Original Research Paper

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Pathology

THERAPEUTIC PLASMA EXCHANGE AT A TERTIARY CARE HOSPITAL IN WESTERN INDIA.

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ABSTRACT **Introduction:** Therapeutic Plasma Exchange is an emerging modality of treatment in various diseases. **Aim:** Analysis of the various indications for Therapeutic Plasma Exchange in a tertiary care sub specialty hospital **Materials And Methods:** In this retrospective single center study between January 2018 and December 2019 evaluation of the indications for Therapeutic Plasma Exchange (TPE) was done. Pre-procedure investigations Complete blood count (CBC), Serum Creatinine, Serum Electrolytes were done. 1 to 1.5 times plasma volume was exchanged. Fresh Frozen Plasma (FFP) or Human albumin 20% were used as a replacement fluid. Acid Citrate Dextrose ratio was used. Injection Calcium gluconate 30ml &Injection Avil 2ml in 100ml of DNS was given. Vitals were monitored. Adverse event, managed accordingly. **Results:** In 65 patients (54 Males,11Females) 328 cycles were performed Indications were Antibody mediated Rejection (ABMR) 61.5%, Atypical Hemolytic Uremic Syndrome (aHUS)24.6%, Prerenal transplant sensitization and Crescentic Glomerulonephritis 4.6% each, FSGS, Post Liver Transplant Rejection and Post Liver Transplant Auto immune cirrhosis 1.5% each. Totally 191(58.2%) procedures were performed for 40 patients of ABMR (M: F- 36:4), 96 (29.2%) procedures for 16 patients (M: F-10:6) of a HUS Adverse effects in 9 patients 7 Males and 2 Females. Out of these 9 patients 8 underwent TPE for ABMR and 1 for aHUS. Shivering and vomiting were the most common adverse effect (N=5). Giddiness in 2, skin rash and leakage in Dual lumen Catheter in 1 each. ABMR, Pre-Transplant Sensitization and FSGS is in category I 1B for TPE, a HUS is under I 2C for TPE and the remaining indications are under category III for TPE. **Conclusion:** Our results are consistent with available American society for Apheresis (ASFA) guidelines 2019 More quality of evidence is required for aHUS patients. TPE is a safe and effective procedure.

KEYWORDS : Therapeutic Plasma Exchange, American Society for Apheresis Guidelines 2019

INTRODUCTION

Apheresis is a process in which blood being removed from a subject is continuously separated into component parts, usually to allow a desired component/s to be retained while the remnant is returned to the subject.[1] Therapeutic Plasma Exchange (TPE) is the removal of plasma and retention of cellular components. The purpose of TPE is to remove the agent in the plasma like toxin, antibody or abnormal protein which produces the symptoms in a patient. During TPE large quantities of plasma is replaced with physiological fluids like Fresh Frozen Plasma (FFP) or Albumin for the maintenance of the intra vascular compartment. TPE is indicated as first line of treatment according to the American Society of Apheresis (ASFA) guidelines where the recommendation is between strong recommendation with high quality evidence to weak recommendation with low quality evidence-Grade 1A to 2C.[2,3]

Aim And Objective Of Study

This was a retrospective clinical research study to evaluate the indications for TPE in a tertiary care sub specialty hospital. This study was approved by the Institutional Review Board. We already obtained informed consent from the participants who were enrolled in this study in accordance with the committee's standards from the individual described herein.

Inclusion And Exclusion Criteria

Study included any gender with <60 years of age with diseases like ABMR, a HUS, pre- transplant sensitization, Crescentic GN, FSGS, Liver transplantation rejection, post liver transplantation auto-immune cirrhosis. Our study excluded malignancy, systemic illness, pelvic inflammatory diseases, thyroid dysfunction, coagulopathy, seropositive patients and pregnant women. Even, patients who were advised TPE but refused to undergo, were excluded from the study

MATERIAL AND METHODS

Analysis of indications was performed in patients referred to the Department of Transfusion Medicine for TPE. The procedure was performed under the supervision of blood bank officer and a nurse

TPE was performed on two types of continuous flow centrifugation machines available in our Transfusion Medicine Department named Spectra Optia and Fresenius Kabi COMTEC. Pre-procedure investigations like Complete blood count (CBC), Serum Creatinine, Serum Electrolytes were done before TPE. The procedure and its probable complications were explained to patients and their relative in their local languages. Patient's height, weight, hematocrit, temperature, pulse, respiratory rate, blood pressure was recorded before starting the TPE after taking informed consent.

A large caliber vein either internal jugular vein, arterio-venous fistula or femoral vein was used for access and return of blood. Patients total blood volume was calculated using the Nadler's formula. In each patient, 1 to 1.5 times plasma volume was exchanged. FFP or Human albumin 20% were used as a replacement fluid depending upon the indication of TPE.

Inlet flow was within the range of 45-55 ml/minute. Acid Citrate Dextrose ratio was kept 1:12 to 1:14 depending on the replacement fluid used. Simultaneously injection Calcium gluconate 30ml in 100ml of DNS was infused throughout the procedure to prevent hypocalcemia. Injection Avil 2ml was also added in DNS to prevent any allergic reactions during the procedure. Blood pressure, pulse rate and respiratory rate were closely monitored during TPE. An adverse event, if happened then managed accordingly.

