

A male Covid-19 convalescent plasma donor with long existence of SARS-Cov-2 antibodies: a case report

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Case Report

ABSTRACT

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Covid-19 Convalescent Plasma (CCP) was one of alternative therapy for Covid-19 patients. The use of convalescent plasma as an adjunct therapy must consider its efficacy, benefits, and risk, both for the patient and the donor. Convalescent Plasma was produced from purified human plasma. Convalescent Plasma was a passive immunity which provide active antibodies. CCP give immunity to the patient through the transfusion of a survivor's antibodies. We were reporting a case of male CCP donor with long existence of SARS-Cov-2. This donor performed up to 16 donations, which was an unusual case in CCP donor. The SARS-CoV-2 antibody titer was analyzed using Elecsys® Anti-SARS-CoV-2 (Roche Diagnostics). The SARS-CoV-2 antibody showed high level of total SARS-CoV-2 antibodies, with the Cut off Indexes (COI) anti SARS-Cov-2 antibody were still quite high (132 U/mL). The highest donor antibody COI (204.6 U/mL) was seen in 11th donation at 6 months after recovery, while the lowest antibody COI (130.8 U/mL) was in 15th donation at 7 months after recovering. Evaluation of donor health status were performed after the 16th donation and analyzed as well. In conclusion, 16 CCP donations of 600 mL resulting in 48 units of 200 mL plasma in 8 months was safe for the donor, with the SARS-Cov-2 antibody titer remained high in the whole period.

Covid-19 Convalescent Plasma (CCP) merupakan salah satu terapi alternatif untuk pasien Covid-19. Penggunaan plasma konvalesen sebagai terapi tambahan harus mempertimbangkan efikasi, manfaat, dan risikonya, baik untuk pasien maupun donor. CCP dihasilkan dari plasma darah yang dimurnikan. CCP merupakan kekebalan pasif yang memberikan antibodi aktif. CCP memberikan kekebalan kepada pasien yang berasal dari antibodi orang yang telah sembuh dari Covid-19. Kami melaporkan kasus pada seorang donor berjenis kelamin yang memiliki antibodi SARS-Cov-2 yang terbentuk dalam jangka waktu yang lama. Donor ini mampu memberikan plasma hingga 16 donasi. Kasus ini merupakan kasus yang tidak biasa untuk donor plasma. Titer antibodi SARS-CoV-2 dianalisis menggunakan Elecsys® Anti-SARS-CoV-2 (Roche Diagnostics). Antibodi SARS-CoV-2 menunjukkan kadar total antibodi SARS-CoV-2 yang tinggi, dengan Cut off Indexes (COI) antibodi anti SARS-Cov-2 (132 U/mL). COI antibodi tertinggi (204,6 U/mL) tampak pada donasi ke-11 pada bulan ke-6 setelah sembuh, sedangkan COI antibodi terendah (130,8 U/mL) tampak pada donasi ke-15 pada bulan ke-7 setelah sembuh. Evaluasi status kesehatan donor dilakukan setelah donasi ke-16 dan kemudian hasilnya dianalisis. Kesimpulan yang dapat diambil pada kasus ini yaitu 16 donasi plasma sebanyak 600 mL, yang menghasilkan 48 unit plasma masing-masing sebanyak 200 mL dalam 8 bulan aman untuk donor walaupun titer antibodi SARS-Cov-2 tetap tinggi selama periode tersebut.

INTRODUCTION

Covid-19 convalescent plasma (CCP) therapy is the administration of plasma donated by Covid-19 survivors.^{1,2} The use of convalescent plasma as an adjunct therapy must consider its efficacy, benefits, and risk.³ Convalescent plasma also was fast to apply,⁴ frontline treatment in epidemics because it was available as soon as there were survivors.⁵ In most studies found potential benefit of convalescent plasma in severe or critically ill patients with few immediate adverse events.⁶ Although several studies and opinions say that the effectiveness of convalescent plasma therapy has not been proven to reduce the risk of death, reduce hospitalization even though it was given in patients with the early of symptoms.^{7,8} Covid-19 convalescent Plasma was still one of the therapy choices in Indonesia under emergency use authorization.

