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Original Article

Transfusion Medicine Section

Therapeutic Plasma Exchange: A Cross-sectional Study from a Tertiary Care Centre, Srinagar, India

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ABSTRACT

Introduction: Therapeutic Plasma Exchange (TPE) is a procedure in which blood is passed extracorporeally through an automated cell separator which separates plasma from cellular components of blood. The plasma (along with diseased component) is removed and replaced with a replacement solution colloid/crystalloid.

Aim: The aim of the study was to assess the outcome of TPE.

Material and Methods: The present study was a hospital-based cross-sectional study conducted in the Department of Blood Transfusion and Immunohematology at Sheri Kashmir Institute of Medical Science Soura Srinagar (SKIMS), over a period of 20 months from February 2021 to September 2022. All the patients sent from various departments for TPE had to fulfill some basic formalities like: informed consent (after explaining the procedure, risks, benefits and alternative treatment options) and some baseline investigations {Complete Blood Count (CBC), Liver Function Test (LFT), Kidney Function Test (KFT), electrolytes, triple serology, coagulation profile, serum protein, Blood grouping etc.,}. The rationale was that the substance to be removed should exist in plasma that contributes to a symptom/disease, large enough (>15000 D) that it can't be removed by conventional therapy and should have prolonged half life. Data was collected in Microsoft Excel and descriptive statistics was used for the analysis of data in terms of frequencies and percentages.

Results: A total of 20 patients underwent TPE. A 12 (60%) of patients were males. A 11 (55%) of patients were in the age group of 20-40 years. Good response (improvement in laboratory (lab) and clinical parameters) was found in 15 (75%) of patients while no response was shown by 5 (25%) of patients. A 3 (15%) of the patients suffered mild adverse [Two patients suffered nausea and vomiting and one patient suffered mild allergic reactions (rashes and urticaria)] reactions which were managed by antiemetic and antiallergic medications.

Conclusion: TPE has placed blood centers and transfusion services in the position of providing direct medical care for a patient. It is a useful treatment modality (usually temporary) used in a variety of life threatening conditions. It is not only safe and effective treatment but also cost effective and alternative to Intravenous Immunoglobulin (IVIG).

Keywords: Adverse event, Apheresis, Intravenous Immunoglobulin

INTRODUCTION

The TPE is a specific apheresis procedure in which blood is passed extracorporeally through an automated cell separator which separates plasma from cellular components of blood (blood purification procedure). The plasma (along with desired/diseased component) is removed and is replaced with a replacement solution colloid/crystalloid (NS, Albumin, Plasma). By removing plasma components (of high molecular weight), TPE can frequently interfere with key pathophysiological processes, thereby curing diseases or preventing further organ damage [1,2]. The procedure was discovered more than a hundred years ago. In 1914, Abel JJ et al., were the first to suggest the term 'plasmapheresis' for the treatment that has since become a well-established procedure in a broad range of conditions [3]. TPE was first implemented in the year 1952 in multiple myeloma to treat hyperviscosity and its varied outcomes [4]. Chwab and Fahey in the year 1960 performed the first TPE to decrease elevated globulin level in a macroglobulinemia patient [5]. By 1970s, TPE had became as a treatment option in various neurological diseases [6-8]. Today TPE is used in >100 conditions. As the range of therapeutic indications for TPE continues to expand, demand for the procedure is also increasing [2,9]. The most recent guidelines of the American Society for Apheresis- Journal of Clinical Apheresis (ASFA-JCA) Committee for relevant diseases and medical conditions has graded and categorised 157 indications and/or therapeutic apheresis modalities [10].

Membrane TPE (mTPE), in which apheresis is based on molecular size, and centrifugal TPE (cTPE), in which apheresis is based on molecular density are typically system using which TPE is performed [11]. Literature has documented that cTPE system has several advantages over mTPE systems based on the various clinical studies and case series: greater PRE, shorter total TPE time, more flexible access options, fewer clotting events, and fewer and less severe AE. Real-world experience shows that switching from mTPE to cTPE is both feasible and advantageous [12]. The risks and complications associated with this procedure are minimal and manageable. 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% [13]. Main complications associated with TPE are vasovagal reactions, vascular access complications (bleeding, haematoma, sepsis, phlebitis, thrombosis), hypovolemia and hypotension, citrate toxicity (M/C with FFP), depletion of clotting factors, proteins and immunoglobulins, infections, mild arrhythmias, haemolysis, hypersensitivity and various allergic reactions.

