ARAŞTIRMA MAKALESİ/ORIGINAL RESEARCH

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Is Convalescent Plasma Just a Theoretical Therapeutic Option for Critically Ill Patients with COVID 19: A Retrospective Cohort Study

Konvelesan Plazma, COVID 19'lu Kritik Hastalar için Sadece Teorik bir Terapötik Seçenek midir: Retrospektif bir Kohort Çalışması

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ABSTRACT

INTRODUCTION: The intensivists seek solutions for critically ill COVID-19 patients. Thus far, there is no specific treatment for SARS-CoV-2 infection because of the absence of evidence. The aim of this study is to describe our first clinical experience with convalescent plasma transfusion in severe COVID-19 patients.

METHODS: The study was conducted from 22 March to 1 June 2020. Adult patients diagnosed with COVID-19 using a polymerase chain reaction and thorax Computerized Tomography were included. The COVID-19 patients were treated in designated Intensive Care Units of our university hospital. The data of critically ill patients who met the plasma transfusion criteria were analyzed. Clinical outcomes were compared before and after treatment for both dead and alive patients.

RESULTS: During the outbreak 401 COVID-19 patients were admitted to the intensive care unit. Convalescent plasma treatment was given to 24 patients. Twenty one patients ended up with death and 3 patients were alive. The duration of ICU stay was 19.10±8.10 days in dead patients, while alive patients stayed 7.67±1.53 days (p=0.026). There was no significant change in mechanical ventilator parameters, SOFA scores and acute phase reactants before and after treatment. There was a significant relationship between the delay of plasma treatment and the time of the death (p=0.006).

DISCUSSION AND CONCLUSION: A positive effect of convalescent plasma treatment on the survival rate, mechanical ventilator parameters, SOFA or acute phase reactants was not revealed. Reporting objective opinion on this subject without randomized controlled studies carries the risk of giving patients false hope for success

Keywords: COVID-19, convalescent plasma, intensive care unit

ÖZ

GİRİŞ ve AMAÇ: Yoğun bakım uzmanları, kritik durumdaki COVID-19 hastaları için çözümler arar. Şimdiye kadar, kanıt bulunmadığından SARS-CoV-2 enfeksiyonu için spesifik bir tedavi yoktur. Bu çalışmanın amacı, şiddetli COVID-19 hastalarında konvelesan plazma transfüzyonu ile ilk klinik deneyimimizi tanımlamaktır.

YÖNTEM ve GEREÇLER: Çalışma 22 Mart - 1 Haziran 2020 tarihleri arasında gerçekleştirildi. Polimeraz zincir reaksiyonu ve Toraks Bilgisayarlı Tomografi kullanılarak COVID-19 tanısı konan yetişkin hastalar dahil edildi. COVID-19 hastaları üniversite hastanemizin belirlenmiş Yoğun Bakım Ünitelerinde tedavi altına alındı. Plazma transfüzyon kriterlerini karşılayan kritik hastaların verileri analiz edildi. Klinik sonuçlar, hem ölü hem de canlı hastalar için tedavi öncesi ve sonrası karşılaştırıldı.

BULGULAR:Salgın sırasında 401 COVID-19 hastası yoğun bakım ünitesine alındı. 24 hastaya konvelesan plazma tedavisi verildi. Yirmi bir hasta ölümle sonuçlandı ve 3 hasta hayattaydı. Yoğun bakımda kalış süresi ölü hastalarda 19,10±8,10 gün, yaşayan hastalarda 7,67±1,53 gün idi (p=0,026). Tedavi öncesi ve sonrası mekanik ventilatör parametrelerinde, SOFA skorlarında ve akut faz reaktanlarında anlamlı bir değişiklik olmadı. Plazma tedavisinin gecikmesi ile ölüm zamanı arasında anlamlı bir ilişki vardı (p=0,006).

