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Review

Role of Convalescent plasma on the immune system and potential therapy for COVID19

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Abstract

New health trouble terrifies the world by spreading 2019 unique coronavirus or severe acute respiratory syndrome coronavirus-2. Coronavirus is an RNA enveloped virus that is present in humans and wildlife. The spread of the illness occurred in many countries. That's why it is called a pandemic. This virus is transmitted by coughs sneezing, and its incubation period is 3-14 days. This disease's symptoms are mild fever, dry cough, sore throat, shortness of breath, tiredness, and muscle pain. The disease is mild in most people, then it progresses to pneumonia and ultimately results in severe pneumonia or multi-organ dysfunction. The recent pandemic has shown that Coronavirus-2 is involved in the mechanism to evade the typical human responses. It has been observed that the innate immune system activates and can reduce the chances of risk regarding lung inflammation. Currently, the imposed cause and the development process of abnormal conditions due to the coronavirus are ill-defined. There are no therapeutic therapies for Corona Virus Disease 2019's patient; only symptomatic treatment is given as supportive therapy. Convalescent plasma therapy has acted as passive immunization globally for this critical situation in the presence of a coronavirus pandemic. FDA has conceded the approval for applying the convalescent plasma to severe patients of COVID19. CP therapy has some adverse effects like fever, itching or skin rash. This review summarizes the CP as the potential therapy for COVID19 and its role on the patient immune system.

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Introduction

During the last twenty years, two coronavirus epidemics have arisen. SARS-CoV evoked a large-scale epidemic in China, including two dozen countries with around 8000 cases and 800 deaths [1]. CoVs are a large family of positive single-stranded (+ssRNA) RNA viruses [2]. The CoVs have become the major pathogens of emerging respiratory disease manifestations.

It was thought that COVID19 was transmitted from animal to human because of the direct exposure of man to the Huanan Seafood Wholesale Market of Wuhan, China. So, it was settled that the virus could be communicated from human to human, which was the subsequent cause of COVID19 [3]. Therefore, it was suggested that isolation is a better way to stop the spread of this virus. Like other respiratory pathogens, including flu, the communication was considered to ensue over the transfer of respiratory droplets from coughing and sneezing. The main transmission source is a respiratory droplet from the infected person or can also transmit through contact. The SARS-CoV-2 has a more complex spreading ability than SARS-CoV with R0 (Basic reproduction number) ranging from 2.2 to 3.58 [4]. The clinical manifestation of the disease includes fever, dry cough, diarrhea, dyspnea, fatigue, severe pneumonia, and fatigue [5]. It has been observed that the innate immune system activates and can reduce the chances of risk regarding lung inflammation.

Recent studies reveal that SARS- CoV 2 damages the epithelial cell of bronchioles and pneumocytes (type II) within the respiratory system and is attached to the angiotensin-converting enzyme 2 (ACE2) receptor. Coronavirus got access to the host via ACE2 receptor. After joining the host cell, it replicates and assembles, and finally, virion release and symptoms appear in person. The COVID19 has a 2-3% case decease rate, with higher rates in elderly patients and patients with multi-morbidities [6]. Currently, the imposed cause and the development process of abnormal conditions due to coronavirus are ill-defined. There are no therapeutic therapies for COVID19 patients; only supportive therapy is given. During this pandemic, convalescent plasma therapy performs passive immunization for this critical situation. FDA has conceded the approval for applying the convalescent plasma to severe patients of COVID19 [7].

