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"COVID-19 AND CONVALESCENT PLASMA THERAPY"

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Abstract:

Introduction: *The novel coronavirus-2 (SARS-CoV-2) is responsible for the COVID-19 pandemic and to-date, has affected more than 200 countries and over 13 million people worldwide with an excess of 550,000 deaths since its emergence in December 2019. Although several treatment approaches are under scientific scrutiny, there is no definitive treatment for SARS-CoV-2 because of a lack of hard evidence. One of the treatment modalities under consideration is convalescent plasma (CP) therapy, a historical therapeutic tool that has been used repeatedly to treat several infections successfully. Herein we discussed the mechanism of CP therapy's mechanism, in addition to pertinent clinical aspects of the therapy, its potential adverse effects, and recent scientific evidence favoring CP therapy.*

Methodology: *The aim of this systematic review was to determine the efficacy of CP therapy in COVID-19 in addition to highlighting the various facets of CP therapy. Multiple search engines including, but not exclusive of, PubMed, Google scholar and science direct were used to look for relevant primary studies using pertinent mesh terms. 54 research articles were identified that focused on the mechanism of action, various clinical considerations, adverse effects of CP therapy, as well as evidence in favor of the use of CP therapy in COVID-19. Articles published between 1990 and 2020 were included in this systematic review as per the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.*

Results: *In the light of these findings, CP therapy appears to be a potentially safe and effective therapeutic modality particularly in the treatment of critically ill patients with COVID-19. In spite of the encouraging outcome of CP therapy in COVID-19 in small nonrandomized clinical trials, larger randomized clinical trials are required before this treatment modality can be employed in the treatment of COVID-19 on a large scale. However, it can be used empirically in critically ill COVID-19 patients as a life-saving measure due to the unavailability of other proven therapeutic modalities. Clinical judgement and risk vs benefit assessment should be done when using CP therapy on an empirical basis.*

Conclusion: *CP therapy appears to be an effective therapeutic approach for the treatment of emerging pathogens, particularly in the absence of definitive antiviral agents or vaccines. The potential antiviral and immunomodulatory effects of CP should be evaluated in COVID-19.*

Keywords: *COVID 19, convalescent plasma, passive antibody therapy, SARS-CoV-2, COVID-19 serum therapy, Serotherapy for SARS-CoV-2.*

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INTRODUCTION:

In December 2019, reports emerged of clusters of patients afflicted with a pneumonia-like illness of unknown etiology in the city of Wuhan, Hubei province, China. The patients affected by the disease displayed features that were remarkably similar to previous outbreaks of coronavirus [Severe Acute Respiratory Syndrome Coronavirus-1 (SARS-CoV-1) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV)], including dyspnea, high-grade fever, and multi-lobular invasive lesions on chest imaging [1,2]. The etiology was later attributed to a novel coronavirus, subsequently named Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), isolated from the affected individuals' respiratory tract secretions [3]. The spectrum of symptoms of Coronavirus disease 2019 (COVID-19) ranges from asymptomatic or mild upper respiratory tract symptoms to severe pneumonia and fulminant ARDS [4]. WHO declared COVID-19 a pandemic on 11th March, 2020 [5]. As of 19th June, 2020, COVID-19 has affected 8,242,999 people across 216 countries with a death toll of 445,535 globally [6].

COVID-19 is a therapeutic dilemma for medical practitioners as there are no vaccines or specific antiviral therapies available at the time of writing this article. At present, the management is mostly aimed at supportive care of the patients, including oxygenation, ventilation, and fluid management [7]. The search for effective therapeutic approaches is underway, with convalescent plasma therapy being one of the treatment options under investigation [8].

Convalescent plasma (CP) therapy, also known as passive immune therapy, has been used in the past to improve the survival rates of patients with the severe acute respiratory syndrome (SARS), the 2009 influenza pandemic (H1N1), avian influenza (H5N1) and Ebola. It involves infusing active patients with plasma from recently recovered patients [9, 10]. In light of the virological and clinical similarities between SARS and COVID-19, as well as rapid availability and evidence of positive outcomes among patients following CP therapy, it appears to be a promising treatment option for COVID-19 [11,12].