TARTIŞMA ve SONUÇ: Konvelesan plazma tedavisinin sağkalım oranı, mekanik ventilatör parametreleri, SOFA veya akut faz reaktanları üzerinde olumlu bir etkisi ortaya çıkmadı. Randomize kontrollü çalışmalar olmadan bu konuda objektif görüş bildirmek, hastalara başarı için yanlış umut verme riskini taşır.

Anahtar Kelimeler: COVID-19, konvelesan plazma, yoğun bakım ünitesi

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of COVID-19 disease. Coronaviruses are RNA viruses. SARS-CoV-2 encodes proteases by means of RNA polymerase (1). The part that mediates the entry of SARS-CoV-2 into the human cell is the angiotensin converting enzyme 2 (ACE2) receptor (2). The SARS-CoV-2 outbreak is a global health emergency. The intensivists seek solutions for critically ill COVID-19 patients. So far, no proven treatment for COVID-19 infection has been found (3). Various immunomodulatory treatments are being investigated, including glucocorticoids, immune plasma and anticytokine therapy in patients with severe Covid-19 disease (4). Convalescent plasma therapy has been previously recommended to H1N1, Middle East Respiratory Syndrome, SARS and Ebola virus disease (5). A meta-analysis of passive immunotherapy observational studies for coronavirus SARS and severe Influenza suggests a reduction in mortality associated with the timely use of blood products from healing patients, especially those with neutralizing antibodies (6).

Protective antibodies are created by survivors of COVID-19 disease. In the absence of a vaccine and specifically targeted drugs, hyperimmune intravenous immune globulin therapy seems to be an effective way to treat the infection (7). However, although it is a valid option, the convalescent plasma therapy in severe COVID-19 illness remains still controversial. It is not a therapeutic procedure approved for COVID-19 in research so far. The aim of our study is to share the first clinical results and our experience of the convalescent plasma transfusion therapy that we applied in critical COVID-19 patients who need follow-up in the intensive care unit (ICU).

METHODS

Following the Ethics Committee approval (protocol no: 2020/514/177/16, date: 13.05.2020), this retrospective study was carried out in COVID-19 ICU' s of our university hospital. The written informed consent was taken from all patients or their family members according to our Ministry of Health regulations. The data of patients were collected between 22 March and 1 June 2020.

Participants:

The inclusion criteria included:

Patients over 18 years of age and 7-10 days after the onset of symptoms

Patients diagnosed with COVID-19 using a polymerase chain reaction

According to Berlin definition (8), patients with

PaO2/FiO2 ratio ≤300

Cases with severe pneumonia showing rapid progression

Presence of bilateral diffuse involvement in computerized tomography findings

Patients with mechanical ventilation and / or respiratory rate >30/min

For patients who are not intubated, despite nasal oxygen support with 5 L/min, oxygen saturation <90% and/or partial oxygen pressure <70 mmHg

Patients completed the 5-day treatment protocol according to the Ministry of Health treatment algorithm (9).

Procedure Preparation:

During the preparation phase, serum immunoglobulin A levels were determined for the patients the day before convalescent plasma treatment. This treatment has not been applied to patients with IgA deficiency. The donors were interviewed and directed to the blood bank. ABO blood types were determined in both donors and recipients. Convalescent plasma transfusion was not used prophylactically. All patients received anticoagulant therapy with enoxaparin twice a day.

Procedures for the donors included (10):

1. All donor candidates had a PCR test result that they were diagnosed with COVID-19 infection.

2. The SARS-CoV-2 molecular test results of two nasopharyngeal swab samples taken before blood donation were found as "negative".

3. Donor candidates who have completed the quarantine process at home had at least 28 days of clinical recovery.

4. Convalescent plasma donors were preferably selected from men, non-pregnant women, and patients who are not transfused.

5. Immune plasma collection could be done up to 3 times in a month.

6. Plasma was collected from donors whose infection screening tests are negative.

7. Microbiological screening tests (HBsAg, anti-HCV, anti-HIV 1-2 RNA, anti-syphilis antibody tests, HBV DNA, HCV RNA, nucleic acid amplification screening tests were performed in donor candidates.

