Impediments that Challenged Therapeutic Plasma Exchange: Experience at a Tertiary Care Hospital in Bangladesh

ABSTRACT

Therapeutic plasma exchange (TPE) is an extracorporeal blood purification technique that removes circulating antibodies, toxin and mediators from the plasma of the patients.

This study was conducted to assess the safety, type and frequency of complications with regard to the indications and technical aspects of the TPE procedure performed in patients.

A total of 127 patients' clinical data treated with 424 TPE cycles over a period of 6 years from June 2016 to July 2022 at the apheresis unit of the Department of Transfusion Medicine, Bangabandhu Sheikh Mujib Medical University in Bangladesh, were enrolled in this retrospective observational study. The median age was 35.26 years (range 19–63) with a male predominance. The indications were mostly ASFA category I (81.895%) and the most common indications were neurological indications including Guillain–Barré Syndrome (GBS) (61.41%), Myasthenia Gravis (MG) (10.24%) followed by Acute Liver Failure (7.09). Venous access was established with the femoral vein maintaining blood flow at 70 ml/min using acid citrate-dextrose solution A (ACD-A) anticoagulant. TPE was frontline therapy in 55.91% of the patients. Human albumin was used as a replacement fluid in 88% and fresh frozen plasma in 12% of the cycles. Incidence of procedural complication was 49% (n = 206) and majority of them were mild (n=191; 45%) with only 3% and 0.47% being moderate and severe, respectively. Mild complications were hypocalcemia (*n* = 127; 29.95%), anxiety (n = 109; 25.70%), restlessness (n = 68; 16.04%) and hypotension (n = 46; 10.85%) in albumin group and anxiety (n=31; 7.31%), hypocalcemia (n=23; 5.42%), muscle cramp (n=23; 5.42%) in FFP group.

Interestingly, complications were almost similar in albumin and FFP groups except for allergic reactions and mild reactions which were mostly manageable and preventable with continuous, cautious monitoring. Our findings suggest that TPE is a relatively safe procedure and severe complications such as hypotension and anaphylaxis is preventable through continuous and dedicated monitoring by expert personnel.

Keywords: Therapeutic plasma exchange, complication, albumin, FFP, hypocalcemia.

INTRODUCTION:

Therapeutic plasma exchange is a procedure in which whole blood of the patient is passed through a medical device that separates plasma from other components of blood. The plasma is removed and replaced with a replacement solution such as a colloid solution (e.g. albumin and/or plasma) or a combination of crystalloid /colloid solution. This extracorporeal blood purification technique could be

done by either a centrifugation device or membrane filtration. It can remove large molecular weight substances (e.g. auto antibodies, alloantibodies, immunoglobulin, immune complexes, myeloma light chains, albumin-bound toxins, unbound toxins, drug metabolites, cytokines, and cholesterol containing lipoproteins) from plasma. The primary objective of this procedure is to reverse a pathological process related to the presence of these substances.[1,2] After its first application in 1960 by Schwab and Fahey to reduce elevated globulin level in a patient with macroglobulinemia, now therapeutic apheresis is being endorsed for a wide spectrum of diseases alone as frontline and/or as second-line adjuvant therapy and the list of indications for TPE has been growing.[3] Since 2010, the American Society for Apheresis (ASFA) publishes a categorized listing of indications for therapeutic apheresis using a systemic review and evidence-based approach to guide clinicians to decide whether to perform this procedure on their patients. The indications for TPE are labeled into four categories by ASFA. Category I includes disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment. Category II includes disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment. Category III is based on the decision-making of individualized cases as the optimum role of apheresis therapy is not yet established. Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful are categorized as IV.[4] Over the last decades, continuous development regarding technical aspects has been seen; as TPE despite being potentially lifesaving, it is also an invasive procedure with risk of adverse reactions and requires close monitoring by experienced teams. Sparse data is available from Bangladesh focusing on complications, rather limited to discussion on neurological cases. [5-8] Many large series either registry-based or multi-centered studies have been conducted to report complications associated with TPE procedures where complications related to TPE were attributed to several factors such as vascular access, choice of replacement fluids, the procedure itself, the use of anticoagulants or the causative disease itself.[9-16] Awareness regarding possible severe complications is one of the major barriers for physicians when considering TPE for their patients. Vascular access can be achieved either by inserting dual lumen venous catheter either into femoral or subclavian vein or by inserting 16-G needle into antecubital vein or an arterio-venous fistula The choice of replacement fluid is dictated by the underlying disease. Albumin is the most commonly used replacement fluid, suitable for the majority of conditions that can be treated with TPE, whereas patients with thrombotic thrombocytopenic purpura (TTP) require the use of Fresh Frozen Plasma (FFP). Citrate anticoagulation is most commonly used with centrifugation devices, and heparin with membrane PE.[7,8] In this retrospective study medical records of patients who underwent TPE since the establishment of the apheresis department were reviewed and an analysis of our experience concerning the indications, tolerance and complications of plasma exchange was done.

