

Therapeutic Plasma Exchange - An Emerging Treatment Modality in Patients with Neurologic and Non-Neurologic Diseases

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ABSTRACT

Introduction: Therapeutic Plasma Exchange (TPE) is a procedure in which the patient's blood is passed through an apheresis machine, where the filtered plasma is removed and discarded with reinfusion of red blood cells along with replacement fluid such as plasma or albumin in to the patient. We present our experience with TPE in treatment of various neurologic and non-neurologic diseases.

Aim: To evaluate TPE as primary therapy or as a first-line adjunct to other initial therapies as mentioned by American Society for Apheresis (ASFA).

Materials and Methods: A retrospective analysis of TPE procedures was done for a period of nine years, from January 2007 to May 2016 in a tertiary care teaching hospital. A total of 584 TPE procedures were performed in 161 patients between

2 to 75 years of age. Clinical and laboratory investigations like ECG, chest X-ray, cardiorespiratory status and serology were carried out before the TPE procedure.

Results: A total of 161 patients were enrolled in the present study. Guillain-Barre Syndrome (GBS) (67.7%, n=109) was the main indication for TPE, followed by Myasthenia Gravis (MG) (13.04%, n=21). Overall incidence of adverse reactions was 9.93%, inadequate vascular access was a common complication encountered in paediatric age group.

Conclusion: Our results show that TPE is not only safe and effective treatment alternative to Intravenous Immunoglobulin (IVIg), it also strongly holds evidence in the improvement of neurological disorders compared to non-neurological disorders. There is need of further detail evaluation on large number of cases for proper evidence based practice.

Keywords: Apheresis, Guillain-Barre syndrome, Myasthenia Gravis

INTRODUCTION

TPE is the removal and retention of plasma, with return of all cellular components to the patients. This is the most common therapeutic apheresis procedure performed [1]. TPE was first employed in 1952 in multiple myeloma to control hyperviscosity; by 1970s TPE had evolved as a treatment modality in number of neurological diseases [2]. The purpose is to remove the agent in the plasma, such as an antibody, toxin or abnormal protein that is causing the clinical symptoms. TPE is also used to replace a normal factor or substance that may be missing or deficient in the patient's plasma. Regardless the purpose, a large quantity of plasma must be removed during TPE and replaced with sufficient physiological fluid (fresh frozen plasma or albumin) to maintain the intravascular compartment. The efficacy of TPE depends on the Plasma Volume (PV) removed in relation to the patient's total PV, the distribution of the pathogenic substance to be removed between intravascular and extravascular spaces, and the synthesis and equilibrium rate of that substance between the compartments. One volume exchange is equivalent to 65% of the initial component removed from the intravascular space, 1.5 PV approximate around 75%, and around 85% achieved with 2 PV exchanges [3].

TPE is an ideal indication for treatment of neurological conditions like GBS and chronic inflammatory demyelinating polyneuropathy and also the non-neurologic conditions like MG, hyperviscosity syndrome, thrombotic thrombocytopenic purpura, haemolytic uremic syndrome, idiopathic thrombocytopenia and in renal, rheumatologic diseases [4].

We analysed our experience related to the indications, complications and outcome of TPE in the treatment of patients belonging to various categories according to the ASFA guidelines considering

apheresis as standard and acceptable, either as primary or as a first line adjunct to other initial therapies.

MATERIALS AND METHODS

The present retrospective study was conducted at Department of Transfusion Medicine (Blood Bank) of a tertiary care hospital, located in Belgavi, Karnataka, India, for a period of nine years i.e., from January 2007 to May 2016. All the patients indicated for TPE by the physician for neurological conditions like GBS (n=109), Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) (n=6) and non-neurological conditions like Thrombotic Thrombocytopenic Purpura (TTP) (n=17), Haemolytic Uremic Syndrome (HUS) (n=8) and MG (n=21) were included in the study. Patients who were not willing to undergo the procedure were excluded. Proper clinical and laboratory investigations like ECG, chest X-ray, cardiorespiratory status and serology were carried out before the TPE procedure. Informed consent was obtained from every patient prior to the procedure, and was explained about the procedure in detail with the probable complications. Total 584 procedures (one to six cycles of TPE) were performed on 161 patients, depending upon the clinical improvement in the patient. TPE was performed on every alternate day using a double lumen femoral catheter COBE Spectra apheresis machine (Manufacturer TERUMO BCT, INC). Patient's total blood volume was calculated as per Nadler's formula [5].