8. The donors' antibody screening (Indirect Coombs) test result was negative.

9. Donors with anti-SARS-CoV-2 titres of the plasma with neutralizing antibody value of 1:80 and above were selected.

Evaluation of patient data:

1. Demographic data

2. Comorbidities

3. The duration of treatment

4. Lung CT findings, presence of regression

5. PaO2/FiO2 ratio

6. Death rate

7. Weaning success

8. Sequential Organ Failure Assessment (SOFA) score

9. Acute phase reactants

Changes in Positive end-expiratory pressure (PEEP), Inspiratory Positive Airway Pressure (IPAP), fraction of inspired oxygen (FiO2), peripheral capillary oxygen saturation (SpO2) and the Horowitz index (PaO2/FiO2) were recorded.

The assessment of Computerized Tomography (CT) images:

All CT examinations were performed with 128 section Philips ingenuity and 16-section Toshiba Alexion as follows: tube voltage, 120 kVp; tube current modulation,120 mA–380 mA; detector configuration, 64 × 0.625 mm or 16 × 0.625 mm; rotation time, 0.5–0.7 s; slice thickness,5 mm; and pitch, 0.984 (11).

Statistical Analysis

Statistical analyzes were performed using IBM SPSS Statistics 25. In the binary comparison of numerical data groups, Independent Samples T test for normal distribution and Mann Whitney-U test for non-normal distribution were used. Chi-Square test was used for the analysis of discrete variables. The results were evaluated with a confidence interval of 95% and a significance was appraised at $p < 0.05$.

RESULTS

A total of 401 criticilly ill COVID-19 patients were admitted to the ICU and 260 patients were death in total. Convalescent plasma therapy was applied to 24 patients. No patients were excluded from the study. Patient demographics, comorbidities and treatment procedure are summarized in Table 1.

Patients whose ages ranged from 35 to 83 years (62.83 ± 11.92) were included in the study. Twenty one patients ended up with death and 3 patients were alive. The mean day of death of the patients was 8.38 ± 5.61 days of ICU hospitalization. The mean number of days spent in the mechanical ventilator after plasma treatment was 7.54 days. The mean ICU length of stay was 17.67 days. Patients ended up with death received convalescent plasma treatment significantly later than alive patients (9.95 ± 5.10 vs 3.0±2.0 days, p=0.004). There were no significant relationship between death and alive patients according to their age, gender, Body Mass Index or hyperension incidence (Table 2). Prolonged mechanical ventilation was observed in death patients (8.38±5.61 vs 1.67±2.89 days, respectively, p=0.031). The duration of ICU stay was 19.10±8.10 days in death patients, while alive patients stayed 7.67±1.53 days (p=0.026).

Forteen patients had at least one comorbidity. The most prevalent comorbidity was hypertension (13 patients, 54.1%). The second most common

preexisting conditions among the patients were diabetes (8 patients, 33.3%). All patients received oseltamivir, favipiravir, hydroxychloroquine and azithromycin treatment. Steroid was given in 2 patients at a dose of 80 mg once daily for 5 days. Thirteen patients received tocilizumab once. Twelve of patients treated with tocilizumab have died (Table 3). Forteen patients had radiological regression in thorax CT findings. The rate of radiological regression among dead patients was 57% whereas the rate was 66% among living patients.

Table 1: Demographic Data, Comorbidities, and Treatment Procedure for all Patients Receiving Plasma