METHODS:

This retrospective observational study was conducted by extracting data manually from the medical records of 127 patients who had been treated with at least one cycle of Therapeutic Plasma

Exchange (TPE) over a period of 6 years from June 2016 to July 2022 at the apheresis unit of Department of Transfusion Medicine, Bangabandhu Sheikh Mujib Medical University in Bangladesh, since its inception. Written informed consent was obtained from all patients before each procedure after explaining the procedural risks in detail. Adult patients who underwent at least one procedure were included and patients with insufficient observation forms were excluded. All procedures were performed by senior apheresis technologists under the supervision of Transfusion Medicine specialists. Vital signs were monitored at the beginning and at the end of each procedure, and patients were monitored for adverse events during all procedures. Information was collected regarding demographic details of the patients (age, gender), indications for TPE, the use of TPE as front/second line treatment, vascular access, complications related to procedure. Vascular access was done either by inserting a dual lumen venous catheter either into femoral artery or inserting 16 G fistula needle into an arterio-venous fistula. Catheter patency was maintained by the instillation of heparin (10,000 U/ml) into catheter lumen. Continuous flow cell separator Com.Tec (Fresenius Kabi, Bad Homburg, Germany) and Haemonetics MCS+ intermittent flow cell separator (Haemonetics Corporation, Braintree, Massachusetts, USA) instruments were used for TPE. Therapeutic plasma exchange was performed every other day for most of the patients and a total of upto 1 volume of plasma was exchanged for each cycle. Estimated plasma volume (EPV) was calculated according to the Kaplan formula, EPV = {(0.065 x body weight (kg) x (1− Hct)} and further modified by taking consideration of patients' height, weight, gender and hematocrit values. 5 % solution of human albumin or Fresh Frozen Plasma (FFP) and 0.9% Normal Saline were used as volume replacement fluid and acid citrate-dextrose solution A (ACD-A) was used as anticoagulant at a ratio of anticoagulant and whole blood about 1:13-1:15 during the procedure. All patient received intravenous calcium supplementation to prevent hypocalcaemia caused by citrate in ACD-A and the dose was 10 ml of 10% calcium gluconate solution per 1000 ml; of 0.9% Normal saline. If there were symptoms of hypocalcaemia such as perioral and limb numbness and tingling, an additional 10 ml 10% calcium gluconate over 10-15 minutes were given. Since the beginning of TPE treatments in our department, all details of therapeutic sessions have been recorded, thus all complications have been noted in our files. In the present study, we assessed the incidence and severity of different complications which occurred in association with TPE. Life-threatening adverse effects were reported as severe complications. Complications which required medical intervention but were otherwise of little clinical significance and resolved completely were classified as moderate. Complications were classified as mild, if they were transient in nature and limited to the duration of the procedure without clinical significance. We recorded only complications directly associated with the procedure. Therefore, adverse events like central line–associated blood stream infections or thrombosis were not recorded. Routine laboratory tests e.g. Complete Blood Count (CBC), blood grouping, S. albumin, S. calcium, S. electrolyte, Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), and International Normalized Ratio (INR) and other baseline tests as appropriate according to diagnosis were done before TPE. The local ethics committee approved this retrospective analysis.

Statistics

All the data were collected through an Excel sheet and statistical analysis was done by statistical software Statistical Package for Social Science (SPSS) version 24. All the data were expressed as numbers and percentages or median and range.