Hence, it is a useful treatment modality (usually temporary) used in a variety of life threatening conditions. It is not only safe and effective treatment but also cost effective and alternative to IVIG in various disease conditions [14]. The aim of the study was to assess the experience and outcome of TPE.

MATERIALS AND METHODS

The present study was a hospital-based cross-sectional study conducted in the Postgraduate Department of Blood Transfusion and Immunohematology at SKIMS Soura, Srinagar over a period of 20 months from February 2021 to September 2022. The study was reviewed by Ethics Committee of college with ref no. IEC/SKIMS Protocol #RP 03/2021.

Inclusion criteria: All the patients with ASFA category-I, II and III indications were included in the study.

Exclusion criteria: The patients with ASFA category-IV indication and patients with <10 years of age were excluded from the study.

Study Procedure

All the patients sent from various departments for TPE had to fulfill some basic formalities like: informed consent (after explaining the procedure, risks, benefits and alternative treatment options) and some baseline investigations (CBC, LFT, KFT, electrolytes, triple serology, coagulation profile, serum protein, blood grouping etc.,). ASFA 2019 guidelines were followed and the main indications for the procedures were: removal of antibodies, removal of immune complexes, hyper-viscosity syndromes, removal of toxins and replacement of deficient plasma components [Table/Fig-1] [10]. The rationale was that the substance to be removed should exist in plasma that contributes to a symptom/disease, large enough (>15000 D) that it can't be removed by conventional therapy and should have prolonged half life. The most common anticoagulant used in TPE is Acid Citrate Dextrose (ACD). The ratio set for ACD to whole blood was 1:9 to 1:14 and the blood flow rates were set to 25-45 mL/min. The speed set for blood pump was 90 mL/min to 130 mL/min [8].

Category	Description	Example
I	Disorders for which apheresis is accepted as a first line therapy	Myasthenia Gravis, and Guillian-Barre syndrome (GBS).
II	Disorders for which apheresis is accepted as second line therapy	Acute Disseminated Encephalomyelitis (ADEM), Autoimmune Haemolytic Anaemia (AIHA)
III	Optimum role of apheresis is not established. Decision making should be individualised.	Systemic Lupus Erythromastosus (SLE), Sepsis.
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful	Amyotrophic lateral sclerosis, Rheumatoid arthritis

[Table/Fig-1]: American Society for Apheresis 2019 guidelines [10].

All TPE procedures were performed using centrifugal intermittent flow cell separator Spectra Optia® Apheresis System (cTPE system). Mostly procedures were done through peripheral access (11.5 FR- Dialysis catheter). The high blood flow required for TPE was attained by placing dual lumen central venous catheter in subclavian or internal jugular vein. The replacement fluid used was 20% albumin, normal saline and fresh frozen plasma.

The volume of plasma to be exchanged was determined by calculating patients total blood volume according to Nadler's formula [15]. TPE is normally restricted to 1 or 1.5 plasma volumes [4]. One Plasma Volume (PV) exchange is equivalent to 65% of the initial component removed from the intravascular space, 1.5 PV approximates around 75%, and 2 PV exchanges achieved around 85% component removal [16]. More than 1.5-PV exchange confers little benefit due to the diminishing return effect, while placing the patient at higher risk for procedural complications [17]. In all TPE procedures, total volumes exchanged during a full treatment with TPE may range from 12 to 49 liters [18].

To prevent citrate toxicity in patients with low calcium levels, injection of calcium gluconate (10 mL of 10%) was given during the procedure. For anaemic patients a preprocedure Haemoglobin (Hb) was built to 7-8 g/dl. In case of paediatric patients with a decreased blood volume, the circuit was primed with RBCs. Patients with haemodynamic instability procedure was with held till haemodynamic condition improved. The duration of procedure ranges from 1 to 3 hours depending on the amount of plasma exchanged.

All medications were preferably given after TPE and dose adjustments were considered as drugs are also removed. Adverse reactions were assessed closely throughout the procedure and postprocedure period.

The frequency of TPE procedures can be disease specific and relates to the type of antibody present and the rate at which it equilibrates (redistributes or rebounds) Efficiency of removal is greatest early in procedure and diminishes progressively during exchange (assuming no redistribution and further production).

