Editorial

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COVID-19 and convalescent human plasma: Prospects and challenges

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COVID-19 (Coronavirus disease 2019) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2),[1] has challenged the global health and economy in recent times. It has established the fragility of our healthcare systems in confronting emergencies related to the spread of new infectious agents that require the rapid development of effective care strategies. The outbreak which originated from a seafood market in the Chinese province of Hubei has matured into a global pandemic with 8.66 million cases and 0.46 million deaths in 216 countries and territories (as of June 20, 2020).[2] Although not confirmed yet, the virus is assumed to be zoonotic due to sequence similarity with a bat-coronavirus.[3]

COVID-19 has diverse manifestations, with the great majority of infected individuals having only minor symptoms or even no symptoms.[4,5] The preliminary data concerning COVID-19 has shown a 2% mortality rate and acute respiratory distress syndrome in 20.1% of patients.[6] Older individuals of male sex and those with previous respiratory conditions seem to be at the highest risk for severe complications.[7,8] Studies have also reported COVID-19's clinical linkages with hypertension, diabetes, and other obesity-associated and cardiovascular ailments.[9-11]

Coronaviruses have a long history of affecting the human population,[12] two significant pandemics in the 21st century, i.e. severe acute respiratory syndrome (SARS)[13] and Middle East respiratory syndrome (MERS)[14] were caused by coronaviruses. The recent SARS-CoV-2 is the seventh coronavirus identified. The other six include SARS-CoV, MERS-CoV, HKU1, NL63, OC43, and 229E, the last four being the least pathogenic.[15]

Even though vaccination strategy is indeed a viable goal, the development of a vaccine necessitates a time frame not compatible with the emergency circumstances we have encountered. It is also a prophylactic strategy that has no use in the therapeutic scenario. In the absence of an established effective therapy, present management involves supportive care, containing invasive and noninvasive oxygen support and the use of antivirals and antibiotics.[16] The World Health Organization (WHO) has recommended that the management of COVID-19 should focus on infection prevention, case identification, and supportive care including fluid management, oxygenation, and ventilation.[17]

With these unprecedented circumstances, the transfusion of convalescent plasma for the treatment of COVID-19 critical patients appears to be a logistically feasible therapeutic approach. The convalescent plasma, extracted from the blood of recovered patients, has antibodies to the SARS-CoV-2 that are effective against the virus. Convalescent plasma is typically collected by plasmapheresis technique to guarantee larger volumes. The key established mechanism of action for convalescent plasma is clearance of viraemia, which usually occurs 10-14 days after infection.[18] Historical precedents exist on the effective use of convalescent plasma therapy. This therapy, called passive

immunization or passive antibody therapy was successfully implemented during the 1918 influenza pandemic in Spain where 1,703 patients were transfused with a human plasma of recovered influenza patients showing positive results.[19] The convalescent plasma has been used during epidemics with other respiratory infections, including the H1N1 influenza virus pandemic in 2009-2010, the SARS-CoV epidemic in 2003, and the MERS-CoV epidemic in 2012. The findings showed promising results such as low viral load,[20,21] presence of antibodies in convalescent plasma,[22] lower mortality rates, and a shortened hospital stay.[18,23,24] In addition to respiratory viruses, the convalescent plasma was used to treat Ebola virus disease as an empirical treatment measure.[25-27] However, because EBOV is a Biosafety Level 4 pathogen (SARS-CoV-2 is Level 3), and because EBOV outbreaks have mostly occurred in resource-poor settings, it has been difficult to carry out high-quality, randomized controlled trials on this subject.

Soon after the COVID-19 pandemic, numerous experts proposed convalescent plasma as a possible therapeutic strategy.[28,29] So far, there are limited studies published to assess the clinical outcome of convalescent plasma transfusions in COVID-19. The first study by Shen *et al.,*[30] from China was a case report where five patients with acute respiratory distress syndrome were transfused with convalescent plasma. Encouraging results were observed after the first week of transfusion with no serious adverse effects of transfusion. In the second pilot study from China, 10 patients were transfused with convalescent plasma showing comparable clinical findings and undetectable viraemia.[31] Although both these studies reported positive outcomes, they had some limitations. During the study duration, the antiviral drugs were also administered to the patients along with other drugs like steroids, hence making it impossible to assess the precise role of convalescent plasma to the outcomes reported. Similarly, the studies were conducted without a control group to which the patient group could have been compared. A third study (also from China) published by Li *et al.,*[32] addressed the limitation of the control group and conducted a randomized control trial on 103 participants with severe COVID-19 manifestations. The results compared the convalescent human plasma transfusion along with standard treatment versus the standard treatment alone and did not significantly increase the time to clinical improvement. The study, like the former two studies, also had the limitation of a small sample size.

However, regardless of the limitations, transfusing plasma through this approach appears to be relatively safe provided the guidelines provided by the World Health Organization on the use of convalescent plasma in a pandemic, are followed.[33] The guidelines highlight the need for quality control and standardization in the selection donor, collection of convalescent plasma, and screening for transfusion-transmitted infection, to maximize therapeutic effectiveness. Notable contra-indications to convalescent plasma are allergy to plasma proteins or sodium citrate, selective IgA deficiency, or use of immunoglobulins in the last 30 days (risk of serum sickness), concurrent bacterial or viral infections, thrombosis, pregnancy, and breastfeeding.[34]

In recognition of these data, the United States Food and Drug Administration[35] allowed the emergency use of convalescent plasma as an Emergency Investigational New Drug (IND) in life-threatening COVID-19 patients. However, this does not take into account the use of convalescent plasma for the prevention of infection.

Currently, more than 4.25 million patients have recovered from COVID-19 across the globe (as of June 20, 2020), presenting a valued resource of convalescent plasma for treatment.[2] The pandemic in Pakistan is well established with more than 166,000 confirmed cases, 3,229 deaths, and 61,383 recovered patients.[2] Following the government's endorsement on the use of convalescent plasma and subsequent issuance of guidelines,[36] convalescent plasma donation was initiated on an experimental basis. The initial findings of the ongoing trial performed on 14 severe COVID-19 patients, reported that 86% (n=12) recovered without the requirement of a ventilator and RNA was negative for six patients (43%) by the eighth day of plasma transfusion.[37]

Although the strategy of convalescent plasma transfusion shows promise, it is an investigational product and there is limited evidence to support its use for COVID-19 treatment. In-depth clinical and laboratory research is imperative to assess the efficacy of convalescent plasma before administering it routinely. This treatment seems to be beneficial for the interim period until an absolute effective treatment is made available.

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