This review article is aimed at highlighting the mechanism of action along with the evidence of the benefit of convalescent plasma as a therapeutic modality in COVID-19 patients, as well as summarizing the clinically relevant details of this approach and describing potential adverse effects.

PASSIVE IMMUNIZATION - A BRIEF HISTORY:

Passive immunization is a classic adaptive immunotherapy and has been a successful treatment modality for several infectious diseases since the 20th century [12,13]. It entails the acquisition of plasma (along with neutralizing antibodies) from patients who have undergone seroconversion and subsequently recovered from an infection followed by its administration to infected patients [10].

In 1880, the principle of passive antibody therapy came to light when it was discovered that rapid immunity against diphtheria could be achieved if animals suffering from active infection were inoculated with existing antibodies from the sera of animals infected with diphtheria. Subsequently, the convalescent sera's additional passive immunomodulatory properties were recognized, which enabled recipients to curb the excessive inflammatory cascade prompted by infectious agents or sepsis [14,15].

Initially, CP therapy was used on an empirical basis during the Spanish flu pandemic's 1917-1918 flu pandemic before the advent of antimicrobials [16]. Since then, it is employed successfully to manage several pandemic and epidemic outbreaks. Convalescent plasma therapy was used during the 2009 influenza A H1N1 (H1N1pdm09) pandemic and the 2015 avian influenza (H7N9) epidemic [9]. A cohort study demonstrated a marked decline in the

relative risk of mortality (odds ratio 0·20 [95% CI 0·06–0·69], p=0·01) for patients infected with H1N1 pdm09 who received convalescent plasma infusions [17]. Furthermore, a multi-center, prospective, double-blind, randomized controlled trial reported a lower viral load and reduced mortality in association with the use of plasma procured from the patients who recovered from influenza A H1N1 pdm09 virus infection [18]. Furthermore, in 2014, WHO issued interim guidelines for the empirical use of convalescent plasma for the treatment of ebola on a large-scale during the 2013-2015 ebola epidemic [19].

Similarly, CP therapy has shown favorable outcomes as a treatment approach for coronavirus-related respiratory syndromes. During the 2003 SARS-CoV outbreak, convalescent plasma was used as a last resort in critical patients whose condition progressively declined despite pulsed methylprednisolone administration [20]. Furthermore, a meta-analysis from 32 studies conducted on SARS-CoV infection showed that the case fatality rate was considerably low among those who received CP therapy when compared to the placebo group [21]. Guidelines for the use of passive antibody therapy as a treatment approach for MERS were formulated in 2015 [22].

These historical precedents of its long-standing success as a treatment modality in various viral epidemics/pandemics strengthen the case for the use of CP therapy for the treatment of COVID-19.

CONVALESCENT PLASMA:

By definition, convalescent plasma is plasma obtained from individuals previously afflicted with a disease who have since recovered. Their sera are rich in protective antibodies against the disease following seroconversion during the course of the illness [23].

Composition:

The composition of plasma is complex and variable. It is an amalgam of water, inorganic salts, organic compounds, and about 1000 proteins like albumin, immunoglobulins, complement, coagulation, and anti-thrombotic factors. Moreover, a vital constituent of plasma is antibodies that are tailored to match the donor's immune system [24, 25]. Therefore, while convalescent plasma may offer a modicum of immunomodulatory effects by hindering the actions of complement, inflammatory cytokines and autoantibodies through anti-inflammatory cytokines and antibodies, there is a risk of adverse transfusion reactions in association with the administration of CP as is the case with other blood-derived products [25, 26].

Mechanism of action:

The mechanism of action of convalescent plasma can be divided into anti-viral and immunomodulatory effects.

Anti-viral effects:

Neutralizing antibodies (NAbs) have a pivotal role in suppressing viremia thereby providing protection against viral diseases. The efficacy of CP therapy has been associated with the concentration of NAbs in the donor's plasma [27].

