Available online at www.medicinescience.org

REVIEW ARTICLE

Medicine Science International Medical Journal

Medicine Science 2022;11(2):920-3

Convalescent plasma therapy in COVID-19

Ayse Uysal[1], Mehmet Ali Erkurt[2], Irfan Kuku[2], Ahmet Sarici[2], Soykan Bicim[2], Emin Kaya[2], Ilhami Berber[2]

[1]Firat University, Faculty of Medicine, Department of Hematology, Elazig, Turkey
[2]Inonu University, Turgut Ozal Medicine Center, Department of Hematology, Malatya, Turkey

Received 17 September 2021; Accepted 05 January 2022
Available online 15.03.2022 with doi: 10.5455/medscience.2021.09.292

Abstract

The coronavirus disease 2019 (COVID-19) affected many people in a short time and 5-10% of them were severely affected by the disease. A variety of treatment methods have been developed for this rapidly spreading disease and vaccine studies have been initiated. One of these treatment methods is convalescent plasma (CP) therapy which is a passive immunization therapy. CP method is based on the principle of giving the plasma containing the antibodies formed against the pathogen to people who have active disease after they have recovered from the disease which is a very effective but short-term solution until a definitive and permanent treatment (vaccine, drug, etc.) is found in pandemic conditions. Here, we presented the use of CP in the COVID-19 pandemic.

Keywords: Convalescent plasma, COVID-19, passive immunization, therapy

Introduction

The coronavirus disease 2019 (COVID-19) caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is detected firstly in Wuhan Province of the People's Republic of China in December 2019, has become a global problem in a short time [1,2]. As of today, SARS-CoV-2 had infected over 180 million individuals worldwide and caused over 3,5 million deaths [3].

The coronavirus disease 2019 (COVID-19) affected many people in a short time and 5-10% of them were severely affected by the disease. A variety of treatment methods have been developed for this rapidly spreading disease and vaccine studies have been initiated. Some of these treatments include antiviral agents as lopinavir/ritonavir, favipiravir, and remdesivir, anti-malaria drug as hydroxychloroquine, anti-cytokine drugs, and systemic corticosteroids. Considering its clinical effectiveness in past viral epidemics or pandemics such as Ebola, measles, mumps, polio, influenza, SARS-CoV-1, and Middle East Respiratory Syndrome [MERS], opinions on the use of convalescent plasma have been reported [4,5]. In the declaration published by WHO in January 2020, it was stated that immune plasma can be used for the SARS-CoV-2 virus when vaccine and/or effective anti-viral drugs are not available [6]. The Food and Drug Administration (FDA) approved the emergency use for hospitalized patients with COVID-19 (August 2020) [7].

Convalescent plasma therapy

Convalescent plasma therapy has been successfully used to treat infectious diseases for a long-time which method based on the principle of giving the plasma containing the antibodies formed against the pathogen to people who have active disease after they have recovered from the disease which is a very effective but short-term solution until a definitive and permanent treatment (vaccine, drug, etc.) is found in pandemic conditions [8,9].

In history, passive immunization therapy was used for diphtheria in 1891. In 1918, CP was also used in the Spanish flu pandemic. It

*Corresponding Author: Mehmet Ali Erkurt, Inonu University, Turgut Ozal Medicine Center, Department of Hematology, Malatya, Turkey
E-mail: erkurtali@hotmail.com

has also been an effective and successful treatment method used in influenza (H1N1) pandemic, and the Ebola outbreak (2015).

More recently, CP has been used in two important coronavirus epidemics before COVID-19 which are SARS-1 (2003) and MERS (2012) epidemics. In SARS patients, the mortality rate and duration of hospital stay were decreased by the KP [8]. In Hong Kong, Cheng et al. investigated 80 patients who were transferred with SARS, CP with earlier administration had a lower mortality rate and better early discharge rate [10].

The expected effect with passive antibody therapy is to neutralize the virus by binding directly and the other mechanisms of action are complemant activation, antibody-dependent cellular cytotoxicity, and/or the initiation of virus elimination via phagocytosis pathways.

The most important of these mechanisms are neutralizing antibodies that prevent virus replication and increase virus clearance. The higher titer of the neutralizing antibody is more likely to be efficacious and associated with a lower risk of mortality in the therapeutic use of CP. Therefore, the neutralizing antibody level is important, and recommended antibody titers are at least 1:160 [4,11,12].

