Ulfa Syafli Nosa et al /J. Pharm. Sci. & Res. Vol. 12(12), 2020, 1527-1531

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Convalescent Plasma – Offers Hope The Recovery Times for COVID-19 Treatment: An Update Review

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Abstract:

The novel Coronavirus infection that was initially found in late December 2019 has attracted great attention worldwide. Globally, thus far the number has increased to more than 50 million confirmed cases of COVID-19, and including more than 1 million deaths were reported. This outbreak has been defined as a pandemic situation, but so far there is still no "specific drug" available. Convalescent plasma therapy has a strong scientific basic and historical perspective to treat the previous viral infections such as Ebola, Middle East Respiratory Syndrome (MERS), and Severe Acute Respiratory Syndrome (SARS). In the current pandemic of Coronavirus disease 2019 (COVID-19), the use of convalescent plasma transfusions could be of great value given the lack of specific preventative and therapeutic options. Here, we provide an overview of convalescent plasma transfusions.

Keywords: Convalescent plasma, COVID-19, SARS-COV-2.

INTRODUCTION

The global pandemic of novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in Wuhan, China, in December 2019, and has since spread worldwide [1]. Globally, as of 11 November 2020, there have been 50,676,072 confirmed cases of COVID-19, including 1,261,075 deaths were reported [2]. SARS-CoV-2 is the seventh coronavirus known to infects humans; SARS-CoV, MERS-CoV, and SARS-CoV-2 can cause severe disease, whereas HKU1, NL63, OC43, and 229E are associated with mild symptoms [1]. The common symptoms of COVID-19 symptoms are fever, fatigue, and dyspnea, while anosmia and ageusia have been reported [3],[4]. Prevalence of comorbidities in COVID-19 patients with underlying disease including hypertension, respiratory system disease, and cardiovascular disease may be risk factors for severe patients compared with non-severe patients [3]. The rapid spread of the virus has stricken global health and the economy [5].

Numerous therapeutics and studies were explored during this outbreak. To date, beyond supportive care, there is currently no specific treatment that has been proven to be effective for Coronavirus disease [6]. Convalescent plasma (CP) or immunoglobulins has been used to treat patients with Machupo virus (Bolivian hemorrhagic fever), Junin virus (Argentinian hemorrhagic fever), Lassa fever, and Ebola virus [7]. Afterward, convalescents plasma has been studied in outbreaks of other respiratory infections, such as H1N1 influenza, SARS, and MERS. Although promising, convalescent plasma is not effective in every disease studied [8]. Currently, several studies showed a shorter hospital stay and lower mortality in patients treated with convalescent plasma than those who were not treated with convalescent plasma for patients COVID-19 [9]. Therefore, to date, it is necessary to conduct more clinical trials that were needed to see if it was useful in COVID-19 [8].

METHODS

A review was conducted by searching PubMed, Google Scholar, Science Direct, and Cochrane database until November 2020. The keywords for searching databases included using a combination of the following keywords: " Convalescent Plasma", "COVID-19", "SARS-CoV-2", Coronavirus". We limited our investigation to English-language journals.

DISCUSSION

COVID-19 convalescent plasma (CP) has emerged as the most recent treatment for COVID-19 that has been collected from individuals who have recovered from COVID-19 [10]. This passive antibody administration through transfusion of convalescent plasma may offer the only short-term strategy for conferring immediate immunity to susceptible individuals [11]. Other proteins such as anti-inflammatory cytokines, clotting factors, natural antibodies, defensins, pentraxins, and other undefined proteins are obtained from donors during apheresis, in addition to neutralizing antibodies (Nabs) [12].

Moreover, transfusion CP to patients who infected may provide further benefits such as immunomodulation via amelioration of severe inflammatory response [13]. Could be the case of COVID-19 which over-activated of the immune system may come with systemic hyperinflammation or "cytokine storm" driven by IL-1β, IL-2, IL-6, IL-7, IL-8, TNF-α, and CCL2. About this inflammatory reaction, pulmonary damage entailing fibrosis, and reduction of pulmonary capacity [14].

To infectious conditions, several convalescent blood products such as intravenous immunoglobulin (IVIG) and monoclonal or polyclonal antibodies have been developed [15]. Nevertheless, it's difficult and expensive to produce and may not yield appropriate infectious control in this emergency condition [15]. Therefore, the use of CP has been widely used in different outbreaks considered the

lack of effective medications or vaccines, and often as last chance or experimental treatment [12].