Convalescent plasma therapy

Convalescent plasma treatment is a passive immunization that acquires immediate, short-term defense against a pathogen (virus) by establishing pathogen-specific antibodies for the patients. After manifesting viral infection, the patient's body produces antibodies that resist the virus. These antibodies are collected from recovered patients and are known as convalescent plasma. Plasma therapy involves extracting plasma, fractioned antibodies, immunoglobulins (IGs), and other therapeutic compounds from immunized or convalescent people [8]. Whereas these antibodies from the recovered patients are injected into newly infected patients, these antibodies counterbalance the virus and boost the patient's immunity. For active CP transfusion, donor plasma is verified for antibodies action and virus-neutralizing activity. ELISA IgG is a test that is used to detect neutralizing activity [9]. The diagram below shows how antibodies from convalescent coronavirus patients are effective for newly infected people (Fig. 1). Usually, 1 liter of blood is taken from the healthier patient, and about 250 ml of plasma is transfused to the sick person after checking the antibodies neutralizing activity [10].

Historical background

The fundamental source of CP transfusion was based in 1880, while it was demonstrated that resistance in contradiction of diphtheria depends on existing antibodies in blood [11]. It was perceived that resistant plasma counterbalances the pathogen and contributes to passive immunization. From the Spanish flu to the present pandemic, it is described that CP therapy decreases the fatality rate. CP therapy has no severe adverse effects but has mild to moderate adverse effects. In the case of coronavirus, research reveals that transfusion of convalescent plasma is harmless and not linked with significant antagonistic effects. So, it is an excellent healthful opportunity to treat and regulate the current pandemic situation.

Rise of Convalescent plasma

Convalescent plasma has been practiced for more than 100 years. It became a potential therapeutic therapy for Spanish flu in 1917-1919, severe acute respiratory syndrome (SARS) in 2003, influenza virus H5N1 flu in 2005-2015 and H1N1 flu in 2013-2015. It is also productive for Lassa fever, measles and sin Nombre virus. In 2014 the WHO approved that convalescent plasma was also functional for new ebolavirus patient [12]. Currently, the exact pathogenesis of COVID19 is ill-defined. There are no treatment therapies for COVID19; only symptomatic treatment is given as supportive therapy. Convalescent plasma (CP) therapy is also effective for this critical situation of coronavirus globally [13]. FDA has conceded the approval for applying the convalescent plasma to severe patients of COVID19 [7,14].

Patient and donor eligibility criteria for CP

A donor and patients eligibility criterion [15] is given in the table 1

Plasma composition and acquisition

Plasma donors must go through definitive pre-donation determination to assure complaisance with present supervision regarding plasma donation [16]. Donors from endemic and tropical areas must be prohibited. Apheresis is the approved technique to take a plasma. This process is established on uninterrupted centrifugation of blood from the giver to grant the choosy plasma collection. The technique competence is about 400-800 ml from a particular apheresis contribution. The plasma should be stored in 200-250 ml units, freeze within 24 hours of collection, and be castoff for more transfusion to the newly infected patient [17]. The essential content of convalescent plasma (CP) is volatile and variable. It includes various blood-derived components, e.g., combination of inorganic salts, organic compounds, water, and a wide range of polypeptides. Later on, it is found that plasma also contains albumin, immunoglobulin, coagulation, complement and antithrombotic [18].

Usually, convalescent plasma (CP) cure acts as a passive immunization for the COVID19 patient. Convalescent plasma contains neutralizing antibodies (NAbs) that can

contribute to the suppression of viral infection. Convalescent plasma therapy involves two basic mechanisms during its mode of action after antiviral transfusion: mechanism and immunomodulatory. Both are explained below:

Antiviral mechanism

Convalescent plasma can contribute to Neutralizing antibodies (nabs) that suppress the viral contamination. Neutralizing antibodies are necessary for virus clearance and also act as a protective agent against viral disease. The adequacy of this therapy is linked with the concentration of nabs in the convalescent plasma. These nabs bind to the S1-RBD (spike one receptor binding domain), S1- NTD (spike 1 N-terminal domain) and S2 [19]. After binding to the receptors, it inhibits the virus entry and assembly. Thus, inhibiting the progression of the virus in the host. Other therapeutic effects of CP include:

- Complement activation
- Antibody-dependent cellular cytotoxicity
- Phagocytosis

In the CP, defensive antibodies also present instead of neutralizing antibodies like immunoglobulin G and immunoglobulin M. These non-neutralizing antibodies (Non-Nabs) drag the virus. Still, they do not disturb its ability to reproduce. It also contributes to the improvement of COVID19 [20].

