ORIGINAL ARTICLE

Therapeutic Plasma Exchange as An Emerging Treatment Modality in Neurologic Disorders – An Experience in Pediatric Population

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ABSTRACT

Objective: Therapeutic plasma exchange (TPE) is a modality to treat neurologic diseases like GBS, CIDP, inflammatory demyelinating disorders of CNS and many others. This study aimed to evaluate the efficacy and safety of TPE either a first line therapy or as an adjunct to other initial treatments in patients with neurologic diseases.

Study Design: It is a descriptive observational study.

Place and Duration of Study: Conducted from October 2021 to December 2023 at Department of Pediatric Neurology, The University of Child Health Sciences and The Children's Hospital, Lahore.

Material and Methods: TPE was performed on alternate days for a total of 3-5 sessions using FRESENIUS KABI apheresis machine and femoral or jugular double lumen catheter. Replacement fluid was fresh frozen plasma (FFP). Patients were assessed before and after TPE for clinical and functional status using GMFCS and MRCS scores and paired t- test was applied to measure it statistically.

Results: 134 procedures were done on 30 patients. Mean age was 7.84 years with 56.6% males. Most common disease was Guillain-Barré syndrome (GBS) (60%), predominantly axonal variant (60%) followed by Neuromyelitis Optica Spectrum Disorder (NMOSD) (16.6%), Anti NMDA receptor encephalitis (10%) and 6.6% each of Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) and chronic inflammatory demyelinating polyneuropathy (CIDP). Improvement in terms of function and motor power was measured both before and after plasmapheresis using Gross Motor Function Classification System (GMFCS) and Medical Research Council Sum (MRCS) score and found a very low p-value of 0.001 in both pairs, which is significant statistically.

Conclusion: TPE is an effective and safe therapeutic modality in pediatric population with neurologic disorders especially in resource constraint settings.

Key Words: *Therapeutic plasma exchange (TPE), Guillain-barre syndrome (GBS), Neurologic diseases.*

INTRODUCTION

Therapeutic plasma exchange (TPE) or plasma Exchange (PLEX) is described as withdrawal and substitution of plasma to eliminate pathogenic material or antibody while reinfusing all the cellular blood components to the patient.[1] It is

commonly performed therapeutic apheresis procedure. During this procedure, patient plasma is passed through a machine to remove the antibodies or harmful substances that are causing the clinical manifestations. To accomplish this objective, a significant volume of plasma must be removed during this procedure and replace it with adequate volume of albumin or blood product such as plasma (FFP), to preserve the blood volume and normal circulation. Various factors influence the effectiveness of therapeutic plasma exchange (TPE), including the proportion of Plasma Volume (PV) exchanged relative to the total PV of child, antibodies distribution across the vascular and outside vascular area, as well as the formation and balance of that antibodies across these spaces. The amount of plasma exchanged with single plasma volume removes approximately sixty-five percent of the original intravascular space component, while approximately 75% removal is achieved with approximately 1.5 PV exchanges, and around 85% removal is achieved with approximately 2 PV exchanges.[2-4]

TPE is a suitable treatment option for various pediatric neuro-immunological diseases such as Guillain-Barre syndrome (GBS), chronic inflammatory demyelinating polyradiculo-neuropathy (CIDP), CNS inflammatory demyelinating disorders like neuromyelitis optica spectrum disorder (NMOSD) including the most recently defined dendrocytopathy (myelin oligodendrocyte glycoprotein antibody associated disease, MOGAD), myasthenia gravis and autoimmune encephalitis.[2,4,5]

American Society for Apheresis (ASFA) has categorized various indications of therapeutic plasma exchange. Category I indications has strong research evidence and include acute inflammatory demyelinating polyradiculo-neuropathy (AIDP/GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), N-methyl D aspartate receptor (NMDAR) encephalitis and myasthenia gravis. Whereas Devic's disease (NMOSD), acute episode of multiple sclerosis, autoimmune limbic encephalitis and pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) are included in category II indications and are recommended as second line treatment.[6-8]

This study is designed to analyze indications, outcome and complications of therapeutic plasma exchange in the treatment of pediatric neurological disorders according to ASFA guidelines which classify various categories in which plasmapheresis is considered appropriate, whether as a primary treatment or as an adjunct to other initial treatments. The objective of this study was to evaluate the efficacy and safety of therapeutic plasma exchange as first line therapy or as an adjunct to other initial treatments in patients with pediatric neurologic diseases.

