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REVIEW

Facts and challenges in convalescent plasma therapy in COVID-19

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Abstract

The present coronavirus disease 2019 (COVID-19) pandemic has brought the focus back onto the passive immunization potential of the Convalescent plasma. This however has many challenges as availability of recovered patients as donors, eligibility of recovered patients for convalescent plasma donation, Safety profile of convalescent plasma. Considering the lack of efficacious treatments for COVID 19 and the epidemic situation with high mortality rate, the evaluation of convalescent plasma therapy in COVID-19 is the need of the hour. In this article, the feasibility and challenges are discussed based on the literature published on role of convalescent plasma therapy in COVID-19. Based on the limited scientific data available, convalescent plasma transfusion (CPT) therapy in COVID-19 patients appears safe, clinically effective, and reduces mortality. However an ongoing clinical study at our Centre should give us a good direction to establish the efficacy of CPT to COVID-19 patients.

Keywords: convalescent plasma therapy; COVID-19; coronavirus; SARS-CoV-2

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Introduction

The recent emergence of coronavirus disease 2019 (COVID-19) pandemic has reassessed the usefulness of historic convalescent plasma transfusion (CPT). Historically, convalescent plasma therapy has been used in various viral diseases such as poliomyelitis, measles, mumps and influenza before vaccines became available [1-5]. A meta-analysis of 1703 patients with H1N1 influenza during the Spanish Flu of 1918 suggested that patients who received convalescent plasma had lower mortality [6]. Conversely, in a double blind, randomized, placebo-controlled trial, convalescent plasma was not found to be superior to placebo in patients infected with Influenza A [7-9]. Furthermore, 84 patients with Ebola virus disease who were transfused with convalescent plasma without known levels

of neutralizing antibodies did not have a survival benefit [10]. Convalescent plasma was also studied during the previous coronavirus outbreak of SARS in 2002 -2004. In a retrospective study of 80 patients by Cheng et al, it was observed that patients who received convalescent plasma before day 14 of illness had better outcomes, defined as early hospital discharge, compared to patients who received it after day 14 of illness (15.6% vs 58.3%; P<0.001) [11].

In this article, the feasibility and challenges in convalescent plasma therapy in COVID-19 are discussed based on the literature published.

Convalescent plasma in COVID-19

Currently, there are no approved treatments for COVID-19. The management plan is supportive care with supplemental oxygen and mechanical ventilation [12]. Multiple trials are being done across the globe to assess the efficacy of various treatment strategies. World Health Organization (WHO) initiated the SOLIDARITY trial in several countries to compare the effectiveness of the following regimens against COVID-19: Remdesivir, Lopinavir/ Ritonavir, Lopinavir/ Ritonavir with interferon beta, and hydroxychloroquine [13]. In a clinical trial, Lopinavir/ Ritonavir did not demonstrate any benefit over Standard of care [14]. United States Food and Drug Administration (USFDA) has recently approved convalescent plasma from patients recovered from COVID 19 for the treatment of severe or life threatening COVID-19 infections [15].

In a small case series, five critically ill COVID-19 patients with acute respiratory distress syndrome (ARDS) were treated with convalescent plasma containing neutralizing antibodies. Infusion of plasma was followed by improvement in clinical status in all five patients, with no deaths and the study reported that three patients were discharged, whilst two continued to be stable on mechanical ventilation [16].

In another small case series of four patients, including one pregnant female, all four patients recovered eventually [17].

In another feasibility study of convalescent plasma therapy, 10 severely ill patients were transfused with 200 ml of convalescent plasma [18]. It was well tolerated with significant increase in neutralizing antibodies and disappearance of viremia in 7 days. Clinical symptoms rapidly improved in 3 days.

Considering the lack of efficacious treatments for COVID 19 and the epidemic situation with high mortality rate, US FDA has approved convalescent plasma for COVID-19 for clinical trials, expanded access and single patient emergency investigational new drugs (IND) [19].

Challenges in convalescent plasma therapy in COVID-19

Majority of the adverse effects associated with plasma transfusion are non-lethal; medically treatable adverse effects commonly associated with transfusion of plasma include TRALI; transfusion associated circulatory overload (TACO); allergic/ anaphylactic reactions; transfusion related transmission of infections (TTI); febrile non-hemolytic transfusion reactions (FNHTR); hemolytic transfusion reactions (HTR); and rarely RBC allo-immunization [20]. Another theoretical risk of using convalescent plasma includes antibody dependent enhancement of infection [21].

Eligibility of donor

The following criteria should be met for potential donors [19]:

- >18 years of age
- Males or nulliparous female donors of weight >55Kg
- Prior diagnosis of COVID-19 documented by a laboratory test (RT-PCR) with symptomatic disease with at least fever and cough and
- Complete resolution of symptoms at least 28 days prior to donation

In addition, donor eligibility criteria for whole blood donation will be followed in accordance to the Drugs & Cosmetics Act 1940 and rules 1945 therein (as amended till March 2020) [22].

These individuals fulfilling the above criteria will be contacted telephonically and explained the details of the study and their extent of participation. They will be encouraged to visit blood bank for further evaluation towards eligibility for blood donation. If requested, they will be provided transport for the same.