Possible Mechanism of Action Convalescent Plasma

In virus clearance, neutralizing antibodies are crucial and have been considered essential in protecting against viral disease. Passive immunity driven by CP can provide these neutralizing antibodies that restrain the infection. The efficacy of this therapy has been associated with the concentration of neutralizing antibodies in plasma from recovered donors [16],[17]. Neutralizing antibodies was discovered to bind to the spike1-receptor binding protein (S1-RBD), N-terminal domain, and S2 in SARS-CoV and MERS, thus inhibits their entry, restricting viral amplification [18]. Furthermore, the phagocytosis, antibody-dependent cellular cytotoxicity, complement activation dan other antibody-mediated pathways may also encourage the therapeutic effect of CP.

Through ELISA and Biolayer Interferometry Binding, a study showed that one SARS-CoV-specific antibody, CR3022, bind with COVID-19 RBD, and more importantly, this antibody with angiotensin-converting enzyme-2 (ACE-2) did not show any competition for the binding to COVID-19 [19]. At the C-terminus residues, the RBD of COVID-19 varies broadly from the SARS-CoV [19]. Even though, this difference does not enable COVID-19 to bind the ACE-2 receptor, does affect the cross-reactivity of neutralizing antibodies [19].

To measure specific neutralizing antibodies in plasma from recovered patients with SARS-CoV-2, a pseudotyped-lentiviral-vector-based neutralization assay showed variations in neutralizing antibodies titers, patients did not develop high titers after infections approximately 30% [20]. These variations are associated with lymphocyte count, C-reactive protein levels in the blood, and age, suggesting that other components from plasma contribute to the recovery of these patients.

There are other protective antibodies in plasma, in addition to neutralizing antibodies, including immunoglobulin G (IgG) and immunoglobulin M (IgM) [11]. Non-neutralizing antibodies that bind to the virus, but do not influence its capacity to replicate, might contribute to prophylaxis and/or recovery improvement [11].

SARS-CoV infection induces IgG antibodies production against nucleoprotein (N) that can be detected at day 4 after the onset of disease and with seroconversion at day 14 [21]. In SARS infection 89% of the recovered patients, showed IgG-specific and neutralizing antibodies 2 years post-infection [22]. Furthermore, on a ninth day after the onset of the disease, the highest concentration of IgM was detected, and in the second week occurred the class switching to IgG [23].

The other study showed that recovered donors from COVID-19 infection had SARS-CoV-2 specific antibody titers ranging between 1.800 and 16.200 and neutralizing antibodies titers were between 80 and 480 [24]. The plasma received from the donors and transfused in the recipients on the same day leads to viral load alleviated [24]. Following the transfusion of CP, the titers of IgG and IgM in the recipients increased in a time-dependent manner [24]. Furthermore, the presence of neutralizing antibodies in the recipients played a vital role in the restriction of viral infection [24]. Another study monitored the kinetics of SARS-CoV-2-specific neutralizing antibodies development during the course of the disease [20]. Before day 10 post-disease onset the titers of neutralizing antibodies in patients infected with SARS-CoV-2 were low and then alleviated, with a peak 10 to 15 days after onset, remaining stable than in all patients [20].

Recommended Dosage

There is not a standard transfusion dose of CP. In different studies for Coronaviruses, the administration of CP ranges between 200 and 500 mL in single or double scheme dosages [14]. Currently, the recommendation is to administer 3 mL/kg per dose in two days [14]. This strategy facilitates the distribution of plasma units (250 mL per unit) and provides a standard option of delivery in public health strategy [14].

Efficacy-Interim Reports of Convalescent Plasma in Infant and Children

There are several case reports have been reported associated CP used in special populations, specifically in infant and children. A case report presented the case of a six-year-old children with diagnosed COVID-19 associated aplastic anemia with severe pancytopenia [25]. The patients used antiviral drugs and immune modulators as therapy at the beginning, but without any positive results [25]. Afterward, the patients undergo a transfusion of convalescent plasma. The patients observed that SARS-CoV-2 was elimination and did not observe any adverse events of the treatment [25]. The other case, of a 4-year-old girl with severe COVID-19 associated pneumonia who presented as febrile neutropenia [26]. The use of convalescent plasma transfusion following steroids and IVIG showed remarkable results, and the patients recovered without the need for any certain treatment [26]. The next case which has been reported an infant with cardiopulmonary failure secondary to unrepaired congenital heart disease exacerbated by COVID-19, and their hypothesized that CP administration may clear SARS-CoV-2 following the failure of remdesivir [27]. Therefore, despite of several cases shown the impact of CP administration in the pediatric population with COVID-19, future more studies will certainly be needed to fully define the efficacy.