RESULT:

In a 6-year period, TPE was performed on 127 patients, for a total of 424 cycles treating a wide variety of medical conditions. Neurologic diseases were the most common indications for TPE, followed by hepatological, nephrological and endocrine diseases. The most common indications were Guillain–Barré syndrome (GBS) (61.41%), Myasthenia Gravis (MG) (10.24%), Acute Liver Failure (7.09%), and Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) (7.3%). All of them belong to ASFA category I except for acute liver failure which is of category III. The number and frequency of TPE procedures depended upon the clinical scenario; some patients required long term maintenance TPE. The number of cycle per patient was relatively large for GBS, MG, post renal transplantation rejection cases (5 cycles per patient), and was relatively small for rapidly progressive glomerulonephritis (RPGN), CIDP, familial hypercholesterolemia (2 cycle per patient). In 104 patients (81.89%), the diagnosis belonged to ASFA category I, where TPE is a recommended first-line therapy. In another 11 patients (7.87%), the diagnosis belonged to ASFA category II, 12 (9.45%) to category III, and none in category IV (Table 1).

Table 1: Indications for TPE

Diagnosis	No. of Patient N	No. of Patient (%)	No. of cycle N	No. of cycle (%)	ASFA category
Guillain–Barré syndrome	78	61.41	287	67.69	I
Myasthenia gravis	13	10.24	47	11.08	I
Acute liver failure	9	7.09	21	4.96	III
Renal allograft rejection	4	3.15	18	4.25	
a. Antibody-mediated rejection	3	2.36	15	3.54	I
b. Donor specific human leukocyte antigen antibodies (suspected)	1	0.79	3	0.71	II
Chronic inflammatory demyelinating polyradiculoneuropathy	6	4.72	12	2.83	I
Thyroid storm in Graves Disease	4	3.15	10	2.36	II

Systemic lupus erythematosus	2	1.57	7	1.65	II
Transplatation associated Thrombotic microangiopathy	3	2.36	7	1.65	III
Rapidly progressive glomerulonephritis with diffuse alveolar haemorrhage	3	2.36	6	1.42	I
Thrombotic thrombocytopenic purpura	1	0.79	3	0.70	I
Familial hypercholesterolemia	2	1.57	3	0.70	II
Multiple Myeloma	1	0.79	2	0.47	II
Lambert-Eaton myasthenic syndrome	1	0.79	1	0.24	II

*American Society for Apheresis (ASFA)

Table 2: Patient Characteristics

Patient Characteristics	Median (range)	N (%)
Age (years)	35.26	(11-70)
Sex(M/F)	86/41	
TPE as frontline treatment	71	(55.91)
Treatment prior to TPE	56	(44.09)
IVIG	8	(6.29)
Steroid	69	(54.33)
Pyridostigmine	13	(10.24)
Others	48	(37.80)

Table 2 above shows that TPE was performed in 86 males and 41 females, with an age range of 11–70 years. TPE was frontline therapy in 55.91 % of the patients (n=71), while 44.09 % of the cases (n: 56) were treated before their trial with TPE. Among them, 54.33 % were treated with corticosteroid (n: 69), 7.87% with pyridostigmine (n= 113), and 6.29% with IVIG (n: 8) prior to TPE. All patients with MG had a history of taking pyridostigmine. IVIG was taken by 5 GBS patients and only one MG and only one CIDP patient.

Figure 1: **Type of replacement fluid used in each cycle.**

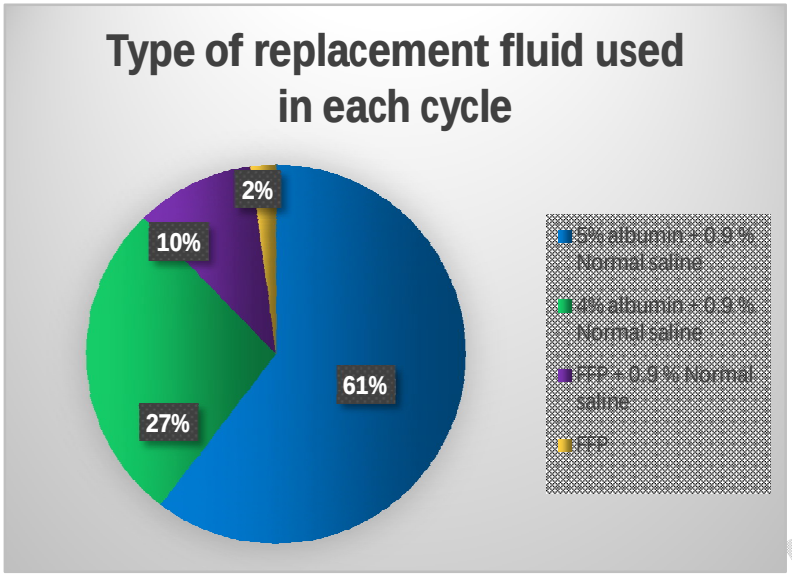


Figure 1 outlines that out of 424 TPE cycle, replacement of half volume were carried out with 5% albumin in 61% cycle and 4% albumin in 27% cycle, respectively in combination with 0.9% normal saline (NS), as the rest half of the replacement fluid. Only 2% were carried out solely with FFP and in 10% cycles, FFP was used along with 0.9% NS. Therefore, human albumin was used in 88% cycle and FFP was used in 12 % cycle.

