Original Research Paper

Volume - 12 | Issue - 10 | October - 2022 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Nephrology

THERAPEUTIC PLASMAPHERESIS – AN EXPERIENCE AT A TERTIARY CARE CENTRE IN SOUTH INDIA

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ABSTRACT **Background:** Plasmapheresis has a therapeutic role in various diseases. Literature evidence for use of Therapeutic Plasma Exchange(TPE) in renal disease is widely available. Literature evidence for utility of TPE in non-renal disease is limited. In this study, we have evaluated outcome with TPE for different renal and non-renal causes. **Methods:** This was a prospective observational study conducted in patients who underwent TPE during a period of eight months. Demographic data, clinical profile, details of plasmaphersis, patient tolerance and complications during the procedure were systematically recorded and descriptive statistics was applied for analysis. **Results:** The study participants (n=93) were divided into two groups as immunological disease group (n=39) and non-immunological disease group (n=54). Patients with yellow phosphorus poisoning constituted the non immunological disease group. Patients who had Guillain Barre Syndrome, Antibody Mediated Rejection, Myasthenia Gravis, Crescentic Anti Neutrophilic Cytoplasmic Antibody associated Glomerulonephritis, Thrombotic Microangiopathy, ABO incompatible Renal Transplantation constituted the immunological disease group. Median duration of hospital stay was 20 days in the overall population and it was significantly longer in patients who underwent TPE for immunological cause ($p<0.0001$) compared to non-immunological cause. The proportion of patients experiencing clinical improvement was significantly higher in non-immunological group ($p= 0.008$). All-cause mortality was numerically higher in immunological group. **Conclusion:** In our study TPE was done more for non-immunological diseases than immunological diseases. It was reaffirmed to be a safe and efficacious procedure in both immunological and non-immunological diseases. Clinical outcomes were better in patients undergoing TPE for non-immunological disease.

KEYWORDS : Therapeutic Plasma Exchange, Guillian Barre syndrome, yellow phosphorous poisoning, Antibody Mediated Rejection

INTRODUCTION

Therapeutic plasma exchange (TPE) interchangeably termed as plasmapheresis is a process involving extracorporeal removal of plasma from other components of blood, discarding and replacing plasma with physiological fluids.[1] Since its introduction in 1952, TPE has been used in many disorders either alone or in combination with other therapies, with improved safety and efficacy[2,3]

TPE targets removal of a single or allied group of high molecular weight (MW) substances (>15 kD) compared to hemodialysis and hemofiltration and reduces the concentration of target molecule(s), thereby providing a therapeutic window for drugs to act[4]

TPE indications were identified and revised by the American Society For Apheresis (ASFA) in 2019 and are divided into four categories, from 1 to 4, based on available literature [5]

TPE is performed either using centrifugation (cTPE) devices that separate the plasma from cellular components based on density or membrane apheresis, based on molecular size (mTPE).[6]

In our study membrane apheresis was done for all patients.This has a lower plasma extraction ratio but compensates with a higher blood pump speed.[7] Nephrologists largely favor mTPE, an adaptation of technology on the dialysis machine. Membrane filtration is nonselective in removing plasma with dissolved "toxins" and useful components.

Membrane size in plasmafilters is smaller than 0.6 micron restricting removal of cellular components

The principal factors influencing the removal of the target substance in plasma are the relative distribution of the substance in intravascular and extravascular compartments, transfer rates of the substance across compartments, plasma half-life, regeneration of the substance, and ratio of plasma volume removed.[8]

The commonest replacement fluid used is Human serum albumin (HSA) though,in certain specific indications plasma is used as replacement to replenish missing plasma components.

Central venous catheters either temporary or tunneled are preferred for membrane filtration.In those patiens with Arterio Venous Fistula or Graft it was used.

Number of TPE sessions varies greatly depending on the type and severity of the disease and also the general condition of the patient[9].

