ABSTRACT
Coronavirus 2 (SARS-CoV-2), which started in December 2019 in Wuhan province in China and caused serious respiratory infections in humans, was accepted as a pandemic on March 11, 2020. The disease from SARS-CoV-2 is called COVID-19. In a short period of five months, approximately 4 million people were infected and 300 thousand people died from this disease. To date, no specific therapeutic agents or prophylaxis for COVID-19 are available, so it is among the passive immunization treatment options with the plasma of patients who recover from the disease. Convalescent plasma therapy has been used in epidemic periods in the past and has been shown to be effective. Neutralizing antibodies in plasma contributes to recovery by inactivating the virus. In the literature, there are 4 publications presenting a total of 21 patients receiving convalescent plasma. They reported that the patients benefited from the treatment of convalescent plasma and that there were no complications. Studies have been initiated about convalescent plasma all over the world and their results are interestingly awaited.

Key Words: Convalescent plasma, COVID 19, Immune plasma, SARS-CoV-2

ÖZ
Çin’de Wuhan eyaletinde Aralık 2019’da başlayan ve insanlarda ciddi solunum yolu enfeksiyonlarına neden olan Coronavirus 2 (SARS-CoV-2) çok hızlı bir yayılım göstererek 11 Mart 2020 tarihinde pandemi olarak kabul edilmiştir. SARS-CoV-2 kaynaklı hastalık tablosuna COVID-19 adı verilmiştir. Beş ay gibi kısa sürede yaklaşık 4 milyon kişi enfekte olmuş ve 300 bin kişi bu hastalıktan kaybedilmiştir. Günümüzde kadar etkili bir profilaksi ve tedavisi bulunamayan hastalıktaki iyileşen hastaların plazması ile pasif bağışıklama tedavi seçenekleri arasında bulunmaktadır. Konvalesan plazma tedavisi geçmişte salgın hastalık dönemlerinde kullanılmış, etkili olduğu gösterilmiştir. Plazmadaki nötralizan antikorlar virüsü inaktive ederek iyileşmeye katkı sağlamaktadır. Literatürde, konvalesan plazma verilen toplam 21 hastanın sunulduğu 4 yaban bulunmaktadır. Hastaların konvalesan plazma tedavisi edinildiğinde fayda görsüllüğü ve herhangi bir komplikasyon olmayışı bildirilmiştir. Tüm dünyada konvalesan plazmaya ilgi başlatılmış çalışmalar olup bunların sonuçları merakla beklenmektedir.

Anahtar Kelimeler: Konvalesan plasma, İmmün plazma, COVID 19, SARS-CoV-2
INTRODUCTION

Coronavirus 2 (SARS-CoV-2), which started in December 2019 in Wuhan province in China and caused serious respiratory infections in humans, turned into a global health crisis. The disease from SARS-CoV-2 is called COVID-19 (1,2). It spread rapidly to the world in a short period of 3 months and was declared as a pandemic by the World Health Organization on 11 March 2020. According to the data of the World Health Organization, the number of patients with SARS-CoV-2 proved is 3,925,815 and the number of deaths is 274,488 in 215 countries on 11 May 2020. According to the data from ministry of health, the number of patients with SARS-CoV-2 proved is 138,657, the number of deaths is 3,786 and the number of people recovering is 92,691 in our country on 11 May 2020. To date, no effective prophylaxis against SARS-CoV-2 or proven treatment options in COVID-19 have been reported. There are studies conducted with various drugs [antiviral drugs (remdesivir, favipiravir, ribavirin, lopinavir/ritonavir), antimalarial drugs (chloroquine, hydroxychloroquine) and interferon-β], but there is currently no definitive treatment. Passive immunization (convalescent plasma transfusion) had been used outbreaks of the SARS-CoV-1 in 2003, the H1N1 influenza virus in 2009-2010, and MERS-CoV in 2012 and shown to be successful and it is usage has been raised again (3,4).

