

Outcomes of therapeutic plasma exchange; one year single center experience

Abstract

Background: Outcome of therapeutic plasma exchange (TPE) in treating different immunological and non-immunological diseases in our unit is not clear. We aimed to study the outcome TPE in different diseases categories during one-year period.

Methods: Prospective cross sectional study of patients referred for TPE during one year period. Demographic, clinical data, number of sessions, volume of plasma exchanged, patient tolerance and complications during or post to the procedure were systematically recorded and descriptive statistics applied for analysis.

Results: 276 TPE procedures were recorded for 57 patients during the study period. Twenty five patients had GBS, 16 patients had MG, 7 patients had ITP, 3 patients had SLE, 2 patients had cryoglobulinemia, 2 patients had CIPD, 1 patient presented with hyperviscosity syndrome and neuromyelitis optica. Forty nine patients experienced improvement while 2 patients showed no improvement and 6 patients died throughout the treatment cycles. In patients with GBS, 23 patients showed full improvement while 2 patients died ($p < 0.001$). In patients with MG, 13 patients showed improvement while 3 patients died ($p < 0.001$). The patients with neuromyelitis optica, cryoglobulinemia, hyperviscosity syndrome and SLE showed complete improvement ($p < 0.223$, $p = 0.049$, 0.223 and 0.011 respectively). Six patients with ITP experienced improvement while 1 patient died ($p < 0.001$). There was no response in patients with CIPD ($p < 0.049$). Sixty four complications were reported out of that 32 procedures reported hypotension, 22 procedures reported allergic reactions and post-procedural fever reported in 10 procedures.

Conclusion: Therapeutic plasma exchange is safe and effective adjuvant treatment for several diseases especially autoimmune diseases with less complications events.

Keywords: outcomes, therapeutic plasma exchange, autoimmune disorder

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Abbreviations: TPE, therapeutic plasma exchange; MPS, membrane plasma separation; EPV, estimated plasma volume; GBS, guillain-barre syndrome; CIPD, chronic inflammatory demyelinating polyneuropathy; MG, myasthenia gravis; ASFA, american society of apheresis; EMG, electromyography; TTP, thrombotic thrombocytopenic purpura

Introduction

Therapeutic plasma exchange (TPE) is an extracorporeal blood purification method that remove high-molecular weight plasma proteins from a blood volume passing through a membrane plasma separation (MPS) or plasma filter.^{1,2} It removes circulating antibodies, immune complexes and toxins from the blood. The patient venous blood is drawn into the extracorporeal circuit and plasma is separated from the cellular component, which is retained. The patient plasma is discarded and replaced with fresh frozen plasma.³ When the replacement is other than plasma, then it is called apheresis. ~1.5 to 2 times patient's plasma volume is exchanged during the procedure. It was introduced to the first time in 1962 for treatment of waldenstrom's macroglobulinemia.⁴ And since then, there has been profound advancement in the technique with advances in transfusion medicine and successful therapeutic using in various immunologically mediated diseases in the last few decades. Initially it had been restricted to

blood bank centers but currently; it is increasingly performed in intensive care units because of the extension of indications and utilization of hemodiafiltration machines that ensure better efficiency and simplicity.^{2,5} The complications are procedure as well as access related. The large extracorporeal blood volume and blood loss in the circuit carry the risk of hypotension and anemia, respectively. Also, blood product transfusion during plasma exchange exposes patients to the additional risks of viral infection and transfusion-related acute lung injury. Furthermore, Catheter-related complications are also reported and include access thrombosis and infection.⁶ Due to paucity of data about the outcome of TPE in our unit, we designed this cross sectional study aiming to assess its outcome in treating different immunological and non-immunological disorders during one year period.

Subject and methods

This study was conducted at Nephrology Unit, Internal medicine Department Zagazig University Hospitals, Egypt. It was designed to be a prospective observational cross sectional study.

Inclusion criteria

In the course of one year (2015), all patients in who therapeutic plasma exchange was indicated to improve the course of the disease and/or their quality of life were included in this study.

Exclusion criteria

- i. Patients indicated for plasma exchange but not fit for the procedure due to presence of complications e.g. severe hypotension, severe anemia.
- ii. Patients not compliant to treatment.

Ethical clearance

Written informed consents was obtained from patients participating in this study after informing them about the steps of study, the complications and the capability to withdraw at any time after approval of Ethical Committee in Faculty of Medicine, Zagazig University.

