Literature Review

Convalescent Plasma Therapy in COVID-19 Patients with Acute Respiratory Distress Syndrome (ARDS)

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Abstract

COVID-19 is caused by SARS-CoV-1, an RNA virus of the betacoronavirus genus, making it the seventh coronavirus infecting humans. Because particular therapies are still in the research stage, no confirmed treatment for this illness has been agreed upon by the World Health Organization (WHO) or other clinical institutes. The reason is that there are many different potential remedies. Antiviral treatments like favipiravir, oseltamivir, and remdesivir have been investigated and tested. On the other hand, the outcomes of the replies of patients who were given these medications are still quite inconsistent. Furthermore, the COVID-19 mortality rate has remained at a level of less than 5.21 percent of cases that have been documented. Patients suffering from COVID-19 may be treated with convalescent plasma, a therapeutic option that utilizes a mix of neutralizing antibodies and other immunological components. Activation of body-dependent cellular cytotoxicity (ADCC) and phagocytic activity against COVID-19 will occur due to this immunological component. This medication also has the potential to reduce the systemic inflammatory response brought on by COVID-19. Clinical improvement was different after 28 days when convalescent plasma was used as a treatment for patients with severe COVID-19 symptoms and emergency conditions compared to patients treated with conventional therapy alone. However, it is not very significant.

Keywords: ARDS, COVID-19, Convalence Plasma Therapy

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INTRODUCTION

In 2019, the Wuhan Province in China was first notified of the sickness known as COVID-19 (coronavirus disease 2019). It soon spread around the planet, and as of the 20th of April 2020, 2.4 million individuals worldwide had been impacted by it. As a direct result of this, the WHO classified it as a pandemic.[1] COVID-19 was infected with SARS-CoV-2, which stands for severe acute respiratory syndrome coronavirus-2. This virus is a species that is a part of the betacoronavirus genus that causes the severe acute respiratory syndrome. This virus is the seventh specimen of a coronavirus that has been identified as being able to infect humans.[2]

Recently, effective therapy for the illness has not yet been developed by WHO or any other clinical institutions have developed one. The research phase of the illness is still in progress since the disease is still in its early stages.[3] Antiviral medications, such as favipiravir, oseltamivir, and remdesivir, have been used in conjunction with one another to treat this condition. However, unfortunately, the medication response was unpredictable. Hence, COVID-19 is still responsible for the deaths of 5.21 percent of all patients.[4]

The use of convalescent plasma (CP) as an antiviral model is one of the neutralizing antibody-containing antiviral models. The therapeutic effects of COVID-19 are thought to arise from three distinct immunological pathways: phagocytosis, complement activation, and antibody-dependent cellular cytotoxicity (ADCC). The therapeutic action against COVID-19 is believed to be mediated via these immunological mechanisms. Defensins, pentraxins, and anti-inflammatory cytokines are thought to reduce severe inflammatory response syndrome (SIRS). SIRS. is the underlying pathophysiology of acute respiratory distress syndrome (ARDS) and

death.[5] The CP treatment was revealed to be effective in treating a variety of viral conditions, for instance Middle East respiratory syndrome (MERS) and Ebola infection, according to the findings of several studies.[6]

In treating COVID-19, CP is beneficial only when used with other therapies. The reduction of viral load, improvement in cytokine response, and reducing mortality are the goals of convalescent plasma treatment. In addition, the CP treatment transfers antibodies from patients who have been successfully in good health caused by a specific agent to patients whom that agent also afflicts. These forms of passive immunity may assist patients in combating their sickness and slowing the rate at which it progresses.[7]

Because it includes antibodies with certain receptor domains, CP attained from COVID-19 patients who have recovered is thought, according to the findings of some research, to have the potential to possess antiviral characteristics.[8] When implementing CP, some elements must be considered, although their exact nature is still unclear. Considerations include the severity of patients who would benefit from CP, the availability of plasma donors, the timing of CP's delivery, and the severity of patients who would not benefit from CP.

The Treatment of CP was reported to generate good consequences in a limited sample of patients suffering from severe COVID-19 symptoms, according to the research conducted by Shen et al. (2020).[9] To determine whether or not this treatment was effective, a task that had become extremely challenging in pandemic conditions before the vaccine's introduction, the research needed to involve a greater number of patients and should have been designed more effectively.[10] This article discusses the studies conducted on CP therapy for ARDS patients carrying the COVID-19 virus.

ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

The early onset of pulmonary edema, bilateral pulmonary infiltration, and poor respiratory system compliance are the characteristics of ARDS, which is not caused by a cardiac etiology. ARDS is an abbreviation for acute respiratory distress syndrome.[11] As this description describes it, ARDS is a severe kind of diffuse lung damage that occurs when all of the following criteria are satisfied:[12]

a. A new clinical cause or a worsening of respiratory symptoms within a week of the onset;
b. A bilateral X-ray opacity in the chest that has nothing to do with fluid accumulation, lung collapse, or nodules;
c. Recognizing breathing failure caused by fluid overload or cardiovascular collapse; and
d. Hypoxemia is defined as having a PaO_2/FiO_2 ratio that falls into one of these three categories:
    1. Low ($200<PaO_2/FiO_2<300$ mmHg)
    2. Moderate ($100<PaO_2/FiO_2\leq200$ mmHg)
    3. Severe ($PaO_2/FiO_2\leq100$ mmHg)

A feature of the heterogeneous illness known as ARDS is an intensification in the pulmonary capillary endothelial cell permeability.[13]

