Plasma Exchange: A Newer Therapeutic Approach

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ABSTRACT

Introduction: Plasma exchange is a therapeutic procedure used to treat a variety of diseases through the bulk removal of plasma. THERAPEUTIC PLASMA EXCHANGE (TPE) is a potentially lifesaving but also invasive procedure with risk of adverse events and complications and requires close monitoring by experienced teams. 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 adjunctto 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 Three years, from January 2018 to December 2020 in a tertiary care hospital. A total of 78 TPE procedures were performed in 22 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 22 patients were enrolled in the present study. Guillain-Barre Syndrome (GBS) (68.18%, n=15) was the main indication for TPE, followed by Myasthenia Gravis (MG) (13.63%, n=3). Overall incidence of adverse reactions was 9.09%, inadequate vascular access was a common complicationencountered in pediatric 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

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 serves to remove pathogenic substances (e.g., autoantibodies or toxic agents) and/or to administer deficient substances present in plasma of healthy donors (e.g., a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, ADAMTS13) though other potential immunomodulatory effects beyond the removal of Ig may be involved. Reported effects of TPE on immune function include T-cell modulation with a shift from in the Th1/Th2 balance with a shift toward Th2, suppression of IL-2 and IFN-γ production. The indications for TPE have been refined over time. TPE is an invasive procedure with often emergent indications, demanding its execution as soon as possible. Thus, a rapid response by experienced staff, with specific equipment, close monitoring, and multidisciplinary management are essential. It is an emerging treatment modality in patients with non-neurological diseases like Myasthenia Gravis, thrombotic thrombocytopenic purpura, hyper-viscosity syndrome and in renal and rheumatologic diseases and neurological conditions like GBS, chronic inflammatory demyelinating polyneuropathy and also other immunological disorders [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 at Jaipur, Rajasthan, India, for a period of three years i.e., from January 2018 to December 2020. All the patients indicated for TPE by the physician for neurological conditions like GBS (n=15), Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) (n=1) and non- neurological conditions like Thrombotic Thrombocytopenic Purpura (TTP) (n=2), Haemolytic Uremic Syndrome (HUS) (n=1) and MG (n=3) 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 78 procedures (one to six cycles of TPE) were performed on 22 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].

Mechanism of plasma removal and exchange

Devices used to perform TPE can be divided into 2 broad categories, those that separate the plasma from the cellular components based on size and those that separate components based on density.

Currently licensed TPE devices can operate with a continuous or an intermittent flow. Both, centrifugal cTPE and membrane-based mTPE devices are available. In most nephrology departments and ICUs, the preferred devices are membrane-based (mTPE), including multifunctional renal replacement therapy (RRT) machines. Devices separating based on size use filters, whereas those separating by density use centrifugation.

The predominant method used for TPE is centrifugation through apheresis machine in transfusion medicine or hematology department that often use citrate for anticoagulation. In these apheresis devices, whole blood is pumped into a rapidly rotating separation chamber. Components separate into layers based upon their density, with the most dense element, RBCs, migrating the furthest from the axis of rotation and the least dense portion, plasma, layering closest to the axis of rotation. Intermediate layers, moving from the axis of rotation outward, are platelets, lymphocytes, and granulocytes. In TPE, the plasma layer is removed and discarded, and the remaining cellular elements are mixed with a replacement fluid and returned to the patient. It is important to realize that there is some mixing that occurs at the interface between the layers in the centrifuge. The implication of this is that some platelets may be present in the plasma layer and, depending upon several factors, there may be a resulting loss of platelets during TPE.

Kinects of plasma removal

The efficacy of TPE depends on 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.

To be efficiently cleared by TPE, the substance should ideally be identified and assayed and have a high molecular weight, low distribution volume (chiefly in plasma), long half-life, and low turnover rate. Of note, the degree of substance removal does not necessarily correlate with the alleviation of the clinical symptoms like in myasthenia gravis.

The fact that a replacement fluid is necessary to perform TPE and that it is administered while the procedure is occurring has implications for the removal of substances circulating in the plasma. Because of the dilution of the plasma by the replacement fluid, the substance of interest cannot be completely removed from the circulation.

One volume exchange is equivalent to 65% of the initial component removed from the intravascular space, 1.5PV approximate around 75% and 85% achieved with 2 PV exchanges. As additional plasma volumes are exchanged, the absolute amount removed becomes lower, although removal of a fixed 60%-70% still occurs. For this reason, routine practice is to exchange only 1-1.5 plasma volumes during a TPE. Treating volumes beyond 1.5 plasma volumes removes smaller, less clinically important amounts of pathologic substance present in the plasma while prolonging the procedure and exposing the patient to more replacement fluid and anticoagulant. The result is an increasing risk of complications without increasing benefit to the patient. There are diminishing returns in treating beyond 1.5 plasma volumes.

