BRIEF RESEARCH COMMUNICATION

Scope, Safety, and Feasibility of Therapeutic Plasma Exchange in Pediatric Intensive Care Unit: A Single-center Experience

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Abstract

Background: Indications for therapeutic plasma exchange (TPE) in the pediatric intensive care unit (PICU) are expanding. We aimed to study the demographics, clinical indications, and outcomes of patients who have undergone TPE in our PICU.

Materials and methods: This is a retrospective study performed among children aged from 1 month to 16 years of age. Demographics, indications, therapeutic response, serious adverse events (SAE), PICU length of stay (LOS), and death during hospitalization were studied as outcome variables.

Results: Therapeutic plasma exchange was performed in 115 sessions on 24 patients for 12 different indications falling under various American Society for Apheresis (ASFA) categories. Therapeutic plasma exchange was performed on ten, four, and ten children for ASFA category I, II, and III indications, respectively. The most common indications were thrombotic microangiopathy (TMA) (8/24) and acute liver failure (ALF) (6/24). During those 115 sessions, a total of five serious adverse events (SAEs) occurred, accounting for 4.3% of the cases. Minor adverse events occurred in 12 sessions (10.4%). Therapeutic response was good in 17 patients (71%) including 5 patients who underwent standard volume TPE (SV-TPE) for ALF. Median PICU LOS was 9 (range 2–120) days. The mortality rate was 12.5% (3/24).

Conclusion: Therapeutic plasma exchange is effective in various clinical conditions involving various organ systems. It is an excellent therapeutic modality in children with ALF, irrespective of the exchange volume and TMA. However, SAEs do occur in the minority.

Keywords: Acute liver failure, American society for apheresis, Paediatric Intensive care, Plasmapheresis, Therapeutic plasma exchange, Thrombotic microangiopathy.

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Highlights

- Therapeutic plasma exchange is a potentially effective treatment option for a range of illnesses in pediatric intensive care unit (PICU).
- Therapeutic response is good, especially in acute liver failure (ALF), irrespective of the exchange volume, complement-mediated thrombotic microangiopathy (TMA), and thrombotic thrombocytopenic purpura (TTP).
- Therapeutic plasma exchange is feasible even in infants.

Background

Therapeutic plasma exchange is an extracorporeal blood purification technique where a patient's plasma is selectively removed and replaced with fresh frozen plasma (FFP), albumin, saline, or a combination of them. Therapeutic plasma exchange works by removing large molecular weight particles like circulating autoantibodies, immune complexes, etc., from the plasma which are implicated in the pathogenesis of certain diseases.[1]

The procedure requires large and durable venous access like a dialysis catheter to withstand high flow rates. Therapeutic plasma exchange is more challenging in pediatric patients than in adults due to difficulty in obtaining vascular access and other technical considerations. Still, its application in the pediatric intensive care unit (PICU) is increasing with evolving evidence to support its use in select conditions. The American Society for Apheresis (ASFA) regularly updates its evidence-based guidelines on the use of therapeutic apheresis in adults and children, the ninth edition (2023) being the latest.[2] Although a large body of literature exists on this subject in adults, data is sparse in children, especially in the Indian context. We aimed to study the demographics, clinical indications, and outcomes of patients who have undergone TPE in our Tertiary Care PICU.

Materials and Methods

This is a retrospective study performed in our tertiary care PICU over 6 years among patients between 1 month and 16 years of age. Demographic details, diagnosis, indication for TPE, procedure

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Table 1: Demographic data

Total number of patients	24
The median age in years (Range)	10.7 (0.6–16)
Median weight in Kg (Range)	31 (6.3–78)
Male: Female ratio	2.4:1
Total number of TPE sessions	115
The median number of sessions per patient (Range)	5 (1–15)
The median duration of each session in hours (Range)	2.5 (2–4)

TPE, therapeutic plasma exchange

details, concurrent extracorporeal therapies, and outcome data were collected from medical records and analyzed. Indications were compared with the ASFA categories of recommendations for therapeutic apheresis. Therapeutic response, serious adverse events (SAE), PICU length of stay (LOS), and death during hospitalization were studied as outcome variables.

