Original Article

Access this article online

Quick Response Code:

Website: www.ajts.org

DOI: 10.4103/ajts.ajts_125_20

Therapeutic plasma exchange an emerging treatment modality: A 3-year retrospective analysis of patients admitted in a multispecialty hospital of North India

Archana Solanki, Ashutosh Singh, Abhishek Chauhan[1], Devisha Agarwal[2], D. Himanshu[3], Tulika Chandra

Abstract:

BACKGROUND AND AIMS: Therapeutic plasma exchange (TPE) is increasingly used throughout the medical field. We aimed to analyze the various aspects of TPE practices at our hospital in terms of clinical indications, technical feasibility, safety, outcome as well as complications associated with the procedures.

MATERIALS AND METHODS: The data included demographic profiles, clinical parameters, and technical characteristics of each TPE procedure. All the information was noted in data spread sheet (Microsoft Excel 2013) for further analysis.

RESULTS: This is a 3-year retrospective study of total 266 TPE procedures carried out on 92 patients with different clinical conditions. Out of them, 55 (59.8%) were male and 37 (40.2%) were female patients. There were six major categories such as (1) neurological, (2) hematological, (3) gastrological, (4) renal, (5) rheumatic, and (6) others. The TPE treatment was highest in neurology group (60.2%), followed by gastrology group (24.4%). Most of the procedures (82.6%) were according to the American society of apheresis 2016 I or II categories (76/92 patients).

CONCLUSION: TPE is beneficial and used as primary or secondary adjunctive therapy for a wide spectrum of various diseases and syndromes. TPE is considered as safe, cost-effective, and life-saving treatment modality in various diseases.

Keywords:

American society of apheresis, citrate anticoagulation, extracorporeal, therapeutic plasma exchange

Departments of Transfusion Medicine, [2]ENT and [3]Medicine, King George's Medical University, [1]Department of Radiodiagnosis, Dr RML Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Address for correspondence:
Dr. Tulika Chandra, Department of Transfusion Medicine, King George's Medical University, Lucknow - 226 003, Uttar Pradesh, India.
E-mail: drtulikachandra@gmail.com

Submitted: 20-08-2020
Revised: 10-12-2020
Accepted: 21-03-2021
Published: 12-06-2021

Introduction

The term "apheresis" derived from Greek word meaning "to remove" or "take away."[1] Therapeutic apheresis (TA) is an extracorporeal therapy used in the treatment and management of various diseases and is achieved either through the removal and discarding of selected blood constituents or through the collection of targeted blood elements with their subsequent *ex vivo* manipulation and return to the patient.[2] Therapeutic plasma exchange (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.[3] TPE is an extracorporeal procedure that involves removing of the patient's plasma and exchanging it with an appropriate fluid. Its use was first reported in the literature as an extra corporeal blood purification

How to cite this article: Solanki A, Singh A, Chauhan A, Agarwal D, Himanshu D, Chandra T. Therapeutic plasma exchange an emerging treatment modality: A 3-year retrospective analysis of patients admitted in a multispecialty hospital of North India. Asian J Transfus Sci 2021;15:46-51.

technique more than a 100 years ago.[4] The ultimate goal of TPE is to remove alloantibodies, autoantibodies, immune complexes, high concentration lipoproteins, toxins, various pathological proteins, and molecules. Thus, TPE plays a key role in the management of various diseases. 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 compartments, 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.[5] Treating volumes in excess of a 1.5-PV exchange confers little benefit due to the diminishing return effect, while placing the patient at higher risk for procedural complications.[6]

According to the recent American Society of Apheresis (ASFA) 2016 guidelines, TPE is beneficial and used as primary or secondary adjunctive therapy for a wide spectrum of various diseases and syndromes. According to it, TPE can be performed to treat 87 diseases with 179 indications. In addition, a Grading for Recommendation Assessment, Development and Evaluation system is also provided for each TPE indication.[7-9]

Thus, TPE is increasingly used, safe and effective treatment modality throughout the world.

Aims

In the present study, we aimed to analyze the various aspects of TPE practices at our hospital in terms of clinical indications, technical feasibility, safety, outcome as well as complications associated with the procedures. We also analyze the utility of TPE according to the new ASFA 2016 guidelines.