The procedure assumes that there is no exchange between the intravascular and extravascular compartments during the procedure. However, this assumption is not valid for all substances, so the amount removed and the concentration in the plasma at the end of the procedure may not match that predicted. For example, IgG is evenly distributed between the intravascular space and the extravascular space and can move between these compartments. During TPE, as the concentration of IgG in the intravascular space decreases, IgG within the extravascular space moves into the intravascular space. After the procedure, the plasma concentration of IgG will be greater than predicted, suggesting that the TPE was not as efficient as expected. This has led some to believe that the removal of such molecules is less efficient and that greater volumes should be treated, but the amount of IgG in the waste bag is actually greater than predicted, indicating that TPE was more efficient than expected due to redistribution during the procedure, with removal of IgG from both the intravascular and extravascular compartments. Because TPE involves the bulk removal of plasma, anything circulating in plasma will also be removed. The procedure is nonselective removing both normal and pathologic plasma components.

For example, during a I plama volume exchange using albumin as replacement fluid, coagulation factor activity decreases and coagulation test may become abnormal. Significant declines in factor 5, F7, F8, F9 and VWF activity occurs. Activities of F8, F9 and VWF return to normal within 4 hours after TPE, whereas the remaining coagulation factors achieve pre- TPE activity levels by 24 hours. the bulk removal and replacement of plasma also has implications for laboratory testing. The removal of Abs from the patient can result in false negative tests for infectious diseases, autoantibodies, alloantibodies, and enzyme and coagulation factor activity. Samples for such testing should be collected before the initiation of TPE. TPE may also remove medications.

It is important to realize that one-third of the replacement fluid administered at the beginning of the TPE will be present by the end, with the majority having been removed. Administering plasma as a replacement fluid at the beginning of a TPE results in exposure of the patient to blood products without benefit.

The most commonly used replacement fluid is 4%-5% human albumin in physiologic saline. This solution has the advantage of avoiding disease transmission and transfusion reactions (e.g., transfusion-related acute lung injury), both of which can occur with plasma. The main disadvantage of albumin is its expense relative to plasma. This replacement fluid is slightly hyperoncotic compared with plasma and may therefore expand intravascular volume. This effect can be beneficial in avoiding hypovolemia. Because the albumin replacement fluid is the most expensive component of a TPE procedure and use of 100% albumin as a replacement does expand intravascular volume, some practitioners will use lower albumin concentrations, such as 70% albumin and 30% saline. When this is done, the albumin and saline are alternated, with the majority of the albumin being given at the end of the procedure to avoid hypovolemia from redistribution of the crystalloid. It should be noted that the use of albumin and saline has been associated with a greater frequency of hypovolemic reactions compared with using albumin alone. When albumin is used as replacement solution, metabolic acidosis may be seen after the TPE session because albumin has an acidic profile.

Plasma is used as a replacement fluid in a limited number of disorders, for example, to replace ADAMTS13 when treating thrombotic thrombocytopenic purpura, to treat coagulation factor deficiencies, and to prevent dilutional coagulopathy in patients with active bleeding. Because of the large volume, the number of donor exposures, and often prolonged duration of therapy, the risk of allergic reactions is higher with plasma than with albumin, and some centers administer antihistamines and/or glucocorticoids when using plasma. When plasma is used as replacement solution, metabolic alkalosis may occur because of metabolism of citrate used as anticoagulant and citrate present in stored plasma. For every citrate molecule metabolized, there is a consumption of hydrogen ions and production of three sodium bicarbonate molecules, thus increasing serum pH levels.

Vascular access

The choice of vascular access for TPE depends primarily on the method used: cTPE typically requires lower blood flow rates (Qb) (50–120 mL/min) than mTPE (150–200 mL/min). A lower Qb enables the use of narrower catheters such as peripheral devices (e.g., 18-Gaugeneedle) or standard double-lumen central venous catheters (e.g., 7 Fr) or a cenral venous line. With a peripheral vein, single-needle access is feasible when using cTPE but might increase the treatment time. Peripherally inserted central catheters are not suitable because their narrow catheter gauge will collapse with the negative pressures exerted during TPE. The mTPE devices often require higher Qb and therefore, wider catheters such as temporary hemodialysis catheters or large-diameter dual-lumen catheters (e.g., 13.5 French). The optimum characteristics of a catheter for TPE include rigid walls, a large diameter, and a short length to reduce resistance and decrease instrumental arms. Machines used for cTPE can concentrate RBCs to a hematocrit of 80% or higher, which allows for more plasma per volume to be processed compared to mTPE devices . A higher Qb is needed with mTPE devices as they usually extract only about 30–35% of processed plasma to prevent RBC damage from a high hematocrit. Thus, with mTPE devices three or four times more plasma volume must be processed to remove similar plasma volume as with cTPE devices.