Treatment course

Patient is admitted to the unit after being diagnosed as he is a candidate for therapeutic plasma exchange. Upon Admission, Re-evaluation with full history taken and full clinical examination was done and recorded. TPE was performed 2 to 4 times weekly using a single volume plasma exchange with intermittent cell separator (Fresenius AS 104 blood cell separator Dialysis machine with NPL-1 filter). Patient's blood counts, electrolytes, serum proteins, coagulation profile, and vitals were checked, and appropriate steps were taken to correct the deranged parameters. The consent for the procedure was taken from the patient or the patient's relatives before the procedure. The procedure was done through femoral or central line access using 12 French double lumen dialysis catheters. Anticoagulation with 25000 units of heparin was attached to the lines according to instructions. The volume of plasma to be replaced was calculated according to patient's weight, types of disease and decided numbers of sessions. Replacement of plasma removed during the session was done with isotonic sterile saline, to makeup one-half of the volume and with 4% purified human albumin and fresh frozen plasma to complete it. The amount of plasma to be exchanged must be determined in relation to the estimated plasma volume (EPV). A simple means of estimating the EPV can be calculated from the patient's weight and hematocrit using the formula; $EPV = (0.65 \times wt [kg]) \times (1 - Hct)$.⁷ A careful monitoring of hemodynamic parameters was done and complications during or following TPE were rapidly recognized and reverted by rationale interventions of medical staff that assisted the procedure. Indications for TPE, number of cycles and sessions, duration of each session, volume of plasma exchanged and patient tolerance to the procedure were systematically recorded. All patients received additional medical therapy including immunosuppressant according to disease specific indication in collaboration with the original referring departments. Protocols for TPE were different and depend on the disease and its severity.

Statistical analysis

Data collected throughout history, basic clinical examination and laboratory investigations. The outcomes measured, coded, entered and analyzed using Microsoft excels software. Then data imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. Continuous data are expressed as the Mean \pm SD & median (range), and the categorical data are expressed as a number (percentage). According to the type of data, the following tests were used to test differences for significance. Continuous variables were checked for normality by using Shapiro-Wilk test. Independent samples Student's t-test test was used to compare two groups of normally distributed data. Differences between means (quantitative variables) were analyzed using ANOVA test. Paired t test was used

to compare two dependent groups of normally distributed data. Wilcoxon signed ranks were used to compare two dependent groups of non-normally distributed data. Categorical data were compared using the Chi-square (χ^2) test or Fisher's exact test when appropriate. All tests were two tailed. $p < 0.05$ was considered statistically significant (S), $p < 0.001$ was considered highly statistically significant (HS), and $p > 0.05$ was considered non statistically significant (NS).

Results

Our unit records showed an average of 276 procedures during the year 2015. Most therapeutic procedures were performed on patients referred from department of neurology and mostly were referred for Guillain-Barre syndrome (GBS), Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) and myasthenia gravis (MG). The clinical outcome of patient underwent TPE was assessed at the end of scheduled TPE session, at 3 months, and at 6 month after last procedure and categorized as improved, no change or worsen.

Patients clinical and demographic characteristics

A total of 57 patient admitted to our unit during the study period were included to this study. They were referred from Neurology, ICU, Nephrology and Cardio-thoracic surgery department. The average age of patients was 36 years with a range from 4-77 years. Twenty eight (49.1%) patients were male and 29 (50.9%) patients were female.

Classifications of patients according to the underlying diseases (Table I)

Table I Demographic and diseases characteristics

MG	16 (28.1%)	2 (7.1%)	14 (48.3%)	
GBS	25 (43.9%)	17 (60.7%)	8 (27.6%)	
CIPD	2 (3.5%)	2 (7.1%)	0 (0%)	21.28
Neuromyelitis optics	1 (1.8%)	0 (0.0%)	1 (3.4%)	
Cryoglobulinemia	2 (3.5%)	2 (7.1%)	0 (0%)	
Hyperviscosity syndrome	1 (1.8%)	0 (0.0%)	1 (3.4%)	0.006
SLE	3 (5.3%)	0 (0.0%)	3 (10.3%)	
ITP	7 (12.3%)	4 (14.3%)	3 (10.3%)	

Patients admitted for TPE were classified according to the underlying disease into the following:

- I. Patients with GBS: Twenty five patients were presented by GBS. Eight patients were female and the remaining 17 patients were male. The protocol of American society of Apheresis (ASFA) for GBS was followed "200-250 ml/kg bodyweight over 10-14 days divided by 5 procedures", 2 patients died during the treatment course, 2 patients needed more than 5 TPE procedures. Every patient has pre and post TPE electromyography (EMG) study. Nerve conduction velocity, latency period, wave amplitude and f-wave were the items of concern in assessment of improvement.
- II. Patients with MG: There were 16 patients presented by MG of these 13 patients were female and 3 patients were male. Seven patients presented for pre-operative (pre-thymectomy) TPE procedures. One patient presented by postoperative MG crisis and 9 patients presented for management of MG crisis. Three patients died during the course of treatment; two of them were female with secondary MG as paraneoplastic manifestation.