Materials and Methods

We conducted a retrospective analysis of the data of the patients underwent TPE procedures at our hospital from June 2017 to June 2020. The data included demographic profiles, clinical parameters, and technical characteristics of each TPE procedure.

All TPE procedures were performed using centrifugal continuous flow cell separator Fresenius separator (COM.TEC), version 4.00.xx (Fresenius Hemocare GmbH, Bad Homburg v. d. H., Germany). Informed consent was taken from each patient undergoing TPE after explaining benefits, other alternative treatments available, and possible risks associated with the procedure. All the TPE procedures were done at bedside in intensive care units of Medicine and Critical Care Medicine departments under close supervision of specialists (apheresis technician, blood bank officer, and treating clinician). Vitals were monitored before, during, and after each procedure. The high blood flow required for TPE was achieved by placing dual lumen central venous catheter in subclavian or internal jugular vein. For peripheral access, a 12 French double lumen femoral catheter was used. The anticoagulant acid-citrate-dextrose type A solution (ACD-A) was used in all TPE sessions. The ratio kept for ACD-A was from 1:9 to 1:14 to whole blood and the blood flow rates were set to 25–45 ml/min. The speed set for blood pump was 90 ml/min and gradually increased up to a maximum of 130 ml/min taking care to prevent clotting due to low speed and filter breakage due to high speed. In all TPE procedures, 1.0–1.5 PVs are normally removed in a single session. The patient's total blood volume was calculated according to Nadler's formula.[10] The number and frequency of TPE are varied from patient to patient and usually decided by underlying disease, response to treatment and treating clinician. The duration of procedure varied from 1 to 3 h depending on the amount of plasma exchange. Five percentage albumin solution is the standard choice as a replacement fluid for TPE but because of its high cost, 5% albumin was transfused only in the patients who could afford it and the dosage was 250 ml albumin in 500 ml of saline infusion. Seventy percentage fresh frozen plasma (FFP) with 30% of normal saline (NS) was infused as a replacement fluid in most of the patients. A 10 ml of 10% calcium gluconate was given during the procedure to prevent citrate toxicity in patient with decreased calcium levels. Medical Research Council Scale was used to assess the grading of muscle power in neurological patients.[11] Nonneurological cases in terms of improvement were noted as a clinical improvement as well as decreased antibody levels postprocedures; however, the titers cannot be measured. Complications and adverse reactions were assessed closely throughout the procedure and postprocedure.

All the information was noted in data spread sheet (Microsoft Excel 2013) for further analysis. The present study was approved by the Institutional Ethical Committee.

Results

This is a 3-year retrospective study from June 2017 to June 2020. A total of 266 TPE procedures carried out on 92 patients with different clinical conditions who were admitted to the hospital during study period. Out of them, 55 (59.8%) were male and 37 (40.2%) were female patients. The patient's age varied from 12 years to 81 years with mean of 34.6 years. The mean number of TPE procedures performed per patient was 3.09.

The mean PV exchanged in patients was 2641.62 ml (minimum 830.42 ml and maximum 3920.49 ml). Seventy percent FFP with 30% of NS was infused as a replacement fluid in most of the patients (90/92). Five percentage albumin was transfused only in 2 (2.17%) patients who could afford it, and the dosage was 250 ml albumin in 500 ml of saline infusion. According to spectrum of diseases, the patients were categorized into six groups. These were (1) neurological, (2) hematological, (3) gastrological, (4) renal, (5) rheumatic and the last group, and (6) others [Table 1]. The TPE treatment was highest in neurology group (60.2%), followed by gastrology group (24.4%) as shown in Table 2. Most of the procedures (82.6%) were according to ASFA 2016 I or II categories (76/92 patients).

The clinical and physical improvement was noted in 42 neurological patients including Guillain–Barre syndrome (GBS), chronic inflammatory demyelinating polyneuropathy, myasthenia gravis (MG), and autoimmune encephalitis. Out of which 35 patients showed Grade-IV improvement in muscle strength (movement against moderate resistance over full range of motion) and remaining seven patients showed Grade III improvement (movement against gravity over almost full range of motion).

