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Use of convalescent plasma in COVID-19, a bioethical perspective

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Abstract
Currently, the COVID-19 pandemic is a huge threat to global health. Several treatments have been proposed for it as well as adjuvant treatments that can allow strengthening of the immune system when fighting the disease. In this work, we review the use of plasma as a treatment for COVID-19, evaluating their risks, benefits, previous use, and bioethical aspects.

Introduction

Convalescent plasma therapy has been used for more than 100 years to treat several diseases, with varying degrees of success. For example, it has been tested against measles, Argentine hemorrhagic fever, influenza, chickenpox, cytomegalovirus infections, parvovirus B19 as well as in the Middle East Respiratory Syndrome (MERS) caused by a specific coronavirus, and in the H1N1 and H5N1 influenza variants (Marano et al. 2016).

The current coronavirus disease 2019 (COVID-19) pandemic has caused a lot of economic and human losses (Burlacu et al. 2020; Briggs et al. 2021); this poses a challenge to public health systems around the world in trying to contain the damage that this terrible disease has generated. On the other hand, the scientific community has been immersed in an unprecedented race to find new therapeutic options (Attia et al. 2021). Given the current world panorama, the convalescent plasma is seen as a therapeutic alternative in patients infected by SARS-CoV-2.

COVID-19 overview

SARS-CoV-2 (a positive single-stranded RNA virus) has been seen to alter the normal immune response, making it deficient and creating an uncontrolled inflammatory response, especially in patients with severe or critical illness. These patients might exhibit lymphopenia, lymphocytic dysfunction, and abnormalities in monocytes and granulocytes, as well as elevated levels of cytokines and an increase in immunoglobulin G (Yang et al. 2020).

Virus transmission between humans is through the respiratory secretions of infected people, especially during expulsion by coughing or sneezing, of small droplets and aerosols that can cross the air. The clinical picture of COVID-19 can manifest a wide variety of clinical symptoms, from an asymptomatic patient to those with multiple systemic compromises, respiratory failure, and death (Tay et al. 2020; Lewis 2020).

In January 2020, the World Health Organization (WHO) declared SARS-CoV-2 a global emergency. The first case reported in Mexico was on February 28, 2020. By January 30, 2021, the Johns Hopkins University of Medicine, through the Coronavirus Resource Center, reported 102,257,414 cases of people infected by SARS-CoV-2 worldwide and 1,841,893 cases in Mexico, of which 156,579 have died from COVID-19, placing Mexico in 3rd place of deaths after the US and Brazil (Johns Hopkins University of Medicine, Coronavirus Resource Center. s. f.).

Plasma, quantity definition, method of obtaining and storage

Plasma is the liquid component of the whole blood. It is preferably frozen within the first six hours after being obtained in a quantity between 150 ml and up to 600 ml. Plasma contains normal levels of stable clotting factors, albumin, and immunoglobulins (Storch et al., 2019). Therapeutic plasmapheresis is the process of separating and removing the plasma from other components of the blood and is considered an adjunctive treatment for diseases; it is based on removing substances such as cytokines or autoantibodies which can be therapeutic in certain situations (Balagholi et al., 2020). Plasmapheresis is performed by 2 fundamental techniques: centrifugation or filtration. With apheresis by centrifugation, the blood is divided into 4 components and separated into layers by their different densities; it is commonly performed by chemists, and its advantage is that there are no limits to the size of the molecules that are being removed. With filtration plasmapheresis, all blood passes through a filter to separate plasma components into red blood cells, white blood cells, and platelets, it is commonly performed by nephrologists and intensivists (Nguyen et al., 2012).

Plasma therapy is generally indicated to replace the deficiency of coagulation factors before invasive surgeries where there is a risk of severe bleeding or in cases where the concentration of the specific factor to be replaced is not enough. In these circumstances the requirements for an effective plasma therapy are laboratory confirmation of any coagulopathy by PTT or PT, fibrinogen level; determination of factor X or XI deficiency; specification of the dose according to the objective of the therapy; control of the efficiency of transfusion by laboratory analysis; and specification of transfusion intervals.

The transfusion is carried out intravenously using peripheral veins with a transfusion device that contains 170-210 micron filters to retain clots. Several units of plasma can be transfused using the same transfusion set (4 plasma for therapeutic use, 2009). In Mexico, before the transfusion, tests such as blood group and RH, HIV serology, hepatitis B, and C viruses and syphilis should be done (Secretaría de Salud, 2007) but certainly, as in other countries, some pathogens may escape from standard screening and inactivation procedures (Udvardy, 2018).

History of the use of plasma as a treatment

When suffering from a disease, the human body generates antibodies against a specific antigen; these antibodies together with the immune system respond to an infection caused by that pathogen (Berry and Gaudet, 2011). However, the antibodies production requires time, and every human being has a different response. For this reason, antibodies collected from patients who suffered from the same disease or artificially generated antibodies can be considered as a way of offering instant immunity to susceptible cases in a short period.

