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Therapeutic Plasma Exchange in Adult Patients with COVID-19 and Severe Pneumonia: Single Center Experience of Eighty Patients

Ağır Pnömonili Erişkin COVID-19 Hastalarında Terapötik Plazma Değişimi: Seksen Hastada Tek Merkez Deneyimi

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ABSTRACT

Aim: Therapeutic plasma exchange (TPE) is a frequently discussed treatment modality in severe coronavirus disease 2019 (COVID-19) patients. It requires an apheresis device and experienced personnel for the application. In this study, we aimed to reveal the characteristics and clinical outcomes of adult patients with COVID-19 who experienced TPE.

Material and Methods: Adult patients who had undergone TPE in our apheresis unit were retrospectively analyzed and COVID-19-positive cases were included in the study. All the medical information about the cases was obtained from the electronic database and technical details of the procedures were gathered from apheresis unit records.

Results: A total of 80 patients with a median age of 60 (19-85) years were included in the study. Severe pneumonia was present in 98.8% (n=79) of the cases. More than three-quarters of the patients had lymphopenia, critically elevated C-reactive protein (CRP), and D-dimer, and 41.0% (n=32) had high ferritin. The median length of stay in the intensive care unit was 26 (5-124) days. The mortality rate observed on the 14th and 28th days following the TPE procedure was 51.3% (n=41) and 75.0% (n=60), respectively. High ferritin level, multiple organ failure (MOF), and intubation were parameters found to be associated with mortality in the multivariate analysis.

Conclusion: The mortality rate observed in patients with COVID-19 who underwent TPE in our study was similar to the cases in the literature without the procedure, while it has been shown that high ferritin levels, intubation, and the presence of MOF increase the risk of mortality.

Keywords: Therapeutic plasma exchange; pneumonia; COVID-19.

ÖZ

Amaç: Terapötik plazma değişimi (TPD), ağır düzey koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19) hastalarında sıklıkla tartışılmakta olan bir tedavi şeklidir. Uygulanması için deneyimli personele ve aferez cihazına gereksinim vardır. Bu çalışmada, TPD uygulanmış olan erişkin COVID-19 hastalarının özellikleri ve klinik sonlanımlarının ortaya konulması amaçlanmıştır.

Gereç ve Yöntemler: Aferez ünitemizde TPD uygulanmış olan erişkin hastalar geriye dönük olarak incelenmiş ve COVID-19 pozitif olan vakalar bu çalışmaya dahil edilmiştir. Olgulara ait olan tüm tıbbi bilgiler elektronik veri tabanından alınmış ve aferez işlemlerine ait teknik detaylar ise aferez ünitesi kayıtlarından elde edilmiştir.

Bulgular: Bu çalışmaya, ortanca yaşı 60 (19-85) yıl olan toplam 80 hasta dahil edildi. Olguların %98,8 (n=79)'inde ağır pnömoni varlığı söz konusu idi. Tüm olguların dörtte üçünden daha fazlasında lenfopeni, kritik düzeyde C-reaktif protein (CRP) ve D-dimer yüksekliği ile %41,0 (n=32)'inde ise ferritin yüksekliği mevcuttu. Yoğun bakım ünitesinde ortanca kalış süresi 26 (5-124) gündü. TPD işlemini takip eden 14. ve 28. günlerde gözlenen mortalite oranları sırasıyla %51,3 (n=41) ve %75,0 (n=60) idi. Çok değişkenli analizlerde ferritin yüksekliği, çoklu organ yetmezliği (multiple organ failure, MOF) varlığı ve entübasyon ihtiyacı mortalite ile ilişkili olarak bulundu.

Sonuç: Araştırmamızda TPD uygulanan COVID-19'lu hastalar için gözlenen mortalite oranı literatürdeki işlem yapılmayan olgularla benzer bulunurken, bu hastalarda ferritin yüksekliği, entübasyon ve MOF varlığının mortalite riskini artırdığı gösterilmiştir.

Anahtar kelimeler: Terapötik plazma değişimi; pnömoni; COVID-19.

INTRODUCTION

The new type of coronavirus disease 2019 (COVID-19) is an infectious disease that first appeared in China at the end of 2019 and quickly spread to all continents, causing it to be declared as a global epidemic by the World Health Organization (WHO). The causative agent of the disease has been identified as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which manifests itself with respiratory symptoms such as fever, cough, and shortness of breath (1). Since the outbreak of the pandemic, many promising treatment options have been tested, but only a few have proven effective to date (2,3). Mortality rates in critically ill COVID-19 cases, on the other hand, are still very high (4,5).

