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COMMENTARY

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Convalescent plasma therapy: A passive therapy for an aggressive COVID-19

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CONVALESCENT PLASMA THERAPY: A PASSIVE THERAPY FOR AN AGGRESSIVE COVID-19

As of 19 May 2020, there are in total 4 986 200 laboratory-confirmed Coronavirus disease-2019 (COVID-19) cases. Two percent (45 425) out of 2 657 390 active COVID-19 cases are critically ill and might be requiring intensive care support.[1,2] Unfortunately, even after 6 months since its first detection, we still do not have any definitive treatment options for COVID-19 pneumonia. Recently, the use of human convalescent plasma is being considered as a potential option for the treatment of COVID-19.[3]

CONVALESCENT PLASMA THERAPY DURING PREVIOUS OUTBREAKS: LESSONS FROM THE PAST EXPERIENCE

The basic concept for use of convalescent plasma in COVID-19 is as a delivery system for viral neutralizing antibodies, that is to confer passive immunity. Given the fact that we do not have reliable targeted drugs or a vaccine yet, the option of convalescent plasma seems reasonable to boost the immune system of infected patients or susceptible population immediately. This is not a new concept, rather this has been utilized for over 100 years, even predating the discovery of antibiotics. With regard to the previous outbreaks, experience with convalescent plasma have shown mixed results.[4-6] Soo et al[4] reported a low mortality rate ($P = .049$) and shorter hospital stay ($P = .001$) in patients with SARS by using convalescent plasma. Contrarily, the use of convalescent plasma therapy has been found to be of uncertain benefit in the 2013 African Ebola epidemic.[6] Many studies have confirmed that not all Ebola survivors have anti-Ebola antibodies and hence plasma extraction from such donors might not be beneficial for the treatment of Ebola disease.[7]

CONVALESCENT PLASMA THERAPY DURING COVID-19 PANDEMIC

Preliminary results on using convalescent plasma in COVID-19 patients have shown positive results.[8,9] Shen et al used convalescent plasma ([IgG] binding titer greater than 1:1000) therapy in five mechanically ventilated patients. There were significant laboratory and clinical improvement in all patients, with three patients even discharged at the time of reporting.[8] Similarly, Daun et al[9] in their 10-patient study with convalescent plasma (neutralizing antibody titers above 1:640) found an increase of oxyhemoglobin saturation, increased lymphocyte counts, and decreased CRP levels. Serum SARS-CoV-2 RNA load was also checked in all patients that confirmed a 100% clearance of viremia, although data were not presented on respiratory tract clearance. Rajendran et al reviewed five studies recently reported on the use of convalescent plasma in COVID-19 patients[10,11] The major findings of this review were (a) reduced mortality in critically ill patients (b) disappearance of SARS-CoV-2 RNA was observed in the majority of patients (c) improvement in clinical symptoms and radiological shadows of the patients after convalescent plasma therapy (d) no significant adverse effects secondary to plasma therapy were noted.

Although the convalescent plasma therapy concept is old, the COVID-19 disease is just 6 months old. Hence, a large degree of uncertainty exists as to donor selection, patient eligibility, indications, and side effects that merit further discussion.[11]

Donor selection and timing of plasma extraction: The U.S. Food and Drug Administration (FDA) has recommended the following guidance for timing of COVID-19 convalescent plasma collection:

- *Scenario A* (*Clinical findings based*): Donors' symptoms should have completely resolved at least 28 days before donation.

- *Scenario B* (*Clinical plus laboratory investigation based*): Donors' symptoms should have completely resolved at least 14 days before donation *AND* negative COVID-19 PCR from nasopharyngeal swab.

RECOMMENDATION FOR SARS-CoV-2 NEUTRALIZING ANTIBODY TITERS

Once it is confirmed that the proposed donor is no longer contagious, the next step would be to see if the donor has sufficient antibody levels to donate? This can be done by measuring SARS-CoV-2 antibody levels to ensure sufficient titers in the donor's circulation. The FDA recommends a SARS-CoV-2 neutralizing antibody titer of at least 1:160 as an inclusion criterion for donor selection. If such a matched unit is not available, the FDA suggests that a titer of 1:80 may be considered acceptable.

FINDING THE BEST CANDIDATE FOR CONVALESCENT PLASMA THERAPY

Convalescent plasma therapy involves many logistical challenges, including the donor's availability and willingness; apheresis center capacity; storage and transportation of plasma concentrate; and testing for the adequacy of antibody titers. Considering the aforementioned limitations and the potential risks, appropriate triage systems should be utilized; hence, plasma therapy use is currently restricted only to critically ill patients. The FDA recommends two clinical indications for the current usage of convalescent plasma therapy in COVID-19 patients[12]

- *Scenario A* (Severe disease) which is defined as one or more of the following: Dyspnea, RR ≥30/min, blood oxygen saturation ≤93%, paO2/FIO2 Ratio <300, and radiological worsening with the appearance of lung infiltrates >50% within 24 to 48 hours.
- *Scenario B* (Life-threatening disease) which is defined as one or more of the following: Respiratory failure, septic shock, or multisystem dysfunction.

