ORIGINAL ARTICLE

UDC: 616.8-08
DOI: https://doi.org/10.2298/VSP241022030V

Factors affecting the effectiveness/productivity of therapeutic plasma exchange in the treatment of immune-mediated neurologic disorders – a pilot study

Faktori koji utiču na efikasnost/produktivnost terapijske izmene plazme u lečenju imunski posredovanih neuroloških poremećaja – pilot studija

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Abstract

Background/Aim. Standard treatment for immune-mediated neurologic disorders (IMNDs) involves the use of immunosuppressive drugs and other therapies. Therapeutic plasma exchange (TPE) is an effective supplementary immunomodulatory approach. Its main goal is to decrease patients' load of pathogenic factors (including autoantibodies) to the levels that will allow clinical improvement. Immunosuppressive medications used simultaneously with TPE reduce the "rebound rise" of autoantibody synthesis. The aim of the study was to evaluate the effectiveness of our own standardized TPE protocol and determine the correlation of TPE treatment outcomes with paraclinical (laboratory) and apheresis parameters/data. **Methods.** The study included 32 patients with myasthenia gravis, Guillain-Barré syndrome or acute polyradiculoneuropathy, and multiple sclerosis. TPEs were carried out using Spectra-Optia® (Terumo-BCT, USA). Properties of our apheresis protocol used for IMND patients were as follows: a) total treatment – five single TPE procedures; b) TPE frequency – every other day; c) removed plasma – one patient's circulating plasma volume (range 2,800–3,100 mL). TPE effectiveness was determined based on recovery of neurologic deficiency and peripheral nerve conduction, positive findings in some paraclinical (laboratory) tests, and apheresis data monitoring. **Results.** Using the described apheresis protocol, a clear positive therapeutic effect was observed in patients treated by TPE procedures with no interruption. TPEs were advantageous in 84.4% of patients (effectiveness rate 89.3%; non-response rate 10.7%), while in 15.6% of cases, treatment was not completed due to patients' severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (followed by coronavirus disease 19 – COVID-19). Patients who completed five single TPEs had evident clinical improvement in terms of disability scale, muscle weakness, or neural conduction deficit. In the follow-up period, no relapses were observed. Significantly reduced values of erythrocyte parameters (especially hematocrit levels) were correlated with higher TPE effectiveness, due to increased plasma/blood cell volume ratio, followed by higher plasma-collection/removal efficacy. Other examined laboratory findings did not show a positive correlation with TPE effectiveness/productivity. Severe adverse events did not occur. There were no relapses in the following 6 months. **Conclusion.** In this study, the reduced levels of erythrocyte parameters (particularly hematocrit levels) were associated with an increased TPE effectiveness. For definitive conclusions, further randomized and larger clinical investigations are needed.

Key words:
blood component removal; guillain-barre syndrome; myasthenia gravis; multiple sclerosis; plasmapheresis; treatment outcome.