The use of convalescent plasma during the COVID-19 period

The first CP experience for the COVID-19 pandemic came from the People's Republic of China where the infection originated as a case or case series. The first dose of CP therapy from a COVID-19 patient was collected on February 1, 2020, that was applied to severely ill patients at a hospital in Wuhan Province on February 9, 2020.

From China, Duan et al. presented a case series outcome of effectiveness of CP therapy in 10 severe COVID-19 patients who treated CP with neutralization activity of >1:640. After the CP infusion, improvement of clinical symptoms, reduction of pulmonary lesions, improvement of lymphocytopenia, amelioration of routine other laboratory criteria (C-reactive protein, alanine aminotransferase, aspartate aminotransferase etc.) were reported [13]. In the other study from China, CP therapy experiences in 5 critically ill patients with COVID-19 who received intensive treatment before the CP. The values of the inflammatory biomarkers and the SOFA score ranged decreased, and respiratory parameters increased, and viral loads also became negative after the plasma therapy [14]. Ye et al. presented the clinical, laboratory, and radiologic improvement in 6 severe COVID-19 patients with CP therapy from Wuhan [15].

As time passed, reports of experience with many cases and randomized-controlled trials began to be published from around the world. Salazar et al. reported an interim analysis of prospective trial' results, 316 patients with COVID-19 who received CP or nor received CP were evaluated which suggests that transfusion of CP in early period decrease the mortality rate [12]. Liu et al presented a retrospective trial from New York City which showed that oxygen requirements and mortality reduced significantly in CP treated group [16]. A randomized placebo-controlled trial from USA and Brazil was presented. The mortality was significantly lower in convalescent plasma group versus control plasma (12.6% & 24.6%, and they suggested that CP therapy was associated with significantly improved survival [17].

In CAPSID trial reported that CP with higher neutralizing antibodies accelerates the clinical improvement and hospital discharge and improves the survival compared to the control group [18]. Klassen and colleagues presented a systematic review and meta-analysis, according to this study, high-titer CP and within 3 days transfusion were decreased the mortality rate [19].

In phase 2, prospective trial from Greece, the death and extubation rate significantly better in CP group. Overall survival statistically significant better CP infusion group ($p < 0.001$). This trial suggested that CP effective therapy in patients with severe COVID-19 [20].

Altuntas et al. presented a multicenter, randomized, retrospective trial from Turkey, this trial established that CP reduces the mechanical ventilation and vasopressor support [21]. Oliveira et al. reported a review which included 24 CP clinical trials mostly advanced phase from several countries. The length of hospital stays, disease severity, and mortality were reduced with CP therapy in critical or severe COVID-19 patients [22]. Erkurt et al. presented 26 severe COVID-19 patients who applied CP therapy. They reported that CP therapy was safety method for severe COVID-19 patients and should be applied in the early period of admission to the hospital [23]. Cizmecioglu et al. reported in their study that CP reduce the length of stay in the hospital [24]. Casadevall et al presented the idea that mortality rates may have increased due to recent declines in CP use [25].

Timing of convalescent plasma administration

One of the factors affecting the effectiveness of CP is the time of the treatment. The early transfusion of CP to patients with COVID-19 provides more therapeutic benefits. A multicenter, cohort study from Argentina demonstrated that CP transfusion within 3 days decrease the mortality rate [26,27].

Convalescent plasma in cancer, immunodeficiency, and elderly with COVID-19 patients

COVID-19 disease affects the cancer patients more than the normal population which the prevalence is 1-2% [28] which increased the mortality and morbidity more than without cancer patients because of immunosuppressive agents, radiation therapy, or underlying disease [29,30]. Cancer patients had a higher risk of severe illness as intensive care unit admission and the mechanical ventilation support compared without cancer [28]. CP may be a treatment option in these critically ill patients with cancer. Tremblay et al. presented a case series with 24 cancer patients (53.8% hematologic malignancy) who were treated with convalescent plasma. They demonstrate that CP may help improve oxygen requirements and decreases CRP significantly [29]. Thompson et al. evaluated 143 patients who had hematologic malignancy and received CP treatment. They reported that 30-day mortality decrease after the transfusion [31].