Another potential indication, though not proposed by the FDA, is the prophylactic use of convalescent plasma in vulnerable populations: [A] patients with multiple medical conditions, [B] health care providers, and [C] individuals with exposure to confirmed cases of COVID-19.

It is unknown how long such protection might last but based on the amount and type of transfused antibody, immunity could last from weeks to months. Another important factor is the timing of plasma therapy infusion. As viremia is expected to be maximum in the first week, the early infusion is likely to give the best response. Possible mechanisms are viral neutralization and antibody-dependent cellular cytotoxicity and/or phagocytosis. This helps in not only clearing the viremia but also could potentially eradicate the reservoir of infected host cells. Currently, the only antibody source available for urgent use is from convalescent plasma from recovered patients. It is anticipated that as more people contract and recover from COVID-19, the number of potential donors will rise.

On 3 April 2020, the FDA cleared the path for the use of this potential lifesaving therapy under any of the following three routes- (a) enrollment in a clinical trial, (b) via the national expanded access treatment protocol, and (c) under a single patient emergency investigational new drug application (eIND). Armed with FDA approval, researchers are now in the process of conducting placebo-controlled trials to test convalescent plasma, at numerous hospitals, including Johns Hopkins, the Mayo Clinic (NCT04325672), and Washington University in St. Louis (Table 1). Lacking a vaccine and with limited antiviral options against SARS-CoV-2, this is an ideal time to try convalescent plasma therapy in COVID-19 patients.

COMPLICATIONS OF CONVALESCENT PLASMA THERAPY IN PATIENTS WITH COVID-19

Preliminary results are very encouraging, and none of the studies have thus far shown any significant adverse reactions. However, as experience is still limited, vigilance for potential side effects of convalescent plasma therapy is advised. As with any other blood product transfusion, there are certain common, predictable, or known side effects that also apply to convalescent plasma therapy, such as transfusion-related infections, serum sickness, fluid overload, and transfusion-related acute lung injury. By following diligent modern blood banking techniques and transfusion precautions, the incidence of these unwanted events can be minimized at any center; and the cumulative risk of any life-threatening reactions is <1%. Although a theoretical risk that of antibody-dependent enhancement of infection, this has not been witnessed to date.; and there are no data thus far to suggest any increased risk of convalescent plasma over ordinary fresh frozen plasma.[13]

FUTURE OF CONVALESCENT PLASMA THERAPY

While awaiting an effective vaccine and/or antiviral agent for COVID-19, experimental therapies are currently being testing in clinical trials.[14] Plasma therapy has so far provided encouraging outcomes, without any serious events. We anticipate an upsurge in the use of convalescent plasma over the next several months, for the treatment of severely ill patients and perhaps with a role earlier in the course of illness and/or for prophylaxis. The American Red Cross, the U.S. government, investigators at Mayo Clinic (www.uscovidplasma.org), and many others across the country are now hard at work identifying appropriate donors and establishing testing to confirm neutralizing antibodies in a timely fashion. As antibody testing is validated, it should help guide the more effective use of convalescent plasma. In addition, efforts are underway to pursue production of a COVID-19 immune globulin, which might provide a more reliable, more effective, and more readily available plasma-based therapy against this formidable virus.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

TABLE 1 Recent trials on convalescent plasma from United States

NCT	Study title	Study characteristics	Conducting authority
NCT04342195	Acquiring convalescent specimens to isolate and identify potent monoclonal antibodies against COVID-19	Observational, cross-sectional, 12 participants	Columbia University
NCT04338360	Expanded access to convalescent plasma for the treatment of patients with COVID-19	Expanded access	Mayo Clinic (all centers of US)
NCT04340050	Pilot study for use of convalescent plasma collected from patients recovered from COVID-19 disease for transfusion as an empiric treatment during the 2020 pandemic at the University of Chicago Medical Center	Interventional (Clinical Trial), Single Group Assignment, 10 participants	University of Chicago, Chicago, Illinois,
NCT04343755	Phase IIa study exploring the safety and efficacy of convalescent plasma from recovered COVID-19 donors collected by plasmapheresis as treatment for hospitalized subjects with COVID-19 infection	Interventional (Clinical Trial), Single Group Assignment, 55 participants	Hackensack Meridian Health, New Jersey, United States,
NCT04344015	The goal of this study is to identify individuals who have previously been infected with COVID-19 and collect plasma from those who meet inclusion criteria for convalescent plasma donation	Interventional (Clinical Trial), Single Group Assignment, 2000 participants	Thomas Jefferson University Hospital, Philadelphia, Pennsylvania,
NCT04343261	Convalescent plasma in the treatment of COVID 19	Interventional (Clinical Trial), Single Group Assignment, 15 participants	Trinity Health of New England, Hartford, Connecticut
NCT04344535	A randomized trial comparing the efficacy and safety of high-titer anti-SARS-CoV-2 plasma vs standard plasma in hospitalized patients with COVID- 19 infection	Interventional (Clinical Trial), Parallel Assignment, 500 participants	Elliott Bennett-Guerrero, Stony Brook University

AUTHOR CONTRIBUTIONS

All authors have seen the manuscript and agree to the content and data. All the authors played a significant role in the paper.

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