Brief Reports

Therapeutic Plasma Exchange; One Year Single Center Experience.

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Abstract

Background: Therapeutic plasma exchange (TPE) or plasmapheresis is a procedure which removes circulating antibodies, immune complexes and toxins from the blood. TPE has been successfully used in various pediatric immunological and non-immunological diseases.
Aim of the study: This work aims to study the outcome of therapeutic plasma exchange in our University Hospitals.
Methods: This is a descriptive study, carried out in a one year including patients who were treated using TPE; clinical data, number of sessions, volume of plasma exchanged, outcomes and complications were recorded and statistically analyzed.
Results: Thirty six patients were included in this study; 13 patients had Guillain Barre Syndrome (GBS), 9 patients had hemolytic uremic syndrome (HUS), 9 patients had nephrotic syndrome, 3 patients had Amyloidosis, and 2 patients had Systemic lupus erythematosus (SLE). Throughout this year we delivered 301 session of TPE , As regard complications; the most common complication was hypofibrinogenemia, Twenty seven patients experienced improvement and 6 patients showed no improvement while 3 patients died during the course of disease treatment.
Conclusion: Therapeutic plasma exchange is a safe and effective adjuvant therapy for many diseases especially autoimmune diseases.

Key words: Plasmapheresis, Outcome, Autoimmune disease, HUS, GBS.

Running title: plasmapheresis in children

Key words: plasmapheresis, Outcome, Autoimmune disease, HUS

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Introduction

Therapeutic plasma exchange (TPE) or plasmapheresis is a procedure which removes circulating antibodies, immune complexes and toxins from the blood. During therapeutic plasma exchange (TPE) whole blood is removed from patient and pass through an extracorporeal medical device, which separates the plasma from the cellular component of the blood [1]. The plasma is removed and replaced with colloid solution (e.g. albumin and-or donated plasma) or a combination of crystalloid and colloid solution. When the replacement is other than plasma then it is called apheresis [2].

Through removal and replacement of plasma, many pathological substances such as pathological antibodies, immune complexes and cytokines are eliminated. It has been presumed that the removal of these substances represents the major mechanism of action of TPE. However, this mechanism does not explain the length of response seen in some disorders. In addition evidence was found that TPE may have immunomodulatory effect beyond the removal of immunoglobulins [3]. About 1.5 to 2 times patient's plasma volume is replaced during the procedure; TPE has been successfully used in various pediatric immunologically and non-immunological mediated diseases, Initially it has been restricted to blood bank centers but in the last two decades; it is increasingly carried out in intensive care units because of the extension of indication and utilization of hemodiafilteration machines that make certain that better efficiency and simplicity [4].

The Apheresis Applications Committee of the American Society for Apheresis (ASFA) periodically evaluates potential indications for apheresis and categorizes them from I to IV in the basis of the available medical literature [5].

The complications are procedure as well as access related. The large extracorporeal blood volume and blood loss in the circuit carry the risk of hypotension and anemia, respectively. Furthermore, catheter-related complications are also reported and include access thrombosis and infection [6].

In this current study we aimed to assess TPE in our unit as a 1st year experience, including indications, doses, complications and outcome.

Methods

This is a descriptive/case series study carried out at our Pediatric Nephrology unit, during one year period; the study included 36 patients indicated for TPE. Informed consent was taken from parents or care-givers of children to be enrolled in the study. The study was approved by the ethical committee of our University.

The study included all patients for whom TPE was indicated to improve the course of disease and their quality of life such as; Guillain-Barre syndrome (GBS), systemic lupus erythematosus (SLE), myasthenia gravis (MG), hemolytic uremic syndrome (HUS), nephrotic syndrome (NS) and thrombotic thrombocytopenic purpura (TTP).

We excluded all patients indicated for TPE but unfit for the procedure, Patients who cannot tolerate central line insertion, Patients who have allergies to fresh frozen plasma or albumin depending on the type of plasma exchange, Patients who were

actively septic or hemodynamically unstable.

Actually exchanged or treated plasma volumes were taken from apheresis protocols; patient plasma volumes (PPV) were calculated according to Sprenger as following:

Plasma volume [l] = 0.065 × body weight [kg] × (1-hematocrit) [1, 8]. Regional anticoagulation with citrate, infused to blood volume with a ratio of 1:32 and target concentration of post-filter ionized calcium 0.25–0.35 mmol/l as described by Calatzis [9].