In 1901, Emil von Behring became the first laureate of the Nobel Prize in Medicine/Physiology for his work in serum therapy, especially testing its application against diphtheria. This opened a new path in the domain of medical science. His work gave rise to the so-called "Behring's Law" that blood and serum from an immunized individual transferred to another individual can cause the latter to be immunized. It has allowed the development of passive immunity concepts, establishing that what is transmitted through the plasma are antibodies that the donor has generated against certain pathology towards the recipient. Based on these findings, the treatment of multiple pathologies evolved (Nobel Prize in Physiology or Medicine, 1901).

The use of convalescent plasma is a passive immunization strategy that has been used in the prevention and treatment of epidemic infections for more than 100 years. In 1907, it was used in Italy for the first time to protect children infected with measles and in 1916 to treat acute paralysis during a polio outbreak in New York, in both cases proving their efficacy (Marson, Cozza, & De Silvestro, 2020). Also, this kind of intervention was recommended as an empirical treatment during the outbreaks of Ebola (Garraud, 2017) and MERS (Mustafa, Balkhy & Gabere, 2018). It has also been used to treat other viral infections (Hui et al., 2018).

In case of prescribing convalescent plasma, antibodies should be administered as early as possible to maximize their effectiveness, because there is the possibility that the number of antigens is much higher than antibodies when the disease becomes severe, thus reducing its effect (Samad et al., 2020).

The use of convalescent plasma in COVID-19

Although preventive measures have reduced the spread of COVID-19 such as social distancing, hygiene, and protection with face masks (Moran et al. ,2021), scientists have been looking for cures for this disease and in 2021, vaccines from different countries were approved for massive use. However, convalescent plasma is still an option in the contention of this disease.

In summary, it has been observed that the use of convalescent plasma reduces the mortality rate, decreasing the viral load and improving the clinical condition; it not only neutralizes the pathogen but also provides immunomodulatory properties that allow controlling the inflammatory cascade that is created due to the infectious agent (Rojas et al., 2020).

Potential convalescent plasma donors must go through a pre-donation check-up to ensure that they fulfill the appropriate conditions: They must be between 18-65 years old, without symptoms, and a negative test for COVID-19 (qPCR or serology) after 14 days of recovery (this test must be performed again 48 hours later), a negative test for COVID-19 by pharyngeal swab and / or blood sample at the time of the donation, neutralizing antibody titer greater than 1:320, and a check that the donor is free of infectious-contagious diseases.

The recommended procedure for obtaining plasma is apheresis by centrifugation; the plasma administration range is between 200-500 ml; currently the recommendation is to administer 3 ml/kg/dose in 2 days. The efficacy of this procedure relies on the neutralizing antibodies concentration in the donor plasma; these antibodies bind to the spike 1 receptor binding protein of the coronavirus (S1-RBD) and to the terminal domain S1 and S2, inhibiting their entry and limiting viral amplification, in addition to other antibody-mediated pathways such as complement activation, cellular cytotoxicity, and phagocytosis that can promote the therapeutic effect of convalescent plasma (Rojas et al., 2020).

It is a therapeutic product with special characteristics and should be stored in a differentiated form from the rest of the blood components, clearly indicated on it: "Convalescent plasma for use in studies related to SARS-CoV-2". The expiration date will be in accordance with the storage practices of blood banks; for fresh frozen plasma being 1 year from the date of collection if stored at -80ºC or less and must be frozen within 8 hours after collection.

In clinical trials, one unit of plasma (200 ml) is used for prophylaxis and two units (400 ml) for treatment. The duration of the effectiveness of the antibodies decreases through time. It is estimated to last from weeks up to a few months. After 40 days from recovery, convalescent plasma no longer has a significant number of antibodies. In a previous use of SARS convalescent plasma therapy, 5 ml per kg was used at a titer of 1:160; in linear proportion 3.125 ml of plasma per kilogram with a titer of more than 1:64 would provide adequate therapy (Alcántara, 2020).

Discussion

Given the current world panorama, in-depth research is needed to assess the benefits of a new treatment option. Convalescent plasma has been used as a therapeutic alternative since ancient times. The use of plasma as a therapeutic modality to treat infectious diseases has been known for more than 100 years, being of great benefit in certain pathologies, while in others being moderately or not effective.

The benefits of this therapy are still uncertain against COVID-19 although the evidence seems to indicate a clinical improvement while its risks are the same as in other cases of transfusions, that is, allergic reactions, possibility of transmission of infectious agents, anaphylaxis reactions, acute lung damage as well as hemolysis among others (https://www.covid19treatmentguidelines.nih.gov/anti-sars-cov-2-antibody-products/convalescent-plasma/ 2020). Overall, plasma donation is safe for patients and adverse effects are rare.