Covid-19 convalescent plasma was produced from purified human plasma. Convalescent plasma was a passive immunity which provide active antibodies. Covid-19 convalescent plasma give immunity to the patient through the transfusion of antibodies.⁹ Convalescent plasma was promising treatment with strong historical evidence, biological plausibility, and limited barriers for rapid development and deployment of this investigational therapy.¹⁰ Convalescent plasma was being considered as a viable treatment for Covid-19 infections because it can provide short-term, immediate immune protection. Convalescent plasma compared to remdesivir and hydroxychloroquine or chloroquine, has demonstrated the least severe side effects.⁹

The antibodies in CCP bind to the SARS-Cov-2 viruses, inhibiting them from binding to cells.⁹ Data from the first 20,000 patients transfused with CCP show it was safe and without excess risk of complications.¹⁰ Convalescent plasma significantly reduces the viral load and increase the level of neutralizing antibody. In most cases the patients showed improvements of symptoms including normalized body temperature, absorption of lung lesions, Acute Respiratory Distress Syndrome (ARDS) resolved, weaned from ventilation within 1 day to 35 days post transfusion.¹¹ Convalescent plasma transfusion substantially improved survival and significantly

reduced hospitalization period and needs for intubation.¹²

The criteria for CCP transfusion include the patient being aged ≥ 18 years, having severe or immediately life-threatening Covid-19, and possessing the ability, or having a proxy with the ability, to provide informed consent. The criteria of disease severity at least one of the following: dyspnea; respiratory frequency ≥ 30 per min; blood oxygen saturation $\leq 93\%$; partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300 ; and/or progression of lung infiltrates by $> 50\%$ within 24–48h. Life-threatening criteria included at least one of the following: respiratory failure, septic shock and multiple-organ dysfunction or failure. Because of supply limit thus, patients were further prioritized by the following considerations, which were flexible according to plasma supply: ABO blood type; duration of symptoms; length of stay, inclusive of admission at a transferring hospital; and baseline functional status and comorbidities.^{10,13,14}

Convalescent plasma both beneficial for early and late-stage infections, but only a limited supply of convalescent plasma was available, because CCP must be harvested from recovering Covid-19 patients before their immunity dissipates.⁹ In Indonesia plasma donors can give CCP repeatedly each 2 weeks if they still meet the specified conditions, but there was not easy to find CCP donors in the country. In most studies, donation of convalescent plasma was generally safe.¹⁵ Although CCP transfusion can provide benefits to recipients, it must also be considered the possibility of side effects might occur in both the patients and the donors.¹⁶ The aim of this case report was to analyze the convalescent plasma donation which has been performed 16 times from a donor with a consistent high antibody titer, which was unusual case.

CASE DESCRIPTION

A male donor (age 43) with a height of 170 cm and bodyweight of 70 kg (total blood volume 4.660 mL and total plasma volume 2.500 mL), gave his first convalescent plasma donation on January 10th 2021 at the Dr. Sardjito Hospital Blood Center, Yogyakarta, Indonesia. This donor donated between January-August 2021, with total 16 times convalescent plasma donor by

plasmapheresis with an average plasma volume of 612 mL per donation. Before donated his first convalescent plasma donation, the donor donated 8 times a unit of whole blood at the regional blood center without any adverse events.

The donor was diagnosed with Covid-19 by positive result of PCR evaluation on December 1, 2020, with symptoms such as cough, fever, and weakness. He was hospitalized in a regional hospital for 11 days, with no history of transfusion, no ventilation, and no previous comorbid. On December 16, 2020, the patient was declared cured of Covid-19 by negative result of PCR evaluation. There were no changes in body weight or health problems during these routine convalescent plasma donations. He reported feeling even to be healthier and there were no disturbances in work performance or in other daily activities. Antibody was determined used Elecsys® Anti-SARS-CoV-2 (Roche Diagnostics) which can be determined Cut off Indexes (COI) * $< 1.0 = \text{non-reactive}$ $\geq 1.0 = \text{reactive}$. In 16th convalescent plasma donation, the COI of anti SARS-Cov-2 antibody were still quite high (132 U/mL). The kinetics of SARS-Cov-2 antibody was shown in Figure 1. The results of laboratory parameters carried out just before donation i.e., routine hematology, haemostasis functions, liver functions, electrolytes, C-Reactive Proteins (CRP), and lipid profiles were normal.

