

Current Status of Plasma Therapy in the Pandemic Corona Virus Disease-19: A Therapeutic Alternative for Patients

**Prabhat Kumar Upadhyay¹, Vishal Kumar Vishwakarma², Manish Kumar^{3*},
Abhishek Tiwari⁴, Varsha Tiwari⁴, Manoj Yadav⁵,
Vijay Kumar Yadav⁵, Sanjeev Kumar Chauhan⁶**

¹Institute of Pharmaceutical Research, GLA University Mathura - 281406, UP, India

²All India Institute of Medical Science (AIIMS), Ansari Nagar East, New Delhi 110029, Delhi, India

³M.M. College of Pharmacy, Maharishi Markandeshwar (Deemed to be University), Mullana-Ambala, Haryana-133207, India

⁴Department of Pharmacy, Devsthal Vidyapeeth College of Pharmacy, Lalpur, Rudrapur (U.S. Nagar), Uttarakhand, India

⁵Department of Pharmacy, Dr. Bhimrao Ambedkar University, Agra-282002 U.P., India

⁶KIET School of Pharmacy, KIET Group of Institutions, Ghaziabad, UP, India

*Correspondence Author: manish_singh17@rediffmail.com

Abstract

Currently, the transfusions of convalescent plasma are widely used in the pandemic corona virus disease-19 (COVID-19). The use of plasma lacks a specific prevention and therapy of this virus disease. Thus, the treatment using plasma has a meticulous interest till specific vaccine is not offered for control and management of viruses. During the infection, severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) identified which is responsible to cause COVID-19. This paper reviews from literature available on Google scholar, pub Med, Scopus database and focused on the use of convalescent plasma as one of the therapeutic alternative for management of COVID-19. The convalescent plasma can be immediately used in such treatment which establishes quick convenience of a capable therapy before validation of the vaccines and specific therapy are for appropriate scaling. Further, literature is searched to develop better convalescent plasma. The development of vaccines and more specific therapeutic agents is based on the availability of extensive data from studies of disease's pathogenesis and its immune response. In addition, margin of safety is requisite to defend the convalescent plasma recipients because of lacking more information on natural history of the disease.

Keywords: Corona virus disease-19, Convalescent plasma, Pathogenesis, Immune system.

Introduction

What is Blood Plasma?

Blood plasma is generally known as plasma, a light-yellow liquid portion of blood. The plasma have a role in the transportation of nutrients in human body from the cells to various tissues and organs. It also carries waste products from biochemical processes to lungs, liver and kidneys for excreting them from the body which were resulting from

cellular metabolism. It plays an important role to transport the blood cells and maintain normal blood pressure. Plasma maintains the homeostasis by establishing acid-base balance in the blood and distributing heat throughout the body¹.

Components of Blood Plasma

Blood plasma has 91-92% of water and 8-9% of solids as whole system. It mainly consists of- (a) The fibrinogen as main coagulant, which helps in the blood coagulation (b) The globulin and albumin as main plasma proteins which help in maintaining osmotic pressure of colloidal blood at about 25 mmHg; (c) The calcium, sodium, potassium, bicarbonate and chloride as main electrolytes which help to maintain the pH of blood (d) Immunoglobulins help in the fighting against infection and other small amounts of enzymes and hormones.

The immunoglobulin is major class of proteins which is obtained from B-lymphocytes of the immune system. These classes include protective antibodies generated against specific viral or bacterial antigens in favour of body's response².

Role of plasma components from recovered patient

When people fight with any type of virus, they generate antibodies that act against attacking virus. Chemically, such antibodies are proteins and secreted from specialized immune cells named B-lymphocytes. They are found in the liquid part of blood or the plasma. It helps in the blood coagulation as per need and also supports immunity. As person infected with virus and recovered, who develops antibodies and stay in the blood for fighting with same virus, if it returns?. Then, antibodies are injected into another diseased person recognize the virus which attacks on the body³ (**Figure 1**).

