Convalescent plasma therapy in patients with coronavirus disease-19 – One year after: A brief review

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Abstract

Multiple therapies have been tested on the present pandemic. Convalescent plasma (CP) is being empirically applied on different trials as a possible treatment to avoid severe presentations of coronavirus disease-19. These treatments have been used before for other infectious diseases with controversial results. The study of this virus is still ongoing, and new information is being gathered daily that could upgrade the approach to get new solutions. Up to this day, vaccines are the most promising therapy to avoid infection, but no successful therapy has been found to cure the actual disease. As we present in this paper, there is controversial information on CP. Still, due to the actual global situation, the medical guild has needed to learn empirically on the road of treating the patients. Results are shown of the most relevant trials that have been made. Furthermore, we mention the trials that are not yet finished for further review.

Key words: Coronavirus disease-19. Pneumonia. Pandemic. Convalescent plasma.

Almost a year has passed since the coronavirus disease (COVID-19) pandemic started. This virus belongs to the family *Coronaviridae* and subfamily *Orthocoronavirinae*¹. One of the first published outbreaks was made in early 2020, when a cluster of patients with pneumonia of unknown cause was linked to a market in Wuhan, China. These patients had a similar acute respiratory syndrome as severe acute respiratory syndrome coronavirus (SARS-CoV1) and Middle East respiratory syndrome coronavirus, but after sequencing this virus, a new type of coronavirus was discovered². It is classified in the same family of viruses as the Middle East respiratory syndrome-CoV and SARS-CoV1, but remarkable differences are being discovered daily. Based on research, cell entry

depends on binding of the viral S (spike) protein to angiotensin-converting enzyme 2 receptor, which is principally found in human lungs³.

Despite efforts to contain the virus, infectious outbreaks spread from China and were declared a pandemic by the WHO on March 11, 2020^{4,5}. Since the beginning of the pandemic, multiple challenges had been assessed. The propagation of this virus worldwide forced most of the affected countries to live under a “new normality,” which includes enforced health prevention systems, governmental measurements, social consciousness and commitment, and medical research to improve clinical approach. Many clinical trials had been realized assessing different drugs and treatments, but to this day, no specific or ideal treatment

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Table 1. Randomized trials using convalescent plasma for COVID-19

Study name	Journal	Date of publishing	Country	Outcome	Observations
Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients	<i>Mayo Clinic Proceedings</i>	September 2020	USA*	Useful	Earlier administration is more likely to reduce mortality
A randomized trial of convalescent plasma in COVID-19 severe pneumonia	<i>New England Journal of Medicine</i>	November 2020	Argentina	Not useful	Total SARS-CoV-2 antibody titers tended to be higher in the convalescent plasma group at day 2 after the intervention.
Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life threatening	<i>Journal of the American Medical Association</i>	August 2020	China	Not useful	Plasma was associated with a negative conversion rate of viral PCR at 72 h in 87.2% of the convalescent plasma group versus 37.5% of the control group (OR, 11.39 [95% CI, 3.91-33.18]; $P < 0.001$).
A pilot study of therapeutic plasma exchange for serious SARS-CoV-2 disease (COVID-19): a structured summary of randomized controlled trial study protocol	<i>Trials</i>	June 2020	USA, Saudi Arabia	Useful	It may reduce the cytokine release syndrome associated with fulminant COVID-19 disease
Convalescent plasma in the management of moderate COVID-19 in India: an open-label parallel-arm Phase II multicenter randomized controlled trial (PLACID trial)	<i>medRxiv</i>	September 2020	China	Not useful	A priori measurement of neutralizing antibody titers in donors and participants may further clarify the role of CP in management of COVID-19

*The United States of America. This table shows a comparison between a selection of randomized trials performed in 2020 assessing convalescent plasma effectiveness. SARS-CoV: severe acute respiratory syndrome coronavirus.

has been found for COVID-19. Because of this, organizations such as the World Health Organization (WHO) are still focusing efforts on preventive actions such as mask use and hand hygiene. Unfortunately, the consequences of an underestimated pandemic are now a daily punishment for people and their governments. As of February 2021, 104,045,835 million people have been affected worldwide, and 2,250,677 have died⁶.

In Mexico, COVID presence was first known on February 27, 2020, when the first imported cases were confirmed, and, to this day, 1,869,708 people have been infected, with 159,100 reported deaths⁷. On March 23, 2020, the government started the “Jornada Nacional de Sana Distancia” with restriction of non-essential activities and social distancing⁸. One of the many concerns regarding the “arrival” of the pandemic in Mexico was due to the high prevalence of chronic diseases in the population, such as hypertension (26%), obesity (36%), and diabetes (14%), which had been related to severe COVID-19 disease and

mortality. The first death due to the virus was confirmed on May 18, 2020⁹⁻¹².

Convalescent plasma (CP) has been assessed as an experimental therapy in virus infections such as influenza, Ebola, and coronavirus associated with SARS¹³. Because of this, CP became a prospect in the treatment of the new coronavirus disease. Studies synthesizing the possible efficacy and safety of CV in different stages of the disease in adult and pediatric patients have been performed to this day¹³⁻¹⁹. The previous studies suggest a durable T-cell response against COVID-19, but the extent to which they can provide protection is limited²⁰. Research about the protection and probability of reinfection with COVID is still going on, and reports vary²¹⁻²³. To this day, no conclusions can be drawn from seroprevalence studies about the duration of immunity, if there is one, to SARS-CoV infection²⁴.

Empirical treatments used during previous pandemics are being analyzed, including antiviral agents, immunosuppressive agents, immunoglobulins, and CP,

alongside many other therapies. Still, plenty of ethical, economic, and social barriers prevent the scientific community from studying possible solutions, making trials a complex pathway. CP had previously been used in several infection outbreaks with some provocative and promising good results. Still, there is not enough evidence to consider that this therapeutic intervention is useful²⁵. In Mexico, small non-randomized studies have reported improvement in patients treated with plasma^{26,27}. CP donor requirements include a previous positive test for COVID-19, a receptor-binding domain-specific IgG titer of $\geq 1:160$, 28 days without symptoms, and in the case of females, no previous pregnancy. Blood antigens must be compatible (ABO-Rh) between donor and recipient.

Studies have been made assessing the effectiveness of CP in patients with COVID, as shown in **table 1**, but still, effectiveness is not completely clear^{18,28-32}. The use of plasma with high titers of anti-SARS-CoV-2 antibodies is appealing. Still, we must consider that we need donors, apheresis machines, trained personal, and money to provide plasma to patients. The recommended therapeutic amount of plasma varies between studies but usually consists of two doses of 200 mL 24 h apart. The response to CV is measured clinically ($\text{PaO}_2/\text{FiO}_2$) or radiologically but can also be assessed by anti-SARS-CoV-2 antibody titer, lymphocyte count, and SARS-CoV-2 viral load¹⁵.

Conclusion

Further studies are needed to determine the efficacy of CP in the disease. However, until now, there is no clear evidence of the therapeutic advantage of plasma in patients with COVID-19. Since there is no ideal therapeutic option to treat patients, plasma, if administered, must be used in the early stages of the infection before the patient is seriously ill.

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Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

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