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Apstrakt

Uvod/Cilj. Standardno lečenje za imunski posredovane neurološke poremećaje (IPNP) uključuje upotrebu imunosupresivnih lekova i drugih terapija. Terapijska izmena plazme (TIP) je efikasan dopunski imunomodulacijski pristup. Njen osnovni cilj je smanjenje „opterećenja" bolesnika patogenim faktorima (uključujući autoantitela) na nivoe koji će omogućiti kliničko poboljšanje. Imunosupresivni lekovi, korišćeni istovremeno sa TIP, smanjuju „povratni porast" sinteze autoantitela. Cilj rada bio je da se proceni efikasnost protokola naše standardizovane TIP i utvrdi korelacija ishoda TIP tretmana sa parakliničkim (laboratorijskim) i afereznim parametrima/podacima. **Metode.** Istraživanjem su obuhvaćena 32 bolesnika sa miastenijom gravis, sindromom Guillain-Barré ili akutnom poliradikuloneuropatijom i multiplom sklerozom. TIP je izvođena korišćenjem aparata Spectra-Optia® (Terumo-BCT, SAD). Svojstva našeg afereznog protokola primenjenog kod bolesnika sa IPNP bila su: a) sveukupni tretman – pet pojedinačnih TIP procedura; b) učestalost TIP – svaki drugi dan; c) uklonjena plazma – jedan volumen cirkulišuće plazme bolesnika (opseg 2 800–3 100 mL). Efikasnost TIP procenjena je na osnovu oporavka neurološkog deficita i provodljivosti perifernih nerava, pozitivnih nalaza u para-kliničkim (laboratorijskim) testovima i praćenja afereznih parametara. **Rezultati.** Korišćenjem opisanog protokola afereze primećen je jasan pozitivan terapijski efekat kod bolesnika koji su bili podvrgnuti TIP procedurama bez prekida. Procedure TIP bile su korisne kod 84,4% bolesnika (stopa efektivnosti 89,3%; stopa izostanka odgovora 10,7%), dok kod 15,6% slučajeva tretman nije završen zbog infekcije bolesnika koronavirusom 2 izazivačem teškog akutnog respiratornog sindroma (*severe acute respiratory syndrome coronavirus 2* – SARS-CoV-2) (praćene koronavirusnom bolešću 19 – COVID-19). Bolesnici kod kojih je sprovedeno pet pojedinačnih TIP imali su evidentno kliničko poboljšanje u smislu skale invaliditeta, slabosti mišića ili deficita neuronske provodljivosti. U periodu praćenja nisu zabeleženi recidivi. Značajno smanjene vrednosti eritrocitnih parametara (posebno nivoa hematokrita) bili su u korelaciji sa većom efikasnošću TIP, zahvaljujući povišenom odnosu volumena plazme/krvnih ćelija, što je bilo praćeno većom efikasnošću prikupljanja/uklanjanja plazme. Ostali praćeni laboratorijski nalazi nisu pokazali pozitivnu korelaciju sa efikasnošću/produktivnošću TIP. Nije bilo teških neželjenih događaja. Nije bilo realpsa u narednih 6 meseci. **Zaključak.** U ovom istraživanju značajno smanjene vrednosti eritrocitnih parametara (posebno nivoa hematokrita) bili su u korelaciji sa većom efikasnošću TIP. Za definitivne zaključke potrebne su buduće randomizovane i veće kliničke studije.

Ključne reči:
afereza; poliradikuloneuritis; miastenija gravis; multipla skleroza; plazmafereza; lečenje, ishod.

Introduction

Therapeutic plasma exchange (TPE) involves removing a portion of the patient's plasma and replacing it with an appropriate fluid—such as plasma, colloids, or crystalloids—and autologous cells. Beneficial effects of TPE can be obtained by changing the "antigen-to-antibody" ratio, reduction of the concentration of immune complexes, and/or modifying the activities of immuno-inflammatory mediators, and sometimes even through a placebo effect [1–4]. During a single TPE procedure, the volume of removed plasma should be 35–55 mL/kg of the patient's body mass – this practically corresponds to one volume of circulating plasma [1, 5]. The applied TPE protocols vary depending on the type of devices (equipment characteristics) used, the category of the disease, and the patient's general condition. More than 150 disorders have previously been documented in which TPEs have been used, although no uniform therapeutic effects have been achieved [2, 5–9]. Nowadays, that number has been reduced to a few dozen indications where the use of TPEs is really justified and undoubtedly effective. For the currently accepted indications given according to the classification of the American Society for Apheresis (ASFA), specific categories of diseases/disorders and the degree of success of TPE are shown [10]. Immune-mediated neurological disorders (IMNDs) are among them. Therefore, TPE should be considered a treatment option for IMNDs, provided that clearly defined clinical criteria are met. Generally, the use of TPE is associated with improving patients' clinical status – recovery of neurologic deficiencies and reducing disease-related complications [1–4]. Although numerous authors consider that the precise determination of exact parameters of the TPE efficacy in the treatment of IMND is still not completely resolved [4, 10–13].

Finally, it should be emphasized that the use of TPE, in combination with immunosuppressive drugs and other medications, should never represent the last approach or option in the treatment of IMNDs.

The aim of this study was to evaluate the effectiveness of our standardized TPE treatment and the correlation of this protocol with paraclinical (laboratory) findings and specific apheresis parameters/data.

