

Convalescent Plasma and COVID-19: Ancient Therapy Re-emerged

Francis Ajeneye

Department of Haematology/Transfusion, Maidstone and Tunbridge Wells Hospital, Pembury, TN2 4QJ, United Kingdom

ABSTRACT

Convalescent plasma has again re-emerged as a therapy during coronavirus disease (COVID-19) outbreaks currently use as a prophylactic or an interventional treatment in infected patients. Convalescent plasma has been used in the 20th century confronting different infectious diseases where there was no other therapy available. Conceivably, this convalescent plasma therapy tends to be proving a game-changing treatment in some COVID-19 patients and could support treatment, in addition to the current interventions before other developed therapies are available for the population.

Key words: Antibodies, Convalescent Plasma, SARS-CoV-2

INTRODUCTION

Convalescent plasma is blood plasma extracted from human patient who has “convalesced” or recovered from infection with a particular disease. Clinical trials with convalescent plasma for COVID-19 have significantly outnumbering those for other infectious disease outbreaks to date. This is primarily driven by continuity of spread of COVID-19. The ongoing investigational studies with convalescent plasma for COVID-19 globally had share some common features in the study design, protocol, such as patient population, disease status, dosage, and primary outcome measures. In the meantime, these studies vary in other features, including randomization, blinding, and sample size which had been lacking in the 20th century clinical trials.

The history of plasma as a treatment began in the 1890s when the German scientist Emil von Behring demonstrated serum therapy, the use of blood from an animal or human who had recovered from a disease to treat that disease in another animal or human. Serum therapy uses the same principle as convalescent plasma today, although scientists could not yet separate plasma from whole blood during this period. In 1901, Behring won the first Nobel Prize in Physiology or

Medicine for his achievement. During influenza outbreak of 1918 is known as the “Spanish flu,” with the fatality rates cut in half for patients who were treated with blood plasma compared to those who were not. The method seemed particularly effective when patients received the antibodies in the early days of their infection, before their own immune systems had a chance to react excessively and causes damage to vital organs.^[1]

The separation of plasma from whole blood became conceivable for the first time by Edwin Cohn, a biochemist, figured out how to separate whole blood in component. A model of the fractionation machine he used is now stored in the Smithsonian’s National Museum of American History.^[2] Plasma on its own is much more stable than whole blood, making it possible to move across borders to provide life-saving transfusions. In addition, plasma had played a crucial component in a ground-breaking treatment for hemophilia, a rare blood disorder where patients lack the clotting factors. By the 1940s and 1950s, antibiotics and vaccines began to replace the use of convalescent plasma for treating many infectious disease outbreaks, but the out-of-date method came in accessible yet again during Korean hemorrhagic fever, also known as Hantavirus.^[3] With no other treatment available,

Address for correspondence: Francis Ajeneye, Department of Haematology/Transfusion, Maidstone and Tunbridge Wells Hospital, Pembury, TN2 4QJ, United Kingdom.

© 2021 The Author(s). This open access article is distributed under a Creative Commons Attribution (CC-BY) 4.0 license.

field doctors transfused convalescent plasma to sickened patients and saved numbers of lives. Convalescent plasma was repeatedly deployed against the 21st century outbreaks novel viruses that spread through communities with no natural immunity, the SARS, MERS, and EBOLA outbreak, where no vaccine and effective antiviral treatment is available.^[4]

Convalescent plasma offers “passive immunity.” Since the infected patients cannot produce antibodies, they can derive them from another person who has successfully recovered from the infection and produce an immuneresponse.^[5,6,7] Unlike a vaccine, the protection does not last a lifetime, but antibodies derived from the recipient can reduce recovery times and even be the difference maker between life and death. Convalescent plasma interacts differently with the immune system than a vaccine. When a person is treated with a vaccine, their immune system actively produces its own antibodies that can activate an immune response when encounters with the target pathogen. This is called active immunity. The mechanism of action of convalescent plasma has yet to be fully understood, several corresponding effects have been hypothesized. The therapeutic effects are thought to be stimulated primarily through blocking the early steps in the viral replication cycle by neutralizing antibodies. Klasse^[8,9] explained, the binding to surface of virus, the antibodies may also inhibit attachment and entry of viral particles to target cells by disrupting interactions between viral envelop glycoproteins and cell surface receptors, or inhibit transfer of genetic materials from viral particles to target cells. However, antibodies in convalescent plasma may facilitate killing of infected virus-producing cells through the mechanism of antibody-dependent cellular toxicity. In addition to the antibodies, convalescent plasma also contains cytokines and other molecules that provide immune-modulatory effects.