MATERIAL AND METHODS

It is an observational study (descriptive type), which was a joint venture of Department of pediatric neurology, Pediatric intensive care unit and Hematology at The Children's Hospital and University of Child Health Sciences, Lahore. It is a prospective study and patients who were consecutively admitted to the Department of Pediatric Neurology and Medical ICU were enrolled between October 2021 to December 2023 after getting approval from Children's Hospital & the Institute of Child Health Review Board (IRB) reference No. 2021-443-CHICH dated 15-09-2021. Written informed consent was acquired before the procedure from parents or guardians after explaining the procedure in detail including probable complications.

Children of both gender were selected who presented with neurological conditions like GBS, CIDP, MOGAD, NMOSD and NMDAR receptor encephalitis who did not responded to first line therapy (steroid and/or IVIG) up to 10 days or in whom the first line therapy is not feasible due to cost issues.[4,7] These children have GMFCS IV or V, requiring mechanical ventilation due to respiratory failure or altered state of consciousness, with weight of more than 10 kg who are hemodynamically stable, without any signs of severe infection, for whom informed consent was obtained from their parents, was taken for PLEX.[8] Children who was less than 10 kg weight, was critically sick with hemodynamic instability/unstable cardiac failure/ severe infection and children with underlying coagulation disorder/ severe active hemorrhage/disseminated intravascular coagulation (DIC) were excluded.[9]

Appropriate medical and diagnostic assessments like electrocardiography, chest radiograph, evaluation of cardiac and respiratory status, baseline renal function test, liver function tests, serum electrolytes, serum albumin and viral screening including hepatitis B, C and HIV was conducted before the TPE procedure. TPE was performed on every alternate day, with total of 3-5 sessions. Vascular access was gained by femoral or jugular double lumen catheter. Procedures was performed by apheresis machine manufactured by Bad Homberg, Germany (FRESINIUS Kabi). Nadler's formula was applied to determine patient's total blood volume and 40-60 ml/Kg of plasma replaced during each session. Fresh frozen plasma (FFP) was utilized as replacement fluid in all patients.[10]

Children who fulfilled the inclusion criteria was picked and parents were informed about the procedure. Written consent was obtained before the procedure. Patient bio-data such as name, sex, medical record number, age at presentation, address, weight and exact diagnosis to be recorded over a proforma. Complete assessment including current clinical and functional status (both pre-and 2 weeks post-TPE procedure), laboratory investigations, neuroimaging like MRI brain and spine, neurophysiological studies (NCS/EMG), serology for NMOSD, autoimmune encephalitis and treatment modalities used will also be recorded.

Statistical analysis: SPSS version 25 was used to analyze the data. The quantitative variables like age, number of TPE sessions done, duration between onset of disease and PLEX were demonstrated as standard deviation and mean. The qualitative variables such as sex, Oxygen dependency, complications of procedure and pre and post-assessment using GMFCS and MRCS score were calculated as percentages and frequencies. The data was categorized based on age and gender. After stratification paired t test was applied, with p-value of 0.05 or lower is graded as statistically significant.

Evaluation criteria:

1. **Gross Motor Function Classification System (GMFCS) [11]**

- GMFCS 1 – No Limitations in walking
- GMFCS 2 – Limitations in walking
- GMFCS 3 - Walks with the aid of assisted walking device
- GMFCS 4–Limited mobility independently; May use motorized mobility assistance
- GMFCS 5 – Dependent on a self-propelled Wheelchair for transportation

An improvement of at least one level in functional class is considered significant.

2. **Medical research counsel sum score (MRCSS)[12, 13]**

It is defined as total MRC sum scores by grading three muscles in each limb (Both upper and lower) bilaterally, with the score ranging from sixty (normal) to zero (quadriplegic). *An improvement of at least 10 points in MRC score is considered significant*. The score demands examination of the three group of muscles listed below bilaterally, each with a score from 0 to 5 according to the given grades of muscle power.

