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Hematology & Transfusion International Journal

Review Article

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Convalescent plasma therapy for Covid 19 - A perspective

Abstract

Convalescent plasma therapy has been used for years. However, its use in Covid-19 is still experimental. While it can be life-saving, its efficacy as well as risks need to be evaluated to establish this as a therapeutic option. Also, for this proper infrastructure and adequate facilities need to be in place before embarking on this journey. However, under current circumstances, convalescent plasma should be strictly only given in the setting of clinical trials.

Volume 9 Issue 2 - 2021

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Received: January 20, 2021 | **Published:** April 08, 2021

Introduction

Convalescent plasma therapy has historically been used for management of a wide range of infectious diseases.[1] This therapy has played an important role in infectious disease outbreaks where treatments and vaccines were not readily available.[2] Though popular for initial management of emerging viruses providing time for development of vaccines and antiviral therapy, its use later in the therapeutic setting has not been defined.[3]

Over the years, the world has been hit by several viruses including Influenza viruses (H1N1, H2N2, H3N2, H5N1), Human Immunodeficiency virus, Ebola virus, Chikungunya virus, coronaviruses (severe acute respiratory syndrome coronavirus SARS-CoV and Middle east respiratory syndrome coronavirus MERS-CoV).[4]

SARS CoV-2 Pandemic:

December 2019 saw the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the city of Wuhan in China. Within months, it had spread across continents to different parts of the world. The first index case of Europe was reported in France on 21 Jan 2020. WHO declared the outbreak to be a public health emergency of International concern on 30 January 2020. On 11 Feb 2020, WHO named the new coronavirus as COVID-19. It was declared as a global pandemic on 11 March 2020.[5] In Pakistan, the first Covid-19 case was reported in Karachi, Pakistan on 26 February 2020 and by 18 March 2020, all four provinces including federal territory had been affected. The cases are rapidly rising and as of June 2, 2020, more than 76398 cases have been reported across the country resulting in 1621 deaths.[6]

Covid-19, a pandemic, has caused concern among the public inciting fear and panic.[7] The fact that no specific treatment has proven effective as yet has further increased the stress and anxiety.[8] Management options are limited, supportive care being the mainstay of treatment.[9] Specific treatment based on antiviral drugs (remdesivir) and IL-6 pathway inhibitors (tocilizumab) are still in clinical trials.[10] Convalescent plasma has shown promising results for management of severe or life-threatening Covid-19.[11]

Convalescent plasma therapy

Transfusion of convalescent plasma is a strategy of passive immunization used since early 20th century.[10] It has proved effective in several pandemics previously such as in Spanish flu, West Nile virus and Ebola virus. Thus, its utility in emergency management of viral pandemics is well established.[12]

Convalescent plasma is obtained by collecting whole blood or plasma from a patient who has survived previous infection and has developed humoral immunity against the pathogen responsible for the disease in question.[13] Convalescent plasma therapy in Covid-19-19 is based on obtaining plasma from previously infected individuals who have now recovered completely and have adequate neutralizing titers of anti-SARS CoV-2 antibodies and transfusing it to serious patients.[14] Donor selection should be based on the neutralizing antibody titer based on plaque reduction neutralization test (PRNT) or ELISA assays.[15] Mechanisms include direct neutralization of the virus, control of an overactive immune system (cytokine storm, Th1-Th17 ratio, complement activation) and immunomodulation of a hypercoagulable state.[16]

Donor selection criteria

Donor selection criteria are variable depending on different institutions and different protocols. All donors must undergo standard pre-donation assessment as per standard national protocols. FDA has defined donor eligibility as evidence of Covid-19 based on diagnostic test (nasopharyngeal swab) or a positive serological test, at least 14 days have elapsed after complete recovery and SARS CoV-2 neutralizing antibody titers of at least 1:160 or 1:80 if no alternative matched donor. All other pre-requisites for plasma donation must be met including screening for TTIs, haemoglobin estimation and ABO RhD testing.[17] The Organizing Committee of The ISBT Working

Party on Global Blood Safety have described the donor eligibility requirements in low and middle income countries. These include confirmation of previous infection with SARS CoV-2 by clinical records or NAT testing, an interval of at least 28 days following complete recovery and all fulfillment of standard selection criteria for blood donation.[18]