RESULTS

Indications for TPE with category and grading is given in the Table 1& Table 2 as per American Society for Apheresis (ASFA) guidelines 2019 Category and Grading for the indications for TPE in our patients Table 3

65 patients (54 Males 11 Females) were referred to the Department of Transfusion Medicine for TPE. Total 328 cycles were performed for these 65 patients with different indications. ABMR accounted for 61.5%, aHUS 24.6%, Prerenal transplant sensitization and Crescentic Glomerulonephritis 4.6% each, Focal Segmental Glomerulosclerosis (FSGS), Post Liver Transplant Rejection and Post Liver Transplant Auto immune cirrhosis 1.5% each. Age wise distribution of the number of patients for Antibody Mediated Rejection (ABMR) 15 patients in the age group of 0-20 years, 20 patients in the age group of 21- 40 years and 5 patients in the age group of 41-60 years Totally 191(58.2%)

procedures were performed for 40 patients of ABMR (M: F- 36:4). In HUS, 96 (29.2%) procedures were performed for 16 patients (M: F-10:6). Adverse effects were observed in 9 patients 7 Males and 2 Females. Out of these 9 patients, 8 underwent TPE for ABMR and 1 for aHUS. Shivering and vomiting were the most common adverse effect observed (N=5). Two patients developed giddiness while 1 developed skin rash and 1 patient had leakage in Dual lumen Catheter. No adverse effect was reported in remained 61 patients. Treatment was continued till clinical improvement was noted by clinicians in all the patients. There was no mortality in any of the patients.

ABMR, Pre-Transplant Sensitization and FSGS is in category I 1B for TPE, a HUS is under I 2C for TPE and the remaining indications are under category III for TPE. Table 3, Figure 1 ,2

DISCUSSION:

Ours is a tertiary care sub-specialty hospital mainly dealing with patients of Nephrology, Pediatric Nephrology, Gastrology and Hepatobiliary Diseases, Obstetrics and Gynecology. Most of the patients referred for apheresis were Post Transplant Antibody Mediated Rejection (ABMR) and atypical Hemolytic Uremic Syndrome. Antibody mediated rejection is known in Post Renal transplant patients. ABMR is category-I 1B for TPE where TPE is the first line therapy with strong recommendation and moderate quality evidence. We performed TPE to ABMR patients for a mean number of 4.7 exchanges per patient. Out of 40 patients only 7 developed adverse reactions.. Second most common indication for TPE was aHUS. Category is 1-2C. First line of treatment however weak recommendation and low-quality evidence. Only 1 patient had developed adverse reaction to TPE out of 16 patients who underwent TPE. Mean 6 exchanges were done.

Acute antibody-mediated rejection (ABMR) is a known to occur after renal transplantation. TPE is done as a treatment for ABMR as efficacy of other methods of treatment is yet to be established[4]. Plasmapheresis removes the unwanted antibodies from the serum. It has an immuno-modulatory effect, reducing B cells and NK cells, and increasing T regulatory cells and T-suppressor-cell function[5] Plasmapheresis along with Intravenous Immunoglobulin (IvIg) improves the graft survival in patients of ABMR[6]

Plasmapheresis should be considered as the first line of treatment for patients of a HUS for removal of antibodies. Plasma exchange, has been the first-line treatment replacing functional complement regulation proteins and/or eliminating complement inhibitor[7]. Early initiation of Plasmapheresis in patients of a HUS shows better clinical improvement.[8] More studies to establish the role of TPE in a HUS to establish its role and provide better quality of evidence is needed.

Similar study was done by Aseem K Tiwari et al where TPE was performed in Neurological Hematological Renal Hepatic and Rheumatological indications and they have observed that the type of indications for which TPE has changed, number of procedures of TPE have increased and patients response rate is better Adverse events have decreased They have concluded that in the last few years there has been a change in the type of indications for therapeutic apheresis and increase in the number of procedures. The response rate and safety of these procedures have also improved[9] This is similar to our study we have also observed that no serious adverse events were observed in any of the patients who had undergone TPE and more patients were referred. In another study by Sreedevi Bobati et al they have observed that HUS holds very low-quality evidence in their study for the use of TPE as only eight cases were reported, hence they felt the need for more evidence to prove the role of TPE in the treatment of HUS in their institution.[10]We have performed 96 TPE procedures on 16 patients and have observed that patients tolerated the procedure well and showed clinical improvement too. In another study by Gajjar et al they have observed that TPE is a safe procedure in pediatric patients Number of exchanges increased. And it is a safe procedure in pediatric patients .[11] In other indications like pre-renal transplant sensitization, Focal segmental Glomerulosclerosis and post liver transplant rejection also TPE was done at our center and patients have tolerated the procedure well. However, the patient pool for these indications was very less.

Limitations: We are a tertiary care sub specialty hospital catering mainly to patients of Nephrology Urology Gastrology and Gynecology Hence our study could not include patients of Neurological diseases in which cases other centers have done TPE.

