

Therapeutic plasma exchange in neuroimmunologic disease: 60 patients experience

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Abstract

Aim: We aimed to determine the results, safety, and applicability of therapeutic plasma exchange (TPE) in neurological diseases.

Materials and Methods: We performed a retrospective analysis in between 2014-2019. In the evaluation of response to treatment (RT), patients were divided into 4 groups: full recovery (RT1), partial recovery (RT2), stationary or worse (RT3), exitus (RT4). TPE treatment was evaluated effective in patients with RT1 and RT2. Patients' data were compared between group 1 (TPE as first line treatment) and group 2 (TPE as additional therapy).

Results: TPE procedure was applied to 199 patients, 1330 times. Sixty neurological patients (mean age 51.5±17.05; 24 female) underwent 356 TPE procedures on average 6.2 sessions. After TPE, functional status was RT1:3, RT2:19, RT3:28, RT:10. TPE was an effective treatment in 36.6% of patients.

Disease distribution Guillain Barre syndrome (n:26), myasthenia gravis (n:8), autoimmune encephalitis (n:6), neuromyelitis optica (n:5), transverse myelitis (n:5), vasculitis (n:3), chronic demyelinating inflammatory polyneuropathy (n:2), multiple sclerosis (n:2), Morvan syndrome (n:1), myeloradiculitis (n:1) and polymyositis (n:1). 7 patients (11.6%) were included in group 1 and 53 patients were in group 2. TPE was started after 9.7 days (±6.9) due to insufficient response. Complications were found in 6 patients (10%). The duration of hospitalization was 28.1 (±13.1) in group 1 and 32.9 (±19) days in group 2 (p: 0.01).

Conclusion: Our experience has supported that TPE is a safe and effective treatment option for a wide range of antibody-related neurological disorders, especially if it is the first treatment option.

Keywords: AFSA; Guillain-Barre syndrome; neurologic disease; neurommunologic disease; plasmapheresis; therapeutic plasma exchange

INTRODUCTION

Therapeutic plasma exchange (TPE) is a process involving extracorporeal removal of plasma from other components of blood, discarding and replacing plasma with physiological fluids. The underlying mechanism is the clearance of pathogenic immunomodulators, such as antibodies and immune complexes and/or reduction of proinflammatory molecules, such as complement components and coagulation factors from circulation (1,2).

Therapeutic plasma exchange has been used in clinical practice since the 1970s and its indications have expanded over the years, especially in neurological diseases. Therapeutic success of TPE in the treatment of Guillain-Barre syndrome (GBS) or myasthenic crisis has

led to its use in other neurological conditions. Although the indications of TPE have been supported by randomized clinical trials in some neurological diseases, most of its use is still based on individual case reports, small case series, and expert opinion papers (Table 1). The lack of a specific guideline as well as the invasive nature of the procedure and concern for complications can still be challenging during decision-making in clinical practice (3-6).

In this study, we reported our single-center experience in TPE procedures applied to patients with neurological diseases, with a special emphasis on the patients' clinical status, hospital stay, complications. we aimed to contribute to the literature and help neurologists in TPE-related decision making.

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Table 1. Category and Grade Recommendations for Therapeutic Apheresis, from Padmanabhan A. et al (13)

Disease	Indication	Category	Grade
GBS	Primary treatment	I	1A
CIDP		I	1B
NMDA-encephalitis		I	1C
MG	Acute, short-term-treatment	I	1B
	Long-term-treatment	II	2B
Multiple sclerosis	Acute attack/relapse	II	1A
	Chronic	III	2B
NMOSD	Acute attack/relapse	II	1B
	Maintenance	III	2C
VGKC antibody-related-diseases		II	1B
ADEM	Steroid-Refractory	II	2C
Rasmussen-Encephalitis		III	2C
Paraneoplastic-NS		III	2C
Paraproteinemic-CDADP	IgG/IgA/IgM	I	1B
	Anti-MAG-neuropathy	III	1C
	Multiple myeloma	III	2C
	Multifocal-motor-neuropathy	IV	1C
PML-associated-with-natalizumab		III	1C
Stiff-person-syndrome		III	2C

MATERIALS and METHODS

This is a retrospective study performed at the Neurology Clinic of Bezmialem Vakif University. Electronic medical records of patients who were undergone TPE between January 2014 and June 2019 were collected. Type of neurological disease was noted. The medical records were analyzed for demographics, relevant medical history, risk factors and medications were reviewed.