Methods

Study design and population

This clinical investigation was designed as a retrospective unicentric pilot study performed in treating patients with IMND at a single center, the University Clinical Center Kragujevac – UCCK, Serbia. The study was conducted on 32 patients (male to female ratio 1 : 1.29) with IMND or autoimmune neurologic diseases: 9 patients had myasthenia gravis (MG), 12 patients had Guillain-Barré syndrome or acute polyradiculoneuropathy (APRN), and 11 patients had multiple sclerosis (MS). The patients were all hospitalized at the Department of Neurology of UCCK. Investigations were carried out from December 2019 to July 2024. The study was approved by the Ethics Committee of the UCCK (approval No. 01/23-130, from

April 10, 2023). The treatment of the subjects was carried out in accordance with the principles of ethics (Declaration of Helsinki) and good clinical practice. Written consent for inclusion in the research was obtained from each respondent.

Standardized TPE protocol

TPEs were performed by Spectra-Optia® (Terumo-BCT, USA), an automated blood cell separator of the last generation. Simply put, this *ex vivo* system separated whole blood (WB) into components – plasma and blood cells. Then, plasma [standard one circulating or total plasma volume (TPV)] was removed, and the remaining cellular components were resuspended in an equivalent/appropriate replacement fluid (human albumin in normal saline) and re-transfused [11].

Parameters monitored and analyzed during TPE procedures were as follows: 1) quantity of processed blood; 2) volume of removed plasma (one TPV); 3) replacement fluid amount and balance; 4) anticoagulant [acid-citrate-dextrose (ACD) formula B – ACD-B] quantity and proportion; 5) vascular access protection, blood flow rate, and single TPE procedure duration; 6) degree of plasma constituent and/or platelet (Plt) loss. Permanent monitoring of blood pressure, pulse, and cardiac rhythm was indicated only in "medically unstable" patients [10, 12–16].

In general, replacing one volume of circulating plasma removes approximately 45–55% of the pathological substrate present in the patient's plasma. A larger exchanged/removed plasma volume may result in coagulopathy, a higher risk of citrate-related adverse events (AEs), as well as plasma protein or electrolyte dysbalance [1, 13, 16]. For the above reasons, in our study, the quantity of removed plasma by a single TPE was standardized and equal to one TPV. Total blood volume (TBV) was defined by Spectra-Optia® software. The value of TPV was calculated by the following formula: TPV = TBV × (1.0–hematocrit), as previously described [12]. The whole (complete) apheresis treatment for these patients was carried out using a constant five single TPE procedures.

Vascular access was typically obtained across a central venous catheter or, rarely, using antecubital veins. Patients were anticoagulated by ACD-B (United States Pharmacopeia – USP XX; 1.8% citrate concentration). The ACD-B to WB ratio was 1:10. The removed plasma was replaced by 20% human albumin in combination with normal saline (removed vs. replaced fluid ratio = 1.0) [12, 13].

Following each reduction of autoantibody intravascular concentration by TPE, they will migrate from the extravascular into the intravascular space (equilibration phase is around 18 hrs). Furthermore, a decrease of antibody plasma concentration due to TPEs can lead to elevated synthesis, followed by higher antibody levels compared to pre-apheresis grade ("rebound" effect), resulting in inferior TPE effectiveness [1–4]. For this reason, TPE procedures in our study were conducted every second day, based on previous experiences, as well as accepted guidelines of the ASFA [10–13, 17, 18].

The plasma collection/removal efficacy (PCRE) was calculated as a ratio by dividing the quantity of removed plasma by the plasma volume processed in the blood cell separator, using the formula PCRE [%] = $(TPV_{removed} : TPV_{processed}) \times 100$. The Plt loss was determined by the quantity of Plts found in the waste bag expressed as the percentage of the initial Plt number in WB, as explained earlier [12, 15].

Thus, the most important attributes and properties of standardized TPE protocol applied in the treatment of our patients were as follows: 1) the whole apheresis treatment consisted of five TPE procedures; 2) single TPE procedures were performed every other (second) day; 3) by using single TPE procedure, one TPV was removed/replaced and with the whole apheresis treatment, TPV of five patients was removed/replaced.