The entry of SARS-CoV-2 into cells is mediated by the interaction of the receptor-binding domain (RBD) of the viral spike (S) glycoprotein with the angiotensin-converting enzyme-2 (ACE2) receptors [28, 29]. Antibodies directed at RBD of SARS-CoV-1, a human coronavirus with 79.5% phylogenetic similarity to SARS-CoV-2 [30], have been linked with potent neutralization of SARS-CoV-1 S-protein-mediated entry. Similarly, the presence of anti-RBD antibodies corresponds with neutralization in SARS-CoV-2 in the plasma [31]. The neutralizing antibodies with the highest potencies are the ones directed at the RBD. Some antibodies may compete with ACE-2 receptors to bind with S-protein [32]. In addition to NAbs, CP contains certain Non-NAbs, including Immunoglobulins G (IgG) and M (IgM), that bind to the virus and may result in an improved recovery along with prophylaxis against future infections. [33]

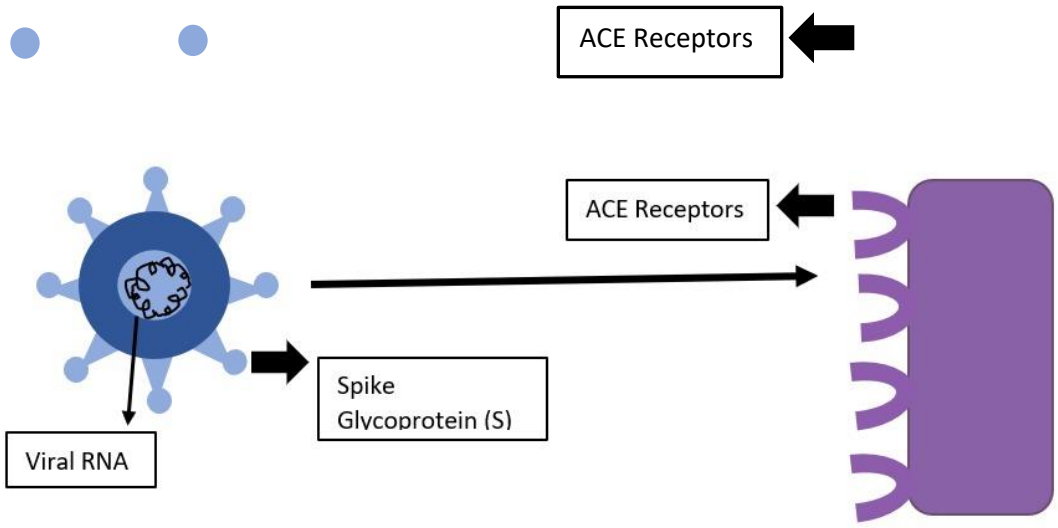

FIGURE 1A: Pathway for SARS-CoV-2 entry into host cells.

FIGURE 1B: Anti-viral effects of CP therapy in COVID-19.

Immunomodulatory effects:

The immunomodulatory effects of convalescent plasma are mediated through various proteins like cytokines, clotting factors, natural antibodies, defensins, pentraxins, and other undefined proteins acquired from the donor's plasma in addition to the neutralizing antibodies. [15] These additional components of the plasma ameliorate severe inflammatory response as well as immunomodulate hypercoagulable states. [26] The most important facets of the immunomodulatory effects of CP therapy in COVID-19 patients have been described below.

The activation of macrophages is the major immunological element being implicated in lung inflammation and damage in association with COVID-19. It is being postulated that the underlying pathophysiology of COVID-19 is likely similar to

macrophage activation syndrome with an innate immune migration of the macrophages to the pulmonary tissue. This theory suggests that the control of immunological pathway may help prevent severe pulmonary damage by hindering the excessive production of cytokines. [34] Blanco-Melo et al observed an upregulation in the production of chemokines by innate immune cells both in ferrets and humans with COVID-19, a finding that supports the aforementioned theory. [35] Although no evidence exists to support the theory that the administration of IVIG inhibits the pulmonary migration of macrophages, previously studies on induced peripheral neurotoxicity showed a reduction in the infiltration of nerves by macrophages in rats treated with IVIG. [36] These findings may account for the favorable outcome in critically ill COVID-19 patients treated with CP. [12, 37]

