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CONCISE REVIEW

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Convalescent plasma therapy in patients with COVID-19

Tuğçe Nur Yiğenoğlu[1] | Tuba Hacıbekiroğlu[2] | İlhami Berber[3] | Mehmet Sinan Dal[1] | Abdülkadir Baştürk[4] | Sinem Namdaroğlu[5] | Serdal Korkmaz[6] | Turgay Ulas[7] | Tuba Dal[8] | Mehmet Ali Erkurt[3] | Burhan Turgut[9] | Fevzi Altuntaş[1,10]

[1]Ankara Oncology Training and Research Hospital, Department of Hematology and Bone Marrow Transplantation Center, University of Health Sciences, Ankara, Turkey

[2]School of Medicine, Department of Internal Medicine, Division of Hematology, Sakarya University, Sakarya, Turkey

[3]School of Medicine, Department of Internal Medicine, Division of Hematology, Inonu University, Malatya, Turkey

[4]School of Medicine, Department of Internal Medicine, Division of Hematology, Selcuk University, Konya, Turkey

[5]Bozyaka Training and Research Hospital, Department of Hematology, University of Health Sciences, Izmir, Turkey

[6]Kayseri Training and Research Hospital, Department of Hematology, University of Health Sciences, Kayseri, Turkey

[7]School of Medicine, Department of Internal Medicine, Division of Hematology, Near East University, Nicosia, Cyprus

[8]School of Medicine, Department of Clinical Microbiology, Ankara Yıldırım Beyazıt University, Ankara, Turkey

[9]School of Medicine, Department of Internal Medicine, Division of Hematology, Namık Kemal University, Tekirdağ, Turkey

[10]School of Medicine, Department of Internal Medicine, Division of Hematology, Ankara Yıldırım Beyazıt University, Ankara, Turkey

Correspondence
Tuğçe Nur Yiğenoğlu, Department of Hematology and Bone Marrow Transplantation Center, Ankara Oncology Training and Research Hospital, University of Health Sciences, Ankara, Turkey.
Email: dr.nuryigenoglu@gmail.com

Abstract

There are currently no licensed vaccines or therapeutics for COVID-19. Anti-SARS CoV-2 antibody-containing plasmas, obtained from the recovered individuals who had confirmed COVID-19, have been started to be collected using apheresis devices and stored in blood banks in some countries in order to administer to the patients with COVID-19 for reducing the need of intensive care and the mortality rates. Therefore, in this review, we aim to point out some important issues related to convalescent plasma (CP) and its use in COVID-19. CP may be an adjunctive treatment option to the anti-viral therapy. The protective effect of CP may continue for weeks and months. After the assessment of the donor, 200-600 mL plasma can be collected with apheresis devices. The donation interval may vary between countries. Even though limited published studies are not prospective or randomized, until the development of vaccines or therapeutics, CP seems to be a safe and probably effective treatment for critically ill patients with COVID-19. It could also be used for prophylactic purposes but the safety and effectiveness of this approach should be tested in randomized prospective clinical trials.

KEYWORDS

convalescent plasma, COVID-19, SARS CoV-2

1 | INTRODUCTION

At the end of 2019, pneumonia patients with an unidentified cause were started to be observed in Wuhan, Hubei Province, China.[1] After the genetic analysis of the virus, it was understood that these pneumonia cases were caused by the 2019 Novel Coronavirus (2019-nCoV).[2] On 11 February 2020; the disease was officially named as COVID-19, by the World Health Organization (WHO).[3] This novel coronavirus was named as SARS-CoV-2 by the International Committee on Taxonomy of Viruses.[4] It was declared a pandemic by the WHO on 11 March 2020. As of 17 April 2020, in the worldwide, there have been 2 175 130 confirmed cases of COVID-19, including 145 184 deaths, as reported to WHO.[3] The mortality rate of COVID-19 is higher than the mortality rate of seasonal influenza in which the mortality rate is reported usually less than 0.1%.[3] Patients with any comorbidity and/or older age are associated with poorer clinical outcomes than younger patients or those without any comorbidity. As the number of comorbidities increases, the clinical outcome gets worse. Smoking, chronic obstructive pulmonary disease, diabetes, hypertension, cardiovascular diseases, and malignancy are reported to be the risk factors for severe COVID-19 and increased mortality.[5] Although there are clinical trials regarding the development of therapeutics and vaccines, there are currently no licensed vaccines or therapeutics for COVID-19. Because of the higher mortality rate and the high number of infected cases, it is important to find a treatment in a short time.