All children included in this study were subjected to full history taking, thorough clinical examination, laboratory investigations in the form of CBC (complete blood count), kidney and liver function tests, PT (prothrombin time), PTT (partial thromboplastin time), CRP , Serum Albumin , Fibrinogen level , Clotting function test, routine urine analysis, urine culture, arterial blood gas analysis (ABG), blood glucose level, serum sodium, serum potassium, and blood culture in addition to special investigation according to the diagnosis such as; (ANA, Anti DNA, C3, C4, and ANCA for SLE cases), (Nerve conduction velocity, Electromyography study (EMG) for Gullian Barrie syndrome) and (C3, LDH, Blood culture, Stool analysis, Stool culture for Hemolytic uremic syndrome).

Statistical Analysis

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0). According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, median and range, the following tests were used to test differences for significance.

Difference and association of qualitative variable by Chi square test (X^2). Differences between quantitative independent groups were done by t test or Mann Whitney, paired by sign test. Chi-Square test X^2 was used to test the association variables for categorical data. r→ spearman correlation: it evaluates the linear association between 2 quantitative variables (one is the independent var. X, and the other is the dependent var., Y), value of "r" ranges from -1 to 1.

Results

In this study we collected data of thirty six children who underwent TPE in our department, they were Thirteen cases (36.1%) of cases had GBS, nine (25%)of cases had NS, nine (25%) of cases had HUS, two (5.6%) of cases had SLE and three (8.3%) of cases had Amyloidosis; with mean age of the studied cases at presentation was 9.43±3.6 with range of (3-14) years and mean weight was 35.5±12.1 with range of (12-58). We used albumin and saline in 26 cases while we used fresh frozen plasma in 9 cases; the type of replacement fluid was selected according to disease and availability.

Throughout this year we delivered 301 sessions of TPE, number of sessions is <5 in 19.4% of cases, 5-10 in of 66.7% of cases and >10 in 13.9% of cases **(Table 1)**.

As regard complications; the most common complication was hypofibrinogenemia after 53 sessions

(17.6%) [we tested for fibrinogen level after every session and when low we start replacement by cryofibronogen and when not available we used plasma; it occurred regardless original disease or age of the patients] , hypotension as it happened in 36 sessions (11.9), followed by hypothermia occurred in 7 sessions (2%) and hemorrhage in three sessions (0. 9%) only. At the end of TPE sessions we had 27 improved cases (75%), 6 cases weren't improved (16.7%) and unfortunately we lost 3 cases ended by death (8.3%).

(Table 2) showed that there is no significant relation between age and outcome, but there is high significant relation between number of sessions and outcome; as the best improvement was in both groups received less than 10 sessions, as regard diseases type there was a significant improvement in GBS, NS and HUS in comparison to those with SLE or amyloidosis.

We found that there is significant change of urea level, Hg, creatinine and platelets while there is no significant change in other laboratory findings **(Table 3)**.

Table 1 : Number of sessions of the studied cases.

Number of sessions		
Mean ± SD	7.1±1.2	
	No.	**%**
<5	7	19.4
5-10	24	66.7
>10	5	13.9

Table 2 : The relation between age, number of sessions and diseases and outcome.

Variable	**Improved (N = 27)**	**Not improved (N = 6)**	**Died (N = 3)**	**Test of Significance**	**P Value**
Age				KW	
Mean ± SD	8.87±3.52	11.2±4.14	12±1.73		
Median	9.5	12	13	4.45	**0.108**
Range	3-14	4-14	10-13		
Number of sessions					
<5	6	1	0	$\chi 2$	**<0.001**
5-10	20	4	0	21	**(HS)**
>10	1	1	3		
Disease Type					
GBS	12	1	0		
NS	8	0	1	$\chi 2$	**<0.001**
HUS	7	2	0	42.71	**(HS)**
SLE	0	0	2		
Amyloidosis	0	3	0		

KW is for Kruskal Wallis test, P value is significant if <0.05

Table 3 : Comparison between on admission and end of relapse laboratory data.

