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Convalescent Plasma Therapy: Solution to COVID-19?

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The entire world is currently suffering from a major threat on human health, imposed by a pneumonia associated with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2), the disease emerging in Wuhan, China in December, 2019, being named as coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) and declared as a pandemic by WHO in March, 2020. Because of the current unavailability of proper medications, drugs, antiviral agents, vaccines or other therapeutic strategies, the ongoing devastating global pandemic, which has already claimed countless lives, has created a high impetus for and turned the spotlight onto exploring the prospect of passive immunization by using convalescent white blood cell and Convalescent Plasma (CP) for the prevention and treatment of patients suffering from COVID-19. Convalescent blood products (CBPs), obtained by collecting whole blood or plasma from a patient who has survived a previous infection and developed humoral immunity against the pathogen responsible for the disease in question, are possible sources of specific antibodies of human origin. Different CBPs have been used to achieve artificially-acquired passive immunity: (i) Convalescent Whole Blood (CWB), CP or Convalescent Serum (CS); (ii) pooled human immunoglobulin (Ig) for intravenous or intramuscular administration; (iii) high-titer human Ig; and (iv) polyclonal or monoclonal antibodies. Apheresis plasma is the preferred therapeutic tool because of several reasons: (i) larger volumes collected per session; (ii) possibility of more frequent donations; and (iii) absence of impact on the hemoglobin of the donor [1].

The protective and therapeutic benefits of transfusing plasma or serum, derived from immune survivors of an infectious disease, were initially studied in animal models at the beginning of the 20th century. It was observed that plasma transfusion from patients recovering from a particular infection were able to neutralize the pathogen and eventually lead to its eradication from the blood circulation. This knowledge was translated into human use in 1916, when 26 patients suffering from acute poliomyelitis were treated with convalescent serum from polio survivors with some favorable outcomes. Studies conducted a century ago during the Spanish influenza pandemic of 1918 to 1920 suggested for the first time the efficacy of CP as a potential therapy for viral infections [2]. Since then, CP therapy, a form of classic adaptive immunotherapy has been applied to the prevention and treatment of many infectious diseases. Over the past two decades, CP therapy has been applied safely with satisfactory efficacy in the treatment of measles, chickenpox, parvovirus B19, 2003 SARS-CoV, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), avian influenza A (H5N1) virus, and influenza A (H1N1) pdm09 virus, the last one to cause 2009 HIN1 pandemic, without however showing significant positive results against 2014 Ebola virus infection, due to the absence of data of neutralizing antibody titration for stratified analysis [3-5]. Public Health England and International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) published a decision-making support tool on potential therapies for MERS-CoV, that highlighted CP and other neutralizing antibody-containing immunotherapeutics (e.g., hyperimmune immunoglobulins and monoclonal antibodies) as the most promising potential treatments for MERS-CoV illness, deserving evaluation in human clinical trial(s). Despite a long history of CP usage, clinical efficacy has not been studied robustly and conclusions are rather weak, likely because CP was mostly applied in critical situations, during massive epidemic/pandemic outbreaks, requiring immediate actions. People have used this technique as the last resort, since the effectiveness of this therapy is governed by many factors like pathogen and treatment protocols, *viz*., timing, volume and dose of administration. It is equally important to understand the antibody characteristics and titers, able to affect the course of disease as well as the role of the immune response of the recipients of CP therapy [6,7].

The COVID-19 pandemic has turned out to be an unprecedented global public health crisis with significant humanitarian consequences. The current treatment of COVID-19 is limited to general supportive care, with provision of critical care like mechanical ventilation, due to the dearth of approved therapies or recognized vaccines. Since the virological and clinical characteristics share similarity among SARS-CoV, MERS-CoV and SARS-CoV2, CP therapy might be a promising

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treatment option for COVID-19 rescue [8]. The Food and Drug Administration (FDA) has proposed that study and application of investigational CP therapy may provide a clinical effect for treatment of COVID-19 during the public health emergency. This has led to broader interest to leverage CP from recovered COVID-19 patients for treatment or prophylaxis of health care workers and other patients. Convalescent plasma has the advantage that while its antibodies limit viral replication, other plasma components can also exert beneficial effects such as replenishing coagulation factors when given to patients with hemorrhagic fevers. The FDA has provided guidelines to set up protocols for collection, preparation and administration of apheresis-collected CP in response to the current pandemic.