STATISTICAL ANALYSIS

Data was collected in Microsoft Excel and descriptive statistics was used for the analysis of data in terms of frequencies and percentages.

RESULTS

During this 20 month study period, a total of 20 patients underwent TPE. A 12 (60%) of patients were males and 8 (40%) patients were females. Maximum patients 11 (55%) were in the age group of 21-40 years and least no of patients 1 (10%) were in the age group of 61-80 years [Table/Fig-2]. ASFA 2019 guidelines were followed and the patients were categorised into ASFA category-I and II [Table/Fig-3]. A 14 (70%) of patient belonged to ASFA category-I and 6 (30%) patients belonged to ASFA category-II. The patients were divided into three groups according to departmental diagnosis [Table/Fig-3]. Most of the patients 12 (60%) were from Neurology Department, 5 (25%) patients were from Nephrology Department and 3 (15%) patients were from other departments. A total of 78 procedures were carried out on these 20 patients. Good response (improvement in Lab and Clinical Parameters) was found in 15 (75%) of patients while no response (no improvement in lab and clinical parameters) was shown by 5 (25%) of patients [Table/Fig-4]. A 3 (15%) of the patients suffered adverse reactions. Out of which 2 (10%) patients suffered nausea and vomiting (managed by antiemetic medications) and 1 (5%) of the patients suffered mild allergic reactions (rashes and urticaria managed by antiallergic medications).

Age group (in years)	Male n (%)	Female n (%)	Total n (%)
10-20	3 (15%)	0	3 (15%)
21-40	5 (25%)	6 (30%)	11 (55%)
41-60	3 (15%)	1 (5%)	4 (20%)
61-80	1 (5%)	1 (5%)	2 (10%)
Total	12 (60%)	8 (40%)	20 (100%)

[Table/Fig-2]: Age and gender wise distribution of the patients.

Department	Total No. of cases (%)	Diagnosis	n (%)	ASFA category
Neurology	12 (60%)	Guillain Barre syndrome (GBS)	5 (25%)	I
		Myasthenia Gravis (MG)	4 (20%)	I
		Acute Disseminated Encephalomyelitis (ADEM)	2 (10%)	II
		Multiple Sclerosis (MS)	1 (5%)	II
Nephrology	5 (25%)	Rapidly Progressive Glomerulonephritis (RPGN)	3 (15%)	I
		Ab mediated Graft Rejection (Renal transplant)	2 (10%)	II
Others Gynaecology and Obstetrics Clinical Haematology General Medicine	3 (15%)	Catastrophic Antiphospholipid Syndrome (CAPS)	1 (5%)	I
		Auto Immune Haemolytic Anemia (AIHA)	1 (5%)	II
		Thrombotic Microangiopathy (TMA)	1 (5%)	I

[Table/Fig-3]: Department wise distribution with ASFA 2019 category of the patients.

Diagnosis	No. of cases	No. of procedures done	Replacement fluid	Outcome
Guillain Barre syndrome	5	20 (4 sessions for each patient on alternate days)	NS, FFP, 20% Albumin	Good response: improvement in muscle power grading, no need for assisted ventilation
Myasthenia Gravis	4	16 (4 sessions for each patient on alternate days)	NS, FFP, 20% Albumin	Good response: improvement in muscle power and facial weakness, improvement in speech, swallowing and chewing, weaning off the ventilator
Acute Disseminated Encephalomyelitis	2	9 sessions (one patient 4 sessions, one patient 5 sessions on alternate days)	NS, FFP	No response (No improvement in lab and Clinical parameters)*
Multiple Sclerosis	1	4 sessions on alternate days	FFP, NS	Good response: Vestibular and ocular motor function improved. Also, improvement in dizziness and imbalance.
Rapidly Progressive Glomerulonephritis	3	13 (two patient 4 sessions each, one patient 5 sessions on alternate days)	NS, FFP, 20% Albumin	Good response: marked improvement in renal function tests, dialysis independent
Ab mediated Graft Rejection	2	9 sessions (one patient 4 sessions, one patient 5 sessions on alternate days)	NS, FFP, 20% Albumin	No response (No improvement in lab and Clinical parameters)*
Catastrophic Antiphospholipid Syndrome	1	4 sessions on alternate days	NS, FFP, 20% Albumin	Good response: decreased levels of serum antibodies
Auto Immune Haemolytic Anaemia	1	4 sessions on alternate days	FFP, NS	No response (No improvement in lab and Clinical parameters)*
Thrombotic Microangiopathy	1	4 sessions on alternate days	NS, FFP, 20% Albumin	Good response: marked improvement in coagulaiion factors, liver enzymes, renal function, platelet count, Hb