TPE procedure was conducted in patients with acute exacerbation of disease in MS and MG, or in the first attack in APRN. Before starting the TPE protocol, MS and MG patients were treated with immunosuppressive therapy, but without an adequate positive response. Evaluation of the effectiveness of comprehensive or complete IMND treatment included: 1) monitoring of clinical improvement/status (based on the disability scale, muscle weakness or neural conduction deficit or disease relapse) and 2) laboratory data research: blood cell count analysis, biochemical parameter testing (aspartate transferase, alanine aminotransferase, C-reactive protein – CRP, total protein and albumin, sodium, potassium, calcium levels), as well as hemostatic activity investigation (prothrombin time, activated partial thromboplastin time), fibrinogen, etc. Quantitative analysis was done by comparing initial (before TPE) and final (after TPE) values in the Expanded Disability Status Scale (EDSS) in MS patients, the Osserman score of improvement in MG patients, and the Hughes Motor Scale (HMS) in APRN patients.

AE was considered severe if it was life-threatening or led to irreversible consequences with organ failure.

Statistical analysis

Statistical analysis was conducted using SPSS software. The normality of data distribution was tested using the Shapiro-Wilk test, given that the sample consisted of 32 patients. For analyzing the procedure's success in relation to patient admission laboratory values, the Student's *t*-test for independent samples or the Mann-Whitney *U* test was applied, depending on whether the data followed a normal distribution.

Results

The investigated sample was composed of IMND patients with an average age of 43.09 ± 14.54 years. Gender, blood group, and patient diagnoses (type of IMNDs) are shown in Table 1.

There was clear evidence of beneficial therapeutic effects with positive clinical outcomes in patients treated with a complete apheresis protocol (five single TPEs on 84.4% of

cases from our total IMND patient pool, with an evident therapeutic-benefit rate of 89.3%). In 15.6% of cases, treatment was not completed due to patients' severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (followed by coronavirus disease 19 – COVID-19) and their transport to a COVID center for adequate treatment. In MS patients, there was an improvement ranging from evident regression of symptoms to complete remission (reduction in EDSS) compared to the onset of disease relapse, particularly concerning walking and vision ability. In patients with APRN and MG, improvement was related to the improvement of muscle strength in all affected muscle groups. It was seen that APRN patients had a considerable improvement in neurological deficits. Moreover, peripheral neural conduction was improved in all APRN patients after TPE treatment.

In the group of nine MG patients, seven went through the whole TPE treatment (five procedures). All of them were estimated as grade III (three patients) and IV (four patients) (after Osserman's classification). The improvement was observed in six patients; in four patients, there was improvement from grades III and IV to grades I and II (by Osserman). In two patients, we recorded complete remission. There was no positive therapy response in one patient. Among the 11 MS patients (10 of them went through the whole TPE treatment), positive therapy response was observed in 7, in different degrees. All patients were in acute exacerbation before starting TPE, with an EDSS score between 5 and 6.5. After TPE treatment, nine patients had a positive clinical response with a reduction of 2–3 degrees in EDSS. One patient was without a positive clinical response after TPE. Twelve APNR patients started the TPE procedure within 7 days after the onset of the acute disease attack. Two patients did not finish the whole cycle due to COVID-19. Four patients were in grade III (walking 5 m with support), four patients were in grade IV (relying on a bed or wheelchair), and two patients were in grade V (requiring ventilatory support), according to HMS. In nine patients, a moderate to significant improvement was observed. TPE resulted in significant walking improvement in grade III patients, two grade IV patients improved their walking ability to grade II, and one of them resulted in HMS grade III. One patient who required ventilator support had a positive response to TPE in terms of clinical improvement in spontaneous breathing ability, but with no walking ability. Unfortunately, one patient in the HMS grade V had no positive therapy response (which led to death due to numerous comorbidities).

In the follow-up period (six months after TPE treatment), there were no relapses or significant worsening in terms of an increase in EDSS or decrease in muscle strength in all groups of IMND patients.

Data related to specific apheretic parameters (processed WB, removed plasma and replacement fluid volumes, fluid balance, and TPE duration) for whole apheresis treatments (five single TPE procedures) are shown in Table 2.

Table 1

IMND patients treated by apheresis procedures

Parameters	n (%)
Gender	
female	18 (56.3)
male	14 (43.7)
Blood groups	
O RhD positive	12 (37.5)
A RhD positive	16 (50.00)
B RhD positive	3 (9.38)
O RhD negative	1 (3.13)
Diagnosis	
myasthenia gravis	9 (28.13)
multiple sclerosis	11 (34.38)
APNR	12 (37.5)

IMND – immune-mediated neurologic disease; APNR – acute polyradiculoneuropathy.
Values are given as numbers (percentages).

