Therapeutic Plasma Exchange in Neurological Disorders: A 9-year Experience

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ABSTRACT

Therapeutic plasma exchange (TPE), is based on the removal of pathogenic substrates from plasma with replacement fluid. Especially in refractory cases to standart treatment protocols, TPE procedures are performed for many neurological disorders. The aim of this study was to analyse the efficacy and safety of TPE in patients with neurological disorders. This retrospective study was conducted between 2012 and 2021 in our tertiary referral hospital, Adult Hematology Clinic and Therapeutic Apheresis Unit. The study included 59 patients with a total of 267 therapeutic procedures. The response to treatment was evaluated with the Medical Research Council (MRC) scoring system. The 59 patients comprised of 30 (50.8%) males and 29 (49.2%) females with a median age of 52 [20-80] years. Of these patients 44.1% were diagnosed with Myastenia Gravis (MG), 27.3% with Guillain Barre Syndrome (GBS), and 8.5% with Multiple Sclerosis (MS). The median number of TPE sessions per patient was 5 (1-7). The overall response rate was 76.3%. Patients with Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIPD), Transverse myelitis (TM), and MG have higher rates than other disease subtypes. The MRC score was significantly higher in the group with response than the group with no symptom regression (p= 0.001). The current study highlighted that TPE is a safe and effective treatment option with mild to moderate and manageable adverse events in patients with neurological disorders. Evaluation of response with the MRC scoring system was beneficial as a reliable quantative response.

Keywords: Therapeutic plasma exchange, Myastenia Gravis, Guillain Barre Syndrome, MRC score

INTRODUCTION

Therapeutic plasma exchange (TPE) is an extracorporeal purification method that removes large molecular weight particles from plasma. The principal mechanism is the removal from the circulation of autoantibodies, immune complexes, cytokines, monoclonal proteins, toxins and other inflammatory mediators.[1]

In the TPE procedure, the patient's blood is passed through an apheresis device and the filtered plasma is removed. Fresh frozen plasma (FFP) or albumin is used as replacement fluid.[2] The purpose of this procedure is to remove from the plasma, the pathogens or circulating immune complexes or high molecular weight substances, which may be responsible for the disease itself or its clinical findings.[3]

TPE was first used in 1952 in a patient with multiple myeloma because of symptoms of hyperviscosity. Then, in the 1970s, it started to be used in a number of neurological diseases.[4,5] This method, which is based on the removal of pathogenic substrates from patient plasma, has been used with increasing indications in hematological, neurological, nephrological and connective tissue diseases in recent years.[1]

Most neurological disorders which are treated with PE are associated with presumed aberrant humoral immune responses. These diseases include myasthenia gravis (MG), Guillain-Barré syndrome (GBS), and chronic inflammatory demyelinating polyneuropathy (CIDP).[4,6]

The American Society for Apheresis (ASFA) has published guidelines for the use of therapeutic plasma exchange for over 30 years. The addition of new TPE indications, retirement of some former indications and the provision of updated recommendations for current indications are reviewed periodically based on current literature.[7] TPE treatment is in category 2 in acute disseminated encephalomyelitis (ADEM), acute multiple sclerosis (MS), and acute neuromyelitis optica (NMO) attacks from CNS demyelinating diseases.[8] It has been recommended that TPE treatment be applied especially in severe MS attacks that do not respond to pulse steroid treatment and are predicted to cause permanent disability.[9]

The aim of this study was to examine the efficacy and safety of TPE in patients with various neurological diseases who were evaluated by the hematology and neurology clinics and were planned to undergo plasma exchange.

PATIENTS AND METHODS

A retrospective review was made of the medical reports of all patients who received TPE for neurological disorders between 2012 and 2021 in the Apheresis Unit of University of Health Sciences Ankara Diskapi Yildirim Beyazit Training and Research Hospital. Inclusion criters were; patiens who were > 18 years and had plasma exchange indication for neurolojical disease . Patients who under 18 years were excluded from the study. No patient had received rituximab combined with plasma exchange

Age, gender, neurological disease, indications for TPE, total TPE cycles, treatments (TPE as front line or second line treatment), treatment responses and complications of TPE were recorded. TPE indications were categorized according to the ASFA guidelines. Clinical outcomes were measured using the Medical Research Council (MRC) neurological assesment scale. The MRC grading system provides the following grades: 0, paralysis; 1, only a trace or flicker of muscle contraction is seen or felt; 2, muscle movement is possible with gravity eliminated; 3, muscle movement is possible against gravity; 4, muscle strength is reduced, but movement against resistance is possible and 5, normal strength.[10] Response is determined as at least one point MRC increase in at least one muscle group after the procedure. The neutrophil count, lymphocyte count and neutrophil/lymphocyte ratio were recorded before any treatment and at 7 days after the last plasma exchange cycle.