Patient #	Age (years)	Gender	DM	HT	COPD	Smoker	BMI>35	Mortality	Duration of ICU stay (days)	Plasma treatment time in ICU (day)	2nd dose plasma treatment	Regression	ECMO	Favipiravir	Tocilizumab
1	66	M	-	+	-	-	-	+	28	18	+	+	-	+	-
2	65	M	-	+	-	-	-	+	19	16	-	-	-	+	+
3	58	M	-	-	-	-	+	+	23	14	+	+	-	+	+
4	35	M	-	-	-	-	-	+	8	7	-	-	-	+	+
5	83	M	-	+	-	-	-	+	16	5	+	+	-	+	-
6	67	M	-	-	-	-	-	+	35	20	+	-	-	+	+
7	59	M	-	-	-	-	-	+	20	12	+	+	-	+	+
8	40	M	-	-	-	-	-	+	20	7	-	+	-	+	+
9	44	M	-	+	-	-	-	+	30	7	-	+	+	+	+
10	58	M	+	+	-	-	-	+	10	8	-	-	-	+	+
11	60	M	-	-	-	+	-	+	8	6	-	+	-	+	+
12	71	M	+	+	-	+	-	+	12	11	-	+	-	+	-
13	71	F	+	+	-	-	-	+	30	20	-	-	-	+	-
14	66	M	+	+	-	-	-	+	20	12	-	+	-	+	-
15	75	F	-	+	+	-	-	+	15	7	+	-	-	+	-
16	74	F	-	-	-	-	-	+	16	12	-	+	-	+	-
17	62	F	-	+	-	-	-	-	11	7	-	+	-	+	+
18	70	M	-	-	-	-	-	+	8	5	-	-	-	+	+
19	80	F	+	+	-	-	-	+	7	4	-	-	-	+	-
20	74	F	+	+	-	-	-	+	9	6	-	-	-	+	-
21	60	M	+	+	-	-	-	+	8	5	-	+	-	+	+
22	63	M	-	-	-	-	-	-	8	5	-	+	-	+	-
23	49	M	+	-	-	+	-	-	9	3	-	+	-	+	+
24	58	M	-	-	-	-	-	+	6	1	-	-	-	+	-

DM: Diabetes Mellitus; HT: Hypertension; COPD: Chronic Obstructive Pulmonary Disease; BMI: Body Mass Index; ICU: Intensive Care Unit

Table 2: Comparison of demographic data, comorbidities, mechanical ventilation and ICU stay times of dead and alive patients

	Death (n=21)	Alive (n=3)	p
Age (years)	63.71±12.33	56.67±7.10	0.349[s]
Treatment day	9.95±5.10(7.0)	3.0±2.0(3.0)	0.004*[m]
Duration for mechanical ventilation (days)	8.38±5.61(8.0)	1.67±2.89(0.0)	0.031*[m]
Duration of ICU stay (days)	19.10±8.10	7.67±1.53	0.026*[s]
Gender			
Male	15	3	0.546[c]
Female	6	0	
DM			
Yes	7	1	1.000[c]
No	14	2	
HT			
Yes	13	0	0.082[c]
No	8	3	

[s] Independent Samples T test: values are given as mean ± standard deviation; [m] Mann Whitney U test: values are given as mean ± standard deviation (median); [c] Chi-square test: valuesaregiven as frequency (percentage); *P<0.05: statistically significant difference

Table 3: The Comparison of Dead and Alive Patients

	Exitus (n=21)	Alive (n=3)	p
Tocilizumab			
Yes	12	1	0.576[c]
No	9	2	
2nd dose treatment			
Yes	6	0	0.546[c]
No	15	3	
Radiological Regression			
Yes	12	2	1.000[c]
No	9	1	
Smoker			
Yes	2	1	0.343[c]
No	19	2	

[c] Chi-square test: values are given as frequency (percentage)

There was no significant change in mechanical ventilator parameters before and after plasma treatment (Table 4). There was no significant difference between SOFA values before and after treatment (5.17±1.81 vs 5.79±1.86, p=0.184). Ferritin, CRP, D-Dimer, procalcitonin and IL-6 values were studied as acute phase reactants. There was no significant difference between the acute phase reactant levels before and after plasma treatment. There was a statistically significant relationship between the delay of convalescent plasma treatment and the time of the death (Table 5, p=0.006).