Adverse events during TPE range from subtle hemodynamic instability, cramps, allergic reactions reactions to more sinister events like thromboembolism, severe anaphylaxis which may be associated with mortality[10].Therapeutic utility of TPE is well established in various autoimmune disorders affecting various organ systems though, in recent years its utility in non immunological causes especially in yellow phosphorus poisoning is well recognised. In this article, we aimed at evaluating the utility and outcome of TPE in patients with various immunological and non immunological causes at a tertiary care hospital in South India using membrane filtration.

Study Design And Methodology

This is a prospective observational study conducted to evaluate the outcome of TPE at a tertiary care hospital between September 2020 and April 2021. Patients undergoing TPE for various clinical condition as per standard protocol and guidelines were recruited([10]).

Patients who warranted TPE but clinically unstable for the procedure due to presence of complications e.g. severe hypotension, overt sepsis were excluded from this study. The objective of this study was to evaluate the utilisation of TPE for immunological and non-immunological diseases, and to compare the clinical outcomes like duration of hospital stay, clinical improvement, and all-cause mortality. Data on demographic variables including age, sex, indication for TPE, site of venous access, complications developed during or following the procedure, total number of sessions, replacement fluids used (albumin, fresh frozen plasma, etc.), outcome data were collected.

After obtaining the written consent from patients, a case report form was used to collect relevant details till the endpoint of either discharge or death. Institutional Ethics Committee approval was obtained. Descriptive statistics was used to describe the age, sex, pre-treatment biochemical parameters. Survival analysis was performed to calculate the duration of hospital stay. Log rank test (with $p < 0.05$) was used to compare the duration of hospital stay between patients undergoing TPE for immunological and non-immunological diseases. Unpaired T-test and Chi-square tests were performed to determine the association in continuous data and ordinal data, respectively.

RESULTS

A total of 93 patients who underwent atleast one session of TPE were recruited in this study. Out of 93 patients, 39 patients underwent TPE for Immunological cause and 54 patients for non-immunological cause as shown in Fig 1. Most common Immunological disease was Guillain Barre Syndrome (GBS) constituting 38.4 % (n = 15) patients, followed by Antibody Mediated Rejection (ABMR) post Renal Transplantation constituting around 35.9% (n = 14) of patients. Smaller proportions of patients with Myasthenia Gravis (MG) crisis, Thrombotic Microangiopathy (TMA), Crescentic Anti Neutrophilic Cytoplasmic Antibodies associated Glomerulonephritis (ANCA GN) and ABO incompatible Renal Transplantation also underwent TPE. Mean age group was significantly higher in patients undergoing TPE for immunological diseases compared to non-immunological diseases (38.5 years vs 26.9 years, $p < 0.05$). Other baseline characteristics are depicted in Table 1.. A total of 362 sessions of TPE were performed for 93 patients. Mean TPE sessions required by patients with non-immunological cause was 3(sd 0.75) and by patients having immunological cause was 5.13(sd 1.17). One Plasma volume was calculated for each patient according to Kaplan formula (0.07X weight in kgX(1- hematocrit%)) with the help of body weight and hematocrit of the patient. All patients with non-immunological disease in this study received 1 plasma volume exchange replacing with equal volumes of fresh frozen plasma and ringer lactate, on an alternate day basis. All patients with immunological disease, received 1.5 times plasma volume exchange replacing with equal volumes of 5% albumin and Ringer Lactate, on an alternate day basis.

Table 1: Baseline Characteristics

Baseline characteristics			
Pretreatment	Immunological disease (n = 37)	Non-immunological disease (n = 56)	
Age (SD)	38.5 (10.7)	26.9 (9.1)	< 0.05*
Sex (male %)	56.4 %	40.7 %	> 0.05
Diabetes	16.2% (n = 6)	12.5 % (n = 7)	> 0.05
Hypertension	18.9 % (n = 7)	10.7 % (n = 6)	> 0.05
Creatinine in mg/dL	2.89 (2.4)	1.5 (0.24)	< 0.05*
Bilirubin in mg/dL	0.6 (0.12)	7.9 (4.34)	< 0.05*
SGOT	20.0 (3.2)	729.1 (785.4)	< 0.05*
SGPT	19.8 (3.2)	615.6 (649.1)	< 0.05*
INR	0.87 (0.11)	4.8 (2.4)	< 0.05*

