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Review article

Emergence of ancient convalescent plasma (CP) therapy: To manage COVID-19 pandemic



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ARTICLE INFO

Article history:

Available online 5 December 2020

Keywords:

Convalescent plasma (CP) therapy
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
Coronavirus disease 2019 (COVID-19)
Passive immune therapy
Antibody-dependent enhancement (ADE)

ABSTRACT

Since December 2019, the human populations of the 195 global countries continue experiencing grave health and life threats due to the current COVID-19 pandemic. As a result of the novelty of the pathogen, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), at present there is lack of preventive as well as therapeutic options for treating and managing the infection. The use of ancient immunotherapeutic technique – the convalescent plasma (CP) therapy, may act as an immediate and available option to control the COVID-19 pandemic. This review provides a concept and understanding on the CP therapy, its potential to control SARS-CoV-2 pandemic. The CP therapy might act as an immediate saviour for society from the virus. Although the CP therapy has exert affirmative result against COVID-19 it has not been recommended for long time use in COVID-19 and this review gives support for its possible application.

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1. Introduction

In December 2019, an infectious type of pneumonia associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak emerged in Wuhan, China and the disease as a result of the infection was later named the coronavirus disease 2019 (COVID-19). Soon the epidemic disease spread rapidly worldwide and was immediately declared a pandemic by World Health Organization (WHO) on March 11, 2020. According to WHO, as of 11 November 2020, in 195 countries, 48,196,862 cases of COVID-19 were reported with more than 1,226,813 deaths notified [1]. So far, the worldwide mortality rate due COVID-19 has been reported to be approximately 4.5% [2]. Frequent symptoms of the COVID-19 are reported to include cough, fever, headache, loss of smell and taste, shortness of breath and fatigue. The majority of affected individuals develop acute respiratory distress syndrome (ARDS) accompanied by a huge cytokine storm within 2–14 days post-viral infection [3]. Study with COVID-19 patients in Beijing showed that, the neutrophil-to-lymphocyte ratio (NLR) was the early identification of risk factors for patients with age \geq 50 years. According to the study, patients who facilitate a NLR \geq 3.13 develop severe illness, and should rapidly accessed to intensive care unit [4]. Furthermore, SARS-CoV-2 can be found in stool, gastrointestinal tract, saliva, and

urine samples from the infected patients. Also, Li et al., in April 2020, detected SARS-CoV-2 from semen of COVID-19 positive patients [5].

There is currently no approved antiviral medication against this novel virus, although, drugs like chloroquine/hydroxychloroquine and, a combination of these old antimalarial drugs with azithromycin or their combination with remdesivir and lopinavir/ritonavir as well, are used [6]. Furthermore, corticosteroid treatment for COVID-19 also took a tiny bit of limelight but due to delayed renal clearance, its use remains controversial [7]. There is now a worldwide recommendation of the use of dexamethasone, another corticosteroid as a drug of choice for patient who have a severe SARS-COV-2 infection hospitalized and in intensive care [8]. Despite dexamethasone hailed as a breakthrough in treating symptomatic COVID-19 patients, dexamethasone has been already described used in acute respiratory distressed patients and has been used widely as well as the use of hydrocortisone [9,10]. Even Zhang et al. propose in a recent article, to improve outcome of COVID-19 situations we should opt for a system-wide strategy, which may vary patient to patient but will provide satisfactory result in health care centers [11].

Currently there's no approved effective vaccine or medication for COVID-19, although the disease spreading like wildfire globally. There is the greatest necessity to find alternative therapeutic strategies for COVID-19. There is certain old treatment, like the convalescent plasma (CP) treatment that could provide some relief for the disease. The classic adaptive immunotherapy, convalescent

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Table 1
Ongoing trials with plasma therapy against COVID-19 as of June 02, 2020 (source: clinicaltrials.gov).

