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NEÜ YAYINEVİ

Efficacy of Convalescent Plasma Therapy in COVID-19 Patients

COVID-19 Hastalarında Konvelesan Plazma Tedavisinin Etkinliği

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Öz

Amaç: Corona Virüs 2019 Hastalığı (COVID-19)'nda şu ana kadar spesifik antiviral ajan olmamasına rağmen tedavi için konvelesan plazma (CP) tedavisi tedavi için kullanılmıştır. Ancak CP tedavisinin prognoz ve mortalite üzerindeki etkinliği halen tartışma konusudur. Bu çalışmada COVID-19 hastalığında CP tedavisinin etkinliğine ilişkin deneyimlerimizin paylaşması amaçlandı.
Hastalar ve Yöntem: Çalışma Mayıs 2020-Şubat 2021 tarihleri arasında standart tedaviye ek olarak CP tedavisi alan 126 COVID-19 tanılı hastada gerçekleştirildi. 126 hasta ilk beş gün içinde (Grup A) ve beş günden sonra (Grup B) CP uygulananlar olarak iki gruba ayrıldı. Bu iki gruptaki hastalar laboratuvar parametreleri, klinik bulgular ve mortalite açısından değerlendirildi.
Bulgular: Toplam 126 hasta Grup A'da 86 hasta ve Grup B'de 40 hasta) tespit edildi. 119 (%94.4) hasta şifa ile taburcu olurken 7 (%5,5) hasta kaybedildi. Ortalama hastane yatış süresi Grup A'da 11.4±0.7, Grup B'de 18.4±1.7 gün olarak bulundu (p<0,001). Lenfosit, PLT, fibrinojen ve CRP'nin tedaviye bağlı ana değişim etkisi istatistiksel olarak anlamlıydı (p<0.001). Ancak, iki grup D-dimer açısından karşılaştırıldığında sonuçlar marjinal olarak anlamlıydı. Basit etki değerlendirildiğinde; Grup A'daki değişim anlamlı değilken, Grup B'deki değişim anlamlıydı. CP tedavisine 5 gün önce veya 5 gün sonra başlanması laboratuvar parametrelerini değiştirmedi. Ancak, D-dimer'daki değişim marjinal olarak anlamlıydı (p=0.058).
Sonuç: Çalışmamızda CP tedavisine erken başlamanın hastanede kalış süresini azalttığı ancak mortalite ve laboratuvar parametreleri üzerine etkisinin olmadığı gösterildi.

Anahtar Kelimeler: Konvelesen plazma, COVID-19, SARS-CoV-2

Abstract

Aim: Convalescent plasma (CP) therapy has been used for treatment, although it has not been Corona Virus 2019 Disease (COVID-19) specific antiviral agent so far. However, the effectiveness of CP treatment on prognosis and mortality is still a matter of debate. In this study, we aimed to share our experiences about the effectiveness of CP treatment in COVID-19.
Patients and Methods: The study was conducted in 126 patients diagnosed with COVID-19 who received CP treatment in addition to standard treatment between May 2020 and February 2021. 126 patients were divided into two groups as those who underwent SP within the first five days (Group A) and after five days (Group B). The patients in these two groups were evaluated in terms of laboratory parameters, clinical and mortality.
Results: A total of 126 patients were identified (86 patients in Group A and 40 patients in Group B). 119 (94.4%) patients were discharged with recovery, 7 (5.5%) patients died. The mean days of hospitalization were found to be 11.4±0.7 in Group A and 18.4±1.7 in Group B (p<0.001). Treatment-related lymphocyte, PLT, fibrinogen and CRP main effect of change was significant (p<0.001). However, the results were marginally significant when the two groups were compared in terms of D-dimer. When the simple effect is evaluated; Group A as not significant, while group B was significant. Starting CP treatment 5 days before or 5 days later did not change the laboratory parameters. However, D-dimer was marginally significant (p=0.058).
Conclusion: In our study, it was shown that early initiation of CP treatment reduced the hospitalization, but had no effect on mortality and laboratory parameters.

Key words: Convalescent plasma, COVID-19, SARS-CoV-2.

