Original Article

Effectiveness of Therapeutic Plasma Exchange in Autoimmune Neurological Diseases in a Tertiary Care Hospital of South India

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Abstract

Background and Objectives: Therapeutic plasma exchange (TPE) is commonly used as a treatment of certain autoimmune neurological diseases, and its main target is to remove pathogenical toxins or autoantibodies. Removed plasma with toxins and autoantibodies is replaced by crystalloids, colloids, and/or normal saline. It is more effective and cost-effective than immunoglobulins. The aim of this study was to know the effectiveness of TPE in autoimmune neurological diseases. **Methods:** This is a prospective study involving 376 autoimmune neurological cases, and the duration of this study was 5 years. All autoimmune neurological patients irrespective of age with complaints of weakness in limbs, respiratory distress, and acute myasthenia gravis (MG) crisis cases were included in the study. The Modified Rankin Score and MG Composite Score were used to analyze the severity of the disease, and the number of TPE procedures or cycles was planned. **Results:** The total number of cases included was 376 (322 newly registered cases and 54 old and relapse cases), and the total number of TPE procedures done was 1491 between the years 2017 and 2021. Male patients were 138 and female patients 238. The most number of cases were of MG, followed by Guillain–Barre syndrome. The mean number of TPE procedures done was 6.1 cycles in myasthenia crisis patients. There was a significant improvement in the patients after the treatment. The Modified Rankin Score and MG Composite Score were 1/6 and 3/50, respectively (P = 0.0321 and P = 0.0298, respectively) after completion of the TPE. **Conclusion:** TPE is the most effective method in cases of neurological autoimmune diseases. Most of the cases show improvement immediately after the first cycle, and more than half of the cases will be able to walk or do their routine activities after 2 or 3 cycles. It is a safe and cost-effective treatment modality with minimal side effects or complications.

Keywords: *Autoantibodies, autoimmune disease, Guillain–Barre syndrome, myasthenia gravis, therapeutic plasma exchange*

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Introduction

Therapeutic plasma exchange (TPE) is the process in which the antibodies or/ and the toxic substances present in the plasma are removed and replaced by harmless plasma substitutes such as Albumin or colloidal solutions or normal saline. TPE removes pathogenic substances such as autoantibodies, lipoproteins, and circulating immune complexes from the plasma and plays a key role in the management of various diseases. TPE can also replenish missing plasma components such as ADAM metallopeptidase with thrombospondin type 1 motif 13 in thrombotic thrombocytopenic purpura (TTP), if fresh frozen plasma is used as exchange fluid. According to the American Society for Apheresis (ASFA) guidelines, plasmapheresis may be useful for the treatment of various neurologic, hematologic, or nephrological diseases. These diseases are categorized into four categories where TPE is indicated.

In Categories I and II, TPE is absolutely indicated whereas in Categories III and IV, TPE is indicated along with the other

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treatment modalities.[1] Disease entities include Guillain–Barre syndrome (GBS), good pasture's syndrome, hyperviscosity syndromes, myasthenia gravis (MG), neuromyelitis optica (NMO), TTP, familial hypercholesterolemia, chronic inflammatory demyelinating polyradiculoneuropathy, pediatric autoimmune neuropsychiatric disorders, renal transplant rejections, and ABO and Rh incompatibility-associated hemolytic disturbances.

The most common reactions associated with TPE which are less severe include urticaria, pruritus, limb paresthesias and pains, muscle contractions, dizziness, nausea, vomiting, transiently elevated temperature, chills or chills with rigors, seizures, and head and chest pain. Plasmapheresis has some severe side effects which may be due to central venous catheterization, clotting disorders, septic complications resulting from impaired immunity caused by the removal of antibodies during the procedure, catheter-associated infections, and those related to transfusion of blood and blood products. Moreover, life-threatening fall in arterial blood pressure, cardiac arrhythmias, and water–electrolyte imbalance are likely to develop but rare. Overall, TPE is a well–tolerated procedure and can be performed safely by central venous or femoral venous catheterization in the intensive care units (ICUs).

Aim of the study

This study is aimed to know the effectiveness of TPE in autoimmune neurological diseases.