Table 3: Procedural details of TPE per cycle

Procedural details	Median (range)	N (%)
TPE duration (minutes)	131	(90-240)
Vascular access		
Femoral vein	408	(96.22)
Antecubital vein	3	(0.70)
Fistula site	13	(3.06)
Blood Flow (ml/min)	70	(50-90)
TPE alone	421	(99.29)
TPE with column adsorbtion	3	(0.70)
Use of intermittent cell separator machine	340	(79.62)
Use of continuous cell separator machine	87	(20.37)
Total calcium administered during TPE (ml)	4.5	(3.5- 15)
Systolic BP (in mm hg)	110	(90-180)
Diastolic BP (in mm hg)	74	(46-120)
Pulse (beats/min, bpm)	88	(80-110)

*bpm= beats per minute

Table 3 shows that duration of TPE varied from 90 minutes to 240 minutes where the use of a continuous flow cell separator machine (n = 87; 20.37%) required a shorter time and an intermittent flow cell separator machine (n = 340; 79.62%) attributed to longer time duration. Vascular access predominantly involved the femoral vein (96.22%). The median blood flow rate was 70 ml/min. In only 3 cases, column adsorption was used and all were in case of acute liver failure. Although the total amount of 10% calcium gluconate used ranged from 3.5 to 15 ml, 4.5 ml were used in a majority of procedures indicating mild symptoms of hypocalcaemia. Systolic BP and diastolic BP ranged from 90 to 180 mm Hg with median of 110 mm Hg and 46 to 120 mm Hg with median of 74 mm Hg. Median pulse rate was 88 bpm (range= 80-110 bpm)

