Review Article

Convalescent plasma therapy for managing infectious diseases: a narrative review

Massimo Franchini

Department of Hematology and Transfusion Medicine, Carlo Poma Hospital, Mantova, Italy

Correspondence to: Massimo Franchini, MD. Department of Hematology and Transfusion Medicine, Carlo Poma Hospital, Mantova, Italy. Email: massimo.franchini@asst-mantova.it.

Abstract: The coronavirus disease 2019 (COVID-19) pandemic in 2020 is one of the worst catastrophic events in human history. A number of therapeutic modalities have been utilized in order to fight the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), although the majority of them failed to demonstrate a beneficial clinical effect. Among the anti-COVID-19 agents being investigated, the convalescent plasma collected from recovered donors has gained a growing interest. Convalescent plasma has been employed for over a hundred years to treat severe acute viral infections when a vaccine or a specific antiviral treatment was not yet available. In this narrative review, we summarize the literature data on the use of convalescent plasma during previous viral outbreaks and pandemics, including influenza viruses, coronaviruses other than SARS-CoV-2 and Ebola virus. A literature search, using the Medline and PubMed electronic database, was performed to retrieve publications on the use of convalescent plasma in previous viral epidemics. In conclusion, the available literature data suggest the safety profile of convalescent plasma and its potential benefit in treating emerging viral infectious diseases. In addition, these data retrieved from previous viral epidemics provide a solid rationale for the employment of plasma from convalescent donors also in COVID-19 patients.

Keywords: Convalescent plasma; infectious diseases; coronavirus; influenza; Ebola

Received: 30 November 2020; Accepted: 15 January 2021; Published: 30 June 2021.

doi: 10.21037/aob-2020-cp-03

View this article at: http://dx.doi.org/10.21037/aob-2020-cp-03

Introduction

Coronavirus (CoV), an enveloped single-stranded RNA virus belonging to the family of *Coronaviridae*, which initially caused enzootic infections, has shown in the past to be capable of crossing the species barrier and infecting humans causing epidemics with different levels of severity (1). Two outbreaks of CoVs in humans have occurred in the last two decades, causing severe acute respiratory syndrome (SARS-CoV) in 2003 and Middle East Respiratory Syndrome (MERS-CoV) in 2012 (2-4). In December 2019, the third outbreak of a rapidly transmitted CoV, named SARS-CoV-2 and causing coronavirus disease 2019 (COVID-19), occurred and on March 11 2020, the World Health Organization (WHO) declared the CoV outbreak as a pandemic (5,6).

This new virus posed a major challenge among physicians because it had no specific pre-existing therapy. As a consequence, the therapeutic efforts were initially focused on optimizing respiratory care, managing thrombotic and inflammatory complications by using anticoagulation and corticosteroids, and repurposing existing antiviral therapies (7). Unfortunately, almost all these initially promising agents (i.e., hydroxychloroquine, lopinavir/ritonavir and remdesivir) failed to demonstrate a beneficial effect (8-10). Considering the lack of effective anti-SARS-CoV-2 drugs and the initial positive experience from China (11), convalescent plasma (CP, i.e., plasma collected from completely recovered patients), an old therapy used with apparent success in many epidemics and outbreaks since the Spanish 1918 flu (12-18), was proposed again also for COVID-19 (19). Although various immune and non-immune mechanisms have been hypothesized to explain the effect of passive immunotherapy

© Annals of Blood. All rights reserved.

by means of CP transfusion, the most important is likely due to the presence of neutralizing antibodies that, thanks to their capacity of inhibiting viral entry into target cells, prevent the deleterious consequences of viral replication.

In this narrative review, we summarize the main literature data on the use of CP as treatment for past viral epidemics other than COVID-19, focusing on severe acute respiratory epidemics and the most recent Ebola outbreak. We present the following article in accordance with the narrative review reporting checklist (available at http://dx.doi.org/10.21037/aob-2020-cp-03).

Search methods

As a search literature strategy, the Medline and PubMed electronic database was searched for publications on CP in previous viral epidemics without time limits using English language as a restriction. The Medical Subject Heading and key words used were: "convalescent plasma", "hyperimmune plasma", "therapy", "SARS-CoV-2", "COVID-19", "safety" and "efficacy", "acute respiratory infections", "viral infections", "Ebola virus", "SARS", "MERS", "Avian influenza", "H5N1", "Spanish influenza A", "H1N1". We also screened the reference lists of the most relevant review articles for additional studies not captured in our initial literature search.

