
Convalescent Plasma Reduces Endogenous Antibody Response in COVID-19: A Retrospective Cross-Sectional Study
Konvalesan Plazma Tedavisi Alan COVID-19 Hastalarında Azalmış Antikor Yanıtı: Retrospektif Kesitsel Çalışma


Ahmet Omma¹, Abdulsamet Erden¹, Serdar Can Güven¹, İhsan Ateş², Orhan Küçükşahin³

¹Ministry of Health Ankara City Hospital, Department of Internal Medicine, Division of Rheumatology, Ankara, Turkey
²Ministry of Health Ankara City Hospital, Department of Internal Medicine, Ankara, Turkey
³Yıldırım Bayezit University, School of Medicine, Department of Internal Medicine, Division of Rheumatology, Ankara, Turkey

Serdar Can Güven, Ministry of Health Ankara City Hospital, Department of Internal Medicine, Division of Rheumatology, Ankara, Turkey
905337112951
drserdarguven@gmail.com
https://orcid.org/0000-0003-1965-9756

Submitted: 30 April 2021
Accepted: 25 July 2021

Conflicts of Interest: None
Financial Disclosure: No funding received
Acknowledgements: None

ABSTRACT
Objective: Aim of this study is to investigate post-COVID-19 antibody titers in patients who received convalescent plasma (CP) in addition to standard of care.

Materials and Methods: Hospitalized COVID-19 patients who received CP in addition to standard of care were retrospectively investigated. Patients who received CP with a recorded total COVID-19 antibody test result after treatment were included. From hospitalized COVID-19 patients who received standard of care with a recorded total COVID-19 antibody
test result, an age, gender and comorbidity matched control group was formed. Total COVID-19 antibody index levels were compared.

**Results:** Thirty-three CP recipients were enrolled in the study. Control group was consisted of 34 age, gender and comorbidity matched standard of care patients. Median(IQR) total COVID-19 antibody index levels were significantly reduced in CP group.

**Conclusions:** Although CP therapy may have benefits on the disease outcome, having a potential to hamper long-term immunity may be a problem.

**Keywords:** COVID-19, convalescent plasma, antibody, immunity
INTRODUCTION
Convalescent plasma (CP) therapy is transfusion of plasma containing polyclonal antiviral antibodies, which was obtained from recently ill donors who fully recovered with sufficient antibody response. Potential mechanisms of action for CP are virus neutralization, antibody dependent virolysis, antibody dependent antigen presentation, antibody dependent cellular toxicity and complement activation(1). Enhancement of viral clearance is the foremost effect expected by CP therapy, therefore administration in early stages of the infection with high viral load and insufficient endogenous immunoglobulin(Ig) response may be more convenient(2,3). CP have previously been used for prophylaxis after contact in viral hepatitis, mumps, measles, polio and used as a therapeutic agent in influenza, Severe Acute Respiratory Syndrome(SARS), Middle East Respiratory Syndrome(MERS)(4-10). Likewise, effectiveness of CP therapy with early administration has also been demonstrated in coronavirus disease 2019(COVID-19). In a retrospective cohort study based on the US national registry, the unadjusted mortality within 30 days after CP therapy was lower among patients who received a transfusion within 3 days after receiving a diagnosis of COVID-19 than among those who received a transfusion 4 or more days after the diagnosis(11). In addition, Libster et al.(12) demonstrated a reduced progression to severe respiratory disease with early CP administration. Contradictory results regarding to efficacy of CP in COVID-19 also exists(13).

Endogenous antibodies produced by the host in COVID-19 have protective effects against reinfection. Although, early administration of CP seems to have beneficial effects on outcomes in COVID-19, it is unclear whether CP therapy alters endogenous antibody production and hampers long-term humoral immunity against the virus. Here in this study, we aimed to investigate post-COVID antibody titers in patients who received CP in addition to standard of care(SOC) treatments and compare to those of the patients who received SOC.

MATERIALS AND METHODS
Study design
This study was conducted as a single-center, retrospective, case-control study. Ethical approval of the study was obtained from the Ethics Committee of Ankara City Hospital.

**Patients**

Hospitalized COVID-19 patients who received CP therapy in addition to SOC approach from Ankara City Hospital, Internal Medicine inpatient clinic between August 15 and December 31, 2020 were retrospectively investigated. COVID-19 diagnosis was confirmed with presence of a recorded positive SARS-CoV-2 real-time reverse transcription polymerase chain reaction (RT-PCR) test from nasopharyngeal swab in every patient. Among patients with a positive PCR, subjects who received a total of at least 400 mL CP obtained from donors (200-250 mL administered on two consecutive days or two alternate days) with a recorded total COVID-19 antibody against S1 antigen (Siemens Atellica-IM Total [COV2T]) test result after PCR positivity were included in the study. Index values of COVID-19 total Ig over 1 was accepted positive for this kit. Our center reported values over 10 as >10, therefore, patients with Ig levels >10 was recorded as 10. Data regarding to demographics and comorbidities were recorded in all CP recipients. From hospitalized COVID-19 patients who received SOC treatment during the same period of time with a recorded total COVID-19 antibody test result, an age, gender and comorbidity matched control group was formed.

**Interventions**

SOC approach comprised oxygen support, hydroxychloroquine, favipiravir, low molecular weight heparin, anticoagulants and additional anti-inflammatory treatment when indicated in accordance with COVID-19 guidelines of the Turkish Ministry of Health (14). Likewise indications for hospitalization, CP therapy administration, intubation and discharge were also set in accordance with Turkish Ministry of Health guidelines (14).

**Outcomes**

Total COVID-19 antibody index levels and days from symptom onset at the time of COVID-19 antibody work up were recorded in both groups.