Table 2

Parameters for single TPE treatments of IMND patients

Procedure parameters	Single TPE procedures				
	1th	2nd	3rd	4th	5th
Removed plasma volume (mL)	2,777 ± 214	2,881 ± 224	2,974 ± 159	3,027 ± 281	2,941 ± 196
Replacement fluid volume (mL)	2,585 ± 196	2,566 ± 321	2,504 ± 323	2,768 ± 124	2,884 ± 288
Processed blood (mL)	6,002 ± 452	5,804 ± 613	5,986 ± 751	5,826 ± 582	5,393 ± 548
ACD-B (mL)	418 ± 32	449 ± 36	437 ± 58	389 ± 49	437 ± 55
Removed vs. replaced fluid ratio	1.05	9.80	1.0	1.04	1.08
Procedure duration (min)	90 ± 18	94 ± 22	89 ± 24	90 ± 16	86 ± 23

TPE – therapeutic plasma exchange; IMND – immune-mediated neurologic disease; ACD-B – anticoagulant solution acid-citrate-dextrose formula B (United States Pharmacopeia – USP XX; 1.8% citrate concentration).
All values are given as mean ± standard deviation, except for fluid ratio, which is shown as a number.

As presented, the value of the processed blood across the device, i.e., the cell separator, ranged from 5,393 ± 548 mL to 6,002 ± 452 mL, with an evident decrease during the last single TPE. The volume of plasma removed/exchanged ranged from 2,777 ± 214 mL to 3,027 ± 281 mL and increased over time with treatments, but with the noted reduction during the fifth single TPE.

The replacement fluid quantity showed a slight decrease in the third single TPE (2,504 ± 323 mL). The fluid balance during a single TPE was constant and amounted to practically 1.0 (range 1.08–9.80). The amount of ACD-B solution used ranged from 389 ± 49 mL to 449 ± 36 mL. The duration of the procedure ranged from 86 ± 23 min to 94 ± 22 min, and this value decreased from the first to the last single TPE. There were no significant differences in the investigated apheresis parameters.

The mean PCRE in this study (using Spectra-Optia®) was high: 83.2 ± 5.2% (range 77–88%), and the Plt loss into the waste bag was minor: 2.1 ± 1.6% on average (range 1.2–4.9%).

Descriptive statistical analysis was done using the minimum and maximum values, as well as mean values ± standard deviation. The impact of the applied procedure on the laboratory values at discharge was analyzed using the Student's *t*-test for paired samples or the Wilcoxon test, depending on whether the data followed a normal distribution. The results of laboratory blood testing at the start and the end of the single TPE procedures are shown in Table 3.

There was a significant decrease in values for RBCs [t = 4.280; df = 21; $p < 0.005$; mean initial value (M1) = 4.56; mean final value (M2) = 3.99], hemoglobin (t = 4.014; df = 21; $p < 0.005$; M1 = 129.91; M2 = 115.04), hematocrit (t = 4.014; df = 21; $p < 0.005$; M1 = 0.40; M2 = 0.35), platelets (t = 2.831; df = 21; $p < 0.05$; M1 = 240.95; M2 = 197.23), total proteins (t = 5.320; df = 21; $p < 0.005$; M1 = 60.36; M2 = 52.05), potassium (t = 2.538; df = 21; $p < 0.05$; M1 = 4.06; M2 = 3.85), and calcium (Z = 3.064; $p < 0.05$; M1 = 2.29; M2 = 2.15), respectively.

As presented, most of the laboratory values decreased. Using the Student's *t*-test for independent samples, we detected a significant difference (initial vs. final values) for red blood cell (RBC) parameters (especially for hematocrit) in patients in whom TPE treatment was realized completely, with subsequent high-quality clinical effects (superior recovery of neurologic deficiency and peripheral nerve conduction). In the treatment of patients in whom apheresis was interrupted (due to COVID-19), the partially realized TPE protocol was unproductive, and laboratory data for them were disqualified and excluded.