Recovery from Covid-19 infection in donors is confirmed by clinical assessment, date of resolution of all symptoms, demonstration of a non-reactive NAT for SARS CoV-2 on nasopharyngeal sample and neutralizing SARS CoV-2 antibody titre of 1:160 or at least 1:80.[7]

Collection of convalescent plasma

Collection of convalescent plasma can be done by plasmaphereseis or by plasma separation from whole blood. Plasmapheresis is extracorporeal separation of blood components by which plasma is removed from the blood of the donor to allow collection of plasma from the donor. Plasmapheresis is the preferred method for collection of convalescent plasma.[13] Collection of donor plasma should only be done at certified and designated blood bank establishments. Authorized devices and equipment for blood collection should be licensed and validated. Collection should be performed under direct supervision of well-trained and qualified blood bank staff and nurses.[14] As per ISBT working group guidelines, 200-450 ml of whole blood should be collected and plasmapheresis volume should be 600ml (plus the anticoagulant).[18] Whole blood collected is centrifuged and plasma is extracted using standard operating procedures. Plasma may also be extracted from whole blood by membrane filtration technique. The convalescent plasma collected should be clearly labeled as "Convalescent Plasma" and results of TTI screening should be endorsed. Inventory should be maintained. Convalescent plasma should be stored separately from other blood products in the inventory. Liquid plasma may be stored for up to 40 days at a temperature of 1°C to 6°C. At time of issuing plasma, it should be checked that the demand has been signed by competent authority. Standard operating procedures are followed for thawing and issue of the plasma. ABO and Rh compatibility between donor and recipient are assessed. Convalescent plasma is sent to the patient bedside by the designated person and is transfused under supervision of medical officer with strict monitoring of vital signs.[13]

Patient eligibility criteria

FDA has elaborated the patient eligibility criteria which includes, laboratory confirmed Covid-19 having severe or immediately life-threatening disease. Severe disease has been defined as one or more of the following: shortness of breath, respiratory frequency $\geq$30/min, blood oxygen saturation $\leq$93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300 and/or lung infiltrates >50% within 24-48 hrs. Life-threatening disease is defined as one or more of the following respiratory failure, septic shock and/or multiple organ dysfunction or failure. Informed consent should be provided by the patient or blood relative.[17]

Use of convalescent plasma for Covid-19

The first report of convalescent plasma against COVID-19 was published in JAMA about 5 critically ill patients with Covid-19 in Shenzhen, China. Their results showed normalization of body temperature within 3 days, decreased SOFA score, increased P_{AO2}/F_{IO2} within 12 days and marked improvement in clinical status following plasma transfusion.[19] Another study from China by Kai Duan et al titled 'Effectiveness of convalescent plasma therapy in severe Covid-19 patients' has studied 10 patients. Each patient was transfused a single dose of 200ml convalescent plasma. The primary endpoint was the safety of convalescent plasma transfusion and secondary endpoint was improvement of clinical symptoms and laboratory parameters within 3 days of transfusion. Outcomes were affected by two key factors; the neutralizing antibody titer (more than 1:80 showed positive results) and timely administration of convalescent plasma transfusion (within 14 days of onset of symptoms showed favourable results). The study showed that convalescent therapy was tolerated well and had potential for improving clinical outcomes and patient survival.[20]

However, these findings are not sufficient to establish the efficacy of convalescent plasma and larger clinical trials need to be conducted. Qing-Lei Zeng in his study Effect of Convalescent Plasma Therapy on Viral Shedding and Survival in Patients with Coronavirus Disease 2019, studied 6 patients with COVID-19 and respiratory failure who received convalescent plasma at a median of 21.5 days after viral shedding was first detected. All tested negative for SARS-CoV-2 RNA within 3 days after infusion, and 5 eventually died. In conclusion, convalescent plasma treatment can end SARS-CoV-2 shedding but cannot reduce the mortality rate in critically ill patients with end-stage COVID-19, and treatment should be initiated earlier.[21]

