Review

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Effectiveness and Controversy of Convalescent Plasma Therapy for Coronavirus Disease 2019 Patients

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Abstract

Since the coronavirus disease 2019 (COVID-19) began to spread, it remains pandemic worldwide. The European Medicines Agency's human medicines committee and Food and Drug Administration have only granted a conditional marketing authorization for remdesivir to treat COVID-19. It is essential to apply other valuable treatments. Convalescent plasma (CP), donated by persons who have recovered from COVID-19, is the cellular component of blood that contains specific antibodies. Therefore, to determine the feasibility of CP for COVID-19, the effectiveness and controversy are discussed in depth here. It is suggested that CP plays a certain role in the treatment of COVID-19. As a treatment, it may have its own indications and contraindications, which need to be further discussed. Meanwhile, it is critical to establish a standard procedure for treatment from CP collection, preservation, transport, to transfusion, and conduct some large sample randomized controlled trials to confirm the transfusion dosage, appropriate time, frequency, and actively prevent adverse outcomes that may occur.

Keywords: COVID-19; Controversy; Convalescent plasma; Effectiveness; Therapy

Introduction

Since a pneumonia caused by sever acute respiratory syndrome corona virus 2 (SARS-CoV-2), named as coronavirus disease 2019 (COVID-19) by World Health Organization, was reported, the virus spreads worldwide with an alarming rate. At the middle of May, 2021, more than 160 million people have been infected, resulting in over 3.3 million deaths in more than 200 countries,[1] and these numbers continue with high-speed increase.

Till today, despite the efforts of scientists around the world, only a few compelling drugs and treatment options, such as favipiravir, remdesivir, chloroquine are available to help prevent or relieve the disease.[2–4] The European Medicines Agency's human medicines committee has only granted a conditional marketing authorization for remdesivir to treat COVID-19 in adults and adolescents from age 12 with pneumonia who require supplemental oxygen,[5] the same as Food and Drug Administration.[6] It is essential to apply other therapeutic options for COVID-19, especially among critical condition. It is undeniable that convalescent plasma (CP) therapy, a century-old medical treatment is being recommended as a feasible and effective option for alleviating the suffering of this disease.[7–9] CP therapy was widely used as a traditional treatment for infectious diseases such as pneumococcal pneumonia and scarlet fever over one hundred years.[10] Plasma was later used to treat other infectious diseases, such as influenza, Argentine hemorrhagic fever, Middle East Respiratory Syndrome, and Zaire ebolavirus.[7,11–13] Several studies have shown that CP could be successfully employed to treat two previous coronavirus infection diseases, including SARS in 2003, and Middle East Respiratory Syndrome (MERS) in 2012.[14] Theoretically speaking, coronaviruses specific neutralizing antibody in CP, which could accelerate virus clearance and prevent entry into target cells, additionally alleviates hypercytokinemia.[15,16] These satisfactory clinical outcomes provided the possibility that CP treatment could be a promising remedy for COVID-19, especially in the case of early administration.[17,18] On account of this novel Beta coronavirus is similar to SARS-CoV and MERS-CoV, based on its genetic proximity.[19]

Regarding the above statement, there are some studies have also shown negative results about CP, even some studies recently argue that no significant differences were observed in clinical status or overall mortality between patients treated with CP and those who received placebo.[20–22]

The potential therapeutic mechanisms of the CP in COVID-19

CP obtained from patients with an established humoral immunity against the pathogen and who recovered. And CP comprises abundant neutralizing antibodies (NAb), which could protect or

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treat other infected patients.[7] Plasma contains a mixture of water, organic compounds, inorganic salts, and more than 1000 proteins. It is found that albumin, complement, immunoglobulins (IVIg), coagulation, and antithrombotic factors in these proteins.[23] Among the CP contains, NAbs are critical in pathogen clearance which have been identified as vital in the protection of against viral diseases and inhibiting infections. NAbs not only to bind to a virus, they bind in a manner that blocks infection. A NAb might block interactions with receptors, or it might bind to viral capsids and thus inhibit genome uncoating. After an infection, it could take some time for the host to produce highly effective NAbs, but these antibodies persist to prevent future contact with the pathogen.[24] The efficacy of CP therapy is related to the concentration of NAbs in plasma from convalescent patient.[25,26]

CP infusion was first introduced against diphtheria in 1880s.[27,28] It was realized that the antibody-mediated therapeutic effect of CP might act via some mechanisms, such as neutralizes pathogens, or provides passive immunomodulatory properties to reduce the excessive inflammatory response.[28,29]

Studies have shown that IVIg, another most important components of CP. In the early 1950s, IVIg from healthy donors or rehabilitation patients provided the choice for the treatment of severe infectious diseases and immune conditions, including primary immune defects, autoimmune diseases, allergies and so on.[27,30,31]

In vitro studies suggested that IVIg may prevent DCs from maturing, which is the key regulators of innate immunity, moreover reduce the production of interleukin-12 (IL-12). On the other side, the production of IL-10 was enhanced which is an inhibitor of inflammatory response.[32] On the whole, the obtained data suggest that CP might suppress inflammatory response caused by dendritic cells (DCs), which could be critical during the hyperinflammatory stimulation phase COVID-19 patients.