A Fresenius 4008-S hemodialysis machine with Fresenius plasma Flux PSu1S or 2S (effective surface area 0.3 m^2 or 0.6 m^2, respectively) plasma exchange filter was used. Fresenius plasma Flux PSu 1S and 2S were used in children aged <4 and ≥4 years, respectively. The procedure was performed as per our standard protocol. Therapeutic plasma exchange was done by the plasma-filtration method using a P1/P2 filter depending on the patient's body surface area. Standard volume TPE (SV-TPE) was defined as 1–1.5 times plasma volume exchange, while high volume TPE (HV-TPE) was defined as >1.5–2 times plasma volume exchange.[3] Patients were considered to have a good therapeutic response if there was improvement or stabilization of clinical and laboratory parameters (where applicable) allowing the clinician to discontinue TPE. Serious adverse events were defined as those occurring during or within 6 hours of completion of the procedure and requiring additional vasoactive agents, mechanical ventilation, cardiopulmonary resuscitation (CPR), or resulting in death. Other adverse events such as simple allergic transfusion reactions and dyselectrolytemia were considered minor. The study was approved by the institutional review board. Continuous variables are expressed as median (range). Categorical variables are expressed as numbers or percentages.

Results

Over a period of 6 years (January 2016 to December 2021), TPE was conducted in 115 sessions for 24 patients. Out of the 24 children, three had weights of 15 kg or less, with two of them weighing 10 kg or less. The youngest child in the cohort weighed 6.3 kg and was 7 months old. The demographic data is tabulated in Table 1. Access sites were the internal jugular (IJ) in 15 (62.5%) including the three children weighing ≤15 kg and femoral veins in 8 (33.3%) and both in 1 patient (4.2%). Minimal bleeding at the access site was seen in 3 out of 24 patients (12.5%) and they responded to compression dressings. A total of one patient (4.2%) had inadequate flows needing fluid administration and adjustment of the catheter tip position.

Among the patient cohort, 14 experienced multiorgan dysfunction syndrome (MODS). Out of the 24 patients, 10 required concurrent renal replacement therapy (RRT), 12 needed mechanical ventilation during their PICU stay, and none were placed on extracorporeal membrane oxygenation (ECMO).

Except for 1 patient with acute liver failure (ALF) who received HV-TPE, other patients received SV-TPE. The replacement fluid was FFP in 14 patients while it was a combination of FFP and 5% albumin in 9 patients. Cryo-poor plasma was used as a replacement fluid in 1 patient with sepsis/MODS. All patients received prophylactic calcium administration post-procedure to prevent hypocalcemia, a common side-effect observed because of the citrate anticoagulant used in FFP. Blood flow rates were set at 3–5 mL/kg/min approximately with a minimum and maximum flow of 50 and 150 mL/min respectively.

Table 2: Indications for TPE and corresponding ASFA categories

Indication	*Number of patients*	*ASFA category*
Thrombotic microangiopathy		
Factor H autoantibody	3	I
Complement factor gene mutation	1	III
Thrombotic thrombocytopenic purpura	2	I
Infection associated	2	III
Acute liver failure – Standard volume TPE	5	III
Acute liver failure – High volume TPE	1	I
Fulminant Wilsons disease	1	I
Systemic lupus erythematosus with severe complications	3	II
Catastrophic antiphospholipid syndrome	1	I
ANCA associated Vasculitis – Diffuse Alveolar Hemorrhage[#]	1	I
Macrophage activation syndrome	2	III
Acute disseminated encephalomyelitis	1	II
Guillain-Barré syndrome	1	I

ANCA, anti-neutrophil cytoplasmic antibodies; TPE, therapeutic plasma exchange

[#]*ANCA associated Vasculitis – Diffuse Alveolar Hemorrhage has been reclassified as Category 3 as per the latest (2023) ASFA guidelines*

Patients in our study received TPE for 12 different indications falling under various ASFA categories (Table 2). Therapeutic plasma exchange was performed on 10 patients for ASFA category I indications (first-line therapy), 4 patients for category II (second-line therapy), and 10 for category III (optimal role not established, decision individualized) indications respectively. The most common indications were thrombotic microangiopathy (TMA) of various causes (8/24 patients) and ALF (6/24 patients). None of the indications fell under ASFA category IV (TPE ineffective or harmful).

