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SCOPE AND SAFETY OF THERAPEUTIC PLASMA EXCHANGE BY CENTRIFUGATION IN PEDIATRIC PATIENTS: EXPERIENCE AT A TERTIARY CARE HOSPITAL IN WESTERN INDIA

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ABSTRACT

Introduction

Therapeutic Plasma Exchange (TPE) is a well-known therapeutic modality for treating various pediatric diseases. However, no special guidelines are available for pediatric patients, and adult guidelines- American Society for Apheresis (ASFA) are followed.

Aim: To study the safety of TPE and analyze the various indications for which it can be done in pediatric patients.

Material and Methods: A 5-year retrospective analysis of the indications and their safety was done from 2018 to 2022.TPE was done by centrifugation

Results: TPE was performed in 120 patients and 926 procedures were done. Antibody-mediated rejection (ABMR) and Atypical Hemolytic uremic syndrome (a HUS) were the most common indications with 42.5% of procedures each. Pre-Renal transplant desensitization (8.3%) and Wilsons disease (2.5%) were other indications. The most common adverse event seen was moderate (53.57%), and allergic reaction to replacement fluid -Fresh Frozen Plasma (FFP) was the most common. Vomiting was the most common adverse event in the severe (42.85%) category and 3.57% of adverse events were mild. The most common indication where adverse events were seen was a HUS followed by ABMR.

Conclusion: TPE by centrifugation is safe in pediatric patients However, a separate guideline for pediatric patients to categorize the indications is required.

Keywords: Antibody-mediated rejection, Atypical hemolytic uremic syndrome, Fresh frozen plasma.

Introduction

Therapeutic Plasma exchange (TPE) is commonly used for the treatment of various diseases in adult and Pediatric patients. TPE is an extracorporeal technique used for removing unwanted pathogenic substances from the plasma and replacing them with crystalloids or colloids. The most common indication for TPE in various centers is for neurological diseases.[1]It is performed by various modalities of centrifugation and filtration. TPE is performed for various indications as per American Society for Apheresis (ASFA) guidelines for various neurological, hematological, renal hepatic, and autoimmune diseases. However, these guidelines are designed for the adult population. TPE is also performed for various neurological, hematological, and renal indications in the pediatric population. These indications are based on the guidelines provided for adult patients. No separate guidelines are available for pediatric patients TPE is technically challenging in pediatric patients because of physiological and technical challenges.[2-4]

Aim

This study aims to analyze TPE's various indications and safety in pediatric patients. This was a retrospective 5-year study from January 2018 – December 2022. This study was approved by the Institutional Review Board. We already obtained informed consent from the participants who were enrolled in this study.

Inclusion and exclusion criteria

The study included any gender <18 years of age with diseases like Antibody-mediated Rejection (ABMR), atypical hemolytic uremic syndrome (a HUS), pre-transplant desensitization, Crescentic GN, FSGS, Liver transplantation rejection, etc. Adult patients and pediatric patients not opting for TPE were excluded from the study.

Materials and Methods:

Analysis of indications was performed in patients referred to the Department of Transfusion Medicine for TPE. Adverse events observed were classified into three categories as per the World Association for Apheresis (WAA) in 3 categories [5]

1)Mild amounting to transient but not requiring any intervention
2)Moderate- Requirement of medication or intervention
3) Severe- Clinically unstable or requiring termination of the procedure

The procedure was performed by an experienced blood bank officer and a nurse. TPE was performed on two types of continuous flow centrifugation machines available in our Department, Spectra Optia and Fresenius Kabi COMTEC. Pre-procedure investigations like Complete blood count (CBC), Serum Creatinine, and Serum Electrolytes were done. The procedure and its probable complications were explained. The Patient's height, weight, haematocrit, temperature, pulse, respiratory rate, and blood pressure were recorded before starting the TPE after taking informed consent. A large caliber vein, either internal jugular vein or arterio-venous fistula, was used for access and return of blood. The total blood volume was calculated using Nadler's formula. In each patient, 1 to 1.5 times plasma volume was exchanged. Fresh Frozen plasma (FFP)or Human albumin 20% was used as a replacement fluid. Inlet flow was 45-55 ml/minute. Acid Citrate Dextrose ratio was kept at 1:12 to 1:14, depending on the replacement fluid used. Simultaneously, injection of Calcium gluconate 30ml in 100ml of DNS was infused throughout the procedure to prevent hypocalcaemia. Injection Avil 2ml was also added in the DNS to prevent any allergic reactions. Blood pressure, pulse rate, and respiratory rate were closely monitored during TPE. Any adverse event, if it happened then managed accordingly. If total body volume was more than 15% of the extracorporeal volume, which was approximately

