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Assessing safety and efficacy of therapeutic plasma exchange in pediatric patients: A single-center experience

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Abstract:

INTRODUCTION: Therapeutic plasma exchange has been widely employed by clinicians for removal of the toxic constituents from plasma by filtration of whole blood and subsequent removal of plasma and reinfusion of cellular components along with a replacement fluid. It has become an accepted therapeutic modality in paediatric patients for numerous indications including but not limited to renal transplant, haemolytic uremic syndrome and Guillain Barre Syndrome. But, data on safety and efficacy are mainly derived from studies in the adult population with very limited data available in the paediatric age group. However, it is technically challenging in children due to their small circulating volume. This study discusses the clinical indications, efficacy, and safety of therapeutic plasma exchange in paediatric population.

METHOD: We retrospectively reviewed the data of children (up to 18 years of age) who underwent TPE between January 2017 and March 2019 at our Hospital. Main features of the TPE procedures i.e. frequency of TPE, site of vascular access, type of replacement fluid used, instrument used, plasma volume processed, priming of the circuit, adverse events if any and outcome of the patients were analysed.

RESULTS AND CONCLUSION: A total of 114 procedures were performed on these 24 patients. Fifteen patients with Category I indication showed good clinical outcome in terms of attainment of target ABO titre and/or decrease in the donor specific antibody. TPE is an effective therapeutic option in selected paediatric disorders. Our series of data on TPE procedures from paediatric perspective has shown safety and efficacy of the therapy.

Keywords:

American Society for Apheresis, pediatric, therapeutic plasma exchange

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Introduction

Therapeutic plasma exchange (TPE) is the filtration and removal of the plasma, with reinfusion of all cellular components to the patient along with physiological replacement fluid.^[1] Replacement involves the use of albumin, fresh frozen plasma (FFP) or both, and saline. TPE ensures the removal

of proteins, antibodies, and toxins causing clinical symptoms from the circulation. The effectiveness of TPE is related to the volume of plasma removed and the concentration of the pathological substance in the blood.^[2] It is recommended that approximately 1–1.5 plasma volumes be exchanged per procedure.^[3] This therapeutic modality has evolved to an accepted therapy for selected indications in pediatric patients. However, it is technically challenging in children due to their small circulating volume.

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Table 1: Demographic details of the patients

Total number of patients for TPE	392
Total number of TPE performed	1314
Patients belonging to pediatric age group	24
Total number of TPE done in pediatric age group	114
Mean age (years) (range)	8.77 (1-18)
Gender	
Males	12
Females	12
Machine used in patients	
Spectra optia	18
Hemonetics MCS+	6
Total	24
Procedures done on individual machines	
Procedures done on spectra optia	83
Procedures done on MCS+	31
Total procedures done	114
Replacement fluid used	
5% albumin with 2 units of FFP	15
Only 4% albumin	2
Only FFP	7

FFP=Fresh frozen plasma, TPE=Therapeutic plasma exchange, MCS

In the recently published American Society for Apheresis (ASFA) guideline, TPE constitutes the majority of the therapeutic apheresis procedures. The number of disorders that can be treated with TPE has significantly increased over the years.^[4] This is true in the case of pediatric patients also. However, data on safety and efficacy are mainly derived from studies in the adult population with only limited data available in the pediatric age group. This is because of the pathophysiology, clinical course, and therapeutic responses that may differ in children.

This study aimed to review the procedure in terms of clinical indications, efficacy, and safety in our pediatric population.

Materials and Methods

Patients

We retrospectively reviewed the data of children (up to 18 years of age) who underwent TPE between 2017 and 2019 at our hospital [Table 1].

Data collection

The patients' data were obtained from the departmental records. The patient's demographic and clinical characteristics such as age, sex, body weight, and indication for TPE were included. Main features of the TPE procedures, i.e., frequency of TPE, site of vascular access, type of replacement fluid used, the instrument used, plasma volume processed, priming of the circuit, adverse events if any, and outcome of the patients were analyzed.

