Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Infection and Public Health 13 (2020) 1818–1822

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: http://www.elsevier.com/locate/jiph

Review Article

Positive aspects, negative aspects and limitations of plasma therapy with special reference to COVID-19

Basavraj Nagoba[a,*], Ajay Gavkare[a], Nawab Jamadar[a], Sachin Mumbre[b], Sohan Selkar[c]

[a] Maharashtra Institute of Medical Sciences & Research, (Medical College), Latur, India
[b] Ashwini Rural Medical College, Solapur-India & Dean, Faculty of Medicine, Maharashtra University of Health Sciences, Nashik, India
[c] Datta Meghe College of Physiotherapy, Wanadongri, Nagpur, India

ARTICLE INFO

Article history:
Received 21 May 2020
Received in revised form 30 July 2020
Accepted 26 August 2020

Keywords:
COVID-19
Convalescent plasma
Positive aspects
Negative aspects
Limitations

ABSTRACT

The principle of plasma therapy can be used for prophylaxis and treatment purpose. In view of non-availability of suitable vaccine for prevention or no established definitive therapy for SARS-CoV-2, plasma therapy is gaining importance in a current pandemic as one of the treatment options for the treatment of COVID-19. Although, it has been reported to be an effective approach in various preliminary studies, convalescent plasma (CP) therapy has several limitations. In this mini review, an attempt has been made to review positive aspects, negative aspects and various limitations of the CP therapy for COVID-19 cases. The results of various studies show that CP therapy may be thought of one of the alternatives but while considering it as a therapeutic approach, in light of beneficial effects, the negative aspects and limitations are to be taken into consideration before its administration as a therapeutic agent.

Contents

* Corresponding author.
E-mail addresses: dr.bsnagoba@yahoo.com, bsnagoba@gmail.com (B. Nagoba).

https://doi.org/10.1016/j.jiph.2020.08.011

Introduction

The COVID-19 pandemic caused by SARS-CoV-2 originated in China in December 2019 has now become a major concern all over the world. Till date, there is no suitable vaccine for prevention or no established definitive therapy for SARS-CoV-2 is available. In a battle against COVID-19, convalescent plasma (CP) obtained from recently recovered cases of COVID-19 cases is gaining attention as one of the treatment options. Human convalescent plasma administration has been reported to be effective in the management of COVID-19 cases in preliminary studies [1–5]. Use of CP therapy is not new; it is known since long and was used for many viral (Varicella-zoster, hepatitis B, Rabies) and bacterial (tetanus, pertussis) diseases [6]. It was also used for SARS-CoV-1 outbreak in 2003 and was found effective when administered before 14 days following onset of symptoms as compared to when administered after 14 days. The mortality rate was also less in those who received CP therapy before 14 days [7]. It was also used for avian influenza (H5N1) virus in 2008 [8], (H_1N_1) virus in 2009 [9], Middle East Respiratory Syndrome (MERS) outbreak in 2012 [10], Ebola virus outbreak in 2014 [11], etc. A recent study by Zhao et al. shows that there is dynamic increase in IgM and IgG antibodies following SARS-CoV-2 infection as the disease progresses with median seroconversion time of 11–15 days explaining the importance of serological testing in the diagnosis and management of COVID-19 patients [12].

The CP rich in neutralizing antibodies obtained from donors who have recovered from recent viral infections has proved to be one of the safe, effective and reliable treatment options in the outbreak of these viral infections. Thus, it is a well established treatment modality to prevent disease in individuals who are exposed to the infective agent or at a risk of infection [13–17]. It has been found that the use of CP for management of severe H_1N_1 infection reduces hospital stay, ICU duration, mechanical ventilation and Extracorporeal membrane oxygenation (ECMO) [9].

Although found effective, CP therapy has several limitations. In this mini review, an attempt has been made to review positive aspects, negative aspects and various limitations influencing the CP therapy in general and in the management of COVID-19 cases in particular.

