of qualified convalescent plasma, apheresis, laboratory detection and transfusion into infected patients.

not least, inactivation of the plasma virus must be done to ensure the safety of convalescent plasma.

6. IMPLICATIONS FOR CLINICAL PRACTICE

Convalescent plasma may have a clinically relevant impact in reducing the rate of mortality and viral load in patients with severe acute respiratory infection of viral etiology. A schematic diagram showed the whole process of convalescent plasma therapy including donation, apheresis, laboratory testing, and application (Fig. 1). The amount of convalescent plasma, titer of the neutralizing, times of transfusion, interval time, and other factors should be controlled tightly according to the situation of a specific patient. The exact amount of convalescent plasma can be adjusted by the titer of neutralizing antibody or IgG and weight of patient (usually 4–5 mL convalescent plasma per kilogram). Some reports suggest that early initiation of treatment may be of critical importance to reducing mortality in patients with SARI of viral etiology,^{24,30,51} but due to the limited amount of convalescent plasma, it was mainly used to treat critically ill patients at early stages or with acute progression or those who might have viremia. Meanwhile, patients with allergic history of blood transfusion or multiorgan failure or at terminal stage should be prohibited from being treated with convalescent plasma. We hope there will be more convalescent patients who are willing to donate their plasma to save more infected patients. This will help related medical departments use multiple convalescent plasmas to investigate and produce COVID-19 human immunoglobulins. What is more, antiviral drugs and vaccines are being studied and we believe Chinese people are powerful enough to fight and defeat the sly SARS-CoV-2.

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