Therapeutic plasma exchange (TPE) is a treatment modality based on separating the plasma from whole blood extracorporeally with the help of an apheresis device and returning the cellular blood components to the patient together with the replacement fluid (6). It is possible to remove the pathological substances from the body and replace missing plasma components with this method. TPE is a well-known treatment modality and it is currently used for many diseases (7).

During the pandemic, TPE has frequently been discussed for COVID-19 patients as a supportive non-drug treatment approach, and especially in severe cases requiring admission to the intensive care unit, it has been used as a remedy for cytokine storm (8-10). However, the literature on the subject is still limited and additional studies are needed.

This study aimed to examine the adult patients with COVID-19 who had undergone TPE in our apheresis unit and to determine the characteristics and clinical outcomes of these patients.

MATERIAL AND METHODS

We retrospectively searched the records of Adana City Training and Research Hospital's Apheresis Unit for adult patients aged 18 years and older who had TPE between Aug 01, 2020, and Sep 01, 2021. Then the medical records of these patients were examined and the cases whose COVID-19 positivity was confirmed by polymerase chain reaction (PCR) test were included in the study. Demographic data, medical information, and all laboratory results of the included patients were gathered from the electronic database of our center, which is routinely used for patient follow-up. However, the technical details of the apheresis procedures were obtained from the patient files stored in the apheresis unit.

An approval letter was obtained from the Clinical Research Ethics Committee of Adana City Training and Research Hospital (date: 04.07.2022, number: 109/2037), and the Helsinki Declaration criteria were considered.

The records were searched for concomitant diabetes mellitus, hypertension, chronic renal failure, and other comorbid chronic diseases for all cases included in the analysis, and the presence of sepsis/septic shock, acute respiratory distress syndrome (ARDS), and multiple organ failure (MOF) was noted. For every patient, the type of hospital unit (any type of inpatient care service or intensive care unit) where the cases were being followed on the first day of the TPE procedure was noted. The existence of pneumonia and the presence of pneumonia the need for oxygen and intubation was searched and the WHO criteria were used for the definition and grading of COVID-19 associated pneumonia. All the treatments other than TPE started for COVID-19 were also noted for all patients. Patients were categorized according to the results of laboratory tests including lymphocyte count, C-reactive protein (CRP), ferritin, and D-dimer. According to the guidelines published by the Turkish Ministry of Health, exceeding certain threshold values in these tests have been defined as poor prognostic indicators, and the thresholds were given as follows: the absolute lymphocyte count below $0.8x10^3/\mu L$. CRP level equal to or above 40 mg/L, ferritin level equal to or above 500 ng/mL, and D-dimer level equal to or above 1000 ng/mL. For all patients included in this study, these critical tests were screened and included in the analysis, considering the results just before the TPE was started (on the day of the TPE procedure or 24 h before).

In addition to demographic, clinical, and laboratory data, the length of stay in the intensive care unit and hospital, and the survival status of the patients who underwent the procedure were noted for further analysis.

Statistical Analysis

SPSS v.25.0 (IBM Corp. Armonk, NY) software was used in the analysis of the data. The compatibility of the variables to the normal distribution was examined by histogram graphics and the Kolmogorov-Smirnov test. Descriptive analyzes were presented using mean and standard deviation, median and minimum-maximum values, numbers, and percentages. Categorical variables were compared with the Pearson chi-square and Fisher's exact tests. Following univariate analyzes, the variables which were found to be significant considering the mortality groups at the end of the 14^{th} day (CRP, ferritin, ARDS, MOF, intubation) and 28^{th} day (D-dimer, sepsis/septic shock, MOF, intubation) were analyzed by including in the multivariate logistic regression (enter method) model. A p-value less than 0.05 was considered statistically significant.

RESULTS

A total of 80 patients who had TPE due to COVID-19 in our apheresis unit were included in the study. The median age of the cases was 60 (19-85) years. The ratio of male patients was 67.5% (n=54), whereas the ratio of female patients was 32.5% (n=26). Hypertension (37.5%, n=30) and diabetes mellitus (23.8%, n=19) were the most frequently noted comorbid diseases in patients who underwent TPE (Table 1). When the procedure was started, 98.8% (n=79) cases had severe pneumonia and 77.5% (n=62) were intubated. The ratio of patients followed in the intensive care unit was 93.8% (n=75), and ARDS was noted in most of them at 65.0% (n=52). The ratio of patients with sepsis/septic shock was 82.5% (n=66), and the ratio of patients with MOF was 38.8% (n=31).

