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Therapeutic Plasma Exchange among Myasthenia Gravis Patients Attended at Referral Neurosciences Hospital in Bangladesh: A Single Centre Experience

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Abstract

Background: Therapeutic Plasma Exchange (TPE) is an effective therapeutic procedure for treating Myasthenia Gravis (MG). **Objectives:** The aim of study was to evaluate demographics, indications, adverse reactions and outcome of therapeutic plasma exchange in myasthenia gravis patients. **Methodology:** This prospective observational study was conducted in the Department of Transfusion Medicine at National Institute of Neurosciences and Hospital (NINS&H), Dhaka, Bangladesh from August 2014 to June 2022. All patients with Myasthenia Gravis who received therapeutic plasma exchange as a treatment during hospitalization were included in this study. Data were systematically recorded and these were variables of demographics, clinical indications, numbers of sessions, volume of exchanged plasma, clinical responses and complications during or after the procedure. **Results:** A total number of 72 patients had undergone 275 sessions of therapeutic plasma exchange among which 52(72.2%) cases were male and the mean age was 39.5±13.11 years. For each patient the number of therapeutic plasma exchange session and volume of plasma exchange were 3.69±1.016 (Range 2 to 7) and 2266.7±361.53 ml (Range 1400 to 3100) respectively. Anti-acetylcholine receptor antibody (Anti-ACR Ab) was positive in 44(61.1%) cases. Myasthenic crisis (n=45, 62.5%) was the most common indication of therapeutic plasma exchange followed by preoperative preparation for thymectomy (n=16, 22.2%) and worsening of myasthenic weakness (n=11, 15.3%). In 275 sessions of therapeutic plasma exchange, overall incidence of adverse reaction was in 26(9.45%) cases. Mild allergy (n=9, 3.27%) and pyrexia (n=5, 1.82%) were most commonly reported. Hypotension was reported in 4(1.46%) cases. Reactions were mild and were reversed by bed side managements. Response to treatment was observed in 80.5% (n=58) patients. 2(2.8%) patients of Myasthenia Gravis died; but death was unrelated to therapeutic plasma exchange. **Conclusion:** Therapeutic plasma exchange is rapidly effective therapy for myasthenic crisis, progressive myasthenia gravis and prior to thymectomy operation and it has adequate safety profile.*[Journal of National Institute of Neurosciences Bangladesh, January 2023;9(1):16-23]*

Keywords: Therapeutic plasma exchange; myasthenia gravis; myasthenic crisis

Introduction

Myasthenia gravis (MG) is a neuromuscular disorder characterized by weakness and fatigability of skeletal muscles. The underlying defect is decrease in the number of available acetylcholine receptors (AChR) at neuromuscular junctions due to an antibody-mediated autoimmune attack[1]. The annual incidence of myasthenia gravis is approximately 30 new cases per million[2]. Approximately 15.0% to 20.0% of these patients will develop myasthenia gravis crisis (MGC)[2].

Myasthenia gravis is commonly (~85%) caused by antibodies that target acetylcholine receptor (AChR). Other antibodies target muscle-specific tyrosine-kinase receptor (~5% of MG) and low-density lipoprotein receptor-related protein 4 (~3% of MG)[3-5]. Myasthenia gravis without any detectable antibodies referred to as

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seronegative Myasthenia gravis (~7% of MG).

Patients often present with diplopia and/or ptosis, with symmetric muscle weakness affecting the bulbar, limb, and axial muscles. Muscle weakness is usually proximal and variable in intensity[6]. In some cases, these patients require emergency ventilation due to weakening of breathing muscles leading to a condition called myasthenic crisis (MGC)[6]. The disease is clinically classified into two main categories like ocular myasthenia gravis, affecting ocular muscles and generalized myasthenia gravis, not limited to ocular muscles. Generalized myasthenia gravis accounts for about 80.0% of all myasthenia gravis[7].