ARDS used to be commonly known as non-cardiogenic pulmonary edema. ARDS causes the alveoli to become filled with fluid exudate, increasing the permeability of the alveolar-capillary barrier so that fluid-containing proteins can enter the alveoli. This is in contrast to congestive heart failure, which results in pulmonary edema due to elevated left heart pressure-related hydrostatic pressure.[14]

Congestive heart failure leads to pulmonary edema. Fluid in the alveoli may lead to hypoxemia, shunting from right to left, and a reduction in respiratory compliance. Although arterial PCO_2 levels are usually within normal limits, there is an increase in ventilation dead space, which is reflected in increased minute ventilation. A common complication of ARDS is pulmonary hypertension, which may trigger a variety of factors, including the accumulation of fibrin inside blood vessels and the narrowing of blood vessels in response to low oxygen levels. This condition may be addressed using positive pressure ventilation and vessel compression techniques.[14]

The pathological phases of ARDS are often described using a standard format that includes three

stages that follow one another and overlap. During the initial stage of lung injury, known as the exudative phase, the pathological abnormalities seen were referred to as diffuse alveolar destruction. The alveolar gap is filled with an edematous fluid containing protein, and hyaline membranes line the alveolar walls. In addition, the epithelium is disturbed, and neutrophils enter the interstitial space and alveoli, which results in the accumulation of macrophages and, in some cases, bleeding. This stage, which lasts for between five and seven days, is followed, in some individuals, by the proliferative phase.[14]

Fibrosis and the hyaline membrane organization have occurred at this point in the process. Decreased neutrophil count and the severity of pulmonary edema are diagnostic of the proliferative phase, which is marked by pulmonary capillary occlusion, interstitial collagen buildup, and alveolar collagen deposition. The proliferative stage is characterized by pulmonary capillary obliteration and interstitial and alveolar collagen accumulation. The fibrotic phase may be seen on radiographs of patients with chronic ARDS (which has lasted for more than two weeks) after this phase has passed.[14]

At first, it was thought that either direct or indirect lung damage caused an excess production of inflammatory mediators in the pulmonary microcirculation. As inflammatory mediators like neutrophils activate and migrate across the surfaces of the alveolar epithelium and vascular endothelium, they produce proteases, cytokines, and reactive oxygen species (ROS). Pathological vascular permeability, a breach in the alveolar epithelial cell barrier, and necrosis of type I and type II alveolar cells are the results of the migration and release of these mediators. The result is a fluid buildup in the lungs, known as pulmonary edema. The reduction in lung compliance and increased gas exchange difficulty were caused by hyaline membrane development and surfactant depletion. Collagen deposition, fibrosis, and illness progression are also the outcomes of fibroblast infiltration.[14]

During the recovery phase, some processes coincide. Anti-inflammatory cytokines slow down activated neutrophils. Proliferation and differentiation of type II alveolar cells into type I alveolar cells strengthen the epithelial lining of the alveoli, allowing for the drainage of fluid from the alveoli into the microcirculation and pulmonary lymphatic system through an osmotic gradient. Alveolar cells and macrophages collaborate throughout the healing process to clear the alveoli of protein debris.[14]

DEFINITION THERAPY OF CONVALESCENT PLASMA

Patients who have overcome an illness and gained humoral immunity are used in convalescent plasma treatment. Humoral immunity is a kind of tolerance to the bacteria that cause sickness. In most cases, donors' plasma is obtained after completely recovered, making it suitable for use in the convalescent period. Water, proteins, and inorganic salts comprise the convalescent plasma's bulk. Antibodies and immunoglobulins directed against an infectious pathogen may inhibit viral replication and lower viremia in those who are already infected. These antibodies may kill viruses by doing two things: blocking the attachment of viruses to endosomes and halting the discharge of virions from infected cells. Third, preventing viral protein cleavage through extracellular proteolysis, and fourth, preventing viral protein entrance into human cells.[15]

SEVERE CATEGORY CLINICAL SYMPTOMS IN COVID-19 PATIENTS

Dyspnea distinct as a respiratory rate above 30 breaths per minute, a blood oxygen saturation below 93%, a PaO_2:FiO_2 portion of 300 mmHg or less, and a percentage of air infiltration into the lungs more than 50% is all indicative of severe COVID-19 symptoms.[16]

CYTOKINE STORM MECHANISM IN COVID-19

Similar in appearance to SARS-CoV is SARS-CoV-2, a dissimilar betacoronavirus. In order to infect cells, both viruses rely on a protein known as angiotensin-converting enzyme 2 (ACE2). ACE2 receptors are another name for these receptors. These receptors may be found in cardiovascular

tissue and in hematological cells such as monocytes and macrophages. Lymphopenia is an essential component of a COVID-19 infection and is linked to the clinical severity of the condition. MERS-CoV uses dipeptide peptidase 4 to infect monocytes and T cells, while SARS-CoV uses dipeptide peptidase 4 to infect primary monocytes and dendritic cells. The possibility of dendritic cell infection by SARS-CoV-2 has also been targeted. It is possible that apoptosis of T cells, which happens when dendritic cells do not work right, also contributes to COVID-19's immunopathology.[17]

In SARS and MERS infections, cytokine release syndrome is a leading cause of illness (CRS). After contracting MERS, a person's blood will show elevated levels of cytokines such as interleukin-6 (IL-6) and others involved in inflammation. Clinical symptoms, such as ARDS, respiratory failure, and CAS, are often reported in COVID-19 and are linked to increased serum IL-6. When IL-6 is present, the inflammatory protein C-reactive protein (CRP) rises, serving as a biomarker for severe betacoronavirus infection.[18]

