Therapeutic Plasma Exchange: Experiences at Square Hospital, Dhaka, Bangladesh

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Abstract: Introduction: The lowering of toxic level due to over dose of drugs or any metabolites is the cornerstone of all effective therapies in patient having such toxic condition. This procedure is basically an exchange technique which is carried out by deploying apheresis machine. Patient’s blood is passed through the machine, which filters plasma and removes and discards; simultaneously reinfuses red blood cells along with replacement of equivalent amount of fluid such as plasma or albumin into the patient. This procedure is commonly known as therapeutic plasma exchange (TPE), and its indication is assessed by the guidelines of ASFA. This study entails the experience in carrying out TPE in square hospitals Ltd, Dhaka, Bangladesh. Materials and Methods: Patients admitted in Square hospital with neurological and non-neurological conditions were assessed for the requirement of TPE and indication as per ASFA guidelines. Patients who consented for the study were included for the analysis. All TPE procedures were carried out in Intensive Care Unit (ICU) and High Dependency Unit (HDU) by blood bank technologists trained in TPE under the supervision of blood bank physician. All patients were assessed throughout the intra-procedure and post-procedure thoroughly to observe and identify any complications or adverse reactions. Results: Total 50 patients were indicated for TPE, of which 25 were male and 25 females with mean age of 39.6 years, range: 09 to 68 years (Table 1). Among the five age group strata, majority of patients (42%) were from 31-45 years followed by 46-60 years (24%) and the details are followed hereafter. Discussion: Plasma exchange (PE), a therapeutic procedure used to treat a variety of diseases through the bulk removal of plasma. Since the initial use, the term has been describing more broadly of several procedures, all of which involve the separation of whole blood into its components with removal modification of one or more of these components. The PE when introduced in clinical practice has significantly reduced the morbidity and mortality of patients with various diseases, TPE has been reported to be of greater potential benefit than IVIG. In our experience, TPE is more effective when initiated within seven days of disease onset, for controlling symptoms of neuro-immunological disorders. Conclusion: The possibility of complications must be weighed carefully before deciding to use plasma exchange therapy. Careful assessment of the patients and expertise in TPE is essential to optimize therapy and minimize adverse consequences.

Keywords: Apheresis, Plasmapheresis, Therapeutic exchange.

1. Introduction

Intoxications due to metabolites or drug overdoses are the occurrences where rapid lowering of the toxic level is a cornerstone of all effective therapies accomplished by an exchange procedure where patient’s blood is subjected to pass through an apheresis machine. The term apheresis, plasmapheresis, and plasma exchange are often used interchangeably as the therapeutic apheresis because of the procedure uses cell separator/Apheresis machine; however, some differences exist between the terms. Of the therapeutic apheresis, plasmapheresis is the most commonly performed procedure [1]. The indications for plasmapheresis are based on recommendations of the working groups consisting of specialists in various fields and dealing with techniques of extracorporeal blood purification. The first consensus guidelines were presented by the American Medical Association in 1985; the recent ones were published by the American Society for Apheresis (ASFA) in June 2016 [2]. As an invasive method, plasmapheresis is not complication free. The incidence of severe, life-threatening complications is estimated at 0.025–4.75% of procedures. The adverse-side effects are associated with large vessel catheterisation, clotting disorders, septic complications resulting from impaired immunity caused by the removal of antibodies during the procedure, catheter-associated infections, and those related to transfusion of blood products [2]. Moreover, life-threatening fall in arterial blood pressure, cardiac arrhythmias and water-electrolyte imbalance are likely to develop. Less severe reactions and symptoms are more common, e.g. urticaria, pruritus, limb paraesthesia and pains, muscle contractions, dizziness, nausea, vomiting, transiently elevated temperature, shivers, seizures, head and chest pains. Taking into consideration all possible adverse events, together with isolated deviations from reference values in laboratory tests, which predominantly include: reduced levels of haemoglobin, thrombocytopenia, hypokalaemia, and reduced concentrations of fibrinogen [3], the total incidence of complications is estimated at 25–40%. The safety of procedures markedly depends on experiences of the therapeutic team and disease severity (stage) [2].