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INTRODUCTION

Corona Virus 2019 Disease (COVID-19), caused by a new type of beta coronavirus called SARS-CoV-2 in Wuhan, China, emerged as a new pandemic at the end of 2019 (1). More than 185 million people have been infected worldwide, and more than 4 million people have died due to this pandemic since then (2). The clinical signs and symptoms of the disease are very variable. Although it is mild in general, it is severe in approximately 14% of cases (dyspnea, hypoxia, severe lung involvement on imaging). Mortality rate is 3-4% (3, 4).

The treatments applied for COVID-19 disease does not have a specific treatment, these treatments are generally supportive treatments. Although different agents (favipiravir, azithromycin, anakinra, tocilizumab, remdesivir, lopinavir/ritonavir, high-dose steroid) are used in the treatment of COVID-19, their efficacy is not satisfactory (5, 6). Therefore, new treatment strategies are needed to alleviate symptoms and reduce mortality. Previous experience with SARS shows that convalescent plasma (CP) therapy elicits a directed neutralizing antibody response against the viral S protein. In addition, these antibodies prevent the entry of SARS-CoV-ACE2 (7). A retrospective study comparing the clinical results of high-dose steroid therapy and CP therapy in SARS patients showed that patients in the CP group had shorter hospitalization and lower mortality (8). Studies demonstrate that CP therapy is a safe method that improves passive immunity in COVID-19 patients (5, 6, 9-11). Despite the positive results of the use of CP in COVID-19 disease, the recently published randomized study shows that it does not have a significant effect on hospitalization and mortality (12). Therefore, the efficacy and safety of treatment, optimum volume, number of transfusions, the interval between transfusions, optimum neutralizing antibody titer should be determined (13, 14).

From this point of view, the changes in the clinical and laboratory parameters of the patients who received CP treatment at different times of the disease were evaluated retrospectively.

PATIENTS AND METHODS

The study was carried out with the ethics committee's approval (2021/133), by the Declaration of Helsinki, between May 2020 and February 2021. One hundred twenty-six patients who received standard therapy plus CP treatment were included in the study. The patients were divided into two groups as Group A and Group B. Group A, refers to the patients who started CP treatment within the first five days, and Group B, refers to the patients who started CP treatment after five days. The patients in these two groups were compared in terms of clinical and laboratory parameters and mortality.

Inclusion and Exclusion Criteria

It was applied to patients diagnosed with COVID-19 by RT-PCR method and did not have IgA deficiency in line with the CP usage criteria of the Turkish Ministry of Health Between May 2020 and February 2021 (15). Patients who were treated with CP in the first five days and patients who were treated with CP for more than five days were included in the study. A study file was created and demographic data of the patients (age, gender, comorbidity), laboratory results obtained at the time of admission (Lymphocyte, platelets (PLT), neutrophil, neutrophil/lymphocyte ratio, D-dimer, fibrinogen, ferritin, C-reactive protein (CRP), lactate dehydrogenase (LDH), hospitalization and survival were recorded. Patients who were diagnosed with COVID-19 and were not treated with CP were not included in the study.

Donor Selection and Plasmapheresis

CP donor selection was selected according to the CP guidelines of the Turkish Ministry of Health (16). Plasma was collected by the plasmapheresis for two doses of 200 ml from each donor. If CP was to be used immediately, irradiation was performed. The plasma that would not be used on the same day was stored at -25°C. The second CP treatment was performed at least 24 hours after the first CP application.

Statistical Analysis

The conformity of the data to the normal distribution was checked with the Shapiro-Wilk's test. Non-parametric tests were used for data that were not normally distributed. For descriptive statistics, it was expressed as Mean ± SEM (Standart error of mean) for continuous variables and as number (%) for categorical variables. Age and hospitalization parameters were compared between groups by independent t-test. A two-way repeated measure analysis of variance (ANOVA) was performed to test for the main effects corresponding to groups (Group A, Group B) and time (Before-After), as well as the interaction between the two (Groups and time: to see the effect of CP treatment on the Before-After change). In addition, a simple effect test was performed for each group. Total survival analyzes were evaluated using the Kaplan-Meier method. For comparison of survival curves between groups, log-rank test was used and

presented with 95% confidence intervals. All tests were applied in two tailed and p<0.05 was considered statistically significant. Analyzes was carried out with Jamovi ver. 1.2.27 software.