Materials and Methods

This was a prospective study done in the department of transfusion medicine and immunohematology at our center. The total numbers of cases included in this study were 376 patients admitted between the years 2017 and 2021 (5-year duration).

After admission, a thorough history was taken and neurological examination was done and a diagnosis was established. The department of transfusion medicine was consulted for the start of TPE. The Modified Rankin Score was used to assess the neurological disability which has a maximum score of 6.[2-4] In addition, for the MG cases, the MG Composite Score was used which has a maximum score of 50.[5] The higher the score, the higher is the disability. Both these scores were used before and after the procedure to know the effectiveness of TPE. All the routine and other required investigations were done before the start of the procedure and serum albumin was repeated before the next cycle. Viral marker screening was done.

A total of 1–6 procedures per patient were planned after taking consent from the patient or the patient attendee; however, the number of procedures was dependent on the clinical improvement of the patient, vascular access, hypotension, or any minor reactions resulting in stoppage of that particular cycle. TPE was performed every alternate day using a double-lumen central venous line or femoral line by using a COBE Spectra plasmapheresis machine, manufactured by Terumo BCT, Inc. with a disposable plasmapheresis kit. Patient information was entered into the machine, and the blood volume was calculated by the machine. All the procedures were carried out in the ICU with a trained technician under the supervision of the medical officer who managed the adverse reactions during the procedure (if any).

Oral calcium was given to the patient to prevent paresthesia and numbness. Low-molecular-weight heparin (anticoagulant) was given 5–10 ml before the start of the procedure. The acid citrate dextrose (ACD) ratio was 1:10 (ACD:whole blood) and the blood flow rate was set between 35 and 65 ml/min and the pump speed was set by the machine depending on the blood flow to the machine (between 80 and 90 ml/min). The duration of the procedure ranged from 60 to 120 min and was dependent on the blood flow. In all the patients , the volume of the plasma removed by TPE is replaced by 100 % colloidal solutions such as 5% albumin or gelofusine.

Ethics

All procedures were done with patient consent and accoring to strict inclusion exclusion criteria. Care has been taken to conceal identity of patient during analysis of results.

Inclusion criteria

1. All neurological patients irrespective of age with any of the above-mentioned complaints such as weakness in limbs, respiratory distress, and acute MG crisis
2. All the patients meeting the eligibility criteria for the procedure
3. All fresh and relapse cases meeting the ASFA guidelines and where TPE is the first line of therapy.

Exclusion criteria

1. Patients who did not consent to the procedure
2. Patients who are on intravenous immunoglobulin treatment.

Categorization of the cases was done based on the ASFA guidelines which groups them into four categories (I–IV). For Category I, apheresis is the first line of treatment; for Category II, it is the second line of treatment; in case of Category III, the optimum role is not established; and in Category IV, apheresis may be ineffective or harmful.

Statistical analysis

Numerical calculation was performed using Microsoft Excel software.

Statistical analyses were performed using IBM SPSS software version 29 (International Business Machines (IBM) Corporation, North Castle Drive , Armonk New York , United States of America (USA)). *P* value was calculated using paired *t*-tests.

Results

In this study, total cases included were 376 (322 newly registered cases and 54 old and relapse cases), and the total number of TPE procedures done was 1491 between the years 2017 and 2021. Male patients were 138 and female patients 238. The male-to-female patient ratio is 1:1.57. The age of the youngest and oldest patients was 9 years and 78 years, respectively. The mean age was 39.87 years. The age- and year-wise distributions of cases are tabulated in Table 1.

In this present study, 147 cases (39.09%) were MG patients and 21 cases (5.58%) were myasthenia crisis patients where the patients developed worsening muscle weakness and respiratory failure. They were intubation and kept on ventilator support on arrival, and TPE was done. GBS/acute inflammatory demyelinating polyradiculoneuropathy (AIDP) cases were 57 (15.15%) during the study period.

Devic's disease or NMO or NMO spectrum disorder cases were 45 in number (11.96%), and transverse myelitis and CIDP cases were 23 each (6.11%). In this study, TPE was done for rare cases such as Morvan's syndrome, osmotic demyelination syndrome, rhombencephalitis, and stiff-person syndrome [Table 2].

