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One year of COVID-19 pandemic: Challenges and lessons learnt on the transfusion of convalescent plasma to COVID-19 patients

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) has affected millions of people worldwide and caused disruptions at the global level including in healthcare services. The pandemic has caused significant socio-economic disruptions at the global level with an impact on healthcare deliveries. Maintaining an adequate and safe blood supply is one of the primary aims of blood centers across the world. COVID-19 has dramatically affected blood collections, working of blood establishments, and clinical use of blood products.

The World Health Organization (WHO) developed and disseminated an interim guidance on maintaining a safe and adequate blood supply during the COVID-19 pandemic [1]. This guidance recommended: (1) mitigating potential risk of transmission through blood transfusion, staff risk, and donor exposure to COVID-19, as well as risk of reduced availability of blood donors; (2) managing blood demand; (3) ensuring undisrupted supply of critical materials and equipment; (4) communicating to ensure that donors, recipients, all staff, relevant stakeholders and the population are properly informed; and (5) collection of convalescent plasma (CP) from patients who have recovered from COVID-19.

Convalescent plasma (CP) administration, as part of treatment to provide immediate immunity, has been used to improve the survival rate of patients with severe acute respiratory syndromes of viral etiology [2]. There are number of studies reported positive outcomes, including decreased mortality in the Spanish Influenza A (H1N1) infections in 1915–1917 [3], the more recent Influenza A (H1N1) infections in 2009/2010 [4], and more importantly, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in 2003 [5]. A systematic review and exploratory meta-analysis by Jenkins et al. performed in 2014 identified 32 studies of SARS coronavirus infection and severe influenza which revealed evidence for a consistent reduction in mortality upon plasma therapy [2].

With the previous experience of use of CP in the outbreak of Ebola virus and interim guidance issued by WHO in 2014 for empirical use of CP in Ebola outbreak and limited clinical data available in the beginning of COVID-19 pandemic, various countries across the world suggested that CP can have a therapeutic benefit in COVID-19 [2, 6, 7]. In the absence of any known effective therapy and considering the potential for local production, COVID-19 CP was becoming a global priority for investigational use. High income countries with established national infrastructures and effective regulatory oversight could produce quality and safe plasma for transfusion that complies with international standards [8] and have initiated controlled clinical studies of COVID-19 CP [9, 10].

But, in low- and middle-income countries, in the absence of a well-organized and nationally regulated blood collection system and limitations of critical resources and manpower, safe blood collection and transfusion was a challenge. Nevertheless, provision of COVID-19 CP in low- and middle-income countries needed to comply with the same principles of product safety and ethics regarding collection and use as in Hospital Infection Control (HIC), and guidance was needed.

The preparation of COVID-19 convalescent plasma (CCP) in various countries started organizing as national initiatives supervised by the Ministries of Health and coordinated by the National Blood Services or blood establishments meeting quality standards to assure that legal and ethical guidelines for human research are applied to COVID-19.

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The eligibility criteria evolved over time in some countries due to testing limitations at certain phases of the pandemic or changes in the definition of a confirmed case. Different countries developed different guidelines about selection of CCP donors. Initially the donors were required to have proof of infection in the form of a positive polymerase chain reaction (PCR) test performed on a nasopharyngeal swab sample and in some countries a positive PCR test and/or antibody test, and be 28 days from infection and symptom free. The latter criteria were changed to complete resolution of symptoms at least 14 days before the donation [9, 11]. The definition of recovery was also variable between countries. The majority of the institutions used a complete resolution of symptoms while some institutions required confirmation of negative SARS-CoV-2 testing and the absence of symptoms. Some institutions relied on the regulatory authorities' definition (e.g., Ministry of Health in India, Singapore, China, Argentina, and Italy).

There are two sources of CCP: (1) volunteer CCP donors with a history of COVID-19 who are now symptom-free and (2) traditional blood donors with an unknown history, who upon testing their donation sample, are found to have antibodies to both Spike and Nucleocapsid proteins. At present, the majority blood centers require the CCP donors to be symptom-free for 14 days and test positive for both Spike and Nucleocapsid antibodies at the time of donation. However, as an additional precaution against contagion in the donor room, prior demonstration of resolution of infection by a non-reactive nucleic acid test (NAT) for SARS-CoV-2 performed on a nasopharyngeal swab sample can be considered for collections of CP between 14 and 28 days after full recovery from symptoms.