Passive antibody therapy involves administering antibodies against a particular agent to a susceptible individual in order to protect or treat an infectious disease associated with this agent. On the contrary, active vaccination requires stimulation of an immune response that takes time to develop. Therefore, passive antibody administration is the only way to immunize susceptible people immediately. Passive antibody therapy has a history going back to the 1890s and was the only method of treating some infectious diseases before the development of antimicrobial therapy in the 1940s.[6] Currently, passive antibody therapy is mainly consisting of pooled immunoglobulin preparations that includes high concentrations of antibodies. On the other hand, CP has been used emergently in epidemics where there is insufficient time to produce immunoglobulin preparations.[7]

Anti-SARS COV-2 antibody containing plasma, obtained from the recovered individuals who had confirmed COVID-19, have been started to be collected by apheresis devices and stored in blood banks in some countries such as Turkey and the United States of America in hopes of reducing mortality rates and reduce the need of intensive care. Therefore, in this review, we aim to point out some important issues related to convalescent plasma (CP) and its use in COVID-19.

2 | TREATMENT OF INFECTIOUS DISEASES WITH CONVALESCENT PLASMA: HISTORICAL EXAMPLES

In the past, plasma-mediated treatments have been used against many pathogens. Passive immunization obtained from sheep serum against diphtheria toxin was first given to a child with diphtheria in 1891 and saved his life. German scientist Emil Adolf von Behring received the 1901 Nobel Prize for his discovery of passive immunization against diphtheria toxin. CPs have been used in epidemics of viral infections like poliomyelitis, measles, mumps and flu.[6]

Experience in the use of CP against coronavirus was obtained from Severe Acute Respiratory Syndrome 1 (SARS-COV-1) outbreaks in 2003. In the retrospective non-randomized study conducted by Soo et al, 40 SARS patients refractory to ribavirin and 1.5 g of pulsed methylprednisolone received either 200-400 mL CP (n = 19) or a further dose of pulsed methylprednisolone (n = 21). In patients who received CP, higher discharge rate up to 22 days from the hospital (77.8% vs 23%; $P = .004$) and lower mortality rate (0% vs 23.8%; $P = .049$) was observed compared to the patients who received steroids. The authors also observed that patients receiving CP after day 16 had a poor clinical response and concluded that CP administration was more effective when given early in the course of the disease.[8] In Taiwan, Yeh et al reported three healthcare workers with SARS-COV-1, who had failed to respond to steroids, ribavirin, intravenous immunoglobulin and protease inhibitors, were treated with 500 mL CP. All of the patients survived after CP transfusion.[9] Besides, Cheng et al evaluated the efficacy of CP in the treatment of patients with SARS in 2003 and found a higher day-22 discharge rate among patients who received CP before day 14 of illness.[10]

CP was also used in the West African Ebola epidemic in 2013. Eighty-four patients received 500 mL of CP. When compared to the historical control group, the CP group had a shorter duration of symptoms than did the control group. From day 3 to day 16 after diagnosis, the risk of death was 31% in the CP group and 38% in the control group. Even though the transfusion of up to 500 mL CP improved the symptoms, no significant survival benefit was observed.[11] Treatment with CP was also reported in three patients with Middle East Respiratory Syndrome (MERS) in South Korea. In this study, 3 of 13 MERS patients with respiratory failure received 4 CP

infusions from recovered MERS-CoV-infected patients, and only two of them showed neutralizing activity. After the infusion of CP with a neutralizing activity titer of 1:80, serological response was achieved but no response was achieved after the infusions of CP with a neutralizing activity titer of 1:40.[12,13]