CONCLUSION:

TPE is Category I, 1B strongly recommended moderate quality evidence for ABMR and weakly recommended with weak quality evidence for a HUS as per ASFA guidelines 2019 We have observed that in a HUS it can be recommended strongly as we have done TPE safely and with good results in all patients of a HUS However more quality of evidence is required for these patients .To the best of our knowledge present study is largest single center study at a tertiary care hospital where TPE was done mainly for renal and hematological indications. It has gradually been seen as an emerging modality of treatment in adults and pediatric patients. It is safe and effective treatment for both.

An apheresis registry to look into the various indications of TPE across the country other than neurological conditions, expansion of the various indications for TPE and its safety will be beneficial.

Legends Of Tables
Table- 1 American Society of Apheresis Category guidelines 2019
Table 2 American Society of Apheresis Grading 2019
Table- 3 Results

Legends Of Figures
Figure- 1, Indications for TPE
Figure- 2, Number of Procedures

Abbreviations
1. TPE: Therapeutic Plasma Exchange
2. ASFA: American Society for Apheresis
3. FSGS: Focal segmental glomerulosclerosis
4.a HUS: Atypical Hemolytic Uremic Syndrome

Conflict Of Interest
None of the authors declare any conflict of interest regarding the publication of this manuscript

Table- 1 American Society Of Apheresis Category Guidelines 2019

Category Definitions for Therapeutic Apheresis
Category Description
I Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone
treatment or in conjunction with other modes of treatment.
II Disorders for which apheresis is accepted as second-line therapy, either as a standalone
treatment or in conjunction with other modes of treatment.
III Optimum role of apheresis therapy is not established. Decision making should be
individualized.
IV Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or
harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances

Table 2 American Society Of Apheresis Grading 2019

Recommendation	Description	Methodological Quality of supporting Evidence	Implications
Grade 1A	Strong recommendation High Quality Evidence	RCTs without important limitations or over-whelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1B	Strong recommendation,moderate quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1C	Strong recommendation, low-quality or very low-quality	Observational studies or case series	Strong recommendation but may change when higher quality evidence

	evidence		becomes available
Grade 2A	Weak recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2B	Weak recommendation, moderate-quality evidence RCTs	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2C	Weak recommendation, low-quality or very low-quality evidence	Observational studies or case series	Very weak recommendations ; other alternatives may be equally reasonable

Table- 3

	Indications	Category	No. of Patients	No. of Procedures
1	ABMR	I 1B	40(61.5%)	191(58.2%)
2	aHUS	I 2C	16(24.6%)	96(29.2%)
3	Pre-Renal Transplant Sensitization	I 1B	3(4.6%)	8(2.4%)
4	Crescentic Glomerulonephritis	III 2B	3(4.6%)	12(3.6%)
5	FSGS	I 1B	1(1.5%)	12(3.6%)
6	Liver Transplant Rejection	III 2B	1(1.5%)	1(0.3%)
7	Post Liver Transplant Auto Immune Cirrhosis	III 2B	1(1.5%)	8(2.4%)

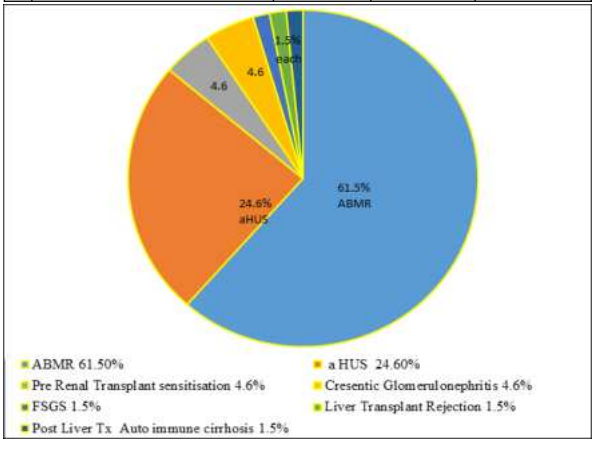

Figure- 1, Indications for TPE

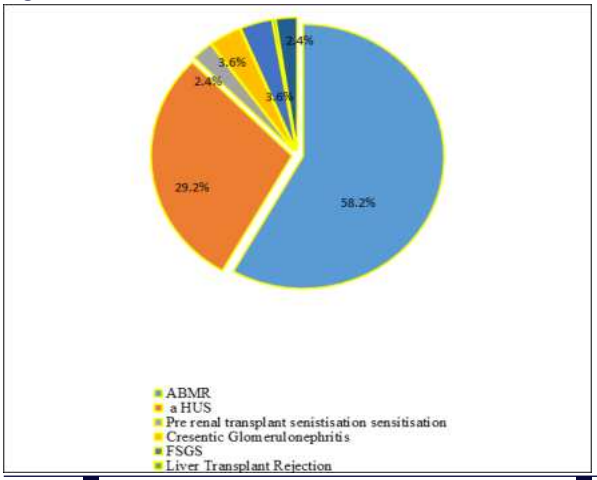

Figure- 2, Number of Procedures

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