CONVALESCENT PLASMA

Fatima Johanna T. Santos-Ocampo, MD, Aileen A. Elorde, MD, Maria Rowena B. Valerio, MD

Introduction

The difference between IVIG and convalescent plasma (CP) is that the former comes from a plasma pool donated by thousands of normal donors in a specified population while the latter is collected from the blood of donors who have recovered from the target disease. By doing so, a high titer of neutralizing antibodies specific to the infectious agent that caused the disease is obtained. Based on meta analyses on the Spanish flu pandemic of 1918, giving of CP became a candidate for prevention of disease in a pre-symptomatic exposed patients or as active treatment for patients who already have the disease.[1]

Mechanism of Action

In all passive antibody preparations, several types of binding antibodies are produced. Some will bind with an antigen to create an antigen–antibody complex that other cells of the immune system will recognize and destroy, while some are neutralizing antibodies. [2]

For COVID-19, it is postulated that neutralizing antibodies play an important role. Common mechanisms may involve one or more of the following: 1) aggregate viruses preventing binding and entry; 2) bind to the viral attachment protein or the cellular receptor and prevent entry; 3) prevent conformational changes necessary for fusion; 4) destabilize the virus and cause release of viral nucleic acid outside the cell; 5) prevent uncoating of the virus capsid; or 6) prevent the release of progeny virus from infected cells.[1,3,4] In COVID-19, the S1 portion of the spike protein in COVID-19 has been characterized and at this time, it is known to allow viral attachment via the ACE2 receptor on the host cell which eventually allows entry into the cell.[5] Neutralizing antibodies present in the CP, specific to either the ACE2 receptor or the S1 protein is postulated to block this from happening.

Its use in symptomatic patients likely “blunts” virus replication while waiting for the host’s immune system to be able to mount a response to the virus.[1]

It is generally agreed that the immunomodulatory mechanism of action can be extrapolated from that of IVIG. Encouraging results from the different case series and reports from China (Appendix 4) seem to be consistent with some anti-inflammatory effects.

Clinical Studies

In this present epidemic caused by SARS-CoV-2, there are 2 completed case series on the use of convalescent plasma. In a pilot study by Duan et al.,

each patient with severe COVID-19 received one dose (200 ml) of convalescent plasma with neutralizing antibody titers at or exceeding a 1:640 dilution between day 11 to day 20 from onset of symptoms. All 10 patients had improvement in symptoms (e.g. fever, cough, shortness of breath and chest pain) within 3 days of transfusion and demonstrated radiological improvement in pulmonary lesions. The study revealed that CP could significantly increase of maintain the neutralizing antibodies at high levels leading to the disappearance of viremia in 7 days. They compared these patients with a historical control group and found significant difference in clinical outcomes ($p<0.001$).[6] In this study all 10 patients on CP also received antivirals with 2 patients on interferon-a. Six patients also received methylprednisolone.

In a case series by Shen et al, 5 critically ill adult patients in China were given two consecutive doses of 200 to 250 ml convalescent plasma (SARS - CoV-2 IgG titers >1000 and & neutralizing antibody titer >40) 1 day apart. These were given between day 10 to day 22, and improvement in clinical status was seen, as evidenced by weaning off mechanical ventilation, reduction in viral load, improvement in oxygenation and clinical stabilization of symptoms. All showed that viral load decreased and became negative within 12 days post transfusion. Transfusion of convalescent plasma in both studies resulted in no serious adverse effects in all recipients. All 5 patients also received antivirals and methylprednisolone.[7]

The first living update of a systematic review of convalescent plasma or hyper-
immune immunoglobulin for people with COVID-19 was published last July 2020 in Cochrane Database. There were 20 completed studies (1 RCT, 3 controlled non-randomized studies of intervention (NRSIs), 16 non-controlled NRSIs) with 5443 participants, of whom 5211 received convalescent plasma. There are 98 ongoing studies, of which 50 are randomized. Overall risk of bias was high because of the study design, severity of disease of the participants and concurrent treatments. Their primary outcome was all-cause mortality and time to death. They could not analyze the results from the RCTs because not all participants had been discharged at the end of their follow-up. For the time to death, those in the convalescent plasma group may be prolonged but the evidence is very uncertain.[8] Piechotta et al. concluded that it is uncertain whether convalescent plasma from patients who recovered from COVID-19 is an effective treatment for people hospitalized with COVID-19. Authors also stated that it is very uncertain whether or not convalescent plasma have an impact on the number of severe complications. It has yet to be determined how much is actually related to the natural progression of the disease, other treatments that the participants received, or to convalescent plasma.