The impact of the applied procedure on the laboratory values at discharge was analyzed using the Student's *t*-test for paired samples or the Wilcoxon test, depending on whether the data followed a normal distribution (Table 3).

The influence of laboratory values at patient admission on procedure parameters is shown in Table 4. By applying the correlation and regression method, i.e., by interpreting the values of the Pearson and Spearman correlation coefficients, a significant and moderately strong to strong correlation was established between the creatinine value and the quantity of removed plasma (r = 0.494; $p < 0.05$), replacement fluid substitution (r = 0.517; $p < 0.05$), processed blood (r = 0.493; $p < 0.05$), and procedure duration (r = 0.434; $p < 0.05$).

In this study, we had only a few mild AEs, such as transitory hypotension (two patients), citrate toxicity (one patient) due to hypocalcaemia (corrected promptly by calcium gluconate), and one patient with an allergic reaction (urticaria) that had been solved with antihistaminic and corticosteroid therapy.

Table 3

The influence of the applied procedure on patients' laboratory data at discharge

Parameters	Initial values	Final values	Stat.	*df*	*p*
WBCs, $\times 10^9$/L	8.76 ± 4.25	11.23 ± 5.11	Z = 1.246	-	0.177
RBCs, $\times 10^{12}$/L	4.68 ± 0.97*	3.86 ± 0.65*	t = 4.280	21	< 0.05
Hemoglobin, g/L	131.22 ± 15.50*	114.88 ± 28.45*	t = 4.014	21	< 0.05
Hematocrit, L/L	0.41 ± 0.04*	0.34 ± 0.04*	t = 4.014	21	< 0.05
Platelets, $\times 10^9$/L	236.85 ± 72.62*	207.32 ± 65.70*	t = 2.831	21	< 0.05
Prothrombin time, s	13.17 ± 1.24	14.65 ± 3.7	t = 1.836	21	0.087
aPTT, s	29.65 ± 8,23	30.05 ± 5.82	Z = 0.416	-	0.655
Fibrinogen, g/L	3.15 ± 1.03	2.67 ± 0.88	Z = 1.511	-	0.138
Glucose, mmol/L	5.61 ± 2.16	6.46 ± 2.46	Z = 1.350	-	0.204
Urea, mmol/L	6.04 ± 2.08	5.45 ± 1.87	Z = 1.296	-	0.158
Creatinine, μmol/L	71.91 ± 12.50	64.92 ± 15.54	t = 0.543	21	0.492
ESR, mm/hr	26.73 ± 8.44	34.92 ± 18.82	t = 0.754	21	0.48
Total proteins, g/L	62.15 ± 8.82*	54.06 ± 6.22*	t = 5.320	21	< 0.05
Albumin, g/L	39.89 ± 5.40	32.91 ± 4.21	t = 0.466	21	0.685
AST, U/L	32.2 ± 18.67	31.58 ± 16.19	Z = 0.134	-	0.899
ALT, U/L	50.48 ± 32.06	44.76 ± 34.31	Z = 0.427	-	0.715
Potassium, mmol/L	4.16 ± 0.30*	3.73 ± 0.32*	t = 2.538	21	< 0.05
Sodium, mmol/L	138.45 ± 6.44	117.65 ± 8.29	Z = 0.361	-	0.788
Calcium, mmol/L	2.47 ± 0.23*	1.92 ± 0.31*	Z = 3.064	-	< 0.05
CRP, mg/L	7.82 ± 6.05	14.68 ± 12.54	Z = 2.121	-	1.125

WBCs – white blood cells; RBCs – red blood cells; aPTT – activated partial thromboplastin time; ESR – erythrocyte sedimentation rate; AST – aspartate aminotransferase; ALT – alanine aminotransferase; CRP – C-reactive protein.
Values are given as mean ± standard deviation. *$p < 0.05$.