DISCUSSION

The definitive protocol for the treatment of Covid-19 has not yet been established.¹⁷ One of the therapies for Covid-19 patients was convalescent plasma.¹⁸ The requirements to become a CCP donor was a high titer of SARS-Cov-2 antibodies, which might reduce the severity of Covid-19 on initial administration to mildly ill infected older adults.¹⁹ Thus, in order to understand the characteristics of an ideal plasma donor, it was important to measure the antibody response after recovery from SARS-CoV-2 infection.²⁰ In Dr. Sardjito Hospital the CCP donor's antibody level was analyzed using qualitative assay method, expressed in COI since the neutralizing antibody tests were not available. This donor showed high SARS-CoV-2 antibody levels still high for 8 months after the donor was infected by SARS-CoV-2. In one study IgG antibodies can last up to 12 months.²¹ 188 patients with Covid-19 classified with asymptomatic to severe infections. They analyzed many components of the immune system over the following 6 months. They demonstrated that the antibodies against the spike protein in the receptor binding domain declines moderately over 8 months comparable to other reports. The memory B cells actually increase between 1 month and 8 months after infection.²² Referring to the study, it was possible that the antibody titer that was still high in this donor was IgG antibody. Study showed by Turner et al., person who had

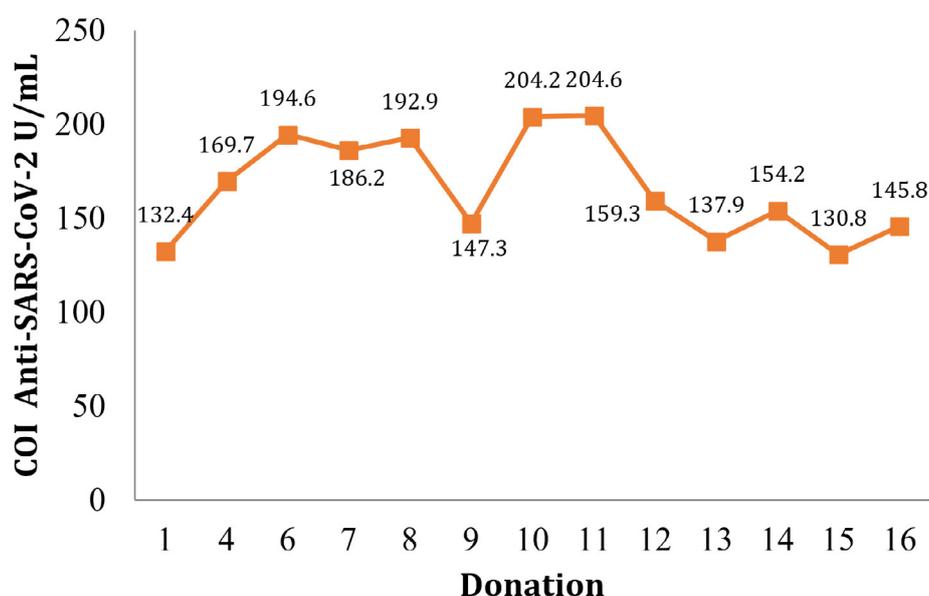


Figure 1. SARS-CoV-2 total antibody indexes during 16 donations (determine by Elecsys®)

experienced mild SARS-CoV-2 infections, in the first 4 months after infection levels of serum SARS-CoV-2 spike protein (S) antibodies rapidly declined and then more gradually over the following 7 months, but remaining detectable at least 11 months after infection. In this particularly study, they showed that there were long lived antibody secreting memory plasma cells in the bone marrow which so far was the best available predictor of long lasting immunity because these plasma cells will stay in bone marrow.²³

Figure 1 illustrates the antibody levels measured in COI over time. The highest donor antibody COI (204.6 U/mL) was seen in 11th donation at 6 months after recovery, while the lowest antibody COI (130.8 U/mL) was in 15th donation at 7 months after recovering. From the interview, this donor routinely does regular exercises (running) 2 times a week. This activity was routinely continued in the period of CCP donations. In the week of the donation with the lowest antibody titer, the donor did not perform any exercises. This might be caused or related to the fact that in regular physical exercise practices, stress hormones and inflammatory responses were decreased, but lymphocytes, monocytes, NK cells and immature B cells were at high levels.²⁴

In this study COI value determined as the manufacturer recommendation.²⁵ Elecsys® Anti-SARS-CoV-2 S (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) was an electrochemiluminescence immunoassay (ECLIA), which has been developed for the in vitro quantitative detection of antibodies, including IgG, against the SARS-CoV-2 S protein in human serum and plasma. This method has better result from common ELISA method. Elecsys® assay demonstrated a reliable performance across various sample populations for the detection of anti-S antibodies.²⁶

The results of laboratory parameters carried before 16th donation were obtained all within normal limits, appropriated with clinical status of the donor. In addition, the donor also felt that there was no significant change in his body and did not complain of symptoms related to the convalescent plasma donations. Sixteen plasma donations of approximately 25% of his plasma volume in a period of 8 months did not have any influence on the total protein levels.