A double lumen 12F venous catheter was placed into the internal jugular or femoral veins. Plasmapheresis was performed using a Prismaflex machine (Gambro, Lund, Sweden) via double lumen HD catheter placed to all patients. The patient's plasma volume was calculated using the following formula: plasma volume (L)=weight×0.065×(1-hematocrit) (7). Twenty percent human albumin (diluted to 5% albumin in isotonic saline) and/or fresh frozen plasma were used as the replacement fluid. All patients underwent calcium and antihistaminic premedication. Vital signs were monitored for adverse events during the procedure.

Total number of TPE procedure and any complication during/after sessions were identified. After completing the TPE sessions, patients' clinical status was categorized according to clinical change after TPE.

This treatment procedure was applied in more than one disease. Therefore, the degree of recovery was evaluated for each disease group separately. Since it is not possible to evaluate all diseases with the same scale, in order to evaluate all patients in terms of recovery, the degree

of recovery was determined as follows: Response to treatment 1 (RT1) = Complete recovery; the patient has completely recovered. RT 2 = Partial recovery; the patient did not recover but is better than applying to the hospital. RT 3 = The patient is the same or worse than the neurological findings on admission to the hospital. RT 4 = The patient died. TPE treatment was evaluated effective in patients with RT1 and RT2.

Also, number of days hospitalized, complications and Category and Grade Recommendations for Therapeutic Apheresis AFSA was recorded.

Complications were divided into 4 (Table 1) according to previously published criteria and classified as follows: 1-mild: no intervention required, 2-moderate: intervention required, but treatment completed, 3-severe: procedure stopped and 4-fatal (8).

Statistical Analysis

Statistical analyses were performed by using SPSS (Statistical Package for Social Sciences) Windows Version 19 software. Descriptive analysis included mean, minimum, maximum, and percentage values, as appropriate. Because of the lack of groups in the study population, comparison tests were not performed.

RESULTS

Of the 314 procedures performed in the Transfusion Medicine department in our hospital between January 2014 and June 2019 and 199 were TPEs. Of these TPEs, 30.2% (n:60) were performed for neurological disease,

27.6% (n:55) for nephrological diseases, 16.5%(n:33) for hematological diseases, 16% (n:32) for gastroenterological diseases, 9.5% (n:19) for other conditions uncategorized (Figure 1).

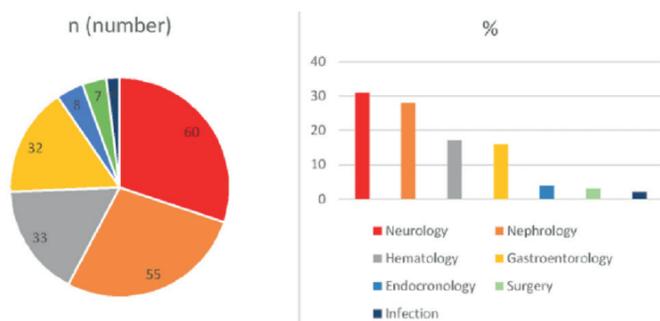


Figure 1. Number (n) and percentage (%) distribution of therapeutic plasmapheresis between sections

All patients underwent a total of 1330 sessions of TPE. Sixty patients underwent TPE with neurological indications and a total of 354 sessions of TPE were applied to this group. The mean age of these patients was 51.4±17.05 (18-84) years, and 51.7% were male. The mean number of sessions was 6.2±2.4 (3-12). TPE was performed 2 different episodes in 7 patients and 4 different episodes in 2 patients.

The diagnosis of the patients were as following: Guillain Barre syndrome (n: 27, 45%), myasthenia gravis (n:9, 15%), autoimmune encephalitis (n: 6, 10%), Neuromyelitis Optica (n: 6, 10%), multiple sclerosis (n: 5, 8.3%), vasculitis polyneuropathy (n: 2, 3.3%), chronic demyelinating inflammatory polyneuropathy (n:2, %3.3), Morvan syndrome (n: 1), myeloradiculitis (n: 1) and polymyositis (n: 1) (Table 2) (Figure 2).