Figure 2: Complications associated with TPE in each cycle

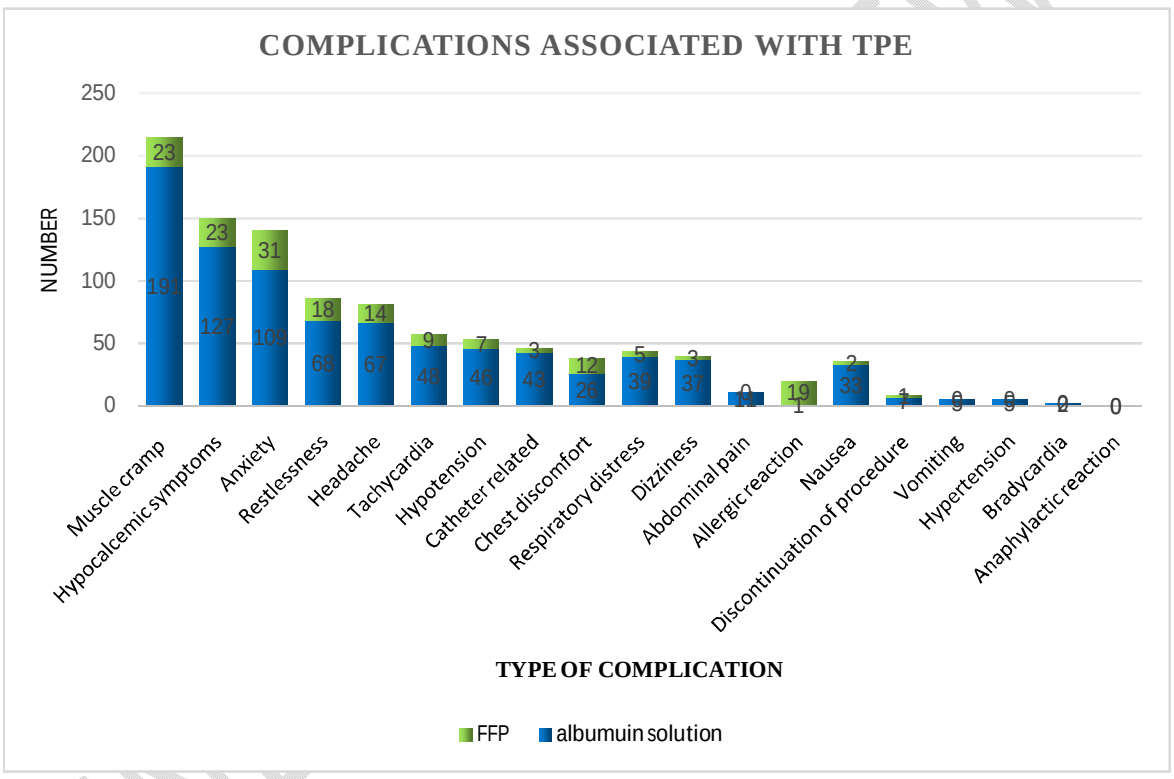
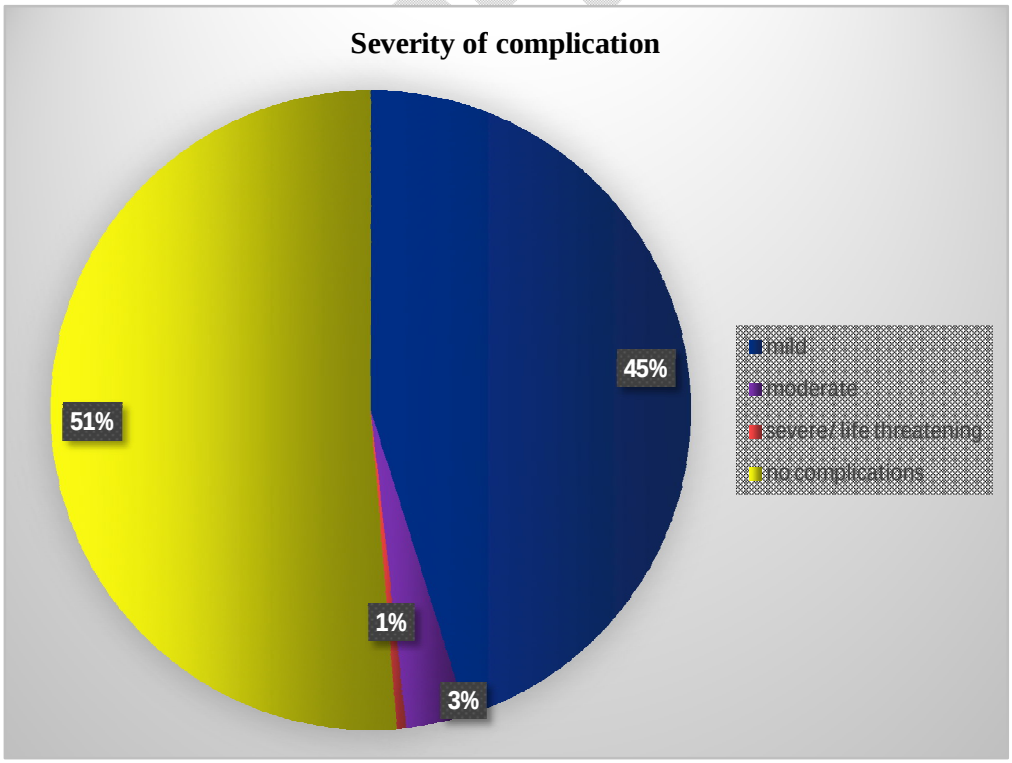


Table 4: Type of complication according to replacement fluid used.

Type of complication	Albumin solution		FFP	
	N	(%)	N	(%)
Hypocalcemic symptoms (tingling, numbness,	127	(29.95)	23	(5.42)

paraesthesia)				
Hypotension	46	(10.85)	7	(1.65)
Allergic reaction	1	(0.23)	19	(4.48)
Anxiety	109	(25.70)	31	(7.31)
Headache	67	(15.80)	14	(3.30)
Nausea	33	(7.78)	2	(0.47)
Hypertension	5	(1.18)	0	
Tachycardia	48	(11.32)	9	(2.12)
Chest discomfort	26	(6.13)	12	(2.83)
Respiratory distress	39	(9.19)	5	(1.18)
Dizziness	37	(8.72)	3	(0.70)
Muscle cramp	191	(45.05)	23	(5.42)
Restlessness	68	(16.04)	18	(4.24)
Abdominal pain	9	(2.12)	0	
Fever	11	(2.59)	3	(0.71)
Discontinuation of procedure	7	(1.65)	1	(0.23)
Vomiting	5	(1.17)	0	
Bradycardia	2	(0.47)	0	
Catheter related	43	(10.14)	3	(0.71)
Anaphylactic reaction	0		0	