During the convalescent plasma donations at Dr. Sardjito Hospital Blood Center, 48 units of convalescent plasma (@ 200mL) have been produced from the donor. Mostly distributed and transfused for patients outside the Dr. Sardjito Hospital, 40 units versus 8 units were used for patients at Dr. Sardjito Hospital. All of 48 convalescent plasma units obtained, have been minor crossmatched at Dr. Sardjito Hospital Blood Center with all of them were compatible with the recipient in need. This indirectly indicated that there were no irregular antibodies in this donor, as the antibody screening was not performed routinely because of efficiency reason.

Actually, not all survivor of Covid-19 can donate CCP, because there were some donor criteria. Each donor must have PCR positive result for Covid-19 and who had been asymptomatic for 14 days. In some region such as USA, Europe donors were negative for anti-human leukocyte antigen antibodies, hepatitis B virus, hepatitis C virus, HIV, human T lymphotropic virus I/II, Chagas disease, West Nile virus, Zika virus, and syphilis^{12,13,27,28} by Nucleic Acid Amplification Screening Tests (NAT).²⁹ Potential CCP donors were prescreened for SARS-CoV-2-specific serum antibodies with the MSH-ELISA anti-IgG assay, only if the titer $\geq 1:320$ donor can donate for plasmapheresis. Microneutralization assay also done to quantify the capacity of donor serum antibodies to inhibit the replication of SARS-CoV-2 viruses; 50% neutralization titers were expressed as the reciprocal serum dilution at which in vitro virus infectivity was halved, relative to a serum-free control infection.¹⁴

To avoid Transfusion Related Acute Lung Injury (TRALI) only male and female donors who have never been pregnant (including having abortions) can donate plasma.^{12,27,28} This was done to avoid the possibility of the presence of antibodies to HLA or granulocyte antigens that appear to occur within 6 h after transfusion. Convalescent plasma donors also never receive blood transfusion before, but if the availability of the donor only women who have been pregnant and individuals who have had blood transfusion should be screened for HLA antibodies and should be negative.²⁸

In this case donor can make donation up to 16 donations in total. Usually plasma (600 mL) was collected from each donor and divided into

two 300-mL units.¹³ Volume of donated plasmas was 500cc, donated plasmas contained antibody titer COI higher than 1.1.¹² The antibody screening (indirect-coombs) test result of CCP donors should be negative. CCP could be donated no more than 3 times in a month, at least once every 7–10 days, based on the date of the first donation that was accepted as the started date. Within a month at most 1800 mL of plasma can be collected from a donor. This donor has high titer antibody, in usual anti-SARS-CoV-2 titers with a neutralizing have antibody level 1:80. Convalescent plasma usually used had a SARS-CoV-2-specific IgG titer >1:1000 and neutralizing titer >40, and >1:640 respectively. The US FDA currently suggests an optimal neutralizing antibody titer >1:160, though 1:80 may be considered acceptable if an alternative was not available.⁶

Many studies demonstrated the safety of CCP transfusions in hospitalized Covid-19 patients, but only few studies have been conducted on the safety of CCP donation and donor related adverse events (DAEs). Research by Joseph et al. mentioned that the safety of CCP donation was comparable to conventional plasma apheresis donation for the type and severity of DAE in similar-risk donors.²⁹ Donor adverse events were include donation-related complications such as local symptoms (hematoma-bruising, arterial puncture, bleeding), complications especially with general symptoms (vasovagal reaction with or without Loss of Consciousness (LOC), complications related to apheresis (hypocalcemia due to citrate use, hemolysis, air embolism).³⁰ In this case, the donor never experienced any of these adverse events during or after donation, therefore did not cause a bad experience for him when donating plasma.

In this case, the donor was someone who lives in an area far from the Blood Center. This donor came with his own car with a journey of approximately 1-hour one-way from his home. This donor voluntarily donates plasma to be given to patients in need for convalescent plasma therapy. The Hospital-Blood Center did not provide any compensation to this donor, either in the form of transportation costs or other costs made by this donor. It can be concluded that this donor was really with their own awareness and intention to help others voluntarily donate plasma without expecting anything in return as voluntary non remunerable donor.

CONCLUSION

In conclusion, 16 CCP donations in eight months were safe for the donor. SARS-Cov-2 antibody titer can be high for at least more than six months.

CONFLICT OF INTEREST

All Authors declare no conflict of interest. All data used in this study under subject consent.

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