As a result of infection with the betacoronavirus, innate immune cells such as monocytes, macrophages, and dendritic cells mature and release inflammatory cytokines like interleukin 6. (IL-6). Both cis signaling and trans-signaling are considered to be the primary traditional ways via which, In the context of cis communication, IL-6 may serve as a messenger. At a complex containing gp130, IL-6 binds to the membrane-bound IL-6 receptor (MIL-GR); subsequent signals are translated by STAT3 and JAKS (Janus kinases) (signal transducer and activator of transcription 3). While gp130 is widely distributed, mlL-6R is exclusively found on immune cells. CRS is induced by the activation of cis signaling, which has pleiotropic effects, meaning it may influence both the adaptive and innate immune systems (B and T cells, neutrophils, macrophages, and natural killer (NK) cells).[19]

To activate trans-signaling, circulating IL-6 binds to the soluble IL-GR (SIL-BR), creating a complex with 9p130 dimer potential on the cell surface. Signaling involving IL-6, SIL-6R, JAK, and STAT3 activates endothelial cells, although these cells do not express mlL-BR. Along with IL-8 and IL-6, the production of monocyte chemoattractant protein-1 (MCP-1) and vascular endothelial growth factor (VEGF) also occurs as a consequence of this process. On the other hand, the amount of E-cadherin produced by endothelial cells is lower. In ARDS, VEGF plays an integral part in the pathophysiology of vascular permeability and leaky hypo physiology, in addition to pulmonary dysfunction, by lowering E-cadherin expression, which can be shown in Figure 1.[20]

SARS-CoV-2 infection-related acute respiratory distress syndrome (ARDS) was fatally established in the clinical data obtained from COVID-19 patients with severe symptoms. This condition was commonly associated with organ failure and lung alveolar damage. Additional investigation found that the condition was associated with cytokine storm, commonly referred to as CRS, which is an increase in the synthesis of cytokines in the body. Cytokines are a class of tiny proteins that have an essential function in the body's immunological response, both to infections and inflammation. However, excessive cytokine synthesis harms tissue as a counterweight to overactive immune responses.[21]

According to several research findings, the first phases of infection are characterized by a pause in the release of cytokines and chemokines. After this, a limited amount of interferons (IFNs) are created, which is subsequently tracked by a rapid rise in the proinflammatory of immune cell-attracting cytokines and chemokines. Furthermore, the process leads to an excessive infiltration of lung tissue, which in turn causes damage to the lung tissue. Additionally, infected cells produce more chemokines to entice inflammatory mononuclear macrophages after activation of other signals (IMM). That leads to an abnormal increase in proinflammatory cytokine production, which only worsens things. IFN-γ and other proinflammatory cytokines drive T cells to commit suicide during the latter stages of the infection, which prevents the virus from being eliminated.[22]

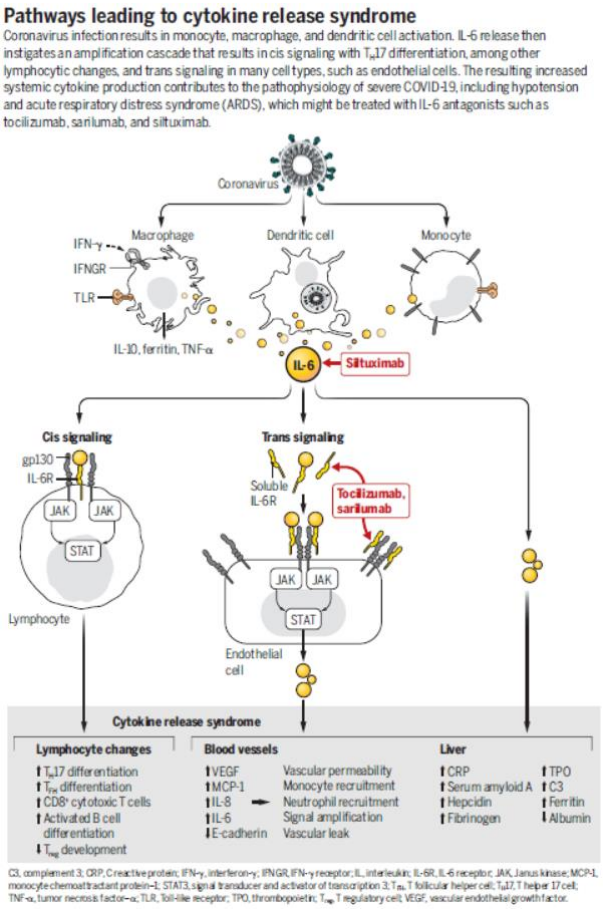

Figure 1. CRS lines on COVID-19[20]

IFN-α and IFN-β, both subtypes of IFN-γ, act as an initial line of guard against viral infections when activated through the JAK-STAT pathway. An infection caused by a coronavirus may induce a strong but delayed response from the immune system's IFNs, which might foster the development of cytokine storms under certain conditions.[23]

One of the proteins produced by the coronavirus, known as the NSP1 protein (non-structural protein 1), inhibits the phosphorylation of STAT1, which stops the production of IFNs in the host cell. STAT1 is the transcription factor responsible for the expression of interferon stimulated genes (ISGs), which are responsible for producing antiviral defensive mechanisms. The composition of M (membrane) and N (nucleocapsid) proteins in coronaviruses allows them to block IFN signaling. One possible approach to getting a target is to disrupt the activity of IRF3, a transcription factor for the IFN gene.[24]

Additionally, irregularities or inhibition of induction IFN brought on by the aging host, and TRAF3's proteolytic degradation may contribute to the pathophysiology of the disease by creating an imbalance between proinflammatory cytokines and responses in aged individuals. These two elements may work together to cause an imbalance in proinflammatory cytokines and reactions in the aged.[24] It is solely for research purposes that leukocyte and cytokine counts are measured in patients with COVID-19.