The use of CP for severe acute viral respiratory infections

von Behring and Kisato were the first investigators in 1980 to provide the basis of passive immunization, then known as serum therapy. Given the early success in 1900s, which earned von Behring the Nobel Prize for Medicine in 1901, passive immunization was rapidly expanded and was used to treat several bacterial infections including *Corynebacterium diphteriae*, *Streptococcus pneumoniae*, *Clostridium tetani*, *Haemophylus influenzae* and *Neisseria meningitidis* (18). In addition, CP was used to fight outbreaks of viral diseases such as poliomyelitis, measles, mumps and acute viral hepatitis A and B (12). Regarding the acute viral respiratory diseases, a meta-analysis by Luke and colleagues reported eight studies involving 1,703 patients with 1918 Spanish influenza pneumonia (H1N1) (14). Although with several methodologic limitations (no study was blinded or randomized and CP was used in many cases without measuring antibody titers), this review showed a pooled absolute reduction of 21% in the mortality rate in patients receiving CP compared to controls (14). During the influenza A (H1N1) pandemic in 2009, the results from a prospective cohort study conducted by Hung and colleagues showed that CP treatment reduced mortality (20.0% in CP-treated group versus 54.8% in control group) (20). Positive evidence was also reported for the 2006 avian influenza A (H5N1) outbreak although mostly based on case reports and case-series (15). Regarding the treatment of previous CoVs, CP was studied in the treatment of SARS during the 2003 outbreak originating in Hong Kong. In a retrospective study, Soo and colleagues compared CP with steroid treatment and observed a significant mortality reduction in CP-treated group which remained also after controlling for co-existing comorbidities (21). Interestingly, Cheng and colleagues retrospectively reviewed 80 patients with SARS infection who had been given CP transfusion and compared those who had been transfused before day 14 following the onset of symptoms to those who received plasma after day 14 (22). The results showed that the group receiving CP earlier had better outcomes (days of hospitalization and death) than the patients who received plasma later. A meta-analysis by Mair-Jenkins and colleagues, including 32 studies of SARS-CoV and severe influenza, reported that CP reduced mortality and it was safe (no relevant adverse events after CP treatment were reported). The reduction of mortality was higher when CP was administered earlier after symptom onset (16). The 2015 MERS-CoV outbreak in South Korea generated a few case reports and case-series that failed to show clinical improvement with the administration of CP (15). Nevertheless, a study conducted by Ko and colleagues found that donor CP containing high titers (≥1:80) of MERS-CoV neutralizing antibody resulted in seroconversion of the recipient post-transfusion whereas seroconversion was not observed with transfusion of low-titer CP (23). This study highlights the importance of the quality of CP in terms of neutralization activity, which plays an important role in the effectiveness of CP.

The use of CP for Ebola virus disease

In addition to the respiratory viral diseases, the recent 2013–2016 West African Ebola virus disease outbreak provided another opportunity to assess the role of CP. A number of non-randomized trials have been published on this issue (17). A study conducted on 84 patients from Guinea receiving CP confirmed the safety of the blood component but failed to demonstrate a survival benefit in the CP treatment arm (24). Another study conducted in Sierra Leone evaluated CP

© Annals of Blood. All rights reserved.

for Ebola treatment in 44 subjects versus 25 non-treated patients and showed an improvement in death rate in patients receiving CP compared to the control group (27.9% versus 44%) with a 2.3 odds ratio (OR) for survival in CP-treated arm (25). In 2014, the WHO has recommended the investigation of CP in the treatment of Ebola virus disease and provided specific protocol guidelines (26). A recent systematic review and meta-analysis on CP therapy for treating severe infectious diseases (SARS-CoV, influenza, Ebola, SARS-CoV-2) including 15 controlled studies showed a significantly lower mortality rate in the group treated with CP compared with the control groups (pooled OR 0.32; 95% CI: 0.19–0.52; P<0.001) (27).

Conclusions

Thanks to the presence of antibodies able to inhibit a specific pathogen, plasma collected from convalescent donors has been frequently used during the last century during several infectious epidemics or pandemics to provide an immediate treatment option while evaluating existing drugs and developing new specific vaccines and therapies. The analysis of the literature data on the use of CP for managing infectious diseases supports its beneficial effect with a high safety profile. In particular, its effectiveness appears to be optimal when administered early and with an adequate titer of neutralizing antibodies. These data have represented a solid rationale for the use of CP treatment during the current SARS-CoV-2 pandemic (28).

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Blood* for the series "Convalescent Plasma". The article has undergone external peer review.