Early clinical experience through case reports and small clinical trials in had shown some promising outcomes. As the pandemic spreads, additional clinical data have become available in many regions outside, as the trials tend to be larger with more robust study designs the efficacy looks promising. This observation is consistent with the generally recognized principle that passive immune therapies, including convalescent plasma, and are most efficacious early in diseases. The data in the same reported by Liu *et al.*^[10] suggested that the survival effect convalescent plasma may begin to manifest more than 1 week after transfusion, and the authors speculated that convalescent plasma may prevent longer-term complications, such as acute lung injury or multi-organ dysfunction syndrome. The country’s first convalescent plasma transfusion trial results have been peer-reviewed and published, showing 19 out of 25 patients improving with the treatment and 11 discharged from the hospital. Houston Methodist became the first academic medical center in the nation to transfuse plasma from recovered COVID-19 patients into two critically ill patients. There was first described in

The American Journal of Pathology. This is the first peer-reviewed publication on convalescent plasma use in the United States.^[11]

The main hypothesis of this trial was that in patients with severe SARS CoV-2 pneumonia, treatment with convalescent plasma would be associated with improved clinical outcomes at 30 days. The use of convalescent plasma did not result in a significant clinical benefit as compared with placebo in patients with severe COVID-19 pneumonia. Our trial ensured that more than 95% of the transfused convalescent plasma units had a total anti-S-CoV-2 antibody titer of at least 1:800 and that the plasma volume infused had a correction factor according to the participant’s weight. This finding is in contrast to the findings of a series of non-randomized studies claiming convalescent plasma to be of substantial benefit and illustrates the importance of randomized, controlled trials, especially in the context of a pandemic.^[12]

The data on the previous use of convalescent whole blood or plasma for the treatment of Ebola Virus are limited.^[7] The largest case series involved eight patients who were treated with convalescent whole blood during the Kikwit outbreak of EVD in 1995; of these patients, seven survived. However, it was not possible to assess whether the low case fatality rate was due to treatment with convalescent whole blood or other factors, such as characteristics of the patients or the period during the illness at which treatment was given. Because of uncertainty about the therapeutic value of convalescent blood products in the treatment of EVD, we conducted the Ebola-Tx trial to assess the safety and efficacy of convalescent plasma for the treatment of EVD in Conakry, Guinea. The study’s authors recognized the important need for controlled clinical trials to determine its therapeutic efficacy, a randomized controlled trial is currently being considered.^[13,14]

Another study looked at the efficacy of convalescent plasma in relation to dose of Ebola Virus, but the levels of neutralizing antibodies were low in many donations. The dose of IgG antibodies showed an association with larger increases in cycle-threshold values after transfusion but no significant association with mortality. Neither outcome showed an association with the estimated doses of neutralizing antibodies received. Further studies are needed to assess the effectiveness of an antibody dose higher than the doses used in this study. Although uncertainty remains about our findings because of the non-randomized nature of the study and the use of historical controls, we could not detect a marked survival effect of the administration of a dose of 200–250 mL of convalescent plasma twice daily. It remains to be assessed whether plasma with high levels of EBOV-neutralizing antibodies, possibly administered repeatedly, would show efficacy and whether sub-groups of patients, such as young children and pregnant women, would be more likely to benefit.^[15,16]

Transfusion of immune plasma is a standard therapy for South American hemorrhagic fevers caused by Arena viruses, and it has been used successfully for treating people infected with other infectious agents. For instance, in Hantavirus infection, convalescent plasma was safe and reduced the case fatality rate to 14% in 29 treated cases versus 32% in 199 untreated cases.^[3] Nevertheless, only anecdotal evidence suggests the possible efficacy of convalescent plasma, and evidence of the efficacy of convalescent whole blood among patients with Ebola virus disease is disputed.

CONCLUSION

The design of robust randomized and controlled clinical trials for convalescent plasma should be consider critical elements, including patient population, outcome measures, study power, required minimal and optimal titers, and dose frequency and volume.^[17,18,19] In this unprecedented time of COVID-19 pandemic, the opportunity is greater than ever to develop convalescent plasma therapy into a safe and effective treatment option, as well as to develop better understanding of the mechanism of action of convalescent plasma therapy in general. The experiences learned through this process will be invaluable in combating future outbreaks of infectious diseases and explore risk factors of hospital deaths in relation to viral shedding and laboratory findings during hospital admission.^[20] The importance of ensuring adequate, accessible, and safe blood and blood components must also be a global priority.