[Table/Fig-4]: Diagnosis, treatment with TPE and outcome of patients.
*as suggested by healthcare provider

DISCUSSION

The TPE is a useful treatment modality used in a variety of life threatening conditions, usually a temporary measure until definitive therapy. In the recent years there has been massive revolution in therapeutic apheresis with tremendous improvement in the patients with various disorders [19]. The effectiveness of TPE is particularly evident in a wide spectrum of diseases supported by strong clinical evidence referred in guidelines from reputed International Societies [18]. In the recent Coronavirus 2019 (COVID-19) times, this TPE has several benefits, in managing severe resistant coronavirus cases by removing toxic cytokines, viral particles and restoring coagulation status, with favorable outcomes [20-22]. However, these cases were not included in the present study. In this study, authors assessed the role of TPE as a treatment modality for both neurological and non neurological diseases. The most common indications for TPE in our study were GBS (25%) followed by MG (20%). The other indications were RPGN (15%), ADEM (10%), Ab mediated graft rejection (10%), and other immunological disorders were (20%). In most of these disease entities, TPE treatment was combined with pharmacotherapy in accordance with current recommendations [23]. A total of 20 patients underwent TPE and a total of 78 procedures were carried out on these 20 patients. Good response (improvement in lab and clinical parameters) was found in 75% of patients while no response (no improvement in lab and clinical parameters) was shown by 25% of patients.

TPE or IVIG is recommended treatment options in GBS, both have been found to be equally effective and significantly better than the conservative treatment [24]. In present study also, GBS was the main indication which showed 25% of cases. TPE is most effective when initiated early usually within once a week of disease onset, for controlling symptoms of neuroimmunological disorders [25,26]. Five patients with other neurological disorders also showed marked treatment response. Four patients of MG had obvious improvement in speech, muscle power and were weaned off the ventilator by the end of 1st week following TPE. Similar results were obtained by Makroo RN et al., [27]. However, two patients with neurological symptoms does not show any improvement after several secessions of TPE rather worsened in their clinical conditions. One of the common indications of our study was RPGN accounting 15% of total cases. TPE in combination with immunosuppression has fiercely improved the results in patients with RPGN. The patients were dialysis independent after completion of treatment (TPE). In catastrophic antiphospholipid syndrome, TPE plays a vital role by removing antiphospholipid antibodies, cytokines, tumor necrosis factor, and complement [28].

Patient was discharged after completing treatment with TPE combined with anticoagulation and steroids. One patient with thrombotic microangiopathy showed marked improvement in lab and clinical parameters such as improvement in coagulation factors, liver enzymes, renal function, platelet count and Hb levels. However, one patient with AIHA does not show any improvement after several secessions of TPE. Apheresis procedures are essentially safe [29]. The risks and complications associated with this procedure are minimal and manageable. American Academy of Neurology while assessing plasmapheresis found that TPE is extremely safe in experienced hands [30]. 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% [13]. Adverse Events (AEs) are considered as mild, moderate and severe. The majority of AEs occurs during the first few sessions are usually mild and affect 2.4% of the patients. Moderate AEs occur in 3% of patients were as severe AEs are rare but may happen in 0.4% of procedures [31]. Potentially life-threatening adverse reactions can be even rarer (0.12% incidence) [32]. In this study, 15% of the patients suffered adverse reactions. Out of which 10% patients suffered nausea and vomiting (managed by antiemetic medications) and 5% of the patients suffered mild allergic reactions (rashes and urticaria managed by antiallergic medications). The percentage of patients that developed complications was low as compared to other studies [33,34].

Limitation(s)

The limitations of study were a small number of patients and procedures. Small scale data is not enough to provide substantial evidence for the impact of TPE on the outcome of different disease conditions. Albumin was not given in two cases as it was not affordable to patients.

CONCLUSION(S)

The TPE has placed blood centers and transfusion services in the position of providing direct medical care for a patient. It is a useful treatment modality (usually temporary) used in a variety of life threatening conditions. The risks and complications associated with this procedure are minimal and manageable.

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