



Therapeutic Plasma Exchange in Neurologic Diseases: An Experience with 91 Patients in Seven Years

Nörolojik Hastalıklarda Terapötik Plazma Değişimi: 91 Hasta ile Yedi Yıllık Deneyim Sonuçları

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ABSTRACT

Introduction: In this study, we report the results of our experience of therapeutic plasma exchange (TPE) for neuroimmunologic disorders performed at our hospital over a seven-year period.

Methods: We retrospectively reviewed the medical records of 91 patients (53 male, 38 female) who had been treated at our center with TPE.

Results: 60 patients with Guillain-Barré syndrome (GBS), 23 with myasthenia gravis (MG), 4 with chronic inflammatory demyelinating polyneuropathy (CIDP) and 1 patient each with polymyositis, septic encephalopathy, acute disseminated encephalomyelitis (ADEM) and Opsoklonus-Myoclonus syndrome (OMS) received TPE. 26.7% of GBS patient's made complete recovery, 61.7% had partial recovery and 11.7% patients died due to respiratory failure. Despite our best efforts and effective TPE treatments, 13.4% of MG patients deceased, however, 78% had full recovery. Three patients with CIDP were discharged with full and 1 patient with partial recovery. The patient with ADEM had partial recovery with TPE at first, but deceased 2 months later due to pneumonia-related respiratory insufficiency. While, patient with polymyositis had slight-partial recovery, we obtained full recovery with TPE in septic encephalopathy and OMS patients. The side effects and complications of treatments with TPE, which included hypotension, hypocalcaemia and anemia, were mild and manageable.

Conclusion: The improvement rates were encouraging and we concluded that significant benefit can be achieved with TPE for the treatment of neuroimmunological disorders. (*Archives of Neuropsychiatry 2014; 51: 63-68*)

Key words: Therapeutic Plasma Exchange, Guillain-Barre syndrome, Chronic Inflammatory Demyelinating Polyneuropathy, Myasthenia Gravis

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ÖZET

Amaç: Bu çalışmada, terapötik plazma değişimi (TPD) ile tedavi ettiğimiz nöro-immünolojik olgulara ait 7 yıllık deneyimizin sonuçları rapor edilmiştir. **Yöntem:** TPD uyguladığımız 91 olgunun (53 erkek, 38 kadın) medikal kayıtları geriye dönük olarak incelenmiştir.

Bulgular: Tanısal olarak sınıflandığında, bu olguların 60'ının Guillain-Barre sendromu (GBS), 23'ünün Miyastenia Gravis (MG), 4'ünün ise kronik inflammatuar demiyelinizan polinöropati (KİDP) tanısıyla TPD aldığı görülmüştür. Birer olguya ise, polimiyozit, septik ensefalopati, akut dissemine ensefalomyelit (ADEM) ve Opsoklonus-Myoklonus sendromu (OMS) tanılarıyla TPD uygulanmıştır.

GBS hastalarımızın %26,7'sinde tam düzelme, %61,7'sinde kısmi düzelme izlenmiş olup, disabilitesi yüksek %11,7 hasta solunum yetmezliği nedeniyle kaybedilmiştir. MG'li hastaların %13,4'ünde tedaviye rağmen ölüm, %78'inde tam klinik düzelme gözlenmiştir. KİDP'li 4 hastamızın üçünde total, birinde kısmi düzelme gözlenmiş, ADEM'li olgumuz TPD ile önce kısmen düzelmiş ancak tedaviden 2 ay sonra aspirasyon pnömonisine bağlı solunum yetmezliği nedeniyle kaybedilmiş, polimiyozitli olgumuzda kısmi, septik ensefalopati ve OMS'li hastalarımızda tam düzelme gözlenmiştir. TPE uygulamasında karşılaştığımız yan etkiler hipotansiyon, hipokalsemi ve anemi gibi hafif ve yönetilebilir düzeydedir.