Recruitment of donor

At the time of discharge, all recovered COVID-19 patients will be counselled. They will be motivated towards donation of convalescent plasma and its probable beneficial effects in the management of COVID-19 patients. These individuals fulfilling the above criteria have be contacted telephonically and explained the details of the study and their extent of participation. They have to be encouraged to visit the Blood Bank for further evaluation towards eligibility for plasma donation.

Screening of eligible donor

1. Donor will be screened, followed by brief physical examination.
2. Donors not fit to donate blood based on the history and examination will be deferred and excluded from plasma donor pool for a time period specified by country regulation.
3. Donors who have had transfusion of blood products in last 8 weeks will be excluded.
4. Donors who have had COVID diagnosis more than 4 months will be excluded from donation.
5. One EDTA sample (5 ml each) and one plain sample (5 ml) will be drawn for the following pre-donation tests as required for convalescent plasmapheresis.
    a. Blood group (ABO grouping and Rh phenotyping) and antibody screening for clinically significant antibodies (Extended Rh, Kell, Duffy, Kidd, MNS) – Antibody screen positive donors will be deferred.
    b. Complete blood count including Hb, Hct, Platelet count, Total and differential leucocyte count. Donors with Hb>12.5g/dl, platelet count >1,50,000 per microliter of blood and TLC within normal limits will be accepted.
    c. Screening for HIV, HBV and HCV by serology or NAT. Donor negative by either test will be included.
    d. Screening for syphilis and malaria by serology. Negative donors will be included.
    e. Total serum protein. Donors with total serum protein > 6gm/dl will be accepted (as per Drugs and Cosmetics (Second Amendment) Rules, 2020)
    f. Presence of IgG and IgM antibodies to COVID-19 by rapid test as per manufacturers' instruction. Donors negative for IgG or positive for IgM antibodies to COVID 19 will be deferred.
6. Titration of anti-COVID-19 (IgG) antibodies and SARS-CoV-2 neutralizing antibodies may be done depending on availability of facilities at the time of testing. Unavailability of antibody titres will not preclude convalescent plasma transfusion. Desired titers for IgG antibodies is 1:640 and for neutralizing antibodies is 1:40. If not done at the time of plasma collection, the donor samples will be stored in aliquots at <-80°C to be tested later.

Plasmapheresis of donors

Donors will be explained the procedure of plasma donation and the adverse events associated with the process. Among the consenting donors and based on the results, accepted donors will be asked to return on a specified date for plasma donation.

Plasma collection will be done by centrifugal separation using any of the apheresis equipment available at the facility. Volume collected will not exceed 500 ml per sitting (as per Drugs and Cosmetics (Second Amendment) Rules, 2020). Throughout the procedure the extracorporeal volume of blood will never exceed >15% of the total blood volume of the donor. Donor adverse events will be managed as per trial site's protocol for Apheresis donations.

A unique donor identification number will be provided to the collected unit as per attached SOP and the unit will be stored as per attached SOP or issued for patient use. The collected plasma will be divided into smaller packs of 200 ml each for easy storage and transfusion and frozen within 8 hours. The plasma will be stored at <-40 degree Celsius.

No pooling of plasma from different donors will be done. Successful plasma donors will be requested to repeat the donation. If the donor agrees for a repeat donation, such donation will be scheduled after at least 2 weeks of the first plasma donation. If there was a loss of red cells at the time of first donation owing to any procedural problems or otherwise the donor will be deferred for a period of 3 or 4 months for male or female donors, respectively. All the donor

selection guidelines described above will apply to repeat donation as well.

In repeated plasmapheresis

1. Total serum protein will be tested before the third procedure if done within four weeks and it should be 6 gm/dl.
2. The quantity of plasma separated from the blood of donor will not exceed 500 ml per sitting and once in a fortnight or shall not exceed 1000 ml per month

Infusion of blood products

For infusion of plasma, standard SOP for transfusion of FFP should be followed with special care to monitor these patients during and post-24 hours of transfusion. All such transfusions must be done using blood transfusion sets. The clinician will send a request for plasma component specifically mentioning the diagnosis and that convalescent plasma is required. An ABO compatible plasma bag of approx. 200mL will be issued maintaining all the blood bank records after thawing at 37°C.

Dose of convalescent plasma

After randomization to intervention arm, one dose of 200 mL convalescent plasma will be transfused. This will be first dose. If the first dose does not lead to any adverse event which contraindicates plasma transfusion, a second dose of 200mL of convalescent plasma will be transfused after an interval of 24 hours from the first infusion.

Hence, the cumulative dose of convalescent plasma for each patient will be 400mL.The second plasma unit will preferably be from a different donor depending on the availability of another ABO compatible plasma unit or else plasma unit from the same donor will be issued [23].

Conclusion

The main findings from available data are as follows: (a) Convalescent plasma may reduce mortality in critically ill patients, (b) Increase in neutralizing antibody titers and disappearance of SARS-CoV-2 RNA was observed in most patients after CPT therapy, and (c) Beneficial effect on clinical symptoms after administration of convalescent plasma. However an ongoing clinical study at our Centre should give us a good direction to establish the efficacy of CPT to COVID-19 patients. Based on the limited scientific data available, CPT therapy in COVID-19 patients appears safe, clinically effective, and reduces mortality.

Conflicts of interests

The author declares no conflicts of interest.

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