# SHORT COMMUNICATIONS

## CONVALESCENT PLASMA FOR COVID-19 INFECTION: EVIDENCE AND CLINICAL APPLICATION

**Ghassan Umair Shamshad, Raheel Iftikhar, Qamar Un Nisa Chaudhry, Jehanzeb Ur Rehman, Parvez Ahmed**

Armed Forces Bone Marrow and Transplant Centre/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

## ABSTRACT

Corona virus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV2) and has currently affected 11 million people worldwide with 0.53 million deaths. While there is ongoing trials and research for newer therapeutic options including antivirals (remdesivir), anti-interleukin 6 (tocilizumab), vaccines and antimalarials; there is renewed interest in the use of old therapeutic tools as well. Convalescent plasma has been used historically for measles, poliomyelitis, Spanish flu pandemic, severe acute respiratory syndrome (SARS1) and Ebola epidemics with conflicting results. With widespread use of convalescent plasma throughout the world as investigational drug for COVID-19, it is important to review past experience with its use in various outbreaks, potential role in COVID-19, and clinical application during current pandemic and challenges faced by resource constrained countries.

**Keywords**: Corona virus, Convalescent plasma, Mortality.



Plasma collected from a person recovering from a known illness is called convalescent plasma and its use to provide passive immunization is called Convalescent plasma therapy. It involves the administration of plasma containing antibodies against a given agent to a susceptible individual for the purpose of preventing or treating an infectious disease due to that agent[1]. Use of Passive antibodies dates back to 1890s and was the only means for treating different infectious diseases before the discovery of antimicrobials. During 1918 influenza virus pandemic, convalescent plasma was used for a large number of patients. A meta-analysis including 1703 patients documented lower mortality in patients receiving convalescent plasma[2]. Literature review showed that convalescent plasma was also used in outbreaks of poliomyelitis, measles and influenza with conflicting results regarding their efficacy. More recently, convalescent plasma was used in 2009-2010 H1N1 Influenza pandemic in patients requiring critical care. Studies by Hung *et al* and Hui *et al* documented lower respiratory virus burden, reduction in circulating pro-inflammatory Cytokines and reduced mortality in patients receiving convalescent plasma. Its use was recommended by world health organization (WHO) in Ebola epidemic of 2014 and a protocol for its use was drafted. Follow-up studies, however failed to document a survival benefit of convalescent plasma in affected patients.

The mechanism of action by which passive immunization works is viral neutralization. Passive antibody therapy is most effective when used for prophylaxis or early in disease course. Exact etiology for temporal variation is unclear but it is hypothesized that this could be due to the fact that passive antibody works by neutralization of initial inoculum which is smaller in early disease course. In recent COVID-19 pandemic, Lancet infectious diseasesand Cunningham *et al*, concluded that use of convalescent plasmais a tried and tested approach and appears to be helpful until definitive and effective treatments are found[3]. A recent case series by Shen *et al*, published in JAMA reported clinical improvement in 5 critically ill patients of COVID-19 and ARDS treated with convalescent plasma. On March 24, 2020. FDA authorized use of convalescent plasmafor investigational use under

**Correspondence: Dr Ghassan Umair Shamshad,** Diagnostic & Procedure Lab, AFBMTC, Rawalpindi Pakistan
*Email: g_umair@yahoo.com*
*Received: 07 Jul 2020; revised received: 10 Jul 2020; accepted: 27 Jul 2020*