The second most common indication was liver failures cases. Out of 32 patients, 24 patients were underwent high volume TPE, in which target is 15% of body weight. In rest of eight patients, normal TPE was performed. Twenty-six patients showed improvement and respond to supportive care. Five patients were died due to underlying morbidity.

TPE were associated with marked improvement in all three Wegener's granulomatosis patients. These patients very well responded to the combination strategy of TPE and immunosuppression. There were six patients of TTP, out of which two were died due to myocardial infarction. Four TTP patients were responded to TPE. All the three patients with organophosphorus poisoning were died due to respiratory failure. One pregnant lady with antiphospholipid syndrome was treated with combination of TPE plus low molecular weight heparin and methyl prednisolone therapy.

Five patients were admitted with diagnosis of sepsis and multiorgan failure, they were treated with combination strategy of TPE and supportive care. Three patients were died with due course of time due to severe underlying morbidity. Total 13 (14.1%) out of 92 patients were died due to associated serious morbidities.

The adverse events occurred in 22.8% (21/92) of patients underwent TPE sessions. Most common adverse events were allergic reactions, paresthesias with tingling, and hypotension [Table 3]. Treatment of all the adverse reactions was done symptomatically. One patient developed severe anaphylactic reaction complaining severe itching, wheezing, swelling of lips and tongue, bronchospasm, formation of hives, and redness all over the body. To treat anaphylactic reaction, injection adrenaline 0.5 ml i.m. in 1:1000, oral pheniramine maleate 5 mg and injection hydrocortisone 100 mg i.v. were given, after 20 min procedure restarted and completed successfully.

Discussion

In the current scenario, with fully automated apheresis machines which are targeted at the most selective possible removal of pathological constituents in the blood, TA has undergone a real revolution in the present years with tremendous clinical improvement in the patients with various disorders.[12] Now, TPE procedures routinely performed at our institution. According to the ASFA 2016 guidelines, the indications for TPE

Table 1: Clinical and demographic detail of 92 patients

Variables	*n* (%) or mean
Total patients	92
Male patients	55 (59.8)
Female patients	37 (40.2)
Age	34.6 (12-81)
Indications for TPE	
Neurological (Guillain- Barre syndrome, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, auto-immune encephalitis)	42 (45.7)
Hematological (thrombotic thrombocytopenic purpura)	6 (6.5)
Gastroenterological (acute liver failure, acute on chronic liver failure, hepatic encephalopathy posthepatitis)	32 (34.7)
Rheumatic (anti phospholipid syndrome)	1 (1.1)
Renal (Wegner's granulomatosis)	3 (3.3)
Other (Oragano-phosphorus poisoning, sepsis with MOF)	8 (8.7)

TPE=Therapeutic plasma exchange, MOF=Multiple organ failure

Table 2: Characteristics of therapeutic plasma exchange treated patients (*n*=92)

Clinical condition	ASFA - 2016 category/GRADE	Number of patients (*n*=92)	Gender	Age, mean (range)	Total sessions (*n*=266)	Number of sessions per patient, mean (range)
Guillain - Barre syndrome	I/1A	34	Male - 28 Female - 6	35.3 (12-81)	131	3.85 (1-6)
Myasthenia gravis	I/1B-I/1C	2	Male - 2 Female - Nil	35 (30-40)	12	6 (5-7)
Chronic inflammatory demyelinating polyneuropathy	I/1B	2	Male - 2 Female - Nil	41 (40-42)	3	1.5 (1-2)
Autoimmune encephalitis	II/2C	4	Male - Nil Female - 4	28.3 (15-40)	14	3.5 (2-5)
Thrombotic thrombocytopenic purpura	I/1A	6	Male - 2 Female - 4	29.3 (18-45)	14	2.3 (1-3)
Wegner's granulomatosis	I/1C-III/2C	3	Male - 1 Female - 2	40.7 (30-54)	14	4.7 (3-7)
Acute liver failure, acute on chronic liver failure, hepatic encephalopathy posthepatitis	I/1A, III/2B, III/2B	32	Male - 17 Female - 15	39.3 (17-70)	65	2.0 (1-8)
Anti phospholipid syndrome	II/2C	1	Male - Nil Female - 1	28	4	4
Sepsis with multi - Organ failure	III/2B	5	Male - 1 Female - 4	32.2 (19-46)	8	1.6 (1-3)
Organo - Phosphorus poisoning	III/2C	3	Male - 2 Female - 1	37.3 (22-50)	8	2.6 (2-4)