180-200 ml, then prime saline was diverted. If hemoglobin was less than 5gm%, then Packed cell volume (PCV) was used to prime the circuit.

Data collection and analysis:
Data extraction from Medical Records of Procedure was done retrospectively for 5 years. Analysis: Mean standard deviation and percentage were calculated. Adverse events were analyzed according to gender, age, clinical diagnosis, and type of replacement fluid. Categorization of various indications as per ASFA guidelines in Number and percentage

Results:
Apheresis by centrifugation was performed in a total of 120 patients, M: F 84:36. In these patients, 926 (Mean 7.72± 10.34) procedures were performed. Mean age 11.1±6.14 years, Mean height 130.77±19.41 cms Mean weight 29.38±13.311 kilograms. Of these 926 procedures, adverse events were seen in 28 procedures (3.0%) TPE was performed for various indications as described in Table 1. The Mean exchanges done were 5.16 for ABMR. In ABMR due to FSGS mean 43 exchanges, for a HUS patient 7.6, for Pre-Renal Transplant desensitization 5.7, and 2.5 was the mean for Wilson's disease.

Table 1. Indications

	Indications	Category	Number of Patients
1	Post Renal transplant ABMR	I 1B	51(42.5%)
2	Atypical Hus	I 2C	51(42.5%)
3	Pre-Renal transplant Desensitization	I 1B	10(8.3%)
4	Wilson's Disease	I 2C	03(2.5%)
5	ABO Incompatible Pre-Renal Transplant	I 1B	01(0.83%)
6	Acute Liver Failure	I 1A	01(0.83%)
7	Membranoproliferative Glomerulonephritis	I 2C	01(0.83%)
8	Lupus Nephritis	II 2C	01(0.83%)
9	Ig A Vasculitis	III 2C	01(0.83%)

Adverse events were seen in 28 procedures out of 926 procedures (3.0%)
According to the indications FFP was the replacement fluid in a HUS & Albumin was the replacement fluid in post-Tx ABMR
Mild: Accounted to 3.57%. One 16-year-old male patient had nausea.
Moderate adverse events: Accounted to 53.57% Age 8-17 years M: F 6 :3 Most common was allergic reaction n= 9. Of these 9 procedures, 8 had Fresh frozen plasma as replacement fluid for a HUS and Human Albumin was in 1 for Post-Transplant ABMR. Vomiting was the next most common adverse event,n=3(2 in a HUS and 1 in Pre Tx-Desensitization). Hypotension (n=2) was seen in a 14-year-old male and a 17-year-old female patient, both had undergone TPE for post Tx ABMR. The male patient also had poor flow in another procedure. Two patients who showed moderate adverse events, both developed one severe adverse event each (Table 2)

Table 2 Moderate Adverse events

Sr no	Type of adverse event	N(Indication)	Replacement fluid
1	Allergic reaction	8(a HUS)	FFP
		1(ABMR)	Albumin
2	Vomiting	2(a HUS)	FFP
		1(Pre-Renal Tx Desensitization)	Albumin
3	Hypotension	2(ABMR)	Albumin
4	Poor flow	1(ABMR)	Albumin