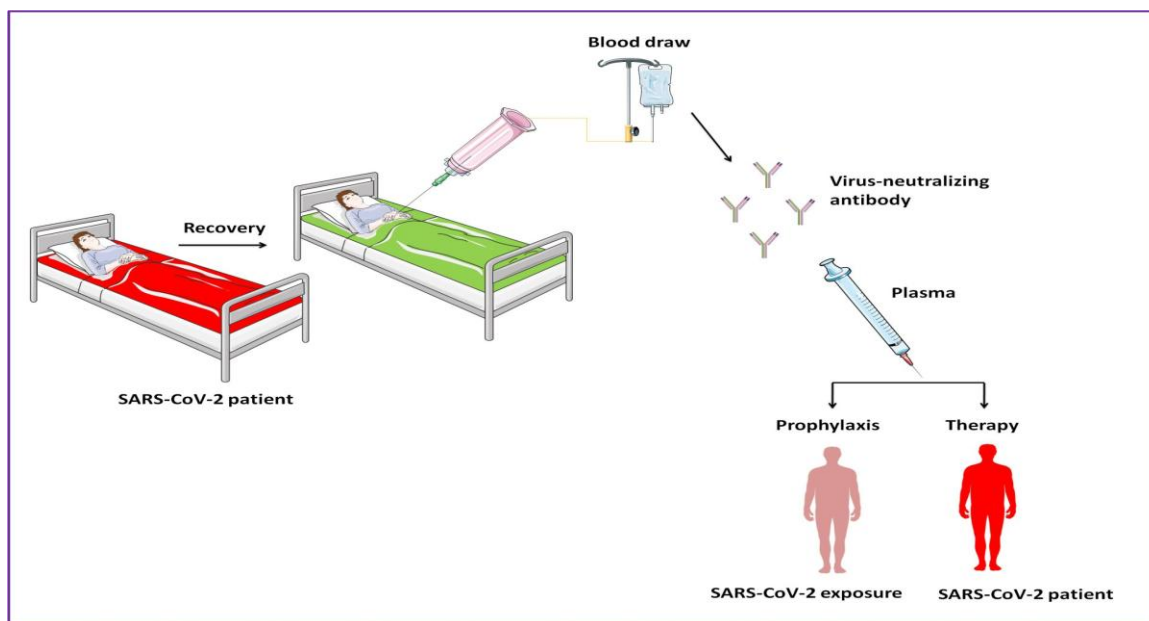


Figure 1: When the people fight the virus they produce antibodies protein that are secreted by immune cells known as B lymphocytes, are found in plasma or the liquid part of blood that helps the blood to clot and supports immunity. Once a person recovers, that person has

developed antibodies that will stay in their blood waiting to fight the same virus. Those antibodies, when injected into another person with disease, recognise the virus as something to attack.

What is convalescent plasma?

The therapy using convalescent plasma is actually transfusion of different components from blood of recovered people who was suffered from COVID-19 virus. These components are transfused to people who are survived at high risk with virus⁴.

Clinical importance of convalescent plasma

The transfusion of convalescent blood and its components is well established tool which is used clinically for controlling the out breaks of infectious disease. From long time, convalescent whole blood, convalescent plasma, and combined human immunoglobulin, high-titer human immunoglobulin, and monoclonal antibodies administered intravenously or intramuscularly in case of passive immune therapy. Currently, the plasma has been collected by aphaeresis technique and used in such therapies⁵. The use of the blood and its components from recovered patients was reported at the time of some infectious diseases in late 1800s⁶. The first viral infection such as Spanish influenza was reported (the pandemic has been observed in 1918–1920). In the clinical studies, the convalescent plasma and blood products were found to have significant use^{7,8}.

A meta-analysis of eight studies of the Spanish flu (1703 patients) exhibited that treatment with convalescent blood products reduced the mortality⁹. The possible use of convalescent plasma for prevention, control and/or therapy was interesting during West African Ebola outbreak due to the lack of vaccines and therapeutics in case of infectious disease and also produced high fatality rate¹⁰.

Several infectious diseases including SARS-CoV-1, MERS-CoV, West Nile Virus, and H1N1 virus have been tried to produce the passive immunity using the convalescent plasma. In spite of long history using convalescent plasma, the clinical efficacy of plasma and its components have not been studied robustly.

The conclusions found are not too effective due to the use of convalescent plasma in critical situations, need of immediate actions and during massive epidemic/pandemic outbreaks. The effectiveness of such convalescent plasma treatment is determined on the basis of pathogenic species and treatment protocols (e.g. timing, volume, and dosing of administration).

The exploratory post-hoc meta-analysis and systematically reviewed literature on the convalescent plasma reported in 2015. The plasma along with immunoglobulin used in the treatment of a variety of infections including severe acute respiratory viral infections. A significant reduction (75%) in mortality was observed by statistically means¹¹. Seven studies on convalescent plasma or intravenous immunoglobulin were reported for SARs¹². One more purposeful study of treatment using convalescent plasma has not been successful to identify adequate high-titer plasma from infected patients for MERS¹³. Kuo-Ming Yeh et al.,

proposed that the use of convalescent plasma along with a serum antibody titer of $>1:640$ for SARS treatment and observed that virus infected patients survived after this treatment¹⁴. The characteristics of antibody and titer values significantly influence the duration of disease. The vaccine and convalescent plasma when administered in new budding viruses that affect immune response of the recipients. The convalescent plasma has been used to manage the safety measures without having the knowledge of viral serotypes or antibody titers.

Clinical use of convalescent plasma in severe COVID-19

In early stages of disease, virus may reduce B lymphocytes and ultimately reduction of IL-6, thus affect the antibody production. It has been observed that there is gradual decrease in Lymphocytes during course of disease, while, an increase in the inflammatory cytokines. Therefore, plasma therapy should be focused on 1) augment immune function in the patients and 2) inhibit the formation of cytokines in the inflammation.