REFERENCES

1. Luke TC, Kilbane EM, Jackson JL, Hoffman SL. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: A future H5N1 treatment? *Ann Intern Med* 2006;45:599-609.
2. Biography. "Edwin Cohn; 2013. <http://www.biography.com/people/edwin-cohn-9252667>. [Last accessed on 2013 Dec 21].
3. Kilgore PE, Ksiazek TG, Rollin PE, Mills JN, Villagra MR, Montenegro MJ, *et al.* Treatment of Bolivian hemorrhagic fever with intravenous ribavirin. *Clin Infect Dis* 1997;24:718-22.
4. Chen L, Xiong J, Bao L, Shi Y, Convalescent plasma as potential therapy for COVID-19. *Lancet Infect Dis* 2020;20:398-400.
5. Casadevall A, Pirofski LA: The convalescent sera option for containing COVID-19. *J Clin Invest* 2020;130:1545-8.
6. Joyner MJ, Bruno KA, Klassen SA, Kunze KL, Johnson PW, Lesser ER, *et al.* Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. *Mayo Clin Proc* 2020;95:1888-97.
7. Joyner MJ, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, *et al.* Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial three-month experience. *medRxiv* 2020;2020:20169359.
8. Klasse PJ. Neutralization of virus infectivity by antibodies: Old problems in new perspectives. *Adv Biol* 2014;2014:157895.
9. Casadevall A, Dadachova E, Pirofski LA. Passive antibody therapy for infectious diseases. *Nat Rev Microbiol* 2004;2:695-703.
10. Liu ST, Lin HM, Baine I, Wajnberg A, Gumprecht JP, Rahman F, *et al.* Convalescent plasma treatment of severe COVID-19: A matched control study. *medRxiv* 2020;5:20102236.
11. Salazar E, Perez KK, Ashraf M, Chen J, Castillo B, Christensen PA, *et al.* Treatment of coronavirus disease 2019 (COVID-19) patients with convalescent plasma. *Am J Pathol* 2020;190:1680-90.
12. Simonovich VA, Burgos Pratz LD, Scibona P, Beruto MV. PlasmAr Study Group. HYPERLINK. Available from: https://www.nejm.org/doi/10.1056/NEJMoa2031304?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed"A randomized trial of convalescent plasma in Covid-19 severe pneumonia. [Last accessed on 2020 Nov 24].
13. van Griensven J, Edwards T, de Lamballerie X, Semple MG, Gallian P, Baize S, *et al.* Evaluation of convalescent plasma for Ebola virus disease in Guinea. *N Engl J Med* 2016;374:33-42.
14. Edwards T, Semple MG, De Weggheleire A, Claeys Y, De Crop M, Menten J, *et al.* Design and analysis considerations in the Ebola_Tx trial evaluating convalescent plasma in the treatment of Ebola virus disease in Guinea during the 2014-2015 outbreak. *Clin Trials* 2016;13:13-21.
15. Mupapa K, Massamba M, Kibadi K, Kuvula K, Bwaka A, Kipasa M, *et al.* Treatment of Ebola hemorrhagic fever with blood transfusions from convalescent patients. *J Infect Dis* 1999;179:S18-23.
16. Bah EI, Lamah MC, Fletcher T, Jacob ST, Brett-Major DM, Sall AA, *et al.* Clinical presentation of patients with Ebola virus disease in Conakry, Guinea. *N Engl J Med* 2015;372:40-7.
17. Epstein J, Smid WM, Wendel S, Somuah D, Burnouf T. Use of COVID-19 convalescent plasma in low- and middle-income countries: A call for ethical principles and the assurance of quality and safety. *Vox Sang* 2020;116:13-4.
18. Bloch EM, Goel R, Wendel S, Burnouf T, Al-Riyami AZ, Ang AL, *et al.* Guidance for the procurement of COVID-19 convalescent plasma: Differences between high and low-middle-income countries. *Vox Sang* 2020;116:18-35.
19. Epstein J, Burnouf T. Points to consider in the preparation and transfusion of COVID-19 convalescent plasma. *Vox Sang* 2020;115:485-7.
20. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet* 2020;395:1054-62.

How to cite this article: Ajeneye F. Convalescent plasma and COVID-19: Ancient Therapy Re-emerged. *Clin Res Hematol* 2021;4(1):1-3.