RISKS OF CONVALESCENT PLASMA THERAPY

Similar to SARS, studies have revealed that viremia peaks during the first week after infection. It is common for patients to develop an immunological response, which may lead to a potentially catastrophic cytokine storm during the second week following the beginning of symptoms. Given that passive immunity via the administration of pathogen-specific antibodies is the basis for CP treatment, there are hidden dangers associated with CP infusion, such as the exacerbation of hyperimmune reactions.[25]

However, one research found that CP treatment could lessen serum cytokine responses depending on when the medication was administered. This conclusion has been corroborated by studies of SARS, lending more credence to the idea that treating CP at an earlier stage is preferable. Therefore, it is crucial to time the administration of CP in COVID-19.[25]

In reality, the titer of the SARS-CoV2 neutralizing antibody (NAT) determines the therapeutic efficacy of CP on COVID-19. A study of people with SARS shows that levels of a certain IgG started to rise in the third week after symptoms began and peaked twelve weeks later. Additional studies have shown that CP with a NAT of 1:160 may reduce mortality from influenza. The CP isolated from patients who are improving 12 weeks after symptom starts with NAT of at least 1:160 is thought to be more potent. The capacity to get CP is limited, however, by factors such as the donor's health, the availability of suitable donors, and the presence of informed permission.[25]

All risks associated with transfusions must be taken into account. Transfusion of CP may lead to various unwanted side effects, including fever, anaphylaxis, chills, hemolysis, circulatory overload, and transfusion-associated acute lung damage. When considering the safety of a CP transfusion, it is essential to remember the risk of transmitting diseases like hepatitis and HIV.[25]

CONVALESCENT PLASMA THERAPY PROCEDURES

The first step was identifying a suitable CP donor from among the COVID-19 patients who had been declared clinically hostile with the PCR test twice in more than a day, indicating that they had fully recovered and been released from the hospital at least two weeks before. Plasmapheresis is used to remove plasma from a patient throughout the healing process. Fresh frozen plasma (FFP) is used to create various plasma products.[26]

Titer IgG antibodies are measured and reported with S-RBD (Spike-Receptor Binding Protein). Only plasma units with IgG titers of at least 1:640 should be used to ensure therapeutic potential, as the Food and Drug Administration (FDA) recommendation.[26]

The CP transfusion dosage for COVID-19 is around 4–13 milliliters per kilogram of the recipient's body weight. It is of the utmost importance that the ABO, the patient blood type, and the ABO type of the dispersed plasma be the same. A convalescent plasma transfusion begins with 10 milliliters given over the first 15 minutes, and the rate of administration is subsequently raised to 100 milliliters per hour while the patient is carefully monitored. When determining an appropriate transfusion rate, it is possible to consider a patient's risk of fluid overload and tolerance.[9]

THE EFFECT MECHANISM OF CONVALESCENT PLASMA THERAPY

Antivirus mechanism

Regarding getting rid of viruses, NAbs are crucial since they can defend against viral infections. Viruses and bacteria may be fought off with the help of passive immunity, which is powered by antibodies. Remember that the plasma concentration of NAbs from the recovered donor influences how well the treatment works. NAbs have been shown to bind to the S1RBD, S1-N, and S2 terminal domains of the SARS and MERS viruses. The entry of these viral proteins is thereby inhibited, and viral multiplication is stymied. Activation of the complement system, antibody-dependent cellular cytotoxicity, and phagocytosis are all antibody-mediated processes that may improve the therapeutic efficiency of CP.[27]

A single SARS-CoV-specific antibody, CA3022, was shown by Tian et al. to bind to the COVID-19 RBD and not compete with ACE-2 for this binding. These results were proved by the SARS-CoV-specific antibody bound to the COVID-19 RBD. Significant differences may be found between COVID-19 RBD and SARS-CoV at the C-terminus residue. Even though COVID-19 cannot form a binding with the ACE-2 receptor, this variation affects the cross-reactivity of NAbs.[27]

Plasma includes NAbs as well as the protective antibodies IgG and IgM. Improved prevention and treatment might be possible using non-NAb antibodies that bind to the virus. IgG antibodies against N are initially seen after the first four days of symptoms in a person with SARS-CoV infection, and seroconversion occurs 14 days after infection. Up to 89% of cured SARS patients showed detectable levels of specific IgG and nabbed two years after infection. IgM levels peaked nine days after sickness onset, while IgG production took over after two weeks.[27]

Donors who had previously been infected with COVID-19 but had recovered showed SARS-CoV-2-specific antibody titers ranging from 1,800 to 16,200 and NAbs titers from 80 to 480, as reported by Shen et al. Infections were reduced in the CP group that had been donated and administered on the same day. After receiving a CP transfusion, the recipient's IgG and IgM titers rose steadily. Defending against viral infection is a crucial function of NAbs. In another study, researchers analyzed the temporal dynamics of the emergence of NAbs that specifically target

SARS-CoV-2. In SARS-CoV2 infect patients, NAbs titers were low before day 10, rose with a peak 10–15 days following the beginning of the disease, and remained constant after that in all patients.[27]