After the introduction of vaccination against SARS-CoV-2, initially selection criteria for CCP donations were 28 days post-vaccination to an individual who has tested positive and symptom free, which was revised later to reduce waiting period after vaccination to 14 days.

There were many challenges in the process of collection and transfusing to the right patients, and as every country evolved through knowledge from the data published over the time, many lessons were learnt by transfusion medicine specialists and clinicians. Few of the key points are as follows:

1. **Comprehensive data** was lacking regarding the regional and national blood supply, the number of units available in hospitals, and hospital usage patterns. This impaired the ability to predict the effect of the pandemic on the blood supply. It impacted a large portion of routine blood supplies of the blood centers across the countries. Additionally, lack of data impaired the blood centers' ability to predict the effect of cancellation of elective procedures and need for blood products.
2. **Donor recruitments:** The information, education, and communication to motivate CCP donors was a challenging task for the transfusion services that were already grappling with issues of motivating and recruiting whole blood donors, more so in lower- and middle-income countries to meet the blood and blood component demands of patients with non-COVID indications such thalassemia, pregnancy, oncology, and other medical and surgical emergencies, more so when there is always a low donor turn over for blood supplies and a challenge to meet the demands. Donors were not having knowledge about convalescent plasma donation when they were under medical supervision during quarantine or treatment.
    a. Movement of donors amid the national lockdowns and recruiting donors for CCP donation was a big challenge faced by many countries, especially in low- and middle-income countries.
    b. There were no qualified lists of CCP donors.
    c. Another donor recruitment challenge was related to timing. Initially, national regulators issued guidelines about requirement of 28-days deferral period after a CCP patient became asymptomatic. Since the epidemic was in its early stages, many COVID-19 convalescent individuals had only recently recovered from their illness. Therefore, the 28-day wait period significantly limited the size of the eligible donor base.
3. **Testing facilities, resources and logistics:** The practice of testing CCP donors for anti-SARS-CoV-2 antibodies before the donation was variable. The lack of licensed tests for anti-SARS-CoV-2 presented challenges to donor recruitment and CCP product characterization. There was a plethora of new serologic and molecular tests in the market for SARS-CoV-2 that had received emergency use authorization (EUA) by various countries' FDAs; however, lack of test availability remained an issue throughout the two phases. Since there were no widely available antibody titer tests to verify CCP product efficacy, guidelines for additional donor samples to be collected and stored for future titer testing were issued by national authorities.

Testing for anti-SARS-CoV-2 antibodies was performed using different testing platforms such as the enzyme-linked immunosorbent assay (ELISA), chemiluminescent assay (CLIA), chemiluminescent microparticle immunoassay (CMIA) and the virus neutralization test. Some institutions relied on a rapid screen test of donors for the presence of anti-SARS-CoV-2 antibodies on the day of donation; some centers used two different testing methods to screen the donors,

either using different testing platforms or different manufacturers. Initially, there was no consensus on IgG antibodies cutoff for different assays but later guidelines were in place for prospective CCP donor eligibility criteria. This could have led to low titer CCP product collection in the beginning of pandemic and could have affected the outcomes of patients leading to skewed data and results of various trials and published studies, especially in resource-constraint countries.

The need for additional personal protective equipment (PPE) put a strain at a time when there were national shortages. Severe supply chain shortages of PPE, disinfectants, paper goods, apheresis kits, and breakdown supports persisted throughout; more during first wave of pandemic. This created pressure on blood centers to find needed supplies, which was affected more where there was lack of prior relationships with vendors. Single source suppliers and just-in-time inventory practices, initially designed to reduce expenditures, exacerbated the situation.