Sonuç: Çalışmamızın sonuçları otoimmün kökenli nörolojik hastalıklarda TPE tedavisinin etkili ve güvenilir bir yöntem olduğunu göstermektedir (*Nöropsikiyatri Arşivi 2014; 51: 63-68*)

Anahar kelimeler: Terapötik Plazma Değişimi, Guillain-Barre sendromu, Kronik İnflammatuar Demiyelinizan Polinöropati, Miyastenia Gravis

Çıkar çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

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Introduction

Therapeutic plasma exchange (TPE) has been used to remove immunoglobulins and other immunologically active substances, such as complements or cytokines, from the blood for the treatment of neurologic diseases in which autoimmunity plays a major role (1). The number of diseases treated with TPE increases with further understanding of the etiopathogenesis of neurologic diseases and improved techniques. It is a standard treatment regimen for some neurologic diseases, such as GBS, MC and CIDP (2,3,4,5,6,7,8). In a recent report of the Therapeutics and Technology and Assessment Subcommittee of the American Academy of Neurology, TPE was established as an effective course of treatment for many diseases; it is offered in cases of severe acute inflammatory demyelinating polyneuropathy (AIDP)/GBS, in the short-term management of CIDP (Class I, Level A), and is probably effective and should be considered for mild AIDP/GBS (9). There have been some other case reports and small studies in which it was claimed that TPE might be effective for some other neurologic diseases such as multiple sclerosis (10), neuromyelitis optica (11), acute disseminated encephalomyelitis (ADEM) (12), Stiff-man syndrome (13), Bickerstaff's encephalitis (14) and hemorrhagic leucoencephalitis (15). Additionally, it has been suggested that TPE may also be successful in treating complications of the central nervous system resulting from systemic hematologic diseases such as thrombocytopenic purpura (16). An alternative treatment option for TPE is intravenous immunoglobulin (IVIG), however, IVIG is very expensive and in many countries is not covered by insurance (17). Plasma exchange typically requires central venous access that can lead to severe complications such as thrombosis, septic infections or pneumothorax. However, TPE is a safe procedure for the treatment of appropriate neurological illnesses in a specialized unit with a high patient volume (9).

Neurologic disorders constitute the largest group of indications for TPE and, the number is increasing due to growing knowledge of pathogenic relevance of auto-antibodies. Although some traditional indications are supported by properly designed randomized trials, others are not. In order to determine the utility of plasmapheresis in different diseases, especially in rarely encountered diseases, we need more results. Therefore, we aimed to make contribution to the literature by reporting our results, considering other publications on this subject.

Methods

We reviewed the medical records of 91 neurologic patients who had been consecutively treated with TPE therapy between January 2004 and June 2011, in the Department of Neurology at Başkent University Faculty of Medicine, Adana Research and Practice Center. During this period, 457 procedures of TPE were applied to 91 patients with neurologic disorders.

The medical records were analyzed for the patients' demographic details (sex and age), types of neuroimmunologic

diseases, treatment modalities, prognoses, and any complications of the treatment.

Neurological indications included GBS, MG, CIDP, polymyositis, septic encephalopathy, OMS and ADEM. There were 38 female and 53 male patients. The mean age was 51.1 ± 16.8 years with a range of 17-80 years (Table 1).

All TPE procedures were done via central venous catheter. The device used in all procedures was COBE Spectra (Lakewood, Colorado, USA) which works with continuous flow. Total blood and plasma volume were calculated by using standard formulation. Albumin-saline, ISOHES, ringer lactate and fresh frozen plasma were selected as replacement fluids according to the patient's clinical and laboratory parameters. The total protein, albumin and calcium levels of all patients were measured before and after each TPE therapy. TPE was given every other day for most of the patients and a total of 1.51 plasma volumes were exchanged per cycle. The mean TPE session number was 5.06 ± 1.73 and the mean plasma volume was 50 ml/kg for each cycle.