Positive aspects of plasma therapy

Clinical efficiency

As far as the clinical efficiency of CP therapy is concerned, the results of preliminary studies are very promising. Shen et al. in their preliminary study on five critically ill COVID-19 cases with severe respiratory failure and receiving mechanical ventilation found that administration of CP containing SARS-CoV-2 antibodies (Abs) with titre more than 1:1000 and neutralizing Abs with titre more than 1:40, along with lopinavir/ritonavir and interferon between day 10 and 22 showed improvement after one week of CP therapy. Their patients showed increase in Ab titre, decrease in viral load, resolution of symptoms of acute respiratory distress syndrome (ARDS) and other symptoms of COVID-19 [1]. In a study by Duan et al. recruiting 10 confirmed cases of COVID-19, administration of one dose of 200 ml of CP from recently recovered donors with the neutralizing Ab titres more than 1:640 along with antiviral agents showed significant improvement in clinical symptoms, decrease in viral load and laboratory values by day three of transfusion of CP. The viral RNA became undetectable in all 10 cases. All 10 patients under study showed reduction in pulmonary lesions on chest CT examination, and clinical improvement as well [2].

In a study by Zhang et al. on four critically ill patients, transfusion of 200–2400 ml of CP ranging from day 11 to 18 resulted in recovery of all four patients from COVID-19 approximately in one week to one month after transfusion of CP [3]. In another descriptive study by Ye et al. in six laboratory-confirmed COVID-19 patients, transfusion of convalescent plasma resulted in resolution of ground-glass opacities and consolidation in five patients and in one patient, it resulted in an elimination of the virus indicating that CP therapy is effective and specific for COVID-19 with no notable adverse effects [4]. Ahn et al. in their study on two confirmed cases of COVID-19 with symptoms of severe pneumonia and acute respiratory distress syndrome, infusion of 500 ml of CP in two divided doses resulted in a favorable outcome after the use of convalescent plasma along with systemic corticosteroids [5] (Table 1 and Fig. 1).

The results of these studies show that administration of CP containing high level of Abs against SARS-CoV-2 virus in the early phase of disease significantly reduces the severity of infection and decreases mortality. The results further show that CP therapy is a simple and effective tool to offer immediate protection by providing passive immunity. It is a more promising treatment option for patients with early symptoms and to prevent disease in those who are exposed to infection [17]. As CP offers immediate protection, i.e. instant immunity with the help of Abs against SARS-CoV-2, it is very much beneficial in immunocompromised individuals [16]. Thus, CP therapy has the potential clinical benefit in the management of COVID -19 cases [18–21].

There are two regions on SARS-CoV-2 spike glycoprotein, which are recognized by sera from COVID-19 convalescent patients. One of them is specific to SARS-CoV-2 and is located in close proximity to the receptor binding domain. The other region is located at the fusion peptide. These two regions are IgG immunodominant regions and spike binding antibodies targeting these regions significantly alter virus neutralisation capacities [22].

Zero percent mortality

Although, the mortality rates of 6.3% in patients receiving plasma therapy before 14 days and 21.9% in patients receiving plasma therapy after 14 days have been reported in patients suffering from SARS-CoV-1 infection [7], no mortality has been reported in the patients receiving CP therapy for SARS-CoV-2 infection in all five studies [1–5] (Table 1).

Beneficial effects of other plasma components

Plasma is a mixture of organic compounds, inorganic salts and water. It has been shown to contain more than 1000 proteins including albumin, immunoglobulins, coagulation and antithrombotic factors, complement components, etc. [23]. These plasma components may exert beneficial effects, e.g. replenishing coagulation factors are useful in patients with hemorrhagic fevers

Table 1
Details of convalescent plasma therapy in patients with COVID-19.