NCT number	Study title	Number enrolled	Phase	Interventions
NCT04359810	Plasma therapy of COVID-19 in critically ill patients	105	II	Biological: convalescent plasma (anti-SARS-CoV-2 plasma) Biological: non-convalescent plasma (control plasma)
NCT04361253	Evaluation of SARS-CoV-2 (COVID-19) antibody-containing plasma therapy	220	III	Biological: high-titer COVID-19 convalescent plasma (HT-CCP) Biological: standard plasma (FFP)
NCT04355897	CoVID-19 plasma in treatment of COVID-19 patients	200	I	Biological: convalescent COVID-19 plasma
NCT04343755	Convalescent plasma as treatment for hospitalized subjects with COVID-19 infection	55	II	Biological: convalescent plasma
NCT04389710	Convalescent plasma for the treatment of COVID-19	100	II	
NCT04397757	COVID-19 convalescent plasma for the treatment of hospitalized patients with pneumonia caused by SARS-CoV-2	80	I	Drug: high-titer anti-SARS-CoV-2 (COVID-19) convalescent plasma
NCT04374565	Convalescent plasma for treatment of COVID-19 patients with pneumonia	29	II	Drug: high-titer anti-SARS-CoV-2 (COVID-19) convalescent plasma
NCT04376034	Convalescent plasma collection and treatment in pediatrics and adults	240	III	Biological: convalescent plasma 1 unit Biological: convalescent plasma 2 units Other: standard of care
NCT04358003	Plasma adsorption in patients with confirmed COVID-19	2000	Not applicable	Device: marker therapeutics D2000 Cartridge (D2000) for use with the Spectra Optia® Apheresis System (Optia SPD Protocol)
NCT04362176	Passive immunity trial of Nashville II for COVID-19	500	III	Biological: pathogen reduced SARS-CoV-2 convalescent plasma Biological: placebo
NCT04388527	COVID-19 convalescent plasma for mechanically ventilated population	50	I	Biological: COVID-19 convalescent plasma
NCT04411602	Feasibility study of anti-SARS-CoV-2 plasma transfusions in COVID-19 patients with SRD	90	I	Drug: SARS-CoV-2 plasma
NCT04377672	Human convalescent plasma for high risk children exposed or infected with SARS-CoV-2 (COVID-19)	30	I	Biological: anti-SARS-CoV-2 human convalescent plasma
NCT04390503	Convalescent plasma for COVID-19 close contacts	200	II	Biological: convalescent plasma (anti-SARS-CoV-2 plasma) Biological: control (albumin 5%)
NCT04412486	COVID-19 convalescent plasma (CCP) transfusion	100	I	Biological: COVID convalescent plasma
NCT04385199	Convalescent plasma for patients with COVID-19	30	II	Biological: convalescent plasma
NCT04392232	A study of COVID-19 convalescent plasma in high risk patients with COVID-19 infection	30	II	Drug: convalescent plasma
NCT04353206	Convalescent plasma in ICU patients with COVID-19-induced respiratory failure	60	I	Biological: multiple doses of anti-SARS-CoV-2 convalescent plasma
NCT04354831	A study evaluating the efficacy and safety of high-titer anti-SARS-CoV-2 plasma in hospitalized patients with COVID-19 infection	131	II	Biological: anti-SARS-CoV-2 convalescent plasma
NCT04364737	Convalescent plasma to limit COVID-19 complications in hospitalized patients	300	II	Biological: convalescent plasma Biological: lactated ringer's solution or sterile saline

plasma (CP) therapy is one option that could be considered in the management of COVID-19 disease based on clinical trial evidences collected (Table 1). One key possible determinant is that CP therapy is dependent on those people who recovered from the infection to donate their immunoglobulin-containing serum, which is to be used in the treatment regimen.

2. Basis of convalescent plasma (CP) therapy

CP therapy involves the use of passive immunization where the administration of antibodies from a given donor to a susceptible person to initiate development of immunity to the recipient against the microbe is initiated [12]. Vaccination involves a

time-dependent defense mechanism within the body, a passive immunization, providing immediate immunity to the recipient. As early as the 1890s to 1940's "passive immune therapy" or "serum therapy" was the main option through which scientists combated several infectious diseases with serum from experimentally immunized animals and human donors were used [13]. CP therapy is, therefore, a remedy that involves passive antibodies and can be efficient as a preventive measure against COVID-19 disease. For the CP to be effective, an adequate amount of antibody has to be administered to the recipient from the donor at very early stages of the COVID-19 disease. Studies have shown that pneumococcal pneumonia, in passive antibody therapy, showed the highest efficacy just after the onset of the symptoms and were ineffective

