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Complications of Therapeutic Plasma Exchange in Patient with Neurological Disorders

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Abstract

Background: Therapeutic plasma exchange (TPE) is a procedure used in neurological disorders where autoimmunity plays a major role. Though it is a relatively safe procedure, severe complications may occur. **Objective:** The aim of the present study was to analyze the incidence of TPE related complications in patients with different neurological disorders. **Methodology:** This prospective study was conducted in 91 patients, in department of Transfusion Medicine at National Institute of Neurosciences and Hospital (NINS) from February 2014 to January 2017 for a period of three (03) years. All admitted patients with neurological disorders advised for TPE were included in this study. **Results:** Age range was from 13 to 70 years with a mean age of 37.14±13.79 years. 67(74%) were men and 24(26.0%) were women. The most common diagnosis was Guillain-Barré Syndrome (GBS) in 79.1 % (n=72) cases followed by myasthenia gravis (MG) in 13.2% (n=12), chronic inflammatory demyelinating polyneuropathy (CIDP) in 6.6 % (n= 6), multifocal motor neuropathy (MMN) in 1.1% (n=1) cases. Total number of 332 TPE sessions was performed with the median of 4 sessions per patient (range 1 to 9). Total 99 (29.8%) adverse reactions occurred in 332 TPE sessions. The most common adverse effect was hypotension (n=35, 10.54 %) followed by allergic reactions (n=29, 8.73 %), access problem (n= 12, 3.61 %) and vomiting (n=8, 2.41 %). Most of the adverse reactions were mild and improved spontaneously or by using simple medications. Out of 332 TPE sessions, 330(99.4%) procedures were completed successfully after managing the adverse reactions. TPE were discontinued in 2 occasions (0.6% of procedures) due to inadequate venous access. There was no mortality related to TPE procedure. **Conclusion:** In spite of few complications, TPE can be considered as a safe method of treatment in neurologic disorders when carried out with all necessary precautions. [Journal of National Institute of Neurosciences Bangladesh, 2017;3(2): 69-74]

Keywords: Therapeutic plasma exchange, Complication, Neurological disorder.

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Introduction

Therapeutic plasma exchange (TPE) is a procedure that reduces the amount of circulating autoantibodies, alloantibodies, immune complexes and monoclonal

proteins by centrifugation and replacement of patient's plasma[1]. Even though both terms are often used synonymously, 'plasma exchange' means separation and removal of plasma from corpuscular blood and the replacement of it with various fluids, while 'plasmapheresis' only refers to the removal of plasma[2].

TPE was first employed in 1952 in patients with multiple myeloma to control hyperviscosity[3]. By the 1970s TPE had evolved as a treatment modality in a number of neurological disorders in which autoimmunity plays a major role including myasthenia gravis, Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP)[4-5]. Usually 1.5 to 2 L or 30 to 40 ml/Kg of plasma is removed at each cycle in most neurological disorders[6]. This requires replacement with plasma expanders like frozen plasma, albumin, saline, or plasma expander solutions[6].

TPE is not complication free. The incidence of severe, life-threatening complications is estimated at 0.025 to 4.75% of procedures[7-8]. The adverse effects are associated with large vessel catheterization, clotting disorders, septic complications resulting from impaired immunity, catheter-associated infections and those related to transfusion of blood products. Life-threatening fall in arterial blood pressure, cardiac arrhythmias and water-electrolyte imbalance can develop.

Less severe reactions and symptoms are more common, like urticaria, pruritus, limb paresthesia, muscle cramp, dizziness, nausea, vomiting, transiently elevated temperature, shivering, seizure, and headache. Abnormal laboratory tests include reduced levels of haemoglobin, thrombocytopenia, hypokalaemia, hypocalcemia and reduced concentrations of fibrinogen[7]. The total incidence of complications is estimated at 25.0 to 40.0%[9-10]. The safety of procedures markedly depends on experiences of the therapeutic team and disease severity. TPE was first introduced in public sector of Bangladesh at National Institute of Neurosciences (NINS) in 2014. Here it had been reported prospectively the three years experience on the complications of TPE in patients with neurological diseases treated in the Department of Transfusion Medicine of NINS.