Therapeutic Plasma Exchange (TPE), as name indicates, is an exchange technique where the patient’s blood is allowed to pass through the Apheresis machine, which filters plasma and is removed and discarded with reinfusion of red blood cells along with replacement of equivalent amount of fluid such as plasma or albumin into the patient. TPE has several
unique characteristics that allow it to be a potentially effective therapy in rapidly achieving this goal. Specifically, TPE allows for the removal of large molecular weight, protein-bound molecules that have a small volume of distribution. Recent information suggests that TPE may be effective in the therapy of patients receiving biologic treatments (for Crohn's disease and rheumatoid arthritis) who develop life-threatening complications due to this therapy. TPE was first employed in 1952 in multiple myeloma to control hyperviscosity; by 1970s TPE had evolved as a treatment modality in number of neurological diseases [1]. TPE is used alone as frontline and/or as second line adjuvant therapy to treat a number of neurologic, renal, hematological, rheumatological, oncological and multi-systemic diseases. 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 decision making of individualized case as 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].

Thus, careful interpretation and analysis of case reports and series are required to assess the potential efficacy of this therapy. Due to the nature of intoxications, drug overdoses or poisonings, no randomized controlled trials on the efficacy of TPE in these conditions is hardly found. The present study thus reviewed retrospectively a 7-year's data from August 2010 to January 2018 to share the experience in conducting the TPE by the Transfusion Medicine Department (Blood Bank) of Square Hospitals Ltd in Dhaka, Bangladesh. The observational data describes the demographic and clinical characteristics of treated patients, and analyze the incidence of plasmapheresis-related complications and discusses the management of the procedures and adverse effect, if any.

2. Materials and Methods

Patients, place and period of study: The patients who were indicated for TPE by the physician for neurological conditions like GBS, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) and non-neurological conditions like Thrombotic Thrombocytopenic Purpura (TTP), HELLP syndrome, Hemolytic Uremic Syndrome (HUS) and Myasthenia Gravis (MG) were included in the study. Patients who did not consented to undergo the procedure were excluded. Relevant clinical and laboratory investigations such as ECG, chest X-ray, cardiorespiratory status and serology were carried out before the TPE procedure. Informed consent was obtained from each patient prior to the procedure, and was explained about the procedure in detail with the probable adverse reactions or complications. A total of 267 procedures were performed on 50 patients, depending upon the clinical improvement of each patient who attended Square hospitals Ltd, a tertiary hospital in strategic location of Dhaka city, Bangladesh between August 2010 and January 2018.

All TPE procedures were carried out in Intensive Care Unit (ICU) and High Dependency Unit (HDU) by blood bank technologists trained in TPE under the supervision of blood bank physician. Throughout the procedure and post procedure all patients were assessed thoroughly to observe and identify any complications or adverse reactions.

Techniques: TPE was carried out daily or on alternate days using intermittent type of cell separator (Haemonetics MCS+, Haemonetics Corporation, Massachusetts, USA) via a double lumen HD femoral catheter. Hemodynamic parameters were monitored throughout the procedure. Estimated plasma volume (EPV) was calculated according to the Kaplan formula, $EPV = \{(0.065 \times \text{bwt in kg}) \times (1−\text{Ht})\}$ where bwt signifies body weight and Ht is Hematocrit. In each session, about 1.0 – 1.5 calculated plasma volumes were exchanged. The ratio of anticoagulant acid citrate dextrose (ACD-A Haemonetics) and whole blood was 1:12 and maintained for every 15-30 minutes intervals. The blood pressure and pulse, changes in appearance, development of symptoms like light-headedness, nausea, paraesthesia and overall status were closely monitored.

Toxicity and fluid replacement: To prevent citrate toxicity a 10% calcium gluconate was given during the procedure according to serum calcium levels and the amount of ACD solution used. The duration of procedure varied from three to five hours depending upon the amount of plasma exchange. As replacement, 5% albumin and normal saline were used for all patients except those suffering from Thrombotic thrombocytopenic purpura (TTP). Fresh frozen plasma (FFP) was used for the patients suffering from TTP. Normal saline was infused in patients who developed hypotension and the procedure was temporarily ceased, and in a few cases institution of pressor amine (dopamine) was required.

3. Results

Total 50 patients were indicated for TPE; of which 25 were male and 25 were females with mean age of 39.6 years, range: 09 to 68 years (Table-1). Among the five age group strata, majority of patients (42%) were from 31-45 years followed by 46-60 years (24%).

