Original Article

Outcome of therapeutic plasma exchange in Myasthenia gravis patients

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Abstract

Aims: The aim of this study was to evaluate the indications, adverse reactions, and outcome of therapeutic plasma exchange (TPE) in myasthenia gravis (MG) patients. **Settings and Design:** Retrospective Observational study. **Methods and Material:** A total of 18 patients of MG had undergone 18 cycles and 87 session of TPE at our Institution, a tertiary care center in Western India. It was performed using a single volume plasma exchange with intermittent cell separator (Freseniouscomtec), subclavian central line access, and with alternate day interval. Outcome was assessed shortly after each session and overall outcome at the time of discharge. **Results:** Total of 68 patients of MG were admitted to Neurology Intensive care unit (ICU) during the study period [January 2016–December 2019]. Out of them, TPE was done in 18 patients. Among the 18 patients, 11 patients had myasthenic crisis and 7 patients had worsening of MG. The mean number of TPE session was 4.2(SD ± 1.2), volume exchange was 2215 ml (SD ± 435); overall incidence of adverse reaction was 33.3%. All patients had immediate benefits of each TPE cycle. Good acceptance of procedure was observed in 72.2% of patients. **Conclusions:** TPE is cost-effective rapid therapy for myasthenic crisis and progressive myasthenia gravis. It reduces ICU stays and improves outcome.

Keywords: Adverse reaction, auto antibodies, Myasthenia gravis, therapeutic plasma exchange

Introduction

Apheresis generally denotes "taking away." Therapeutic apheresis is a blood processing technique which selectively removes certain cell type or component of blood and include therapeutic plasma exchange (TPE), therapeutic cytoreduction, in line cellular immunomodulation, and plasma treatment. All these procedures are used as a primary or secondary treatment for certain disease.[1]

Myasthenia gravis (MG) is a well-known autoimmune disease of neuromuscular junction characterized by antibodies against postsynaptic nicotinic acetylcholine receptors. The hallmark feature of MG is fluctuating weakness in ocular, bulbar, limb, and respiratory muscles. The annual incidence of MG is approximately 30 new cases per million and approximately 15–20% of these patients will develop myasthenia gravis crisis (MGC).[2] As per the consensus of American Society for Apheresis, TPE is a well-established treatment modality for myasthenic crisis and myasthenia exacerbation (Class III evidence, Category I).[3-6]

TPE is an extracorporeal blood purification technique designed for separation of plasma and removal of large molecular weight substances such as pathogenic autoantibodies, immune complexes, cryoglobulins, and toxins that have accumulated in the plasma.[7] The fluid volume removed must be replaced to avoid volume depletion. Albumin, saline, or combination of the albumin and

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Received: 30-05-2020 **Revised:** 09-09-2020
Accepted: 06-10-2020 **Published:** 31-12-2020

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_1026_20

How to cite this article: Dogra A, Rana K, Rathod C, Prakash S. Outcome of therapeutic plasma exchange in Myasthenia gravis patients. J Family Med Prim Care 2020;9:5971-5.

saline are used as a substitution fluid.[8] TPE removes antibodies to acetylcholine receptor, leading to short-term improvement in muscular strength and motor performance by improving neuromuscular transmission.[9] Rebound overproduction of antibodies occurs because of sudden removal of antibodies from the circulation. So, concurrent use of immunotherapy (e.g., glucocorticoid) is advisable along with TPE.[10] In a country like India, where majority of people are from middle and lower socioeconomic class, cost of the therapy is an important factor while choosing treatment option. TPE is relatively cheaper mode of treatment as compare to IVIG. Although studies showed equal efficacy of IVIG and TPE in MGC, an expert consensus suggests that plasma exchange is more effective and works more quickly in the treatment of impending or manifest myasthenic crisis.[11,12]

Role of primary care physician in myasthenia gravis

In our country, majority of the patient first present to the primary care physician for majority of their problems. So, knowledge of MG and myasthenic crisis as well as their treatment option is important. Early referral to the tertiary care facility where all the treatment option are easily available is important. As MGC is an emergency condition and early treatment prevents fatal outcome.

In this retrospective study, we analyzed our experience of TPE in MG patients in relation to indications, complications, outcome, and various aspect of procedure.

Subjects and Methods

This was a retrospective observational study to evaluate indications, complications, and outcome of TPE in patients with MG, admitted in the Neurology Intensive Care Unit in a tertiary care hospital in Western India over a span of 36 months from January 2016 to December 2019. TPE (average cost is 11,000/cycle) was initiated and monitored by the Department of Immunohematology and blood transfusion.

