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Review Article

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Investigational Role of Convalescent Plasma in the Management of COVID-19 Disease in Inpatient & Outpatient Settings

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Abstract

Introduction: Historically, both convalescent plasma & hyperimmune globulin have been tried & tested in multiple viral outbreaks in order to confer passive immunity. These products are obtained from previously infected subjects who have fully recovered and are opined to have generated optimal immune response (polyclonal antibodies to the causative pathogen at sufficient titre and biologic activity) to confer passive immunity in the recipient. Neutralizing antibodies are the main active component of such products. In this article practical aspects of obtaining and administering convalescent plasma and evidence-base for its use in the management of COVID-19 disease in inpatient & outpatient settings is presented.

Method: A comprehensive search of PubMed & EMBASE from March 2020 to July 2022 was made using 3 search items: COVID-19, convalescent plasma, and hyperimmune globulin. The search items were combined using the Boolean operator. Societal guidelines reviewed at the time of writing this article include: US Food and Drug Administration (FDA), Association for the Advancement of Blood & Biotherapies (AABB), American Society of Hematology (ASH), International Society on Thrombosis and Haemostasis (ISTH), and National Institute for Health and Care Excellence (NICE) in the United Kingdom.

Results: Administering COVID-19 convalescent plasma can confer immediate passive immunity that may help shorten the duration of the COVID-19 disease &/or diminish its severity thus preventing life-threatening complications. Besides FDA issued EUA of considering convalescent plasma therapy in immunocompromised individuals with severe COVID disease, other investigational indications for convalescent plasma therapy include a) individuals exposed to SARS-CoV-2 who have not yet become ill (i.e. post-exposure prophylaxis), and b) individuals who are at high-risk of exposure or high-risk of severe disease if exposed (i.e. pre-exposure prophylaxis). Convalescent plasma has recently been successfully tried in the outpatient setting to help reduce disease severity and the incidence of hospitalizations.

Conclusion: Convalescent plasma therapy remains an investigational approach to treating severe COVID disease both in inpatient and outpatient settings. Whereas more data is needed to establish its indications, safety, and relative efficacy in novel COVID-19 variant infection cases, its use in immunocompromised individuals with severe COVID disease remains a valid therapeutic consideration.

Keywords: COVID-19; Convalescent plasma; Hyperimmune globulin

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Introduction

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Method

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Discussion

Prior to the COVID-19 pandemic, convalescent plasma had been used in multiple viral outbreaks with mixed success. The best evidence for its efficacy comes from a randomized control trial in patients with Argentine Hemorrhagic Fever (caused by Junín virus, an arenavirus) [1]. In this RCT, 217 patients were assigned to receive 500 mL of convalescent plasma or control plasma within eight days of symptom onset. The results demonstrated a reduced mortality in the convalescent plasma group (1 versus 16.5 percent). A 2015 meta-analysis of a number of low-quality observational studies also suggested reduced mortality in convalescent plasma groups when used for other coronaviruses, such as Influenza viruses & Severe Acute Respiratory Syndrome Virus (SARS) [2].

US Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19 infection in August 2020, and since over 250,000 units of COVID-19 convalescent plasma have been administered. By late 2021, however, the interest in the use of COVID-19 convalescent plasma has dwindled. The most recent FDA revision of the EUA accordingly limited the authorization for COVID-19 convalescent plasma use in the treatment of COVID-19 infection in patients suffering from an immunosuppressive disease or receiving immunosuppressive treatment [3]. Emergence of SARS-CoV-2 virus variants that are less susceptible to existing vaccines and monoclonal antibodies however has rekindled this interest and restarted the debate concerning indications, efficacy, and safety of COVID-19 convalescent plasma.

Although the precise mechanism for viral clearance of SARS-CoV-2 virus is unknown, in virology it is generally understood that neutralizing antibodies bind to the virus potentially reducing its cellular entry and enhancing its clearance via antibody-dependent phagocytosis or antibody-dependent cellular toxicity [4,5]. In previously unexposed or unvaccinated COVID-19 patients, it may take as long as 2-3 weeks for immune system to mount an adequate antibody response [6]. Administering COVID-19 convalescent plasma can thus confer immediate passive immunity that may at least in theory help shorten the duration of the illness &/or diminish its severity thus preventing life-threatening complications [7,8].

Two of the four major structural proteins of SARS-CoV-2 virus seem to be the main antigenic targets: spike protein (S) and nucleocapsid protein (N). Binding of spike protein to the angiotensin-converting enzyme 2 (ACE2) receptor present on respiratory epithelial cells and gastrointestinal cells allows cytoplasmic viral entry [9]. Anti-S antibodies by blocking cytoplasmic viral entry might thus reduce the severity &/or duration of COVID-19 infection [10]. Although less well understood, by interacting with viral nucleic acid (RNA), anti-N antibodies appear to contribute to the assembly of functional virions [11]. IgM anti-S & anti-N begin to appear during the first week & continue to rise during the second week. IgG anti-S & anti-N typically appear by the third week. It appears that, compared to the intensive care unit (ICU) patients, the immunoglobulin class switch tends to occur earlier in non-ICU patients [12].