Table 4: Comparison of Mechanical Ventilation Parameters, Horowitz Index and Acute Phase Reactants before and after Convelescent Plasma Treatment

	Before treatment (n=24)	After treatment (n=24)	P
PEEP	8.92±4.23	8.96±4.12	0.973[s]
IPAP	17.58±6.41(18.0)	18.08±6.30(20.0)	0.587[m]
FiO_2	75.21±15.43	72.71±20.16	0.632[s]
SpO_2	91.38±4.39	91.13±5.69	0.865[s]
Horowitz Index	90.33±26.88(86.5)	99.88±42.55(85.0)	0.710[m]
SOFA	5.17±1.81(4.5)	5.79±1.86(6.0)	0.184[m]
Ferritin	634.57±452.25(516)	612.27±483.34(459)	0.860[m]
D-Dimer	7776.5±9168(3910)	4933.2±6809(2490)	0.255[m]
CRP	131.09±192.4(75,8)	95.05±95.7(79.7)	0.668[m]
PRC	1.80±4.1(0.39)	2.38±5.0(0.61)	0.479[m]
IL-6	829.76±1195.6(256.65)	435.75±657.3(145)	0.432[m]

[s] Independent Samples T test: values are given as mean ± standard deviation
[m] Mann Whitney U test: values are given as mean ± standard deviation (median)

PEEP: Positive End-Expiratory Pressure; IPAP: Inspiratory Positive Airway Pressure; FiO2: Fraction of Inspired Oxygen; SpO2: Peripheral Capillary Oxygen Saturation; SOFA: Sequential Organ Failure Assessment; CRP: C-Reactive Protein; PRC: Procalcitonin; IL-6: Interleukin-6

Table 5: The Effect of Variables on Exitus

ANOVA[a]

Model		df	F	Sig.
1	Regression	4	7.558	.001[b]
	Residual	19		
	Total	23		

a. Dependent Variable: Exitus

b. Predictors: (Constant) the day for plasma treatment

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	.177	.129		1.365	.188
	the day for plasma treatment	-.077	.025	-1.224	-3.060	.006

[a] Dependent Variable: Exitus

DISCUSSION

In this retrospective cohort study, 24 intensive care patients diagnosed with Covid 19 received convalescent plasma treatment. A high mortality rate has been observed in patients having plasma therapy. There was no significant improvement in mechanical ventilator parameters, intensive care SOFA scores and level of acute phase reactants.

Currently, all efforts to prevent the spread of COVID-19 are insufficient. Convalescent plasma therapy has been used for the treatment of many infectious diseases and its effectiveness has been reported. However, we have limited information about its use in COVID-19 patients. Immunotherapy with IgG is being tried to neutralize the virus that causes COVID-19.

Based on consolidated clinical data from five independent studies of 27 patients, plasma therapy, in addition to antimicrobial or antiviral drugs, has been reported to be an effective therapeutic option with promising evidence for safety, improvement of clinical symptoms and reduction of mortality (12). Four of these 5 studies took place in China. One study was conducted in

South Korea. Mortality has not been reported in the aforementioned studies. However, high mortality rate was observed in our study. There may be several reasons for this. The possibility of a mutation and a new virus strain appear as a reason (13). This situation cannot be ignored and herd immunity may become ineffective. This seems to be one of the most likely causes of plasma treatment ineffective in our patients. Another factor may be the global ethnic and geographic differences in patients living in different countries and geographies (14). Due to different genetic backgrounds, patients may exhibit different outcomes.

In addition, an injury that was not reflected in the clinical reality, may have occurred in our patients. It results by a direct infusion of a significant amount of complementary protein and coagulation factors by convalescent plasma therapy. Besides, the precise role of complement-mediated tissue damage due to plasma transfusion is uncertain. This factor may also cause mortality.

Antibody-dependent enhancement traditionally occurs when antibody levels are not sufficient to completely block viral entry but to opsonize the virus. More than half of the patients included in our study had comorbidity. Therefore, there may not be enough time for opsonization. Thus, it may have been effective fort he increase in mortality rate.