Convalescent plasma means recovering from an illness or operation. Convalescent plasma refers to the plasma collected from individuals who recovered after infection and developed antibody. Giving the convalescent plasma transfusion to the hospitalized patients for therapeutic purposes due to active virus infection can be defined as “passive immune transfer”. Previous transfusions have been shown that passive immunization reduces damage to target organs and neutralizes pathogens directly (5-7).

It has been stated by both the World Health Organization and the American Food and Drug Administration (FDA) that it is possible that convalescent plasma, serum or immune globulin concentrates can be effective against COVID-19 infection when vaccines and/or effective anti-viral drugs are not available (8,9).

COVID-19 Immune Plasma Collection

This section was prepared by using the T.C. Ministry of Health, General Directorate of Health Services, Department of Blood and Blood Products COVID-19 Immune (Convalescent) Plasma Supply and Clinical Use Guide and the FDA’s guide to the use of COVID-19 convalescent plasma. Since COVID-19 convalescent plasma will be collected by apheresis, it should be collected from individuals who meet the donor eligibility criteria for plasma collection and donor eligibility criteria for the transfusion-transmitted infections. For this reason, it should provide the necessary conditions for “Whole Blood Donation” (8-10);

1. Short physical examination, filling the blood donor registration form, blood donor interrogation form, apheresis donor informed consent form, COVID-19 immune plasma donor interrogation form, and the “COVID-19 Immune Plasma Voluntary Donor Consent Form” which shows that COVID-19 immune plasma donation is done on a voluntary basis.

2. The donor candidates, microbiological tests (serological as HBsAg, anti-HCV, anti-HIV-1-2 and anti-syphilis Ab tests and do if HBV-DNA, HCV-RNA, HIV-1,2-RNA Nucleic Acid Amplification Scanning (NAT) test must be done.

To Become COVID-19 Immune Plasma Donor;

1. Demonstration of the presence of COVID-19 infection (PCR test positivity studied from the nasopharyngeal swab sample) or test positivity for SARS-CoV-2 antibodies if not tested at the time of suspected COVID-19.

2. At least 14 days have passed since the recovery of COVID-19 clinical findings.

3. Demonstration that COVID-19 infection has healed [At least 2 PCR test results negativity (one of the tests must have been done within the last 48 hours) from the nasopharyngeal swab samples]. If 28 days have passed since the clinical improvement, the test negativity requirement is not required (This period is recommended by the FDA as 14 days).

4. Immune plasma donors should preferably be selected from men, women who are not pregnant (birth / abortion / induced abortion), and people who have not received a blood transfusion. Women who have given birth or miscarriage and those who have had blood transfusions should be screened for HLA antibodies and shown to be negative in order to be donors.

Processes to be Applied to COVID-19 Immune Plasma Product

1. Measurement of SARS-CoV-2 neutralizing antibody titers (if possible).
   - It is recommended that the neutralizing antibody titer is ≥ 1/80 (recommended as ≥1 / 160 in the FDA guide).
   - After the threshold value corresponding to this value has been defined in the literature with the ELISA test, those with antibody values above this threshold value should be selected.

2. In order to maximize transfusion safety, it is recommended that the plasma received is subjected to “Pathogen Inactivation”.

3. Apheresis method should be chosen for plasma donation. Immune plasma donation can be made up to 3 times in a
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month, once every 7-10 days, provided that the date of the first donation is accepted as the start date. In this context, 200 to 600 mL plasma can be collected from donors by ignoring the amount of anticoagulant solution. If more than 200 mL of ingredients are collected, the components should be individually labeled as a 200 mL divided component. Plasma components taken for traceability should be labeled (COVID-19 Immune Plasma) with the provision of Türk Kızılay using the ISBT coding system and witness samples should be stored in accordance with national legislation in terms of traceability.

4. COVID-19 immune plasma should be irradiated if the plasma collected after collection is to be used within 6 hours without being frozen. For the components that will not be used within six hours, freezing should be started within the first 6 hours after the completion of the apheresis process in accordance with the “National Standards for Blood Service Units” guide.