The ratio kept for the anticoagulant acid citrate dextrose was 1:10 whole blood and the blood flow rate were set to 25-40 ml/minutes. The speed set for blood pump was 90 ml/minutes and gradually increased up to a maximum of 130 ml/minutes taking care to prevent clotting due to low speed and filter breakage due to high speed. For every 15-30 minutes intervals, the blood pressure and pulse, changes in appearance, development of symptoms like

light-headedness, nausea, paraesthesia's and overall status were closely monitored. A 10 ml of calcium gluconate was given during the procedure to prevent citrate toxicity in patients with low calcium levels [3]. The duration of procedure varied from one to three hours depending upon the amount of plasma exchange. Exchange of 1-1.5 PV given to the patients and were transfused with three units of FFP. Albumin is the standard choice alternate to FFP but because of its high cost, albumin was transfused only in the patients who could afford for it and the dosage was 250 ml albumin in 500 ml of saline infusion. Normal saline or FFP was infused in patients who developed hypotension and the procedure was temporarily ceased. All TPE procedures were carried out in ICU by blood bank technicians trained in TPE under the supervision of blood bank medical officer and the physician. Complications and adverse reactions were assessed thoroughly throughout the procedure and post procedure. Medical Research Council Scale was used to assess the grading of muscle power in neurological patients [6].

The present study was approved by the Institutional Ethical Committee.

RESULTS

Total 161 patients were indicated for TPE, of which 107 were male and 54 were females with mean age of 40.25 (range 2 to 75 years) [Table/Fig-1]. The indications, frequency of TPE performed and category, grade of recommendation are listed in [Table/Fig-2]. Neurological cases accounted to 71.4%, with 67.7% cases of GBS followed by the 3.7% cases of CIDP. Non-neurologic cases accounted to 28.6%, with 13.04% cases of MG followed by 10.5% of TTP and HUS with 4.9%. A close correlation between clinical and functional improvement was noted in 115 neurological patients, out of which 105 patients showed Grade-IV improvement in muscle strength (movement against moderate resistance over full range of motion) and remaining 10 patients showed Grade-III improvement (movement against gravity over almost full range of motion). The result of plasma exchange in terms of improvement in the clinical condition of the patient was excellent in all the neurologic compared to non-neurologic patients. Non-neurological cases in terms of improvement were noted as a result of decreased antibody levels post procedures, however the titres cannot be measured.

Age group	Male	Female	Total
0-20	24	19	43
21-40	46	07	53
41-60	23	21	44
61-80	14	07	21
Total	107	54	161

[Table/Fig-1]: Age and sex distribution.

Indications	Frequency of TPE procedures performed	Category and Recommendation grade (according to ASFA guidelines)
I. Neurology diseases GBS and CIDP	five exchanges daily or alternate-day intervals.	Both Category – I Grade- 1A and 1B
II. Non Neurology Diseases TTP and HUS Myasthenia Gravis	Treated as emergency: TPE within four hours. For myasthenic crisis: five exchanges at daily or alternate-day intervals. Before thymectomy : three to five exchanges at alternate-day intervals; 48-hour gap between last plasma exchange and surgery.	Category – I and II Grade- 1A and 2C Category – I, Grade- 1A For moderate-severe Category – I, Grade- 1C For Pre-Thymectomy

[Table/Fig-2]: Indications for TPE, with frequency of procedures, categories and grading according to ASFA guidelines.
Guillain-Barre syndrome (GBS), Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Thrombotic thrombocytopenic purpura (TTP) and Haemolytic uremic syndrome (HUS)

The number and frequency of TPE procedures depended upon the clinical improvement of the patients as some required long term maintenance. Complications like inadequate vascular access was common in paediatric age group patients (3.7%) and in few cases, machine error were reported due to machine breakdown (18.6%). Incidence of adverse reactions accounted to 9.93% (16); most common was hypotension (4.9%), followed by fever with chills (2.4%), nausea (1.2%) and allergic reactions (1.4%). No mortality occurred while performing TPE procedures.