RESULTS

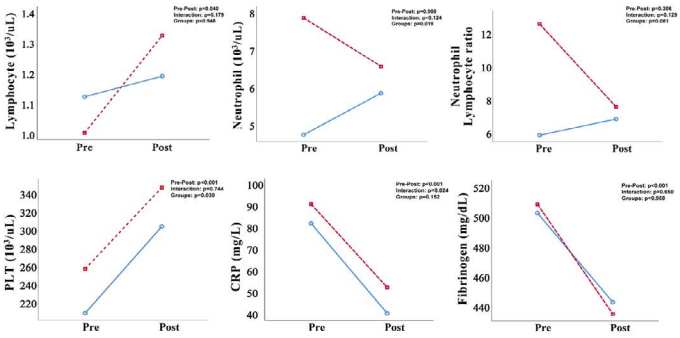
The male/female ratio of 126 patients was determined as 77/49. The mean time of CP treatment was 3.61±0.28 days from the hospitalization. One unit of CP was performed in 19 patients, two units in 107 patients, and three units in 5 patients. No comorbidity was found in 50 (39.68%) patients, while 76 (60.3%) patients had at least one comorbidity. The average hospitalization of the patients was 13.62±0.76 days. No complications were observed during and after CP treatment. Sixteen (12.7%) patients were taken to the intensive care unit, and 7 (5.5%) of these patients were intubated. One hundred-nineteen (94.4%) patients were discharged with recovery, 7 (5.5%) patients died (Table 1).

The patients were divided into two groups: those who received CP treatment within the first five days (Group A; n: 86) and those who received CP treatment after five days (Group B; n: 40). While the time of CP treatment was 1.87±0.14 days in Group A, it was 7.35±0.44 days in Group B. Treatment-related lymphocyte [F (1,124) =4.306, p=0.040, η2=0.034], PLT [F (1,124) =110.404, p<0.001, η2=0.471], fibrinogen [F (1,124) =19.189, p<0,001, η2=0.134] and CRP [F (1,124) =34.649, p<0.001, η2=0.134] main effect of change (before and after CP treatment) was significant. In contrast, the main effect of D-dimer and group interaction was marginally significant [F (1,124) =0.107, p=0.058, η2=0.029]. When the simple effect is evaluated; Group A [F (1,85) =0.602, p=0.440, η2 =0.007] as not significant, while group B [F (1, 39) =4.186, p=0.048, η2 =0.097] was significant. The mean of neutrophil [F (1, 124) =5.619, p=0.019, η2 =0.043] and PLT [F (1, 124) =4.791, p=0.030, η2 =0.037] were significant between groups. In addition, the neutrophil/lymphocyte ratio [F (1, 124) =3.096, p=0.081, η2 =0.043] was marginally significant between groups (Table 2) (Figure 1).

Table 1. Demographic and clinical characteristics of the all patients (CP: Convalescent plasma)

Parameters	COVİD-19 patients (n:126)
Gender	
Male	77 (61.1%)
Female	49 (38.9%)
Age (years)	63.75 ± 1.26
Comorbidity (n:76)	
Diabetes mellitus	21 (27.6%)
Hypertension	29 (38.15%)
Cadiovascular diseases	7 (9.2%)
Respiratory disease	12 (15.7%)
Chronic renal diasease	6 (7.8%)
Chronic liver diasease	1 (1.3%)
Malignancy	10 (13.15%)
Hospitalization (Day)	13.62 ± 0.76
CP application time (Day)	3.61 ± 0.28
Intensive care unit need	16 (12.7%)
Number of CP applied	
1 unit	19
2 unit	102
3 unit	5

Figure 1. Changes in hematological and biochemical parameters between groups (A-solid line and B-dash line) and time (Pre-Post).