3 | TREATMENT OF COVID-19 WITH CONVALESCENT PLASMA

CP has been used in the recent global outbreak for the treatment of patients with COVID-19 in China. In the study conducted by Shen et al, 5 critically ill COVID-19 patients refractory to steroid and antiviral treatment, received 400 mL CP from 5 different donors. All the donors had SARS-CoV-2-specific ELISA antibody titer higher than 1:1000; and neutralizing antibody titer greater than 40. After CP transfusion; in 4 (80%) of 5 patients, the body temperature normalized within 3 days; the Sequential Organ Failure Assessment Score decreased, and PaO_2/FiO_2 increased within 12 days (range, first 172-276 and then 284-366); viral loads decreased and became negative within 12 days; ELISA and neutralizing antibody titers increased. After 12 days, acute respiratory distress syndrome (ARDS) improved in 4 patients (80%); after 2 weeks, 3 patients extubated; 3 of the 5 patients (60%) were discharged from the hospital and the other two patients were stable after 37 days.[14] In a recent study, researchers treated 10 critically ill COVID-19 patients with antiviral therapy and steroid, plus a dose of 200 mL CP that had a neutralized antibody titer of at least 1:640. Researchers prospectively compared symptoms and laboratory findings 3 days after CP infusion. Among all patients, CP was well tolerated. It significantly increased neutralizing antibodies at a high level; within 7 days, viremia disappeared; clinical symptoms resolved rapidly in 3 days. There was an improvement in lymphocyte count and in SaO_2; on radiological examination, they reported that lung lesions changed significantly within 7 days.[15] Although these studies involve a small number of patients, available information suggests that CP administration is safe and reduces the viral load.

On March 24, the American Food and Drug Administration (FDA) published a recommendation with the "COVID-19 Convalescent Plasma Research - Emergency" declaration. FDA stated that certain standards have been established for donation and that CP use is allowed for patients under certain conditions. Of note, FDA does not allow the use of CP for prophylaxis. With the "Blood Regulatory Network", WHO suggested using CP when vaccines and anti-viral drugs are not available in the treatment of critically ill patients with COVID-19.[16]

Turkish Ministry of Health allowed the use of CP in severe COVID-19.[17] Therapeutic apheresis centers licensed by the Ministry of Health and Turkish Red Crescent carry out activities for obtaining CP from donors. In Turkey, multidisciplinary working groups which have been attended by a large number of scientists were formed. These groups provide information and experience sharing among themselves by following donor selection, product standard, treatment management, patient-donor follow-up, and scientific developments in the world. CP administrations are carried out under the control of intensive care, infectious disease specialists and pulmonologists.

4 | CONVALESCENT PLASMA: THE MECHANISM OF ACTION

The exact mechanism of CP in COVID-19 has not been clearly identified yet. However, previous studies revealed that the mechanism of action of CP in other viral infections such as Ebola virus and Respiratory Syncytial Virus is mainly viral neutralization. The other mechanisms are antibody-induced cellular cytotoxicity, complement activation and phagocytosis. Neutralizing antibodies delivered with CP can provide control of the viral load. Non-neutralizing antibodies may also contribute to prophylaxis and/or enhance recovery.[18,19]

5 | STEPS OF THE CONVALESCENT PLASMA COLLECTIONS

The regulations of every single step of CP collections is very important. Starting from assessment of donor to the administration of CP to the patients, all of the steps should be organized carefully and should be performed by experienced health workers.

5.1 | Donor eligibility

The criteria for eligibility of CP donors may vary between countries. According to the FDA, individuals who meet the following criteria can be a CP donor[16]:

1 Recovered from COVID-19, blood donor tests were done and suitable for donation;
2 Evidence of COVID-19 documented by a laboratory test either by a diagnostic test (eg, nasopharyngeal swab) at the time of illness, or a positive serological test for SARS-CoV-2 antibodies after recovery, if prior

diagnostic testing was not performed at the time COVID-19 was suspected.
3 Complete resolution of symptoms at least 14 days prior to donation.
4 Male donors, or female donors who have not been pregnant, or female donors who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies.
5 When measurement of neutralizing antibody titers is available, neutralizing antibody titers of at least 1:160 is recommended. A titer of 1:80 may be considered acceptable if an alternative matched unit is not available.