**Statistics**

Statistical analyses were made using Statistical Package for the Social Sciences version 22 (SPSS Inc., Chicago, IL, USA). Normality of variables was investigated by Shapiro-Wilks test. Continuous variables were presented with median and interquartile range (IQR). Categorical variables were presented with number and percentages. The Mann-Whitney-U was used for comparison of continuous variables according to normality. For comparison of categorical variables, chi test was used. p values < 0.05 were considered statistically significant.

**RESULTS**

Out of 67 CP recipients in addition to SOC, 33 patients with a total COVID-19 antibody test result were enrolled in the study. Control group was consisted of 34 age, gender and comorbidity matched SOC patients with a total COVID-19 antibody test result.

Demographics, comorbid diseases, duration of symptoms at the time of COVID-19 antibody work up and total COVID-19 antibody titers were presented in Table 1. No significant differences were observed in demographics and frequency of comorbid diseases between groups. Days from symptom onset at the time of antibody work-up was 28.5(29.75) in SOC group and 25(12.5) in SOC plus CP group (median(IQR), p = 0.292). In SOC plus CP group the interval between CP administration and antibody work-up was 21(12.5) days (median(IQR)). Median(IQR) total COVID-19 Ig levels were significantly reduced in CP group (Table 1).

**DISCUSSION**

Our results demonstrated significantly reduced total COVID-19 antibody response in CP recipients.
CP is obtained from recovered COVID-19 patients who developed humoral immunity, containing neutralizing antibodies (NAbs) for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) capable of pathogen clearance from peripheral circulation and pulmonary tissues (15). NAbs particularly bind to the S1-receptor binding domain (S1-RBD) of the S protein which binds to angiotensin converting enzyme receptors, preventing the entrance of virus to the cell. Furthermore, CP contains various IgG and IgM type non-neutralizing antibodies (Non-NAb) similar to fresh frozen plasma. In addition to enhancing viral clearance, both NAbs and non-NAbs have immunomodulatory effects via limiting immune complex formation and complement cascade activation (16, 17). Furthermore, both NAbs and non-NAbs in CP reduces innate immune activation, regulates the activation of these cells by downstream of the Fcγ receptors in B lymphocytes and antigen-presenting cells (APC). Again, by regulating the T lymphocyte interaction with these cells, it causes humoral tolerance against SARS-CoV-2 and reduces antibody formation (18). Theoretically, CP administrations during active infection period may suppress the endogenous antibody response due to these aforementioned effects on both B lymphocytes and innate immunity. Our results demonstrated reduced levels of COVID-19 antibodies in CP recipients after median 28.5 days from symptom onset in SOC group and 25 days in CP group. Since CP is generally administered within first week of symptoms and Ig G half-life in circulation is 10 to 21 days, we may assume that even with considerable presence of exogenous COVID-19 antibodies in circulation, index COVID-19 antibody levels were still lower in CP group possibly indicating deterioration in endogenous antibody production (19).

CP therapy may enhance viral clearance and provide better disease outcomes particularly when administered in early stages of infection (12, 20). However, an altered long-term humoral immunity due to suppression of endogenous antibody production may be speculated as a risk for CP therapy. Therefore, it should not be overlooked that after immunoglobulins in CP were metabolized by the host, an absence of immunological memory for SARS-CoV-2 may occur (21).

Small sample size and retrospective nature of the study was major limitations. Disease severity at admission or onset of CP treatment was not evaluated. Furthermore, there may be undetected variations in Ig levels of CP solutions since Ig levels were not measured. Finally, our center reported COVID-19 total Ig values over 10 as >10, therefore, patients with higher Ig levels could not be measured which would further reflect the altering effects of CP on endogenous Ig production. Nevertheless, to our best knowledge, this is the first study to evaluate effects of CP therapy on endogenous antibody production in COVID-19. In conclusion, although CP therapy may have benefits on the disease outcome, having a potential to hamper long-term immunity and increase the risk of reinfection may be a problem, since the pandemic is still far from being under control globally.

Authors' contributions: All authors contributed to the design and implementation of the research, to the analysis of the results, to the writing of the manuscript and approved the final form.

REFERENCES
<table>
<thead>
<tr>
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<th>Standart of care group (n: 34)</th>
<th>Convalescent plasma plus standart of care group (n: 33)</th>
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<tbody>
<tr>
<td>Gender, male, n (%)</td>
<td>25 (73.5)</td>
<td>23 (69.7)</td>
<td>0.728</td>
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<tr>
<td>Age, years, median (IQR)</td>
<td>54.50 (25)</td>
<td>52 (17)</td>
<td>0.730</td>
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<td>Presence of any comorbid disease, n (%)</td>
<td>22 (64.7)</td>
<td>14 (42.4)</td>
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<td>Hypertension, n (%)</td>
<td>12 (35.3)</td>
<td>10 (30.3)</td>
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<td>Diabetes, n (%)</td>
<td>8 (23.5)</td>
<td>6 (18.2)</td>
<td>0.590</td>
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<td>Asthma or COPD, n (%)</td>
<td>1 (2.9)</td>
<td>1 (3)</td>
<td>0.983</td>
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<td>CHD, n (%)</td>
<td>6 (17.6)</td>
<td>3 (9.1)</td>
<td>0.305</td>
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<td>Total COVID-19 antibody index levels, median(IQR)</td>
<td>10 (0.06)</td>
<td>7.71 (7.71)</td>
<td>0.023</td>
</tr>
<tr>
<td>Days from symptom onset at the time of COVID-19 antibody work-up, median(IQR)</td>
<td>28.5 (29.78)</td>
<td>25 (12.5)</td>
<td>0.292</td>
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