ORIGINAL ARTICLE

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Effect of Immune Plasma Therapy on Prognosis and Mortality in COVID-19 Patients

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Abstract

Objective: Since the exact treatment was not known in the coronavirus disease 2019 (COVID-19) pandemic, one of the traditional methods, immune plasma therapy, was also widely used. Our aim with this study is to examine the effect on prognosis and mortality of the patients hospitalized in the intensive are unit with the diagnosis of COVID-19 and receiving immune plasma therapy.

Methods: We retrospectively analyzed the files and electronic media records of 209 patients over the age of 60 or between the ages of 18-60, with comorbid diseases and who received immune plasma therapy in the intensive care units of our hospital's anesthesiology and reanimation clinic, whose diagnosis of COVID-19 was confirmed by polymerase chain reaction test. As a control group, we analyzed the files of 50 patients with similar demographic data who were not given immune plasma therapy. We recorded demographic data of the patients, the day of admission to the intensive care unit, the number of days of hospitalization, comorbid diseases, duration of symptoms and lab parameters of leukocyte count, lymphocyte count, neutrophil count, C-reactive protein, procalcitonin, creatine, D-dimer, fibrinogen, ferritin, interleukin-6; also PaO_2/FiO_2 ratio, oxygen requirement and ventilation status before and after immune plasma treatment. We statistically analyzed these data in terms of mortality and prognosis prediction in patients diagnosed with COVID-19 who received immune plasma therapy.

Results: Despite significant improvement in laboratory findings, 62.2% (n=132) of the 209 patients in our study group and 62% (n=31) of the control group died.

Conclusion: Immune plasma therapy does not provide benefit as a rescue treatment and does not reduce mortality in patients with severe COVID-19.

Keywords: COVID-19, immune (convalescent) plasma therapy, mortality

INTRODUCTION

Immune plasma convelesan plasma (CP) therapy, which is a passive vaccination strategy used in the treatment of infectious diseases, is also used in coronavirus disease 2019 (COVID-19) patients. We examined the effect of CP treatment on prognosis and mortality in the intensive care unit patients of our hospital.

At the beginning of the COVID-19 epidemic, the pathogenesis of the agent was not fully known, and there were no effective and safe drugs for the treatment of the agent. Conventional interventions previously applied for various infections have been experimented. One of these interventions is immune plasma therapy CP, a passive vaccination strategy used in the treatment of infectious diseases. CP is obtained by taking apheresis from live individuals who developed antibodies against the pathogenic agent after they have been exposed to the disease. In the COVID-19 Situation Report published by the World Health Organization on January 28, 2020, it was stated that immune plasma can also be used for severe acute respiratory syndrome coronavirus 2 virus (1,2). Immune plasma therapy is routinely

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given to the patients admitted to the intensive care unit due to COVID-19 as an emergency passive vaccination strategy in the case of indication (3).

METHODS

This study was carried out by evaluating the files and electronic media records of 221 intensive care inpatients who were diagnosed with COVID-19 following the diagnosis guideline of the COVID-19 science board (3) and were given immune plasma therapy in the intensive care units affiliated to the University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital Anesthesiology and Reanimation Clinic in between 20.04.2020 and 30.12.2020, with the approval of the ethics committee of our hospital, dated 19/04/2021 and decision number 167. We conducted our study retrospectively and observationally. According to the immune (convalescent) plasma guideline of the Ministry of Health, adults over the age of 60 years, patients between the ages of 18 and 60 years with severe comorbidity, and patients without immunglobulin A deficiency who were diagnosed with COVID-19 and given immune plasma therapy, were examined. Informed consent was obtained from the patients who could cooperate and from the first degree relatives of the patients who could not cooperate. Patients who did not consent to the study, patients under the age of 18, pregnant women, patients whose treatment was interrupted due to the patient's death, patients who were transferred to the service while their treatment was ongoing, and patients whose adequate clinical data could not be reached were excluded from the study. Demographic data, co-morbidities, number of hospitalization days, duration of symptoms, and number of mortality of the patients included in the study were recorded. In addition, white blood cell count, lymphocyte count, neutrophil count, C-reactive protein (CRP), procalcitonin, creatine, D-dimer, fibrinogen, ferritin, IL-6, PaO_2/FiO_2 ratio, oxygen requirement, and ventilation status were evaluated before and after immune plasma treatment.

The recorded data were statistically analyzed in terms of mortality and prognosis prediction in patients diagnosed with COVID-19 who received immune plasma therapy using either alone or more than 1 parameter together.

In order to be a control group in terms of mortality, a total of 50 patients with a diagnosis of COVID-19 who were admitted to our intensive care unit in the same period of time and did not receive immune plasma therapy were evaluated. The mortality rate of the patients was recorded.