Immunomodulating mechanism

According to F(ab')2's action method, activated complement contributes significantly to inflammation throughout the body, neutrophils moving to the pulmonary, and tissue damage. Some antibodies block complement cascades (C3a and C5a), lending credence to this theory. Additional research has shown that plasma IgG inhibits the effects of cytokines, including IL-1ß and TNF-α that can be seen in Figure 2.[27]

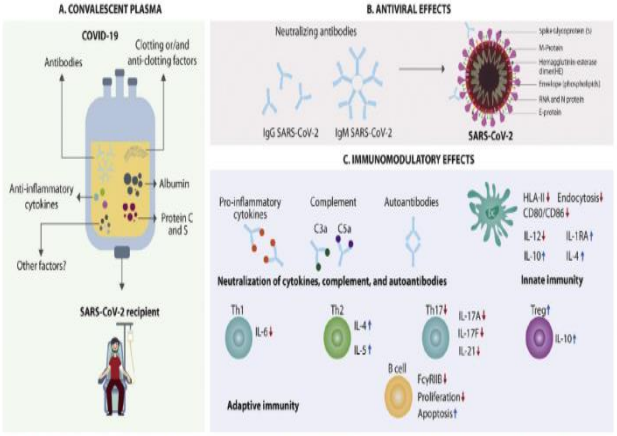

Fig. 1. Schematic representation of convalescent plasma components and its mechanisms of action. A. Main convalescent plasma components. B. Antiviral effects of NAbs. IgG and IgM are the main isotypes, although IgA may be also important, particularly in mucosal viral infections. Other non-NAbs may exert a protective effect. The humoral immune response is mainly directed towards spike (S) protein. C. Anti-inflammatory effects of CP include network of autoantibodies and control of an overactive immune system (i.e., cytokine storm, Th1/Th17 ratio, complement activation and regulation of a hypercoagulable state) (see text for details). N: Nucleoprotein; M: Membrane; E: Envelope.

Figure 2. Convalescent plasma effect mechanism[27]

The interaction of NAbs with Fc and complement receptors is the mechanism behind antibody-dependent enhancement (ADE), whereby infection severity is increased despite the relatively low levels of NAbs in macrophages and other cells that are beneficial for virus reproduction. Given the potential for ADE to have a detrimental impact affecting individuals with latent infections, it is essential to keep this occurrence in mind while treating COVID-19 patients by promptly administering convalescent plasma.[27]

FcRn performs part-time regulation of IgG function. Antibody trafficking within the cell and subsequent excretion on the cell's rear surface are made possible by these receptors by blocking the breakdown and removal of IgG through a pinocytosis process. When FcRn is fully saturated, immunomodulatory pathways may be activated, which might benefit patients receiving convalescent plasma.[27]

Fc-ɣ receptors are found on almost every kind of immune cell. These receptors are essential for regulating and suppressing lymphocyte and other immune cell activities. When IgG activates the Fc receptor, the immune system is inhibited as a consequence of enhanced regulation of FcRIIB.[27]

IgG plays a critical role in reducing inflammation by inhibiting dendritic cell maturation and activating B-catenin. Research suggests that IgG may boost production of Th2 cytokines including IL-4 and IL-10 while reducing the number of Th1 cells, as well as FN- γ and TNF-α synthesis and TNF-α levels. By suppressing dendritic cells, which in turn stops signals to B cells, IgG limits the expansion of Th17 cells and reduces antigen presentation on T cells.[27]

Efficacy of Convalescent Plasma Therapy in COVID-19 Patients with ARDS

Individuals diagnosed with ARDS who also met the criteria for severe pneumonia with rapid viral load progression, mechanical ventilation, and antiviral and methylprednisolone treatment were included in the COVID-19 case series published by Shen et al. (2020). Patients having a neutralization titer of higher than 40 and an antibody specificity (IgG) titer of greater than 1:1000 (final dilution with ELISA) against SARS-CoV-2 are given convalescent plasma transfusions.[9]

Within three days of receiving plasma transfusion, four out of five patients had normalized body temperatures, and in the 12 days that followed, PaO_2/FiO_2 rose (before 172–276, after 284–366). Antibody titers and neutralization levels improve following a transfusion (80–320 before 40–60 days), and virus loads drop and become negative within 12 days.

Table 1. Analyzing Pre and Post Convalescent Plasma Transfusion Viral Load, Clinical Index, and Laboratory Results[9]