Additionally, IVIG preparations constitute of autoantibodies that hinder any reaction pertaining to autoreactive antibodies within the recipient, a reaction that appears to be integral for the control of auto-antibody reactions in patients afflicted with autoimmune diseases. [38,39] Evidence from a recent study demonstrated that critically ill patients with COVID-19 tested positive for anti-cardiolipin IgA, anti- β2-glycoprotein I IgA and IgG antibodies, further bolstering the suggestion that the administration of CP in COVID-19 patients may neutralize such auto-antibodies, thereby minimizing the risks of thrombotic events in critically ill COVID-19 patients. [40,41]

Furthermore, a study showed that insufficient complement levels in mice infected with SARS-CoV were associated with higher levels of viral load, higher levels of inflammatory chemokines and cytokines as well as a greater degree of pulmonary immune cell infiltration. These observations suggest that the activation of complement system is the cornerstone of systemic inflammation and pulmonary neutrophilic migration and infiltration, perpetuating tissue damage. [42] Certain antibodies within CP have the ability to inhibit the complement cascade and to curb immune complexes from developing. [43,44]

Moreover, research shows the neutralization of cytokines such as IL-1β and TNFα by IgG transferred to the recipient via CP infusion. [45]

Acquisition and transfusion of plasma:
Various aspects of acquiring plasma for CP therapy need to be considered, particularly the optimal time of donation, the selection criteria for donors, the pre-donation screening of donors and the process of acquiring plasma i.e. apheresis. Similarly, the optimal dosage of plasma to be infused, the optimal treatment time point, indications and contraindications of CP therapy are significant variables that need to be defined with respect to transfusion of plasma during CP therapy.

Optimal Time For Plasma Donation [8]:
Following the onset of infection, IgM antibodies are formed by day-7 and can be detected in the blood until day-21, while the production of IgG antibodies starts by day-14, and they are detectable in the blood for a longer period. The concentration of antibodies is the highest on day-21 because the immune system starts developing antibodies on the day of infection with an escalation in their production by day 14 and a further substantial increment by day 21. Hence, IgG-rich plasma for CP therapy is usually collected 14 days after the date of recovery.

Selection Criteria For Donors [46]:
The guidelines for the recruitment of potential convalescent plasma donors are generally consistent worldwide. Individuals fulfilling the inclusion criteria are accepted as donors whereas others are deferred from donating plasma.

To be eligible to donate plasma, a donor must fulfill all 6 of the following criteria:
A: Must be more than three weeks' post-onset of symptoms with complete resolution of symptoms at least 14 days before the donation.
B: Must be in line with the discharge/isolation relief standards and follow the appropriate therapeutic schedule.
C: Must be aged between 18 and 55 years.
D: Must weigh ≥50 kgs. if male and ≥45 kgs. if female.
E: There should be no history of transfusion-transmitted infections (TTI).
F: Medical practitioners must clinically assess all eligible donors according to treatment.

On the contrary, a potential donor who falls under any one of the following criteria is to be deferred:
A: Pregnant patient or patient with a history of transfusion whose HNA and HLA antibodies are positive.
B: Declared physically unfit to donate blood by the examining clinician.

Pre-Donation Screening [12, 47]:
In addition to the inclusion above criteria, an eligible donor must have a negative rt-PCR (reverse transcriptase polymerase chain reaction) for SARS-CoV-2 14 days after recovery from COVID-19. Rt-

PCR for SARS-CoV-2 must be repeated 48 hours after the initial test and at the time of donation. Furthermore, all donors must undergo a standard assessment before donation to ensure that the donation follows the current regulations of plasma donation. The donor is bled if they fulfill the criteria for selection. Following the donation, the plasma is screened for Transfusion Transmitted Infections (TTI): Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), HIV, and syphilis, among others. The plasma reactive for viral markers is discarded while the non-reactive plasma is labeled and stored for use.