Severe: Accounted to 42.85%. N=9 patients (M: F 7:2) seen in 12 procedures. One 7-year-old male patient undergoing TPE for a HUS developed an allergic reaction(moderate) in his 1st procedure and developed hypertension (severe) during his second procedure. He underwent only 2 cycles of TPE Another patient who had developed 2 moderate adverse events (hypotension and poor flow) developed chest pain in his 6th cycle. ECG and Spo2 were normal. Pulse was rapid 124/min. Vomiting n=2 was seen in ABMR with Albumin as replacement fluid. One patient, 8 yr male, developed rash where TPE was performed for aHUS with FFP. One 5-year-old male patient became unconscious during his 13th cycle for aHUS with FFP. Another 7-year-old female patient developed hypotension and was shifted to the Critical care unit during her 7th cycle for aHUS with FFP. One 5-year-old male patient developed convulsions during his 4th cycle for aHUS.The patient was treated for the same and was stable later. One 12-year-old female patient became breathless after her 5th procedure for ABMR with Albumin

All the adverse events were managed by the clinicians and there was no mortality because of TPE. There were machine errors in 3 procedures (Table 3)

Table 3 Severe adverse events

Sr	Adverse event	Age	Sex	Replacement fluid	Indications
1	Vomiting	14	Male	Albumin	ABMR
2	Vomiting	08	Male	Albumin	ABMR
3	Convulsions	05	Male	FFP	a HUS
4	Loss of consciousness	05	Male	FFP	a HUS
5	Hypertension	07	Male	FFP	aHUS
6	Chest pain	14	Male	Albumin	ABMR
7	Breathlessness	12	Female	Albumin	ABMR
8	Hypotension	07	Female	FFP	aHUS
09	Poor flow	14	Male	FFP	ABMR

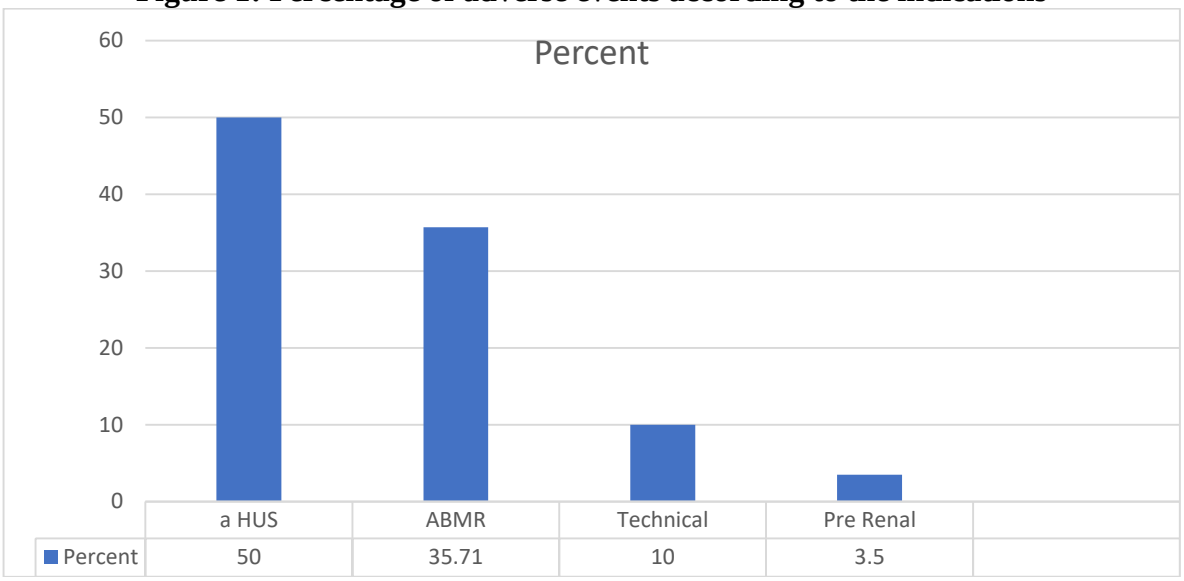
Technical error in the machine in 3 procedures

Table 4 Percentage of adverse events

Adverse events	Number of procedures	Percentage
MILD	01(ABMR)	3.57
MODERATE	15(a HUS =9, ABMR=4, Pre-Renal Tx Desensitization=1)	53.57
SEVERE	09(a HUS =5, ABMR=4)	42.85
	03Technical error in the machine	