the traditional IND regulatory pathway (21 CFR 312). A Cochrane review published in May 2020 by Valk *et al*, failed to document evidence supporting clinical benefit of convalescent plasma for patients with COVID-19[4]. A recently published first randomized trial concluded that for severe and critically ill patient, use of convalescent plasma did not significantly improve 28-day survival, however there was early viral clearance, shorter ICU stay and early discharges. Although trial was prematurely terminated due to lack of patient recruitment[5]. Despite FDA approval for use as investigational treatment and ongoing trials across the world, there are various challenges regarding use of convalescent plasma in resource constrained countries like Pakistan. Most important being lack of regulatory use of convalescent plasma. Due to excessive media hype, biased opinions and undue expectations, convalescent plasma has been used injudiciously and unregulated across the country without enrolling patients in clinical trial. Moreover, there have been unfortunate incidences of sale of plasma by recovered donors. Other challenges include, limited availability and absence of proper consent of COVID 19 recovered donor, lack of testing facilities for detection and quantification of viral neutralization antibodies to select optimal donor, non-availability of nucleic acid testing and methods for viral inactivation of apheresis product, financial constraints, and deficiency of skilled manpower and apheresis kits on a large scale.

Clinical application of convalescent plasma requires enrollment and administration in a centre approved for clinical trial. Informed consent should be obtained and the donor should fulfill all the criteria of a healthy blood donor as per AABB/WHO guidelines (with the exception of the history of acquiring COVID-19 during last 4-8 weeks)[6]. Prior diagnosis of COVID-19 should be documented by a SARS-CoV-2 real time polymerase chain reaction (RT-PCR). Donor should be clinically asymptomatic for at least 21 days prior to donation, in addition to the mandatory requirements of blood donation screening (HBsAg, anti-HCV, anti-HIV, syphilis and malaria). The blood samples should be tested for SARS-CoV-2 by nucleic acid testing (NAT) / RT-PCR. Testing for presence of neutralizing antibodies (preferably quantitative titers greater than 1:320) is a mandatory requirement. Plasma collection should preferably be by apheresis, as larger volumes (800-1200 ml) of convalescent plasma can be collected and can be used for more than one patient. Plasma collection by apheresis can be repeated after 2 weeks gap from same donor. Alternatively, plasma can be separated from whole blood by centrifugation, but the volume obtained is less and this method cannot be utilized again on the same donor before 12 weeks. It is important that donor experience is pleasant and comfortable so other recovered patients are encouraged to donate. In the absence of further clinical evidence, 200-250 mL of convalescent plasma is given to patient and can be repeated after 3-5 days if required; whereas, for pediatric patients, a dose of 10 mL/kg can be used.

As passive immunization is more effective for prophylaxis and when given early in disease course, can lead to reduction in mortality. Preferably, convalescent plasma should be administered to patients with mild disease who are at risk of disease progression (like immuno compromised, one or more prior organ dysfunction) or patients with moderate to severe illness with aim to prevent disease progression and requirement for ventilatory support. In a resource constrained country like Pakistan, pros and cons of convalescent plasma therapy must be weighed. It is important to balance pros of possible clinical efficacy versus cons of cost, donor availability, and risks of plasma infusion. Different clinical trials are ongoing and will be helpful in refining clinical application of convalescent plasma. A clinical trial registered at Clinical trials. Gov NCT 04352751 by Shamsi *et al*, is currently recruiting patients in Pakistan and results are awaited. There is need to have well designed prospective randomized trial comparing convalescent plasma to control group in ongoing pandemic, without

which clinical efficacy of convalescent plasma will continue to remain in question.

## CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

## REFERENCES

1. Arabi YM, Hajeer AH, Luke T, Raviprakash K, Balkhy H, Johani S, et al. Feasibility of using convalescent plasma immunotherapy for MERS-CoV infection, Saudi Arabia. Emer Infect Dis 2016; 22(9): 1554-60.
2. Luke TC, Kilbane EM, Jackson JL, Hoffman SL. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? Ann Intern Med 2006; 145(8): 599-609.
3. Cunningham AC, Goh HP, Koh D. Treatment of COVID-19: old tricks for new challenges. Springer; 2020.
4. Valk SJ, Piechotta V. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a rapid review. Cochrane Database Systematic Rev 2020; 5 (5): CD013600.
5. Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: A randomized clinical trial. J Am Med Assoc 2020; e2010044.
6. Organization WH. Blood donor selection: guidelines on assessing donor suitability for blood donation: World Health Organization; 2012.