Statistical Analysis

The Windows version of SPSS 15.0 was used for the statistical analysis. Descriptive statistics include numerical variables such as mean, standard deviation, minimum, maximum, or median, interquartile range, and numbers and percentages for categorical variables. The chi-square test was used to compare rates between independent groups. Student's t-test was used to compare 2 independent groups when the numerical variable satisfied the normal distribution condition, and the Mann-Whitney U test was used when it did not. The Friedman test was used to perform dependent group analyses since the differences in the numerical variables did not meet the requirements for a normal distribution. Wilcoxon analysis and Bonferroni correction were used to interpret the subgroup analyses. The accepted statistical alpha threshold for significance is $p=0.05$.

RESULTS

Two hundred twenty one patients were evaluated for the study. Seven patients were excluded due to lack of data, 2 patients died on the first day of transfusion, and 2 patients were excluded due to transfer to another center, and the total of 209 patients were included in the analysis. Of the patients, 139 (66.5%) were male and 70 (33.5%) were female, with a mean age of 66.2±12.5 (22-95%). 83 (39.7%) of the patients had diabetes mellitus, 111 (53.1%) hypertension, 55 (26.3%) coronary artery disease, 18 (8.6%) left ventricular hypertrophy, 21 (10%, 0 had malignancy, 30 (14.4%) chronic obstructive pulmonary disease, 20 (9.6%) CRF, 3 (1.4%) liver-C. The symptom duration of the patients before the immune plasma treatment was 8.6±5.3 (1-31%) days. The number of patients who received 1 dose of immune plasma treatment was 69 (33.0%), the number of those who received 2 doses of immune plasma treatment was 48 (23.0%), and the number of those who received 3 doses of immune plasma treatment was 92 (44.0%). Of the patients who received CP treatment, 79 (37.8%) survived and 130 (62.2%) died (Table 1).

The mean age and CRF rate of the deceased patients were found to be statistically significantly higher than those of the surviving patients.

Thirty-one (62%) of 50 patients who did not receive immune plasma therapy and were evaluated in the control group resulted in death. There was no statistical difference in mortality in patients who received CP treatment compared with the control group (Figure 1).

There was a significant increase in leukocyte count in the patients who died. The lymphocyte level of the patients was lower than before the treatment, and the neutrophil level was

higher. These significant differences were observed more clearly in the patients who died.

Procalcitonin, CRP, and creatinine were significantly higher in deceased patients compared to surviving patients. D-dimer, fibrinogen, and ferritin levels decreased in all of the patients we examined. Since IL-6 was not routinely evaluated in every patient, sufficient data could not be obtained. Therefore, we could not take IL-6 levels into consideration.

An increase in the PaO_2/FiO_2 ratio was observed in all patients during the treatment process, but there was no increase in those who passed away; however it was observed that there was an increase in those who survived.

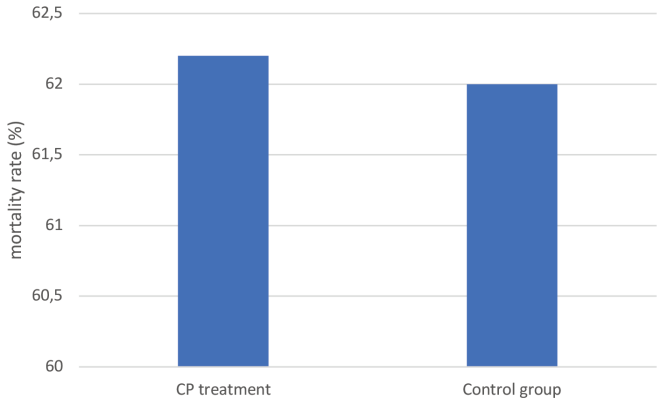

Figure 1. Mortality rates between groups

Although minor and major complications can be seen in immune plasma therapy, no complications were observed in our patients.

DISCUSSION

In our study, we obtained results that CP treatment had no effect on mortality. Although there are articles with different opinions on the treatment of CP in the literature, it is seen that in those studies, CP treatment was applied to patients at different stages of the disease. Only severe cases receiving non-invasive or invasive mechanical support in the intensive care unit were the focus of our study, and we found that CP treatment had no effect on mortality in these cases. There are studies in the literature indicating that it may not be effective as a rescue agent and may not reduce mortality in critically end-stage patients (4,5). This result supports the conclusion that plasma therapy was not beneficial in the patients in our study.

In the literature, Leukocyte elevation, lymphopenia, and neutrophilia are observed in COVID-19 patients. In our patients with severe COVID-19, no improvement was observed in leukocyte, neutrophil, and lymphocyte levels with CP treatment.