Possible Adverse Events of Convalescent Plasma

In influenza A (H1N1), SARS-CoV-2, and MERS-CoV epidemics, studies did not find any adverse events related to CP administration. In the Ebola case, the administration of CP related to mild adverse reactions such as nausea, skin erythema, and fever [16]. To date, there are several studies associated with the evaluation of the safety of CP administration in COVID-19 have been reported. Despite several studies reported that no adverse event occurred, but the other studies reported presence of adverse events of CP administration in COVID-19 patients. The first studies have been reported that overall <1% rate of a

serious adverse event in 5000 hospitalized adults with severe or life threatening COVID-19 [28]. The other study involved 51 participants with a severe or life-threatening disease in which two participants reported transfusion-related adverse events following CP transfusion [29]. Thus, whereas the administration of CP still seems safe, in addition, to have good efficacy for treatment COVID-19, it needs more evaluation and reports associated the safety of this one of therapeutic options to control this current pandemic.

Table 1. Summary of case series studies the use of convalescent plasma in Covid-19 patients

Reference	Number of patients	Timing of Administration	Volume of CP transfused	CP antibody profile	Summary of outcomes observed post-transfusion
Shen et al., 2020 [24].	5	10-22 days (range)	400 mL	SARS-CoV-2-spesific antibody titer > 1:1000 neutralizing antibody titer > 1:40	- Increase in Pao_2/Fio_2 within 12 days - Decrease in viral loads within 12 days - Increase in SARS-CoV-2-spesific and neutralizing anitbody titers - Resolution of ARDS within 12 days - Mechanical ventilation weaned within 14 days - Discharged between days 51-55 - Remained mechanically ventilated
Duan et al., 2020 [30].	10	16.5 days (median)	200 mL	Neutralization antibody titer >1:640	- Clinical symptoms were significantly within 3 days - Increase in O_2 saturation within 3 days - Trend in increased lymphocyte counts - Trend in decreased C-reactive protein - Imaging showed varying degrees of absorption of lung lesions within 7 days - Undetectable viral load
Zhang et al., 2020 [31].	4	15.5 days (mean)	200 mL-2400 mL	Not measured	- Negative qRT-PCR - Imaging showed absorption or partial absorption, of lung lesions - Discharged between days 18-43 - Remained hospitalized with multiorgan failure