Reporting Checklist: The author has completed the narrative review reporting checklist. Available at http://dx.doi.org/10.21037/aob-2020-cp-03

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/aob-2020-cp-03). The series "Convalescent Plasma" was commissioned by the editorial office without any funding or sponsorship. MF serves as an unpaid Guest Editor of the series and serves as an unpaid editorial board member of *Annals of Blood* from July 2020 to June 2022. The author has no other conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

1. Chen Y, Liu Q, Guo D. Coronaviruses: genome structure, replication, and pathogenesis. J Med Virol 2020;92:418-23.
2. Kuiken T, Fouchier RA, Schutten M, et al. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. Lancet 2003;362:263-70.
3. Drosten C, Günther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. New Engl J Med 2003;348:1967-76.
4. de Groot RJ, Baker SC, Baric RS, et al. Commentary: Middle East respiratory syndrome coronavirus (MERS-CoV): announcement of the Coronavirus Study Group. J Virol 2013;87:7790-2.
5. Peeri NC, Shrestha N, Rahman MS, et al. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? Int J Epidemiol 2020;49:717-26.
6. Mahase E. Covid-19: WHO declares pandemic because of "alarming levels" of spread, severity, and inaction. BMJ 2020;368:m1036.
7. Boban M. Novel coronavirus disease (COVID-19) update on epidemiology, pathogenicity, clinical course and treatments. Int J Clin Pract 2021;75:e13868.
8. Lyngbakken MN, Berdal JE, Eskesen A, et al. A pragmatic randomized controlled trial reports lack of efficacy of hydroxychloroquine on coronavirus disease 2019 viral

© Annals of Blood. All rights reserved.

kinetics. Nat Commun 2020;11:5284.
9. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395:1569-78.
10. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med 2021;384:497-511.
11. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 2020;323:1582-9.
12. Casadevall A, Dadachova E, Pirofski L. Passive antibody therapy for infectious diseases. Nat Rev Microbiol 2004;2:695-703.
13. Luke TC, Casadevall A, Watowich SJ, et al. Hark back: passive immunotherapy for influenza and other serious infections. Crit Care Med 2010;38:e66-73.
14. Luke TC, Kilbane EM, Jackson JL, et al. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? Ann Intern Med 2006;145:599-609.
15. Marano G, Vaglio S, Pupella S, et al. Convalescent plasma: new evidence for an old therapeutic tool? Blood Transfus 2016;14:152-7.
16. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis 2015;211:80-90.
17. Wooding DJ, Bach H. Treatment of COVID-19 with convalescent plasma: lessons from past coronavirus outbreaks. Clin Microbiol Infect 2020;26:1436-46.
18. Stevens RW, Rivera CG, Saleh OA. Time to Treat: Applying Lessons Learned from Other Viral Syndromes to SARS-CoV-2. Mayo Clin Proc Innov Qual Outcomes 2020;4:759-763.
19. Salazar E, Christensen PA, Graviss EA, et al. Treatment of Coronavirus disease 2019 patients with convalescent plasma reveals a signal of significantly decreased mortality. Am J Pathol 2020;190:2290-303.
20. Hung IF, To KK, Lee CK, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. Clin Infect Dis 2011;52:447-56.
21. Soo YO, Cheng Y, Wong R, et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. Clin Microbiol Infect 2004;10:676-8.
22. Cheng Y, Wong R, Soo YO, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis 2005;24:44-6.
23. Ko JH, Seok H, Cho SY, et al. Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. Antivir Ther 2018;23:617-22.
24. van Griensven J, Gallian P, de Lamballerie X. Convalescent plasma and the dose of Ebola virus antibodies. N Engl J Med 2017;376:1297.
25. Sahr F, Ansumana R, Massaquoi TA, et al. Evaluation of convalescent whole blood for treating Ebola virus disease in Freetown, Sierra Leone. J Infect 2017;74:302-9.
26. WHO. Use of Convalescent Whole Blood or Plasma Collected from Patients Recovered from Ebola Virus Disease for Transfusion, as an Empirical Treatment during Outbreaks. Interim Guidance for National Health Authorities and Blood Transfusion Services. World Health Organization, 2014 (version 1.0). Available online: http://www.euro.who.int/__data/assets/pdf_file/0011/268787/Use-of-Convalescent-Whole-Blood-or-Plasma-Collectedfrom-Patients-Recovered-from-Ebola-Virus-Disease-for-Transfusion,-as-an-Empirical-Treatment-during-Outbreaks-Eng.pdf
27. Sun M, Xu Y, He H, et al. A potentially effective treatment for COVID-19: A systematic review and meta-analysis of convalescent plasma therapy in treating severe infectious disease. Int J Infect Dis 2020;98:334-46.
28. Brown BL, McCullough J. Treatment for emerging viruses: Convalescent plasma and COVID-19. Transfus Apher Sci 2020;59:102790.

doi: 10.21037/aob-2020-cp-03
Cite this article as: Franchini M. Convalescent plasma therapy for managing infectious diseases: a narrative review. Ann Blood 2021;6:17.

© Annals of Blood. All rights reserved.