Variable	On admission	End of relapse	Paired t test	P value
TLC 10^3/dl				
Mean ± SD	11. 8±7.5	13.5±5.9	**Wilcoxon rank**	0.164
Median	10.8	11.8	1.39	
Range	1.2-25.2	7.3-26.5		
HB g/dl				
Mean ± SD	8.8±2.8	11.5±1.9	30.63	0.04
Median	9.7	11		(S)
Range	4 -13.8	8-16.7		
Platelets 10^3/dl				
Mean ± SD	152.2±184.8	265.2±180.6	**Wilcoxon rank**	0.044
Median	132	206.5	3.44	(S)
Range	48-176	48-629		
Urea mg/dl				
Mean ± SD	100±106.4	13±21.7	**Wilcoxon rank**	<0.001
Median	24.4	15	20.65	(HS)
Range	8.3-391	40-77.1		
Creatinine mg/dl				
Mean ± SD	3.8±4.25	1.0±2.7	Wilcoxon rank	0.046
Median	0.6	0.83	2.44	(S)
Range	0.25-11.6	0.1-8.2		
Calcium mg/dl				
Mean ± SD	9±1.4	9.3±1.1	1.08	0.287
Median	9.6	9.3		
Range	6.3-12.5	7.2-12.5		
Fibrinogen mg/dl				
Mean ± SD	372.2±115.6	379.8±186.7	**Wilcoxon rank**	0.913
Median	360	351	0.931	
Range	195-613	193-820		

Discussion

Therapeutic plasma exchange has been successfully used in various pediatric immunologically and non-immunological mediated diseases in the last few decades. There has been profound advancement in the technique with advances in transfusion medicine; the outcomes of plasmapheresis as a therapeutic modality reported in pediatric nephrology literature are mainly based on case reports in individual diseases [7]**;** So the current study was conducted on 36 children patient admitted to our unit in order to assess the outcome of therapeutic plasma exchange on the treatment of several immunological and non-immunological diseases.

The present study included 5 different disease identities; patients with GBS, HUS, NS, SLE and Amyloidosis. This study revealed that about 36.1% of cases indicated for TPE had GBS, 25.0% of cases had NS, 25% of cases had HUS, 8.3% of cases had Amyloidosis and 5.6% of cases had SLE, about 75% of cases showed improvement after therapy, 16.7% didn't improve and 8.3% died.

At the present study the complications reported were hypofibrinogenemia as most common complication (treated with plasma or Cryoprecipitate whenever available) was followed by hypotension; there was significant relation between complications and number of sessions. This finding matches Zöllner S and his colleagues who found that Hypofibrinogenemia occurs in 20% of patients after TPE [10]; significant declines in procoagulant coagulation factors such as factor V (FV), FVII, FVIII,

FIX, FX, and VWF activity occur. However, coagulation factors are replenished at different rates fibrinogen, achieves 66% of pre-apheresis levels by 72 h, Currently, there are no consensuses or national guidelines regarding hemostasis management in patients undergoing TPE treatments [11].

The present study reported that there was high significant relation between the disease and outcome. Regarding the patients who were presented by GBS (36.1%) every patient was evaluated pre and post TPE by electromyography (EMG), nerve conduction velocity, latency period, wave amplitude, f-wave and other laboratory investigation as the items of concern in assessment of improvement. It was found that about 12 cases improved (92.3%), one case not improved and no case died during the treatment course. These results agreed with the study of Ghonemy et al [11] which included (57 patients) 25 patients had GBS, 16 patients had MG, 7 patients had ITP, 3 patients had SLE, 2 patients had cryoglobulinemia, 2 patients had CIPD, 1 patient presented with hyper viscosity syndrome and neuromyelitis optica. About 49 (88.9%) patients experienced improvement while 2 patients showed no improvement and 6 patients died. In patients with GBS full improvement was reported in (92%), patients with MG improvement rate were (81.2%). The patients with neuromyelitis optica, cryoglobulinemia, hyper viscosity syndrome and SLE showed complete improvement. Sixty four complications were reported out of that 32 procedures reported hypotension, 22 procedures reported allergic reactions and post-procedural fever reported in 10 procedures. Also these results were consistent with the study of Sajid et al [3] which was done to assess about 105 cases who underwent plasmapheresis for various disorders as the main indication for TPE was Guillain Barre Syndrome (GBS) (31%) followed by Myasthenia Gravis (23%), Rapidly progressive glomerulonephritis (22%), Haemolytic uremic syndrome, Thrombotic thrombocytopenic purpura (20%). GB cases showed the most improvement.

In comparing TPE and intravenous immunoglobulin (IVIG) in treating GBS; TPE was the first modality to treat the disease favorably and many major RCTs had confirmed its efficacy. One of the RCT compared TPE, IVIG and TPE followed by IVIG in 383 GBS patients and found all three modalities to be equivalent [13 and 14]; in our university our protocol is to start IVIG and if failed after 15 days we shift to TPE or use only TPE if IVIG is not available. In addition a systematic meta-analysis reported that TPE was the only treatment for GBS and found to be superior to supportive treatment. Furthermore, TPE was more beneficial when applied within the first 7 days of disease. During the hospital stay, plasma exchange slightly decreased the risk of severe infections, cardiovascular instability and cardiac arrhythmias. Plasma exchange also had long-term benefits [15].