All included patients were receiving anti-viral therapy (favipiravir and/or hydroxychloroquine) and prophylactic anticoagulant therapy in accordance with the algorithm recommended by the Turkish Ministry of Health, and TPE was started in addition to these treatments.

The results of laboratory tests performed just before the initiation of the TPE and are known to have prognostic

significance were summarized in Table 2. Accordingly, the presence of lymphopenia at levels exceeding the critical threshold was remarkable in 82.5 % (n=66) of all cases. Similarly, more than three-quarters of the patients had critically elevated CRP and D-dimer. Ferritin levels above 500 ng/mL, which is considered the critical threshold, were recorded in 41.0% (n=32) of the cases.

During the procedure, only fresh frozen plasma was used as the replacement fluid in half of the cases 50.0% (n=40), while fresh frozen plasma and albumin were used together in the other half 50.0% (n=40). The number of procedures applied to the patients ranged from 1 to 11. While only one session of TPE was performed in 28.8% (n=23) cases, 2 sessions were performed in 22.5% (n=18) and 3 sessions were performed in 27.5% (n=22). Only 1 case had 11 procedures performed, and the ratio of patients who had more than 3 procedures was 21.3% (n=17).

Considering the clinical outcomes of the patients, for a total of 75 patients followed in the intensive care unit, the median length of stay was 26 (5-124) days. When all patients were evaluated together, the mortality rate observed on the 14th day following the TPE procedure was 51.3% (n=41) and it was 75.0% (n=60) on the 28th day.

Patients with different clinical features were compared for mortality rates and the results of the univariate analysis were summarized in Table 3. Regarding the mortality on the 14th day of TPE, statistically significant results were obtained for critical elevations in CRP (p=0.039) and ferritin levels (p=0.021), the presence of ARDS (p=0.005), the presence of MOF (p<0.001), the presence of intubation (p<0.001), and hospitalization at the intensive care unit instead of inpatient care service (p=0.018). The mortality rate on the 28th day was worse according to elevated D-dimer levels (p=0.013), the presence of ARDS (p=0.001), the presence of MOF (p<0.001), the presence of sepsis/septic shock (p=0.002), the presence of intubation (p<0.001), and hospitalization at the intensive care unit (p<0.001). According to statistical analysis, mortality rates did not increase in the presence of concomitant diseases such as hypertension, diabetes mellitus, and chronic renal failure.

According to the results of univariate analyses, the variables of CRP, ferritin, ARDS, MOF, and intubation showed statistically significant differences between mortality groups at the end of the 14th day (Table 3). These variables that were found to be significant as a result of univariate analyzes were included in the multivariate logistic regression model. And, it was found that ferritin level >500 ng/mL (OR: 3.68, 95% CI: 1.03-13.10, p=0.044), presence of MOF (OR: 5.07 95% CI: 1.27-20.10, p=0.021) and intubation (OR: 12.39 95% CI: 1.13-135.24, p=0.039) increased the mortality risk at 14th day (Table 4).

Regarding mortality rate on the 28th day, the variables of D-dimer, sepsis/septic shock, MOF, and intubation showed statistically significant differences between mortality groups (Table 3). These variables that were found to be significant as a result of univariate analyzes were included in the multivariate logistic regression model and according to the results of the multivariate logistic regression model, it was determined that the presence of intubation during the procedure (OR: 8.45, 95% CI: 1.64-43.35, p=0.010) increased the risk of mortality (Table 4).

DISCUSSION

The patients who underwent TPE due to COVID-19 at our center were examined retrospectively, and the clinical features of these patients, their prognostic status according to some certain blood tests considered critical during COVID-19, and clinical outcomes such as the length of stay in the intensive care unit and mortality rate were displayed in our study.

It was observed for all cases that the TPE procedure was used as a supportive therapy in addition to the treatment algorithm recommended in the guidelines published by the Turkish Ministry of Health for COVID-19 patients. When the literature on the subject was examined, the predicted mechanism of action for TPE was found to be the reduction of auto- and allo-antibodies, inflammatory mediators, and some other proteins in the plasma, thereby reducing the destructive and uncontrolled cycle that progressed in a cascade (11,12). Although some articles have suggested that plasma exchange reduces viral load in patients with COVID-19, no published source has been found in the literature to date that TPE and SARS-CoV-2 load decreases.