Author	Country	Study design	No. of cases	Dose of CP	Outcomes	Mortality
Shen et al. [1]	China	Case Series	5	Two consecutive doses of 200–250 ml (Total 400 ml)	Decrease in viral loads, increase in SARS-CoV-2–specific antibody titres, improvement of clinical status	Nil
Duan et al. [2]	China	Clinical trial	10	One dose of 200 ml	Improvement in clinical symptoms and radiological findings, decrease in viral loads, increase in Ab titres	Nil
Zhang et al. [3]	China	Case Series	4	200–2400 ml	Clinical recovery of all patients	Nil
Ye et al. [4]	China	Case Series	6	Two consecutive doses of 200–250 ml	Decrease in viral loads, increase in Ab titres, improvement in clinical symptoms and radiological abnormalities	Nil
Ahn et al. [5]	South Korea	Case Report	2	Two consecutive doses of 250 ml (Total 500 ml)	Decrease in viral loads, increase in Ab titres, improvement in clinical symptoms	Nil

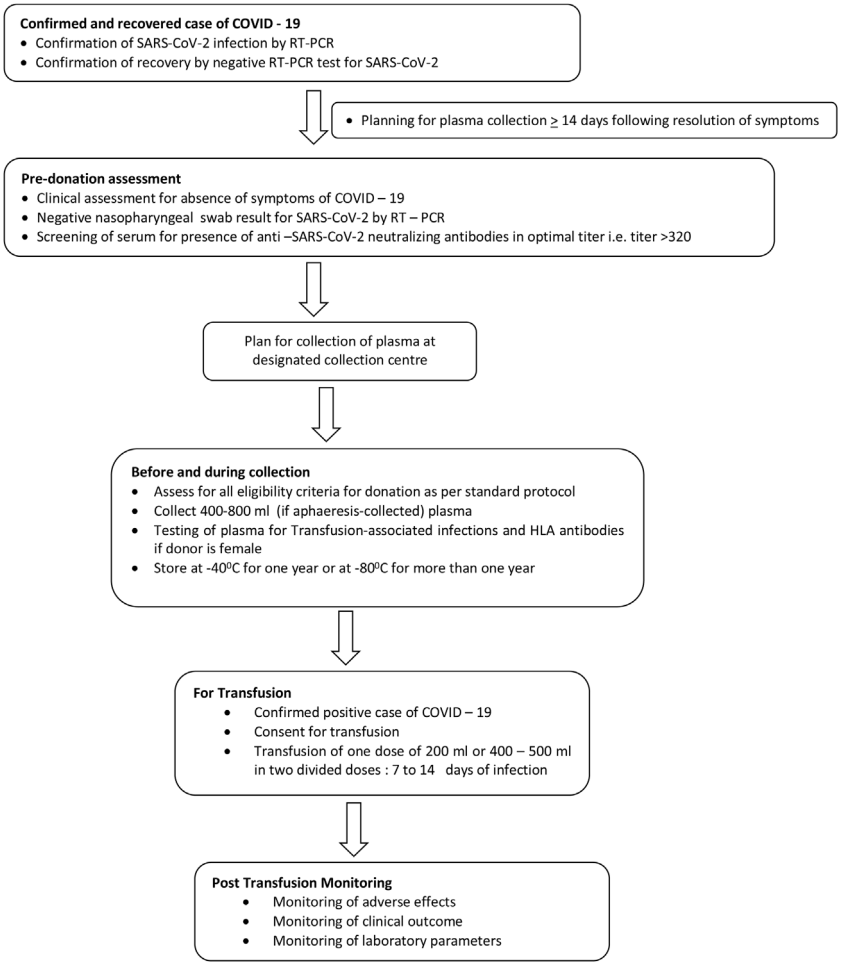

Fig. 1. Anti-SARS-CoV-2 plasma workflow for plasma collection and transfusion.

as in ebola virus infection [24,25]. Plasma proteins, especially albumins contribute to maintain colloidal osmotic pressure of body fluid compartments. It has been also shown that plasma from healthy donors has immunomodulatory effects through anti-inflammatory cytokines and antibodies by blocking complement activation, inflammatory cytokines and autoantibodies [26].