Methodology

This was a cross-sectional study. This study was conducted in the Department of Transfusion Medicine at National Institute of Neurosciences & Hospital (NINSH), Dhaka, Bangladesh. Ninety one patients with neurological diseases were treated by TPE from February 2014 to January 2017 for a period of three years at NINSH, Dhaka, Bangladesh. In 2014 and 2015 TPE were done only in stable patients without ventilator support. Patients from different neurology ward were sent to transfusion medicine department and after each session of TPE they were transferred back to respective ward. From 2016, with the help of portable ventilator we began TPE in patient with respiratory failure. Continuous flow cell separator Comtec, Fresnious Kabi, Germany and Cobe Spectra, USA instruments were used for TPE. For most of the patients TPE was done on every alternate day. A total of 1- 1.5 volume of plasma was exchanged for each session depending on patients height, weight, gender and hematocrit values. Acid citrate dextrose solution A (ACD-A) was used as anticoagulant. Pre exchange routine laboratory tests included CBC, RBS, ECG, Blood grouping, SGPT, s. total protein, s. albumin, s. creatinine, s. calcium, s. magnesium, s. Electrolyte, HBsAg, Anti HCV, Anti HIV, VDRL, PT, APTT. In TPE, 5% human albumin and normal saline were used as replacement fluid in 16 cases. 5% human albumin, normal saline and fresh frozen plasma were used in 3 cases. To reduce the cost of TPE we used only fresh frozen plasma and normal saline in 72 patients. To avoid dehydration, 1 litre normal saline was given previous night of the procedure. Injectable antihistamine IM was used routinely to avoid allergic reaction of FFP. 10% Calcium gluconate was also given routinely according to serum calcium level, number of FFP, and amount of ACD solution used. Venous access was established through antecubital vein by 17G fistula needle in both arms in most cases. Central venous catheter was used in patients with inadequate peripheral venous access. All procedures were done by doctors and lab technicians. Written informed consent was taken from all patients prior to each procedure. Routine monitoring of the patient was done throughout the procedure like pulse, blood pressure, temperature, respiratory rate and oxygen saturation.

Results

Ninety one patients were included into this study over a period of three years. Of the 91 patients, 67 (74%) were men and 24 (26%) were women. Age range was from 13 to 70 years with a mean age 37.14± 13.7 years. The most common diagnosis was Guillain-Barré Syndrome (GBS) in 79.1 % (n= 72) cases followed by Myasthenia Gravis (MG) in 13.2 % (n= 12), chronic inflammatory demyelinating polyneuropathy (CIDP) in 6.6 % (n= 6), multifocal motor neuropathy (MMN) in 1.1 % (n= 1) cases (Table 1).

Table 1. Indications and demographic details of patients undergoing TPE

Diagnosis	No of cases	Gender (M/F)	Mean Age (in years)
GBS	72(79.1%)	52/20	35.1
MG	12(13.2%)	8/4	47.6
CIDP	6(6.6%)	6/0	41.7
MMN	1(1.1%)	1/0	42
Total	**91(100%)**	**67/24**	**37.14±13.7**

GBS= Guillain-Barré Syndrome, MG= Myasthenia Gravis, CIDP= chronic inflammatory demyelinating polyneuropathy, MMN= multifocal motor neuropathy; M/F=Male/Female

Total numbers of TPE sessions were 332 in 91 patients. The number and frequency of TPE procedure depended upon the clinical scenario and economic status of the patient. Median number of TPE sessions per patient was 4 in this study and total number of TPE cycle per patient ranged from 1 to 9 (Table 2).

Table 2: Distribution of Patients according To Number of TPE Sessions

Number of TPE Cycle	Number of Patients	Total No of TPE sessions
1	6	6
2	8	16
3	13	39
4	56	224
5	5	25
6	1	6
7	1	7
8	0	0
9	1	9
Total	**91**	**332**