Atypical hemolytic uremic syndrome (aHUS) is mostly because of gene mutations of complement and its regulators, leading to cascade of activation of the alternative complement pathway, As these genetic mutations are helpful while using TPE can help different types by supplementing deficient factor

[16]. Regarding the present study, patients with HUS 7 patients out of 9 (77.7%) improved and 2 patients did not improve. These results are consistent with a systematic meta-analysis which had reported that plasma exchange is still the most effective treatment of choice in patients with HUS and should be considered as early as possible in the disease course. The study reported remarkable decline in mortality with the use of TPE which has changed this fatal disease to a mostly curable illness. This role of plasma exchange might be due to its role in the removal of potentially toxic substances from the circulation. Plasma exchange rather than infusion should be considered first-line therapy in situations that limit the amount of plasma that can be infused, such as renal impairment or heart failure [17].

Children with primary focal segmental glomerulosclerosis developing NS are treated with steroids as first-line, then by calcineurin inhibitors can be used, and rituximab. TPE may be considered if previous treatments failed [18] in this study found that 9 patients had NS, 8 patients (88.9%) improved. These results agreed with Franke et al [19] who treated nine children with cyclosporine-resistant primary FSGS with plasma exchange (PE) and they concluded that PE and PIA are a useful option for treatment of steroid- and cyclosporine-resistant FSGS, particularly if applied early in the course of the disease.

TPE is not currently among induction or maintenance therapy guidelines for treatment of Lupus Nepheritis (LN) but is reported in current European guidelines as a treatment option in the setting of rapidly progressive glomerulonephritis [20] in this study found that 4 patients with SLE, 2 patients controlled and other 2 patients died. This matches the study of David et al. [21] enrolled patients with SLE who received TPE; the overall outcome was improvement in 41 (62.12%) patients and the study concluded that TPE is safe and effective in patients with severe manifestations of autoimmune diseases. By the same manner Hans et al. [22] reported clinically significant improvement in the patients with SLE after plasma exchange suggesting that it can be an important component of treatment in patients of SLE with acute life threatening complications in addition to conventional high dose steroid and cytotoxic drug therapy.

Number of sessions in our current study was in 66.7% of cases from 5-10 sessions; applied every other day to give time for fibrinogen level to be available. we depend on disease improvement as previous studies showed that number of sessions on some protocols use a set number of procedures, usually 5 or 6, daily or every other day, while other protocols guide number of treatments based on improvement [5].

In trail to reduce rate of vascular line infections we use strict antiseptic measures and using Taurolock (Taurolouidine Citrate) in locking the line and it prevent infection as no one case of catheter related infection reported in our cases depending on many studies that demonstrated the effectiveness and safety of the Taurolouidin citrate [23].

Conclusions

We concluded that TPE is a helpful therapeutic tool in management of serval pediatric illnesses special success showed in GBS, followed by HUS and that the

most common complication was hypofibrinogenemia. We recommend using TPE as an effective adjuvant therapy and to share experience of different pediatric centers to raise the skill and decrease complications.

List of abbreviations

ASFA	Apheresis Applications Committee of the American Society for Apheresis
ANA, Anti-DNA, ANCA	Antinuclear antibody Anti-
ABG	Arterial blood gas
CBC	Complete blood count
C3, C4	Complement 3 and 4
CRP	C reactive protein
EMG	Electromyography Study
GBS	Guillain-Barre syndrome
HUS	Hemolytic Uremic Syndrome
LDH	
MG	Myasthenia Gravis
NS	Nephrotic Syndrome
PTT	Partial Thromboplastin Time
PT	Prothrombin Time
r	Spearman Correlation
SLE	Systemic lupus erythematosus
Taurolock	Taurolouidine Citrate
TPE	Therapeutic Plasma Exchange
TTP	Thrombotic Thrombocytopenic Purpura
X^2	Chi square test

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Statements

Ethics approval and consent to participate

This study protocol and the consents were approved and deemed sufficient by the Ethical Committee of Pediatric nephrology unit, Children Hospital, Zagazig University and informed written consent was obtained in every case from their legal guardians.

Consent for publication

The contents and material of the manuscript have not been previously reported at any length or being considered for publishing elsewhere.

Availability of data and material

"Not applicable"

Conflict of interest

The authors declare no conflict of interest.

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