- III. Patient with neuromyelitis optica: One female patient was presented by neuromyelitis optica with positive antibodies with no response to steroids and immunosuppressant.
- IV. Patients with SLE: Three female patients diagnosed with SLE presented with anemia, thrombotic thrombocytopenic purpura and lupus nephritis were subjected to TPE treatment.
- V. Patients with cryoglobulinemia: Two male patients with cryoglobulinemia with increased plasma viscosity were subjected to TPE. No deaths recorded among those patients during the course of treatment.
- VI. Patients with Chronic Inflammatory Demyelinating Polyneuropathy (CIDP): Two male patients with their age above 65 years old were presented with CIDP and scheduled for 5 TPE procedures. Both had had EMG study before and after TPE.
- VII. Patients with Thrombotic Thrombocytopenic Purpura (TTP): Seven patients presented as TTP patients with low platelets. ASFA protocol was applied to perform TPE procedures until the achievement of 150000 platelets counts and decrease of LDH level to at least twice normal.
- VIII. Patients with hyperviscosity syndrome: one female patient presented with hyperviscosity syndrome and planned for TPE till the correction of plasma viscosity readings and subsiding her symptoms.

Numbers of TPE sessions in the presenting diseases

The required numbers of TPE sessions were varied according to the disease type. Patients with Neuromyelitis optica had the highest

numbers of TPE sessions with mean of 10 sessions followed by patients with SLE by mean numbers of 8±4.8 sessions. While patients with ITP had an average numbers of 7.3±3.2 sessions. Patients with hyperviscosity syndrome had the lowest numbers of TPE sessions by mean of only 1 sessions followed by patients with MG by means numbers of 3.3±3.1 sessions. While patients with cryoglobulinemia had means number of 4±4.1 TPE sessions followed by patients with CIPD by means numbers of 5±0 sessions.

Outcome of the studied subjects

Out of total 57 patients underwent therapeutic plasma exchange, 49 patients (86%) experienced improvement while only 2 (3.5%) patients showed no improvement. There were 6 patients (10.5 %) died throughout the treatment cycles. In patients with MG, 13 out of 16 patients (81.25%) showed improvement while 3 patients (18.75%) died during the course of TPE (p<0.001). In patients with GBS, 23 out of 25 patients (92%) showed full improvement while only 2 patients (8 %) died during the treatment course (p<0.001). In patients with CIDP, there was no improvement through the treatment course (p<0.049). The only one patient with neuromyelitis optica showed complete recovery of the disease (p<0.223). Similarly, all patients with cryoglobulinemia (2 patients), hyperviscosity syndrome (1 patient) and patients with SLE (3 patients) showed complete clinical and laboratory improvement (p=0.049, 0.223 and 0.011 respectively). 6 of 7 patients with ITP experienced improvement (85.71%) and the remaining 1 patient died during his treatment course (p0.001). See Table 2. Patients with younger age group showed highly significant good response to treatment course in comparison to patients with older age group. (p 0.012). See Table 3.

Table 2 Outcomes in the studied patients

	All patients (No.57)	Patients with improvement (No.49)	Patients without improvement (No.2)	Expired patients		
				(No.6)	×2	P
MG	16	13 (81.25%)	0 (0%)	3(3%)	26.06	<0.001
GBS	25	23(92%)	0 (0%)	2(2%)	58.44	<0.001
CIPD	2	0(0%)	2(100%)	0(0%)	6	0.049
Neuromyelitis optica	1	1(100%)	0 (0%)	0(0%)	3	0.223
Cryoglobulinemia	2	2 (100%)	0 (0%)	0(0%)	0.6	0.049
Hyperviscosity	1	1 (100%)	0 (0%)	0(0%)	3	0.223
SLE	3	3 (100%)	0 (0%)	0(0%)	9	0.011
ITTP	7	6(85.71%)	0(0%)	1(14.28%)	13.29	<0.001

Table 3 Outcomes and Age

Age	Improvement (No. 49)	No-Improvement (No.2)	Death (No.6)	F	p
Mean±SD	34.4±16	64±1.4	47.3±15.7	4.809	0.012
Range	4-77 years	63-65 years	24-64 years		

Replacement fluids used during the procedure

Through total of 276 procedures, Albumin/Saline replacement fluids were used in 225 procedures (81.5%). While in the remaining 51 procedures (15.5%), fresh frozen plasma was used as a replacement fluid.