The following elements are essential parts of a CP program: (i) screening of recovered COVID-19 patients to identify available donors who meet the eligibility criteria to donate convalescent serum; (ii) assuring that plasma donation will be safe for the recovering patient/donor, adopt the approved serological assays to detect SARS-CoV2 in serum and measure viral neutralization; (iii) determining antibody levels in eligible donors preferably with high neutralizing antibody titers, the recommended titer >1:320 by FDA; (iv) identifying blood banking facilities to process the plasma donations, proper handling of plasmapheresis and selecting specific product to be prepared (fresh plasma or lyophilized plasma); (v) determining the amount of plasma to be collected and product volume; and (vi) establishing a dosage schedule, based on the knowledge of SARS-CoV2 antibodies, as well as a registered documentation for possible future donations [9].

The convalescent donors between the age groups of 18 and 65 are considered as subjects, having no infectious symptomatology and showing negative test for COVID-19 after 14 days of recovery. These tests must be repeated 48 h later and at the moment of donation. Symptoms of infection must have completely resolved by 14 days prior to donation. If female, donors must either have never been pregnant, or been tested negative for Human Leukocyte Antigen (HLA) antibodies since their most recent pregnancy. Antibody titers ≥160 are recommended, but if an ABO-compatible unit is unavailable, ≥80 is acceptable. As CP production requires high quality standards, it must be free from any infection, hence tests for Human Immunodeficiency Virus (HIV), hepatitis B, hepatitis C, syphilis, human T-cell lymphotropic virus 1 and 2 and *Trypanosoma cruzi* (if living in an endemic area) should be carried out. Donors from endemic areas for tropical diseases (e.g., malaria) should be excluded [10,11]. In addition to molecular tests, it is critical to recognize the emotional situation, to explore susceptibilities, and guarantee not to exploit the donors. Only voluntary donors are expected to be involved in CP therapy; no remuneration of donor by health care setting or patient, other than facilitating the travel is permissible by health authorities according to WHO guidelines. Informed consent of the donor should be obtained with provision of full privacy and confidentiality of donor. The information in this regard should be written and structured in accordance with WHO recommendations. The donor hemovigilance form should be filled for each donor as recommended by Safe Blood Program authorities. There is no standard transfusion dose of CP, which may range between 200 and 500 mL in single or double scheme dosages. Currently, the recommendation is to administrate 3 mL kg^{-1} per dose in two days, which facilitates the distribution of plasma units (250 mL $unit^{-1}$). Studies have not yet established what minimum neutralizing antibody titer is necessary for therapeutic benefit from CP. Depending on the volumes needed and the neutralizing activity of donated CP, preparations could be pooled or used individually, and the plasma may be treated with pathogen reduction technology [12].

Apheresis is the recommended procedure to obtain plasma. This procedure is based on a continuous centrifugation of blood from donor to allow selective collection of plasma. The efficiency of this technique is around 400-800 mL from a single apheresis donation. This amount of plasma could be stored in units of 200 or 250 mL, and frozen within 24 h of collection (by storing at -80^{0}C) to be used for further transfusions [12].

Convalescent plasma is reported to reduce viral load and was safe when administered in China during this current outbreak. There were no severe adverse effects reported from transfusion of CP in these recipients [13]. Rajendran et al. (2020) [14] suggested that CP may reduce mortality in critically ill patients, with observable beneficial effect on clinical symptoms after administration of CP. They also noted increase in neutralizing antibody titers and disappearance of SARS-CoV2 RNA in almost all the patients after CP therapy, thereby reducing mortality. They also recommended well-designed large multicenter clinical trial studies to establish the efficacy of this therapy for COVID-19 patients. Duan et al. (2020) [13] transfused a dose of 200 mL of CP obtained from recent donors with the neutralizing antibody titers above 1:640 to patients, in addition to supportive care and antiviral agents. It was found that CP therapy was well tolerated without adverse effects and could impressively lower down the viral load, improve the clinical outcomes in the form of increased lymphocyte counts and decreased C-reactive protein, along with disappearance of viremia in seven days. However, it is necessary to optimize the dose and time point as well as ensure clinical benefit by investigating larger, well-controlled trials. It seems mandatory to conduct randomized controlled trials to confirm the usefulness of this intervention in both hospitalized patients with mild/severe symptoms and those in intensive care unit.