Additional immunomodulation such as intravenous immunoglobulin (IVIG), steroids, cyclophosphamide, cyclosporine, mycophenolate mofetil (MMF), rituximab, and anakinra, was received by 13 patients (54.2%) out of which three received a single immunosuppressant and the rest received varying combinations of these agents. Steroids (10/13) and IVIG (6/13) were the most commonly used. These agents were given either prior to, concurrent, or post-TPE depending on the primary disease, the severity of the illness, and the response to various therapies.

During a total of 115 sessions, five serious adverse events (SAEs) (4.3%) transpired in 5 patients. Among these events, three took place during the procedure, necessitating the termination of the session, while two occurred within a span of 6 hours. It's worth noting that three of these incidents were likely attributed to hypervolemia secondary to rinse back volume, leading to one or more of the following conditions: hypertension, cardiac failure, pulmonary edema, cardiac arrest, and seizures. All these

Table 3: Therapeutic response in various ASFA categories

ASFA Category	*Indication*	*Good response (n)*	*Poor response (n)*	*Total (n)*
I	TMA - Factor H autoantibody	2	1	3
	TMA - Thrombotic thrombocytopenic purpura (TTP)	2	0	2
	Acute liver failure – High volume TPE	1	0	1
	Fulminant Wilsons disease	0	1	1
	Catastrophic antiphospholipid syndrome	0	1	1
	ANCA associated Vasculitis – Diffuse Alveolar Hemorrhage[#]	1	0	1
	Guillain-Barré syndrome	1	0	1
Subtotal *n* (%)		7 (70%)	3 (30%)	10
II	Systemic lupus erythematosus with severe complications	2	1	3
	Acute disseminated encephalomyelitis	1	0	1
Subtotal *n* (%)		3 (75%)	1 (25%)	4
III	TMA - Complement factor gene mutation	1	0	1
	TMA - Infection associated	1	1	2
	Acute liver failure – Standard volume TPE	5	0	5
	Macrophage activation syndrome	0	2	2
Subtotal *n* (%)		7 (70%)	3 (30%)	10
Total		17	7	24

ANCA, anti-neutrophil cytoplasmic antibodies; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; TPE, therapeutic plasma exchange

[#]*ANCA associated Vasculitis – Diffuse Alveolar Hemorrhage has been reclassified as Category 3 as per the latest (2023) ASFA guidelines*

children needed short-term invasive ventilation and supportive measures and were successfully extubated within 24 hours. One child developed hypotension during the 4th session needing fluids and vasoactives for 12 hours, the cause of which was unclear. All these four children survived. The 5th patient was an adolescent with macrophage activation syndrome (MAS) and MODS probably due to an undiagnosed connective tissue disorder who was hemodynamically unstable and severely ill prior to TPE; he worsened further after TPE initiation and succumbed after 6 hours of TPE. None of the SAEs were in children ≤10 kg.

Minor adverse events occurred in 12 sessions (10.4%) which included hypocalcemia in six, hypokalemia in four, and allergic reactions in two sessions. None of these occurrences warranted termination of the session.

Therapeutic response was good in 17 patients (71%) (Table 3). The median PICU LOS was 9 (range 2–120) days, and the mortality rate was 12.5% (3/24 patients).

Discussion

Therapeutic plasma exchange in children needs close monitoring because of the potential for hemodynamic instability and other complications during the procedure. So, all TPE procedures in our hospital are done only in the PICU. In this retrospective study on TPE in children admitted to our PICU, 24 children underwent 115 sessions of TPE over 6 years. The median age was 10.7 years (Range 7months–16years) and the median weight was 31 kg (Range 6.3 kg–78 kg) which is comparable to other similar studies done in children.[4–7]

Patients in our study had a wide spectrum of diseases involving various organ systems receiving TPE for different indications. Ten patients each had indications in ASFA categories one and three as per the 8th edition of ASFA guidelines which was the latest at the time when this study was conducted.[8] However, as per the 2023 guidelines, 9 patients belong to ASFA Category I, whereas 11 belong to ASFA Category III as diffuse alveolar hemorrhage (DAH) secondary to ANCA-associated vasculitis (AAV) has been moved to Category III from Category I.[2] This change is based on the recent evidence that TPE in AAV has been shown to have no mortality benefit and increased infection risk.[2] All patients who underwent TPE for Category III indications had either failed conventional therapies or had rapidly progressive disease.