The procedure was done mostly through a peripheral venous access (PVA). In 79 (87%) patients access was gained through peripheral venous system. Central venous access (CVA) was used in 12(13.0%) patients. FFP and normal saline were used in 73(82%) cases as replacement fluid. Human albumin and normal saline were used as replacement fluid in 16(17.6%) cases and FFP, human albumin and normal saline were used in 2(2.2%) of the cases. Overall response rate (complete plus partial response) was 74(81.0%) cases. There was no response in 17(19.0%) of the cases. There was no mortality related to TPE procedure. Adverse reactions was occurred in 99(29.8%) cases out of 332 TPE. Common complications were hypotension (10.54%), allergic reactions (8.73%), access problem (3.61%) and vomiting (2.61%). The most common adverse effect was fall in the arterial blood pressure (n=35, 10.54 %). 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, injection hydrocortisone 200 mg given IV and 500 ml normal saline was given IV running. These measures were sufficient to stabilise blood pressure in 34 cases. In 1 patient, institution of pressor amine (dopamine) was needed. The all 35 TPE cycles were completed after restoring normal blood pressure. Allergic reactions were observed during 29 procedures (8.73%) despite of giving antihistamine IM routinely prior to the procedure. Itching, rash or urticaria was noticed. 9 of them subsided spontaneously. 5 patients needed additional antihistamine. 15 patients received injection hydrocortisone in a single bolus. The all 29 TPE cycles were completed successfully. Access problems observed in 12 (3.6%) patients resulted from complete or partial occlusion of fistula needle. In 10 patients, needle had to be replaced. TPE were discontinued in 2 occasions due to inadequate venous access. 8(2.41%) patients vomited for one episode. 5(1.51%) patients complained of nausea but did not vomit. Injecton ondansetron IV was given in all these 13 patients and all of them settle down.1 patient complained of vertigo. He did not require any medication. During 2(0.6%) procedures, body temperature was increased. Fever subsided after using paracetamol. Despite of giving calcium on routine basis in each procedure, 2 (0.6%) cases developed hypocalcemia. Additional injectable 10% calcium gluconate were needed to correct hypocalcemia. Patients also reported symptoms like restlessness, sweating, heart burn, discomfort, parasthesia. The complaints were of mild and subsided spontaneously or by simple medications (Table 3).

Table 3: Complications during Therapeutic Plasma Exchange

Adverse effect	Frequency	Percentage
Hypotension	35	10.54
Allergic reaction	29	8.73
Access problem	12	3.61
Vomiting	8	2.41
Nausea	5	1.51
Restless	2	0.60
Heart burn	2	0.60
Pyrexia	2	0.60
Hypocalcemia	2	0.60
Vertigo	1	0.30
Sweating	1	0.30
Total	**99**	29.8

Discussion

TPE has significantly reduced the morbidity and mortality of patients with various diseases. The low risk to benefit ratio encouraged its use in many different conditions, with mostly excellent therapeutic results[11-14]. However, the initial enthusiasm with therapeutic results of TPE in some clinicians soon replaced by fear of the potentially life-threatening complications of the treatment[15-16].

The results show that PE carries a low risk of adverse reactions. Total 99(29.8%) adverse reactions occurred in total 332 TPE. Common complications were hypotension (10.54%), allergic reactions (8.73%), access problem (3.61%) and vomiting (2.61%). There was no procedure related mortality in our study though several investigators have reported deaths associated with TPE. The incidence of death associated with PE has been estimated to 0.05%[17]. The incidence of severe, life-threatening complications is estimated at 0.025–4.75% of procedures[18].

Hypotension is one of the most common cardiovascular complications of plasma exchange. Volume and protein depletion are the most likely causes of hypotension and can usually be avoided by volume expansion or a slower rate of withdrawal[19]. A primary hypotensive effect of the procedure, unrelated to volume changes, has also been postulated[19]. Also the nature of the underlying illness is important in determining the risk of this complication[20]. In this study the most common adverse effect was fall in the arterial blood pressure (n= 35, 10.54 %). Temporary cessation of the procedure, injection hydrocortisone 200 mg and 500 ml normal saline were sufficient to stabilize blood pressure in 34 cases. In 1 patient, dopamine was needed. The all 35 TPE cycles were completed after restoring normal blood pressure. Incidence of hypotension is variable in different series dealing with neurological patients[20-22]. The usual incidence of TPE related hypotension is 2.6% to 8.1%[23]. Gafoor et al[24] reported 32.2% episode of hypotension during TPE in a tertiary care hospital in South India.

Abnormalities of cardiac rate or rhythm may be present, including bradycardia, extrasystoles, atrial fibrillation, and tachycardia. They are often brief and usually selflimited, although fatal cardiac arrest has occurred[20]. The true incidence is difficult to determine since most centers, including our own, do not routinely employ cardiac monitoring during plasma exchange. The exact cause of cardiac rhythm disturbances is unclear, but chelation of calcium ion by citrate probably plays a role since[25]. The nature of the underlying illness is important in determining the risk of this complication. Patients with Guillain-Barré syndrome and associated autonomic nervous system dysfunction frequently experience cardiac arrhythmias irrespective of the form of treatment[26]. In this study, there was no episode of clinically significant isolated change in the heart rate requiring pharmacological treatment.