To remove the autoantibodies or toxins from the plasma of the patients, it requires 2–6 procedures of TPE which varies from patient to patient and other parameters. The average number of TPE procedures per patient was 4.61 procedures [Table 3]. Most number of procedures were done in MG patients.

Table 1: Age- and year-wise distribution of cases

Age group (years)	2017	2018	2019	2020	2021
9–18	4	7	13	3	2
19–28	7	13	19	11	9
29–38	15	29	38	26	17
39–48	13	26	34	18	13
49–58	6	7	9	6	4
59–68	5	4	4	4	2
69–78	2	3	2	1	0
Total	52	89	119	69	47

All the patients were given 100%–110% of replacement fluids, and the most preferred fluid used was Gelofusine as it was cheaper than albumin and easily available (>90% of cases). In some patients, where there were financial constraints, 50%–75% was replaced by Gelofusine and 25%–50% was with normal saline (8%). In patients whose serum albumin was below 2.5 g/dL, replacement was done with one unit of albumin diluted in 500 ml of normal saline and the remaining replacement was done with Gelofusine (2%). We did not prefer fresh frozen plasma as replacement fluid in any of the cases due to the cost and FFP transfusion-associated complications.

Most of the patients tolerated the procedure well without any complications. A few minor complications occurred in some patients (43%, n = 43 cases) during or after the TPE, and most of the complications were nonlife threatening and were easily manageable. These complications were hypotension (48.83%, n = 21 cases), paresthesia, tingling and numbness in the upper or lower limbs (41.86%, 18 cases), allergic reactions (4.65%, n = 2 cases), fever (2.33%, n = 1 case), and abdominal cramps (2.33%, n = 1 case).

Most of the patients tolerated TPE well and responded gradually after every TPE cycle. Patients Rankin score and MG composite score improved. Overall, 11 patients expired after the first TPE cycle and out of the 11 patients, six patients reported to the hospital in myasthenia crisis and respiratory failure. Three patients had associated comorbidities and sepsis [Table 4]. Among the remaining two cases, one case was multiple myeloma and the other was ADEM. The overall survival rate seen in this study was 97%.

Table 2: Year-wise cases with diagnosis and American Society for Apheresis categorization

Diagnosis	ASFA category	Year wise					Total cases (diagnosis wise) (%)
		2017	2018	2019	2020	2021	
Myasthenia gravis	I	31	39	45	24	8	147 (39.09)
Myasthenia gravis crisis	I	2	6	9	3	1	21 (5.58)
GBS/AIDP	I	9	17	17	14	7	57 (15.15)
NMO/NMOSD/Devic's disease	II	2	10	16	12	11	45 (11.96)
TM	I/II	1	5	10	4	3	23 (6.11)
CIDP	I	1	6	7	3	6	23 (6.11)
LETM	I/II	1	6	6	4	3	20 (5.31)
ADEM/postinfectious encephalomyelitis	II	3	-	4	1	2	10 (2.65)
MGUS	I	-	-	-	2	2	4 (1.06)
Acute-onset quadriparesis/tetraparesis	I	-	-	1	1	1	3 (0.79)
Peripheral neuropathy	II	-	-	1	1	-	2 (0.53)
Morvan syndrome/MFC	I	-	-	1	-	1	2 (0.53)
Early morning paralysis	II	-	-	1	-	-	1 (0.265)
Multiple myeloma	III	1	-	-	-	-	1 (0.265)
Osmotic demyelination syndrome/CPM	III	-	-	-	-	1	1 (0.265)
Rhombencephalitis	II/III	-	-	-	-	1	1 (0.265)
Postinfectious cerebellitis	II/III	-	-	1	-	-	1 (0.265)
Stiff syndrome/stiff-person syndrome	III	1	-	-	-	-	1 (0.265)
Total cases per year		52	89	119	69	47	376 (overall cases)

GBS: Guillain–Barre syndrome, AIDS: Acute inflammatory demyelinating polyradiculoneuropathy, NMO: Neuromyelitis optic, NMODS: Neuromyelitis optica spectrum disorder, TM: Transverse myelitis, CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy, LETM: Longitudinal extensive transverse myelitis, ADEM: Acute disseminated encephalomyelitis, MGUS: Monoclonal gammopathy of undetermined significance, MFC: Morvan's fibrillary chorea, CPM: Central pontine myelinolysis, ASFA: American Society for Apheresis

