Original Article

Indications and Outcomes of Therapeutic Plasma Exchange in Critically ill Children at a University Children Hospital.

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ABSTRACT

Introduction: Therapeutic plasma exchange (TPE) is an extracorporeal therapy, used in a wide spectrum of diseases. The aim of our study is to analyze the indications and outcomes of TPE in critically ill children at a University Children Hospital.
Methods: This is a retrospective study including all patients admitted to pediatric intensive care unit (PICU), who underwent TPE starting from 2018 to 2022. Demographic data, vital signs, laboratory investigations at PICU admission and upon discharge were recorded. The number of PE sessions needed for each patient, volume of exchange, replacement fluid, site of IV access, complications during sessions, and the outcomes were documented.
Results: Seventy-five critically ill pediatric patients who underwent 450 TPE sessions were enrolled. Guillain-Barré syndrome (GBS) was the commonest indication for TPE in 45(60%) patients, 23(30.7%) of them were with severe motor axonal degeneration subtype. Severe autoimmune hemolytic anemia (AIHA) with failed first line of management accounted for 21(28%) children. The mean number of TPE sessions needed for every patient was 6±4 sessions. TPE sessions related complications were minimally significant. Mortality was 12% of the study group and related to respiratory support.
Conclusion: TPE carries the hope for cure of many autoimmune disorders, even as a first line of therapy in many conditions. GBS patients account for the majority of our TPE indication, and a satisfactory outcome was observed in AIHA patients. Further studies are needed to augment our results that more than 5 TPE sessions are sometimes needed in selected severe GBS patients.

Keywords:
Pediatric Guillain-Barré syndrome; Intravenous immunoglobulin; Plasma exchange; Acute motor axonal neuropathy.

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INTRODUCTION

Therapeutic plasma exchange (TPE) is an extracorporeal blood purification technique, which removes large molecular weight particles such as autoantibodies [1] It separates plasma from whole blood, removes plasma with its ineligible plasma components, and plasma is replaced with fresh frozen plasma (FFP) or albumin [2, 3].TPE is widely used in the management of a variety of disorders, including hematology, nephrology, rheumatology, and neurology diseases [4]

In 2019, the American Society for Apheresis (ASFA) published a categorized list of indications of therapeutic apheresis using an evidence-based approach. The guidelines of ASFA are the main reference in the decision-making of indications, even in pediatric patients [3].

Indications of TPE in pediatrics may vary according to the age and the nature of the disease, including neurological disorders e.g., acute disseminating encephalomyelitis (ADEM) and Guillain-Barré Syndrome (GBS), hematological diseases e.g., thrombotic microangiopathy associated with stem cell transplantation and renal diseases e.g., hemolytic uremic syndrome (HUS) [5]. It removes pathogenic circulating autoantibodies, immune complexes, cytokines, and toxins from blood [6].

Complications in adults are uncommon (<6%) and usually minor, in-contrary to children who encounter higher incidence (55%) of apheresis related complications. Hypotension is the most common complication (14%), but only less than 5% of the patients who developed hypotension required fluid therapy. Other common complications included symptomatic hypocalcemia (9.7%) and allergic reactions (4.4%). Anemia, vascular access related thrombosis, and infections were reported in 1.7% to 2.5% of the patients. Hypocalcemia was usually observed when FFP (with citrate as an anticoagulant) was used as a replacement fluid [7].

TPE shows an additional survival benefit in several critically ill conditions with a significant decrease in mortality rate even in non-renal diseases. Although the procedure of apheresis is technically identical in adults and children, differences in vascular access and extracorporeal volume cause obstacles in pediatric patients. Although there are many studies on plasma exchange, indications, and technical problems in adult patients, there are limited publications for the pediatric population [8].

METHODS

This is a descriptive retrospective study, including all patients admitted to Pediatric Intensive Care Unit (PICU) of a University Children Hospital who underwent TPE from January 2018 to June 2022. Regarding the follow up of cases, this was a retrospective descriptive study from the PICU files, unfortunately not all patients are later followed, however, those whom we contacted later we are fine with progressive improvements with no further morality in the followed group.