Tolerance to CP therapy

As far as tolerance to CP therapy is concerned, the CP transfusion is well tolerated by all patients and could potentially improve the clinical outcomes in severe COVID-19 cases although associated with some adverse effects [2,18].

Negative aspects of plasma therapy

Adverse reactions

Adverse reactions ranging from mild fever to allergic reactions to life–threatening bronchospasm, transfusion related acute lung injury and circulatory overload in patients with cardiorespiratory disorders, renal impairment and aged individuals have been reported [14,17,20,21,27]. Non infectious hazards of transfusions - like transfusion reactions such as transfusion related dyspnea and severe allergic reactions with associated bronchospasm, which can further exacerbate respiratory symptoms in COVID-19 patients. Transfusion - like reactions such as transient elevation of body temperature by 0.5 °C–1.5 °C within two hours of transfusion [14,18,28].

Immunological reactions

Administration of plasma may cause severe allergic reactions. Response to donor plasma/serum ingredients may lead to serum sickness and anaphylaxis. These reactions may be associated with bronchospasm [14,17,18,27].

Risk of transfusion associated infections

Although very rare, administration of CP carry the risk of transmission of potential pathogen, i.e. another infectious agents such as hepatitis B virus (HBV), hepatitis C virus (HCV), Human Immunodeficiency virus (HIV), *Treponema pallidum* as well as SARS-CoV-2 itself. Hence, screening for presence of these pathogens is obligatory to avoid the risk of transfusion associated infections [14,18,21].

Risk of reinfection

Administration of CP, i.e. passive Abs may suppress/attenuate the humoral immune response of recipient thereby inhibiting the synthesis of specific Abs against SARS-CoV-2 (pathogen specific Abs). This may make an individual susceptible to reinfection by SARS-CoV-2 [17,18,29].

Other adverse reactions

CP therapy has been reported to cause an evanescent facial red spot in one patient under study [2]. Phlebitis and generalized jaundice have also been reported to occur in some patients [14].

Antibody dependent enhancement (ADE)

There is a remote possibility of antibody dependent enhancement of disease process. ADE is a process in which antibodies present in donor's plasma may exacerbate disease by enhancing entry of virus into host cell and multiplication of virus [14,18].

Important limitations of plasma therapy

Although CP transfusion has been found effective in fighting severely infected cases of COVID-19, it is associated with several limitations. The important limitations of plasma therapy are as follows:

Lack of neutralizing antibodies in patient plasma

The patients recently recovered from the SARS-CoV-2 infection can be effective donors for preparation of plasma for treating COVID-19 cases. The most important requirement for this is that donor must have a high titre of neutralizing antibodies in their plasma. The studies show that not all patients recovered from SARS-CoV-2 infection have desired levels of antibodies in a convalescent stage. Around 30% of patients recovered from SARS-CoV-2 produced very low titre of antibodies. Another problem is that these antibodies last only for a short duration which is to be measured in weeks or months [14,18,30,31].

Large infusion volumes

Another important limitation of CP therapy is the requirement of large infusion volumes. Different studies show that transfusion of 200 ml–2400 ml CP is required for treatment purpose [1–5]. There is no standardization of transfusion dose of CP and different doses have been used in different studies. Depending on the patient, a dose of 200 ml–2400 ml was used by Zhang et al. [3]. However, Duan et al. infused one unit of 200 ml of CP [2] (Table 1).

Time of administration

Another important limitation is time of administrations of CP to infected patients. It is expected to be more effective, if administrated before the development of humoral immune response to SARS-CoV-2. Hence, testing recipient (patient) for neutralizing antibodies would be beneficial in identifying the best recipient for treatment purpose [21].

Waning of plasma Abs

As mutations are common in SARS-CoV-2 there is a possibility of waning of plasma Abs [21].

