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THE ERA OF COVID-19: WILL CONVALESCENT PLASMA AND INTRAVENOUS IMMUNOGLOBULINS BE THE ANSWER

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ABSTRACT: Since the World Health Organization (WHO) declared severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) infection a pandemic in December 2019, observational and interventional studies have been underway to investigate potential therapeutic options to treat and prevent the progression of coronavirus disease (COVID-19). Most COVID-19 patients develop mild to moderate symptoms. However, elderly patients suffering from chronic comorbidities and immunocompromised patients are susceptible to more severe life-threatening presentations. Convalescent plasma and intravenous immunoglobulins (IVIg) are two attractive options for managing and preventing severe COVID-19. However, current literature does not confirm nor deny the efficacy of the convalescent plasma and IVIg against COVID-19. Moreover, there is much concern considering the safety of blood-derived immune products. For these reasons, the current clinical guidelines do not recommend for or against the use of blood-derived immune products for managing COVID-19 cases. This article summarizes recent evidence on the safety and efficacy of the convalescent plasma and IVIg in COVID-19 patients.

INTRODUCTION: Coronavirus disease (COVID-19) is a contagious disease caused by severe acute respiratory syndrome- Corona virus-2 (SARS-CoV-2). The World Health Organization (WHO) declared COVID-19 a pandemic by the end of 2019 [1]. AS of February 2021, there have been 105,658,476 confirmed cases of COVID-19, including 2,309,370 deaths worldwide [2]. Corona virus disease is spread primarily via respiratory droplets with other modes of transmission being possible but not established, such AS feco-oral transmission or contact with contaminated surfaces [3]. Most COVID-19 patients present with mild to moderate respiratory symptoms. Elderly patients, those suffering from chronic comorbidities, and immunocompromised patients are at higher risk of developing more severe life-threatening diseases. Most patients diagnosed as COVID-19 patients present with fever, chills, myalgia, sore throat, cough, dyspnea, nausea, vomiting, dysgeusia, headache, rhinorrhea and anosmia.

More serious complications include thromboembolic events, severe pneumonia, acute kidney injury, encephalopathy, and myocarditis [4, 5]. Being a novel virus, clinical trials are ongoing to establish evidence-based efficacious treatment for COVID-19. Management of COVID-19 has been

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mainly focused on infection prevention, early detection and monitoring; supportive care and nonspecific anti-SARS-CoV-2 treatment have been recommended. Mild cases that do not warrant patient hospitalization are good candidates for supportive home-based care using paracetamol as an analgesic and antipyretic.

All hospitalized patients should receive thromboembolic prophylaxis. Remdesivir is approved for the management of hospitalized cases that require minimal oxygen supplementation. Dexamethasone can be added to the treatment regimen of hospitalized patients with increasing oxygen requirements. Dexamethasone can also be used alone when remdesivir is not available [6, 8]. The available guidelines do not recommend for or against the use of blood-derived immune products such as convalescent plasma or intravenous immunoglobulins (IVIg) to manage COVID-19 patients. This review aims to summarize current data on the potential benefit of convalescent plasma and IVIg in COVID-19 patients.

Convalescent Plasma: Convalescent plasma is similar to fresh frozen plasma or plasma frozen 24 h after phlebotomy. The main difference is that convalescent plasma is collected from donors who were infected and completely recovered from specific infections. Convalescent plasma has been used for fighting viral outbreaks since the early 20th century [9]. Plasma from donors who have recovered from COVID-19 may contain antibodies to SARS-CoV-2 that help suppress the virus and modulate the immune response [10, 11]. During the COVID-19 pandemic, almost 100000 units of convalescent plasma have been administered under emergency use authorization [11]. Convalescent plasma is collected by apheresis and can be immediately transfused to recipient or frozen to be administered later. Donors should have a confirmed diagnosis of SARS-CoV-2 infection with plasma collected at least 14 days after full recovery. Samples are tested for common transfusion-transmitted infections, and samples collected from male donors or nullipara females are preferred to decrease the risk of transfusion-related acute lung injury [12]. At least 200-600 ml plasma is collected per donation. When administered, transfusion of plasma collected from at least 2 different donors is preferred to ensure effectiveness [13]. Salzar *et al.* administered 300 ml of convalescent plasma to 25 patients with confirmed severe or life-threatening COVID-19. Patients were assigned a clinical status score on a 6-point scale at baseline and were reassessed using the same scale on day 7 and day 14 after plasma transfusion. No transfusion-related adverse events were reported during the first 24 h after transfusion. One patient developed a rash 1 day after transfusion. Two patients developed thromboembolic events that were attributed to COVID-19 rather than a transfusion-related adverse event. By days 7 and 14 after plasma administration, nine and 19 patients, respectively, improved from baseline in the modified six-point World Health Organization ordinal scale [14].