Thrombotic microangiopathy and acute liver failure were the most common primary diagnosis for which TPE was initiated. This is similar to the studies by Haque et al., Weiss et al., and Hans et al. where the majority of TPE was for ASFA category I, and the most common indication were TMA.[7,9,10] In contrast to our study results, 'Sepsis/MODS'(ASFA category III) was the predominant indication in studies done by Keskin et al., Sik et al. and Duyu et al.[6,11,12] A significant portion, specifically two-thirds, of our study population exhibited non-renal indications for TPE. This trend is becoming more acknowledged, as noted by Margabandhu et al.[13]

The therapeutic response was good in 17 patients (71%) which is comparable to other studies (Table 3).[14–17] Of note, good therapeutic response was observed in 70% of Category III patients including 5 patients who received SV-TPE for ALF and one patient with DAH and AAV. Among the numerous indications, children with complement-mediated TMA and TTP appear to have responded well (5/6 patients, 83%). This response rate was similar to that reported by Hans R et al. (87.5%) in pediatric patients with atypical hemolytic uremic syndrome.[14] Likewise, in children with ALF, the response was favorable wherein TPE was used as a bridge to liver transplantation (2/6 patients) or till spontaneous recovery of the native liver (4/6 patients) irrespective of whether SV-TPE or HV-TPE was done. These findings in pediatric ALF are consistent with an extensive review conducted by Alexander and Deep.[3]

Among the seven children who had a poor therapeutic response, three had received TPE for category I, one for category II, and three for category III indications. Three patients among them died during the hospital stay (1 patient each with Infection-associated TMA, MAS, and fulminant Wilson disease) and 1 patient was discharged against medical advice and had later died (TMA-Factor H antibody). Three patients improved with concomitant immunosuppression/ immunomodulatory therapy (1 patient each with catastrophic antiphospholipid syndrome, severe systemic lupus erythematosus, and MAS).

The incidence of SAEs ranges between 0.5 and 1.1% in various registry-based studies.[18–20] These data are predominantly from adult patients and the definition of SAE varies between studies. Only a few studies have studied SAE specifically in children. The incidence of SAE was 4.3% in our study, which is comparable between 3.8 and 7.7% in the population studied by Haque et al. and Hans et al. respectively.[7,14] Our results are in contradiction to the Hans et al. study where SAE has occurred only in 1% of the cohort.[10] The discrepancy is likely due to the sicker cohort and the use of membrane apheresis in our study in contrast to their stable patients and the use of centrifugal apheresis. We had three SAEs secondary to hypervolemia due to rinse back volume which is best avoided when blood priming is used and in conditions such as acute kidney injury, myocardial dysfunction, and acute lung injury that are known to be associated with complications secondary to volume overload.[10] The incidence of minor adverse events was 10.4% which is similar to that reported by Stegmayr B et al. (10.3%).[19]

Compared to other previously mentioned studies where the mortality rate ranged from 18 to 37.5%, the mortality rate was lesser in our study population (12.5%).[4–7,11]

The study's limitations include that it is a single center study with a retrospective design. Further, illness severity and mortality risk scores at admission could not be computed because of the lack of certain data.

As more and more diseases with immunological mechanisms are discovered, the scope of TPE is likely to expand. Most of the currently available literature on children is from retrospective studies done in single centers. Well-constructed, prospective, collaborative clinical trials need to be planned to further explore the scope and limitations of TPE in children.

Conclusion

The results of our study suggest that TPE is effective in diseases involving various organ systems and the outcomes are fairly good even in ASFA category III indications. It appears to be an excellent therapeutic modality in children with ALF irrespective of the exchange volume, complement-mediated TMA, and TTP. It is technically feasible even in infants and children ≤10 kg. However, SAEs do occur in a minority.

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