Indicators	Patient				
	1	2	3	4	5
Clinical characteristics					
Body temperature, ℃					
Just before transfusion	38.6	39.0	37.6	38.3	39.0
Day 1 posttransfusion	38.5	36.8	37.7	37.9	39.0
Day 3 posttransfusion	38.1	36.6	37.0	36.6	36.8
Day 7 posttransfusion	37.8	37.2	36.5	37.9	36.8
Day 12 posttransfusion	37.0	36.8	36.6	36.8	37.9
SOFA score[a]					
Just before transfusion	5	10	3	3	2
Day 1 posttransfusion	4	12	4	3	2
Day 3 posttransfusion	6	10	3	2	2
Day 5 posttransfusion	5	11	2	2	2
Day 7 posttransfusion	3	7	2	2	1
Day 12 posttransfusion	2	4	2	1	1
PAO_2/FiO_2[b]					
Just before transfusion	276	209	172	188	205
Day 1 posttransfusion	300	134	184	242	292
Day 3 posttransfusion	220	230	164	233	304
Day 7 posttransfusion	245	206	220	290	230
Day 12 posttransfusion	284	316	342	322	366
Ct value[c] (viral load proxy)					
On admission to hospital	23.0	19.7	18.9	38.0	28.0
Lowest value during hospitalization[d] (highest viral load)	19.2	19.7	18.9	26.6	26.5
Just before transfusion	28.5	22.0	33.0	26.6	35.9
Day 1 posttransfusion	30.0	23.7	38.5	28.0	Negative
Day 3 posttransfusion	34.4	25.0	Negative	Negative	Negative
Day 7 posttransfusion	38.0	32.0	Negative	Negative	Negative
Day 12 posttransfusion	Negative	Negative	Negative	Negative	Negative
Mechanical ventilation					
Onset, days before transfusion	11	2	12	9	2
Removal, days posttransfusion	Intubated	Intubated	2	9	9
ECMO					
Onset, days before transfusion	Not received	1	Not received	Not received	Not received
Removal, days posttransfusion	NA	5	NA	NA	NA
Laboratory findings					
C-reactive protein, mg/L (normal range <8)					
Before transfusion	163.4	242.8	65.0	156.0	173.1
Day 1 posttransfusion	146.2	223.0	108.3	NT	186.8
Day 3 posttransfusion	115.1	75.2	78.7	160.8	233.7
Day 5 posttransfusion	31.3	10.4	74.7	NT	260.4
Day 7 posttransfusion	31.2	13.9	6.2	9.6	5.5
Day 12 posttransfusion	5.3	33.1	NT	5.8	3.2
Procalcitonin, ng/mL (normal range <0.1)					
Before transfusion	1.2	7.3	0.1	0.2	0.2
Day 1 posttransfusion	1.3	19.7	0.1	0.08	0.4
Day 3 posttransfusion	1.6	13.9	0.09	0.07	1.5
Day 5 posttransfusion	0.9	1.8	0.08	NT	0.9
Day 7 posttransfusion	1.1	0.1	0.04	0.04	0.09
Day 12 posttransfusion	0.4	0.2	NT	0.04	0.07
IL-6, pg/mL (normal range 0-7)					
Before transfusion	70.5	438.2	63.9	79.1	87.8
Day 1 posttransfusion	74.9	NT	118.5	39.3	NT
Day 3 posttransfusion	34.5	1045.0	67.0	25.8	797.9
Day 5 posttransfusion	24.1	334.1	590.5	NT	NT
Day 7 posttransfusion	30.8	29.8	174.3	34.0	69.9
Day 12 posttransfusion	6.1	31.8	NT	2.7	54.9
Length of hospital stay, d	Remains hospitalized	Remains hospitalized	53	51	55
Current status as of March 25, 2020	Stable, still receiving mechanical ventilation	Stable, still receiving mechanical ventilation	Discharge home	Discharge home	Discharge home

Note: Ct=cycle threshold; ECMO=extracorporeal membrane oxygenation; NT=not tested.

[a] The SOFA socre is calculated using 6 systems: respiratory, coagulation, hepatic, cardiovascular, central nervous system, and kidney. A socre of 0 is given for normal function through to 4 for most abnormal for each system. The worst values on eacj day are recorded, and the final SIFA socre is the sum of the score of each system.

[b] PAO_2/FiO_2 ratio was defined as the ratio of the partial pressure of arterial oxygen to the percentage of inspired oxygen.

[c] Cycle threshold is the number of polymerase chain reaction cycles required for gone amplification. A higher Ct value is correlated with a lower viral load.

[d] Lowest value (highest viral load) between hospital admission and plasma transfusion.

Four patients with ARDS showed improvement by the 12th day after transfusion, and three patients could discontinue mechanical breathing after the second week of treatment. After 53, 51, and 55 days in the hospital, three of the five patients have been discharged, and 37 days after getting the blood transfusion, both of the remaining patients are doing well. Table 1 shows the variations in parameters before and after a CP transfusion.An experiment was conducted and recorded by Simonovic et al. (2020) in which people with severe pneumonia caused by COVID-19 were randomly allocated to receive either CP or a placebo. Thirty days after the intervention, the patient's clinical state was evaluated using a six-point ordinal scale to determine the study's result.[28]

One hundred and five of the 228 convalescent plasma patients were given a placebo. The median antibody titer for SARS-CoV-2 in recovered individuals is 1:3200. (at now, between 1:800 and 3:1200) A severe study is defined by the presence of hypoxemia. Every patient is followed up with regularly. At day 30, there was no statistically significant difference between the two groups (control and convalescent plasma; odds ratio, 0.83; 95% CI=0.52–1.35; *P*=0.46). Those who were given convalescent plasma had a 10% death rate, whereas those who were given a placebo had an 11% mortality rate. Both groups had the same drawbacks.[28] A comparison of the clinical outcomes of patients treated with convalescent plasma and those treated with a placebo is shown in Figure 3.