Mean age was 62.15±1.6 years in Group A, while it was 67.2±1.9 years in Group B, and it was not statistically significant (p=0.061). Hospitalization was found to be 11.40±0.7 days in Group A and 18.4±1.7 days in Group B, and it was statistically significant (p<0.001) (Table 2). Patients who needed intensive care and died were patients in Group B.

While the median age of the patients who needed intensive care was 70.19±2.41, the median age of the patients who did not need intensive care was 62.82±1.38 and statistically marginal significant (p=0.050).

While the median age of the patients with comorbidity was 68.37±1.35, the median age of the patients without any comorbidity was 56.74±2.05 (p<0.001). Hospitalization was found to be 15.58±1.11 days in patients with comorbidity and 10.64±0.77 days in the other group, and it was statistically significant

Table 2. Evaluation of the characteristics of patients in Group A and Group B. According to repeated measurement analysis; †: Within-subjects effects p<0.05; ‡: interaction effect p<0.05; ¶: between-subjects effects p<0.05 and other parameters: p>0.05. Age (p>0.061) and hospitalizasyon (p<0.001). (PLT: Platelets; CRP: C-reactive protein; LDH: lactate dehydrogenase)

Parameters	Group A (n=86)		Group B (n=40)	
	Before Mean ± SEM	After Mean ± SEM	Before Mean ± SEM	After Mean ± SEM
Lymphocyte (10^3/uL) †	1.13±0.07	1.19±0.06	1.01±0.08	1.33±0.21
Neutrophil (10^3/uL) ¶	4.75±0.25	5.86±0.29	7.87±2.13	6.57±0.46
Neutrophil/ Lymphocyte □	5.89±0.6	6.86±0.65	12.59±5.6	7.6±0.94
PLT (10^3 /uL) †¶	210.1±8.3	305.4±11.8	258.8±22.3	348.3±27.4
Fibrinogen (mg/dL) †	502.8±13.9	443.1±13.8	508.7±20.9	435.2±18.2
D-dimer (ng/mL) ‡	693.2±224.1	582.4±103.7	526.2±108.9	873.8±246.7
CRP (mg/L) †	82.4±6.4	40.9± 4.1	91.4±9.9	52.94±7.12
Procalcitonin (ug/L)	0.23±0.04	0.24±0.05	0.3±0.05	0.2±0.02
LDH (U/L)	336.6±13.4	321.8±9.6	360.7±22.9	355.4±27.6
Ferritin (ug/L)	612.4±59.0	631.7±53.8	616.4±103.6	674.3±115.5
Age (years)	62.15±1.6	67.20±1.9		
Hospitalization (Day)	11.40±0.7	18.40±1.7		

(p=0.001).

All patients (n=122) had a mean of 27.8±0.92 (95% CI 25.9-29.6) days in the 30-day total survival analysis, and there was no difference between groups A and B when comparing the survival curves of those with CP. Median values of survival analysis by subgroups: Grup A (n=4) Survival: 26 ± 2.29 (95% CI 21.51-30.48); Grup B (n=2) Survival: 25 ±1.63 (95% CI 21.79-28.20); Overall: 26 ± 1.54 (95% CI 22.96-29.03) Chi-Square/ P: 0.021/0.886) (Table 3).

DISCUSSION

CP treatment came to the fore with the therapy to 5 severe COVID-19 patients who were resistant to steroid and antiviral treatment by Shen et al (17). It was started to reduce the mortality rate and the need for intensive care by collecting the plasma with anti-SARS COV-2 antibody from individuals diagnosed with COVID-19 and recovered by the plasmapheresis method. On the other hand, studies have started to be published showing that CP treatment in COVID-19 disease is beneficial in non-randomized studies and that it is not beneficial on the course of the disease in randomized studies (12). From this point of view, the effect of CP treatment on the clinical and laboratory findings of the patients was evaluated in this study.