The diagnosis of myasthenia gravis is based on results of clinical examinations as well as tests such as edrophonium test, antibody tests, electrodiagnostic tests like repetitive nerve stimulation test, single fibre EMG, diagnostic imaging and pulmonary function test[6]. Acute or severe patients generally receive short term disease stabilizing therapies such as therapeutic plasma exchange (TPE) and intravenous immunoglobulin (IVIG)[8,9]. Management of acutely ill patients is important, because it can lead to respiratory failure and death[9].

Therapeutic plasma exchange (TPE) is an extracorporeal blood purification technique that reduces the amount of circulating autoantibodies, alloantibodies, immune complexes and monoclonal proteins by centrifugation and replacement of patient's plasma[10]. The fluid volume removed must be replaced to avoid volume depletion. Albumin, saline, or combination of the albumin and saline are used as a substitution fluid[11]. Therapeutic plasma exchange was first employed in 1952 in patients with multiple myeloma to control hyperviscosity. By the 1970s TPE had evolved as a treatment modality in a number of neurological disorders in which autoimmunity plays a major role including myasthenia gravis, Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP) [12,13].

Therapeutic plasma exchange removes antibodies to acetylcholine receptor, leading to short-term improvement in muscular strength and motor performance by improving neuromuscular transmission[14]. Although studies showed equal efficacy of IVIG and therapeutic plasma exchange in MGC, an expert consensus suggests that plasma exchange is more effective and works more quickly in the treatment of myasthenic crisis[15-16].

As per the consensus of American Society for Apheresis, Therapeutic plasma exchange is a well-established treatment modality for myasthenic crisis and myasthenia exacerbation[17-19]. Therapeutic plasma exchange is also considered before thymectomy in myasthenia gravis patients[20]. Many myasthenia gravis patients require chronic long-term maintenance therapeutic plasma exchange in conjunction with medical management[20]. In Bangladesh, there is no large scale study regarding Therapeutic plasma exchange in MG patients. The aim of this study was to evaluate demographics, indications, adverse reactions and outcome of therapeutic plasma exchange in myasthenia gravis patients.

Methodology

Study Settings and Population: This study was conducted in the Department of Transfusion Medicine at National Institute of Neurosciences and Hospital (NINS&H), Dhaka, Bangladesh from August 2014 to June 2022. All patients with myasthenia gravis who received therapeutic plasma exchange as a treatment during hospitalization were included in this study.

Study Procedure: At the beginning following parameters were checked and appropriate steps were taken to correct them: CBC, SGPT, serum creatinine, serum calcium, serum magnesium, serum total protein, serum albumin, serum electrolytes, RBS, ECG, Blood Grouping and Screening and vital parameters. After each session necessary investigations were done like CBC, serum Calcium, serum Albumin, serum total Protein. All the available data were systematically recorded and these were variables of demographics, clinical indications, numbers of sessions, volume of exchanged plasma, clinical response and complications during or after the procedure. Patients were divided into defined MG subgroups for analysis. All patients included in the analysis were assessed using in the Myasthenia Gravis Foundation of America (MGFA) clinical classification system, briefly summarized here; Class I: any ocular muscle weakness but all other muscle strength is normal, Class II: mild weakness affecting non ocular muscles, Class III: moderate non ocular muscle weakness, Class IV: severe weakness affecting non ocular muscles, Class V: Intubation ± mechanical ventilation. Classes II to IV may be sub divided further, with indicating that weakness predominantly affects limb and /or axial muscles and indicating that weakness predominantly affects oropharyngeal and/or respiratory muscles. All patients were admitted in ward/cabin/HDU/ ICU of NINS&H. They were brought into Transfusion Medicine department in the morning before starting procedure. Patient with respiratory failure were supported by portable ventilator. After completion of procedure they were shifted to their respected department.

Assessment of Clinical Status: Clinical status was assessed before starting therapeutic plasma exchange and reassessed before each session of TPE and finally before discharge from hospital, using Myasthenia Gravis Foundation of America (MGFA) clinical classification. Patients were categorized as class I to class V of MGFA classification. Response to therapeutic plasma exchange was categorized as "Yes" or "No" using MGFA classification also. For ICU /HDU patient, extubation from ventilator after therapeutic plasma exchange was considered as "yes" and for patients from ward or cabin is considered "yes" when MGFA clinical classification system findings suggested at least 1 grade improvement after therapeutic plasma exchange. When no improvement of MGFA grade and maximum symptoms persisted, then they were categorized as "No" response to therapeutic plasma exchange.