During the application of the TPE procedure, there is a need for a replacement fluid and it has been hypothesized that the use of plasma instead of albumin may replace some of the protective factors preserving microcirculation, which are depleted during the disease (such as protein C and ADAMTS-13: a disintegrin and metalloproteinase with

Table 1. Clinical characteristics of patients undergoing therapeutic plasma exchange (n=80)

Comorbid diseases, n (%)	
Diabetes Mellitus	19 (23.8)
Hypertension	30 (37.5)
Chronic Renal Failure	4 (5.0)
Follow-Up in the Intensive Care Unit, n (%)	75 (93.8)
Intubation, n (%)	62 (77.5)
Acute Respiratory Distress Syndrome, n (%)	52 (65.0)
Sepsis/Septic Shock, n (%)	66 (82.5)
Multiple Organ Failure, n (%)	31 (38.8)

Table 2. Laboratory values of patients before therapeutic plasma exchange

Laboratory Test (n*)	Median (Min-Max)	Critical Threshold for Poor Prognosis**	Rate of Patients over the Critical Threshold
WBC, $10^3/\mu L$ (n=80)	13.7 (1.0-33.7)		
Lymphocyte, $10^3/\mu L$ (n=80)	0.4 (0.1-18.1)	<0.8	82.5% (n=66)
C-reactive protein, mg/L (n=79)	86 (2-17300)	>40	81.0% (n=64)
Ferritin, ng/mL (n=78)	424 (17-20880)	>500	41.0% (n=32)
D-dimer, ng/mL (n=74)	2320 (1-14340)	>1000	75.7% (n=56)

*: the number of patients who have been tested, **: poor prognosis criteria of the Turkish Ministry of Health

Table 3. Mortality rates according to the characteristics of patients on the 14th and 28th days of therapeutic plasma exchange

	Total number	14th day mortality	p*	28th day mortality	p*
Gender, n (%)					
Male	54 (67.5)	27 (50.0)	0.747[a]	39 (72.2)	0.408[a]
Female	26 (32.5)	14 (53.9)		21 (80.8)	
Lymphocyte, n (%)					
<0.8 x10^3/µL	66 (82.5)	36 (54.6)	0.200[a]	52 (78.8)	0.089[a]
>0.8 x10^3/µL	14 (17.5)	5 (35.7)		8 (57.1)	
D-dimer, n (%)					
<1000 ng/mL	18 (24.3)	8 (44.4)	0.420[a]	10 (55.6)	**0.013[a]**
>1000 ng/mL	56 (75.6)	31 (55.4)		47 (83.9)	
CRP, n (%)					
<40 mg/L	15 (18.9)	4 (26.7)	**0.039[a]**	10 (66.7)	0.428[a]
>40 mg/L	64 (81.0)	36 (56.3)		49 (76.6)	
Ferritin, n (%)					
<500 ng/mL	46 (58.9)	18 (39.1)	**0.021[a]**	33 (71.7)	0.525[a]
>500 ng/mL	32 (41.0)	21 (65.6)		25 (78.1)	
ARDS, n (%)					
No	28 (35.0)	8 (28.6)		14 (50.0)	
Moderate	35 (43.7)	20 (57.1)	**0.005[a]**	30 (85.7)	**0.001[b]**
Severe	17 (21.3)	13 (76.5)		16 (94.1)	
Multiple Organ Failure, n (%)					
No	49 (61.2)	16 (32.7)	**<0.001[a]**	30 (61.2)	**<0.001[b]**
Yes	31(38.8)	25 (80.7)		30 (96.8)	
Sepsis/Septic Shock, n (%)					
No	14 (17.5)	4 (28.6)	0.062[a]	6 (42.9)	**0.002[a]**
Yes	66 (82.5)	37 (56.1)		54 (81.8)	
Intubation, n (%)					
No	18 (22.5)	2 (11.1)	**<0.001[b]**	5 (27.8)	**<0.001[a]**
Yes	62 (77.5)	39 (62.9)		55 (88.7)	
Follow-up Unit, n (%)					
Inpatient Care Service	5 (6.2)	0 (0.0)	**0.018[b]**	0 (0.0)	**<0.001[b]**
Intensive Care Unit	75 (93.7)	41 (54.7)		60 (80.0)	

a: Pearson chi-square test, b: Fisher's exact test

Table 4. Logistic regression analysis for mortality rates on the 14th and 28th day of therapeutic plasma exchange