Indication-wise distribution of adverse events showed 50% in a HUS patient,35.71% in ABMR,10% due to technical problems, and 3.5% in pre-renal transplant desensitization. (Figure 1)

Figure 1: Percentage of adverse events according to the indications



Discussion

To our knowledge, we have the largest number of Pediatric Nephrology patients being treated at our tertiary care super-specialty hospital in India. We have performed the maximum number of TPE procedures in pediatric patients, which is 926 procedures on 120 patients in 5 years. The most common indications for TPE were for category I & Post Tx ABMR, and a HUS were the most common indication for apheresis. This was followed by pre-renal transplant desensitization, Wilson's disease, ABO incompatible pre-renal transplant desensitization &Acute Liver failure. TPE is category I, which is the first line of treatment as per ASFA guidelines. In a retrospective 6-year study on pediatric patients by Balasubramanian KK, TPE was performed mostly for Hemolytic uremic syndrome [6]. In another retrospective study of 19 years by Hans R et al, they also performed TPE most commonly for hematological indications, followed by renal and other indications. They performed 672 procedures in 99 patients.[7] Our patient pool is larger than both these studies. All have followed the ASFA guidelines which are designed for adult patients. No separate guidelines are available for pediatric patients. TPE is challenging in pediatric patients as the body volume is less, veins are small and the course of disease is different from adult patients. Hence a separate guideline is necessary for pediatric patients In our study, adverse events were seen in only 3% of the procedures. The most common adverse event was of moderate type and allergic reaction to replacement fluid (FFP) was the most common. The most common indication where adverse events were seen was a HUS The reason for this may be that more exchanges are needed for these patients. In our study, mechanical obstruction to blood flow was not observed in many cases. This could be attributed to the use of a central venous line or an arteriovenous fistula, along with proper heparin flushes administered under aseptic precautions after the procedure. Small Body volume poses a challenge in pediatric patients which was overcome by diverting prime saline and Packed cell volume priming in patients with low hemoglobin Calcium gluconate infusion prevented citrate toxicity. Hypotension was seen with both Albumin or FFP as replacement fluid. Hence replacement fluid was not the reason for hypotension. Severe adverse event in a patient due to loss of consciousness was treated by the pediatric nephrologists. One patient developed convulsions which were treated effectively with Diazepam. One patient developed chest pain however it may have been due to anxiety as all investigations were normal. In a patient who was breathless after the procedure nasal oxygen and propped-up position made the patient comfortable. Technical errors were seen in just 10% of all adverse events, implying that the machines are competent. This is comparable to the study by Hans R et where 5% adverse events were seen and allergic reaction to replacement fluid was the most common followed by hypotension.[7] In another 10-year study similar to our study however the incidence of adverse events is higher in theirs which is 9%, they performed TPE by filtration whereas we performed TPE by centrifugation.[8] Our rate of

adverse events is comparable to a study by Chowdhary Mohit et al. where the incidence of adverse events was 2.2%. They observed that hypotension and vascular occlusion were the most common adverse events. This is also comparable to another study by Ozake M et al. where they studied the role of TPE in 22 pediatric patients who underwent 135 procedures in all, and a similar percentage of adverse events were noted.[9,10]. In a study by Taylan et al where TPE was performed by filtration, adverse events were seen in 11% of procedures, and the most common indications were ABMR and a HUS, which is similar to our study. However, adverse events were less in our study [11]Comparison between centrifugal TPE and TPE by filtration will be beneficial in proving which method is safer.

Conclusion:

This study is unequivocally the largest single-center investigation in western India regarding therapeutic plasma exchange (TPE) in pediatric patients. It demonstrates that TPE by centrifugation is a safe procedure when physiological and technical challenges are effectively managed. Furthermore, distinct guidelines for apheresis in pediatric patients must be established, as their clinical disease trajectories and progression are markedly different from those of adults**.**

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