Despite the ability of enhancing T helper 2 cell (Th2) depend on IL-33 in DCs.[33] IVIg from CP might promote proliferation and survival of Tregs by regulating the balance between CD4+/CD8+ T cells. Additionally, patients treated with IVIg showed a reduction in T helper 1 cell (Th1) cells and low levels of interferon γ and tumor necrosis factor α with the increase of Th2 cytokines including IL-10 and IL-4.[34] Although the exact mechanism remains unclear, one hypothesis is that CP plays an important role in inhibiting inflammation by supplementing plasma with Nabs and IVIg.

The accessibility of the CP in COVID-19

Although the high rate of COVID-19 infection, the high recovery rate, the relatively low mortality rate (the mortality rate fluctuated between 0.3% and 0.66%),[35,36] provides more CP donors.[35,37] However, the CP donors must meet several strict criteria[38–41] to ensure the antibodies against SARS-CoV-2 [Table 1].[42] Furthermore plasma immunoglobulins G and M (IgG and IgM) with high anti-SARS-CoV-2 titers are preferred, as determined by enzyme linked immunosorbent assay (ELISA). The other concern is that the donors worry about antibodies in plasma be drawn and not be able to deal with reinfection. It is clearly that the level of specific neutralizing antibody decreases naturally since the half-life of antibodies. Cao and his colleagues showed that the neutralizing antibody to SARS-associated coronavirus after recovery decreased sharply at 4 months, reaching very low levels in 25.6% (IgG) and 16.1% of patients at 36 months.[43] A paper about patients with the MERS-CoV and workers exposed the healthcare showed that the MERS-CoV IgG seroreactivity was very low (2.7%), and the antibodies titers subsided rapidly in 3 months.[44] The similar study form Stefansson and colleagues reported that the stable SARS-CoV-2 immunity for at least 4 months with limited loss of antibodies. Although the studies about half-life of SARS-CoV-2 antibodies need future extended.[35]

At the same time, the characteristics of humoral immune response will give us a great deal of confidence. The kinetics of the humoral immune response after infection comprises two waves of antibodies. The first wave is primary immune response, with naive B cell activating, and differentiating into antibody-secreting cells that produce antibodies to corona virus. The second wave elicited when the same antigen stimulates the memory B cells (generated during the primary response), leading to more proliferation and differentiation and production of greater quantities of specific antibody than are produced in the primary response [Figure 1]. So maybe we do not have to worry too much about the decline of antibody concentration, even after plasma donation.

A variety of views on CP treatment for COVID-19

During the early phase of COVID-19 pandemic, several clinical trials were conducted using CP to treat COVID-19 [Table 2]. An Open-label, Expanded Access Program initiated by Joyner and his colleagues, the results supposed that the CP treatment induced mortality in 7 and 30 days in patients included a high proportion

Table 1: The eligibility criteria[38–41]

Conditions	Contents
Condition of necessary	a. Confirmation of previous infection with SARS-CoV-2 by a record of a validated diagnostic test at the time of illness.
	b. Complete resolution of symptoms at least 14 days before the donation.
	c. Standard selection criteria for whole blood or plasma donation according to local requirements and standards (age, weight, collection frequency, vital signs, freedom from deferral criteria) in line with "WHO Blood Regulators Network (BRN): Donor selection in case of pandemic situations."
	d. Non-reactivity of blood samples for transfusion transmitted infections including HIV, HBV, HCV, syphilis (for whole blood) and locally transmitted infections using approved serological and/or nucleic acid tests, consistent with local requirements for collection of blood components for transfusion.
Condition of reference	e. Male donors, female donors who have never been pregnant, or female donors who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies.
	f. One dose of 200 mL of inactivated CP with neutralization activity of >1:640 was transfused into the patients within 4 h following the WHO blood transfusion protocol.

SARS-CoV-2: sever acute respiratory syndrome corona virus 2; WHO: world health organization; HIV: human immunodeficiency virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HLA: human leukocyte antigen; CP: convalescent plasma.