ASFA=American society of apheresis, GRADE=Grading for recommendation assessment, development, and evaluation

Table 3: Adverse reactions in patients undergoing therapeutic plasma exchange sessions

Adverse reactions	Number of patients, *n* (%)
Allergic reaction	10 (10.9)
Paresthesias and perioral tingling	5 (5.4)
Hypotension	3 (3.3)
Catheter block	2 (2.2)
Severe anaphylactic reaction	1 (1.1)
Nil	71 (77.1)
Total	92

are divided into four categories, namely, Category I includes diseases, in which TPE is considered as the first-line therapy such as MG, GBS, TTP, and fulminant Wilson's disease, etc., Category II, in which TPE is considered as standalone therapy or in conjunction with other modes of treatment, for example, catastrophic antiphospholipid syndrome, overdose mushroom poisoning, cold-agglutinin disease, ABO-incompatible kidney transplant, multiple sclerosis, and systemic lupus erythematosus, etc., Category III, wherein the optimum role of TPE is not established yet the treating physician may make his/her own judgment to go for the procedure like pure red cell aplasia, cardiac neonaltal lupus, Rasmussen encephalitis, atopic dermatitis, etc., and Category IV, diseases in which the published evidence suggests TPE to be either ineffective or harmful, for example, inclusion body myositis, lupus nephritis, amyloidosis, etc.[7] ASFA also adopted a grading recommendation proposed by Guyatt *et al*.[8,9] According to that, Grade 1A is strong recommendation, high-quality evidence, Grade 1B is strong recommendation, moderate quality evidence, Grade 1C is Strong recommendation, low quality evidence, Grade 2A is weak recommendation, high quality evidence, Grade 2B is weak recommendation, moderate quality evidence, and Grade 2C is weak recommendation, low quality evidence.

Our patients in the present study mostly belonged to Category I or II as per criteria laid down. The most common indications were GBS, MG, and liver failure patients. GBS was the main indication in the present study, which comprised 34 patients accounting to 36.9%. All patients showed improvement in terms of muscle power grading and patients under assisted mechanical ventilation were recovered without the need for ventilation, independent walking with and without assistance were noticed by 5 weeks and were assessed till 6 months. TPE or intravenous immune globulin (IVIG) is 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.[13] 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 7 days of disease onset, for controlling symptoms of neuroimmunological disorders.[14] In the largest series of TPE on neurological disorders by Gafoor *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.[15]

Eight patients with other neurological disorders also showed marked improvement. Two patients of MG had tremendous improvement following TPE. They were weaned off the ventilator by 4th day of treatment. Similar results were obtained by another study.[16]

The second most common indication was liver failures cases. Acute liver failure can develop in a normal liver (known as fulminant hepatitic failure) or in the setting of chronic liver disease. The most common causes are acetaminophen toxicity or viral hepatitis. In our study, the most common cause was viral hepatitis. The mortality rate in fulminant hepatitic failure is 50%–90% due to acute metabolic disturbances, hepatic encephalopathy, and severe coagulopathy. The standard treatment is supportive care as a bridge to liver transplantation. These patients were provided high volume or normal volume TPE and supportive treatment. TPE can remove albumin-bound toxins as well as unbound toxins including aromatic amino acids, ammonia, endotoxin, indols, mercaptans, phenols, and other factors which may be responsible for hepatic coma, hyperkinetic syndrome, and decreased systemic vascular resistance and cerebral blood flow.[7] In the present study, out of 32 patients, 20 patients were underwent high volume TPE, in which target is 15% of body weight. In rest of 12 patients, normal TPE was performed. In a study conducted, Stahl *et al*. showed that both high volume and normal volume TPE found equally effective in acute liver failure patients.[17] Thus, the TPE is safe and well tolerated, and it improves coagulation profile and liver function tests in critically ill liver disease patients.[18]

TPE was associated with marked improvement in all three Wegener's granulomatosis patients. These patients very well responded to the combination strategy of TPE and immunosuppression. Cyclophosphamide (500 mg, i.v.) and methylprednisolone 1000 mg, i.v. daily for 3 days followed by oral prednisolone 60 mg daily for 4 weeks. TPE in combination with immunosuppression has dramatically improved the outcome in patients with WG.[19,20]