The indications of TPE were compared with various categories mentioned under ASFA guidelines.^[4]

Therapeutic plasma exchange procedure

TPE was performed using MCS+ (Hemonetics, USA) or Spectra Optia (Terumo BCT, USA) aphaeresis system. Spectra Optia uses details of gender, height, and weight to determine the total blood volume (TBV) of the patient using Nadler's formula.^[5] The estimation of treatment results involves calculating the plasma volume to be removed which is calculated using the following formula: $= (70 \times \text{bodyweight in kg}) \times (1 - \text{hematocrit})$.^[6] A total of 1–1.5 volume of plasma was exchanged, depending on patients' weight and hematocrit. The replacement fluids used were albumin 5% and/or FFP according to the indication for TPE. As per the manufacturer's recommendation, for Spectra Optia citrate-based anticoagulants are preferred. The MCS+ TPE protocol also continuously monitors extracorporeal volume (ECV). The MCS+ TPE protocol gives a warning once ECV reaches 15% of the total estimated patient's blood volume (the parameter "ECV Warning" is set in Haemo Calculator). The message "ECV limit reached" is displayed with an audible alarm and the same can be then attended.

Priming with red cells was considered in patients if ECV exceeded 10% of TBV. It is also recommended in cases where the extracorporeal red cell volume (ERCV) of the patient is >10% of the total red cell volume. The ERCV for the TPE disposable set is 68 ml in spectra optia. This is often indicated in younger patients <20–25 kg. For priming in the author's institute, the entire apheresis system is first primed with the normal saline. Thereafter, the centrifuge chamber and the tubings are filled with the red cells from the donor wherein the donor unit is connected to the access/draw line through the blood administration set, and an empty bag is connected to the return line.

In anemic patients, the option of partial "rinse back" is also available in spectra optia. "Rinse back" was avoided in small children who have been red cell primed so as to prevent the circulatory overload. In one patient, 4% albumin was used for priming of the kit as per the physician's request.

A double lumen hemodialysis central venous catheter was used through the jugular, subclavian, or femoral vein according to the patient's vascular anatomy.

Results

Demographic data

From 2017 to 2019, a total of 392 patients underwent 1314 TPE procedures. Out of these 24 patients were younger than 18 years. A total of 114 procedures were performed on these 24 patients. There were 12 male and 12 female

patients. The mean age was 8.77 ± 5.9 years and the mean body weight was 24.3 ± 17.27 kg [Table 1].

Indications of therapeutic plasma exchange and American Society for Apheresis category

Various indications for which patients underwent TPE are summarised in Table 1. According to the latest ASFA guidelines,^[4] desensitization for renal transplant belongs to Category I, Grade 1B indication of TPE. Antibody-mediated rejection (AMR) postliver transplant, atypical hemolytic uremic syndrome (aHUS) and Guillain Barre Syndrome (GBS)-postintravenous immunoglobulin belong to Category III and Grade 2C for TPE.

Therapeutic plasma exchange procedure

Out of the total 114 procedures performed, 31 procedures were performed on MCS+ (Hemonetics USA) and 83 were on spectra optia (Terumo BCT, USA). For patients with a weight of <25 kg ($n = 9$), TPE was performed on spectra optia compulsorily. For patients with a weight more than 25 kg TPE ($n = 15$) was performed on hemonetics MCS+ or spectra optia.

In this study, except for one patient all other patients underwent more than one TPE session. The mean TPE session per patient was 4.7 ± 4.05 .

Priming with red cells was done in nine patients. In these patients, ECV exceeded 10% of intravascular volume. In one patient, 4% albumin was used for priming of the kit as per the physician's request. Five percent albumin with 2 units of FFP was used as the replacement fluid in 13 out of 15 patients who were admitted for desensitization therapy in ABO-incompatible renal transplant and both the patients of GBS. Only albumin was used as a replacement fluid in two patients for desensitization therapy in renal transplant with an anti-human leukocyte antigen antibody. Only FFP was used in seven patients who were suspected cases of AMR postliver transplant and atypical hemolytic uremic syndrome (HUS).