- Arm - abduction at shoulder, flexion at elbow, extension at wrist
- Leg - flexion at hip, extension at knee, dorsiflexion at ankle

Grades of muscle power:

Grade V: Power normal

Grade IV: Movements possible against some resistance

Grade III: Against gravity movements, but not resistance

Grade II: Movements possible only if gravity eliminated

Grade I: Only flicker of contraction possible

Grade 0: Complete paralysis/No movement

RESULTS

134 procedures were executed on 30 patients, started from October 2021 till December 2023. Study population has a mean age of 7.84 ± 3.6 years (range 2-14 years) and majority of patients presented between 5-10 years with slight male predisposition (56.6%). Mean hospital stay was 38.1 ± 15.0 days **(table 1)**. Majority of patients (53.3%, n=16) had their first session of PLEX

between 2-4 weeks of onset of illness, while 30% (n=9) and 16.7% (n=5) had their first session after 4 weeks and before 2 weeks respectively. Five sessions of plasmapheresis were done in majority (60%) of patients **(table 1)**. Most common indications of plasmapheresis were GBS (60%), predominantly axonal variant (60% of all GBS cases), followed by NMOSD (16.6%), NMDAR encephalitis (10%) and 6.6% each of myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) and CIDP **(fig 1)**. Intravenous immunoglobulin (IVIG) was given in 23.3% (n=7) as the first line treatment while intravenous methylprednisolone (IVMP) was given in 36.7% (n=11) without significant improvement. Mechanical ventilation was required in 56.7% (n=17) and all these patients had disease related autonomic dysfunction. After PLEX, 16 patients (94%) were weaned off from ventilator. There was significant improvement in motor power and function in 61% (n=11) patients of GBS, while 66.7% (n=2) patients with NMDAR encephalitis had improved GCS and GMFCS after sessions of plasmapheresis **(fig 2)**.

TABLE 1: Demographic profile of patients undergoing plasmapheresis, n= Number of patients

	Mean ±Std	**7.84 ±3.6yrs (Range 2-14 years)**	
		Frequency (n)	**Percentage**
Age of Patients	< 5 years	04	13.3
	5 to 10 years	19	63.3
	10 years	07	23.3
Gender	Male	17	56.6
	Female	13	43.3
Number of Plasmapheresis sessions (per patient)	3 sessions	4	13.3
	4 sessions	8	26.7
	5 sessions	18	60
Mean Hospital Stay	Mean ±Std	36.4±14.8 days	

There were five confirmed cases of NMOSD, who received IVMP as first line treatment without clinical response. After PLEX, improvement in motor power seen in 2 cases. One case had visual impairment only (no light perception initially) that was improved and patient started face recognition, maintain an eye contact and follow an object at 3 feet post-PLEX. There was 100% (n=2) improvement in MOG AD, who had bilateral visual impairment due to optic neuritis and 50% (n=2) in CIDP that was improved from bed bound state to achieve ambulation after undergoing 5 sessions of plasmapheresis. Improvement in terms of function and motor power was measured both before and after plasmapheresis using GMFCS and MRCS score, paired t-test was applied and found a very low p-value of 0.000 in both pairs, which is significant statistically **(table 2)**.

Complications were seen in 53.3% procedures, hypotension being the most common (26.7%) complication followed by allergic reaction (20.0%) and fever (6.7%). There was no procedure related mortality.

TABLE 2: Paired t-Test applied on GMFCS and MRCSS pre and post TPE

	Paired differences					**t**	**df**	**Sig. (2 tailed)**
	Mean	**Std. deviation**	**Std. error mean**	**95% confidence interval of the difference**				
				Lower	Upper			
Pair 1: Pre TPE GMFCS – Post TPE GMFCS	1.100	1.094	0.200	0.692	1.508	5.508	29	0.000
Pair 2: Pre TPE GMFCS – Post TPE GMFCS	11.700	10.195	1.861	-15.507	-7.893	-6.286	29	0.000