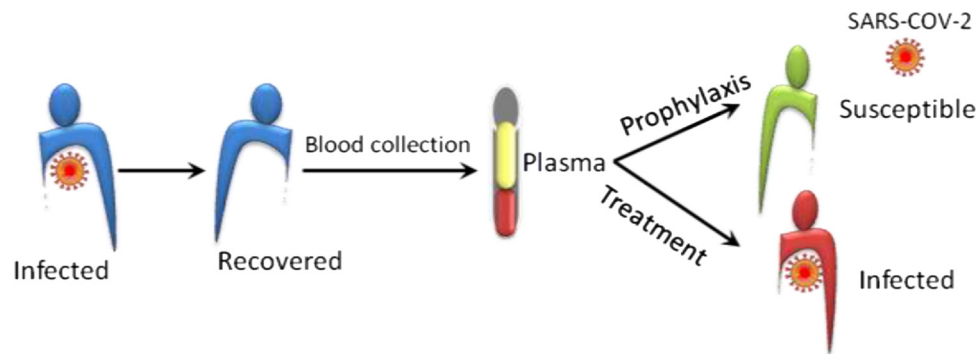


Fig. 1. Outline of convalescent plasma (CP) therapy against COVID-19 disease.

when the therapy was started on the third day after the onset of pneumonia [14]. However, the plasma donor patient has to have fully recovered from COVID-19 disease before donating the plasma (Fig. 1). After collection of immunoglobulin containing serum from a COVID-19 recovered donor, this is administered to COVID-19 patients as well as to the individuals who are exposed to COVID-19 virus. The passive immune therapy would in these instances act as both therapeutic as well as a prophylactic treatment. The CP therapeutic procedure will be more impactful when there are sufficient numbers of donors in a community with immunoglobulin containing serum. Based on previous pieces of evidence, the knowledge of antibody titers or other serological properties available, it is likely that CP therapy can benefit many COVID-19 patients.

3. Use of convalescent plasma (CP) therapy against viral diseases in past

CP therapy has been successfully applied in the past to control outbreaks of several viral diseases like measles [15], poliomyelitis [16], and mumps [17] as well as to control influenza viral infections [18]. Luke et al., 2006 summarized reports from eight cohort studies that administered convalescent sera to 1703 patients during the 1918 H1N1 pandemic to have been beneficial as it lowered the mortality rate successfully [19]. Recently, this ancient immune therapy has also been found satisfactory against diseases such as severe acute respiratory syndrome (SARS), influenza A (H1N1) during the 2009 pandemic, avian influenza A (H5N1), as well as from Ebola viral infections. Hung et al., in 2011 reported that during the 2009–2010 H1N1 influenza virus pandemic, individuals exposed to plasmapheresis technique showed reduced respiratory viral burden as well as controlled cytokine storm as a positive response to passive immune therapy [20]. In the study of Zhou et al. and Wu et al., CP therapy was able to decrease mortality rate when it was used against H5N1 and H7N9 avian flu outbreak in [21,22]. According to Zhou et al., in 2007 a 31-year-old male patient with confirmed with H5N1 infection from Southern China and showed a decreased viral load in his lungs just 8 hours after on the onset of CP therapy over Oseltamivir therapy which had been found as a H5N1 inhibitor [21]. The mechanism through which CP therapy could be functioning is believed to be through triggering the individuals' humoral immune response and therefore maintain normal immunoglobulin levels in infected patients. CP Therapy involves passive immunization where a donor with antibodies in his/her plasma is able to confer immunity to the recipient.

Another case study by Wu et al. in 2015, during the 2014–15 H7N9 outbreak in Zhejiang Province, shows where a 45 years old man treated with CP from a lady donor where within 3 days of onset of symptoms fully recovered. After 4 days of CP treatment (200 mL, containing a neutralizing antibody titer of 1:80), RT-PCR analyses consistently failed to detect the H7N9 virus in the sputum specimen

of the patient [22]. A study with 64 patients during the 2013, Ebola epidemic in Freetown, Sierra Leone, West Africa, where convalescent blood was used from recovered patients as an emergency treatment method to combat the epidemic, showed a remarkable decrease in patient viral loads. Out of 44 patients that were treated with the CP therapy, 1 dropped out of the study and 31 recovered while 12 succumbed to the disease with a case fatality rate of 27.9%. Interestingly, in patients on CP treatment, the viral load decreased within the first 24 h after the administration of convalescent blood. Patients those who have received CP therapy also showed a longer survival rate than those who had not received the therapy [23]. On the contrary, a study had been conducted a comparative study by Griensven et al. in 2016 with a total of 514 EBOV-positive patients. Out of which 102 EBOV-positive patients were enrolled for the convalescent-plasma therapy, but ultimately 58 patients were got confirmation of cure as they tested EBOV-negative [24]. According to Kraft et al., 2015, depicted case study showed two Ebola virus-infected patients had responded positively on treatment with CP. Both of these patients showed negative EBOV RNA on days 22, 24, and 25 with lower AST, ALT, and creatinine concentrations as well as a higher level of IgG and IgM in their plasma [25].