Many COVID-19 infection survivors are known to have not generated sufficiently strong immune response and thus may not have optimal plasma antibody titres to confer therapeutic benefit in recipients. In one study, about 30 percent of patients had very low titre of neutralizing antibodies; in about 6 percent, the antibodies were actually below the limits of detection [4]. Male sex, advanced age, and severity of illness necessitating hospitalization are generally associated with high-titre antibody responses in studies [4,13,14]. Of these parameters, in one study, having been hospitalized was the strongest predictor of having higher antibody levels [14]. Given these variables, it is important to measure antibody titres prior to transfusing the convalescent plasma.

Antibody titers can either be measured via serologic-binding assays or less commonly by functional bioassays. Serologic-binding assays measure antibody binding to a target antigen by either using a chemiluminescence assay (more sensitive) or an enzyme-linked immunosorbent [ELISA]-type assay. These are often reported qualitatively i.e., positive/reactive vs. negative/nonreactive. Bioassays on the other hand assess the effect of plasma on virus viability (also called viral neutralization). These are reported as Plaque Reduction Neutralizing Titre (PRNT). Whereas serologic-binding assays are easier to automate & scale, bioassays are more representative of clinical efficacy. Bioassays nonetheless are difficult to standardize across different laboratories, have slow turnaround times, logistically complex, and therefore not as commonly employed as serologic-binding assays. Improvements in testing for SARS-CoV-2 however remains an ongoing hot topic for research [15-18]. In order to be labelled as high-titre convalescent plasma intended for use in hospitalized patients, the FDA's revised EUA recommendations have so far approved nine assays, with each

system reporting results in unique units [19].

Convalescent plasma is similar to standard Fresh Frozen Plasma (FFP) or Plasma Frozen within 24 hours after phlebotomy (PF24). In the context of COVID-19, this implies obtaining plasma from qualifying donors at least 10-14 days following complete resolution of symptoms. Although convalescent plasma can be obtained from whole blood units in the lab, it is typically obtained by a procedure called plasmapheresis in a blood donation centre. This 1-2 hour procedure typically involves obtaining whole blood from a donor, separating plasma from the formed elements, returning at least the red blood cells to the donor, and either immediately transfusing the harvested plasma to the recipient or freezing it for later administration. Since red blood cells are transfused back, the donors are less likely to become transiently anaemic with repeated apheresis. A single apheresis donation can provide 2-4 units of convalescent plasma. Conversely, only one unit of plasma can be yielded from one unit of donated whole blood. Collecting convalescent plasma by method of apheresis is therefore strongly preferred. Apheresis however is technically complex and costs considerably more. It thus may not be the most practicable method in low- and middle-income countries [20].

After collection convalescent plasma undergoes infectious disease screening like any other blood donation. The presence of SARS-CoV-2 virus itself, however, is not tested as respiratory viruses are not known to be transmitted by transfusion [21]. Concerning pathogen inactivation treatment on plasma to further reduce infectious risk, most countries do not perform this routinely. This is because pathogen inactivation of plasma overall does not appear to significantly impact clinical efficacy. Whereas the norm is to transfuse ABO-compatible convalescent plasma, some institutions allow out-of-group plasma transfusion in carefully selected cases (e.g., group A units might be transfused in group B patients provided they have low Titre of anti-B). For previously pregnant female donors, testing for antibodies against human leukocyte antigens (anti-HLA) is recommended. Since almost a third of parous females are expected to have anti-HLA antibodies, testing these antibodies is necessary to mitigate the risk of transfusion-related acute lung injury (TRALI) [22].

Otherwise, healthy individuals can donate plasma by plasmapheresis as frequently as twice a week (at least two days apart) [23]. One preliminary study suggested that high titers of antibodies to SARS-CoV-2 circulate in donors for at least 16 weeks; hence they can continue to donate convalescent plasma during this period [24]. Another study suggested that antibody titers only remain high between 4-8 weeks [25]. A yet another study demonstrated that anti-RBD antibody titers remained relatively stable over 10 weeks and declined thereafter [26]. The optimal length of time for which a donor may continue to donate convalescent plasma thus remains unclear. FDA recommendations nonetheless simply state that the donation should be within 6 months of the diagnosis.

Since the primary mechanism of action of convalescent plasma is antibody-mediated viral clearance, antibody Titre in the transfused plasma is probably the most important determinant of its efficacy. Under the EUA in USA, by June 2021, only high-tire convalescent plasma was allowed to be transfused [27]. Unfortunately, the antibody profile resulting solely from COVID-19 vaccination has not been sufficiently studied. Given that plasma from vaccinated individuals ("vax-plasma") is still under study, optimally vaccinated individuals who have never suffered SARS-CoV-2 infection do not qualify for convalescent plasma donations presently.

The optimal dose of COVID-19 convalescent plasma is similar to the standard dose of plasma transfusion, i.e. 1-2 units (approximately 200 to 250 mL per unit); paediatric dosing is based on body weight. It so appears that convalescent plasma is most effective if given fairly early during the course of the COVID-19 illness (ideally, within three days of symptom onset). A meta-analysis from early 2021 concluded convalescent plasma to confer survival benefit when administered within three days of diagnosis (OR, 0.44; 95% CI 0.32-0.61) [28]. This is because in late cases when COVID-19 infection has already caused organ damage, administering convalescent plasma is not anticipated to modify the disease course [7].