A review of the literature by Rajendran et al. Using electronic databases (PubMed, Embase, and Medline), a 2020 study of convalescent plasma reviewed five papers reporting 27 individuals. The amount of recovered plasma utilized in each study had a different dosage. There was a single 200 mL CP dose utilized in a Chinese study, and the antibody titer was more than 1:640, while another Chinese study utilized a dose of 2400 mL in a male patient who was 73 years old. Convalescent plasma was administered to the patient during the sixth and 50th days following the start of symptoms or hospitalization.[29]

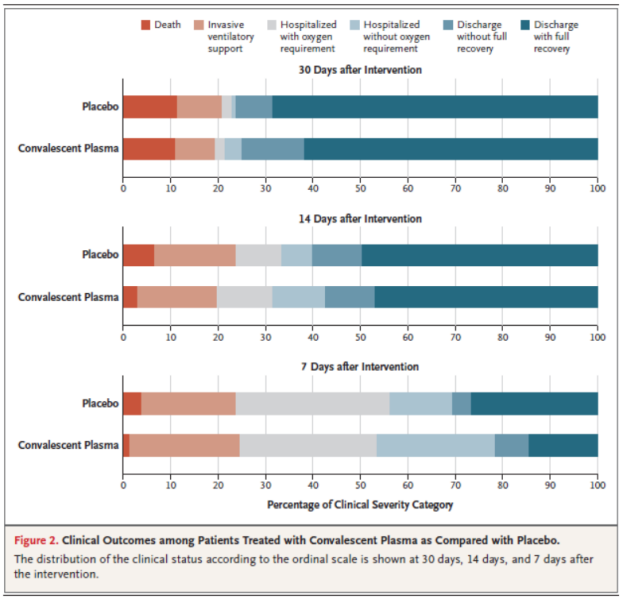

Figure 3. Comparing the Clinical Outcomes of Patients Treated with Convalescent Plasma with a Placebo[28]

Seventeen of the 21 patients receiving convalescent plasma treatment required mechanical ventilation due to the severity of their symptoms. Seventeen ARDS patients were given ECMO therapy. While hospitalization duration data was lacking, hospital discharge times were documented in almost all trials (15 total).[29]

All five investigations showed a considerable and unfavorable decline in viral load between day one and day 30 following plasma injection. In a concise amount of time, almost all patients returned to baseline clinically, with improvements in temperature regulation, absorption of lung lesions, ARDS, and the ability to wean off of mechanical ventilation. After receiving a blood transfusion, the recovery time might range from 1 to 35 days.[29]

CONVALESCENT PLASMA THERAPY IN PREGNANT WOMEN WITH COVID-19

Particular attention should be paid to controlling COVID-19 in pregnant women because of the risk of teratogenic consequences from antiviral drugs and immunosuppression caused by pregnancy. Recovery plasma EBM was studied by Franchini et al (2021) in a clinical setting during pregnancy (see Table 2). Twelve pregnant women were reported as case reports in the research. Preeclampsia affected two women, but six mothers reported feeling OK.[30]

Table 2. Synopsis of Convalescent Plasma Treatment for COVID-19 in Expectant Mothers.[30]

Author, Year [Ref]	Design	Country	Age, y	Gestational Age	Severity of Disease	Comorbidity	Procedures	CP Treatment				Other Medications	Outcome	
								Units Tranfused	NAbT	Days Hospitalization	AR		Maternal	Fetal/Neonatal
Grisolia, 2020 [17]	CR	Italy	29	24 w and 2 d	Mild ARDS	Class I obesity	VD	2	160	+1, +4	None	Ceftriaxone, azithromycin, hydroxychloroquine, methylprednisolone, LMWH	Maternal well-being	Full-term, well neonate with VD
Zhang, 2020 [25]	CR	China	31	35 w and 2d	Severe ARDS	--	CD (35 w), IMV, ECMO	1	NR	+17	None	Lopinavir/ritonavir, ribavirin, imipenem, vancomycin	Maternal survival	Neonatal death due to intrauterine asphyxia
Anderson, 2020 [26]	CR	USA	35	22 w and 2 d	Severe ARDS	Type 2 DM, asthma, class III obesity	Forego delivery (25 w)	1	NR	+1	None	Remdesivir, ceftriaxone, azithromycin, hydroxychloroquine, hydrocortisone, LMWH	Maternal well-being	Normal ongoing pregnancy
Donzelli, 2020 [22]	CR	Italy	34	27 w and 4 d	Severe ARDS	--	IMV, PP, tracheostomy, CD (30 w)	2	NR	+2, +3	None	Clarithromycin, ceftriaxone, betamethasone, LMWH	Maternal well-being	Normal ongoing pregnancy
Jacobson, 2021 [27]	CR	USA	42	26 w	Severe ARDS	--	CD (29 w), IMV, PP, ECMO, tracheostomy	1	NR	+2	None	Remdesivir, dexamethasone, azithromycin, ceftriaxone	Discharged with home oxygen	Neonatal adrenal insufficiency, then good condition
Magallanes-Garza, 2020 [23]	CR	Mexico	33	27 w and 4 d	Severe ARDS	--	VD (39 w), IMV	2	NR	+4, +5	None	Lopinavir/ritonavir, LMWH, azithromycin, ceftaroline, methylprednisolone	Maternal well-being	Neonatal GR
Pelayo, 2020 [24]	CR	USA	35	37 w and 2 d	Severe ARDS, PE	Asthma, class III obesity, ileal carcinoma, HCV	IMV, CD (36 w)	1	NR	NR	NR	Methylprednisolone, remdesivir, heparin, vancomycin, ceftriaxone	Discharged to acute inpatient rehabilitation unit	Neonate intubation due to hypoxia, then positive outcome
Jafari, 2020 [18]	CR	Iran	26	36 w and 1 d	Moderate ARDS	--	CD (36 w)	NR	NR	NR	NR	Favipiravir, meropenem, azithromycin, hydroxychloroquine	Maternal well-being	Neonate well
Easterlin, 2020 [20]	CR	USA	22	23 w and 6 d	Severe ARDS	Tuberous sclerosis, nephrectomy, leiomyosarcoma	CD (25 w), PP, tracheostomy	NR	NR	NR	NR	Azithromycin, hydroxychloroquine, remdesivir, tocilizumab, LMWH	Pre-eclampsia, postdelivery critically ill condition	Critically ill preterm neonate with severe respiratory failure
Soleimani, 2020 [16]	CR	Iran	30	21 w and 2 d	Severe ARDS	Class II obesity	--	2	NR	+10, +11	NR	Lopinavir/ritonavir, LMWH, azithromycin, methylprednisolone	Maternal well-being	Normal ongoing pregnancy
Lam, 2020 [19]	CR	USA	30	23 w and 1 d	Severe ARDS	Type 2 DM, hypertension, pre-eclampsia	CD (25 w)	NR	NR	+1	NR	Remdesivir, dexamethasone, azithromycin, ceftriaxone	Pre-eclampsia, discharged on day +28	Neonate intubation due to hypoxia, stable condition
Yaqoub, 2020 [21]	CR	Qatar	33	32 w	Severe ARDS	Asthma, gestational diabetes	CD (32 w(, IMV, ECMO	2	NR	+5	NR	Lopinavir/ritonavir, tocilizumab, hydroxychloroquine, azithromycin, ceftriaxone	Clinical improvement, discharged on day +40	Neonate intubation due to hypoxia, then positive outcome