Bridging the gap between COVID 19 positive and recovered cases

There is an addition of a large number of COVID 19 positive cases every day in almost all countries; however, the number of cases being recovered from SARS-CoV-2 infection is comparatively very less. Hence, it is very difficult to meet the requirement of large quantity of plasma needed to treat large number of cases being added every day. The bridging of this gap between recovered cases and new cases appears to be very difficult, because of which this treatment option may not be feasible in terms of availability of large quantity of convalescent plasma.

Basic administrative and logistical barriers

The important barriers include identifying, consenting, collecting and testing donors. Identifying/finding donors with robust humoral response (donors with high levels of desired antibodies) is an important hurdle. Lack of suitable assay method for detection of neutralizing antibodies may hamper the identification of suitable/ideal donors. Written informed consent for donations of plasma by patients recently recovered from COVID-19 disease may be an another important hurdle [14,18] (Fig. 1).

Donors eligibility criteria

Donors consenting for donation of plasma must meet the eligibility criteria for standard blood donation. Donors must be negative for SARS-CoV-2 test and must be free from COVID-19 symptoms. Donor dependent variability in Abs specificities and titre of antibodies in CP is another problem associated with different individuals [18,21]. Donated plasma should be compatible with the A-B-O blood type of the recipient [14] (Fig. 1).

Conclusion

The review of various earlier studies show that CP therapy is beneficial in the management of various viral infections, including COVID-19. It may be thought of one of the alternatives, especially for the treatment of viral infections for which no suitable vaccine or established antiviral therapy is available. However, while considering it for therapeutic approach, in light of beneficial effects, the negative aspects and limitations are to be taken into consideration before its institution as a therapeutic agent.

Funding

No funding Sources.

Competing interests

None declared.

Ethical approval

Not required.