Duan *et al.* administered one dose of 200 ml convalescent plasma after a median of 6 days after symptoms onset to 10 patients diagnosed as severe confirmed COVID-19 patients. Four patients suffered from other chronic comorbidities. Convalescent plasma transfusion resolved patients' fever, cough, dyspnea and chest pain. Convalescent plasma administration improved hemoglobin oxygenation and decreased the need for mechanical ventilation and oxygen supplementation. Convalescent plasma was associated with subsequent increase in lymphocyte count in 7 patients. Convalescent plasma had a neutralizing effect on SARS-CoV-2 RNA which became undetectable 2 to 6 days after convalescent plasma transfusion. No adverse events were reported after administration of convalescent plasma [15].

The convalescent-plasma-for-COVID (Con COVID) study assessed the effect of administering 300 ml of convalescent plasma with SARS-CoV-2 antibody titer of at least 1:80 to hospitalized COVID-19 patients in the Netherlands. The study was discontinued because patients' SARS-CoV-2 antibody titer was equivalent to convalescent plasma donors. The investigators were concerned that convalescent plasma transfusion would not benefit the recruited patients [16]. Bradfute *et al.* measured neutralizing antibody and total antibody titer before and after administration of convalescent plasma to 12 patients with confirmed SARS-CoV-2 infection. Convalescent plasma was collected from donors with confirmed completely recovered COVID-19 and administered at 1 unit (200 ml) per patient. Convalescent plasma transfusion was well

tolerated without any serious adverse events. Neutralizing antibody titers were low in convalescent plasma units to be administered and were not correlated to neutralizing antibody activity in recipients after transfusion [17].

The conflict of efficacy results of convalescent plasma in the reported studies could be attributed to the huge variability in antibody titer in the plasma of convalescent donors. It is recommended to screen convalescent plasma units before transfusion to measure antibody titer in donated units and subsequently adjust the volume administered to ensure effectiveness. Moreover, convalescent plasma was administered at different time points after symptoms onset. There are postulations that earlier administration of convalescent plasma might have better outcomes in terms of effectiveness. Although plasma transfusions may lead to transfusion-related adverse events such as fever, allergic reaction, hypotension, circulatory overload, and hemolysis, the available studies showed that most patients well tolerated convalescent plasma.

Intravenous Immunoglobulin (IVIg): Significant positive outcomes have been observed by the administration of IVIg in patients with SARS and Middle East respiratory syndrome (MERS) [18, 19]. Considering the presence of an exaggerated immune response among many COVID-19 patients, as well as the similar pathogenesis between severe acute respiratory syndrome (SARS) and COVID-19, it seems understandable that IVIg may modulate inflammatory response in COVID-19 patients [20, 21].

A single batch of IVIg is prepared from the serum of 1000-15000 donors. Surprisingly, Intravenous immunoglobulins act as both pro-inflammatory and anti-inflammatory agents in a dose-based fashion. Intravenous immunoglobulins are used as a replacement in antibody deficiencies at a dose of 200-400 mg/Kg body weight administered every 3 weeks. Moreover, IVIg are used as immunomodulatory agents in inflammatory disorders at a dose of 2g/Kg/ month [22]. Intravenous immunoglobulins are used in the management of immune cytopenia, hypogammaglobulinemia due to myeloma and chronic lymphocytic leukemia, primary antibody deficiency, systemic lupus erythematosus, vasculitis, Kawasaki syndrome, toxic epidermal necrolysis, myasthenia gravis, and Guillain-Barre syndrome [23, 25]. It is postulated that IVIg would be beneficial in immunomodulation of hyperactive immune system during cytokine storm reported in patients with life-threatening COVID-19. Zeng *et al.* studied the production of immunoglobulin G (IgG) in males and females suffering from different COVID-19 grades of severity.