Table 3: Average number of therapeutic plasma exchange procedures

Diagnosis	Number of TPE procedures	Mean number of procedures per disease
Myasthenia gravis	2–6	5.2
Myasthenia gravis crisis	1–7	6.1
GBS/AIDP	2–5	5.1
NMO/NMOSD/Devic's disease	3–5	4.6
TM	4–6	4.3
CIDP	5–6	5.3
LETM	3–5	4.6
ADEM/postinfectious encephalomyelitis	3–6	4.8
MGUS	3–7	3.9
Acute-onset quadriparesis/tetraparesis	3–6	4.3
Peripheral neuropathy	3–5	4.4
Morvan syndrome/MFC	5	5
Early morning paralysis	5	5
Multiple myeloma	6	6
Osmotic demyelination syndrome/CPM	5	5
Rhombencephalitis	5	5
Postinfectious cerebellitis	4	4
Stiff syndrome/stiff-person syndrome	4	4

GBS: Guillain–Barre syndrome, AIDP: Acute inflammatory demyelinating polyradiculoneuropathy, NMO: Neuromyelitis optic, NMOSD: Neuromyelitis optica spectrum disorder, TM: Transverse myelitis, CIDS: Chronic inflammatory demyelinating polyradiculoneuropathy, LETM: Longitudinal extensive transverse myelitis, ADEM: Acute disseminated encephalomyelitis, MGUS: Monoclonal gammopathy of undetermined significance, MFC: Morvan's fibrillary chorea, CPM: Central pontine myelinolysis

Discussion

MG is an autoimmune condition in which antibodies to AchR or to functionally associated molecules in the postsynaptic membrane bind at the neuromuscular junction, resulting in localized or generalized weakness of the skeletal muscles.[6] Muscular weakness fluctuates throughout the day, worsens with exertion and exercise, and improves on taking rest. Approximately two-third of patients have symptoms involving the extraocular muscles that progress to include other bulbar muscles and limb musculature, resulting in a generalized MG. MG affects muscle power symmetrically in most cases, except for eye involvement, where there can be a marked asymmetry with involvement of any individual or group of extraocular muscles.[7] MG has an incidence of 8–10 cases per 1 million persons annually and a prevalence of 150–250 cases per 1 million population worldwide.[8,9]

The first description of GBS dates back to 1859, when Landry published a description of a case with ascending paralysis.[10] The clinical and biological picture was later completed in 1916 by French neurologists Georges Guillain, Jean Alexandre Barré, and Andre Strohl.[10] GBS is an acute autoimmune disease that reaches maximum severity within 2–5 weeks. GBS affects the peripheral nervous system and is characterized by progressive involvement of muscles innervated by the cranial nerves, reduction or abolition of the deep tendon reflexes, and possible impairment of the autonomic nervous system, sometimes with respiratory failure and albuminocytological dissociation.[10] Due to the respiratory and autonomic nervous dysfunction, the disease has the potential to be fatal even when patients are treated at centers that provide optimal care. Guillain-Barré syndrome is a broad category that encompasses several types of acute immune-mediated polyneuropathies, the most common of which is acute inflammatory demyelinating polyradiculoneuropathy (AIDP), Acute autonomic neuropathy and Miller Fisher syndrome (MFS) is a more rare variant of GBS.[10]

In this study, most of the cases were in the age group of 19–38 years which is in line with the other authors. In this study, the most number of cases were of MG followed by GBS, NMO, transverse myelitis, chronic inflammatory demyelinating polyneuropathy, etc., According to the ASFA guidelines 2019, for all the above-mentioned diseases, TPE is the first line of therapy. In this study, 147 MG cases and 21 myasthenia crisis cases were included, altogether 168 cases (44.68%) which is higher when compared to other studies such as Szczeklik *et al*. where they reported 33.3% of MG cases, Nieto Aristizábal *et al*. reported 37.4% of the MG cases, and Uslu and Gursoy reported 15% of MG cases.[11-13]