Whether higher antibody levels are a response to more severe disease is currently not completely resolved.

Most patients with COVID-19 have already established antibody responses. For this reason, the retionale of antibody infusion is still questioned (15). Failure to decrease the number of dead patients in our study confirms these concerns.

It has been reported that in monkey models with productively SARS COV infected lungs, immunoglobulins cause acute lung injury by reducing inflammation-resolving response (16). These results indicate that patients may have severe lung damage with immunoglobulin therapy. Thus only 3 patients survived in our study. Here, we revealed that hyperimmune globulin treatment had no positive effect on survival. In two previous double-blind randomized controlled trials, hyperimmune IV immunoglobulin has been reported to be ineffective for H1N1 (17, 18). Similarly, in a nonrandomized, comparative study with 84 patients infected with Ebola virus, a total of 500 ml of plasma infusion was given in 2 times (19). In accordance with our results, the treatment was not associated with a significant improvement in survival.

It has been reported that the application of immune IgG antibodies belonging to patients who have recovered from COVID-19 collected from

close circles to sick people may affect the effectiveness of the treatment (9). In the plasma treatment protocol put into practice by our health ministry, it is stated that donor plasma can be given from the whole country, not from the same city. This may have affected the effectiveness of the antibodies used in our study.

We need to standardize the selection of potential donors with high circulating levels of neutralizing antibody. However, as Saverino (20) states, in clinical practice, it remains uncertain.

The cut-off values of the COVID-19 specific IgG to be used are also unclear. However, the superiority of convalescent plasma transfusion therapy to standard therapy or the effect of a synergistic effect on standard therapy on clearance and clinical improvement of viremia is unclear. The effectiveness has not yet been determined by controlled clinical trials for SARS-CoV-2. There is great uncertainty regarding appropriate patient selection, valid indications, and possible side effects. The case series published with the highest number of patients at the time of writing this article belonged to Duan et al. (21) They completed their study with 10 patients. Based on the data of 24 patients examined in our study, the results support that convalescent plasma therapy may not provide a significant benefit. The most reliable way to discuss the efficacy on this issue is to conduct randomized controlled studies in critically ill patients with COVID-19.

A prospectively planned single-arm intervention study analyzing a total of 32 patient data and seven case series were shared in a Cochrane review (22). The efficacy of healing plasma has not been clearly established, since inconsistent results were reported. However, in all these studies, it was stated that the quality of reporting was low and the risk of bias was high. Convalescent plasma treatment is not recommended following the onset of a cytokine storm. This outbreak should be a driving force forward for several modalities or methods of treatment (23). Our practice has changed based on our experience. We started using immune plasma therapy in COVID 19 clinical course earlier. It is now given as earlier treatment method in selected cases instead of a rescue therapy. Plasma treatment was given on the 7th day in patients who died. In contrast, living patients were eligible to receive convalescent plasma treatment on day 3 after ICU admission.

Limitations of the Study

The most important limitation of this study was that it was a retrospective, observational cohort study. Controlled randomized trials are needed to demonstrate the effectiveness of plasma therapy. There was a restriction with plasma supply at the beginning of the pandemic. As we could not reach

plasma, we gave it late. In some patients we planned plasma treatment on 25th or 30th days. Therefore sudden deaths occurred after cytokine storm. Coagulation disorders were another reason for our high mortality rate.

Conclusions

In this observational retrospective study, a positive effect of convalescent plasma treatment on the survival rate was not revealed. Despite a radiologic regression, no significant difference was observed in mechanical ventilator parameters, SOFA or acute phase reactants. Reporting objective opinion on this subject without randomized controlled studies carries the risk of giving patients false hope for success.

Compliance with Ethical Standarts

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Ethics Committee Approval: Ethical approval was obtained. Sağlık Bilimleri Kartal Dr. Lütfi Kırdar Şehir Hospital, Univesity Clinical Research Ethics Committee (13.05.2020 date and 2020/514/177/6 number)

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