It was reported that there was no significant difference between males' and females' production of IgG in mild and moderate COVID-19. However, females diagnosed with severe COVID-19 showed higher titers of anti- SARS-CoV-2 IgG compared to males suffering from severe COVID-19. Moreover, females showed higher IgG production compared to males in early phases of SARS-CoV-2 infection which may attribute to the fact that males are more susceptible to development of severe COVID-19 complications compared to females [26]. A study tested the *in-vitro* cross-reactivity of two available IVIg products to SARS-CoV-2. The study assumed the presence of common antigens between seasonal human beta-coronavirus and novel SARS-CoV-2. The study showed positive reactivity of already existing IVIg to SARS-CoV-2, SARS and MERS [27]. These results together with the immunomodulatory action of IVIg encouraged conducting trials to assess the use of IVIg as a promising treatment option of COVID-19.

There were conflicting results reported on the potential outcome of IVIg administration to COVID-19 patients. Eighty-four patients were randomly assigned to either IVIg or control groups. Thirty minutes before administration of IVIg, patients received 25 mg diphenhydramine, 500 mg paracetamol, and 100 mg hydrocortisone. Intravenous immunoglobulin was administered at a dose of 400 mg/Kg/day for 3 days. The mean time to administration of IVIg was 3.84 days after patient admission. Administration of IVIg significantly decreased the median hospital stay by 3 days without affecting the need for mechanical ventilation, the need for intensive care unit (ICU) admission, or the length of ICU stay. Both groups did not differ in laboratory findings (inflammatory markers, complete blood picture, liver and kidney function tests). The shorter the time from admission till IVIg administration, the shorter the

length of hospital stay was [28]. A propensity score matching retrospective study was designed to assess the impact of IVIg in non-severe COVID-19 patients in Shanghai. Four different dosing regimens of IVIg (10 gm/day for 3 days, 10 gm/day for 5 days, 20 gm/day for 3 days, or 20 g/day for 5 days) were administered to a total of 45 patients within a median of 2 days after hospital admission. Intravenous immunoglobulin administration did not affect time to viral clearance, fever duration, need for antibiotic therapy, mortality, or hospital stay length. The authors concluded that there was no added benefit from IVIg administration to non-severe COVID-19 patients [29].

Shao *et al.* studied 325 confirmed COVID-19 cases who received IVIg (174 patients) or standard of care (151 patients). Generally, administration of IVIg did not affect 28-day or 60-day mortality or median survival of COVID-19 patients. Patients receiving IVIg had significantly longer hospital stay, and their worse clinical status at baseline explained their longer disease span compared to the control group. However, subgroup analysis showed that there was a significant reduction in 28-day mortality and improvement in inflammatory markers in critically ill COVID-19 patients receiving IVIg compared to non-critically ill COVID-19 cases. The authors concluded that early administration (less than 7 days after patient admission) of a high IVIg dose (greater than 15 gm/day) would benefit critically ill COVID-19 patients [30]. A study on 54 lots of IVIg prepared from plasma collected before the COVID-19 outbreak showed that IVIg collected before the pandemic lack *in-vitro* SARS-CoV-2 neutralizing antibodies. Moreover, older donors provide plasma with higher antibody titers mainly due to higher infection rates with increasing age. Given the long time needed to prepare IVIg from donated plasma or blood, the absence of SARS-CoV-2 neutralizing antibodies in batches of IVIg used in early studies on COVID-19 patients might explain the lack of observed efficacy of IVIg [31].

CONCLUSION: There is a conflict in the results of interventional and observational studies of the efficacy of convalescent plasma and IVIg to prevent COVID-19 progression. On the other hand, studies showed promising safety profiles for both convalescent plasma and IVIg in COVID-19. Further studies on homogenous groups of patients in terms of age and comorbidities are necessary. The efficacy of convalescent plasma administered at different timings should be studied and compared. Future studies on the use of convalescent plasma should consider standardization in terms of donor selection and antibody titer per unit transfused.

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