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Should timing be considered before abandoning convalescent plasma in covid-19? Results from the Turkish experience

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ABSTRACT

Introductions: Results with convalescent plasma therapy in coronavirus disease 2019 (COVID-19) have been contradictory. Timing seems to be an important factor for COVID-19 convalescent plasma(CCP) to be effective. Aim of this study is to compare disease outcomes in hospitalized COVID-19 patients who were treated with CCP within first three or seven days of symptoms to patients with symptoms longer than seven days.

Material and methods: A multicenter retrospective study was conducted to evaluate disease outcomes in hospitalized COVID-19 patients who received CCP in addition to standard of care (SOC) approach. Patients were subgrouped according to time of CCP administration; within three days of symptoms, seven days of symptoms and after seven days of symptoms. A control group was formed from age, gender and comorbidity matched hospitalized patients who received SOC treatments without CCP. Length of hospital stay, rates of anti-inflammatory treatment initiation, intensive care unit (ICU) admission and mortality was set as outcome measures.

Results: A total of 223 patients were enrolled in this study, 113 patients received CCP (38 within three days, 63 within seven days, 50 after seven days of symptom onset). Rate of anti-inflammatory treatment initiation was significantly lower (38.1 % vs 62.7 %, p = 0.002, relative risk, 0.60,73; 95 % confidence interval [CI], 0.42 to 0.85) and length of hospital stay was significantly shorter (median(IQR) 8(4) days vs 9.5(5.25) days, p = 0.0025) in patients who received CCP within seven days of symptom onset when compared to SOC group.

Conclusion: CCP therapy may provide better outcomes when applied within seven days of symptoms.

1. Introduction

Convalescent plasma therapy is collection and transfusion of plasma from those who have recovered from a given infection, in this case coronavirus disease 2019 (COVID-19) [1–3]. In addition to protective effects of neutralizing antibodies (NAbs), COVID-19 convalescent plasma (CCP) therapy also have anti-inflammatory and immunomodulatory activity, limiting immune complex formation and complement cascade activation [4]. Nevertheless, enhancement of viral clearance is the foremost effect expected by CCP therapy, therefore administration in early stages of the infection with high viral load and insufficient endogenous immunoglobulin response hypothetically may be more convenient [5,6].

Contradictory results with CCP therapy have previously been reported [7–9]. In their randomized controlled study, Simonovich et al. [7], did not observe any significant benefit with CCP therapy in COVID-19 patients with mean symptom duration of eight days. On the other hand, Libster et al. [10] demonstrated that early and high-dose administration of CCP therapy reduced progression to severe respiratory failure, even in elderly patients, a patient group considered to be prone to have worse outcomes.

Timing seems to be an important factor to obtain utmost effects from CCP therapy. To further elucidate this issue, in our retrospective cohort study, we aimed to compare disease outcomes in hospitalized COVID-19

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patients who were treated with CCP within first three or seven days of symptoms to patients with symptoms longer than seven days.

2. Material and methods

In this multi-center study, data of hospitalized COVID-19 patients who received CCP therapy in addition to standard of care (SOC) approach from Ankara City Hospital, Internal Medicine inpatient clinic and Yıldırım Beyazıt University, Yenimahalle Training and Research Hospital inpatient COVID-19 clinic between August 15 and December 31, 2020 were retrospectively analyzed. COVID-19 diagnosis was confirmed with presence of a recorded positive *Severe Acute Respiratory Syndrome Coronavirus 2 (*SARS-CoV-2) real-time reverse transcription polymerase chain reaction (RT-PCR) test from nasopharyngeal swab in every patient. Patients who received a total of at least 400 mL CCP (200−250 mL administered on two consecutive days or two alternate days) were included in the study (SOC plus CCP group). Among hospitalized COVID-19 patients during the same period of time who did not receive CCP in addition to SOC, an age, gender and comorbidity matched control group was formed (SOC group). Age younger than 18 years, pregnancy, presence of an immunosuppressive condition prior to COVID-19 and need for invasive mechanical ventilation or vasopressor agents to maintain median arterial pressure >65 mmHg or intensive care unit (ICU) admission in the first 24 h of admission were set as exclusion criteria in both groups.