Our study showed that initiation of CP treatment in the early period shortened the hospitalization but had no effect on survival. Liu et al. in a retrospective study of 39 patients, it was shown that the survival rate increased (18). In a randomized controlled study investigating clinical improvement up to 28 days after CP treatment, it was shown that 52% of patients who received CP treatment and 43.1% of the control group recovered, and no significant difference was observed in 28-day mortality (18, 19). In a randomized controlled trial of 464 COVID-19 patients conducted in India, 235 patients received CP therapy plus standard therapy, and 229 patients received standard therapy. It has been shown that CP treatment is not associated with disease severity and mortality rate (20). In a similar study of 241 patients, it was found that CP treatment did not significantly affect hospital stay and mortality (21). In the study of Cizmecioglu et al., which included 50 COVID-19 patients, it was shown that CP treatment performed in the first five

Table 3. Analysis of overall survival and comparison of survival times between groups.

Groups	Median		95% Confidence interval		Log rank
	Estimate	Std. error	Lower bound	Upper bound	Chi-Square / P value
Group A (n=4)	26.00	2.29	21.51	30.48	
Group B (n=2)	25.00	1.63	21.79	28.20	0.021 / 0.886
Overall	26.00	1.54	22.96	29.03	

decreased the hospitalization (22). In a recently published randomized trial involving 228 patients with severe COVID-19 pneumonia, it was shown that the use of CP compared to placebo in patients did not provide significant clinical benefit, did not affect 30-day mortality, and had no effect on other clinical and laboratory parameters (12). Some studies have shown that CP transfusion within the first 14 days results in good clinical results. A similar study determined that CP treatment in the first three days positively affected mortality (19, 23). Although definitive results regarding the effectiveness of CP have not been obtained in the literature, it has been shown in our study that it has no effect on mortality, but early application reduces the length of hospital stay.

The effect of the initiation time of CP therapy applied to COVID-19 patients on laboratory parameters had no effect in general. In other words, starting CP treatment 5 days before or 5 days later did not change the laboratory parameters. However, D-dimer was marginally significant. While D-dimer was 693.22 ng/mL before CP in Group A, it was 526.22 ng/mL in Group B. After-CP was found to be 582.45 ng/mL in Group A and 873.8 ng/mL in Group B. When these data were evaluated, it was thought that CP treatment had a negative effect on D-dimer if the onset time was above 5 days.

Studies on CP transfusion dose are planned with one unit (200 mL) for prophylaxis and one to two units for treatment. Although the duration of activity of antibodies is unknown, it is estimated to last from weeks to several months (24). In our study, one CP was applied to 19 patients, two CP to 102 patients, and three CP to 5 patients. Second unit CP therapy was required in the vast majority of patients. When 126 patients were evaluated, it was concluded that 1 unit of CP treatment was insufficient.

In the study, when the patients in need of intensive care were compared with the other patients, it was determined that the patients in need of intensive care were older and were found to be compatible with the literature. COVID-19 patients with co-morbidity have been shown to have a poor prognosis (25). Sixty percent of the patients in our study had at least one other disease, and seven patients who died were patients with the other disease. In addition, patients with comorbidities had longer hospitalization. In the group with additional disease, D-Dimer elevation and lymphopenia did not improve after CP. D-Dimer elevation and lymphopenia are associated with poor prognosis in COVID-19. It seems consistent with the literature that CP treatment did not affect laboratory parameters in the group with co-morbidity, except for the length of hospital stay (26).

The risks of CP treatment are similar to those of standard plasma. Risk of infection with another infectious disease agent (viral transmission or bacterial contamination), immunological reactions, non-hemolytic transfusion reactions (chills, fever, urticaria), transfusion-related overload (27). Our study shows that CP is a safe method without any complications during and after CP transfusion.

Our study has some limitations. Initially, other antiviral agents and steroid treatments were administered to the patients during their hospitalization. Secondly; The study was carried out retrospectively, and the antibody titer ratios of the CP used could not be studied for technical reasons. As a third, patients who did not receive CP treatment as a control group could not be included, so they were compared in terms of transfusion time and needed for intensive care.

As a result; the effectiveness of CP treatment, as in our study and other studies, is still the subject of study. Our study showed that although early CP treatment reduced the hospitalization, it did not affect survival. Although CP treatment seems effective in non-randomized studies, randomized studies show that CP use is ineffective. Therefore, we believe that randomized controlled studies are needed.

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