Apheresis:
The preferred mode of acquiring plasma for CP therapy is apheresis. During apheresis, the blood from donors is subjected to continuous centrifugation within the apheresis machine to allow a selective collection of plasma. Around 400-800 mL of plasma is collected per apheresis donation, which can be separated into 200-250 mL units and frozen within 24 hours to be utilized when needed. [33]

There are multiple reasons for apheresis being the preferred procedure for collecting plasma. These include the possibility of frequent donations and collecting larger volumes of plasma per session. Furthermore, since red blood cells are reinfused, apheresis does not have any effect on the donor's hemoglobin levels [23].

Optimal dosage:
The optimal dosage of convalescent plasma in COVID-19 is yet to be determined. The doses of the convalescent plasma administered described in the literature vary from study to study. In a case series study, ten patients with critical COVID-19 received a single dose of 200 mL of convalescent plasma with the neutralizing antibody titers above 1:640 [12], while another study reported the administration of 2400 mL of convalescent plasma to an elderly male. [48] The dosage of CP used in COVID-19 is usually 4-5 mL/kg. (200-500 mL) [46]. The most recent trial that tested the efficacy of CP therapy in COVID-19 patients reportedly administered 4-13 mL/kg. of convalescent plasma [49].

Optimal treatment time point:
Based on current literature, the viral load peaks in the first week of most viral illnesses, while a primary immune response is mounted by the 10th-14th day. Hence, the infusion of convalescent plasma during the initial phases of the disease seems more beneficial [43]. In a case-series study, the meantime from the onset of symptoms to CP infusion was 16.5 days (IQR, 11.0 d - 19.3 d). Patients who received a CP infusion after the 14th-day post-onset of infection (DPOI) showed less dramatic improvement than those who were administered CP before the 14th DPOI [12]. A case series of 5 critical patients afflicted with COVID-19 underwent CP infusion between 10th and 22nd DPOI, followed by the mitigation of symptoms in all patients. [48] Although these studies provide irrefutable evidence for early CP therapy, randomized clinical trials need to be carried out to determine the optimal treatment time point.

Indications Of Cp Therapy: [46, 48, 49]
Convalescent plasma can be infused under the following conditions:
A: Within three weeks of the onset of symptoms with a positive SARS-CoV-2 RT-PCR.
B: Patients with severe or life-threatening disease as assessed by clinicians.
C: Patient with long-term positive SARS-CoV-2 RT-PCR (> 4 weeks).

Severe COVID-19 is defined as respiratory distress, respiratory rate ≥30 breaths/minute, oxygen saturation at ≤ 93% on atmospheric oxygen, Arterial partial pressure of oxygen: Fraction of inspired oxygen (PaO2: FiO2) ≤ 300 or lung infiltrates > 50% within 24-48 hours. Life-threatening COVID-19 is described as respiratory failure requiring mechanical ventilation, septic shock, or multi-organ failure (Other than the lungs) that requires ICU monitoring.

Contraindications Of Cp Therapy: [46]
CP therapy is contraindicated in patients with:
A: Congenital IgA deficiency.
B: History of allergy to plasma infusion, human plasma protein products, sodium citrate, and other severe allergies. Methylene blue virus inactivated plasma is strictly contraindicated in methylene blue allergy.
C: Advanced critical stage of COVID-19 with irreversible multi-organ failure.

Evidence favouring cp therapy in covid-19:
Convalescent plasma therapy is becoming increasingly popular as a treatment modality for COVID-19. Multiple successful studies have already been carried out to explore the role of CP infusion as a potential treatment option for COVID-19 while some are underway.

The pertinent details of significant studies highlighting the success of CP therapy as a treatment modality in COVID-19 are mentioned in table 3.4 A.