DISCUSSION

In the present era of technological world, with available upgraded apheresis machines which are targeted at the most selective possible removal of pathological components in the blood, therapeutic apheresis has undergone a real revolution in the recent years with tremendous improvement in the patients with various disorders [1]. American Academy of Neurology while assessing plasmapheresis found that TPE is extremely safe in experienced hands [4]. In the present study, all the neurologic patients showed improvement in terms of muscle power grading and clinically patients under assisted mechanical ventilation were recovered without the need for ventilation, independent walking with and without assistance were noticed by four weeks and were assessed till six months. The non-neurologic patients showed improvement with drop in the antibody levels post the TPE procedures, the antibodies level were not identified nor measured meticulously.

GBS was the main indication in the present study, which comprised of 109 patients accounting to 67.7%. TPE or IVIG are recommended treatment options in GBS, both have been found to be equally effective and significantly better than the conservative treatment for recovery from the disability [7]. However, in GBS with axonal involvement, TPE has been reported to be of greater potential benefit than IVIG. TPE is most effective when initiated within seven days of disease onset, for controlling symptoms of neuroimmunological disorders [8]. In the largest series of TPE on neurological disorders by Gafoor VA et al., they had enrolled 203 GBS patients in their study and similar to our study, found that TPE as cost effective alternative to IVIG and is safe in treating various immune mediated neurological disorders [9].

MG was the second most common indication with 13.04% of cases. Pinching AJ and Peters AK first described TPE as a form of treatment for MG in 1976 [10]. MG treatment modalities include acetylcholinesterase inhibitors, thymectomy, immunosuppression and either TPE or IVIG. Patients diagnosed with MG either seropositive or negative for the antibodies, responded well to TPE procedure before surgery when compared to any other adjunct therapies [7]. Clinically the effects are seen within 24 hours of TPE and are more effective with immunosuppressants, there are no adequate randomized control trials to prove the effects, but many cases report benefit from plasma exchange over IVIG with improvement in ventilator status. Similar to present study, Kumar R et al., noted tremendous improvement in patients with MG and in those who experience exacerbations in spite of treatment with steroids and oral immunosuppressants [11].

TTP in the present study responded well to the TPE procedures. TPE has decreased the overall mortality from >90% to <10% over the period of time [12]. Sidhu D et al., have reported that anaphylactic reactions to plasma are very common in TTP cases. They suggested substituting octaplas for FFP or, alternatively, using albumin with slowly increasing amounts of FFP to mitigate the risk of further anaphylactic adverse events [13].

HUS holds very low quality evidence in our study for the use of TPE as only eight cases were reported, hence there is a need for further evaluation of the role of TPE in the treatment of HUS in our institution and still under trial.

The overall incidence of adverse reaction reported in the literature range from 1.6% to 25% with severe reaction occurring in 0.5%-

3.1% [11]. In our study, overall incidence of adverse reactions was 9.93%. The most common being hypotension, followed by fever with chills, nausea and allergic reactions which were managed easily. Complications like inadequate vascular access were most commonly observed in 11 children. In children, TPE procedures are associated with multiple and unique challenges, hence experience based upon the adult clinical practice are extrapolated, which may not be evidence based [14]. Although complication can occur, most of these are rapidly recognized and reversed and are rarely serious.

Improvement in apheresis machines has made TPE a very safe treatment. TPE shortens the course of hospitalization and reduces the mortality and incidence of permanent paralysis.

LIMITATION

The present study holds few limitations. It was based on single-centre data hence a large trial of TPE is required to compare our findings, also there are variations in the algorithms, methodology and technologies which differ from center to center.

CONCLUSION

This is, to the best of our knowledge, largest series of TPE in neurologic and non neurologic cases from North Karnataka. None of the institutions are practicing TPE in this region. TPE can be performed safely in children and has been shown to be effective, as it is purely based on the experienced hands. Careful assessment of the patients and expertise in TPE is essential to optimize therapy and minimize adverse consequences.

Our results show that TPE is a safe and effective alternative to IVIG in patients who cannot afford it. To understand the scenario across the country about effectiveness and statistical data of the TPE procedures, it is mandatory to establish Indian apheresis registry.

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