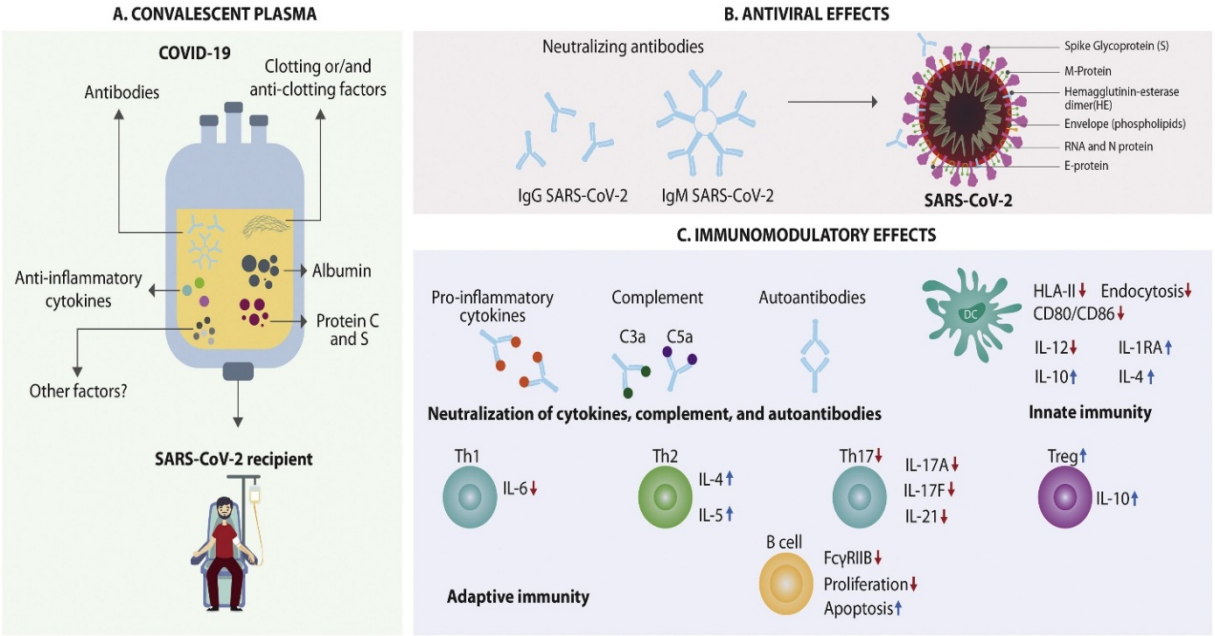

Fig 1. Components of convalescents plasma in schematic and mechanisms of action. A). The main components of convalescents plasma. B. Nabs antiviral effects. IgG and IgM are the primary isotypes, whilst IgA is may be also essential in mucosa viral infections, particularly. Non-NAbs may utilize a protective effect. The humoral immune response is notably directed towards spike (S) protein. C. CP anti-inflammatory effects include network of autoantibodies and control of an overactive immune system.
(Adapted from : Rojas, M., Rodríguez, Y., Monsalve, D. M., Acosta-Ampudia, Y., Camacho, B., Gallo, J. E., ... & Mantilla, R. D. (2020). Convalescent plasma in Covid-19: Possible mechanisms of action. *Autoimmunity Reviews*, 102554)

Convalescent Plasma in Treating COVID-19

Shen et al., for the first COVID-19 study to report a promising outcome of CP for treating COVID-19, all five patients who were treated in China with convalescent plasma between days 10 and 22 of admission improve clinically after receiving treatment [24]. All five patients had severe pneumonia with rapid progression, low Pao_2/Fio_2, and were receiving mechanical ventilation and various steroids and antivirals [24]. Patients exhibited normalized body temperature, improved Pao_2/Fio_2, and Sequential Organ Failure Assessment (SOFA) scores along 1 week after infusion [24]. In the other study Duan et al., present a series of 10 severely ill COVID-19 who all received one 200 mL transfusion of convalescent plasma with high titers of neutralizing antibodies (N1:640) at a median of 16.5 days [30]. The primary endpoint in this study was safety, which was demonstrated as all patients tolerated plasma transfusion without severe adverse events [30]. The secondary endpoints included amelioration of clinical symptoms and improvement in laboratory values by day 3 post-transfusion [30]. Afterward reported increases in neutralizing antibody titer, oxygen saturation, and lymphocyte count; and decreases in C-reactive protein, SARS-CoV-2 viral load, and lung lesions on radiological examination [30]. The other reports, Zhang et al., describe 4 critically ill patients who were transfused between 200 and 2400 mL of convalescent plasma ranging from day 11 to day 18 of admission [31]. All 4 patients were considered recovered from the COVID-19 infection; however, recovery/discharge ranged anywhere from approximately 1 week to 1-month post initial transfusion so the temporal relationship between convalescent plasma and clinical improvement is difficult to reconcile [31]. As of 11 November 2020, a total of 166 records were identified from Clinicaltrials.gov and 17 of the studies were completed [32].

CONCLUSION

The novel coronavirus infection that was initially found in late December 2019 has attracted great attention worldwide. Currently, there is no established treatment to combat this potentially fatal disease. The history of convalescent plasma therapy dates back to the early 20th century and has a strong scientific basis to treat previous viral infections such as Ebola, Middle East Respiratory Syndrome (MERS), and Severe Acute Respiratory Syndrome (SARS). Based on our included studies, convalescent plasma therapy in COVID-19 patients showed promising results as it improved clinical symptoms and parameters, and is it well tolerated. However, well-design clinical trials and further investigations of CP therapy are warranted for COVID-19 patients in the future.

Acknowledgment

The author would like to thank all supervisors and colleagues. The review compiled here are collected over a period of time and may have been reproduced verbatim. Apologize to all researchers if inadvertently failed to acknowledge them in the references.

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