4. **Operations:** Setting up of CCP collection facilities as a new service by some centers during the pandemic and integrating CCP production planning into operations was a challenge. COVID-19 convalescent plasma protocols had to be deployed rapidly early in the pandemic despite the lack of any evidence from high-quality clinical trials and/or published data on its efficacy and safety. Starting a CCP collection programme required regulatory permissions in some countries, test development and/or acquisition, validation, protocol set-up, and continuous training. This occurred while many centers were busy maintaining blood inventory and implementing COVID-19-related safety precautions and social distancing, which slowed the facility's operations. The challenge was further augmented with the difficulties in predicting the pandemic's effect on the blood supply and the regional and national needs. Early and ongoing collaboration between all stakeholders involved in the multi-disciplinary project was an important factor to overcome these challenges early. It was vital for ensuring early interest within the organizations and acceptance of various internal stakeholders to work together to achieve rapid acquisition and staff's commitment to adapt to the rapid and continuous changes in the operations during the pandemic. This involved regulatory authorities, national blood services, hospital blood banks, and treating hospitals.
5. **Donor, staff, and society concerns:** Insufficient knowledge of COVID-19 and protection measurement required for the collecting staff was reported as a challenge. Inconsistent national communications regarding disease risk and mitigation, blood donation safety, and the need for PPE led to confusion of donors and staff [12]. There were concerns of CCP donors on their health, post-COVID-19 illness, and their worries that CCP donations could affect their immunity to reinfection (both COVID-19 and non-COVID-19), resulting in donor's hesitation to donate CCP in hospital-based blood facilities. The motivation and continuous reassurance of the recovered patients to donate CCP by the treating physicians led to improved numbers of CCP donations in most of the centers.
6. **Education and training:** Several institutions faced challenges with the limited number of trained staff and lack of experience in collecting CCP, as its collection facilities needed to be established quickly. Several institutions were dependent on the clinicians and trial coordinators in the hospitals to recruit donors from recovered patients, assess and consent patients for CCP in the trial environment. There was a need for continuous training, especially with the successive changes in the CCP donor eligibility criteria. Training a small group of hospital-based clinicians to obtain consent from the patients was found to be useful.

In India, National Blood Transfusion Council issued the National guidance to Blood Transfusion Services in the light of COVID-19 on March 25, 2020 and revised second interim document on June 25, 2020 [13]. The permission was granted for use of CP under the ambit of Indian Council of Medical Research (ICMR) trial (Placid trial) as early as April, 2020 and, it was authorized as an "off-label/Emergency Use Authorization" therapy by the Drug Controller General, India. Subsequently, it was incorporated in the "Clinical guidance for management of adult COVID-19 patients" AIIMS/ICMRCOVID-19 National Task Force/Joint Monitoring Group, Ministry of Health and Family Welfare, Government of India on June 15, 2020, for patients with moderate disease who are not improving (oxygen requirement is progressively increasing) despite use of steroids with special prerequisites of ABO compatibility and crossmatching of the donor plasma and suggested dose was variable ranging from 4 to 13 mL/kg (usually 200 mL single dose given slowly over not less than 2 hours [14]. Although guidelines suggested that neutralizing titer of donor plasma should be above the specific threshold (plasma IgG titer against S-protein receptor-binding domain, RBD, above 1:640 should be used) but it was not available in the beginning of pandemic. Donor eligibility criteria for whole blood donations were in accordance to the Drugs & Cosmetics Act 1940 and rules 1945.

To summarize, convalescent plasma therapy is one of the promising therapies used for COVID-19 patients, to be administered in hospital settings only. COVID-19 convalescent plasma donors are recovered patients, with

heterogeneity in patient profiles and viral dynamics in the host which lead to biological variability of the products, so each CP unit is a "Batch" in itself. Early and rapid deployment of a CCP collection programme during COVID-19 pandemic, at a time when the blood establishments were struggling in meeting blood supply, has brought up very unique challenges at different levels in all countries. These challenges included wide range from the lack of resources, short supplies, personnel loss, to operational challenges and the need for inter-organizational collaboration; most importantly, recruitment of recovered patients who are eligible to donate blood and CCP, while handling staff, donors, and society concerns. The World Health Organization recommended that blood services should take steps to assess, plan, and respond to the emerging challenges appropriately and proportionately after undertaking a data-driven risk assessment [15]. The role of professional organizations in sharing experiences and providing guidance and recommendations is paramount. Till the time, any specific therapy is developed for any new viral contagion; convalescent plasma therapy has proved to be the bridging therapy, as seen earlier with Ebola virus outbreak and now with COVID-19; more so with the emergence of variants in local demography.

To conclude, with the challenges faced and lessons learnt in this pandemic across the globe, convalescent plasma collection programme should be established as potential therapeutic options on an international level which can be utilized as pandemic preparedness in developing infrastructures and framework in facing similar pandemics in the future so that convalescent plasma therapy can readily and timely be available to patients.

Keywords: Anti-SARS-CoV-2 antibodies, Challenges, Convalescent plasma, COVID-19 pandemic, Lessons

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Author Contributions

Sadhana Mangwana – Conception of the work, Design of the work, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

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Conflict of Interest

Author declares no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.