We included all critically ill children aged more than 1-month up to 14 years old who underwent TPE. Data were collected from patients' files, including

the age, sex, consanguinity, relevant family history, and diagnosis of the underlying disease, indication of PICU admission, duration of PICU stay, need for mechanical ventilation and its duration, indication of TPE, number of TPE sessions done, and adjuvant medical therapy used (IVIG, steroids). EMG and NCV were done to 59 % of patients, which were diagnosed with acute flaccid paralysis and GBS, while those with aHUS were within the 41 percent who weren't in need for it.

In our enrolled group of patients, TTP was diagnosed mainly clinically with no documented ADMS 13 levels in their files. All our enrolled patients had TPE for their management, of the 75 patients, Steroids were used in 45 children (60 %), while Intravenous immunoglobulins (IVIG) as an immune-modulator either before TPE with unsuccessful results or as an adjuvant therapy after TPE were used in 32 patients (42.7%).

For all enrolled patients, a central venous catheter was placed into the jugular, or femoral veins. TPE was performed in most of the patients using the GAMBRO Prismaflex machine (SN.PA5870, 2010, Sweden), the TPE 1000 filter was used for patients weighting <10 kg and TPE 2000 filter for those more than 10 kg. Older patients weighing more than 35 kg were candidates for using the centrifugal machine using the NIGALE XJC 2000 centrifugal plasma separator machine (SN.1511024, 2016, Germany). We aimed to exchange 1–1.5 times the estimated plasma volume, with a filtration rate of 10–50 mL/kg/hour over 1–1.5 hours. The plasma volume to be used was calculated using the estimated plasma volume (EPV) formula. EPV = [0.07 × weight (kg)] × [1- hematocrit]. Most sessions were performed using the membrane plasma separation method, other sessions were done by cell separator centrifugation method.

The replacement fluid used was either FFP in aHUS and TTP or physiological albumin 5% in normal saline for the rest of cases. Heparin was used for anticoagulation of the TPE circuit with 35 IU/kg loading dose and maintenance of 15- 20 IU/kg in plasma membrane separation method and citrate in centrifugal methods.

The number of TPE sessions for each patient was tailored individually for every patient by following-up the course of the disease and the clinical improvement. The patients were monitored for their vital signs during the TPE procedure. Complications associated with TPE such as allergic reactions, hypocalcemia and hypotension were recorded.

STATISTICAL ANALYSIS

Data was coded and entered using Microsoft Excel 2013. Data analysis was performed using the Statistical Package for Social Science (SPSS) version 21 (SPSS, Armonk, New York: International Business Machines Corporation).

Simple descriptive statistics: arithmetic mean ± standard deviation (For normally distributed data /median (IQR) (For non-normally distributed data) were used for summary of quantitative and frequencies (%) were used for qualitative data.

Bivariate relationship of qualitative data was displayed in cross tabulations and comparison of frequencies was performed using the chi-square test or fisher exact test wherever appropriate.

Pearson correlation was used to assess the linear association of the normally distributed quantitative data. The level of significance was set at probability of (P-value) < 0.05.

RESULTS

Seventy-five critically ill pediatric patients were enrolled in this retrospective descriptive study conducted in the PICU of a University Children Hospital, these patients had TPE sessions over the past 5 years from 2018 to 2022 as a line of their management.

Our study group included 41(54.7%) males and 34(45.3%) females. Mean age was 6.8 ± 3.8 years, mean body mass index (BMI) was -.04 ± 4.23, mean weight z-score was 1.25 ± 2.03 and mean PRISM score on admission was 7 ± 4.

The common indications for TPE in our study group were neurological causes as shown in table1. Laboratory findings, demographic data, diagnosis, vitals at presentation, management lines and EMG findings are shown in **Tables 2, 3** and **Figure 1**.The mean number of TPE sessions per patient was 6 ± 4 ranged from 1 as in the 5 AIHA patients, to 30 sessions in some GBS patients with severe neurological affection even after their first line of management. The median number of sessions was five and the total number of sessions for all patients was 450 sessions. The most common site for central venous line (Mahurkar) used for TPE was the right internal jugular vein (72%), followed by the left one (26.7%), and the least common line in our patients was the femoral route (1.3%).