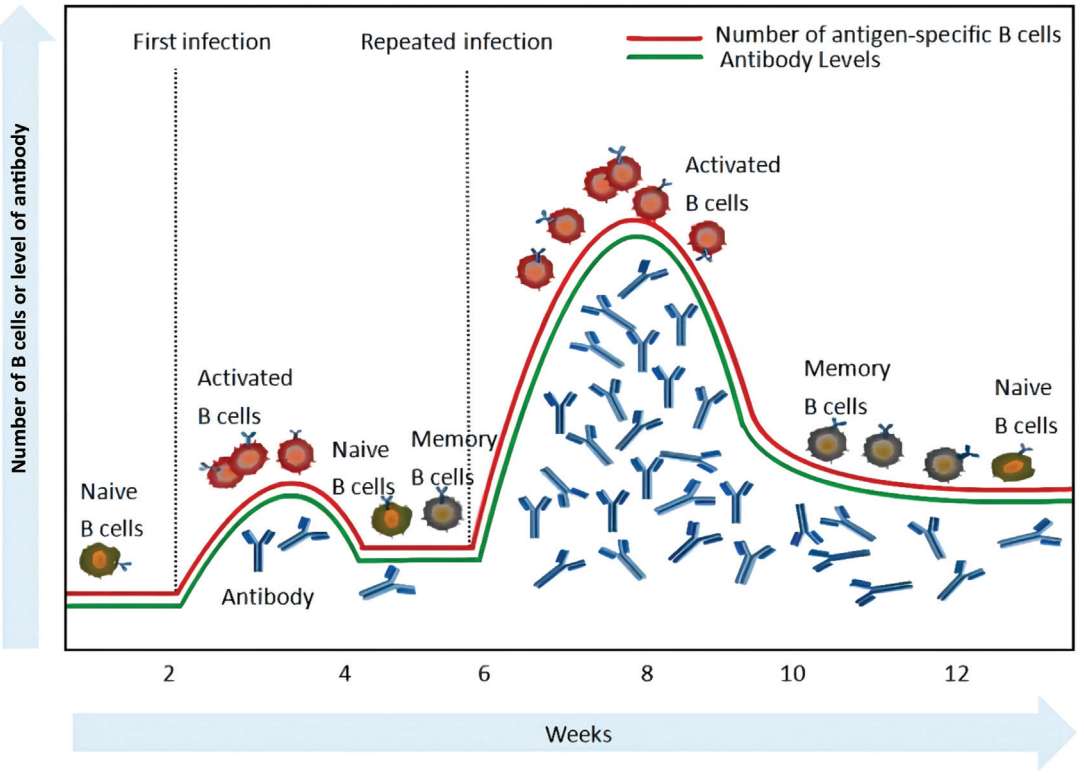

Figure 1: The number of B cells and level of antibody in first and repeated infection.

Table 2: A comparison of views on the CP treatment of COVID-19

Author	Country	Study design	Individuals included	Outcomes	Limitation	Reference
Joyner et al.	America	Case series	35322	Transfusion with higher antibody levels reduced mortality compared to low antibody levels Transfusions within three days yielded greater reductions in mortality	Not a RCT Different standard of treatment Antibody levels were unknown	[45]
Duan et al.	China	Clinical trial	19	Reduced the viral load and improved clinical outcomes	Only one dose of 200 mL of inactivated CP A small sample The median time of CP transfusion was 16.5 d.	[40]
Shen et al.	China	Case series	5	Reduced the viral load and increased the antibodies	A small sample Case-fatality rates were unknown.	[9]
Agarwal et al.	India	RCT	464	Not associated with a reduction in severe COVID-19 or all caused mortality Negative conversion of SARS-CoV-2 RNA on day 7 post-enrolment improved	Without the antibody level before transfusion The donors only had a median titer of 1:40. The uneven level of multi-center medical care	[21]
Simonovich et al.	Italy	RCT	334	No significant differences in clinical status or 30-day mortality No difference in ferritin and D-dimer levels at day 14	All enrolled patients had severe COVID-19 pneumonia excluding patients with mild-to-moderate or life-threatening cases of COVID-19.	[20]
Li et al.	China	RCT	103	No significant differences in clinical improvement within 28 days No significant differences in 28 days mortality No significant differences in time from randomization to discharge The rate of negative viral PCR at 24, 48 and 72 hours were higher.	Early termination of the trial A small sample	[22]
Joyner et al.	America	Retrospective cohort study	3082	Not receiving mechanical ventilation, transfusion of CP with higher anti–SARS-CoV-2 IgG antibody levels was associated with a lower risk of death.	Limited participation and limited availability of data The lack of precision in details and missing data	[49]

CP: convalescent plasma; COVID-19: coronavirus disease 2019; RCT: randomized, controlled trial; RNA: ribonucleic acid; PCR: polymerase chain reaction.