Table 4

The influence of patients' laboratory data upon admission to the hospital on the parameters of the procedure

Parameters	Removed plasma		Replacement fluid		Processed blood		Procedure duration	
	r/ρ	*p*	*r*/ρ	*p*	*r*/ρ	*p*	*r*/ρ	*p*
WBCs	-0.216	0.335	-0.115	0.612	-0.171	0.447	0.102	0.651
RBCs	0.033	0.885	0.143	0.527	0.099	0.661	0.178	0.427
Hemoglobin	0.087	0.701	0.205	0.359	0.160	0.477	0.303	0.170
Hematocrit	-0.043	0.851	0.108	0.634	0.142	0.530	0.020	0.931
Platelets	0.106	0.640	0.075	0.740	0.060	0.791	0.100	0.658
Prothrombin time	-0.083	0.715	-0.018	0.935	-0.278	0.210	0.078	0.729
aPTT	0.422	0.050	0.301	0.174	0.286	0.197	-0.229	0.306
Fibrinogen	0.017	0.942	0.027	0.904	0.110	0.625	-0.064	0.778
Glucose	0.028	0.899	0.019	0.935	-0.020	0.931	-0.034	0.882
Urea	0.057	0.802	0.156	0.488	0.105	0.641	0.372	0.088
Creatinine	0.494	0.020*	0.517	0.014*	0.493	0.020*	0.434	0.043*
eGFR	0.225	0.315	0.151	0.502	0.279	0.208	0.271	0.223
Total proteins	-0.248	0.266	-0.318	0.149	0.109	0.630	-0.171	0.446
Albumin	0.052	0.820	-0.030	0.894	0.205	0.360	-0.378	0.083
AST	0.088	0.698	0.127	0.573	0.137	0.544	0.043	0.850
ALT	0.082	0.718	-0.021	0.927	-0.097	0.667	0.130	0.565
Potassium	0.098	0.663	0.071	0.753	0.165	0.464	-0.086	0.704
Sodium	0.091	0.688	0.067	0.766	0.010	0.966	-0.056	0.804
Calcium	0.109	0.629	-0.056	0.806	0.221	0.323	-0.155	0.492
CRP	-0.024	0.915	-0.169	0.453	0.180	0.423	-0.016	0.942

eGFR – estimated glomerular filtration rate. For other abbreviations, see Table 3. *$p < 0.05$.

Discussion

As mentioned, the rationale for the use of TPE in the treatment of IMNDs is based on the acceptance of the fact that numerous autoimmune and inflammatory diseases result from immune system dysregulation or malfunctioning, leading to the production of destructive autoantibodies or excessive inflammation [1, 14]. Through the depletion of these pathogenic factors in the bloodstream, TPE interrupts disease development/progress and offers therapeutic benefits. This study aimed to provide an answer as to whether the use of TPE results in an improvement in the overall clinical condition and laboratory parameters of IMND patients. The precise assessment of the advantageous effects of TPE procedures was definitely affected by the incomplete understanding of the pathogenesis of the majority of IMNDs and the lack of simple and well-established laboratory tests to quantify the pathogenic substrate in the patient's blood and/or removed plasma [1, 11, 13].

Although TPE is a relatively invasive procedure compared to intravenous immunoglobulin (IVIG), the rationale for choosing TPE over IVIG can vary depending on the specific clinical setting and the patient's general condition. Various factors may impact this choice in favor of TPE. TPE has a quicker action, which is important in the acute attack of the disease. Moreover, patients with renal or cardiovascular conditions are more appropriate for TPE than for IVIG treatment. Finally, TPE can be an alternative in patients who did not respond adequately to IVIG [19–23].

Thus, Liu et al. [20] reported that TPE treatment showed better short-term clinical effectiveness than IVIG therapy in patients with MG. The results of TPE published by Kumar et al. [21] also confirmed tremendous improvement in patients with MG and in those who experience exacerbations despite treatment with steroids and oral immunosuppressive medications.

In the study by Tombak et al. [24], 19 out of 21 MG patients had improvements with TPE, with 14 in the "complete responses" group (the neurological deficit was improved completely after TPE) and 5 in the "partial responses" group (some response, but the neurological deficit did not disappear completely). Two patients were in the "nonresponse" group (there was no response after the performed TPE treatment), possibly because they were admitted too late after the onset of symptoms. They died shortly after the start of the procedure due to respiratory failure. In this study, the overall response rate of TPE in IMNDs was 81%, with mild to moderate and manageable side effects. Comparable data are presented in a study by Yeh and Chiu [25] for 30 MG patients using the double filtration plasmapheresis method. According to them, the success rate in the TPE treatment of MG patients ranges from 55% to 100%.