Other interventional trials in several countries are currently being conducted. (Appendix 4)

Recommended Dose

The appropriate volume for transfusion has not yet been determined. Based on previous pandemics and expert opinion, a volume from 200 to 600 ml (to 8 to 10 ml/kg, with a maximum of 600 ml) once per day and up to three consecutive days has been suggested. [8,9,10]

Improvement of clinical signs & symptoms and decrease in values of clinical markers of inflammation were seen when plasma transfusion was started anywhere from day 10-day 22.[6,7]

A more restricted recommendation comes from the Italian Society of Transfusion Medicine and Immunohematology (SIMTI) and Italian Society of Hemapheresis and cell Manipulation (SidEM), that states that the optimal period to give immune plasma transfusion is within 7 days from the onset of symptoms as this coincides with peak of viremia within first week.[8] At the same time, there is evidence that giving it within the first 2 weeks may still be beneficial. Administration of immune plasma beyond 3 weeks from the onset of the disease seem to render it ineffective.[9]

Adverse Effects

There can be mild reactions like evanescent red spots as reported by Duan et al.[6] Other non-infectious hazards of tranfusions are allergic transfusion reactions and transfusion associated circulatory overload (TACO).[8] The risk for these adverse effects are likely to be no different from those of standard plasm transfusion. However, it may carry some risk of transfusion related acute lung injury (TRALI)[11] considering its use in active treatment of individuals with pulmonary disease. The specific risk of transfusion-transmitted SARS-CoV-2 is highly unlikely if one considers that only 1% of symptomatic patients have been reported to have detectable SARS-CoV-2 RNA in their blood and only asymptomatic plasma donors are recruited. Since there is yet no proof of COVID-19 infection via blood transfusion, its significance is largely theoretical.

There is a theoretical possibility of antibody-dependent enhancement (ADE) following transfusion of human anti-SARS-CoV-2 plasma.[12] ADE refers to a process whereby there is enhancement of disease in the presence of antibodies to a different strain of the virus causing the disease. As there is more than one strain of SARS-CoV-2 that have been identified, occurrence of this phenomenon has been offered as a possible reason for the geographic variation in disease severity

Conclusion:

Use of convalescent plasma in COVID-19 early in the disease process or for prophylaxis is a potentially safe and effective treatment. However, even in a pandemic, when it could be utilized as the most direct and simplest antibody

treatment, a risk-benefit assessment must be carried out when used in critically ill patients with significant pulmonary disease. Its efficacy may also be affected by the variability of the levels of neutralizing antibodies present in a particular donor plasma. Well-controlled clinical trials are still needed to confirm its efficacy and safety for different application in COVID-19.

REFERENCES:

1. Burton DR. Antibodies, viruses and vaccines. Nat Rev Immunol. 2002; 2:706–713.
2. Janeway CA, Travers P, Walport M, Shlomchik M (eds). Immunobiology. Fifth ed. New York: Garland Publishing; 2001.
3. Marasco WA, Sui J. The growth and potential of human antiviral monoclonal antibody therapeutics. Nat Biotechnol. 2007; 25: 1421–1434.
4. Reading SA, Dimmock NJ. Neutralization of animal virus infectivity by antibody. Arch Virol. 2007; 152:1047–1059.
5. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. Lancet. 2020; 395:565-574. doi: 10.1016/ S0140-6736(20)30251-8.
6. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A. 2020; 117:9490-9496. doi: 10.1073/pnas.2004168117.
7. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA. 2020; 323:1582-1589. doi: 10.1001/jama.2020.4783. [Epub ahead of print].
8. Piechotta V, Chai KL, Valk SJ, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database of Systematic Reviews, Issue7. Art. No.:CD013600.DOI: 10.1002/14651858.CD013600.pub2.
9. Bloch EM, Shoham S, Casadevall A, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. J Clin Invest. 2020; 130:2757-2765. doi: 10.1172/JCI138745.
10. Accorsi P, Berti P, de Angelis V, et al. “osition paper on the preparation of immune plasma to be used in the treatment of patients with COVID-19. Blood Transfus. 2020; 18:163-166. doi: https://dx.doi.org/10.2450%2F2020.0124-20.
11. US Food and Drug Administration. Recommendations for investigational COVID-19 convalescent plasma. Available from: https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma. Accessed on March 30, 2020.
12. Gajic O, Rana R, Winters JL, et al. Transfusion-related acute lung injury in the critically ill: prospective nested case-control study. Am J Respir Crit Care Med. 2007; 176(9): 886–891.
13. Wan Y, Shang J, Sun S, et al. Molecular mechanism for anti-body-dependent enhancement of coronavirus entry. J Virol. 2020; 94(5): e02015-19.