Despite the potential utility of passive antibody treatments, there have been few concerted efforts to use them as initial therapy against emerging and pandemic infectious threats. The absence of large trials certainly contributes to hesitance in employing this treatment and suspicion regarding its success. The most effective formulations are still largely unknown. In addition, there are several other challenges that restrict the application of CP therapy. While in case of a large-scale pandemic or epidemic, it may be easier to find available donors and recruit them to collect their plasma, the situation may be difficult in cases where the infection is confined or localized with lesser people being affected, so that CBP supplied may appear less effective due to possible strain variation of the pathogen in question. Proper identification, selection and recruitment of potential donors can also be difficult, as convalescent subjects must also meet donor selection criteria, in compliance with national policies and routine procedures [1]. Often it is found that only a small number of donors voluntarily come forward and there is a high reluctance on the part of potential donors. There is a prevalent stigma and fear among the donors (especially in the developing countries, which lack sound health care systems) that they might again catch infection if they come to the hospitals to donate plasma. Many people infected once with coronavirus often suffer from immense trauma and psychological stress, since they were either ostracized in the society or not properly looked after by health care workers when admitted to the hospitals. Health care workers in such cases will have to take the responsibility to deal with the COVID-19-infected patients sympathetically, remove their fear and anxiety and encourage them to donate plasma

after discharge from the hospitals. As with any other blood product transfusion, there are certain predictable or known side effects that also apply to CP therapy, such as transfusion-related infections, serum sickness, fluid overload and transfusion-related acute lung injury [15]. By following diligent modern blood banking techniques and transfusion precautions, the incidence of such unwanted events can be minimized.

CP therapy has so far provided encouraging outcomes, without any serious events. It is anticipated that there would be an upsurge in the use of CP for COVID-19 treatment till the world comes up with an effective vaccine. The American Red Cross, the U.S. government and investigators at Mayo Clinic are all working hard in identifying appropriate and eligible donors, setting proper donor criteria and establishing blood processing and testing capabilities to confirm neutralizing antibodies in a timely fashion. As antibody testing is validated, it should help in increasing the more effective use of CP. Sufficient serologic assays are also being developed to ensure large-scale screening. However, as experience is still limited, vigilance for potential side effects of CP therapy is advised. There are some issues that need to be considered in determining the advisability of implementing a large-scale CP transfusion program: (i) lack of high-quality studies (i.e., randomised clinical trials); (ii) risk of transmitting infections to transfusion service personnel (e.g., when handling laboratory specimens from infected recipients for pre-transfusion testing); (iii) need for adequate selection of donors with high neutralizing antibody titers; (iv) suitable risk assessment when considering relaxation of the selection criteria against risk impact of excluding donors; (v) case-fatality rates in CP trials, influenced not only by risk factors of the patients, but also by the specific supportive care offered by clinical centers [16,17]. Other critical factors to consider when designing treatment protocols include timing of administration relative to onset of illness; timing of donation relative to resolution of symptoms; severity of illness of the donor; pre-transfusion serology of the recipient; and antibody titers of the donor [11]. The outcome measures should be tailored to the population being studied. Proper guidance would be needed to direct blood centers and plasma fractionators to begin prioritizing collections from COVID-19-convalescent donors; expedite the availability of these products for therapeutic use; create a data collection, analysis and regulatory infrastructure to identify factors that predict therapeutic efficacy [18]. To conclude, deploying passive antibody therapies against the rapidly increasing number of COVID-19 cases will provide an unprecedented opportunity to perform clinical studies of the efficacy of this treatment against SARS-CoV2. If the results of rigorously conducted investigations, such as a large-scale randomized clinical trial demonstrate efficacy, the use of this therapy could help in changing the course of this pandemic and serve as savior of human lives.

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