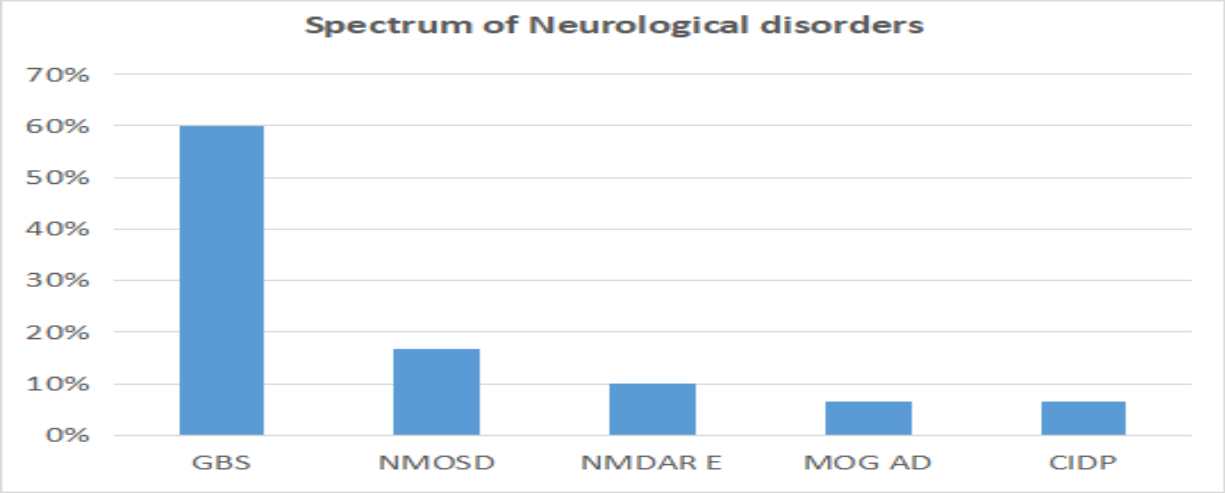

Fig 1: Spectrum of neurological disorders in which TPE was performed

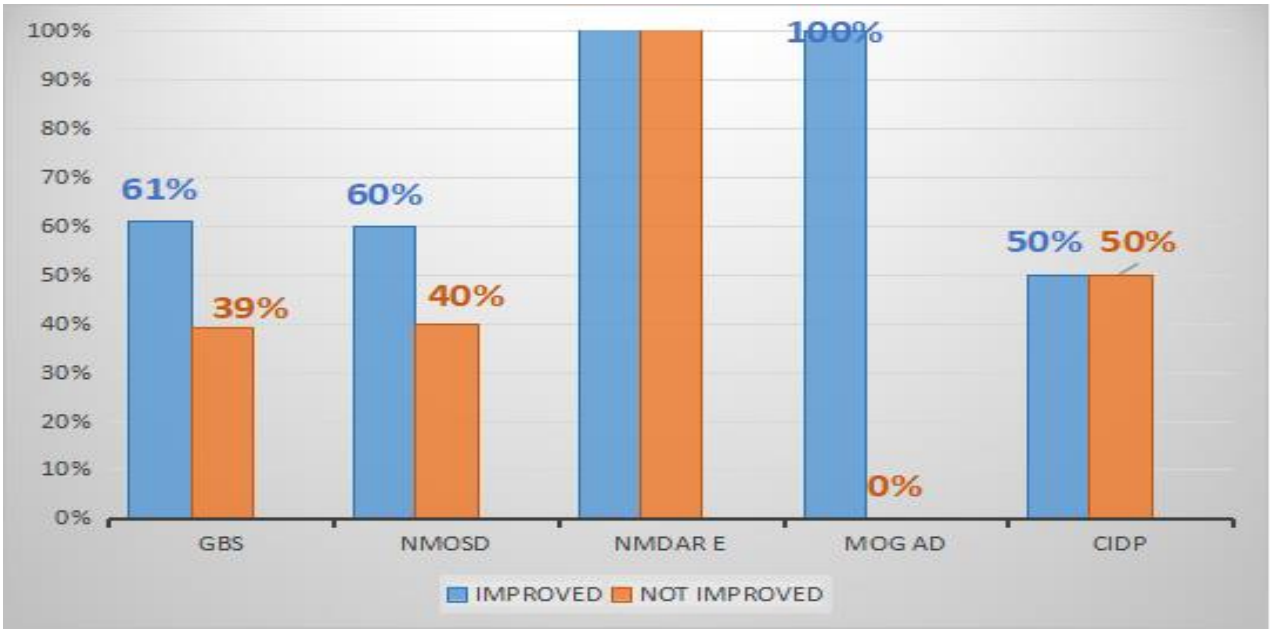

Fig 2: Outcome in different neurological disorders after plasmapheresis

DISCUSSION

In the present study, we shared our experience regarding usefulness of plasmapheresis is in immune mediated neurologic disorders, in which it is used as either first line treatment or an adjuvant treatment modality in cases who were refractory to IVIG or IVMP. The main indication of the PLEX was GBS in the present study (62.6 %), which is similar to many other studies like one done in India comprised of 109 GBS patients out of total, accounting to 67.7%.[2] We used 2 weeks follow up to evaluate improvement which was also been practiced in other studies.[14] The mean hospital stay in our patients was 36.4 ± 14.8 days which is almost similar to GBS patients in Bangladesh

undergoing PLEX.[15] This significantly prolonged hospital stay is due to the fact that patient preparation like pre requisite laboratory investigations, arrangement of blood products and execution of PLEX sessions on alternate day are time taking processes and main factors for this prolonged stay.

Majority of our patients (53.3%) were having their plasmapheresis sessions within first 2-4 weeks of disease onset is because of delayed presentation or referral to our center and sometimes its related with time taking diagnostic workup and arranging prerequisites for PLEX procedure. However, the ideal time to start TPE is initial 7 days from the disease onset with better outcome but it still provides beneficial effect if started within the first 4 weeks from disease onset.[2,7] Our 2 patients with NMDAR encephalitis showed significant clinical improvement, which is comparable to Chinese study that enrolled 19 patients of NMDAR encephalitis, conducting a total of 118 plasmapheresis procedures, exhibited significant improvement ($P < 0.05$).[9]

The response rate of NMOSD patients is 60% in our experience. Clinical data from other center also demonstrate 50% response in NMOSD having visual impairment.[7] This is worthwhile to mention that PLEX have been proved to be an effective therapy in steroid non-responder cases of NMOSD, having response rate of 74%.