In the literature, experiences of CP therapy in patients with primary and/or secondary immunodeficiency are limited and include a small population. The results of these studies, CP was a safe and effective therapeutic option in COVID-19 patients with

immunodeficiency [32]. CP transfusion improved the clinical status and viral clearance in patients who experienced protracted severe COVID-19 symptoms with secondary immunodeficiency due to therapies that suppress B-cell proliferation [29].

In solid organ transplantation, the effectiveness of CP was demonstrated by improving clinical symptoms and reducing the oxygen requirements in the majority of the patients with COVID-19 [33].

In the literature, the effect of CP is higher in young patients than in old patients. Yoon et al reported that the risk of mortality decreases 4-fold in patients younger than 65 years old [34]. Nevertheless, the other trial of CP in older adult patients reports that the early transfusion of high-titer CP against infected elderly patients (75 years of age or older) decreased the progression of Covid-19 to severe illness [27].

Risk of convalescent plasma

In clinical trials, CP transfusion well tolerated and not occurred fatal adverse events [5]. Blood product transfusion associated adverse events as allergic/anaphylactic reactions, acute hemolytic transfusion reaction, transfusion related lung injury (TRALI) or transfusion associated circulatory overload (TACO) can be occurred and in studies the most reported side effects are transfusion reaction [35]. TRALI and TACO are more common in patient with COVID-19 infection than the normal population, which is attributed to increase the vascular permeability, cardiac and pulmoner damage. The other possible side effect is thrombotic events that may be caused by direct infusion of coagulant factors with plasma or by complemant-mediated tissue damage. Antibody dependent enhancement (ADE) of infection is the possible theoretical side effect. However, in SARS-2 CoV-2 ADE is not defined and reported.

Donors' selection

According to the FDA, CP donors have recovered from COVID-19. The diagnostic test at the time of illness or, the presence of SARS-CoV-2 antibodies after recovery were documented. Before the donation, complete recovery of symptoms at least 28 days or at least 14 with negative diagnostic test from one or more of nasopharyngeal swab samples or blood. Male donors or non-pregnant female donors should be selected firstly, or female donors who have been tested after their most recent pregnancy and have been evaluated as negative for HLA antibodies. The neutralizing antibody titers should be at least 1:160.

Conclusion

Convalescent plasma may be a treatment option in critically ill patients especially in infections whose treatment is not clear. In COVID-19 infections, CP has been very effective when applied in the early period of infections and which decrease the duration of hospital stay, increase the clinical improvement.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