CCP donation is regulated and executed by Ministry of Health in our country and plasma samples are distributed to medical centers countrywide in case of necessity. The general procedure comprises obtaining plasma from voluntary donors between the ages of 18–65 who had COVID-19, 28 days after their symptoms completely disappeared. HAEMONETICS (Haemonetics, Boston, Massachusetts, USA) device is used for the convection of plasma supply after initially confirming that the index antibody (SARS-Cov-2 IgG) titer is > 1.1 in these plasma samples. Each patient receives CCP harvested from a single donor, pooling from multiple donors is not applied. CCP treatment was administered to patients in our study in accordance with these national regulations.

SOC approach comprised oxygen support, hydroxychloroquine, favipiravir, low molecular weight heparin, antiaggregants and additional anti-inflammatory treatment (tocilizumab, anakinra, systemic steroids) when indicated in accordance with COVID-19 guidelines of the Turkish Ministry of Health [11]. Likewise, indications for hospitalization, CCP therapy administration, intubation and discharge were also set in accordance with Turkish Ministry of Health guidelines [1,11].

Data regarding demographics, comorbidities, COVID-19 related symptoms, treatment agents for COVID-19, length of hospital stay, presence of anti-inflammatory treatment initiation, ICU admission and death were recorded in all subjects using a standardized case-report form. All data were checked by 2 physicians (OG and AC), and then a third researcher (EKG) determined any differences in interpretation between the 2 primary reviewers.

CCP receivers were evaluated as a single population, additionally patients who received CCP subgrouped into three according to symptom duration at the time of CCP administration: Patients with symptom duration shorter than seven days, patients with symptom duration shorter than three days and patients with symptoms longer than seven days. Outcomes in all CCP recipients and in subgroups were compared with outcomes in SOC group with pairwise comparisons. Outcomes in CCP recipients within seven days of symptoms were also compared to those in CCP recipients after seven days.

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 either with median and interquartile range (IQR) or mean ± standard deviation, according to normality. Categorical variables were presented with number and percentages. The Mann-Whitney-U test or the Student-t test was used for comparison of continuous variables according to normality. For comparison of categorical variables, the Pearson's Chi-Square test was used. Relative risk (RR) values and their 95 % CI were calculated through crosstabs. P values <0.05 were considered statistically significant.

All procedures in this study were approved by Ankara City Hospital Ethics Committee and were therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

3. Results

A total of 223 patients were enrolled in this study: 113 patients with administration of CCP and 110 patients with SOC. Demographics, comorbidities and COVID-19 symptoms are presented in Table 1. No significant differences were observed in age, gender and comorbidities. None of the patients had been recorded to have any adverse reactions with CCP therapy. Median (IQR) days from symptom onset to initiation of SOC treatment was 2(3) in SOC alone patients and 2(2) in all CCP patients.

Outcomes of patients are presented in Table 2. No significant differences were observed in length of hospital stay and rates of anti-inflammatory treatment need, ICU admission and mortality between patients who received CCP therapy and who did not. Among patients who received CCP therapy, 55.7 % received in first seven days of symptoms while 44.3 % received after seven days. Need to anti-inflammatory treatment rate was significantly lower (38.1 % vs 62.7 %, p = 0.002, relative risk, 0.60,73; 95 % confidence interval [CI], 0.42 to 0.85) and length of hospital stay was significantly shorter (median (IQR) 8 (4) days vs 9.5 (5.25) days, p = 0.0025) in patients who received CCP within seven days when compared to SOC group. Rates of anti-inflammatory treatment administration (38.1 % vs 94 %, p < 0.001) and ICU admission (6.3 % vs 28 %, p = 0.002) were also significantly lower in patients who received CCP within first seven days of symptoms when compared to patients who received after seven days. Likewise, need to anti-inflammatory treatment rate (28.9 % vs 62.7 %, p < 0.0001; 2.6 %) and length of hospital stay (median (IQR) days, 7 (1.5) vs 9.5 (5.25), p = 0.003) were significantly lower in patients who received CCP within first three days when compared to SOC group.