[16] CIDP is an acquired inflammatory autoimmune polyneuropathy involving peripheral nerves. We experience 50% improvement in CIDP patient, as severe cases do not respond to TPE where axonal loss has occurred.[10] Significant short term outcome in functional improvement and nerve conduction have been seen between 33% and 66% of patients of CIDP using PLEX in a review of available trials.[11] The treatment response in CIDP was 42% in another study.[17] There was favorable outcome in 100% cases of MOGAD with optic neuritis (MOGAD ON) that is correlating with an international multicenter study involving 92 MOGAD ON attacks treated with PLEX reveal substantial improvement in all attacks except for one.[18]

Overall incidence of adverse reactions in our study was 42.9%. In Indian study complications were seen in 14 patients (35%) which was managed adequately. The reported incidence of adverse reactions in the literature ranges from 1.6% to 25%.[19] The most common adverse reaction was hypotension associated with plasmapheresis procedures in our patients like reported in other studies.[9,20]

Limitations: The sample size was relatively small. Single volume exchange was used in most of the patients. Majority patients (87.3%) were done after initial 2 weeks of onset of illness, which may be a factor for suboptimal outcome in clinical condition. Long term follow up was not done.

CONCLUSION

Therapeutic plasma exchange (TPE) has demonstrated significant clinical and functional improvement in pediatric immune mediated neurological disorders, both as first line treatment and as adjunct in patients refractory to steroids or IVIG, especially in resource constraint settings, if timely executed. It can be performed safely in children by taking care of volume shifts and calcium supplementation. Thorough patient assessment and expertise in TPE are crucial for optimizing therapy and reducing adverse outcomes.

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Author's Contribution

MAA: Conception, study design, data collection and manuscript writing
AA: Data collection and interpretation
NM: Data interpretation and manuscript writing
MZR: Data interpretation and manuscript review
NS: Manuscript editing
TS: Review and final approval of manuscript

All the authors have approved the final manuscript draft and accept the responsibility of research integrity.