Data collection

Inclusion criteria: All patients with MG who received TPE as a treatment during hospitalization.

Exclusion criteria: Patient with MG who did not received TPE during hospitalization.

The study did not need approval by the ethics committee as per the local regulations for the retrospective case study.

Total 68 patients of MG were admitted at our hospital during the study period. 18 (26.4%) of them received TPE. They were submitted to a total of 18 cycles and 87 sessions of TPE. Clinical data, lab parameters, outcome data were obtained from the inpatient medical records and discharge cards of patients admitted in the Department of Neurology. Clinical diagnosis of MG was supported by repetitive nerve stimulation tests (RNS), Antiacetylcholine receptor (Anti AChR) antibodies, and neostigmine test. All the patients were classified according to the Myasthenia Gravis Foundation of America (MGFA) scales. Age, gender, age-onset of MG, precipitating cause for MC, clinical deficit before TPE, level of serum anti-AChR binding antibodies, and the disease status at discharge were analyzed as shown in Table 1.

Before the procedure, following parameters were checked and appropriate steps were taken to correct them: Hemogram, Creatinine, blood urea, liver function test, electrolytes, serum proteins, coagulation profile, and vital parameters. The consent was taken from the patient/patients relatives before the procedure. TPE was performed using a single volume plasma exchange with intermittent cell separator (Fresenius Comtec,) machines by femoral or central line access using 12 French double lumen dialysis catheter. TPE was done on alternate day basis for 8–10 days. Anticoagulation with citrate (ACD) was used systemically. Isotonic saline, albumin and fresh frozen plasma (FFP) were used as a replacement fluid. Isotonic saline was used to make one-half of the volume and 4% purified human albumin and fresh frozen plasma were added to complete it. During and after the procedure, hemodynamic parameters were monitored and unwanted events were identified and reverted by rational interventions. 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. To avoid citrate toxicity, 10 ml of 10% calcium gluconate was infused over 15 min approximately halfway through the procedure. Daily monitoring of hemogram, serum electrolytes, total protein, and albumin were done. After each session, outcomes in terms of clinical improvement was measured. The amount of plasma to be exchanged was determined by following formula: Estimated plasma volume (EPV) = (0.65 × weight [kg]) × (1 − Hematocrit).[13]

Results

A total of 18 (26.4%) patients of MG or MGC, who were on mechanical ventilation received plasma exchange during the study period. A total of 18 cycles and 87 sessions of TPE were done. Among the 18 patients, 13 (72.2%) were females and 5 (27.8%) were male. The mean age of onset was 35.5 years with age group ranging from 17 to 56 years. All the cases were classified by using MGFA clinical classification. Cases were classified as class Iva (4 cases- 22.2%), class IVb (7 cases-38.9%) and class V (7 cases-38.9%). Indication for TPE were MGC in 11 patients (61.1%) and progressive weakness despite optimal treatment in 7 (38.8%) patients. The mean number of TPE session were 4.2 (Standard deviation ± 1.2).

The mean volume of plasma exchanged was 2215 ml (SD ± 435) and mean time duration of each session was 207 min (SD ± 25). Side effects were mild such as citrate toxicity in 3 (16.7%), hypotension in 2 (11.1%), catheter-related problems in 8 (44.4%), and anaphylactoid reactions to FFP in 3 (16.7%) procedures. No

Table 1: Characteristic details of patients, procedure and outcome

Cases	Gender	Sex	MGFA	Anti AChA	Triggering Factor/Comorbididty	Cycles	Sessions	Adverse reactions	Outcome
1	Male	17	V	8.33	Lower respiratory tract infection	1	5	hypocalcemia	CSR
2	Female	23	Iva	7.43	Drug defaulter	1	5	-	PR
3	Female	27	IVb			1	5	hypocalcemia	MM2
4	Female	43	IVb		Lower respiratory tract infection	1	5	Allergic reaction	MM3
5	Male	27	IVb	5.4	Drug defaulter	1	5	-	MM2
6	Male	28	V		Recent surgery	1	5	-	CSR
7	Female	18	Iva	6.21		1	5	Allergic reaction	MM2
8	Female	32	V		Drug defaulter	1	5	-	MM3
9	Female	45	Iva		Lower respiratory tract infection	1	5	-	MM2
10	Female	38	IVb	5.34		1	5	Vasovagal hypotension	MM3
11	Female	42	V		Recent surgery	1	5	-	CSR
12	Male	54	IVb	11.12	Acute gastroenteritis	1	5	-	MM3
13	Female	36	IVb	7.89		1	5	-	MM3
14	Female	35	V			1	5	- hypocalcemia	MM2
15	Female	37	Iva	8.10		1	5		CSR
16	Male	56	V		Lower Respiratory tract infection	1	2	-	death
17	Female	45	IVb	4.52	Lower respiratory tract infection	1	5	-	CSR
18	Female	36	V	3.6	Hypothyroidism	1	5	-	MM2

infection was observed, and no death occurred in consequence of TPE. Good TPE acceptance occurred in 72.2% of cases.