**Patient Selection for COVID-19 Immune Plasma Use**

There are no definitive treatment algorithms for immune plasma therapy in COVID-19 cases. For this reason, choosing the appropriate treatment becomes important. In studies conducted in China for the COVID-19 clinical course, hospitalizations were generally between the fourth and fifth days, clinical and laboratory values worsened between the seventh and tenth days, and the patient needed intensive care after the seventh and eighth days, and the patient’s antibody production started during the seventh and tenth days. It is the period when it started the war against the virus and studies have shown that cytokine storm during this period. Therefore, immune plasma therapy is reported to be effective between the seventh and fourteenth days from the onset of clinical symptoms (8, 10,11). Based on these data, both the FDA and the Ministry of Health published an immune plasma treatment guide in COVID-19 cases.

**According to this;**

- Laboratory tests showing that COVID-19 is positive
- Severe or life-threatening COVID-19 condition

**Severe disease is defined as one or more of the following:**

- Persistent fever (7 days)
- Dyspnea ,
- Respiratory rate ≥ 30 / min ,
- Blood oxygen saturation 93%,
- Arterial partial oxygen pressure /inspiratory oxygen fraction <300,
- Oxygen saturation <93% despite nasal oxygen supply of 5 liters /minute and above,
- An increase in lung infiltration > 24% within 24 to 48 hours,
- Sepsis Related Organ Failure Assessment Score (SOFA Score) ≥ 2
- Blood lactate level > 2 mmol /L
- Need of a vasopressor
- Patients with rapid clinical progression, those with poor prognostic parameters (lymphopenia; increased C-reactive protein, elevated level of erythrocyte sedimentation rate, elevated level of ferritin, elevated level of lactate dehydrogenase, elevated level of D-dimer)
- Organ failure, respiratory failure, septic shock condition requiring intensive care treatment

**Life-threatening disease is defined as one or more of the following:**

- Respiratory failure,
- Septic shock,
- Multiple organ dysfunction or failure

**Be informed by the patient or the healthcare representative.**

**Possible Risks of Immune Plasma Treatment**

To date, immune plasma transfusion appears to be safe in patients with COVID-19. Plasma transfusion risks are the same as for any blood product transfusion (12);

- Accidental infection with the infectious pathogen,
- Severe lung injury in patients with transfusion-related acute lung injury (TRALI)
- Includes general reactions such as transfusion-associated circulatory overload (TACO). In addition, it concerns the development of antibody-dependent tissue damage and the suppression of natural antibody development against the SARS-CoV 2 virus. However, up to now, these problems have not been encountered in immune plasma transfusions against the SARS-CoV 2 virus.

**COVID-19 Convalescent plasma experiences**

There are 4 publications in the literature that share their experience with the use of COVID-19 convalescent plasma. Four patients presented by Zhang B and colleagues (13) gave convalescent plasma at different doses and times when they were in the shock, connected to the mechanical ventilator. They reported that all patients recovered after plasma treatment and did not see any complications related to plasma transfusion.

Duan et al.(14) reported that 10 patients with convalescent plasma had an increase in oxygen saturation and improvement in infection parameters within 3 days. 200-400 mL plasma was collected from the forty donors with the Baxter CS 300 cell separator device by apheresis method. Plasma was treated with methylene blue and light treatment for 30 min for virus inactivation. No serious complications were seen after
plasma treatment. Shen et al. (15) treated 5 COVID-19 cases, Ahn et al. (16) treated 2 COVID-19 cases with convalescent plasma. They reported that there was a clinical and laboratory improvement in cases, and no complications related to plasma transfusion developed.

Convalescent plasma therapy is used worldwide. There are 61 studies registered in Clinical Trials, which investigates the reliability, efficacy and complications of Convalescent plasma on 10 May 2020. According to the data of “uscovidplasma.org” in the USA, 7205 COVID-19 convalescent plasma transfusions were performed on 7 May 2020. Experiences in our country are also increasing and their effectiveness will be evaluated better after evaluating these data.

In conclusion, COVID-19 convalescent plasma has not yet been proven to provide clinical benefit in patients affected by this disease. It is not known whether this treatment will help COVID-19 patients or have any harmful effects, but it is one of the only treatments we currently have.

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