The replacement fluid used was as 5% solution of human albumin or FFP. Depending on patient weight, height and hematocrit value, a total of 1-1.5 volumes of plasma were exchanged. This procedure was performed using continuous flow cell separators Braun Diapact CRRT, or Fresenius Comtec, according to the center preference. A central venous catheter was used for the TPE procedure, with a 12 F double-lumen catheter inserted through the subclavian or jugular vein.

All procedures were performed by senior apheresis nurses. The patients were monitored and vital signs recorded at the beginning and end of each procedure. Adverse events were monitored and recorded during all procedures.

Ethical Approval and Informed Consent

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. As a standard of care/action of our hospital, the patient records confirmed that all the study patients gave informed consent at the time of hospitalization and before the administration of any intervention. Written informed consent was obtained from all patients.

The study was approved by University of Health Sciences Turkey, Ankara Dışkapı Yıldırım Beyazit Training and Research Hospital Ethics Committee (protocol no: 109/29, date: 19.04.2021).

Table 1. Demographic , disease and treatment characteristics of the patients

(n= 59)	
Age (years) (median,min-max)	52 [20-80]
Gender (n,%)	
Female	29 (49.2%)
Male	30 (50.8%)
Diagnosis	
MG	26 (44.1%)
GBS	14 (27.3%)
MS	5 (8.5%)
Others	14(23.7%)
The number of TPE treatment sessions (median,min-max)	5 [1-7]
MRC score (median,min-max)	2 [0-5]
ASFA category	
I	45 (76.3%)
II	14 (23.7%)
Previous treatment before TPE (n=12)	
IVIG	5 (41.6%)
Steroid	6 (50%)
IVIG+steroid	1 (8.3%)
Replacement fluid	
FFP	33 (55.9%)
5% human albümin	26 (44.1%)
Side effect/complication	
No	39 (66.1%)
Yes	20 (33.9%)
Side effect/complication (n=21*)	
Hypotension	13 (%65)
Hypertension	4 (%20)
Tacchycardia	3 (%15)
Catheter-related	1 (%5)

* In 1 patient there was seen to be more than one side effect/complication
MG= Myasthenia Gravis, GBS= Guillain-Barre syndrome, MS= Multiple Sclerosis, FFP= Fresh frosen plasma IVIG= Intravenous Immunoglobulin TPE= Therapeutic plasma exchange ASFA= The American Society for Apheresis MRC= Medical Research Council

Statistical Analysis

Study data were analyzed using SPSS 27.0 software. Mean, standard deviation, median minimum, maximum values, frequency (n) and percentage were used in the descriptive statistics of the data. The distribution of variables was assesed with the Kolmogorov-Smirnov test. The Independent Samples t-test and Mann-Whitney U-test were used in the analysis of quantitative independent data, and the Wilcoxon test for dependent quantitative data. The Chi-square test was applied to qualitative independent data, and the Fischer test was used when the Chi-square test conditions were not met.

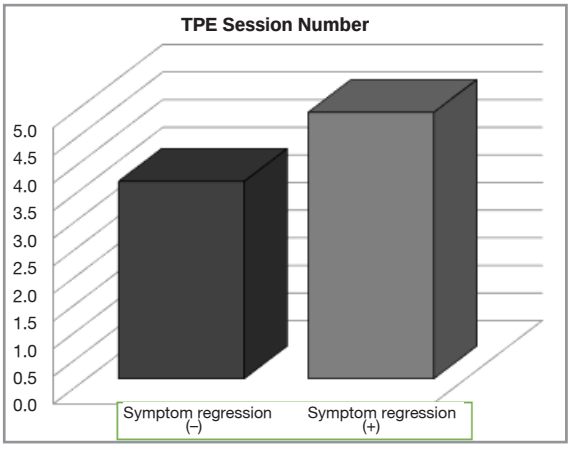

Figure 1. The relationship between the number of TPE sessions and the effectiveness

RESULTS

Evaluation was made of 59 patients, The demographic features, indications and side effects/complications are shown in Table 1.

FFP was used as replacement fluid in 33 (55.9%) and human albümin was used in 26 (44.1%) cases. TPE was applied as front-line therapy to 79% and as second line therapy to 21%. In the second line therapy group, patients had received steroid (50%), IVIG (41.6%) and IVIG+steroid (8.3%) medications as front line therapy before TPE.