The relative risk reduction for ICU admission with CCP therapy within first seven days of symptoms when compared to SOC was 39.27 % and the number needed to treat to avert an ICU admission was 4 (95 %

Table 1
Demographics, frequency of symptoms and comorbidities in patient groups.

	SOC (n:110)	SOC plus CCP (n:113)	p
Male, n(%)	66 (60)	74 (65.6)	0.397
Age, years, median(IQR)	57.50 (17)	57 (19)	0.817
Initial symptoms, n(%)			
Cough	54 (49.1)	70 (61.9)	0.053
Fever	44 (40)	48 (42.5)	0.707
Dyspnea	53 (48.2)	46 (40.7)	0.261
Headache	12 (10.9)	22 (19.5)	0.075
Diarrhea	4 (3.6)	4 (3.6)	0.979
Arthralgia	11 (10)	21 (18.6)	0.068
Myalgia	49 (44.5)	48 (42.5)	0.756
Nausea and vomiting	27 (24.5)	9 (8)	0.001
Anosmia	6 (5.5)	5 (4.4)	0.723
Ageusia	18 (16.4)	8 (7.1)	0.03
Comorbidities, n(%)			
Any co-morbidity	73 (66.4)	72 (63.7)	0.679
Hypertension	48 (43.6)	49 (43.4)	0.967
Diabetes	25 (22.7)	24 (21.2)	0.788
Asthma or COPD	7 (6.4)	8 (7.1)	0.831
CHD	23 (20.9)	22 (19.5)	0.789
Renal disease	3 (2.7)	3 (2.7)	0.973

SOC: standard of care, CCP: COVID-19convalescent plasma, n: number, COPD: chronic obstructive pulmonary disease, CHD; coronary heart disease.

Table 2
Pairwise comparisons of outcomes between convalescent plasma recipient groups and standard of care treatment group.

	SOC (n:110)	CCP (n: 113)	CCP within 3 days (n: 38)	CCP within 7 days (n: 63)	CCP after 7 days (n:50)	p SOC vs CCP	p SOC vs CCP within 3 days	p SOC vs CCP within 7 days	p SOC vs CCP after 7 days	p CCP within 7 days vs after 7 days
Length of hospital stay, days, median (IQR)	9.5 (5.25)	9 (6)	7 (1.5)	8 (4)	11 (5.25)	0.961	0.003	0.025	0.007	<0.0001
Need to anti-inflammatory treatment, n(%)	69 (62.7)	71 (62.8)	11 (28.9)	24 (38.1)	47 (94)	0.987	<0.0001	0.002	<0.0001	<0.0001
Intensive care unit admission, n(%)	14 (12.7)	18 (15.9)	1 (2.6)	4 (6.3)	14 (28)	0.495	0.075	0.186	0.018	0.002
Mortality, n(%)	6 (5.5)	7 (6.2)	0 (0)	2 (3.2)	5 (10)	0.814	0.142	0.492	0.292	0.135

SOC: standard of care, CCP: COVID-19 convalescent plasma, n: number, IQR: interquartile range, anti-inflammatory treatment comprises tocilizumab, anakinra and systemic steroids.

CI, 3–11). The relative risk reduction with CCP therapy within first three days of symptoms when compared to SOC was 53.85 % and the number needed to treat to avert an intensive care unit admission was 3 (95 % CI, 2–6).

4. Discussion

Our results demonstrated reduced rates of ICU admission and anti-inflammatory therapy administration with CCP therapy in patients who received CCP within seven days of symptom onset. Furthermore, hospital stay shortened when therapy induced within three or seven days of symptom onset when compared to SOC.

COVID-19 pandemic on goes without any curative therapy. Since need for hospitalization and ICU admission is a prominent concern, early interventions to prevent worse outcomes come forward.

CCP is obtained from recovered COVID-19 patients who developed humoral immunity, containing neutralizing antibodies for SARS CoV-2 capable of pathogen clearance from peripheral circulation and pulmonary tissues [12]. Potential mechanisms of action for CCP are virus neutralization, antibody dependent virolysis, antibody dependent antigen presentation, antibody dependent cellular toxicity and complement activation [13].