For patients with GBS and CIDP, we considered a mean improvement in the disability grade, measured 4 weeks after the end of the TPE therapy and based on the 7-point Hughes Disability Grade Scale (18) and a mean improvement in the Osserman scale (19) for myasthenic patients, as the primary outcome measure. We have already been using the Hughes Disability Grading Scale for the monitoring of efficacy of TPE for the inflammatory neuropathy patients, the scores were taken from the patients' files. In addition, for the resolution of crises in myasthenic cases, we considered the duration of ventilation, time needed for independent walking, residual disabilities, and death, 4 weeks after treatment as secondary outcome measures. We also recorded the complications due to TPE. The approvals for off-label treatments were used.

Table 1. Diagnostic and demographic details of the patients treated with plasmapheresis

Diagnosis	Number of the patients	Mean age \pm SD	Sex (Female/Male)
GBS	60	52.5 \pm 15.86	27/33
CIDP	4	49.3 \pm 17	2/2
MG (prethymectomy)	9	41.1 \pm 18.8	5/4
MC	14	51.6 \pm 15.6	3/11
ADEM	1	28	0/1
Septic Encephalopathy	1	18	1/0
Polymyositis	1	51	0/1
OMS	1	49	0/1

GBS: Guillain Barré Syndrome, CIDP: Chronic Inflammatory Demyelinating Polyneuropathy, MG: Myasthenia Gravis, MC: Myasthenic Crisis, ADEM: Acute Disseminated Encephalomyelitis, OMS: Opsoclonus Myoclonus Syndrome

Results

GBS

The clinical diagnoses, the disability levels accordingly (18), and demographic features of the patients are summarized in Table 1 and 2. Twenty (33.3%) patients with GBS were not able to walk without assistance (Hughes 3), 25 patients (41.7%) were confined to a wheelchair or bed (Hughes 4), and 15 patients (25%) were in need of mechanical ventilation (Hughes 5). In all cases, TPE therapy was started within 10 days after the onset of the disease. Table 3 summarizes the prognoses of these patients. In a four-week therapy period, during which all patients also received physical therapy and rehabilitation, 16 patients (26.7%) experienced complete recovery (≥ 4 degree improvement in grades), 37 patients (61.7%) showed partial improvement (2-3 degree improvement in grades) and, when they were discharged, all of them were able to walk unaided or with little support. Seven GBS patients died (11.7%) with higher initial Hughes scores and respiratory failure. Among deceased patients from GBS, only 4 completed all the TPE sessions, 2 received only 1

session, and 1 received 2 sessions. Two of deceased patients suffered from acute motor sensory axonal neuropathy (AMSAN), and 5 of them had AIDP. Fifteen of 60 GBS patients were classified as acute motor axonal neuropathy (AMAN), among which there were no deaths.

CIDP

All of the CIDP patients required assistance with walking when first admitted to hospital and they either had not benefitted from at least 3-month corticosteroid treatment, or it had caused marked blood glucose elevation. However, after TPE therapy, all of them improved significantly. One of the patients was already on a cyclic TPE treatment since 2 years; he had not benefitted from steroid treatment which he had received at another center for 1 year, but we were able to achieve significant improvement with 5 cycles of TPE in one of his exacerbation periods. Another male patient, who was initially treated with IVIG successfully, had to be treated with cyclic TPE due to insurance problems and marked improvement was recorded. One female patient was treated with methylprednisolone for 3 months with no improvement, but prominent recovery was achieved with 6 cycles of TPE. A second female patient was treated for 3 exacerbations of CIDP with TPE due to steroid-related severe blood glucose elevation and unresponsiveness to IVIG in the 6th months of her diagnosis. Additionally, all the patients with CIDP were on azathioprine treatment (2 mg/kg/day).