There were six patients of TTP, of which four were responded well and two were due to myocardial infarction. Shepard *et al*. carried out a multiapproach study on about forty patients with TTP, of which 17 patients were treated with plasma exchange, 15 with exchange transfusions, and 6 with both types of therapy. The complete response rates in each category were 88% for plasma exchange (15 patients), 47% for exchange transfusions (seven patients), and 67% for exchange transfusions and plasma exchange (four patients).[21] Furthermore, Coppo *et al*. showed that daily therapeutic TPE transformed the historically fatal prognosis of acquired, anti-ADAMTS13 antibody-mediated TTP leading to the current overall survival rates of 80%–85% in TTP.[22]

In catastrophic antiphospholipid syndrome, TPE plays an important role by removing antiphospholipid antibodies, cytokines, tumor necrosis factor, and complement.[23] FFP as a replacement fluid in TPE also provides natural anticoagulants such as antithrombin and protein C and S. The patient was treated with combination strategy of anticoagulation (LMW heparin 0.8 mg/kg) plus glucocorticoid (methyl prednisolone 1000 mg for 3–5 days) plus TPE (4 cycles).

Five patients were admitted with diagnosis of sepsis and multiorgan failure. The main treatment of these patients was supportive in nature such as antimicrobial agents, hemodynamic support, and ventilator support. TPE improved by removing inflammatory and antifibrinolytic mediators and replenishing anticoagulant proteins and ADAMTS 13.[7] Thus, TPE reverse pathobiological derangement and restore hemostasis. Despite all the efforts, only two patients were survived.

The three cases were admitted as a case of organophosphorus poisoning. The organophosphorus is chemicals in insecticide used extensively in farming. Organophosphorus pesticide self-poisoning is an important clinical problem in rural regions of the developing world like India and kills an estimated 200,000 people every year.[24] Organophosphorus pesticides inhibit esterase enzymes, especially acetylcholinesterase in synapses and on red-cell membranes, and butyrylcholinesterase) in plasma and acetylcholinesterase inhibition results in accumulation of acetylcholine and overstimulation of acetylcholine receptors in synapses of the autonomic nervous system, central nervous system, and neuromuscular junctions.[25] All three patients had severe signs and symptoms of poisoning such as tachycardia, hypertension, confusion, and muscle paralysis. Severe acute organophosphorus pesticide poisoning is a medical emergency. Treatment must ensure that the patient has a patent airway and adequate breathing and circulation. Treatment of these patients includes resuscitation and giving oxygen, a muscarinic antagonist (atropine, 1–3 mg as bolus), fluids (0.9% NS), and an acetylcholinesterase reactivator (pralidoxime chloride, 2 g i.v., an oxime that reactivates acetylcholinesterase by removal of the phosphate group) and TPE. Total eight cycles were given in three patients. Despite all extensive efforts, all three were died due to respiratory failure.

The percentage of patients that developed adverse reaction was low as compared to other studies.[26,27] The most common adverse event was allergic reaction followed by paresthesias and perioral tingling as in Table 3. No deaths could be associated with any TPE procedures and most of the allergic

reactions were being associated with FFP transfusion. The adverse events report of the World Apheresis Association Registry included 50,846 procedures in 7142 patients showed hypotension in 15%, tingling 58%, and urticaria 17% of total cases. They categorized them as mild, moderate, severe, and fatal according to the necessity for treatment.[28]

Conclusion

The present study includes a total 266 TPE procedures carried out on 92 patients with different clinical conditions who were admitted to the hospital. Our patients in the present study mostly belonged to Category I or II as per criteria laid down. According to spectrum of diseases, the patients were categorized into six groups. These were (1) neurological, (2) hematological, (3) gastrological, (4) renal, (5) rheumatic, and (6) Others the most common indications were GBS, MG, and liver failure patients. The most common adverse event was allergic reaction followed by paresthesias and perioral tingling and were mild in nature. Thus, an appropriate use of TPE in different clinical settings can provide a cost-effective, safe, and lifesaving treatment therapy, especially in developing countries.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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