More researches have been focused on pathogenesis of disease and immune response. They will develop better treatment using the convalescent plasma. The use of convalescent plasma gives quick accessibility of treatment whereas vaccines and other treatments for definite purposes are evaluated. The convalescent plasma obtained from donor who is a person recovered from COVID-19. The plasma may be mainly capable when it is used for the prophylaxis or administered to patient for the short duration after onset of disease's symptom marked by 14 days.

The protection against virus may persist from the weeks to months^{8,15}. It has been reported that there are more than 1.6 million cases observed while, more than 300,000 COVID-19 patients recovered, who are dependent on available source as convalescent plasma till date. There is no specified dose of convalescent plasma (CP) in its transfusion. The CP administration between 200 and 500 mL in single or double doses observed in different studies of infectious diseases with the corona viruses (Table 1). More recently, the medical advice is to manage 3 mL/kg per dose during two days¹⁶. This approach makes easy the distribution of plasma units (250 mL per unit) and gives a standard option delivery to the patient in the favour of public health.

Table 1 Convalescent plasma in patients with respiratory infection by SARS-Cov-2 SARS-CoV: Severe acute respiratory syndrome coronavirus.

Infectious Agent	Patient Condition Study Design	# Patients	Timing of Administration	Volume Transfused	Antibody Titer	Patient Outcomes	Reference
SARS-CoV-2	Severely ill Case Series	10	16.5 days (median)	200 mL (x1)	>1:640	Improved oxygenation and reduced inflammation and viral load	Duan et al., 2020 [4]
SARS-CoV-2	Severely ill Case Series	5	10–22 days (range)	200 mL (x2)	>1:1000	Body temperature normalized within 3 days in 4/5 patients SOFA score decreased, and PAO ₂ /FIO ₂ increased within 12 days ARDS resolved in 4 patients at 12 days	Shen et al., 2020 [26]
SARS-CoV-2	Severely ill Case Series	4	15.5 days (mean)	200–2400 mL		All 4 patients recovered	Zhang et al., 2020 [27]
SARS-CoV-2	Case Series	6	3 days	200–250 mL (x2)		Reduction of viral load and increase of SARS-CoV-2 IgG and IgM antibodies	Ye et al. (2020) [28]

Currently, pandemic disease has been occurred due to multiplication of SARS-Cov-2 observed in human host and the use of CP appreciably reduces mortality, case of fatality rates¹⁷, and some extent to mild adverse events (Table 2)¹⁸⁻²².

Table 2 Adverse events to convalescent plasma in epidemics

Viral etiology	Adverse events	Author
SARS-CoV-2	Self-limited facial erythema in 2/10 patients. No major adverse events.	Duan et al. (2020) [4]
SARS-CoV-2	None	Ye et al. (2020) [28]
SARS-CoV-2	None	Anh et al. (2020) [29]
SARS-CoV-2	None	Zhang; et al. (2020) [27]
SARS-CoV-2	None	Shen et al. (2020) [26]

Three case series were observed in China using convalescent plasma for the treatment of COVID-19 (total patients were nineteen (Table 1). Some critically ill patients found in China who have received the attention on the use of convalescent plasma. This results to better oxygenation, reduction in the inflammation or viral load²³⁻²⁵. In COVID-19 study; nine patients were included. They have received the convalescent plasma with a dose of 200 mL using neutralizing antibody titers of ratio >1:640. The median time between when illness starts and convalescent plasma transfusion was observed to 16.5 days. The patient sex habited clinical symptoms with enhancement in the oxy-hemoglobin saturation within 3 days of illness. The lymphocyte counts become increase from $0.65 \times 10^9/L$ to $0.76 \times 10^9/L$. The C-reactive protein (CRP) becomes decrease from 55.98 mg/L to 18.13mg/L. It has been observed that neutralizing antibody became enhanced in all patients. The viral load was undetectable in 7 out of 9 patients suffered from previous viremia.

It has been observed from the various reports that administration of the CRP is safe and has no correlation with main adverse episodes in COVID-19. Therefore, CRP is a high-quality contestant which is evaluated as a therapeutic alternative to control current pandemic due to high acceptability and potential efficacy.

Conclusion

The therapy with convalescent plasma is promising strategy for emerging and re-emerging pathogenic viruses, in that situation when effective antiviral agents or vaccines are not available. The instant use of convalescent plasma gives a promising treatment whereas there is a need of more specific vaccines and other therapeutic alternative. Moreover, the development of plasma, vaccines and other therapeutic alternatives are based on the production of exhaustive data on disease' pathogenesis as well as immunity. It has been

proposed that the information about COVID virus should be added for defending such recipients of convalescent plasma with elevated margin of safety.

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