The total number of TPE cycles in this study was 1491 (376 cases) which is more when compared to the studies done by Schmidt *et al*., where 912 TPEs were performed in 185 patients.[14] In the study done by Arslan *et al*.,[15] they reported 658 TPEs in 158 patients over a 3-year period, followed by a study from Colombia done by Cordoba JP *et al*[16] reporting 500 TPE sessions in 68 patients over a period of 5 years, a study from India reporting in 492 TPE procedures performed in 125 patients, and the study by Stegmayr *et al*.[17] who reported on 388 TPE in 122 patients. The mean number of TPE cycles done was 6.1 in myasthenia crisis patients followed by multiple myeloma and other disease entities, which is in tandem with many authors according to the meta-analysis done by Ipe *et al*.[18]

A few minor complications occurred in some patients (43 cases – 11.43%) during or after the TPE, and most of the complications were nonlife threatening and were easily manageable. Hypotension occurred in 48.83% of the cases when compared to the study done by Nieto-Aristizabal *et al*.,[12] where 56.6% of cases had hypotension. In the study done by Szczeklik W *et al*.,[11] hypotension was noted in 7.3% of cases.

Paresthesia, tingling, and numbness in the upper or lower limbs noted in 18 cases – 41.86%), allergic reactions (2 cases – 4.65%), fever (1 case – 2.33%), and abdominal cramps (1 case – 2.33%) which are higher in this study when compared to the study done by Nieto-Aristizabal *et al*.,[12] where paresthesias accounted for 1.08%, allergic reactions 0.81%, fever 0.54% and abdominal cramps 0.54%. However, the sample size in Nieto Aristizábal *et al*. is very less (54 cases) when compared to the present study of 376 cases.[12] The effectiveness of TPE is tabulated in Table 5.

Table 4: Pre- and post-therapeutic plasma exchange scores and improvement

Score	Mean preprocedure score	Mean postprocedure score	Overall improvement seen in patients	*P*	Expired cases
Modified Rankin Score (*n*=376)	5/6	1/6	365/376	0.0321	11
Myasthenia Gravis Composite Score (*n*=168)	41/50	3/50	159/168	0.0298	9

*Maximum score is 6 for Modified Rankin Score, #Maximum score is 50 for Myasthenia Gravis Composite Score

Table 5: Comparison of effectiveness of therapeutic plasma exchange in neurological diseases

Author name/ study name	Year	Sample size (number of patients)	Effectiveness (%)
Gajdos *et al*.[19]	1997	87	63
Qureshi *et al*.[20]	1999	51	71
Jensen and Bril[21]	2008	18	78
Sarkar *et al*.[22]	2008	19	80
Saeteng *et al*.[23]	2013	86	88
Murthy *et al*.[24]	2005	23	93
Guptill *et al*.[25]	2011	103	93
Nagayasu *et al*.[26]	2005	51	100
Present study	2024	376	97

In the present study, relapse cases were 54 out of the 376 cases and 11 deaths (2.90%), which is almost close to the study done by Nieto Aristizábal *et al*. where they reported 59 relapse cases and 3 deaths, respectively.[12]

Limitations of this study

1. Some of the patients left against medical advice before completion of all the cycles as per plan or protocol, which had decreased the effectiveness of overall TPE
2. Some of the patients had electrolyte imbalances, albumin depletion, etc., which delayed the process as per the protocol (alternate-day procedure)
3. In some of the cases, clinical severity was roughly calculated instead of point to point
4. We have done the TPE procedures with COBE Spectra Terumo BCT. Better version instruments such as TRIMA Optia would have reduced the number of cycles, time taken per procedure, and improved effectiveness.

Further research

A multicenter study with different TPE instruments would give much better idea about the effectiveness of the TPE.

Conclusion

TPE is considered a safe, cost-effective treatment modality for autoimmune neurological diseases. Proper workup with the routine and mandatory investigations before the procedure will reduce the complications and increase the effectiveness of the procedure. More than half of the patients, who have a severe disease, will be able to walk after 2 or 3 cycles and are most satisfactory for the patient. As far as our search of literature, this study is the largest in a tertiary care center in south India. TPE can be used in dermatological, rheumatological, and hematological conditions and also in renal diseases to remove the autoantibodies.

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Conflicts of interest

There are no conflicts of interest.

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