AUTHORS	STUDY DESIGN	PARTICIPANTS	CLINICAL STATUS OF PARTICIPANTS	DETAILS OF CP THERAPY	ADJUNCT THERAPY (NON-CP)	OXYGEN / VENTILATORY SUPPORT	OUTCOMES	MORTALITY	ADVERSE EFFECTS
Ye et al [50]	Case series.	6.	Severely ill with deterioration after standard treatment.	200-600 mL of CP in 1-3 consecutive transfusion.	Arbidol (n=6).	Supplemental oxygen (n=4)	Clinical and radiological improvement. Reduction of viral load.	0%	None.
Zhang et al [48]	Case series.	4	Critically ill. ARDS (n=3).	200-400 mL of CP in 1-2 consecutive transfusion. 1 patient received 2400 mL of CP divided into 8 consecutive doses.	Methylprednisolone (n=1) ANTIVIRALS: Arbidol (n=3) Lopinavir-Ritonavir (n=4) Oseltamivir (n=2) Ribavarin (n=2)	Invasive mechanical ventilation (n=4).	Clinical improvement, resolution of viremia and Reduction of the need for mechanical ventilation.	0%	None.
Shen et al [37]	Case series.	5	Critically ill with ARDS.	2 consecutive transfusions of 200-250 mL of CP (400 mL of CP in total) with antibody titer > 1:1000.	Methylprednisolone (n=5) ANTI-VIRALS: Lopinavir-Ritonavir (n=4) Favipiravir (n=2) Darunavir (n=1) Arbidol (n=1)	Invasive mechanical ventilation (n=5).	Mitigation of clinical symptoms within 3 days. Improvement of pulmonary function (PaO2:FiO2) and reduction in viral load within 12 days. Weaned from mechanical ventilation (n=3) within 2 weeks.	0%	None.

Ahn et al [51]	Case report.	2	Critically ill with ARDS.	2 doses of 250 mL CP (Total 500 mL of CP) at a 12-h interval.	Methylprednisolone (n=2) Hydroxychloroquine (n=2) ANTI-VIRALS: Lopinavir-Ritonavir (n=2).	Invasive mechanical ventilation (n=2).	Clinical and paraclinical improvement within days of CP therapy. Resorption of pulmonary lesions. Complete resolution of viremia within 20-26 days. Extubation by day 24 (n=1) ventilatory weaning with tracheostomy (n=1).	0%	None.
Duan et al [12]	Clinical trial.	10	Critically ill. All admitted to the ICU.	Single dose of 200 mL CP with neutralizing antibody titres > 1:640.	Methylprednisolone (n=6) Arbidol (n=9) Ribavarin (n=3) Remdesivir (n=1) Oseltamivir (n=1) Peramivir (n=1)	Invasive mechanical ventilation (n=3). High flow nasal oxygen (n=3). Low flow nasal oxygen (n=2).	Amelioration of clinical status and laboratory parameter (lymphocyte count and C-Reactive protein). Oxyhemoglobin levels by day 3. Reduction of viral load. Variable degrees of improvement radiological picture by day 7.	0%	No serious adverse effects. Evanescent facial red spot (n = 1).
Li et al [49]	Randomized clinical trial	103; CP group: n=52, Control group: n=51. (Calculated sample size:	Severely ill (n=45). Critically ill (n=59).	Single dose of 200 mL CP.	Antivirals: CP group: n=41. Control group: n=44. Steroids: CP group: n=21. Control group: n=16.	Invasive mechanical ventilation (CP group: n=14, Control group: n=11). High flow nasal oxygen (CP group: n=21, Control group: n=23).	Overall, the primary outcome rate between CP and control groups was statistically significant [Rate of improvement of clinical status within 28 days: CP Group: 51.9% (n=27),	Statistically insignificant 28-day mortality benefit. [CP group: 15.7%, Control	2 instances of adverse reactions post transfusion. A definite non-severe allergic transfusion reaction +