Table 2. Distribution of diseases		
	TPE were given 1st line	TPE were given second line
Number of patients	7	53
Diagnosis	GBS- AMAN (n:1) MG (n:1) NMO (n:1) Autoimmune encephalitis(n:1) Mononeuropathy multiplex (n:1) Morvan syndrome (n:1)	GBS (n:26) - AİDP: 18 - AMAN :2 - AMSAN: 3 - MFS: 3 MG (8) Multiple sclerosis (n: 5) NMO (n:5) Autoimmune encephalitis (n:5) Vasculitis polyneuropathy (n: 2) CIDP (n:2) Myeloradiculitis (n: 1) Polymyositis (n: 1)
Side effects /complication	None	Catheter infection (n:2) Anaphylaxis (n:1) Thrombocytopenia (n:1)
Response to treatment	Full recovery: 3 Stationary: 2 Death: 2	Full recovery: 0 Stationary: 24 Partial recovery: 19 Death: 8

TPE was chosen as the first treatment method in 7 patients (11.6%) with more severe clinical progression. Two of these patients were MG, one autoimmune encephalitis, one mononeuropathy multiplex caused by vasculitis, one NMO, one GBS, one Morvan syndrome. In the remaining 53 patients, IVIG and / or steroid were the first treatments. TPE was started after an average of 9.7 days (± 6.9; 4-30) due to insufficient response.

The overall response rate in neurology patients was 36,6%. The functional status after TPE was RT3 at 45% (n:27),

RT2 at 33,3% (n:20), RT4 at 16,7% (n:10) and RT1 at 5% (n:3) (Figure 3).

The duration of hospitalization was 28.1 (±13.1; 10-50) days for patients who underwent direct TPE (group 1) and 32.9 (±19; 6-120) days for patients who underwent TPE as the second treatment (group 2) (p: 0.01).

The number of patients who had plasmapheresis with the diagnosis of GBS was 27 (45%). Of these, 2 had died, 10 had partially recovered, and 13 had had a stationary disease.

TPE was started directly in one of the patients intubated in the first day, and IVIG was preferred as the first treatment in the other patients. Ten patients were intubated under IVIG treatment and then TPE was initiated.

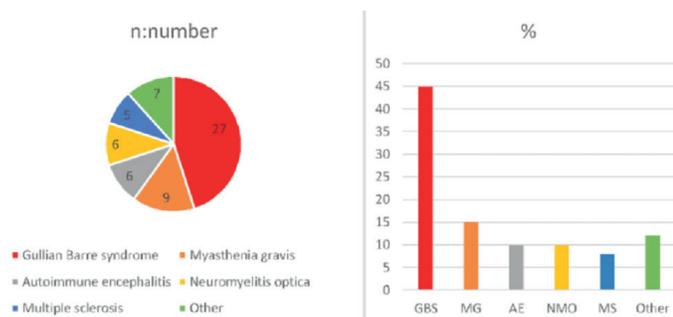


Figure 2. Distribution of diseases and number (n) and percentage (%) of patients undergoing TPE

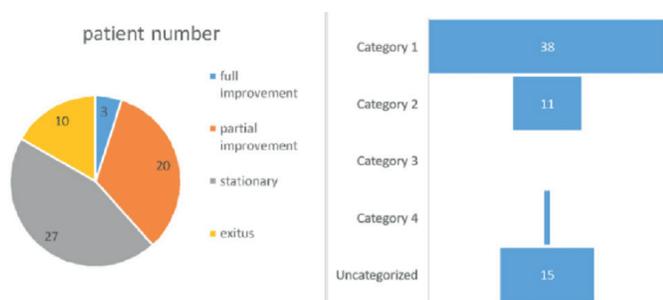


Figure 3. Neurological status of patients and distribution according to AFSA classification

TPE was applied to 9 MG (15%) patients. The mean number of sessions was 5.1 (3-7). All had bulbar and/or respiratory difficulty, 5 patients were intubated. In one of our patients who were intubated because of significant and severe bulbar involvement and her diagnosis was Muscle-specific tyrosine-kinase-antibody-positive myasthenia gravis (MuSK-MG), TPE was applied 3 times with a few months intervals and partial recovery was detected each time. Two patients underwent direct TPE (group 1), one was ex and one was fully recovered. One of the remaining patients died, 2 were stationary, 3 were partially improved in MG.