Figure 3: **Severity of complication**



Procedural complications are shown in figure 3 and table 4, where the most frequently observed complication in TPE cycles was, muscle cramp (n = 191; 45.05%), followed by symptoms of hypocalcaemia (n =127; 29.95%), anxiety (n =109; 25.70%), restlessness (n =68 ; 16.04%) and hypotension (n = 46; 10.85%) whenever albumin solution was used as replacement fluid. Anxiety (n=31; 7.31%), hypocalcemic symptoms (n=23; 5.42%), muscle cramp (n=23; 5.42%) were seen commonly with FFP. Allergic reaction was more common with FFP (n=19, 4.48%) than with albumin (n=2; 0.47%). All patients with allergic reaction were treated with IM antihistamine, but only 11 of them required IV hydrocortisone in a single bolus, and procedures were completed successfully. Complications leading to premature discontinuation of the procedure occurred in 7 cycles (1.65%) with albumin, and in only one cycle with FFP. Discontinuation occurred due to problems associated with femoral catheter blockage or inadequate vascular access leading to reduced blood flow and hypotension. However, no mortality was reported during TPE itself. Hypotension was defined as fall of mean arterial blood pressure (BP) more than 20 mm Hg from baseline. Whenever hypotension was noticed, procedure was stopped temporarily for a few minutes and 500-1000 ml IV 0.9% normal saline was given running. This measure was sufficient enough to stabilize blood pressure in all cases except 3 cycles leading to discontinuation. During restlessness and respiratory distress, counseling was done and O_2 was given via nasal cannula at 2-4 L/min, respectively. 7.78 % patient (n=33) complained of nausea but only 1.17% (n=5) vomited. All of them were given IV antiemetic and all procedures were completed. Chest discomfort/heart burn (n = 26; 6.13%) was observed when calcium supplement was given at relatively faster rate. During procedure, fever was reported in 2.59% (n=11) of cycle in the albumin group and only 0.71% (n=3) of the FFP group of total 424 cycle, total incidence of procedural complication was 49 % (n = 206) and majority of them were mild (n = 191; 45 %). Moderate and severe type were of only 3 % (n = 13) and 0.47 % (n=2), respectively.

DISCUSSION:

The initial fear and doubt within the referring physician community at the beginning of the establishment of the apheresis unit in our hospital is slowly being replaced with enthusiasm towards Therapeutic Plasma Exchange (TPE). This is evident by the growing number of TPEs performed in our department over the few years. This optimistic attitude is reflected in our current study by showing moderate complications in only 3 % of the procedure and severe complications in 0.47% of the procedure. In another study on 4587 TPE cycle, the overall incidence of complications related to PE was 4.75%, with the incidence of severe complications of only 0.12%.[17] In an Indian study on 517 procedures, the complications occurred in 60 % of the patients and in 10.8% cycle.[18] In a similar set up of TPE in Korea like ours, the overall frequency of complications was 11.1% (n=293/2647) of which symptomatic hypocalcaemia was the most common (2.3%).[19] In contrast to these findings, overall rates of complications were higher in our study; however, hypocalcaemic symptoms (tingling sensation, paraesthesia and numbness) were the most common, secondary to muscle cramps which can be caused by immobilization and cautionary posture adopted to prevent displacement of femoral catheter. Hypocalcemia is most likely to stem from the use of acid-citrate-dextrose (ACD-A) solution,