Procedure of Therapeutic Plasma Exchange: The patients received TPE with 275 sessions in department of Transfusion Medicine at NINS&H, Dhaka, Bangladesh. Therapeutic plasma exchange was performed with 1 to 1.2 volume plasma exchange with continuous flow (Fresenius Comtec/Optia/Cobe Spectra) machine, with intermittent flow (Haemonetics) machines by using double/try lumen femoral dialysis catheter. TPE was done by alternate day basis for 8 to 10 days. Acid Citrate Dextrose (ACD) is used for anticoagulation. Isotonic saline, fresh frozen plasma (FFP), 5% albumin (few cases) were used as a replacement fluid. During procedure haemodynamic parameters were closely monitored and adverse reactions were treated accordingly. To avoid citrate toxicity 10 ml of 10.0% calcium gluconate was used in 10 ml normal saline within 10 minutes or infused by drip throughout the procedure (usually 40 ml in 40 to 60 ml normal saline for better result). Before giving FFP, antihistamine injection (pheniramine meliate) was given routinely. Indications for therapeutic plasma exchange, number of cycles and sessions, duration of each session, volume of plasma exchanged and patient tolerance to the procedure were systematically recorded.

Statistical Analysis: Statistical analyses were performed with SPSS software, versions 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Continuous data that were normally distributed were summarized in terms of the mean, standard deviation, median, minimum, maximum and number of observations. Categorical or discrete data were summarized in terms of frequency counts and percentages.

Ethical Consideration: This study was conducted in accordance with the principles of good clinical practice and declaration of Helsinki. Ethical permission was obtained from the Institutional Review Board (IRB) of National Institute of Neurosciences & Hospital, Dhaka, Bangladesh. All procedures of the present study were carried out in accordance with the principles for human investigations (i.e., Helsinki Declaration) and also with the ethical guidelines of the Institutional research ethics. Formal ethics approval was granted by the local ethics committee. Participants in the study were informed about the procedure and purpose of the study and confidentiality of information provided. All participants consented willingly to be a part of the study during the data collection periods. All data were collected anonymously and analyzed using the coding system.

Results

A total of 72 patients of MG or MGC, who were admitted in NINS&H either in ward, cabin, HDU or ICU received plasma exchange during the study period. Of 72 patients 75 cycles and 275 sessions of TPE were done, among them 52(72.2%) were male and 20(27.8%) were female. Age ranging from 12 to 65 years, mean age was 39.5±13.11 years. All the cases were classified by using MGFA clinical classification; cases were classified as class II - 10 cases (13.9%), Class III- 11 cases (15.3%), class IV - 6 cases (8.3%), and class V - 45 cases (62.5%). The mean numbers of TPE session were 3.69±1.016 (range 2 to 7). The mean volume of plasma exchange was 2266.7±361.53 ml (1400 to 3100). (Table 1) Mean time duration of each session was 105 minutes (range- 90 to 120 minutes) in continuous flow machine and 210 minutes (range- 180 to 240 minutes) in intermittent flow machine (Table 1).

Table 1: Demographic and TPE Characteristics

Characteristics	Values
Age in Years (mean±SD)	39.5±13.11
Gender	
• Male	52(72.2%)
• Female	20(27.8%)
Number of TPE session (mean±SD)	3.69±1.016
Volume of plasma exchange in ml (mean±SD)	2266.7±361.53
Duration of each session (in minutes)	
• Continuous flow machine (mean±SD)	105.2± 6.1
• Intermittent flow machine (mean±SD)	209.5 ±11.8

Indications for TPE were MGC (MGFA clinical classification class V) in 45(62.5%) patients. TPE was done in 11(15.3%) patients due to progressive

weakness (MGFA clinical classification Class III or class IV) despite optimal treatment. 16(22.2%) patients underwent a short course of TPE (2 to 3 procedure) as preoperative preparation of thymectomy, they were classified as class II or Class III according to their symptoms. 3 cases of post-operative thymectomy patients were readmitted for worsening of symptoms (Figure I).