Note: AR=adverse reactions to CP infusion; ARDS=acute respiratory distress syndrome; CD=Cesarean delivery; CR=case report; d=days; DM=diabetes mellitus; ECMO=extracorporeal membrane oxygenation; GR=growth restriction; IMV=invasive mechanical ventilation; LMWH=low-molecular weight heparin; NAbT=neutralizing antibody titer; NR=not reported; PE=pulmonary embolism; PP=prone positioning; VD=vaginal delivery; y=years; w=weeks.

The future outlook for each mom is laid forth in detail. Survival, clinical progress, oxygenation, and recuperation are all parts of a full prognosis. Two infants were described as healthy, four as experiencing mild sickness, two as being in severe condition, one as having passed away, and three as not being noticed. All three pregnancies were healthy, and the baby is expected to do well.[30]

Eleven women and one mother experienced severe ARDS before beginning CP treatment. No co-morbid conditions were reported in any of the five patients. In our sample, five mothers had several chronic diseases, whereas the other two had simply obesity as a chronic illness. In CP treatment, gestational age may be anywhere from 21 weeks and 36 weeks and two days. Steroids (n=8), heparin (n=7), hydroxychloroquine (n=5), human monoclonal antibodies (tocilizumab, n=2), and antivirals from the analog family of nucleotides (redeliver, n=5) were all used throughout the patients' hospital stays. Three of these nine patients had tracheostomies, and three had extracorporeal membrane oxygenation/ECMO. Six patients required invasive mechanical ventilation.[30]

SARS-CoV-2 seems to exacerbate clinical symptoms in both mothers and their babies. Premature delivery, maternal death, fetal death in utero, and newborn mortality are expected outcomes of pregnancies interrupted by SAR-COV-2. There was a 5% maternal and 6% infant mortality rate, respectively. Although passive immunotherapy with CP transfusion is often deemed appropriate in patient groups with such specific characteristics, only twelve cases of CP recorded in pregnant women were described. The average gestational age was 27.9 weeks, with a range of 22–36 weeks, and the average age of the patients was 32.0 years (range, 22–42 years). However, most reported cases (i.e., in the third trimester of pregnancy) were in women younger than 35. Research shows that third-trimester SARS-CoV-2 infections are dangerous.[31,32] Critically ill patients with moderate to severe ARDS have always been given CP. The high proportion of invasive operations (7/12.58.3%) needed to cure life-threatening hypoxia demonstrates the severity of respiratory disorders. These procedures include invasive mechanical ventilation, tracheostomy, and extracorporeal membrane oxygenation.

According to previous research, COVID-19 in pregnancy and an accompanying illness showed a greater risk of having complications with their pregnancy. Seven of the twelve pregnant women polled had several medical problems (most commonly obesity, diabetes, and asthma). Six of nine doctors agree that two CP units are necessary for clinical improvement (56%). There is a wide range (1–17 days) between hospital admission and the first transfusion in a CP unit, although typically, it takes two days. The antiviral advantages of plasma hyperimmune are maximized when it is infused as soon as possible after hospitalization (ideally within 72 hours).[33–35]

Unfortunately, only two CP units have the anti-SARSCov-2 neutralizing titer, a key metric for assessing CP effectiveness. However, CP transfusion has not been linked to adverse effects, demonstrating its safety as a treatment option. In addition to hyperimmune plasma, several other medications, such as 1) antibiotics; 2) steroids; anticoagulants employing low molecular weight heparin (LMWH); 3) hydroxychloroquine; and 4) antiviral medicines employing lopinavir, ritonavir, or remdesivir, are utilized. These medications are used either in conjunction with hyperimmune plasma or as a second-line therapy after the initial one has been in every case investigated and recorded; the only person who prevailed was the mother.

According to a review of the relevant data, convalescent plasma treatment during pregnancy with severe COVID-19 benefits both mother and baby. Since current research is based on a single case report, they may be biased. Well-designed and well-funded registries and research, including pregnant women, may help comprehend CP's role in treating COVID-19 throughout pregnancy.

CONCLUSION

Patients with severe COVID-19 symptoms and emergencies responded more quickly (within 28

days) to convalescent plasma therapy than standard medical care. Convalescent plasma might be looked into when managing COVID-19. However, further clinical studies are still required to offer more concrete evidence of convalescent plasma effectiveness.

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CONFLICT OF INTEREST

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