as an anticoagulant in our centre, and its occurrence is reduced with frequent and prophylactic administration of 10% inj. calcium gluconate. Although, hypocalcemic episodes are more like to occur with the use of FFP as it, itself contains more ACD-A. This was not observed in our study as the frequency of hypocalcaemia in the FFP group was 5.42 % compared to 29.95% in the albumin group. However, this could also be due to smaller sample size in the FFP group (12%). In our centre, the use of FFP was mostly restricted to patients with thrombotic thrombocytopenic purpura and acute liver failure due to the risk of transfusion-transmitted infection and allergic reaction. Fever was present in 11(2.59%) cycles in the FFP group and only 3 cycles (0.71%) in the albumin group. In the majority of cases, fever was self limiting, therefore, whether it was due to access infection or due to the procedure itself could not be found out. However, fever coincided with positive RT PCR for COVID-19 in 4 patients during the COVID-19 pandemic. In the study of Mokrzycki and Kaplan, access-related infections occurred in 0.3% of procedures.[11] Our study reveals that 45% of complications are mild, transient-nature and manageable and about 51% of cycles showed no complication. The frequency of hypotension was low with the use of a continuous flow centrifugation machine. Hypotension could be related to factors such as extracorporeal volume and duration of procedure, vasovagal reaction, and inadequate replacement. Previous studies have also shown that TPE may also induce shock, persistent arrhythmia, pulmonary embolism, vascular perforation, severe hemolysis, transfusion-related lung injury, and heparin-induced type II thrombocytopenia.[20-22] Although no such severe complications occurred in our study, they should be considered by clinicians and future researchers.

Fresh frozen plasma as a replacement was used more commonly than in other countries (29.1%). The French registry reported an FFP use in 17.1% [23] and the 2000 International Apheresis Registry found FFP used in only 1/6 of albumin uses.[24] Similarly, FFP used in our study is about 12% to avoid its known side-effect (i.e. transfusion transmitted infection and allergic reaction). Although no anaphylactic reaction was encountered in our study, whenever, FFP is used as a replacement fluid, it is necessary to be vigilant to avoid escalation of allergic reaction as its frequency is more in comparison to the use of albumin solution as a replacement fluid. However, human serum albumin might contain trace amounts of globulins and other plasma constituents which might provoke anaphylactoid reaction.[25] In France, the use of albumin with a plasma expander such as starch is most common,[23] because this colloid solution can maintain blood pressure stability with less risk of allergic reactions.[26] It may be beneficial to try the combination of substitution fluids in the future. For vascular access, the use of the antecubital vein is more common in Japan and Europe, and the use of a central catheter is more common in the United States and Korea.[19,24] Femoral catheter was the most preferred access site in our study, although the longer duration of the femoral catheter due to the procedure on an alternate day led to blockage or reduced blood flow in many instances. The indications for TPE are constantly evolving. Bangabandhu Sheikh Mujib Medical University (BSMMU) is a tertiary referral hospital with all subspecialties. Therefore, our patient population is a representative case-mix of both stable as well as critical patients requiring TPE. With regard to the American Society for Apheresis (ASFA) categories, we found excellent adherence to the current guidelines. As in our centre, 81.89% of the patients had an ASFA guidelines category I disease,

where TPE is a recommended first-line therapy, 7.87% had a category II disease and 9.45 % had a category III disease. These figures are much higher than those reported in a large analysis of plasma exchange in U.S. children's hospitals, where only 9% the children had a category I and 2.2% a category II disease. Category I comprised of predominantly Guillain–Barré Syndrome (GBS) (61.41%), Myasthenia Gravis (MG) (10.24%). An international randomized trial compared TPE, IVIG and TPE followed by IVIG in 383 adult patients with severe GBS and found all three modalities to be equivalent.[27] Due to differences in disease prevalence and the lack of financial support indications and procedure details may vary. Initially, neurological patients for whom Intravenous Immunoglobulin (IVIG) is not a feasible option are mainly the one who proceeded with TPE. At present, TPE has proved itself to be an equally effective treatment option and in some cases the only lifesaving option. To reduce the cost, we use albumin or FFP in combination with 0.9% normal saline. This study reports our experience with the highest number of TPEs from Bangladesh ensuring safety, reliability and advantages of this potentially lifesaving procedure. It is evident from our analysis that a successful TPE requires teamwork and close patient monitoring to minimize the mild adverse reactions that usually happen and prevent its further precipitation into a severe form that rarely occurs. Further exploration into predictors of complication and assessment of outcome is recommended. Although limited by its retrospective design, our results; including a large number of treatment cycles indicate that TPE is a relatively safe method of treatment, provided it is carried out by experienced staff, and used for appropriate indications and optimum technique with all necessary precautions.

Ethical Clearance:

Informed written consent from the patients before each procedure and departmental permission were obtained prior to beginning this study. Therefore, this study was exempted from ethical clearance due to its retrospective and observational nature.

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