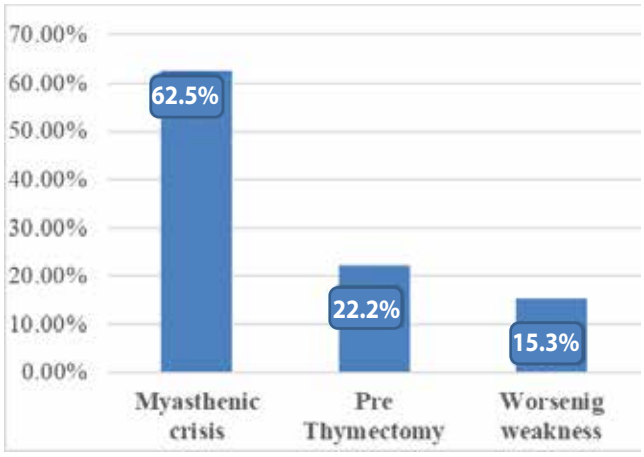

Figure I: Indication of TPE (n=72)

Acetylcholine receptor antibody (ACR Ab) were positive in 44(61.1%) and negative in 16 (22.2%) patients. ACR Ab status was not known in 12(16.7%) patients (Figure II).

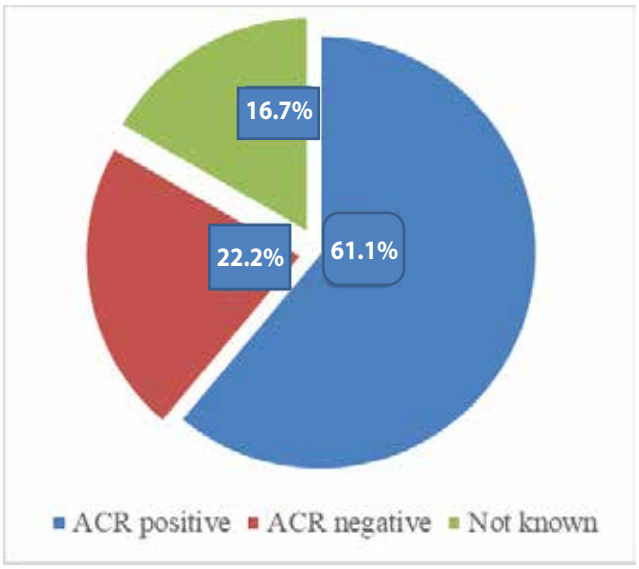

Figure II: ACR (Anti Acetylcholine Receptor) antibody status (n=72)

The outcomes of TPE was recorded and had found that majority had a good response which was 80.5% cases and the rest of 19.5% cases were failed to give good response (Figure III). The median duration of hospital stay was 23 days in ICU/HDU and 15 days in ward/cabin.

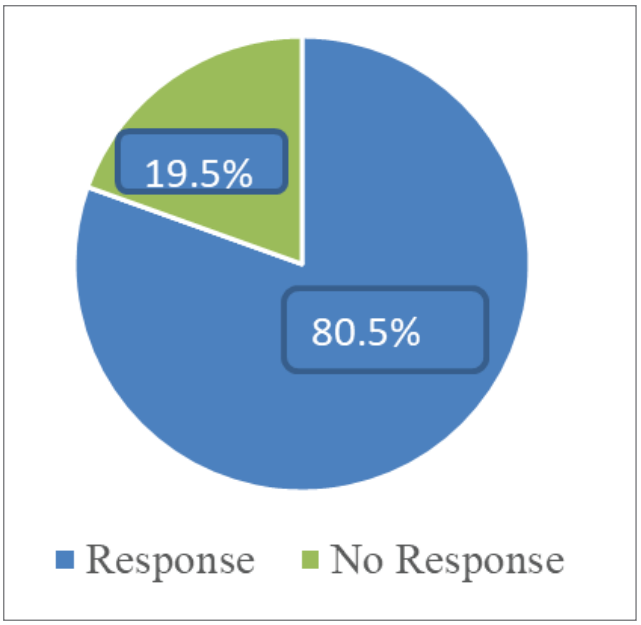

Figure III: Outcomes of TPE (n=72)