of critically-ill patients. Another CP treatment of hospitalized COVID-19 patients provided evidence that both earlier transfusion time and higher antibody levels are associated with reduced mortality.[45] Shen et al. reported that five critically-ill patients with COVID-19 and acute respiratory distress syndrome, administration of CP were followed by improvement in their clinical status. After plasma transfusion, body temperature normalized, the sequential organ failure assessment score decreased, and a ratio of the partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) increased at different times. Neutralizing antibody titers corresponding increased and viral loads also decreased and became negative following the transfusion.[9] A similar and promising result was found in another program.[40] Liu et al. studied 39 patients with life-threatening COVID-19 to assess effectiveness of CP, using a retrospective, propensity score-matched case-control trial. The result showed the rate of oxygen requirement in CP group was less than that in controls and survival improved in plasma recipients.[46] No significant transfusion-related mortality or morbidity was observed in this cohort, neither in other larger multicenter, national cohort.[47,48] The potential harms, however, allergic reactions relate to plasma transfusion, although rare, could occur.[46]

In a retrospective study, Joyner et al. reported that among COVID-19 patients who were not receiving mechanical ventilation, the high antibody levels in CP was associated with a lower death rate. In addition, patients who received plasma within 3 days after receiving a diagnosis of COVID-19 had a lower risk of death than those who received transfusions later in the disease course.[49]

Subsequently, several clinical trials showed other negative results about CP treatment. A randomized trial, initiated by Simonovich et al. reported that neither significant difference was observed in clinical status, overall mortality between patients treated with CP and those who received placebo, no difference in ferritin and D-dimer levels at day 14.[20] In addition, a multicenter randomized controlled trial in India found no difference in 28-day mortality or progression to severe disease among 464 moderate COVID-19 patients, 235 patients treated with CP along with best standard of care compared with 229 patients in control group. But a higher proportion of participants in the intervention arm showed negative conversion of SARS-CoV-2 RNA on day 7 post-enrolment.[21] In another randomized clinical trial in China, 52 patients received standard treatment and CP transfusions, the other 51 patients received standard treatment only. There existed no significant difference in the time to clinical improvement in 28 days.[22]

The deficiencies and counter measure of the CP in COVID-19

In the present study, there are some potential risks and deficiencies.[48] One theoretical complication is antibody-dependent enhancement (ADE), existing in several kinds of viral infection, an antibody mediated proinflammatory disease enhancement.[50] These antibodies from donors may abnormally stimulate complement receptors or fragment crystallizable, aggregate chemokines and proinflammatory cytokines to the infected site and cause severe tissue damage.[51,52] More than that, the presence of Nabs may exacerbate viral endocytosis or phagocytosis into host cells, potentializing viral replication.[53] This effect was first identified in dengue virus and other viral diseases, but there were not so many ADE cases reported CP treatment for patients with SARS, MERS, or SARS-CoV-2.[9,40,48,51,54] However we could not deny completely the possibility that ADE may exist in SARS-CoV-2.

As mentioned above, the second shortcoming is that the antibodies in CP supply shorter-term protection, partly because of the half-life of antibodies in CP.[55] In spite of the CP treatment protect patients with COVID-19 for a little time, clinically the short-term therapy may protect severe patients from critical situations by disappearance of viremia, and improved clinical symptom, and keep them out of danger. And this shortcoming may be resolved by multiple transfusions, which can provide longer protection.[9,40]

The third critical factor is the transfusion time point. A better treatment outcome suggested that patients with SARS who received CP treatment before day 14, highlighting the importance of transfusion time point.[56] But these studies are small scale and non-randomized, and the appropriate transfusion time point needs further research to determine in the future. Also, for different types of patients, the dosage of transfusion should be taken into account.

Conclusions

Despite a favorable historical record (especially in SARS and MERS), few controlled trials have been performed to evaluate the efficacy of CP, in large part due to its emergency application in times of epidemics. However, this time COVID-19 have reached over 160 million people worldwide, and it has kept on for a long time. Therefore, we had the opportunity to conduct more clinical trials and analyses. During our research, better result may be observed when CP used in earlier time, with higher titer antibodies and not in too serious stage of the disease. There are also other factors affecting the mortality rate, such as older age, impaired organ function, including acute kidney injury and acute cardiac injury, are strongly correlated with increased mortality in COVID-19 patients.[57,58] We speculate that CP plays a role in the treatment of COVID-19, but it is not the only one. As a treatment, it may have its own indications and contraindications, which need to be further discussed.

The exploration of scientific problems is endless, and we should not give up or affirm it because of temporary success or failure. As can be seen from the case of plasma in the recovery period, we should neither myth this method nor abandon it because some studies are negative. Clinical problems should be viewed rationally and dialectically and explored in depth.

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Authors' Contributions

Zhanjun Shu designed the study. Peipei Wu, Qianqian Qian and Li Zhou conducted the research; Dandan Du, Mengxuan Ding, Tao Peng and Ke Fang analyzed the data. Zhanjun Shu, Peipei Wu, and Qianqian Qian wrote the paper. All authors revised the manuscript and approved the final manuscript.

Conflicts of Interest

None.

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