		200. Early termination due to non-availability of new participants).				Low flow nasal oxygen (CP group: n=15, Control group: n=15).	Control Group: 43.1% (n=22); Time to improvement: 2.15 days (95% CI, −5.28 to 0.99 days) in CP group.] However, addition of CP therapy to standard treatment in critically ill patients did not yield a statistically significant improvement [Clinical improvement within 28 days: CP group: 20.7% (n=6/29), Control group: 24.1% (n=7/29).] Furthermore, no significant difference was noted between CP group and control group with respect to major secondary outcomes [28-day mortality rate, 28-day discharge rate (CP group: 51%, Control group: 36%.) Conversely, CP group had a higher negative rt-PCR rate 72 hours' post-infusion (CP group: 87.2% Control group: 37.5%)].	group: 24.0%).	probable non-severe febrile nonhemolytic transfusion reaction in the severe COVID-19 group (n=1) 2-hours post-transfusion and a possible severe transfusion associated dyspnea in the critical COVID-19 group (n=1) 6-hours post-transfusion. Both patients improved with appropriate treatment.

Clinical Use of Convalescent Plasma In COVID-19:

Overall, the literature highlights the promising therapeutic effects of CP therapy in treating critical COVID-19 patients. However, randomized clinical trials are required to explore the efficacy of CP therapy as almost all of them employed other therapeutic modalities as an adjunct to CP therapy, and none of these studies were controlled except the one by Li et al. which in turn was underpowered due to the incomplete sample size.

Potential adverse effects of cp therapy:

Overall, CP therapy was tolerated quite well by all the participants in the studies analyzing the efficacy of CP therapy. No fatality or serious adverse effect was reported in association with convalescent plasma use in COVID-19 patients. A minor side effect was reported by Duan et al., where one patient administered with convalescent plasma developed minimal evanescent facial red spot. Additionally, Li et al. observed transfusion reactions in two patients following plasma infusion. In both instances, the patients improved with appropriate treatment [12, 49, 52].

Some of the known adverse effects of CP therapy reported with the use of the treatment modality include Transfusion transmitted infections (TTI), Immunological reactions like serum sickness, Transfusion-related acute lung injury (TRALI). [53]

A theoretical risk concerning this treatment approach is the concern of Antibody-Dependent Enhancement of infection (ADE) that entails the antibodies facilitating viral entry into the host cells or the enhancement of infection by viral toxicity. It is postulated that ADE occurs if the antibody levels are inadequate to block viral entry completely but are sufficient for opsonization. Antibody-coated viruses are hauled into Fcγ receptor-bearing cells (macrophages and monocytes). Since pulmonary macrophages play a pivotal role in inflammation due to COVID-19, ADE's risk should be considered. It is hypothesized that ADE is why adults who have been exposed to prior strains of viruses can develop worse infections than children. This has been observed in COVID-19 as well. Although it is not definitively known if ADE may occur with CP therapy in COVID-19, it is a pertinent concern in patients who are under consideration for CP infusion. [54]

The risk vs. benefit analysis must be done to minimize the risk of potential adverse reactions in each case.

CONCLUSION:

To recapitulate, treating a novel pathogen such as SARS-CoV-2 is a dilemma for medical practitioners due to the inexistence of definitive therapies or vaccines. Until definitive treatment options can be formulated, CP therapy can be used as an effective treatment modality. Considering the existing literature, convalescent plasma therapy has proven to be a very promising treatment option for patients afflicted with COVID-19. During this pandemic, the therapy has been used to treat numerous people globally successfully. Considering the rapidly expanding COVID 19 patients' pool, and the encouraging reports from non-RCT studies, CP therapy appears to be effective and safe, though further trials are needed to determine its efficacy and safety-index definitively. However, it can be used in emergency conditions as a life-saving measure in critical patients until further studies are done.

RECOMMENDATIONS:

Considering the promising effects of CP therapy, we recommend that large randomized clinical trials should be carried out to assess the efficacy and safety-index of this treatment modality more accurately. Furthermore, nation-wide plasma acquisition facilities should be established for stockpiling and distributing plasma on an urgent basis and a national registry for COVID-19 recovered patients should be established for donors to be approached for voluntary donation as needed. Lastly, awareness programs should be established to recruit more people by appealing to their sense of goodwill to contribute to critically ill-treatment.

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