Table 1. Comparison of the patients in the study group by demographic data, duration of symptom and number of CP doses

		Alive		Mortality		
		n	%	n	%	p#
Sex	Male	51	64.6	88	67.7	0.641
	Female	28	35.4	42	32.3	
Age (mean ± SD)		61.8±12.8		68.9±11.6		**<0.001***
Comorbidity	Diabetes mellitus	25	31.6	58	44.6	0.063
	Hypertension	43	54.4	68	52.3	0.766
	Coronary artery disease	16	20.3	39	30.0	0.121
	Cerebrovascular disease	7	8.9	11	8.5	0.921
	Malignancy	6	7.6	15	11.5	0.358
	Chronic obstructive pulmonary disease	7	8.9	23	17.7	0.077
	Chronic kidney disease	1	1.3	19	14.6	**0.001**
	Lung disease	1	1.3	2	1.5	1.000
Symptom duration	Median (IQR)	7 (4-11)		8 (5-12)		0.089**
Number of CP	1	25	31.6	44	33.8	0.933
	2	19	24.1	29	22.3	
	3	35	44.3	57	43.8	

#chi-square test, *Student t-test, **Mann-Whitney U test, CP: Convelesan plasma, SD: Standard deviation

Procalcitonin, CRP, ferritin, D-dimer, and fibrinogen levels increase, resulting in thromboembolic events in COVID-19. As the severity of the disease increases, the PaO_2/FiO_2 ratio decreases. In our study, we have observed all these situations that are in parallel with the literature. We obtained significant findings regarding the improvement in these values with CP treatment.

Since IL-6 is not a routine parameter in our hospital's protocol, we could not reach sufficient data. In the light of these circumstances, we observed that we do not have enough data to examine the effect of immune plasma therapy on IL-6 levels.

In the literature, it is stated that CP treatment should be given within 14 days from the onset of symptoms (6-8). In our patients, we found that the mean time to start treatment was 8.6 days from symptom onset. Although we started the treatment at the right time, we attribute no change in mortality to the fact that the patient population consists of severe cases. This situation does not contradict with the literature.

Complete data on neutralizing antibody titers in immune plasma units were not available in our study, limiting its power to assess the correlation between donor plasma quality and efficacy. Although we applied immune plasma therapy ranging from 200 mL to 600 mL in our patients, the neutralizing antibody titer in the existing plasma is not known. *In vivo* studies have shown that the effects of neutralizing antibodies in immune plasma are not only limited to viral clearance but also include acceleration of infected cell clearance and are considered important in protection against viral diseases. Treatment efficacy was correlated with the titer of neutralizing antibodies in immune plasma (8). For this reason, we think that it would not be accurate to evaluate the treatment efficacy and mortality according to the number of immune plasma doses received by our patients.

In terms of being a guide in a possible COVID-19 pandemic in the future, we can state the following: CP treatment is not beneficial when applied with traditional methods. However, further studies are required for determining its effectiveness at high titers by measuring antibody titers.

Study Limitations

There are several limiting factors in our study. First, patients are not given immune plasma therapy alone. In addition, the standard treatment protocol recommended by the Ministry of Health for patients diagnosed with COVID-19 was applied. We consider that concomitant treatments will affect the correct assessment of CP effectiveness, another factor is that the neutralizing antibody titer level in the immune plasma is not routinely measured. This situation prevents us from evaluating the effectiveness and quality of the treatment. The fact that our patients did not know the duration of symptoms before the time of admission to the hospital and that our patients could not give reliable information about this period is another important limiting factor in this study. The effects that occur due to the fact that the patient group we included in the study consists of intensive care treatment, mostly intubated patients, the presence of concomitant diseases, the antibiotics applied due to superimposed infections or prophylaxis, and the complicated mixed treatments used for the COVID-19 virus, when the treatment is not known exactly, are multifactorial. Although efforts are made for standardization, many factors cannot be ruled out. These are inevitable limiting factors in these type of studies.

CONCLUSION

Immune plasma therapy has no effect on mortality in severe COVID-19 cases. CP treatment does not benefit patients under non-invasive/invasive mechanical support and does not affect mortality outcomes in patients with severe COVID-19 diagnosis according to symptom duration and immune plasma dose level.

CP therapy may be helpful in the beginning. However, for patients with severe COVID-19, this study found no benefits to immune plasma therapy.

Ethics

Ethics Committee Approval: This study was carried out by evaluating the files and electronic media records of 221 intensive care inpatients who were diagnosed with COVID-19 following the diagnosis guideline of the COVID-19 science board (3) and were given immune plasma therapy in the intensive care units affiliated to the Ministry of Health Prof. Dr. Cemil Taşcıoğlu City Hospital Anesthesiology and Reanimation Clinic in between 20.04.2020 and 30.12.2020, with the approval of the ethics committee of our hospital, dated 19/04/2021 and decision number 167.

Informed Consent: Informed consent was obtained from the patients who could cooperate and from the first degree relatives of the patients who could not cooperate.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.D., F.G., N.T., T.Y., Concept: E.D., F.G., N.T., Design: E.D., F.G., N.T., Data Collection or Processing: F.G., N.T., T.Y., Analysis or Interpretation: E.D., F.G., Literature Search: E.D., F.G., N.T., T.Y., Writing: E.D., F.G., N.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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