Complications during the procedure

During the total of 276 procedures, total of 64 complications

were reported. 32 procedures reported occurrence of hypertensive attacks, 15 procedures reported allergic reactions (either due to fresh frozen plasma or albumin) while urticarial reaction was reported in 7 procedures and post-procedural fever was reported in 10 procedures. Regarding the types of fluid used for replacement therapy, we have found that using normal saline/albumin replacement therapy had more frequent complications in comparison to using fresh frozen plasma. See Table 4.

Table 4 Complications and their relation to types of replacement fluid

Type of complications	Number of complications -64	FFP	Saline/human albumin
Hypotension	32 (50.%)	6 (9.3%)	26 (40.6%)
Allergic reaction	15 (23.4%)	4 (6.25%)	11 (17.18%)
Urticarial only	7 (10.9%)	2 (3.12%)	5 (7.8%)
Fever post procedure	10 (15.6%)	5 (7.8%)	5 (7.8%)

Discussion

TPE is an effective therapeutic option for treating serious manifestations of systemic autoimmune diseases, such as myasthenia gravis, Guillain-Barre syndrome, lupus, and idiopathic thrombocytopenic purpura and a valid option for those patients with diseases refractory to conventional treatments.⁸ When plasma is removed, it takes with it the antibodies that have been developed against self-tissue in an attempt to reduce the attack on the patient's own body. Plasmapheresis carries with it the same risks as any extracorporeal procedure but is otherwise generally safe. The primary objective of the study is to assess the outcomes of plasmapheresis unit, Zagazig, University, Egypt during one-year period, so as to evaluate the efficacy and safety of TPE in treating certain conditions.

57 patients with different conditions that needed supportive treatment with therapeutic plasma exchange were included in this study. They included 8 different disease identities. Patients with GB syndrome had the highest number of patients (25 patients by incidence of 43.9% of all patients). The majority of the patients showed clinical improvement (92% of patients) after 5 procedures. Improvement was documented by nerve conduction studies as investigatory method of assessment and by clinically by motor and sensory examination of the patients. There were only 2 deaths during their course of treatment, one of them died by intracerebral hemorrhage due to severe hypertension and the other one was died due to hospital acquired pneumonia in immunocompromised patient. The duration needed by the patients to walk without assistance was greatly reduced in our patients mostly due to early presentation to our unit, which was mostly within the first week. One patient with history of diabetes mellitus, and other patient presented with severe form required intubation showed delay in improvement to walk without assessment yet both of them showed complete recovery. No patient showed relapses within the 6 months follow up period. 3 patients included in our study were children with age ranged from 8-14 years old and all of them showed improvement after the 3rd procedure and only one patient needed to complete the 5-procedure course.

Hughes et al.⁹ stated improvement rate at (97%) while NobuhiroYukiet al.¹⁰ Stated improvement rate at (87%). Meena Sidhu

et al.¹¹ Raphaël¹² and Van Doorn¹³ are in agreement with our results and encouraging the initiation of treatment within the first week and notable decrease in recovery time and early achievement of clinical milestones. In patients with myasthenia gravis, which included 16 patients, the improvement rate was 81.25%. This was in agreement with studies done by Nagayasu et al.¹⁴ who stated remission rate at (79%), and Sarkar et al.¹⁵ who stated remission rate of 80%. The difference at improvement rate could be attributed to the total number of cases studied. And here we quote: "All patients had immediate benefits of each TPE cycle good acceptance of procedure was observed in 78.3% of patients and concluded: TPE may be considered as one of the treatment options especially in developing countries like ours as it is relatively less costly but as effective for myasthenic crisis as other modalities.¹¹

Ralf et al.¹⁶ and Linda et al.¹⁷ are in agreement with our results and stated that all patients had immediate benefits of TPE with good tolerance and relatively less costly but effective than other modalities. While Skeie et al.¹⁸ stated that their study failed to show pronounced difference between TPE and IVIG, yet it may be due to relative small sample size of their study. In our single case of neuromyelitis optica, there was total clinical improvement. The patient was non-responsive to steroids and presented late and she needed a longer duration of TPE procedures, yet improvement was notable after the 3rd procedures, but complete improvement needed a total of 10 procedures. In agreement with our results, Watanabe et al.¹⁹ stated improvement rate at (50%) with paid special attention to the fact that the patient's condition was steroid resistant. While Wang et al.²⁰ stated improvement rate at (88.8%) of studied subjects.