Complications encountered in the study group were hypertension in 18(24%) patients treated with steroids, hypotension during TPE sessions in 3(4%) patients, citrate use related hypocalcemia in 3(4%) patients, and severe bradycardia and pre-arrest during the TPE session in 1(1.3%) patient.

Nine (12 %) patients of the enrolled group died as a complication of their primary disease, three patients with severe bulbar GBS, 1 TTP patient, 1 myasthenia gravis patient, 2 AIHA patients, one of *the AIHA was* secondary *to* severe combined immune deficiency (SCID), and 2 with aHUS. Of the sixty-six living patients, six showed recurrences of their primary diseases, and one suffered post respiratory arrest hypoxic insult.

In our study group, no statistically significant relation was found between patients' mortality and their age, sex, nor patients' different diagnoses. However, a statistically significant relationship was found between patients' mortality and complications related to their management as hypotension or hypocalcemia related to TPE sessions or hypertension as a sequel of steroids use ($p = 0.038$). Also, patients presented on admission with increased respiratory rates, and those who needed MV had significant relationship to mortality ($p<0.001$). Moreover, high PRISM score (mean >11.7) at PICU presentation and elevated ALT (mean = 41.5 IU/L) showed a significant relationship to mortality ($p<0.01$ & 0.006 respectively). Neither the number of PE sessions done nor the rest of laboratory tests at presentation were related to mortality **Table 3**.

The number of TPE sessions across various diagnoses varied significantly with a higher number of sessions needed in GBS patients ($p =0.019$). On the other hand, there was no relation between the

number of PE sessions needed and the age of the patient, PRISM score at admission, nor the need for mechanical ventilation.

Almost of patients in this study had TPE with the membrane separation technique either for their weights or their hemodynamic state, while few older patients who was hemodynamically stable had TPE with the centrifugation technique, that's why we couldn't address the difference in results between both modalities.

Table 1: Indications of PICU admission and diagnoses of the study group.

		Count (n= 75)	%
Cause PICU admission	Acute Flaccid Paralysis	45	60.0%
	Severe pallor	21	28.0%
	Disturbed conscious level	3	4.0%
	Purpura	1	1.3%
	Acute kidney injury	3	4.0%
	Ptosis	1	1.3%
	Convulsions	1	1.3%
Diagnosis	Guillian-Barré Syndrome	43	57.3%
	Auto-immune Hemolytic Anemia	18	24.0%
	Thrombotic Thrombocytopenic Purpura	3	4.0%
	Myasthenia Gravis	2	2.7%
	Atypical Hemolytic Uremic Syndrome	4	5.3%
	Dermatomyositis	1	1.3%
	Acute Demyelinating Encephalomyelitis	1	1.3%
	Systemic Lupus Erythematosus	2	2.7%
	Rasmussen Encephalitis	1	1.3%

Table 2: Laboratory data of the study group.

	Mean	Median	Minimum	Maximum	Standard Deviation	Percentile 25	Percentile 75
Hemoglobin	9.03	10.00	1.50	14.00	2.92	6.20	11.00
TLC	10.72	10.00	1.40	27.00	4.92	7.60	13.00
PLT	299	302	7	814	151	225	374
HCT	28.07	30.00	13.00	48.00	8.68	18.89	35.00
Urea	39	29	6	400	53	17	44
Creatinine	1.0	.5	.2	20.0	2.4	.4	.6
ALT	29	23	8	84	15	15	43
AST	32	23	5	198	31	15	33

TLC: Total leucocytic count; PLT: platelets; HCT: hematocrit; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