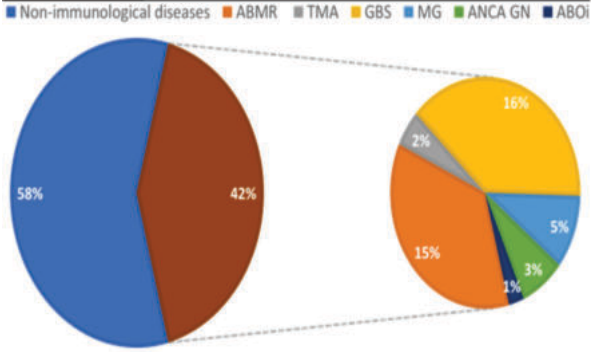

Fig 1: Disease Spectrum Of Patients Undergoing TPE

Median duration of hospital stay was 20 days (CI: 19 - 22) in the overall population as shown in Fig. 2a. Log rank test was done to compare the duration of hospital stay between patients undergoing TPE, for immunological and non-immunological disease. Median duration of hospital stay is significantly longer in patients with immunological diseases compared to non-immunological diseases [27 days (24 – 32) vs 18 days (17 – 19), $p < 0.001$] as shown in Fig. 2b.

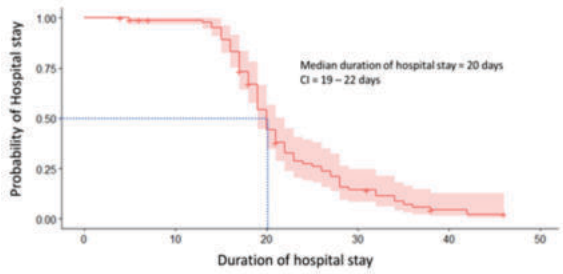

Figure 2a: Duration Of Hospital Stay In The Overall Population

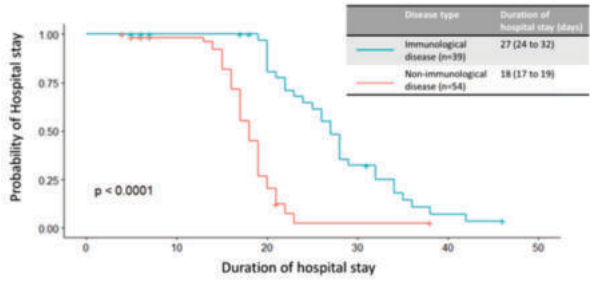

Fig 2b: Duration Of Hospital Stay In Patients Undergoing TPE For Immunological And Non-immunological Diseases

TPE was beneficial in 73.1 % patients. On applying Chi-square test clinical improvement was found to be significantly higher with TPE in non-immunological disease compared to those with immunological diseases (88.3% vs 58.9%, $p = 0.008$). All-cause mortality was 18.3% and it was numerically higher in patients undergoing TPE for immunological diseases than for non-immunological disease (20.6 % vs 16.7 %, $p > 0.05$) as shown in Tab 2.

Table 2: Clinical Improvement And All-Cause Mortality

	Clinical improvement		All-cause mortality	
Immunological disease	58.9 %	P = 0.008	20.6 %	P > 0.05
Non-immunological disease	88.3 %		16.7%	

Clinical outcome, mean duration of hospital stay and all-cause mortality in immunological diseases (n = 39) are depicted in Table 3. The incidence of adverse event in the study population was 33.3 %. The incidence of adverse event was numerically higher in non-immunological disease (38.8 % vs 30.3 %, $p > 0.05$) with hypotension being the most common event. Other adverse events reported were anaphylaxis and hypocalcemia. No other major adverse events were reported .