Immunomodulation

CP infusion plays a crucial role in the immune system in COVID19 infection by involving different immune cells (T-cells and B-cells) and mechanisms. The immune system is altered by an agent, either immune system stimulation or suppression known as immunomodulation, and these agents are called immunomodulators. Convalescent plasma therapy act on the immune system and show humoral immune responses [21]. Some are explained below:

F (ab) 2 mechanisms: The recent pandemic has shown that Coronavirus-2 is involved in the mechanism to evade normal human responses. It has been observed that the innate immune system activates and can reduce the chances of risk regarding lung inflammation. A recent report described that patients with coronavirus illustrate positively for anticardiolipin IgA antibodies and anti-beta two glycoprotien1 IgA and IgG antibodies [22]. These reports reveal that CP in COVID19 neutralizes this kind of auto Abs that decreases the probabilities of suffering from thrombotic disease, especially in critical patients [23] Antibody-dependent enhancement (ADE) is a mechanism in which severity of contagion raises in the subsistence of prior poor Nabs that contribute to the reproduction of the virus in macrophages and other immune cells through communication with Fc or complement receptors [24]. These antibodies also prohibit the complement cascade and restrict the production of immune complexes[18]. CP in coronavirus should be directed with attention since ADE may develop as an adverse response in a patient with the vigorous stage of COVID19 [25].

Fc mechanisms: FcRn is a life-threatening controller of IgG half-life. This receptor performs its function by preventing, depriving and clearing IgG by granting antibody flow within the cell for its evacuation [26]. It is described that permeation of this receptor by intravenous immunoglobulin may account as the most likely mechanism to clear autoantibodies in certain autoimmune situations by decreasing their lifetime. So the getting saturation of FcRn grants further immune-modulatory pathway in patient CP [27].

Fc gamma receptors are present in the whole immune system, which inhibit the activity of immune cells and lymphocytes. Their activation by IgG activates the over-regulation of Fc-gamma RIIB linked with inhibitory effects. It is reported in B cells where over-regulation of Fc-gamma RIIB has been linked with management effectiveness for acute refusal afterward transplantation. It is also demonstrated that sialylation of these receptors is necessary for the inhibition of immune cells. Convalescent plasma transfusion may help suppress immune responses by Fc gamma receptors, and it is a major consideration in the supervision of COVID19 [28].

Dendritic Cells: In the case of dendritic cells, these are the antigen-presenting cells (APC) and regulators of innate immunity. In vitro studies reveal that the direction of intravenous immunoglobulin may invalidate the evolution of dendritic cells and minimize the production of IL-12. This may lead to the large production of IL-10. Other studies show that IVIg stimulates the synthesis of IL-33 that develops IL-4 generating basophils. IVIg also speeds up the invention of IL-4 and IL-13 corresponding to IL-33 [29].

CP infusion in the convalescent patients in the presence of coronavirus may increase the anti-inflammatory characteristics of dendritic cells, which is critical in exaggerated inflammatory stimuli in coronavirus patients [30].

T cells: Even though the capacity of stimulating Th2 by IL-33 within the dendritic cells. It is demonstrated that IVIG varies the equilibrium among CD4+ and CD8+ T cells. In addition to it also speed up the proliferation and continuance of Tregs. It is also reported that CP therapy decreases the antigenic presentation of T-cells by suppression and prohibition of dendritic cells. This process is autonomous [31]. Different reports also described that decreased stimulation of T-cells was autonomous of IgG sialylation, monocytes or B- cell. It is described that IVIG decreases the stimulation of CD8+ t cells and T-cell receptor blockade, leading to diminished communication among effectors and target cells. The administration of IVIG also synchronizes cytotoxicity.