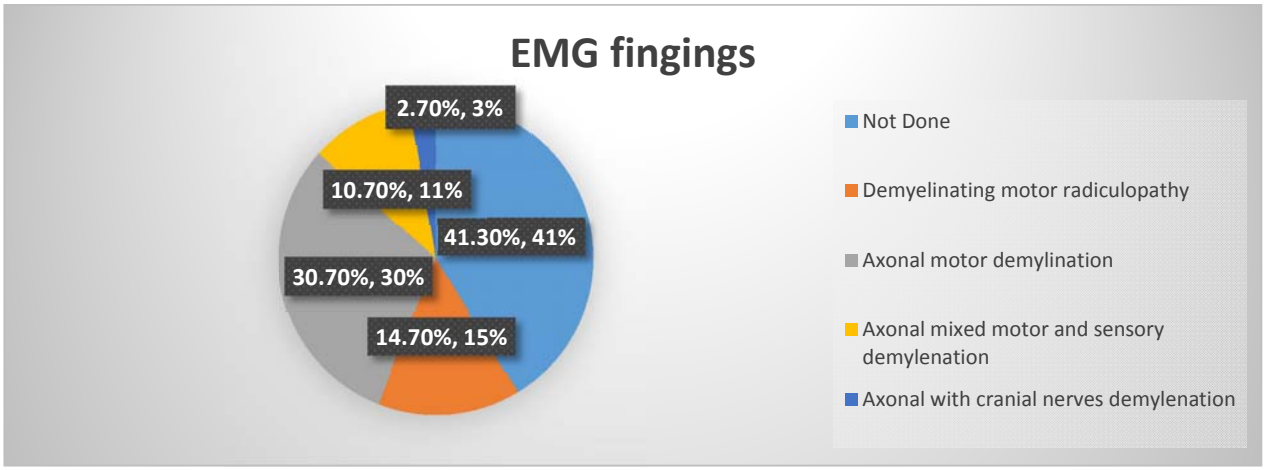

Figure 1: The Nerve conduction velocity and electromyographic findings of the study group.

Table 3: The relation between patients' mortality, demographic data, diagnosis, vitals at presentation, management lines and EMG findings.

		Prognosis						P value
		Living		Died		Total		
		N	%	N	%	N	%	
Sex	**Male**	35	85.4%	6	14.6%	41	100 %	0.499
	Female	31	91.2%	3	8.8%	34	100 %	
Consanguinity	**Negative**	58	87.9%	8	12.1%	66	100 %	1.000
	Positive	8	88.9%	1	11.1%	9	100 %	
Family history	**Negative**	64	90.1%	7	9.9%	71	100 %	0.068
	Positive	2	50.0%	2	50.0%	4	100 %	
Diagnosis	**Guillian-Barré Syndrome**	40	93.0%	3	7.0%	43	100 %	0.190
	Autoimmune hemolytic anemia	16	88.9%	2	11.1%	18	100 %	
	Thrombotic Thrombocytopenic Purpura	2	66.7%	1	33.3%	3	100 %	
	Myasthenia Graves	1	50.0%	1	50.0%	2	100 %	
	Atypical Hemolytic Uremic Syndrome	2	50.0%	2	50.0%	4	100 %	
	Dermatomyositis	1	100 %	0	0.0%	1	100 %	
	Acute Demyelinating Encephalomyelitis	1	100 %	0	0.0%	1	100 %	
	Systemic Lupus Erythematosus	2	100 %	0	0.0%	2	100 %	
	Rasmussen Encephalitis	1	100 %	0	0.0%	1	100 %	
Complications of management	**No**	46	92.0%	4	8.0%	50	100 %	0.038
	Hypotension	1	33.3%	2	66.7%	3	100 %	
	Hypertension	15	83.3%	3	16.7%	18	100 %	
	Hypocalcaemia	3	100 %	0	0.0%	3	100 %	
	Bradycardia and pre-arrest	1	100 %	0	0.0%	1	100 %	
Steroid	**No**	25	83.3%	5	16.7%	30	100 %	0.470
	Yes	41	91.1%	4	8.9%	45	100 %	
Intravenous immunoglobulin	**No**	36	83.7%	7	16.3%	43	100 %	0.286
	Yes	30	93.8%	2	6.3%	32	100 %	
Mechanical ventilation	**No**	51	98.1%	1	1.9%	52	100 %	<0.001
	Yes	15	65.2%	8	34.8%	23	100 %	
Pulse	**Normal**	47	90.4%	5	9.6%	52	100 %	0.443
	Tachycardia	19	82.6%	4	17.4%	23	100 %	
Blood pressure	**Normal**	56	91.8%	5	8.2%	61	100 %	0.095
	Hypotension	4	66.7%	2	33.3%	6	100 %	
	HTN	6	75.0%	2	25.0%	8	100 %	
Respiratory rate	**Normal**	51	100 %	0	0.0%	51	100 %	<0.001
	Tachypnea	15	62.5%	9	37.5%	24	100 %	

NCV and EMG: Nerve conduction velocity and Electromyogram. P value <0.05: Significant.