14th day Mortality	OR (95% CI)	p
CRP (>40 mg/L)	1.22 (0.25-5.83)	0.797
Ferritin (>500 ng/mL)	3.68 (1.03-13.10)	**0.044**
ARDS (No)		0.945
ARDS (Moderate)	1.24 (0.25-5.97)	0.786
ARDS (Severe)	1.02 (0.14-7.44)	0.984
MOF (Yes)	5.07 (1.27-20.10)	**0.021**
Intubation (Yes)	12.39 (1.13-135.24)	**0.039**

28th day Mortality	OR (95% CI)	p
D-dimer (>1000 ng/mL)	3.39 (0.76-15.04)	0.107
Sepsis/septic shock (Yes)	1.01 (0.18-5.70)	0.985
MOF (Yes)	6.87 (0.71-66.01)	0.095
Intubation (Yes)	8.45 (1.64-43.35)	**0.010**

CRP: C-reactive protein, ARDS: acute respiratory distress syndrome, MOF: multiple organ failure, OR: odds ratio, CI: confidence interval

a thrombospondin type 1 motif, member 13) (9,13). In parallel with these suggestions, we found that fresh frozen plasma was used as the replacement fluid in half of our patients who underwent TPE, whereas albumin was used together with fresh frozen plasma in the other ones.

Nearly all of the study population had severe COVID-19 related pneumonia, of which more than half developed ARDS and we found that the presence of intubation at the start of TPE increased the mortality rates. Different sources have reported ARDS and cytokine storm syndrome as the main causes of death for patients with COVID-19 infection (14-16). However, approximately half of the patients presenting with cytokine storm syndrome develop ARDS (17). Therefore, early recognition and control of uncontrolled immune reactions are essential in these patients. Ferritin, CRP, and D-dimer levels are clues used to detect the severity of systemic inflammatory responses (18). In our study population, CRP levels in 81.0% (n=64), D-dimer in 75.7% (n=56), and ferritin levels in 41.0% (n=32) were found to be above the critical threshold values that predict poor prognosis and this suggests the presence of intensive cytokine storms during the TPE procedure in most of our population. Additionally, our statistical analysis revealed a relation between mortality rate and increased levels of ferritin, which is in parallel with the previously reported literature (19,20).

Unfortunately, we do not have a control group with whom the included cases could be compared, who were positive for COVID-19 and did not undergo TPE. However, the follow-up rate in the intensive care unit of our current study population is 93.8% (n=75), and the mortality rate reported in the literature for patients who need follow-up in the intensive care is around 50% (21,22). In a study published in Turkey, on the other hand, this rate was reported as 78% (23). The mortality rate observed for the

patients who underwent TPE was 75.0% (n=60) on the 28th day of the procedure in our study, and this rate is similar to the cases in which the procedure was not performed compared to the literature. As a matter of fact, it was also concluded in a similar observational study published in Iran that TPE could not reduce mortality rates (24). These findings contradict the literature reported on the effectiveness of TPE to date and needs to be confirmed by further observation and prospective studies (9,25,26).

In this study, most of the research population consisted of cases with poor prognostic features according to both clinical and laboratory characteristics. The median age of these cases is 60 years, and when considered from the perspective of the attending physician, there is a relatively young patient group who have exhausted all the treatment options. It appears that TPE is applied as a last-resort treatment in these cases. Current literature for recommendations on the selection of COVID-19 patients for TPE is scant, and it is unclear which patient will be selected at which stage of the disease. Therefore, studies involving large case series on the subject are urgently needed.

CONCLUSION

In this study, we found that elevated ferritin levels, intubation, and the presence of MOF increase the risk of mortality in TPE applied patients with COVID-19 and severe pneumonia. However, the mortality rates did not seem to be much different in our TPE treated patient population considering the literature on TPE naïve patients with COVID-19.

Although the development of vaccines and new treatments has come a long way in the pandemic process, for some patients, COVID-19 is still a deadly disease that progresses to the critical illness stage. Prospective studies in which the best treatment algorithms will be developed will primarily be led by a retrospective analysis of the existing data and it is thought that our study and findings will lead to larger-scale, multicenter prospective studies on the subject and that TPE will maintain its importance as a supportive treatment approach in critically ill patients.

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Adana City Training and Research Hospital (04.07.2022, 109/2037).

Conflict of Interest: None declared by the authors.

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