Different studies show that IVIG decreases Th17 cells' propagation and less synthesis of IL-17A, IL-17F, IL-21 and CCL-20 [32]. However, intravenous immunoglobulin materializes to suppress the Th17/Treg ratio linked with gestation loss. It is possible that convalescent plasma also plays a parallel role in the case of COVID19 [18].

B-cells are censorious in adaptive immunity as they produce antibodies and cytokines. B-cells' propagation and continuance are arbitrated by the B-cell activating factors (BAFF). In a study, it is reported that CP contains Nabs and BAFF [20]. This could demonstrate the decreased proliferation and the high apoptosis rates of B-cells. In dendritic cells (DCs), downregulation of certain molecules is due to the transfusion of IVIG. This is similar to B cells that reveal depletion in antigen-presenting activity after IgG internalization. This can

happen with the decreased IL-2 synthesis by T cells. These processes contribute to immunosuppression of inflammatory response in the case of COVID19 just after the CP transfusion.

Other Immune cells: Another immune cell dominant immunological influence that is suspicious and linked with the inflammatory response and lung damage in coronavirus infection is the stimulation of macrophages. It has been proposed that the activation of macrophages characterizes patients with COVID19 as a syndrome-like disease linked to innate immune cell relocation to lung tissues. The prohibition of immunological pathways contributes to the increased cytokines production and avert pulmonary damage. Different reports describe an over-regulation of chemokines for immune cells (innate) in the case of COVID19 infection [18]. It is reported that macrophages served with intravenous immunoglobulin express more synthesis of IL-10 along with less IL-12. This indicates the up-gradation of anti-inflammatory macrophages [33]. In the case of COVID19, convalescent plasma transfusion in the initial phase of infection prohibits innate immune cells transfer and evade lung damage.

Limitations of convalescent plasma

When plasma from the healthier patient of COVID19 is infused into the coronavirus's newly infected patient, this transfusion is usually safe. Still, it can cause minor, moderate and severe adverse effects. Some adverse effects are explained below:

Minor reactions

Usually, no adverse effects are noted when CP is transfused. But occasionally, minor symptoms are detected like fever, itching or skin rash. If there is too immediate transfusion, more critical symptoms appear. Hyperpyrexia just after the transfusion is present. Consistently inflammation of veins (phlebitis) and generalized jaundice (hyperbilirubinemia) is noted after the CP infusion [34,35].

Moderate to severe transfusion related effects

- The patient body may react with serum components, e.g. serum cytokines
- Anaphylaxis
- Another infectious particle is transmitted to the patient
- Transfusion associated circulatory overload (TACO) in patients with heart and breathing diseases, progressive age and kidney deficiency.
- Antibody dependent enhancement (ADE) of the infection is a theoretical apprehension of SARS-CoV-2. ADE can exist in many viral diseases in the presence of definite antibodies [15,36].

Conclusion

SARS-CoV-2 appears frequently and unexpectedly, rapidly spread and cause severe infectious diseases; they develop a nonstop danger to human's health. It is settled that the virus can be communicated from human to human, which is the subsequent cause of the spread of COVID19. Therefore, it was suggested that isolation is the better way to stop the spread of this virus. Viral pathogenicity, the body's inflammatory response, also plays a vital role in the case of SARS-induced lung damage. Therefore, in cases of CoV pneumonia, the regulation of cytokine development and inflammatory response is significant because they are accountable for the gathering of cells and fluids. This approach is complex because we have not yet visibly established an immune response that can be precisely repressed without sacrificing favorable host protection. It has been observed that the innate immune system activates and can shrink the chances of risk regarding lung swelling. During this pandemic, convalescent plasma (CP) therapy acts as passive immunization for this critical situation of this coronavirus outbreak globally. Until now, there is no treatment for coronavirus infection is available. However, effective antiviral therapy or vaccination is under evaluation and development.