Venous access used were femoral vein ($n = 10$, 41.6%), internal jugular vein ($n = 12$, 50%), arterio-venous fistula ($n = 1$, 4.2%), and permacatheter ($n = 1$, 4.2%).

Clinical outcome

Fifteen patients with ASFA Category I indication showed good clinical outcome in terms of attainment of target ABO titer and/or decrease in the donor-specific antibody [Table 2].

Of the 6 patients with ASFA Category III indication for AMR postliver transplant, 4 patients succumbed and 1 had a graft failure. The mortality was due to sepsis in these 4 patients and was not related to the procedure itself. Two patients of aHUS and GBS respectively had left against medical advice (LAMA) after one session of TPE each. The outcome could not be assessed in these patients. The patient with GBS had made Grade 3 neurological improvement (completes the available test range of motion against gravity but tolerates no resistance) according to the Medical Research Council Manual Muscle Testing scale.^[7]

Therapeutic plasma exchange procedure and complications

Hypotension was noted in two patients. The first patient had hypotension in two consecutive procedures and the other patient had a single episode of hypotension. Both were managed symptomatically with no sequel. Catheter-related complications were seen in two patients. Following a catheter exchange for a catheter occlusion, the TPE was completed without further complications.

Discussion

There is relatively little evidence-based data on TPE use in pediatrics. The indications for TPE are often derived from adult studies. Nevertheless, improvement in the techniques and availability of different central venous catheters and ports have paved the way for a better outcome in these pediatric patients. However, since the pediatric population is a special population, special

Table 2: Indication for therapeutic plasma exchange in patients as per the American Society for Apheresis and clinical outcome

Indication	Number of cases	ASFA category	Clinical outcome
Desensitization for renal transplant	15	I	Target ABO titer and decrease in the donor-specific antibody was achieved in all
Antibody-mediated rejection postliver transplant	6	III	1 - graft failure 4 - mortality 1 - decrease in the donor-specific antibody was achieved
HUS, infection-associated	1	III	LAMA
GBS (post-IVIG)	2	III	1 - LAMA 1 - neurological improvement
Total	24		

ASFA=American Society for Apheresis, IVIG=Intravenous immunoglobulin, LAMA=Left against medical advice, GBS=Guillain-Barre Syndrome, HUS=Hemolytic uremic syndrome, ABO blood group

consideration with regards to technical, procedural, vascular access, and anticoagulation have to be taken into account for the selection of the procedure. Also, the children undergoing TPE exhibit some degree of anxiety, which may often require a special approach to cater to their needs. This may include an individual approach to each patient's interests, psychosocial background, and better and innovative communication. As a protocol, in the author's institute, the parents or guardians are effectively counseled about the procedure, its side effects, and any discomfort the child may experience.

Disorders treated with TPE vary based on the age groups and depending upon the specialty and expertise of the hospital in pediatric patients. In our study, the major indication for TPE in the pediatric age group was desensitization for renal transplant. In comparison, the most common indications in other studies were, sepsis/organ failure, thrombotic thrombocytopenic purpura, and chronic inflammatory demyelinating polyneuropathy, HUS, renal diseases, lupus nephritis, and Focal Segmental Glomerulosclerosis.^[8-12]