4. Application of CP therapy against corona virus diseases

Cheng et al. (2005) reported that during outbreaks of severe acute respiratory syndrome (SARS), they applied CP within 7 days after onset of symptoms on 80 patients in Hong Kong and the patients showed complete recovery and discharged from the hospital within 22 days of hospitalization. CP was applied to patients who were PCR-positive but serologically negative for the virus. The results showed the treatment with CP contributed to better prognosis and 61% of patients from this treatment group showed positive response [26]. Likewise, in 2005, a group of scientists and doctors applied CP on patients in a Taiwan hospital just after the onset of symptoms and it was noticeable that patients responded positively with an increased IgM and IgG concentrations and accompanied by decreased viral loads [27]. Current reports suggest that China, also opted for CP therapy in patients infected with COVID-19. The plasma was collected from person who had recovered from COVID-19 [28,29] and used to treat COVID-19 patients. Recently, as of May 27 2020, a 65 years old male patient in Hubballi, Karnataka, India was admitted to hospital with COVID-19 disease and went through CP therapy twice with a total volume of 200 mL plasma where this patient is said to have responded positively [30]. The use of CP therapy within 14 days after the onset of symptoms has been established as a recommended beneficial treatment procedure for treatment as well as for prophylactic treatment [30]. Duan et al. propose that CP on a single dose of 200 mL derived from a recently recovered person with an antibody titer ratio of 1:640, is the ideal and effective dose to be administered immediately after

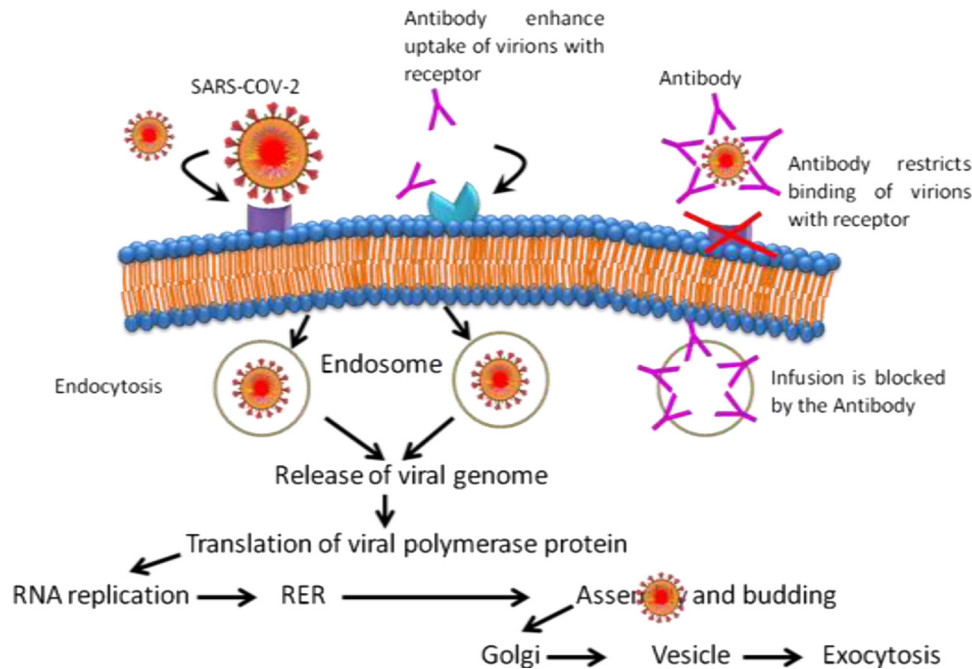


Fig. 2. Schematic presentation of SARS-CoV-2 infection through antibody-dependent enhancement.

the onset of symptoms [31]. In April 2020, Shen et al. reported that 5 critically ill patients with COVID-19 and acute respiratory distress syndrome (ARDS) (age group-36–65 years: 2 women) were subjected to CP therapy Hospital in Shenzhen, China. It has been seen that administration of CP, which contained neutralizing antibody improved their clinical status. Following CP therapy, within 3 days they showed a normalised body temperature. Within 2 weeks of CP therapy patients were weaned from mechanical ventilation and they were discharged from the hospital after treatment length of 53–55 days [32].