Overall incidence of adverse reaction was 26 (9.45%). Allergic reaction was the commonest side effect, of which mild allergy was noticed in 9(3.27%) cases and severe allergy (urticaria) in 1(0.36%) case. Pyrexia occurred in 5(1.82%) cases and hypotension in 4(1.46%) cases. We encountered 2(0.73%) catheter related problem. Hypocalcaemia occurred 2(0.73%) cases; vasovagal attack in 1(0.36%) case. 1(0.36%) patient vomited for one episode. 1(0.36%) patient complained of nausea but did not vomit (Table 2).

Table 2: Adverse reactions following TPE sessions (n=275)

Adverse effect	Frequency	Percent
Allergic reaction	9	3.27
Pyrexia	5	1.82
Hypotension	4	1.46
Catheter related problem	2	0.73
Hypocalcemia	2	0.73
Nausea	1	0.36
Vomiting	1	0.36
Urticaria	1	0.36
Vasovagal attack	1	0.36
Total	**26**	**9.45**

Discussion

TPE has significantly reduced the morbidity and mortality of patients with various diseases. The low risk to benefit ratio encouraged its use in many different conditions, with mostly excellent therapeutic results[21-24]. The usefulness of TPE in MG was first described by Pinching and Peter in 1976 applying TPE in 3 patients with improvement of muscle weakness and fatigue[25].

TPE removes Ach Receptor antibodies from circulation. Clinical and functional outcomes correlate with decline in the antibody level[26-27]. The beneficial effect of TPE can be seen within days and lasts for 3 to 6 weeks[28]. Few studies demonstrated faster response rate with TPE as compared to IVIG[29-33]. There was no procedure related mortality in our study though several investigators have reported deaths associated with TPE. The incidence of death associated with PE has been estimated to 0.05% cases[34]. The incidence of severe, life-threatening complications is estimated at 0.025 to 4.75% of procedures[35].

The most common adverse effect was mild allergy (n=9, 3.27 %). Allergic reactions were observed despite of giving antihistamine IM routinely prior to the procedure. Itching, rash or urticarial rash was noticed. All of them needed additional antihistamine. Only 1 patient received injection hydrocortisone in a single bolus due to severe allergy with urticarial rash. TPE cycles were completed successfully. The likelihood and nature of allergic reactions in TPE depend on the materials used to replace discarded plasma[36]. Fresh frozen plasma is most likely to induce allergic reactions ranging from mild episodes responsive to antihistamines to anaphylaxis[36]. A significantly higher incidence of allergic reactions occurs in patients requiring FFP. Human serum albumin might contain trace amounts of globulins and other plasma constituents which might provoke anaphylactic reaction[37]. Gafoor et al[38] reported 2.2% episode of allergic reaction during TPE in a tertiary care hospital in South India. As we used mostly FFP as replacement fluid, the incidence of allergic reaction is higher than many previous studies although our results are comparable with those reported from other studies, where most reactions were limited to rigor or urticaria [36-37,39-40].

Hypotension was defined as fall of mean arterial blood pressure (BP) more than 20 mm Hg from baseline. In this study there was fall in the arterial blood pressure in 4(1.46%) cases. Temporary cessation of the procedure, injection hydrocortisone 200 mg and 500 ml normal saline were sufficient to stabilize blood pressure in 3 cases. In 1 patient, dopamine was needed. TPE cycles were completed after restoring normal blood pressure. Hypotension is one of the most common cardiovascular complications of plasma exchange[41]. A primary hypotensive effect of the procedure, unrelated to volume changes, has also been postulated41. Also the nature of the underlying illness is important in determining the risk of this complication[42]. Incidence of hypotension is variable in different series dealing with neurological patients[42-44]. The usual incidence of TPE related hypotension is 2.6% to 8.1% cases[45]. Abnormalities of cardiac rate or rhythm may be present, including bradycardia, extrasystoles, atrial fibrillation, and tachycardia. They are often brief and usually self-limited, although fatal cardiac arrest has occurred[42]. In this study, there was no episode of clinically significant isolated change in the heart rate requiring pharmacological treatment.