Table 3: Clinical Outcomes And All-cause Mortality In Patients With Immunological Diseases Undergoing TPE

Disease	Average hospital stay	Clinical improvement	All-cause mortality
ABMR (n = 14)	26.9 days (SD = 8.1)	50%	14.3%
C4D positive (n = 10)	28.2 days (SD = 9.1)	50%	20%
C4D negative (n = 4)	23.8 days (SD = 4.0)	50%	0%
Post transplant < 5yrs (n = 8)	23.5 days (SD = 5.2)	50%	0%
Post transplant > 5yrs (n = 6)	31.5 days (SD = 9.5)	50%	33.3%
GBS (n = 15)	23.6 days (SD = 11.5)	66.7%	33.3%
AIDP(n = 6)	31 days (SD = 5.0)	83.3%	16.7%
AMAN (n = 7)	19.3 days (SD = 12.5)	57.1%	42.8%
AMSAN (n = 2)	16.5 days (SD = 14.8)	50%	50%
MG (n = 4)	28 days (SD = 12.5)	50%	50%
Others (n = 6)	23.3 days (SD = 4.6)	83.3%	0%

DISCUSSION

TPE is used to treat large number of immunological and non-

immunological diseases involving neurological, haematological, renal and hepatopancreatic systems. The effectiveness of TPE for various indications have been evaluated across multiple clinical trials, case series and case reports. In the latest ASFA guideline (8th Edition) published in Journal of Clinical Apheresis(JCA) comprises 84 fact sheets for relevant diseases and medical conditions, with 157 graded and categorized indications and/or TA modalities[8]

Median duration of hospital stay in the overall study population was 20 days and it was longer for immunological diseases when compared to non-immunological diseases. Average duration of hospital stay in GBS patients was longer in our study population compared to available literature (23.6 days vs 14 days)[11]. In Tekdon et al the predominant population undergoing TPE were for non-immunological conditions similar to our population[12]

TPE was found to be safe and effective procedure when performed early in case of yellow phosphorus poisoning induced hepatotoxicity and has shown survival benefit. It can be used as bridging therapy for Liver Transplantation. In our study about 88.3% of patients who presented with yellow phosphorus induced hepatic failure showed significant clinical improvement after TPE, similar to Varghese et al[13][14]. TPE appears to be a promising non transplant option to treat toxin induced fulminant hepatic failure[15] and can be done in any hospital having with hemodialysis and blood bank facilities with high dependency unit. In our study, all- cause mortality in cases of yellow phosphorus poisoning was 16.7%, whereas it was 21% in Varghese et al[13]. Therapeutic efficacy of TPE in yellow phosphous poisoning with early stages of hepatotoxicity was seen in 78% of the study population in the study by Archana et al[15]. In this modern era, TPE has emerged to improve survival in patients with acute liver failure and has proven to be the standard of care especially in a resource limited setting[17].

In this study, among the immunological diseases, GBS was the predominant disease which required TPE similar to available literature[18] [19]. The proportion of clinical improvement was around 90% in the available literature[19] [20], whereas it was only 66.7 % in our study population. In this study all-cause mortality among immunological disease group was 20.6% whereas it was 23.1%.Mortality depends on the factors like severity of primary disease, time of presentation to hospital, standard of care, hospital acquired infections etc. TPE proved to be a safer procedure in our study with no major complications and adverse events like hypotension, anaphylaxis and hypocalcemia were found in 33% of the study population with majority seen in patients who underwent TPE for non-immunological diseases (yellow phosphorus poisoning) probably due to the choice of replacement fluid Fresh Frozen Plasma since all patients in that group had severe coagulopathy. Incidence of adverse events during TPE in our study was similar to study by Sajad et al[18]. The major limitation of this study was not including those patients not undergoing TPE as comparator arm to evaluate and compare the efficacy of TPE.

CONCLUSION

This study evaluates the utilisation and outcome of TPE in a tertiary care hospital. The demographics and clinical outcomes of patients were similar to the available literature. Low dose TPE was found to be beneficial in yellow phosphorus poisoning. TPE could be a relatively cost effective treatment for GBS. Although, TPE appears to be a safe and effective option in various disease spectrum, randomised controlled trials against active comparators are essential to conclude the effectiveness of TPE.

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