Overall 45/59 (76.2%) patients responded to TPE. In the group diagnosed with MG, the indications for TPE remained stable as they were preoperatively. According to the MRC scoring system, the mean score in the unresponsive group was 0.0 and 2.0 in the responding group. The TPE response score was significantly higher (p= 0.001) in the group with response than in the group without symptom regression. TPE efficacy was determined in the fifth cycle in 14 (23.7%) patients, in the fourth cycle in 14 (23.7%), in the thirth cycle in 11 (18.6%), in the second cycle in 5 (8.4%) and in the first cycle in 1 (1.6%) patient.

The demographic and clinical characteristics of patients with and without regression in symptoms following TPE are given in Table 2.

Table 2. Demographic and clinical characteristics of patients with and without regression in symptoms with TPE

	Symptom regression (–) Mean±sd /n %	Symptom regression (+) Mean.±sd /n %	p
Age			
	51.0±15.9	51.9±16.4	0,735[m]
Gender			
Female	7 / 50	22 / 48.9	0,942[X2]
Male	7 / 50	23 / 51.1	
TPE session number	3.6±1.3	4.8±0.9	0,000[m]
MRC score			
	0.0±0.0	2.1±1.1	0,000[m]
ASFA cathegory			
I	11/78.6	34 / 75.6	1,000[X2]
II	3 / 21.4	11 / 24.4	
TPE replacement fluid			
FFP	7 / 50	26 / 57.8	0,609[X2]
5% Human Albumin	7 / 50	19 / 42.2	
Complication			
(–)	9 / 64.3	30 / 66.7	0,732[X2]
(+)	5 / 35.7	15 / 33.3	

m= Mann-Whitney U test / X2= Chi-Square test (Fischer test) FFP= Fresh frosen plasma TPE= Therapeutic plasma exchange
ASFA= The American Society for Apheresis

While the mean number of TPE sessions was 4.8±0.9 in the responding group, it was 3.6±1.3 in the unresponsive group. The number of sessions was significantly higher in the response group (p= 0.001).

Neutrophil, lymphocyte and neutrophil/lymphocyte ratios were evaluated from the hemogram findings of the patients before any treatment and at 7 days after TPE was completed (Table 3). In the group without symptom regression, the lymphocyte count after TPE decreased significantly compared to before TPE (p= 0.043). The lymphocyte increase after TPE was significantly higher in the group with symptom regression than the group without symptom regression (p= 0.02).

The complications were generally mild to moderate and manageable. The catheter-related complication was fibrin sheaths, causing catheter dysfunction. The TPE procedure was terminated in only 1 patient due to complication, and no mortality developed related to the TPE procedure.

In current study, MG was the most common indication for TPE. The response rate was 88.4% in MG diagnosed patients. In 3 of the MG patients, TPE indication was to maintain the preoperative stable condition. Although the evaluation of these patients as non-responders caused a slight decrease in the success rate, the response rate was 100% in patients with MG when these patients were excluded. GBS was the second most common TPE indication with a rate of 14%. The response rate was 57.1% in GBS diagnosed patients. In addition, the response rate in patients with MS and NMO (central nervous system diseases) was found to be lower than in patients with CIDP (peripheral nervous system diseases) or MG (neuromuscular junction disease). Response rates according to diagnosis given in Table 4.

DISCUSSION

TPE is a procedure used in many diseases where an immune etiology is known or suspected. Through filtration, it reduces from circulation the antibodies and substrates that cause immune-mediated diseases, and thus the symptoms of the disease can be controlled.[11,12] This procedure is used in many immune-mediated neurological diseases. Randomized controlled studies have demonstrated the efficacy of TPE in neurologic disorders.[13] GB, CIPD, MG, MS and ADEM can be given as exam-

Table 3. Neutrophil, lymphocyte counts and neutrophil/lymphocyte ratios the patients before any treatment and at 7 days after TPE was completed

	Symptom regression (–) Mean±sd / n %	Symptom regression (+) Mean.±sd / n %	p
Neutrophil			
Before TPE	7937.9±6450.0	6178.7±4235.7	0.123[m]
After TPE	8919.3±5564.1	6809.3±4102.4	0.202[m]
Before/After Change	981.4±3179.7	638.4±4231.3	0.543[m]
In-group exchange p	0.116[w]	0.230[w]	
Lymphocyte			
Before TPE	2150.7±1741.4	1445.4±610.7	0.281[m]
After TPE	1789.3±793.3	2110.5±1226.6	0.569[m]
Before/After Change	-361.4±1346.9	666.3±1128.8	0.0043[m]
In-group exchange p	0.777[w]	0.002[w]	
NLR			
Before TPE	5.9±4.5	5.4±5.8	0.577[m]
After TPE	6.8±8.7	5.7±8.6	0.129[m]
Before/After Change	1.0±7.0	0.3±8.1	0.564[m]
In-group exchange p	0.778[w]	0.605[w]	

[m]: Mann-Whitney U test/ [w]: Wilcoxon test

ples of neurological diseases in which immunity plays a role in the etiology.[11]

In the ASFA guideline, GBS, MG and CIPD have category I and MS and NMO have category II indication for TPE.[7] MG, GBS, and CIPD are the most common TPE indications among neurological diseases, followed by MS.[14]

In a multicenter study of TPE in neurological diseases, Kaynar et al.[11] reported an overall response rate of 82%. The most common indications were GBS and MG, respectively.