During 5(1.82%) procedures, body temperature was increased. Fever subsided after using paracetamol. TPE sessions were completed successfully. Catheter related problem was observed in 2(0.73%) patients resulted from complete or partial occlusion of femoral catheter. In 1 patient, catheter had to be replaced. There was no haematoma, bleeding or infection at catheter site. Gafoor et al[38] reported 7.0% incidence of access related problems during TPE. Due to access problem, 4.0% to 5.0% of PE may have to be terminated[38,46]. Infection may also be related to the mode of venous access employed during plasma exchange or to the type of replacement fluids used[35]. The lower incidence of serious infection in neurological patients supports the concept that the underlying illness plays a major role in determining the likelihood of this complication. In our study, there was no procedure related infection.

Despite of giving calcium on routine basis in each procedure, 2(0.73%) cases developed hypocalcemia Additional injectable 10% calcium gluconate were needed to correct hypocalcemia. None of the patients experienced severe hypocalcemia with the development of cardiac arrhythmia.

Only 1 patient vomited for one episode. 1 patient complained of nausea but did not vomit. Injection ondansetron IV was given in these 2 patients and they settled down. Frequent complications experienced during plasma exchange are nausea, paresthesia and occasional muscle cramp probably due to chelation of ionized calcium by infused citrate anticoagulant[44]. Nausea has been reported during as many as 15% and paresthesia in 9.0% of exchanges utilizing concentrated

citrate solution such as ACD-A[44]. Other study reports vary on the occurrence of these symptoms[34-35]. These symptoms can be partly avoided by adding calcium to the replacement fluids, slowing the infusion of citrated blood, or by using anticoagulant solutions with a lower concentration of citrate[44]. In this study regular parenteral replacement of calcium was responsible for a low incidence of hypocalcemia (n=2, 0.73%). Patients also reported symptoms like restlessness, sweating, heart burn, discomfort, parasthesia. Their complaints were mild and subsided spontaneously without any medication. Response to TPE was assessed by comparing clinical status before starting the treatment and at the time of discharge from hospital using MGFA clinical classification grading. In this study, 80.5% (n=58) patients responded to treatment. All of them were ambulatory at the time of discharge with mild to moderate symptoms. 19.5% (n=14) patients did not responded to TPE. 2 patients died but not due to TPE, 1 patient died after thymectomy operation and another patient died 2 days after TPE. Definitive treatment of MG requires immunosuppression or immunomodulation therapy such as IVIg or TPE[47-48]. Immunomodulation is used when rapid improvement is required, i.e., MG exacerbation[28,49-51] preoperative optimization of strength prior to thymectomy[52] and in patients who cannot tolerate or do not respond to immunosuppressive medications[28,47,51]. The benefits of immunomodulation with TPE and IVIg have been demonstrated in several studies[28,51,53-54].

Conclusion

TPE is a safe therapeutic procedure with acceptable mild adverse reactions. It is a rapidly effective therapy for myasthenic crisis and progressive myasthenia gravis. Before thymectomy operation TPE should be considered to avoid post-operative myasthenic crisis.

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Contribution to authors: Ara F, Islam S, Fatema K were involved in the procedure and collect data. Hasan MS, Ara F, Sonia SF were involved in reporting data analysis and writing the manuscript. Yusuf MA, Alam MB and Mohammad QD were revised the manuscript. All the authors have read and approved the final version of the manuscript.

Data Availability
Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate
Ethical approval for the study was obtained from the Institutional Review Board. As this was a prospective study the written informed consent was obtained from all study participants. All methods were performed in accordance with the relevant guidelines and regulations.

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