5. Pros and cons for employment of CP in population

CP therapy for COVID-19 may be beneficial for prophylactic as well as for treatment purposes. CP could provide basic protection against those who are at high risk of the disease. The use of CP for the treatment of many infectious viral diseases has already been established and these facts have been presented and discussed in the article. Nevertheless, this procedure may also introduce some risks to the individual upon whom CP is going to be administered. People may experience any inadvertent upward effects including immunological reactions and blood-borne pathogenic infections related to blood transfusion. Before donating convalescent plasma, it is recommended that the donor should have recovered fully from the disease and have met the eligibility criteria set for donating serum [33]. All transfusions should involve modern, sanitized techniques applicable to facilities involved in human blood transfusions. Infected persons with compromised lung functions are prone to develop transfusion-related acute lung injury (TRALI) due to plasma transfusion [34] and such potential donors are discouraged from donating blood. Care should be taken when donors who are on medication due other chronic diseases and should not be allowed to donate blood. The donor should be capable of generating high neutralizing antibody titers as per the FDA recommendations, i.e. a titer of $>1:320$ for eIND [33]. High-titer value of antibody fortifies specificity against SARS-CoV-2 while binding and ensures the neutralization of the viral particles [35]. Care on the selection of the dose of CP should be taken into consideration for an optimal positive response for both prophylactic and treatment purposes.

Furthermore, the use of CP therapy may cause antibody-dependent enhancement (ADE) or immune enhancement as a result of infectivity and virulence of the pathogen. In ADE, binding of viral proteins to antibodies, triggers cell entry of the pathogen as well as its subsequent replication [36]. Ricke and Malone have shown that COVID-19 disease may increase its severity as well as progression in an in vivo system through the ADE (Fig. 2). Antigenic drift in viruses contributes to sudden immunological dysfunction as well as cytokine storm that ultimately for instance lead to the in vivo progression of the COVID-19 [37]. Employment of ADE mechanism may be one of the reasons behind the high severity of SARS-CoV-2 among the older population. Age and production of antibodies are inversely proportional. Older people take longer to produce sufficient amount of antibodies to neutralize the virus, which, gives the infectious virus time to change its antigenic determinants. Also employment of ADE is positively correlated with viral load of the virus, i.e. there will be a large increase in number of viral body in the in vivo system. The use of ADE in favor of successive virulence is the main disquiet for the development of vaccines against SARS-CoV-2. While SARS-CoV-2 already employs ADE for the establishment of its virulence after host cell entry, then the use of CP therapy for both prophylactic as well as therapeutic purposes may cause some concern.

6. Conclusion

CP therapy is an old immunological technique and its application in SARS-CoV-2 is not new. While CP can provide immediate protection as well as a complete cure from COVID-19 disease, it may have disadvantage in that it be rejected by certain individuals due to several intolerances (e.g. hemolytic transfusion reactions, anaphylactic reactions, transfusion-related acute lung injury), allergic reactions and many other reasons (e.g. delayed hemolytic transfusion reactions). It is advisable that, whenever the procedure is going to be administered to the patients, there must be evidence that the donor has fully recovered, not of serious chronic medications and that the blood has been cleared for donation with enough antibody titer for effective clearing of the infectious virus and that the patients is less likely to have allergic response. With the evidence on CP therapy

available, we hope that this therapy could be found useful against SARS-CoV-2 for providing immediate protection. CP has the potential application for prophylactic use as well as in the treatment of severely SARS-COV-2 infected persons.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgement

The authors express gratitude to the Department of Pharmacology, University of the Free State, Bloemfontein, Republic of South Africa. Dr. Darssama and Dr. Tripathy are further thankful to the Department Research Directorate (DRD) at University of Free State for providing them with the opportunity to do their postdoctoral fellowships in the Department of Pharmacology at same University.

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