A certain number of authors have described the functional impact of TPE on the immune system in patients with different immune-mediated disorders, such as lupus, MS, acute disseminated encephalomyelitis, or APRN. It causes a modification of lymphocyte proliferation capacities and modulation of antibody production [26–28]. Furthermore, it induces the reconstitution of certain subpopulations of lymphocytes (regulatory T cells) [28, 29] and the improvement of the functional capacities of monocytes and macrophages [30]. In brief, TPE is an extracorporeal blood purification technique allowing the removal of pathogenic macromolecules from the blood. It has been successfully used for several decades in managing IMNDs.

Together, these therapeutic approaches form part of a comprehensive system for treating severe IMNDs, intending to reduce disease activity and enhance patient clinical outcomes.

Thanks to the increased number of studies, indications are based not only on assumptions but also on facts.

Our pilot study confirms the positive clinical effects (recovery of neurologic deficiency and peripheral nerve conduction) of the TPE treatment used in IMND patients. Namely, favorable effects of treatment were manifested by the return of weakened reflexes, normalization of motor functions, disappearance of speech, and swallowing dysfunction, with positive findings in certain paraclinical (laboratory) tests. Overall, 89.3% of patients with positive therapy responses after TPE had different degrees of improvement, which is comparable with results revealed by several previous studies [31, 32].

According to our study, TPE is a potent and well-tolerated method for treating IMNDs. Beneficial therapeutic effects were observed in patients undergoing five single TPE procedures (without interruption). TPEs were completed in 84.4% of patients (the therapeutic-benefit rate was 89.3%). Superior treatment efficacy in our study was observed in patients with significantly inferior RBC parameters (primarily hematocrit levels) as a result of an elevated ratio of the plasma vs. blood cell volume and higher PCRE values (up to 88%). It is comparable to our earlier results and data from the literature for PCRE [12, 15]. With increased creatinine values on admission, the values of all considered procedure parameters rose. Considering the normal WBC values during TPE, we can assume that this was a transient increase in CRP values due to the placement of a central venous catheter or urinary catheter, which can cause a slight increase in CRP. Therefore, we believe these values are not directly associated with the TPE procedure.

The timing of the TPE is also important for some IMNDs – the TPE treatment started as early as possible (within 7 days after the onset of the disease) and was followed by antibody reduction and superior clinical improvement in APRN patients [11]. The importance of optimized apheresis timing was determined as a significant factor of the TPE efficacy in our earlier studies and also in data from the literature [9–11, 13]. In the therapy of a certain number of patients (15.6%), TPE treatment was not completed, as mentioned, due to patients' SARS-CoV-2 infection, followed by COVID-19, and their transport to a COVID center for proper treatment.

Despite the benefits of TPE, several studies have evaluated some potential AEs and complications, including those related to replacement fluids or anticoagulant solutions, cardiovascular vulnerability, vascular access, normal plasma constituents, or Plt reduction/loss, etc. [11, 15–18]. Finally, the use of TPE procedures is not possible without updated medical education of personnel (apheresis team members) and experience related to work with extracorporeal circulation [11, 14].

In this study, we observed only a small number of mild AEs, such as transitory hypotension in two patients, citrate toxicity in one patient (with mild tingling in the legs as a result of hypocalcemia), and mild to moderate urticaria in one patient. There were no serious AEs related to TPE treatment during this study.

Conclusion

The effectiveness of immunomodulatory drugs plus TPE therapy varies and, to some degree, depends on the type of immune-mediated neurological disorders and the patient's condition. Reduced levels of red blood cell parameters (particularly hematocrit levels) were associated with an increased TPE effectiveness, primarily due to an increased plasma-to-blood cell volume ratio, followed by superior plasma collection/removal efficacy values. Other paraclinical and laboratory findings did not correlate positively with TPE efficacy. The patient tolerated the TPE treatment well without severe adverse events. No relapses were found within a 6-month follow-up period. For definitive conclusions, further randomized, controlled, and larger clinical trials are needed.

Conflict of interest

The authors declare no conflict of interest.

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Received on October 22, 2024
Revised on December 16, 2024
Revised on January 24, 2025
Accepted on January 29, 2025
Online First May 2025