MG

Twenty three patients with MG were treated with TPE therapy; 9 (F/M: 4/5) received TPE therapy during the preparation stages of thymectomy, and 14 (F/M: 3/11) were treated for either MC's (6) or severe bulbar signs and myasthenia-related respiratory insufficiency (8). The patients with bulbar signs were treated with TPE to quickly stabilize the clinical outlook and to prevent deterioration of their clinical status because of newly started 1 mg/kg prednisone daily. Their Osserman gradings are shown on Table 4. Three patients died in myasthenic group; 1 due to infection in the early post-thymectomy period (day 4); 2 due to MC. Last 2 died in their second crises and, they had needed 10 sessions of TPE for the resolution of their first crises: One of them had congenital lung anomaly, and critical illness neuropathy was observed in the second. In addition, second crises of these patients were more severe and they died in the initial 1-2 sessions of TPE.

Table 2. Demographics, electrophysiological subtypes (for the cases with GBS) and Hughes grading's of the cases with demyelinating polyneuropathy treated with TPE

Number of the patients	AIDP n=35	AMAN n=15	AMSAN n=10	CIDP n=4
F/M	16/19	8/7	3/7	2/2
Mean Age	52.5±13.2	52.6±21.1	58.1±19.2	49.3±17
Grade 0	0	0	0	0
Grade 1	0	0	0	0
Grade 2	0	0	0	1
Grade 3	13	4	3	3
Grade 4	14	7	5	0
Grade 5	8	4	2	0
Grade 6	0	0	0	0

GBS: Guillain Barre Syndrome, TPE: Therapeutic Plasma Exchange, AIDP: Acute Inflammatory Demyelinating Polyneuropathy, AMAN: Acute Motor Axonal Neuropathy, AMSAN, Acute Motor Sensory Axonal Neuropathy, CIDP: Chronic Inflammatory Demyelinating Polyneuropathy

Table 3. Details of the prognoses of cases after the treatment with TPE

Diagnosis	AIDP	AMAN	AMSAN	CIDP	MG	ADEM	Polimyositis	SE	OMS
No of patients	35	15	10	4	23 (9 patients with prethymectomy)	1	1	1	1
Full recovery	12	3	1	1	9	0	0	1	1
Partial covery	18	12	7	3	3	0	1	0	0
Exitus	5	0	2	0	2	1	0	0	0

AIDP: Acute Inflammatory Demyelinating Polyneuropathy, AMAN: Acute Motor Axonal Neuropathy, AMSAN: Acute Motor Sensory Axonal Neuropathy, CIDP: Chronic Inflammatory Demyelinating Polyneuropathy, MG: Myasthenia Gravis, ADEM: Acute Demyelinating Encephalomyelitis, SE: Septic Encephalopathy, OMS: Opsoclonus Myoclonus Syndrome

The targeted neurological deficits of the remaining 12 patients were improved by TPE therapy. Nine had a complete recovery, while the bulbar signs were resolved in 3 patients with MC. None of our myasthenic patients received IVIG treatment.

In addition, 7 patients from the prethymectomy group and 7 patients from MC group were found to be positive for AchR antibodies, and 1 patient in the MC group was positive for anti-titin. The mean duration of the disease was estimated to be 12 months in the MC patients and 18 months in the prethymectomy group.

Polymyositis

A 51-year-old man has complained severe quadriplegia since 6 months. Elevation of creatine kinase and pseudomyotonic discharges on electromyography were shown. Muscle biopsy revealed necrotizing myopathy. We performed 7 sessions of TPE therapy on alternate days, but the patient achieved only slight improvement in a 4-week period. IVIG therapy also proved ineffective. However, the patient made a complete recovery after a 3-month azathioprine therapy with 2.5 mg /kg/day.

Septic Encephalopathy

An 18-year-old girl showing a confused state of mind was examined in the intensive care unit. She had facial cellulitis and it had progressed into septic state. She made a full recovery with 3 cycles of TPE.