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Table1: Patient and donor eligibility criteria for CP

Donor eligibility	**Patient eligibility**
Lab tests, e.g. RT-PCR document SARS-Cov-2 infection	Documented confirmed COVID19 infection by RT-PCR
Gross settlement of signs at least 14 days before donation	• severe symptoms are present (dyspnea, oxygen saturation < 93%, respiratory rate >30 per minute • Life-threatening signs are present (lung failure, septic shock and multiple organ failure)
Negative test result for SARS-CoV-2	Transfusion, usually at 7-14th day of infection, is recommended
The female donor should not be pregnant or have been tested as negative for HLA Ab to refuse TRALI	Oxygen saturation level <90% while transfusing 5L/minute and more oxygen provision is needed by nasal canula
Well-distinct SARS CoV 2 NAbs titer	If Fast evolution of illness and poor prognostic parameters are present
The blood group should be matched with a recipient	Mechanical ventilation is required
Indirect comb test should be negative	Screening for IgA deficiency is negative

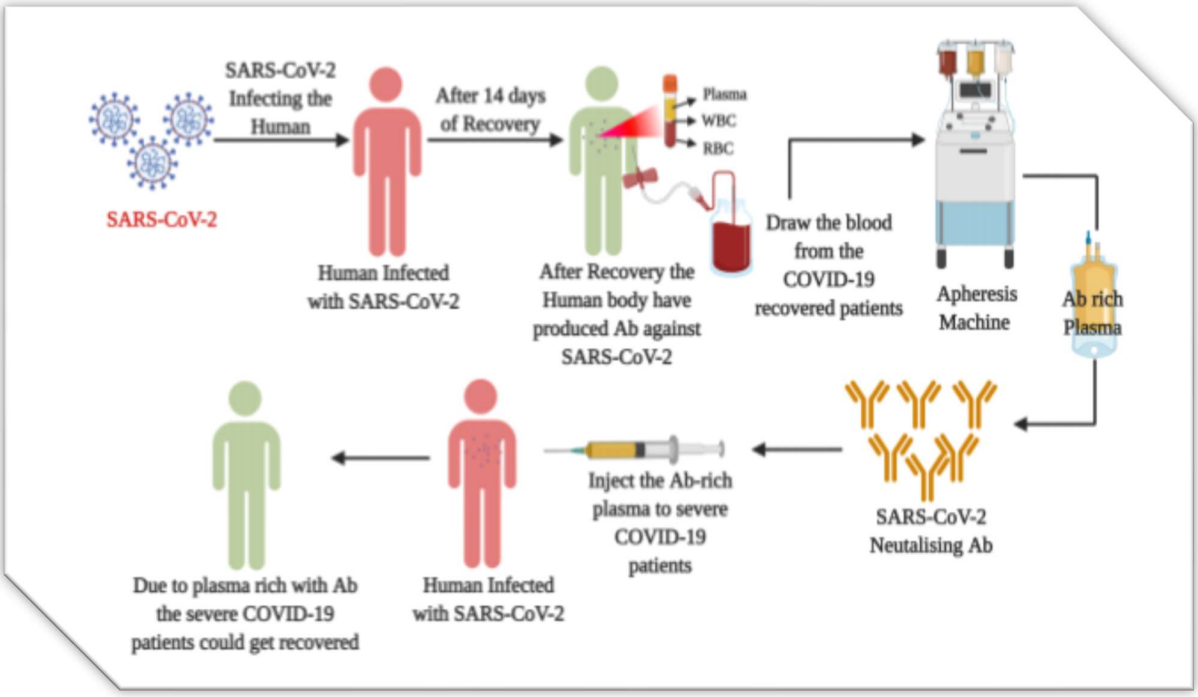

Fig 1. Schematic mechanism of convalescent plasma therapy for Covid- 19