The Food and Drug Administration (FDA) has approved the emergency use of the convalescent plasma in the United States considering the possible benefits of this therapy, which include an improvement in symptoms, a reduced need for supplemental oxygen and mechanical ventilation, and possibly a reduction in mortality. The data suggest that the use of convalescent plasma from patients with COVID-19 that have high antibody titer is more likely to be effective in reducing mortality in hospitalized patients (FDA).

In South America, several countries have implemented specific protocols to administer convalescent plasma to people with COVID-19. Those developed by Bolivia and Venezuela (Nina Garcia & Cussi Coronel, 2020; Sánchez et al., 2020) attract attention. In Mexico, there are some protocols recruiting patients to be treated with convalescent plasma (NCT04356482; NCT04405310).

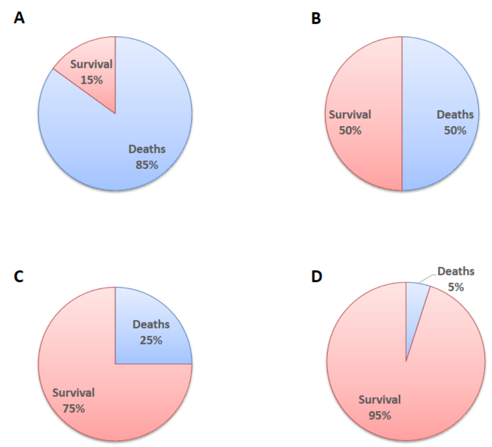

Figure 1. Examples of different percentages of deaths and survival to decide whether to try the use of convalescent plasma

A bioethical aspect of the use of convalescent plasma

The Mexican Ministry of Health reports that the morbidity rate of SARS-CoV-2 is 16.18 per 1000 patients (consulted on January 30, 2021). However, morbidity could be higher due to persistent under-diagnosis in this nation.

Medicine as science has had the ultimate goal of safeguarding human health by all means but always respecting the four principles of bioethics: autonomy, beneficence, justice, and non-maleficence (Holm 2002). In relation to COVID-19 and convalescent plasma, one paradoxical situation we are facing nowadays is that this blood product is stored in blood banks without being used due to the lack of authorized research protocols in hospitals where it is obtained. For example, the average activity of the Blood Bank of the "Mónica Pretelini Sáenz" Maternal-Perinatal Hospital (HMPMPS), Health Institute of the State of Mexico (ISEM), Toluca, Mexico, shows that since the beginning of this pandemic (approximately March 2020) 1,100 packages of blood and 550 of plasma would have accumulated. Applying the morbidity data and probability reasons, at some point, a patient infected with SARS-CoV-2 has donated blood or plasma that has been stored and administered to a patient without knowing this condition because the COVID-19 test is not a routine test before the donation. Furthermore, we can assume that this phenomenon is occurring throughout the world.

Taking into account the bioethical principles of respect for autonomy, nonmaleficence, beneficence, and justice, imagine the circumstance in which there is one patient with COVID-19 intubated in an Intensive Care Unit (ICU) with a mortality of 60% and the physician in charge has the possibility to ask for plasma donors from recovered patients and all but a physician agree to give a single dose of the convalescent plasma; due to the discordance the plasma cannot be infused. The opposed physician argues that the convalescent plasma has not been added into an international flowchart to treat COVID-19. With a COVID-19 mortality higher than 60% when intubated until when do we have to wait for a randomized, double blind trial with convalescent plasma before trying to get a reduction in the mortality using convalescent plasma? At what point not transfusing plasma is more harmful than trying this procedure? (Figure 1).

Are we applying the principle of beneficence by letting the disease advance towards possible death without using a possible tool that has been used in several diseases? Are we applying the principle of autonomy by not telling the patient or his/her family about the existence of a possible treatment with convalescent plasma? Do they deserve the right to take the risks? The principle of nonmaleficence is clear, as the treatment with convalescent plasma is well known and under usual conditions the risks are low.

Under substantial uncertainty during aggressive and unknown diseases, waiting too long for the perfect clinical assay could condemn hundreds of patients. Notwithstanding, the scientific evidence on the use of this therapy is still limited. However, multiple studies are currently being carried out throughout the world on the use of convalescent plasma for the treatment of SARS-CoV-2 infection (Table 1). It is expected that the results of these investigations will begin to appear in 2021 (Wooding & Bach, 2020).

Conclusion

Convalescent plasma can be a therapeutic alternative in patients with COVID-19 that improves symptoms and prognosis, and it does not have a statistically significant adverse effect on mortality rates. Based on the evidence mentioned above, convalescent plasma against COVID-19 should be considered, at least as a compassionate therapy, particularly in emergency cases of patients admitted to hospitals, despite the absence of an authorized protocol, considering that the attempt to safeguard life is more important than the existing technical limitations. We strongly recommend to health institutions that they can facilitate the prompt approval of the different protocols necessary to start the use of this complementary therapy.

Acknowledgments

Authors thank the students affiliated to the Latin American Scientific Association (ASCILA) for their valuable comments in improving this manuscript. No potential conflict of interest was reported by the authors.

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