Tombak et al.[15] reported a multicenter study of TPE in neurological diseases in 63 patients. An average of 8 TPE sessions were applied and the overall response rate was 81%. The most common indications were GBS and MG, respectively. The response rates were 19 of 21 patients in MG and 18 of 21 patients in GBS.

Consistent with the literature, the overall rate of regression in neurological symptoms was 76.3% in the current study. The median number of TPE sessions was higher in the responsive group. Based on this result, it may be advisable to continue with TPE sessions in patients who do not respond in the early period. However, there is no clear information in the literature about how many sessions should be applied in total. It would be more accurate to decide on the number of TPE sessions according to the clinical condition and response of each patient.

In the study by Korkmaz et al. 16 of 3203 patients with an average of 5 TPE sessions. FFP was the most common replacement fluid, followed by 5% human albumin. Similarly, in the current study, FFP was used most frequently as the replacement fluid.

MRC is an ordinal scoring of muscle weakness, which forms the basis of the Mayo Clinics and manual muscle testing grading systems, and the MRC system is the most widely used system worldwide. There are studies in the literature in which this scoring system has been used to evaluate the effectiveness of plasma exchange in neurological diseases.[2,17] It was an expected result that the current study findings obtained with the MRC score and the score determined between the responding and unresponsive groups were statistically significant.

When the non-responsive group of patients was analyzed, the majority of the patients had diseases with central nervous system involvement (except

Table 4. Response rates according to diagnosis

Diagnosis	Patients (n)	Symptom regression (–) (n)	Symptom regression (+) (n)	Response rate %
Myasthenia Gravis	26	3	23	88.4
Guillain-Barre syndrome	14	6	8	57.1
Multiple Sclerosis	5	2	3	60
Neuromyelolitis Optica	4	1	3	75
Encephalitis	4	1	3	75
Transvers Myelitis	3	1	2	66.6
Chronic Inflammatory Demyelinating Polyradiculoneuropathy	2	0	2	100
Lambert -Eaton syndrome	1	0	1	100

GBS patients). In addition, the mean score of the responding patients increased by 2.1±1.1, suggesting that mobilization was achieved and the improvement, was objective and effective, considering the MRC score.

Leukocytes and associated subtypes are well-known indicators of systemic inflammation. Neutrophils play a major role in innate immunity. The lymphocyte count is assumed to reflect the degree of host responsiveness to the immune system18. In a study comparing the efficacy of NLR and plasma exchange in GBS, NLR was significantly higher in patients with poor response than in patients with good responses.[19] In another study of 71 patients, which investigated the factors predicting the response to plasma exchange in autoimmune neuropathies, 61 were diagnosed with GBS and 15 with CIPD. The results of this study showed that low NLR value was a predictor of poor response to plasma exchange is in GBS patients.[20]. In the current study, however, no significant difference was found in the TPE-responsive and non-responsive groups in respect of NLR values. In addition, the significant increase in the lymphocyte count after TPE in the group with regression in symptoms compared to the group without regression can be considered as a new parameter for antipicated response.

In a multicenter study evaluating TPE in neurological diseases 115 patients underwent an average of 5 sessions, using 66% central venous catheter and 34% peripheral venous access for the procedure. Complications were observed in 18.3% of the patients, as related to catheter placement (8.7%), hypotension (3.5%), hypocalcemia (3.5%), and allergic reaction (1.7%).[21] Seyhanlı[22] et al. analyzed 11 years of TPE experience of 207 patients with neurological diseases, and the most common side-effects were allergic reaction and hypotension. In the current study, the use of a central venous catheter, was prefered for all patients because the access line is better in terms of patient comfort in possible repetitive session applications. The most common complication was hypotension, which was consistent with similar studies.

Conclusion

The results of this study show that the efficacy of TPE was remarkably high with mild to moderate managable side-effects.

Performing the TPE response evaluation with the scoring system was beneficial as a quantative assesment of the reliability of the efficacy. An elevated lymphocyte count can be used as a cheap and easily accessible parameter for the prediction of response. Based on current data, TPE continues to be a reliable and effective treatment option in neurological diseases.

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