There were 11 patients in the demyelinating diseases (MS and NMO) group. These patients had an average of 6.8 sessions (5-12) of TPE. Plasmapheresis was performed directly in a patient with a very poor vision of optic neuritis, but there was no improvement in vision. Pulse steroid was applied to the other patients before TPE was performed. Only 2 of the remaining patients recovered partially and rest remained stationary.

TPE was performed in 6 patients with autoimmune encephalitis. Pulse steroid and/or IVIG treatment was applied in all of this patient group. Since the seizures continued, treatment was continued with TPE. However, only one patient showed significant improvement after TPE. One of the remaining 4 patients recovered partially and 3 died.

Polymyositis/dermatomyositis takes place in category IV in ASFA guideline. In our 1 patient, polymyositis resistant to other therapies, TPE was performed before cardiac surgery.

TPE was started after an average of 9,7 days ($\pm 6,9$; 4-30) due to insufficient response or progression. Complications were found in 6 patients (10%). One was anaphylaxis, one was thrombocytopenia, two were catheter infections, two were hypotension. None of them were serious, all were mild and moderate complications. No one had died due to complications of TPE.

The number of TPE did not show a statistically significant difference between groups. The duration of hospitalization was 28,1 ($\pm 13,1$; 10-50) days for patients in group 1 and 32,9 (± 19 ; 6-120) days for patients in group 2 ($p:0,01$).

Seventy-nine percent of the cases were in category I (n:38), 18,3 % were in category II (n:11).

There were 36 patients (%60) in ASFA category 1 (GBS, CIDP, MG) and 7 patients (%11,7) in category II (MS, NMO), 1 patient (%1,7) in category IV (polymyositis) according to the American Society for Apheresis (ASFA) 2010 guidelines (Figure 2). There were 15 patients (transverse myelitis, autoimmune encephalitis, vasculitis, Morvan syndrome) who were not included in ASFA (9,13).

DISCUSSION

We retrospectively evaluated therapeutic plasmapheresis procedures in our university hospital center. Approximately one-third of TPE procedures performed in our apheresis center was performed to neurology patients. Although these rates vary according to the characteristics and specialization of the centers, similar rates are generally reported (14-16).

According to the data of many centers in both America and Europe, GBS is the most commonly used plasmapheresis among neurological diseases (16,17).

In our series, almost half of the patients had GBS. In all of our GBS patients, we used IVIG as the first-line treatment, and we performed TPE for the patients who progressed with this treatment. Almost one-third of the patients were intubated just before starting the TPE procedure. Half of the patients had stable neurological status, one third had improved and 4 had died. In our series, there were no patients who had a complete recovery after TPE. In fact, TPE for GBS treatment, recommended by AFSA, is category I-evidence level 1A as the first-line treatment (13). Here, it may be effective for all of our patients to choose TPE as the second-line treatment in patients with severe progression.

Plasmapheresis was performed in two CDIP patients who progressed despite steroid and IVIG treatment, one of which showed partial improvement and one died. Although the efficacy of TPE in CIDP has been demonstrated in several controlled trials (17,18), it is recommended at the level of category I, level 1B in patients with severe episodes and progressing despite the appropriate dose and duration of treatment (13).

Among the neurological diseases, TPE was applied first in myasthenia gravis patient. In 1979 Newsom-Davis performed TPE in 7 myasthenia gravis patients and reported complete recovery in all of them (21). In the ASFA guidelines, TPE is recommended for category I, grade 1B in the acute short-term treatment of myasthenia gravis. The efficacy of TPE in MG varies from 55 to 100% in the literature (12). In our series, TPE was performed in 9 MG patients, 5 of whom were intubated. Only one of these patients improved completely. We preferred TPE in patients with poor prognosis who could not be treated adequately with IVIG and standard MG treatment, as in GBS, and this may explain lower full recovery rates compared to other studies.