OMS

A 49-year-old man with rapid, dysrhythmic and uncoordinated involuntary eye movements and ataxia by 4-day was hospitalized. It is known that most adults with OMS have neoplastic, infectious, metabolic, or idiopathic etiologies. We excluded the possibility of a cancer with appropriate investigations. After the treatment failed with steroids (1 g/day for 5 days), we got full recovery by 5 courses of TPE on alternate day.

ADEM

A 28-year-old man was referred with 2-month duration of severe quadriplegia, he was unresponsive to 7-day high-dose methylprednisolone pulses and also, IVIG (35 gram/day) for 5 days had been failed. He received 7 sessions of TPE on alternate days, and underwent respiratory physiotherapy. Marked improvement was achieved in breathing problems, and the patient was removed from mechanical ventilation. He

was discharged as quadriplegic but, 2 months after he was hospitalized with pneumonia due to aspiration, and he died.

Results

Thirty-one of our 91 patients made a complete recovery, and 49 showed partial improvement. Despite our best efforts, 11 of our patients died.

During the procedures, no patient mortality was related to the TPE therapy. A total of 7 patients; 3 GBS patients, 2 MG patients and 2 CIDP patients experienced adverse events. In our patients, only one of them had tetany due to hypocalcaemia during apheresis, and the procedure was stopped until the calcium levels were restored. Mild and manageable complications such as hypotension and hypocalcaemia were also observed in these 7 patients.

Discussion

It is believed that cross reaction between the antibodies against a microbial agent and the neuronal tissues cause GBS (20). GBS is a major cause of acute neuromuscular paralysis with an annual incidence of 1.3-2 per 100 000 throughout the world (21), and is treated both medically and supportively. Medical treatment methods include IVIG and plasmapheresis, although TPE was introduced as a possible alternative treatment in 1978 (22), and was shown to offer significant benefit by a randomized trial published in 1985 (23). In a study comparing the effects of TPE, IVIG, and a combined regimen of TPE followed by IVIG, no difference was found in terms of clinical outcome between the three groups (24). The Cochrane systematic meta-analysis reported that TPE was the only treatment for GBS found to be superior to supportive treatment (25). Furthermore, TPE was more beneficial when applied within the first 7 days of the disease, although it was still effective when performed within the first month (25). Sixteen (26.7%) of our GBS patients made a complete recovery, 37 (61.7%) had partial recovery improvement with 2-3 degrees on the Hughes scale after TPE at the end of first month, and 7 (11.7%) died. However, no other treatment modalities have been adequately tested in these deceased GBS patients. Yucesan et al. reported that their all 6 patients with GBS improved with TPE treatment and their recovery rate was 100% (7). In our experience, the recovery rate of GBS patients was 88.3%, but our study population was 10 times larger with 60 GBS patients. In the report of Van Doorn et al. related to GBS patients treated with TPE, 3-10% of patients died and 20% were unable to walk after 6 months (26). In our study group, 11.7% of GBS patients deceased; these proportions are similar with the literature.

Overall, we may say that TPE is effective for GBS and improved therapeutic strategies are urgently needed for the unresponsive cases. When we followed TPE with IVIG therapy, significant improvement was seen in the GBS patients, and in particular in those with AMAN. However, a study by the Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome

Table 4. Osserman grading's of the patients with Myasthenia Gravis

Numbers of patients	n=23
F/M	7/16
Mean age (year)	46.1±17.1
Grade 1	5
Grade 2A	2
Grade 2B	1
Grade 3	9
Grade 4	6

Trial Group showed that IVIG and TPE were equally effective in the treatment of GBS, although sequential application did not yield any additional benefit (24). However, in the Miller-Fischer variant of GBS, neither IVIG nor TPE is recommended; owing to the benign nature of the disease, the regimens are not found to be superior to supportive therapy alone (27). We considered scores of 1-3 in the Hughes Scale as showing good prognosis, and higher scores were accepted as poor prognostic factors.