DISCUSSION

Therapeutic plasma exchange in children carries the hope for cure of many autoimmune disorders. Through removing the offending autoantibodies from the circulation, TPE could be the first line management in many situations **[9].** TPE in children can be used for specific indications, which are constantly evolving, and its utilization appears to have increased over the last decade. However, there is lack of evidence-based data about pediatric use, and pediatric literature is mostly derived from single center studies. Even though indications and possible complications are mainly based on adult studies. Yet, it is a highly specialized procedure and should be performed by experienced staff to minimize the risk of complications **[5, 10].**

In the past 5 years, GBS accounted for 60% of our study cases, which matches the ASFA guidelines (Category I), followed by AIHA (28%) (Category II and III) **[3].** Although IVIG in GBS has comparable results to TPE **[11]**, Ten of

our severe GBS patients have received IVIG before PICU admission with no remarkable improvement; instead, they experienced deterioration of their ongoing disease that required further management by TPE. Most of these severe GBS patients had NCV findings of axonal demyelination or degeneration, which usually show failure of response with the standard course of IVIG **[12, 13].** Hence, TPE as a first line of management in those patients will be much more beneficial and cost effective , as achieved in 13 cases of our sever GBS , where TPE was the first line of management, with combined decision from Neurology and PICU teams . In this study 9.3% of the cases had reported complication during TPE sessions, in the form of hypotension, citrate induced hypocalcemia and bradycardia in one patient.

The number of TPE sessions needed for every patient varied according to his disease condition. In some of our GBS patients the maximum number of PE sessions needed per patient was thirty sessions. Although previous literature reported that further PE sessions did not make much difference **[14]**, we performed 5 sessions for those patients on every other day basis, then we spaced for 2 weeks and observed for signs of improvement, after which we decided if the patient was still in need for another 5 sessions or not.

Apart from the three mortalities, all other 40 GBS patients showed dramatic improvement of their conditions on PICU discharge. Mortality in our patients was related to respiratory failure. The severity of their conditions, need of mechanical ventilation and nosocomial infections from prolonged mechanical ventilation were the common causes of mortality.

The limitation of our study is the retrospective design in a single center. Despite this limitation, data on pediatric TPE is very limited, and we believe that our contribution will be useful.

CONCLUSION

Still, GBS accounts for most of our study patients with special focus on the need for more than five sessions in some resistant axonal subtype patients. Due to the lack of evidence-based data regarding pediatric TPE practice, more studies are needed to confirm the need of more than 5 TPE sessions especially for those GBS variant patients.

ABBREVIATIONS

ADEM	acute demylenating encephalomyelitis
aHUS	atypical Hemolytic uremic syndrome
AIHA	Autoimmune Hemolytic Anemia
ASFA	American Society for Apheresis
CBC	Complete Blood Count
EPV	Estimated Plasma Volume
GBS	Guillain-Barré syndrome
Hb	Hemoglobin
HTN	Hypertension
IVIG	Intravenous immunoglobulin
PICU	Pediatric Intensive Care Unit
SCID	Severe Combined Immunodeficiency
SLE	Systemic Lupus **Erythematosus**
TLC	Total Leucocytic Count
TPE	Therapeutic Plasma Exchange
TTP	Thrombotic Thrombocytopenic Purpura

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STATEMENTS

Ethics approval and consent to participate

Research ethics committee, Faculty of medicine, Cairo University, Registration no.: MS-383-2021

Consent for publication

All authors read and approved the final manuscript.

Availability of data and material

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

MA collected the data, EE analyzed and interpreted the data, SA supervised and revised the work and NE contributes in writing the manuscript. All authors read and approved the final manuscript.

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