References

1. Samudrala P K, Kumar P, Choudhary K, et al. Virology, pathogenesis, diagnosis and in-line treatment of COVID-19. Eur J Pharmacol. 2020;883: 173-375.
2. Gavriatopoulou M, Ntanasis-Stathopoulos I, Korompoki E, et al. Emerging treatment strategies for COVID-19 infection. Clin Exp Med. 2021;21:167-79.
3. WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int/ access date 2th Agust 2021
4. Brown B L and McCullough J. Treatment for emerging viruses: Convalescent plasma and COVID-19. Transfus Apher Sci. 2020;59:102790.
5. Franchini M and Liumbruno G M. Convalescent Plasma for the Treatment of Severe COVID-19. Biologics. 2021;15:31-8.
6. WHO Blood Regulators Network (BRN): Interim Position Paper on blood regulatory response to the evolving outbreak of the 2019 novel coronavirus SARS-CoV-2. http://www.transfusion.ru/2020/04-03-3.pdf access date 2nd August 2021
7. Recommendations for Investigational COVID-19 Convalescent Plasma. https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-applications-inds-cber-regulated-products/recommendations-investigational-covid-19-convalescent-plasma access date 2nd Agust 2021
8. Casadevall A and Pirofski L A. The convalescent sera option for containing COVID-19. J Clin Invest. 2020;130:1545-8.
9. Casadevall A and Scharff M D Return to the past: the case for antibody-based therapies in infectious diseases. Clin Infect Dis. 1995;21:150-61.
10. Cheng Y, Wong R, Soo Y O, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis. 2005;24:44-6.
11. Joyner M J, Carter R E, Senefeld J W, et al. Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19. N Engl J Med. 2021;384:1015-27.
12. Salazar E, Perez K K, Ashraf M, et al. Treatment of Coronavirus Disease 2019 (COVID-19) Patients with Convalescent Plasma. Am J Pathol. 2020;190:1680-90.
13. 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;117:9490-6.
14. 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.
15. Ye M, Fu D, Ren Y, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. J Med Virol. 2020;92:1890-901.
16. Liu S T H, Lin H M, Baine I, et al. Convalescent plasma treatment of severe COVID-19: a propensity score-matched control study. Nat Med. 2020;26:1708-13.
17. O'Donnell M R, Grinsztejn B, Cummings M J, et al. A randomized double-blind controlled trial of convalescent plasma in adults with severe COVID-19. J Clin Invest. 2021;1;131:e150646.
18. Korper S, Weiss M, Zickler D, et al. High Dose Convalescent Plasma in COVID-19: Results from the Randomized Trial CAPSID. medRxiv. 2021;2021;05:21256192.
19. Klassen S A, Senefeld J W, Johnson P W, et al. The Effect of Convalescent Plasma Therapy on Mortality Among Patients With COVID-19: Systematic Review and Meta-analysis. Mayo Clin Proc. 2021;96:1262-75.
20. Pappa V, Bouchla A, Terpos E, et al. A Phase II Study on the use of convalescent plasma for the treatment of severe COVID-19- A Propensity Score-Matched Control Analysis. Microorganisms. 2021;11;9:806.
21. Altuntas F, Ata N, Yigenoglu T N, et al. Convalescent plasma therapy in patients with COVID-19. Transfus Apher Sci. 2021;60:102955.
22. Oliveira F A, Nucci M P, Rego G N A, et al. Convalescent plasma therapy in COVID-19 critically ill patients during advanced phases of clinical trials and their preliminary results. Einstein (Sao Paulo). 2021;19:eRW6186.
23. Erkurt M A, Sarici A, Berber I, et al. Life-saving effect of convalescent plasma treatment in covid-19 disease: Clinical trial from eastern Anatolia. Transfus Apher Sci. 2020;59:102867.
24. Akay Cizmecioglu H, Goktepe MH, Demircioglu S, et al. Efficacy of

convalescent plasma therapy in severe COVID-19 patients. Transfus Apher Sci. 2021;60:103158.

25. Casadevall A, Dragotakes Q, Johnson P W, et al. Convalescent Plasma Use in the United States was inversely correlated with COVID-19 Mortality: Did Plasma Hesitancy cost lives? medRxiv. 2021;2021.04.07.21255089.

26. González SE, Regairaz LR. Salazar M, et al. Timing of convalescent plasma administration and 28-day mortality for COVID-19 pneumonia. medRxiv 2021;02.02.21250758.

27. Libster R, Pérez Marc G, Wappner D, et al. Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults. N Engl J Med. 2021;384:610-8.

28. Desai A, Sachdeva S, Parekh T, et al. COVID-19 and Cancer: Lessons From a Pooled Meta-Analysis. JCO Glob Oncol. 2020;6:557-9.

29. Tremblay D, Seah C, Schneider T, et al. Convalescent Plasma for the Treatment of Severe COVID-19 Infection in Cancer Patients. Cancer Med. 2020;9:8571-8.

30. Aries J A, Davies J K, Auer R L, et al. Clinical outcome of coronavirus disease 2019 in haemato-oncology patients. Br J Haematol. 2020;190:64-7.

31. Thompson M A, Henderson J P, Shah P K, et al. Convalescent Plasma and Improved Survival in Patients with Hematologic Malignancies and COVID-19. medRxiv 2021;2021.02.05.21250953.

32. Senefeld J W, Klassen S A, Ford S K, et al. Therapeutic use of convalescent plasma in COVID-19 patients with immunodeficiency. medRxiv 2020;2020.11.08.20224790.

33. Rahman F, Liu S T H, Taimur S, et al. Treatment with convalescent plasma in solid organ transplant recipients with COVID-19: Experience at large transplant center in New York City. Clin Transplant. 2020;34:e14089.

34. Yoon H A, Bartash R, Gendlina I, et al. Treatment of severe COVID-19 with convalescent plasma in Bronx, NYC. JCI Insight. 2021;22;6:142270.

35. Avendaño-Solà C, Ramos-Martínez A, Muñez-Rubio E, et al. Convalescent Plasma for COVID-19: A multicenter, randomized clinical trial. medRxiv. 2020;2020.08.26.20182444.