Promising effects of convalescent plasma were demonstrated in SARS CoV-1 when patients received therapy within 14 days of symptom onset [14]. CCP also reported to be advantageous for reducing mortality in COVID-19 particularly when administered within seven days of symptom onset [6,15]. Similarly, *American Association of Blood Banks* (AABB) recommends administration of CCP as close to symptom onset as possible [16]. On the other hand, Simonovich et al. did not report any beneficial effect with CCP in a subgroup of patients who received the therapy within 72 h, questioning the role of CCP in management of COVID-19 [7]. However, Libster et al. [10] demonstrated prominent effects in mildly affected elderly patients with early high dose administration of CCP. The relative risk reduction with convalescent plasma was 48 %, and the number needed to treat to avert an episode of severe respiratory disease was 7 (95 % CI, 4–50) [10]. A retrospective cohort study based on the United States national registry revealed that the unadjusted mortality within 30 days after transfusion was reduced in patients who received CCP within 3 days after diagnosis of COVID-19 (point estimate, 22.2 %; 95 % CI, 19.9–24.8) in comparison to those who received CCP four or more days after the diagnosis (point estimate, 29.5 %; 95 % CI, 27.6–31.6) [9]. In our study, the relative risk reduction for ICU admission was 39.27 % when CCP administered within seven days of symptom onset and was 53.85 % when treatment initiated within three days of symptom onset. Coherent with the literature, our results were in favor of early administration of CCP.

CCP administrations are not standardized in means of dose adjustment since efficacy of neutralizing antibodies were affected by various unpredictable factors such as donor viral load and immune response [17–19]. Generally single unit is applied (approximately 200 mL) and additional doses may be administered up to maximum three units within 24−48 h according to disease course. General approach was administration of a total of 400 mL CCP in this study.

CCP therapy may have adverse effects such as transfusion related acute lung injury (TRALI), transfusion related circulatory overload, infection transmission and immune reactions most of which may potentially increase the burden of pulmonary disease in COVID-19 patients [18,20]. Nevertheless, Libster et al. reported no side effects even in elderly patients [10]. Likewise, none were observed in our study. Since these adverse events have not been observed to be increased following CCP transfusion, CCP seems to confer similar risk to transfusion of non-immune plasma.

Retrospective nature of the study, small sample size, lack of randomization and propensity score matching were major limitations for our study. Even so baseline demographics and frequency of comorbid diseases were similar between CCP and SOC groups. Other limitations were lack of categorization for signal-to-cut off ratios for anti–SARS-CoV-2 IgG antibody levels in CCP solutions and lack of evaluation of symptom severity. Timing of symptom onset is a crucial point in CCP therapy. However, symptom perception may vary from patient to patient which may have been affected timing of CCP administration.

In conclusion, as an overall safe treatment approach, CCP therapy particularly with early administration may provide better outcomes. Since COVID-19 is yet to have a proven curative therapy, CCP may be considered as an effective adjuvant agent in management.

Authors' contributions

All authors substantially contributed to study design and acquisition, analysis and interpretation of the data. All authors revised the final version of the work and approved for publication in agreement on all aspects of the study.

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CRediT authorship contribution statement

İhsan Ateş: Conceptualization, Methodology, Project administration, Supervision, Writing - review & editing. **Abdulsamet Erden:** Conceptualization, Methodology, Project administration, Supervision, Formal analysis, Data curation, Writing - review & editing. **Serdar Can Güven:** Formal analysis, Writing - review & editing. **Elif Kübra Gürler:** Investigation. **Adem Çağlayan:** Investigation. **Özge Güçbey:** Investigation. **Hakan Apaydın:** Investigation. **Enes Seyda Şahiner:** Investigation. **Hamit Küçük:** Conceptualization, Investigation. **Özkan Varan:** Conceptualization, Investigation. **Ahmet Omma:** Conceptualization, Methodology, Project administration, Supervision. **Orhan Küçükşahin:** Conceptualization, Methodology, Project administration, Supervision.

Declaration of Competing Interest

The authors report no declarations of interest.

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