5.2 | Pre-donation evaluation of donors

Real-time reverse transcriptase-PCR (RT-PCR) is currently a favored assay for the detection of coronavirus. However, RNA detectability was low in samples collected before day-7 and during days 15-39. For this reason, coronavirus pre-donation screening tests should be supported by antibody detecting tests.[20] Each donor must meet all eligibility criteria and be evaluated by all test required for normal blood donation. Female donors with a history of pregnancy should be screened for HLA antibodies to minimize the risk of transfusion-related acute lung injury (TRALI). In addition, a blood sample should be obtained for antibody testing before referring the donor to an apheresis procedure. Unfortunately, neutralizing antibody assays are not available in most centers. Quantitative assays (eg, ELISA) are available but commercially available assays have not been optimally validated. In addition, the relationship between total anti-SARS-CoV-2 antibodies and neutralizing anti-SARS-CoV-2 antibodies is not clear. There is also uncertainty as to whether total antibodies or subclasses (eg, IgM, IgG, or IgA) are the optimal measures, and which antigen is most informative.[21,22] Limited data are currently available on the ELISAs. In a previous study, the efficacy of the antibody test for the detection of IgM and IgG, has shown a sensitivity and specificity of 88.7% and 90.6%, respectively. The antibody titer will differ according to the duration between the collection time and onset of infection. In previous studies, seroconversion has been observed to occur between 8 and 21 days after the onset of symptoms.[22-25] In a study conducted in 173 patients with COVID-19, the seroconversion rate for total antibodies (Ab), IgM and IgG was 93.1%, 82.7%, and 64.7%, respectively. The median seroconversion time for total Ab, IgM and then IgG were day-11, day-12 and day-14, separately. The presence of antibodies was <40% within 1-week since onset but rapidly increased to 100.0% (total Ab), 94.3% (IgM), and 79.8% (IgG) since day-15 after onset. RNA detectability decreased from 66.7% in samples collected before day-7 to 45.5% during days 15-39. The authors suggested that combining RNA and antibody detections significantly improved the sensitivity of diagnosis for COVID-19 in the first 1-week since onset.[26] Currently, the findings that have been reported suggest that CPs that are collected ≥14 days after resolution of symptoms contain high titers of antibodies.[22-25] According to FDA if testing can be conducted, neutralizing antibody titers should be at least 1:160 but a titer of 1:80 may be considered acceptable if an alternative matched unit is not available.[16]

5.3 | Donor recruitment

Blood centers may play a role in recruitment of donors in collaboration with partner hospitals. In Turkey, therapeutic apheresis centers licensed by the Ministry of Health and Turkish Red Crescent carry out activities for obtaining CP from donors.

5.4 | Collection of convalescent plasma at apheresis centers

Donors who have successfully completed pre-donation evaluation are directed to the apheresis centers. CP should be collected by apheresis to take larger volumes in short intervals. Approximately 200-600 mL plasma can be collected with apheresis devices depending on the total blood volume of the donor. The collected plasma volume (excluding the anticoagulant solution) should not exceed 750 mL for each procedure. With the consent of the donor, an appointment can be arranged for plasma donation again. The donation interval may vary between countries. CP is stored by freezing or applied within 6 hours without freezing. Freezing should be started within the first 6 hours after the apheresis process is completed. Plasma components should be labeled using the ISBT128 coding system for traceability. The collected products can be individually labeled as 200 mL of divided ingredients and defined as 1 unit. Barcoded products should be stored at or below minus 18/25° in a separate storage cabinet. Appropriate patients can be given 200-400 mL of CP in accordance with the clinical research protocol. ABO blood group should preferably be compatible. For pathogen inactivation process; amotosalen + UV light, riboflavin + UV light, methylene blue or a solvent/detergent may be used. But we would like to highlight that there has been no study that compared Anti-SARS-CoV-2 CP that had undergone pathogen inactivation

process to those of not. In order to maximize transfusion safety, it is recommended that the CP should undergone pathogen inactivation process. It should be irradiated if it will be given to the patient without being frozen within 6 hours after the plasma collection. Otherwise, the frozen plasma does not need to be irradiated.

6 | THE DOSE OF CONVALESCENT PLASMA

In the previous studies, the dosing of CP is highly variable. In clinical trials, one unit of plasma (200 mL) has been planned for use for prophylaxis and one to two units have been planned for treatment. The antibodies' duration of efficacy is unknown but is estimated to last in weeks to a few months.[25,27,28] In previous use of CP therapy in SARS, 5 mL/kg of plasma at a titer of 1:160 was used.[10] A quarter or half of the treatment dose was used for prophylactic purposes in earlier studies. According to linear proportionality, 3.125 mL/kg of plasma with a titer of >1:64 would provide an equivalent immunoglobulin level to one-quarter of 5 mL/kg plasma with a titer of 1:160.[7]

In pediatric transfusions, dose by body weight should be used. COVID-19 is rarely symptomatic in the pediatric age group. Therefore, every procedure in this age group should be performed within the scope of clinical research in cooperation with national and international health authorities.