Plasma exchange can be done by continuous flow centrifugation (CFC), for example, spectra optia or intermittent flow centrifugation (IFC) technology e.g., MCS+. In IFC, the therapeutic apheresis is done in interrupted cycles that include withdrawal of whole blood, separation of required components, and reinfusion of the remaining components. Essentially, the whole blood is processed in batches of small volumes to be tolerable by the patient, once the separation of that blood is completed, the separation chamber must be emptied to repeat the cycle. This process involves a large ECV. The ECV of the apheresis procedure would include not only the tubings but also the ancillary devices such as the blood warmer. Besides a large ECV, hemodynamic fluctuation, and longer duration of the procedure are other disadvantages associated with IFC therapeutic apheresis. CFC on the other hand is uninterrupted or continuous flow for withdrawal, separation, and reinfusion. The complications, therefore, are of a much lesser degree when compared to IFC. IFC also has some advantages, besides being a relatively portable machine, which enables the equipment to be shifted at the patient bed site, they have a distinct advantage wherein it helps the patient to metabolize the anticoagulant citrate dextrose solution formula A (ACD-A) during the draw cycle before the next dose of ACD-A is infused during return cycle. Regardless of the type of instrument (IFC or CFC), ECV will represent a larger fraction of the TBV in the paediatric population as compared to an adult population. This would mean a greater volume deficit persists throughout the procedure until the "rinseback" is performed on the patient after the end of the procedure. To calculate this volume deficit, the TBV of the child needs to be determined which varies

with the lean body mass. TBV can be roughly calculated on the basis of age and weight of the patient wherein the TBV of child more than 3 months old is 65–75 ml/kg, infants younger than 3 months old is 80–100 ml/kg and in adult males is 75–80 ml/kg. Sophisticated instruments like spectra optia uses the Nadler formula to calculate the TBV based on gender, height, and weight of the patient.^[5] However, for patients <25 kg, the machine does not calculate the TBV and the same needs to be entered based on the rough estimate according to the weight of the patient and departmental standard operation procedures. Based on our experience with both the systems, in experienced hands, and selecting appropriate subjects according to the above-mentioned limitations, both IFC and CFC instruments can yield very promising results.

In patients with a weight <25 kg, in order to prevent hypotension related to excessive ECV, a 4 log leukoreduced and Anti human globulin cross-match compatible packed red cell (PRC) was used as a priming fluid to prime the kit as part of the departmental protocol. The ECRV in the TPE disposable is 68 ml. In the author's institute, In one patient, 4% albumin was used for kit priming as part of the primary physician's discretion. This was a patient of ABOi renal transplant, who had a negative pretransplant donor-specific antibody. Since blood is one of the potential sources of alloimmunization in transplant patients, the same was avoided.

The frequency of TPE sessions is an important aspect that determines the clinical outcome and clinical response in patients with various clinical conditions. In our study, the TPE sessions for all patients were done daily except in patients for GBS for whom it was done every other day which was in accordance with the ASFA guidelines for various indications of TPE.^[4]

While selecting the vascular access device, the factors that are considered are the urgency of the TPE, the expected frequency and duration of the procedure, and the ease of catheter care. Since the veins of young children may not be able to accommodate peripheral access, a double lumen hemodialysis central venous catheter was preferred for the procedures. In the current study, the most commonly used venous access for TPE procedures was internal jugular vein (50%) followed by a femoral catheter (41.6%). Internal jugular veins are preferable in children as they achieve a better flow rate by reducing the mechanical problems associated with agitation and movements. Other studies have also mentioned the use of a central venous catheter but fail to mention the site of venous access used.^[9,11-13] Arteriovenous fistula was used as venous access in one patient ($n = 1$, 5.88%).

Citrate is often preferred in pediatric intensive care unit setting as the use of heparin as an anticoagulant can lead

to bleeding and heparin-induced thrombocytopenia. Citrate itself may cause adverse effects related to hypocalcemia and hypomagnesemia. The young or sick children may not be able to inform the operator of the usual paraesthesia that occurs with citrate toxicity. Furthermore, these children may not have classical symptoms and often develop abdominal pain, emesis pallor, and hypotension. In optia devices, the maximum infusion rate of ACD-A is limited. If a maximum ACD-A infusion rate of 1.2 ml/min/L/TBV is reached, the device switches into a warning mode. Here, it is possible to proactively adapt the infusion rate through inlet flow. For patients with a weight of <25 kg, TPE was performed on spectra optia compulsorily. This is because there is a very low ECV of the disposable set. In optia device, as per manufacturers' recommendation, the circuit was primed using 4 log leukoreduced and AHG cross-match compatible PRC or albumin. Other advantages of this equipment are the user-friendly graphical interface and continuous feedback during the procedure minimizing the risk of adverse iatrogenic events.