References

[1] Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 critically ill patients with COVID-19 with Convalescent plasma. JAMA 2020;323:1582–9.
[2] Duan K, Bende L, Cesheng L, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A 2020;117:9490–6.
[3] Zhang B, Liu S, Tan T, Huang W, Dong Y, Chen L, et al. Treatment with convalescent plasma for critically ill patients with SARSCoV-2 infection. Chest 2020;158:e9–13.
[4] Ye M, Fu D, Ren Y, Wang F, Wang D, Zhang F, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. J Med Virol 2020, http://dx.doi.org/10.1002/jmv.25882.
[5] Ahn JY, Sohn Y, Lee SH, Cho Y, Hyun JH, Baek YJ, et al. Use of convalescent plasma therapy in two COVID-19 patients with acute respiratory distress syndrome in Korea. J Korean Med Sci 2020;35(14):e149, http://dx.doi.org/10.3346/jkms.2020.35.e149.
[6] Nagoba BS, Pichare AP. Medical Microbiology and Parasitology. 3rd ed. New Delhi: Elsevier; 2016.
[7] Cheng Y, Wong R, Soo YOY, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis 2005;24:44–6.
[8] Zhou B, Zhong N, Guan Y. Treatment with convalescent plasma for influenza A (H5N1) infection. N Engl J Med 2007;357(14):1450–1.
[9] Hung IF, To KK, Lee CK. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. Clin Infect Dis 2011;52(4):447–56.
[10] Mustafa S, Balkhy H, Gabere MN. Current treatment options and the role of peptides as potential therapeutic components for Middle East Respiratory Syndrome (MERS): a review. J Infect Public Health 2018;11(1):9–17.
[11] Gulland A. First Ebola treatment is approved by WHO. BMJ 2014;8:349–5539.
[12] Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clin Infect Dis 2020, http://dx.doi.org/10.1093/cid/ciaa344.
[13] Luke TC, Casadevall A, Watowich SJ, Hoffman SL, Beigel JH, Burgess TH. Hark back: passive immunotherapy for influenza and other serious infections. Crit Care Med 2010;38(4):66–73.
[14] Zhou XZ, Zhao M, Wang FS, Jiang TJ, Li YG, Nie WM, et al. Epidemiologic features, clinical diagnosis and therapy of first cluster of patients with severe acute respiratory syndrome in Beijing area. Zhonghua Yi Xue Za Zhi 2003;83:1018–22.
[15] Özdemir Ö, Melek Arsoy HE. Convalescent (Immune) plasma therapy with all aspects: yesterday, today and COVID-19. Erciyes Med J 2020;42, http://dx.doi.org/10.14744/etd.2020.36528.
[16] Marano G, Vaglio S, Pupella S, et al. Convalescent plasma: new evidence for an old therapeutic tool? Blood Transfus 2016;14(2):152–7.
[17] Anudeep TC, Jeyaraman M, Shetty DU, Raj MH, Ajay SS, Somasundaram R, et al. Convalescent plasma as a plausible therapeutic option in nCOVID-19—a review. J Clin Trials 2020;10, http://dx.doi.org/10.35248/2167-0870.20.10.409.
[18] Sullivan HC, Roback JD. Convalescent plasma: therapeutic hope or hopeless strategy in the SARS-CoV-2 pandemic. Transfus Med Rev 2020, http://dx.doi.org/10.1016/j.tmrv.2020.04.001.
[19] Liu G, Li S. Convalescent plasma: a valid option in the treatment of COVID-19? Insights Clin Cell Immunol 2020;4:001–2, http://dx.doi.org/10.29328/journal.icci.1001012.
[20] Bloch EM, Shoham S, Casadevall A, Sachais BS, Shaz B, Winters JL, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. J Clin Invest 2020, http://dx.doi.org/10.1172/JCI138745.
[21] Roback JD, Guarner' J. Convalescent plasma to treat COVID-19 possibilities and challenges. JAMA 2020;323(16):1561–2.
[22] Poh CM, Carissimo G, Wang B, Amrun SN, Lee CY, Chee RS, et al. Two linear epitopes on the SARS-CoV-2 spike protein that elicit neutralising antibodies in COVID-19 patients. Nat Commun 2020;11:2806, http://dx.doi.org/10.1038/s41467-020-16638-2.
[23] Benjamin RJ, McLaughlin LS. Plasma components: properties, diff ;erences, and uses. Transfusion 2012;52(Suppl. 1):9S–19S, http://dx.doi.org/10.1111/j.15372995.2012.03622.x.
[24] Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. J Clin Invest 2020, http://dx.doi.org/10.1172/JCI138003.
[25] Kraft CS, Hewlett AL, Koepsell S, et al. Nebraska biocontainment unit and the Emory serious communicable diseases unit. The use of TKM-100802 and convalescent plasma in 2 patients with Ebola virus disease in the united States. Clin Infect Dis 2015;61(4):496–502.
[26] Lünemann JD, Nimmerjahn F, Dalakas MC. Intravenous immunoglobulin in neurology–mode of action and clinical efficacy. Nat Rev Neurol 2015;11:80–9, http://dx.doi.org/10.1038/nrneurol.2014.253.
[27] Gajic O. Transfusion-related acute lung injury in the critically ill: prospective nested case control study. Am J Respir Crit Care Med 2007;176:886–91.
[28] Hendrickson JE, Hillyer CD. Noninfectious serious hazards of transfusion. Anesth Analg 2009;108:759–69.
[29] Uhr JW, Baumann JB. Antibody formation. The suppression of antibody formation by passively administered antibody. J Exp Med 1961;113:935–57.
[30] Herman AO. SARS-CoV-2 Antibodies Undetectable in Some Recovered Patients. https://www.jwatch.org/fw116548/2020/04/13/sars-cov-2-antibodies-undetectable-some-recovered (Accessed 20 May 2020).
[31] Wu F, Wang A, Liu M, Wang Q, Chen J, Xia S, et al. Neutralizing antibody responses to SARS CoV-2 in a COVID-19 recovered patient cohort and their implications. medRxiv preprint 2020:1–20, http://dx.doi.org/10.1101/2020.03.30.20047365.