Each sessions of TPE resulted in immediate improvement of clinical status in every patient. The median duration of ventilatory support following TPE was 12 days and Intensive care unit stay (ICU) was 16 days. Longest duration of ICU stay was 25 days. Disability at the time of discharge was minimal and all patients were discharges in a stable and ambulatory condition. However, at discharge clinical status was recorded as complete stable remission in one patients; pharmacological remission in one patient, taking low-dose of cholinesterase inhibitors (MM2) in 6, with low-dose cholinesterase inhibitors and some immunosuppressor (MM3) in 5. Death was registered in one patients, but it was not directly related to TPE.

Discussion

The usefulness of TPE in MG was first described by Pinching and Peter in 1976. They used TPE in 3 patients and found partial recovery in muscle weakness and fatigue.[14] They also suggested that humoral mechanism was responsible for neuromuscular junction disorder.

TPE directly removes Ach Receptor antibodies from circulation. Clinical and functional outcomes correlates with decline in the antibody level.[15,16] The beneficial effect of TPE can be seen within days and lasts for 3–6 weeks. A randomized controlled trial by The Myasthenia Gravis Clinical Study Group showed equal efficacy of TPE as compared to IVIG for the treatment of MG exacerbation.[17] One meta-analysis showed that TPE provides rapid short-term benefits in patients with MGC.[18] Few studies demonstrated faster response rate with TPE as compared to IVIG.[19-21] In Juvenile MG, PLEX is more favored therapy than IVIG because of rapid onset of action.[22]

In our study, TPE was indicated for MGC in 11 (61.1%) patients and progressive worsening despite treatment in 7 (38.8%). Similar to previous study, most common triggering factor for MGC was infection in 6 (54.5%), drug defaulter in 3 (27.3%), and emergency surgery in 2 (18.2%) patients. Among the infections, respiratory tract infection was commonest cause (5 patients - 83.3%) and one patient had gastrointestinal infection.[23,24] One patient presented with MGC as a presentation of MG (5%). Some studies has shown MGC as a presentation of MG in 13–20% patients.[23,25,26]

In our study, the incidence rate of adverse reaction was 33.3%. This was comparable to previous study in which adverse reaction was reported from 1.6% to 25%.[18,27,28] The complications observed were either related to vascular access or related to composition of replacement fluid. The complications related to vascular access include infection, thrombosis, dissecting hematoma, air embolism, and pneumothorax (0.2–0.4%). Citrate-related complications include hypocalcemia and metabolic alkalosis (1.5–9%) and clinically manifest as paresthesia, nausea, vomiting, muscle cramps, hypotension, and rarely arrhythmia because of QT prolongation.[29] Apart from this, hypotension or vasovagal reaction occurs in roughly 0.4–4% of procedures because of preexisting hemodynamic instability and anaphylactoid reactions to FFP up to 21%.[30,31]

In our study, we encountered catheter blockage in 8 procedures (44.4%), citrate toxicity occurred in 3 (16.7%), hypotension in two (11.1%), and anaphylactoid reaction in 3 (16.7%). Hypotension was managed by fluid replacement and anaphylactic reaction by intravenous hydrocortisone and diphenhydramine.

There was one death of a patients, who presented with MC secondary to septicemia. The case fatality rate for TPE is 3 to 5 per 10,000 and is because of respiratory or cardiac complication like arrhythmia.[32]

Conclusion

We found that TPE is highly efficacious, cheaper short-term therapy for MG. Outcome in patients with myasthenic crisis are favorable and it reduces ICU stay by early weaning from ventilator.

Key Points

- Therapeutic plasma Exchange is cost-effective short-term therapy for myasthenic crisis.
- Adverse reactions are less if proper protocol is followed.
- Early initiations of TPE can reduces number of ICU days.
- TPE is a short-term therapy, patient with MG requires long-term immunosuppressant.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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