According to the ASFA 2019 guidelines, during an acute attack of demyelinating diseases is a category II indication (13). In our series, 11 patients diagnosed with the demyelinating disease (5 MS and 6 NMOSD) underwent TPE during an acute attack.

Schilling S et al, 13 adult patients with a poor prognosis MS patient performed TPE and they found 71% good or very good outcome (22). In the publications of Özkale M et al, 3 pediatric NMO patients underwent TPE and had complete recovery (23). Both the MS and NMO patients did not respond to high-dose steroid and IVIG treatments. These patients underwent 7-10 sessions of TPE in their acute attacks. Approximately one-third recovered, and the rest remained clinically unchanged.

In our series, autoimmune encephalitis was the third most frequent disease group. According to ASFA 2019 guidelines, NMDA receptor encephalitis is a category I, grade 1C indication (AFSA). However, other types of autoimmune encephalitis, which is a very heterogeneous group, are not included in this recommendation guideline. In our series, there was no NMDR encephalitis. The only one was GABA-R encephalitis, the others were seronegative autoimmune encephalitis. Only our patient with GABA-R encephalitis showed partial recovery with TPE, others did not benefit from this treatment and half died during this process. However, in the literature, very good results of TPE application in AE treatment have been reported (24,25). This may be since most of our group was seronegative.

There is no clear optimal treatment regimen in polymyositis. The first treatment in many patients is steroid. In one randomized controlled trial (26), plasma exchange was no more effective in improving muscle strength or functional capacity than sham apheresis (26,27). Polymyositis/dermatomyositis takes place in category IV in ASFA guideline (13). In our one patient, polymyositis resistant to other therapies, TPE was performed before cardiac surgery for aortic stenosis. TPE was preferred because she could not use other treatment options because of serious heart failure findings before surgery and the patient's symptoms improved significantly after TPE.

TPE was started after an average of 9,7 days ($\pm 6,9; 4-30$) due to insufficient response or progression.

Complications such as hypocalcemia, coagulopathy, thrombocytopenia, anemia, thrombosis, infection, Ig deficiency, reaction to the contents of replacement fluid, atypical reaction to ACE inhibitor, hypokalemia, metabolic alkalosis, hypotension has been reported in the literature. The incidence of complications associated with TPE is between 4,3-50% in the literature. Few studies have reported TPE-related deaths between 0,005-11%. In our series, there was no death during or due to TPE (28-32).

In our cases, major complications were detected in 10% of patients associated with TPE in neurological patients. In fact, premedication with calcium, antihistamines and/or steroids is recommended if required. However, in our center, all of the neurological patients underwent premedication with antihistaminic medicine and calcium replacement, which have caused a low complication rate.

The number of applied TPE did not show a statistically significant difference between groups.

In fact, it is expected that TPE should be hospitalized for a longer period time because the interventional procedure requires special tools and trained personnel. Considering these conditions, IVIG is preferred as the first-line treatment in many centers. In our center, for many patients, it had also been IVIG or steroid the first choice according to the disease. But, in the literature, the results of the comparisons made regarding the length of hospital stay in patients receiving IVIG alone and TPE alone are inconsistent. Many studies find the TPE group longer, same and shorter (33-38).

Although the lack of patient numbers restricts us from drawing a clear conclusion from this assessment, we found that patients who received TPE as their first treatment option were hospitalized shorter than the other group. Three patients showed complete neurological recovery and all of them had TPE as the first-line treatment.

LIMITATIONS

This work had some limitations because it was performed retrospectively; hence, the clinical severity of neurological disease and recovery scoring could not be reliably reported.

CONCLUSION

In conclusion, TPE is a safe, fast, and effective method used in experienced centers. Based on the literature and our results As can be expected, patients who underwent direct TPE were hospitalized for a shorter time than patients who had TPE added as second-line treatment. TPE is an effective alternative treatment option for well-chosen patients with neurological diseases. Although some tertiary centers have experience in this area, as the experience of the centers and patient profiles are different, centers should identify and share their data with similar studies.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: The study protocol was approved by the Clinical Research Ethics Committee of Bezmialem Vakif University (02/09/2020-10192).

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