7 | PATIENT SELECTION

There are several clinical trials that are ongoing that have very different eligibility criteria from the severely affected to post exposure individuals.[29] The patient selection may vary between countries. The FDA allowed the use of CP to patients who met the following criteria[16]:

- Laboratory confirmed COVID-19
- Severe or immediately life-threatening COVID-19.
  - Severe disease is defined as one or more of the following:
    - Dyspnea,
    - Tachypnea ≥ 30/min,
    - blood oxygen saturation ≤ 93%,
    - $PaO_2/FiO_2 < 300$,
    - lung infiltrates >50% within 24-48 hours
  - The life-threatening disease is defined as one or more of the following:
    - respiratory failure,
    - septic shock,
    - multiple organ dysfunction

8 | PROPHYLAXIS

There is no clear indication and evidence of benefit by using CP for prophylaxis for those who have been exposed to SARS-CoV-2, this issue is still controversial and FDA does not allow the use of CP for prophylaxis outside of approved clinical trials.[7,16] However, historically, it has been stated that passive antibody therapy is most effective when administered prophylactically or used early after the onset of symptoms.[30,31] The new, phase 2-3 trial is recruiting patients and still evaluating the use of post-exposure prophylactic plasma in COVID-19 patients who have had close contact exposure, but have not yet presented symptoms.[32]

9 | RISKS OF CONVALESCENT PLASMA

The risks of CP administration are similar to those of standard plasma. Infection with another infectious disease agent (viral transmission or bacterial contamination), immunological reactions such as serum disease, non-hemolytic transfusion reactions (tremors, fever, urticaria), transfusion-associated circulatory overload and TRALI can be observed.[33] No serious adverse events have been reported in any study of CP. Two observational studies during the SARS-CoV-1 outbreak did not report any complications related to CP.[8] In developed countries, for HIV, hepatitis B and hepatitis C viruses, the risk of transfusion-transmissible infection is less than one infection per two million donations.[34] The risk of TRALI is generally less than one for every 5000 transfused units, but in COVID-19, the risk of TRALI is one of the major concerns about CP because most of the critically ill patients have ARDS and disseminated intravascular coagulation. Both of these situations are risk factors for the development of TRALI.[35] Specific risk about Anti-SARS-CoV-2 CP is transfusion-transmitted SARS-CoV-2. This remains theoretical because there has been no report of SARS-CoV-2 transmission by blood transfusion. This risk is particularly important in prophylactic use since critically ill patients are already infected. In addition, only 1% of symptomatic patients have been reported to have detectable SARS-CoV-2 RNA in their blood.[36,37] Between January 25 to March 4, 2020; 2430 blood donations were screened in Wuhan and only one (0.04%) donor was found to be positive for SARS-CoV-2 RNA. Between December 21 to January 22, 2020; 4995 blood donations were screened and a second (0.02%) donor was found to

be positive for SARS-CoV-2 RNA.[38] The other theoretical risk of CP is an antibody-dependent enhancement (ADE). Antibodies that developed during a previous infectious disease caused by a different viral serotype may exacerbate clinical severity.[39] Previous infection with other types of coronavirus may arise the concern about the risk of ADE in COVID-19 and the geographic variation in disease severity may be attributed to this mechanism.[40] In the current pandemic, there has been no report about the worsening of the clinical situation that has been attributed to ADE after CP infusion. Similarly, there has been no report about ADE after the use of CP for SARS and MERS. The other theoretical risk of CP is the attenuation of the development of a natural immune response, especially when administered for prophylaxis. CP treatment is recommended only in academic or comprehensive centers that can manage potential treatment-related complications, such as TRALI.

In conclusion, SARS-CoV-2 continues to spread worldwide. The exact treatment of COVID-19 disease is currently unknown. Even though limited published studies are not prospective or randomized, until the development of vaccines or therapeutics, CP seems to be a safe and probably effective treatment for critically ill patients with COVID-19. At least preliminary results of multicentre randomized controlled clinical trials should be waited. Meanwhile, in this pandemic, scientists should be encouraged to collaborate on common research protocols, rather than conducting independent researches. International multicenter randomized controlled trials are needed. CP use should be encouraged to be made within the scope of clinical trials in cooperation with national and international health authorities.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

ORCID

Tuğçe Nur Yiğenoğlu https://orcid.org/0000-0001-9962-8882

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