In CIDP, efficacy of TPE was confirmed in two small controlled trials (4,5). The use of TPE is recommended in any patient with CIDP who cannot walk unaided or has a more severe deficit (Class I, Level A) (9), who has compromised respiratory function, whose disease cannot be controlled adequately with two months of corticosteroid therapy with a dosage of 1-1.5 mg/kg every other day (8). Recently, due to a change in policy implemented by the Ministry of Health in Turkey, social security did not cover the IVIG treatment for CIDP patients and thus, those patients who did not respond to corticosteroids had to be treated by regular TPE's for a while. We achieved significant improvement with our 4 CIDP patients using TPE therapy. Although there were not enough patients to determine how beneficial TPE is in the treatment of patients with CIDP, we suggest that it might be an effective treatment choice for CIDP patients who do not respond well to corticosteroids and have unpredictable blood glucose elevation.

MG is a relatively rare disease with a variable prevalence of 5 to 15/100.000 (28,29,30). About 15% to 20% of patients with MG experience MC at some point in the course of their disease. Current statistics still report a mortality rate of 3% to 8% related to MC's, despite newer treatment and intense medical care (30). Infections, including lower and upper respiratory tract infections, are responsible for at least 70% of MCs (31). MC is traditionally defined as an acute respiratory failure due to worsening MG, requiring admission to an intensive care unit (32,33). The basis of the action of plasmapheresis in MC is that it rapidly eliminates the pathological antibodies via mechanical separation or more recently, by immunoadsorption or double filtration techniques (34,35,36). A standard course in myasthenia exacerbation entails 5 to 6 exchanges on alternating days utilizing 2 to 4 L per exchange (34,35). Although there is inadequate data to evaluate the use of plasmapheresis in the treatment of MC or the prethymectomy period in MG, in the last report of the American Academy of Neurology, TPE appears to be just as beneficial as IVIG therapy in patients with MG (9). In addition, a Cochrane review compared the efficacy of IVIG with plasma exchange, other treatments and placebo; it was concluded that IVIG and TPE are equally effective on MC (36). The efficacy of TPE in MG varies from 55 to 100% in various reports (37,38,39). In addition, although it was shown that TPE was optimal when it was performed 4 sessions in one course, the number of sessions can be changed according to the patients' clinical response. For advanced MG, a daily schedule was reported to be more effective than an alternate-day regimen. Although plasma

exchange procedures are mostly done via plasmapheresis, in clinical practice, immunoadsorption can also be used, and may in fact be a superior method in MC cases (40). We treated 18 MCs of 14 patients with TPE, and 16 of these crises were resolved, 2 died in the initial TPE sessions of their second crises. In the report of Yucesan et al., all of the 30 MG patients treated with TPE improved. It is important to note that, one of our deceased myasthenics had congenital lung problems and critical illness neuropathy was observed in the second and, during their first crises, 10 sessions of TPE was needed for considerable improvement. The efficacy of TPE in MG varies from 55% to 100% in various reports and our results were similar to that in the literature. Co-morbid diseases may increase the mortality.

The side effects of plasmapheresis include pneumothorax, hypotension, hypocalcaemia and septicemia, pulmonary embolism, bleeding from the catheter region or obstruction, anemia, thrombocytopenia, and impairment of coagulation parameters (2). We recorded hypotension, hypocalcemia and anemia in our patients. These results were similar to those of the study by Yucesan et al., which was also carried out in Turkey. They also reported a case with septicemia due to venous catheter used for TPE. From these points of view, it can be said that TPE is a safe procedure when performed in experienced units, and may be preferable for controlling symptoms in the early stages of neuroimmunological disorders in which autoimmunity plays a major role in the pathogenesis.

Despite all clinical observations, further prospective research are necessary to establish the role of plasmapheresis in mild AIDP/GBS, long-term management of CIDP, treatment of neuropathy associated with IgM gammopathy, MCs and the prethymectomy period of MG, and in fulminant central nervous system demyelinating diseases.

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