Concerning the optimal timing for convalescent plasma administration, a meta-analysis demonstrated maximum benefit when the transfusion is made within three days of diagnosis (OR, 0.44; 95% CI 0.32-0.61) in inpatients [28] and within nine days in outpatients [29]. What is clear is that convalescent plasma administration in late disease is not beneficial.

Currently there is no data available to advise whether repeat dosing of convalescent plasma is appropriate. One theoretically predictable advantage of repeat dosing however is compensation for the variability in donor antibody titers. Some ongoing clinical trials, particularly of critically-ill patients, therefore, are allowing for repeat dosing. Repeat dosing may also be reasonable in individuals who have evidently benefitted from the first dose of convalescent plasma but continue to harbour active disease.

Whereas the duration of efficacy of convalescent plasma therapy is unknown, based on the experience with other antibody-based therapies, it is postulated to confer adequate viral neutralization for several weeks to a few months. In most patients, this is likely sufficient time to recover from COVID-19 infection & generate optimal endogenous immune response to the virus. In appropriately selected patients (severe COVID disease in immunocompromised individuals), convalescent plasma therapy should be instituted in conjunction with other disease-specific and supportive care interventions. Although preliminary data suggests that convalescent plasma may be less effective against certain novel SARS-CoV-2 variants, its use is still deemed appropriate in immunocompromised individuals despite possibly reduced efficacy [30,31]. This is because convalescent plasma is polyclonal, and some of the antibodies may still recognize the mutated versions of the SARS-CoV-2 spike protein. High-tire convalescent plasma recently collected from donors who have recovered from a contemporary or recently circulated variant is another consideration to envisage efficacy.

Besides FDA issued EUA of considering convalescent plasma therapy in immunocompromised individuals with severe COVID disease, other investigational indications for convalescent plasma therapy include a) individuals exposed to SARS-CoV-2 who have not yet become ill (i.e. post-exposure prophylaxis), and b) individuals who are at high-risk of exposure or high-risk of severe disease if exposed (i.e. pre-exposure prophylaxis) [32,33].

Interestingly, convalescent plasma has recently been tried in the outpatient setting to determine if helps reduce disease severity and thus the incidence of hospitalizations. In an RCT, 1181 adult outpatients were randomly assigned to either receive high-Titre convalescent plasma or control plasma within nine days of symptom onset [29]. In the convalescent plasma group, 17 of 592 (2.9 percent) participants got hospitalized; in the control plasma group, 37 of 589 (6.3 percent) got hospitalized (absolute risk reduction, 3.4 percent [95% CI 1.0-5.8]; relative risk reduction, 54 percent). Higher rates of pneumonia were seen in the control group. The three deaths reported in the RCT all involved individuals who received control plasma and were later hospitalized. Establishing an outpatient convalescent plasma transfusion service nonetheless entails several managerial challenges, e.g., transport, infection control, staffing infrastructure, etc [34].

Many factors can affect the demand and supply of convalescent plasma. Concerning supply, once an outbreak starts to dwindle, the number of recently affected individuals with high neutralizing antibody titers (i.e. donors) fall. Concerning demand, it may simply wane as other more efficacious therapies become available. As COVID-19 pandemic appears to come in waves, it seems appropriate to take steps to maintain the supply by a) immunizing selected individuals to generate high-Titre units, b) immunizing animals (as is done with rabies immune globulin from horses), c) generating immortalized lymphocytes to yield polyclonal or monoclonal neutralizing antibodies, and d) establishing banking units for use in the next wave.

Besides convalescent plasma, other antibody-based therapies include hyperimmune globulin and monoclonal antibodies (mAbs). Hyperimmune globulin is a licensed product manufactured from thousands of convalescent plasma donations and consists of a concentrated immune globulin fraction [35]. In a clinical trial setting, a single dose of hyperimmune globulin may be considered as a reasonable alternative to convalescent plasma. Its main advantage is higher Titre of antibodies and ease of storage and shipping, allowing transfer to regions of active outbreaks. The main disadvantage is the high cost of preparation thus limiting its potential availability in low- and middle-income countries. Administration of mAbs directed against a single antigen is another way of providing passive immunity to COVID-19 patients. The main advantage of mAbs is avoidance of exposure to plasma, which can cause transfusion reactions [36]. Disadvantages include reduced efficacy when viral mutations occur, high production cost, and poor availability. Whereas no RCT has ever compared the relative efficacies of different antibody-based therapies, polyclonally, relatively lower production cost and thus potentially greater availability are the major advantages of convalescent plasma [37].

Conclusion

Convalescent plasma therapy remains an investigational approach to treating severe COVID disease both in inpatient and outpatient settings. Whereas more data is needed to establish its indications, safety, and relative efficacy in novel COVID-19 variant infection cases, its use in immunocompromised individuals with severe COVID disease remains a valid therapeutic consideration.

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Conflict of Interest

No conflict of interest.

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