In our study, there were 2 patients with CIDP who showed no improvement during their treatment course with TPE. Kaynar et al.²¹ agreed with our results that CIDP patient included in their study showed no response to TPE. While Meena Sidhu et al.¹¹ and Kaya et al.²² both reported that patients with CIDP included in their studies showed total improvement after using TPE. The difference in the result between our study and these other studies may be due to the severity of disease in our patients. The 2 patients showed affection of lumbar vertebrae and intervertebral discs in between and one patient had uncontrolled diabetic with severe form of poly neuro-radicalopathy.

In our single 42 years old female patient with hyperviscosity syndrome, there was a good response to the single TPE procedure and improvement was confirmed by hematology department staff. This is in agreement with other study done by Zarkovic et al.²³ and Marvin Stone²⁴ Both agree with our results and in addition, Zarkovic et al.²⁴ stated that single plasmapheresis procedures with one plasma volume replacement showed a dramatic improvement in such patients. Regarding the two cryoglobulinemia cases, they showed immediate improvement, one patient was HCV+ve. However, Rockx MA²⁵ and Clark WF²⁵ in their Meta analysis study; they reviewed 11 studies in using Plasma exchange for treating cryoglobulinemia and concluded that these studies weakly support the use of plasma exchange largely on a mechanistic basis.

In patients with ITP, there were initial decline in total platelet counts after the first Procedure and slight increment of serum LDH above the initial level. Within the 2nd and 3rd Days of treatment, platelet counts start to rise and serum LDH level begins to decline with improvement rate by 87.5 %. Altuntas et al.²⁶ reported success rates at (77%). Also, Korkmaz et al.²⁷ reported cure rate at (85-87%) in their study. Yet Korkmaz et al.²⁷ and Marn Pernat et al.²⁸, emphasis that treatment must be started as soon as possible to obtain a good clinical response. Regarding the 3 female patients with SLE, they showed improvement rate at (100%) after an adjuvant TPE procedures together with immunosuppressant medications. It was indicated because of SLE flaring in the form of class 3-lupus nephritis (biopsy proven) and thrombotic thrombocytopenic purpura. The average of TPE was 8 procedures and the 3 Patient showed no relapses during the 6 months follow up. Guillermo et al.⁸ Reporting (100%) cure rate within their 31 patients with refractory autoimmune diseases and concluded that TPE is an effective modality for treatment of SLE exacerbation with relative good clinical outcome. Morgan et al.²⁹ concluded that TPE is a good modality in treatment of severe lupus nephritis that fails to respond to conventional therapy.

Improvement noticed in cases included in the study may be due to successful removal of auto antibodies present in patient's circulatory system. Patients undergoing plasmapheresis manifested less effects of immune complex deposition in combination with immune therapy either corticosteroid and/or cytotoxic drugs which aim to reduce inflammatory process and inhibit immune system activity. In other study done by Bambauer et al.³⁰ they concluded that using of cyclosporine and TPE to control symptomatic disease in patients with flares resulted in quicker resolution of symptoms and decreased doses of cytotoxic drugs. Also we can quote that early presentation, high index of suspicion among treating physicians and early introduction of TPE along with dialysis and appropriate immunosuppression may be promising in effectively decreasing morbidity and improving outcome in patients with immunological renal disease.³¹ Regarding the complications of the procedure, we conclude that most complication reported were hypotension, nausea and allergic reaction either due to the fresh frozen plasma or human albumin all of which never seriously endangered the patients' life, or affected patient's mortality. Shemin D et al.³² agreed with our results keeping in mind that the study conducted with total number of TPE procedure of 1727, and relative similar rates of complication.

Conclusion

Therapeutic plasma exchange is almost safe and effective adjuvant treatment for several diseases especially autoimmune diseases. It is

very effective modality of treatment in patients with neurological disorders like MG, GB and neuromyelitis optica. Also it is an effective treatment in hematological disorders like ITP and hyperviscosity syndrome. Also it was used effectively in patients with severe lupus nephritis (in conjunctive with immunosuppressant medications) and in patients with cryoglobulinemia. The complications of TPE were rare and can be easily managed throughout the procedure cycles. Further extended studies with large numbers of patients are highly advised to confirm safety and effectiveness of TPE on treatment of different specific disorders.

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None.

Conflicts of interest

The author declares there is no conflict of interest.

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