Anticoagulation

Anticoagulation for TPE aims to achieve a delicate balance between preventing circuit failure with loss of expensive blood components and preventing bleeding. Systemic heparin and regional citrate are the most common anticoagulants, while epoprostenol can also be used, when citrate is unavailable, and heparin is contraindicated. The risk of bleeding during TPE is lower with citrate than with heparin. Symptomatic hypocalcemia is also more common with citrate and can be prevented by prophylactic calcium administration.

Clinical response

The expected benefits and potentially deleterious effects of TPE are dependent on the timing of the procedure with respect to the onset of the illness, the volume of fluid exchanged, the type of replacement solution, and the frequency and intervals of plasma removal. The individual criteria for "clinical response" are highly disease specific, ranging from changes in individual or multiple hematological parameters, antibody concentrations or biochemistry to improvement of clinical signs and symptoms. The impact of TPE can be rapid or slow and may last for weeks to months, depending on the underlying disease. However, long-term effects, including psychological well-being and the risk of chronic organ dysfunction beyond the acute illness are rarely reported.

The American Society of Apheresis clinical guidelines

The ASFA is a professional society composed of physicians, scientists, and allied health professionals. It was founded in 1982 when the Society of Hemapheresis Specialists, an allied health organization, and the American Society for Apheresis Symposia, a physician and scientist organization, merged. Since that time, a goal of ASFA has been to advance the "science of apheresis medicine."

To provide practical, evidence-based guidance to the apheresis practitioner and to encourage critical science in the field of apheresis medicine, ASFA has published guidelines on the use of therapeutic apheresis in clinical practice. The latest guidelines on therapeutic apheresis in 2019. They identified four categories of use: first-line therapy (Category I), second-line therapy (Category II), role not established (Category III), and ineffective or harmful (Category IV). 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 22 patients were indicated for TPE, of which 15 were male and 7 were females with mean age of 40.56 (range 2 to 75 years). The indications, frequency of TPE performed and category, grade of recommendation are listed in [Table 1]. Neurological cases accounted to 72.72%, with 68.18% cases of GBS followed by the 4.54% cases of CIDP. Non-neurologic cases accounted to 27.28%, with 13.64% cases of MG followed by 9.09% of TTP and HUS with 4.55%. A close correlation between clinical and functional improvement was noted in 16 neurological patients, out of which 14 patients showed Grade-IV improvement in muscle strength (movement against moderate resistance over full range of motion) and remaining 2 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 titers cannot be measured.

Indications	Frequency of TPE procedures performed	Category and Recom- mendation 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	Treated as emergency: TPE within four hours.	Category – I and II Grade- 1A and 2C

TTP and HUS	For myasthenic crisis: five exchanges at daily or alternate- day intervals.	Category – I, Grade- 1A For moderate-severe
Myasthenia Gravis	Before thymectomy : three to five exchanges at alternate-day intervals; 48-hour gap between last plasma exchange and surgery.	Category – I, Grade- 1C For Pre-Thymectomy

Table 1: 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 (4.54%) and in few cases, machine error were reported due to machine breakdown (18.18%). Incidence of adverse reactions accounted to 9.09% (2); including hypotension (4.54%), and fever with chills (4.54%). 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 15 patients accounting to 68.18%. 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 13.63% 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 immunosuppressents, 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 9.09%. Complications like inadequate vascular access were most commonly observed in 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.

CONCLUSION

Plasma exchange is a therapeutic procedure used to treat a wide variety of diseases through the bulk removal of plasma. Whereas the mechanism of action has been thought to be the removal of pathologic Igs, there is evidence suggesting an immunomodulatory effect. The procedure is safe, with the majority of reactions and complications being mild, easily treated, and of limited duration. Unfortunately, the published evidence supporting the use of plasma exchange is of limited quality. To assist the practitioner in the determining the appropriate use of plasma exchange and other apheresis treatments, and to promote additional studies of the role of apheresis, the ASFA has created evidence-based guidelines that have been accepted internationally as indications for the use of apheresis in clinical medicine. TPE 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.

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.

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