Replacement fluid during TPE is an important consideration and frequently varies across institutions. There are no fixed guidelines on the ideal replacement solution that needs to be used.^[14] Replacement fluids include FFP, albumin, normal saline, or a mixture of fluids. Citrate toxicity is more profound in FFP replacement as compared to albumin replacement. This is much more exaggerated in children and sick individuals who have hepatic and renal dysfunction. If TPE is performed daily there is a risk of coagulation factor depletion (especially fibrinogen level, which should be monitored) and so plasma supplementation may be considered in these situations.^[9] In our study, 5% albumin with 2 units of FFP was used as the replacement fluid in 13 patients (desensitization and GBS) as more than 3 sessions of TPE were planned in these patients. Only FFP was used in cases of AMR postliver transplant and aHUS. Only albumin was used in two patients for desensitization as less than were sessions were planned in these patients. In a retrospective study by Özkale *et al.* among ($n = 22$) children with neurological disease, TPE was done using FFP was used as replacement fluid.^[14] The most common indications among these pediatric patients were inflammatory polyneuropathy followed by acquired diseases to the central nervous system. Other indications reported were autoimmune encephalitis and paraneoplastic limbic encephalitis. The authors reported a nil mortality rate during TPE.^[14]

In a study done by Özkale *et al.* the complication rate was found to be 2.2% which consisted of transient events including hypotension and allergic reactions which were similar to our study.^[14] The hypotension in young patients is usually due to hypovolemia but may seldom occur

due to hypocalcemia or vasovagal reaction. The usual protocol in the author's institute is to halt the procedure for a while until the vitals reach the baseline value. As a dictum, the vasovagal reactions are associated with bradycardia whereas hypovolemia is usually accompanied by tachycardia. In our study, the most frequent adverse events noted were hypotension in two patients and catheter-related complications (venous access malfunction) in two patients. Both were managed symptomatically with no sequelae. Catheter-related complications were also the most common complications seen in the pediatric age group in a study by Carter and Benador.^[13] In another study by Cortina *et al.*, one patient had developed transfusion-related lung injury following a TPE session.^[11]

In terms of efficacy, the procedure was most effective as a part of the desensitization protocol in prerenal transplant patients. In our study, 15 patients were prospective renal allograft recipients. In all these patients, the target ABO titer and decrease in the donor-specific antibody were achieved. Desensitization is a category I indication for TPE.^[4] One patient of GBS had symptomatic relief, i.e. improvement in motor strength but mild motor weakness was still present even after TPE. The other patient of GBS and the patient with aHUS left against medical advice and therefore TPE efficacy could not be assessed in these patients.

Six patients underwent TPE for AMR postliver transplant. In five of these patients, TPE was not very effective [Table 2]. All these cases were category III indications for TPE according to ASFA guidelines.^[4]

Limitations of this study include its retrospective design, the inclusion of a small number of patients, and the fact that it is a single-center analysis. TPE outcome in two patients could not be assessed as the patient's LAMA due to financial constraints. As TPE was used in combination with immunosuppressive therapy, the therapeutic effect of TPE alone could not be evaluated in this study.

Conclusion

Our study concludes that TPE is an effective therapeutic option in selected pediatric disorders. Our series of data on TPE procedures from pediatric perspective has shown the safety and efficacy of the therapy. TPE is a safe procedure when in experienced hands and hence well-trained staff is imperative to minimize complications. Following evidence-based guidelines for TPE, the procedure was the most effective in patients for desensitization and titer reduction before renal transplant which were Category I indication of TPE. Overall the pediatric group tolerated the procedure well with no major adverse events.

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Conflicts of interest

There are no conflicts of interest.

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