The likelihood and nature of allergic reactions depend on the materials used to replace discarded plasma[27]. Fresh frozen plasma is most likely to induce allergic reactions ranging from mild episodes responsive to antihistamines to anaphylaxis[27]. A significantly higher incidence of allergic reactions occurs in patients requiring FFP. Although most of these reactions were associated with the use of FFP, one should bear in mind that human serum albumin might contain trace amounts of globulins and other plasma constituents which might provoke anaphylactoid reaction[28]. In this study allergic reactions were observed during 29(8.73%) procedures; 9 of them subsided spontaneously; 5 patients needed additional antihistamine; 15 patients received injection hydrocortisone in a single bolus. All 29 TPE cycles were completed successfully. Gafoor et al[24] reported 2.2% episode of allergic reaction during TPE in a tertiary care hospital in South India. As it has been used mostly FFP as replacement fluid, the incidence of allergic reaction is higher than many previous studies although our results are comparable with those reported from other studies, where most reactions were limited to rigor or urticaria[27-30].

In this study, access problem were observed in 12 (3.6%) patients resulted from complete or partial occlusion of fistula needle in PVA site. In 10 patients (3%) needle had to be replaced. There was no haematoma, bleeding or infection at cannula site. There was no complication from central venous access (CVA). Gafoor et al[24] reported 7% incidence of access related problems during TPE. Due to access problem, 4 to 5% of PE may have to be terminated[31].

The most frequent complications experienced during plasma exchange are nausea, paresthesia and occasional muscle cramp probably due to chelation of ionized calcium by infused citrate anticoagulant[22]. Nausea has been reported during as many as 15% and paresthesia in 9% of exchanges utilizing concentrated citrate solution such as ACD-A[22]. Other study reports vary on the occurrence of these symptoms[17-18]. These symptoms can be partly avoided by adding calcium to the replacement fluids, slowing the infusion of citrated blood, or by using anticoagulant solutions with a lower

concentration of citrate[22]. In this study regular parenteral replacement of calcium was responsible for a low incidence of the symptoms of hypocalcemia (paresthesia, tingling) even in patients treated with FFP. None of the patients experienced severe hypocalcemia with the development of cardiac arrhythmia.

Alteration of several hematologic laboratory values are common, but are seldom associated with clinical signs or symptoms. Reduction of platelet count is an almost constant finding after plasma exchange though anemia and leukopenia are not common[22]. Fibrinogen level is consistently lowered after exchange, Fibrinogen levels recover considerably within four hours and return to normal within one to two days after a single exchange[22,29]. Vitamin K-dependent coagulation factors and factor VIII are also severely depressed, but return to normal within 24 and 4 hours, respectively[29]. Depletion of coagulation factors can be avoided by using FFP as the replacement fluid. In our study there was no bleeding episode probably because we used mostly FFP as replacement fluid and TPE were done in alternate day basis. Basic-Jukic et al[29] report bleeding in 0.06% of procedures where Rossi et al[30] report on hemorrhage in 0.2% of treatments.

Serious, occasionally fatal infections have occurred in patients treated with plasma exchange. This complication is at least in part due to depletion of immunoglobulins and complement by the procedure[32]. Adjunctive immunosuppressive therapy can further prolong this compromised state by inhibiting immunoglobulin production and slowing recovery from depressed levels[33]. Infection may also be related to the mode of venous access employed during plasma exchange or to the type of replacement fluids used[18]. The lower incidence of serious infection in neurological patients supports the concept that the underlying illness plays a major role in determining the likelihood of this complication. In our study, there was no procedure related infection. Similarly, no serious infections occurred in two studies describing plasma exchange for multiple sclerosis, or in one series with patients treated for motor neuron disease[34-36].

Conclusion

The possibility of complications must be weighed carefully before deciding to use plasma exchange therapy. Certain factors are clearly useful in assessing the likelihood of complications in a particular patient, including the mode of venous access, the frequency of exchange, the replacement fluid to be used, the need for adjunctive immunosuppressive therapy, and the nature of the underlying illness. Our results derived from a large number of procedures indicate that PE is a relatively safe method of treatment when carried out with all necessary precautions. Continuous observation, proper monitoring of patients and trained personnel are essential for procedure-related safety.

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