Limitations

Convalescent plasma therapy is still experimental and its efficacy and safety have not been completely established. Lack of definitive evidence in form of randomized controlled trials on large number of patients is lacking, thus proven efficacy has not been established. Following discharge of patients, there is no follow-up to determine any long term complications. Data being collected shows encouraging results and may prove useful in selective patients. However, there are still certain issues and limitations that need to be addressed in implementing use of convalescent plasma therapy on a large scale. Developing countries like Pakistan face greater challenges. The first patient, a 53 year old coronavirus patient at Liaquat Medical University, Karachi, Pakistan recovered from convalescent plasma therapy in May 2020. Following this, plasma therapy trials have begun in different parts of the country. Eight approved clinical trial facilities for convalescent plasma are working across the country.[22]

Limitations include the lack of central authority and leadership, absence of a central registry limiting timely donor availability with ABO and Rh compatibility, unavailability of standard validated tests for detection of donor antibody titers, scarcity of apheresis equipment, financial, administrative and logistic constraints coupled with limited number of blood banks and standard facility for plasma preparation. Potential hazard of convalescent plasma therapy is the risk of transmission of infections to the recipients as well as healthcare workers. Another threat is the probability of transmitting more viral particles of the causative agent to the recipient that could lead to worsening of the clinical condition.[14] The already established complications of transfusion may also affect convalescent plasma therapy. Contraindications to plasma therapy include allergy to plasma proteins, sodium citrate toxicity or selective IgA deficiency.[16]

Way forward

In developing countries, like Pakistan, it is pertinent to establish a donor registry. Awareness programs need to be implemented to recruit donors. Central and regional fully equipped authorized blood bank facilities for collecting, storing and issuing donations are necessary for proper implementation of convalescent plasma therapy program. Trained personnel and adequate apheresis

Citation: Mahmood A, Mahmood R, Khan M, et al. Convalescent plasma therapy for Covid 19 - A perspective. *Hematol Transfus Int J.* 2021;9(2):28–30. DOI: 10.15406/htij.2021.09.00247

equipment should be available to provide these services to a large numbers. Facility of apheresis is not present on a mass level, so in order to implement these services, convalescent plasma will have to be extracted from whole blood donations. Standardized method for preparation and storage of plasma should be practiced and strictly followed. Administrative, logistic and financial aspects need to be considered. National regulatory authority has to monitor all processes from selection of donor to transfusion of convalescent plasma to the patient as well as post-transfusion follow-up. In resource-constraint countries, it is important to collaborate with NGOs and local and international funding agencies for logistic and financial assistance and implementation of plasma therapy program. Services for Banking of donor plasma in donor banks for later use needs to be in place.

Stringent donor selection criteria have to be followed. Selection of donors should be based on neutralizing antibody titers assessed by standard testing techniques. Testing facilities for determining antibody titers need to be established. It is pertinent to rationalize the use of convalescent plasma to avoid potentially harmful effects of transfusion. Clinical assessment of patients by senior physicians should be done to determine patient suitability for convalescent plasma. Multidisciplinary team including critical care specialist, anaesthetist, medical specialist and transfusion specialist should be the final authority to make a risk benefit analysis to ensure judicious use of plasma therapy. All these facilities are not available in our country except for a few specialized centers. It is important to establish these services, provide standard adequate equipment and develop expertise for proper plasma collection. Proper screening should be done to ensure non-reactivity of plasma for transfusion transmitted infections including HBV, HCV, HIV, syphilis and malaria using regularized in vitro diagnostic systems. Special consideration should be given in elderly population eligible for convalescent plasma therapy in order to avoid well established complications like transfusion associated circulatory overload (TACO) commonly encountered in this age group. Vigilant monitoring of the transfusion should be carried out by trained personnel for timely recognition of any transfusion reaction or transfusion-related complication.

It is important to conduct well controlled trials to determine the efficacy of this treatment and any adverse effects in our population. Registry should be maintained of all Covid-19 patients along with their outcome. There is also a need to assess combination therapies and other alternative therapeutic regimes to compare response and outcome of convalescent plasma therapy with other therapies. Long term follow-up of patients receiving convalescent plasma therapy for monitoring late side effects is also warranted. Further research needs to be initiated to manufacture plasma derived and purified immunoglobulin products for commercial availability.

Acknowledgments

None.

Conflicts of interest

The authors declare no conflicts of interest.

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