Table 1: Demographics of patients undergoing TPE

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Frequency (%)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-15</td>
<td>2 (4)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>16-30</td>
<td>11(22)</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>31-45</td>
<td>21(42)</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>46-60</td>
<td>12(24)</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>61-75</td>
<td>4 (8)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>25</td>
<td>25</td>
</tr>
</tbody>
</table>

Table- 2 shows the blood group of the patient undergone TPE procedure. Of the total 50 patients, majority of patients (94%, 47 of 50) were positive for various ABO groups; only two (4%, 2 of 50) was O negative and one (2%, 1 of 50) was B negative. Patients by positive blood groups, majority were B positive (38%, 19 of 50), followed by O positive (28%, 14 of 50).
Table 2: Blood Group of the patients

<table>
<thead>
<tr>
<th>Blood Group</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B positive</td>
<td>19(38)</td>
</tr>
<tr>
<td>O Positive</td>
<td>14(28)</td>
</tr>
<tr>
<td>A Positive</td>
<td>8(16)</td>
</tr>
<tr>
<td>AB Positive</td>
<td>6(12)</td>
</tr>
<tr>
<td>O Negative</td>
<td>2(4)</td>
</tr>
<tr>
<td>B Negative</td>
<td>1(2)</td>
</tr>
</tbody>
</table>

The most frequent indications for performing TPE are shown in Figure-1. The neurological diseases group comprised of 58% (29 of 50) patients with Guillain-Barré syndrome (GBS); hematological disease group had 28% (14 of 50) patients with TTP and one patient 2% (1 of 50) with HUS. Other indications for TPE were HELLP Syndrome in 8% (4 of 50) patients, MG in 2% (1of 50) patient and Hyper Triglyceridemic Pancreatitis in 2% (1 of 50) patient.

Figure 1: Indicating syndrome of patients undergone TPE

The indications of TPE for a disease or condition of the patients were categorized as per published guidelines of the ASFA (2016). There were 82%, (41 of 50) in category I, while 18%, (9 of 50) were in category III (Table-3).

Table 3: Indications for TPE with categories according to ASFA guidelines

<table>
<thead>
<tr>
<th>Indication</th>
<th>Category (according to ASFA guideline)</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBS</td>
<td>I</td>
<td>29 (58)</td>
</tr>
<tr>
<td>TTP</td>
<td>I</td>
<td>14 (28)</td>
</tr>
<tr>
<td>HELLP Syndrome (post partum)</td>
<td>III</td>
<td>4 (8)</td>
</tr>
<tr>
<td>HUS</td>
<td>III</td>
<td>1 (2)</td>
</tr>
<tr>
<td>MG (Pre-thymectomy)</td>
<td>I</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Hyper Triglyceridemic Pancreatitis</td>
<td>III</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Note: Guillain-Barre syndrome (GBS), Thrombotic thrombocytopenic purpura (TTP), Myasthenia Gravis (MG) and Haemolytic uremic syndrome (HUS). A total of 267 TPE sessions were performed and the mean number of TPE sessions performed per patient was 5.34 (range 1-13) sessions which are shown in Figure-2. Majority of patients had episodes below 10; while a few patients had more than 10 episodes.

Complications associated with TPE procedures were presented in Table 4. Of the total procedures, over 88% (232 over 267) were carried out without any apparent complications. During the TPE procedure, adverse effects were observed in 11.99% patients (32 over 267). The life threatening adverse reactions, however, occurs in 1.12% (3 of 267 episodes) cases only. The most common adverse effect was 2.62% (7 of 267) was the fall of Arterial blood pressure, not requiring pressor amines followed by catheter related complication in 2.25% (6 of 267) like catheter blockage, and anxiety/agitation requiring sedation was 1.87% (5 of 267). Rest of patients had symptoms of hypocalcaemia and allergic reaction (1.5% each), fever (1.12%), fall in the arterial blood pressure requiring pressor amines/shock (0.75%) and anaphylactic reaction (0.38%). However, the majority of them were mild. There was no procedure related mortality in our study, but 1 TTP patient was reported death after first cycles due to disease related complication.

4. Discussion

Plasma exchange (PE), a therapeutic procedure used to treat a variety of diseases through the bulk removal of plasma.
Since the initial use, the term has been describing more broadly of several procedures, all of which involve the separation of whole blood into its components with removal modification of one or more of these components. The PE when introduced in clinical practice has significantly reduced the morbidity and mortality of patients with various diseases, and especially of those with thrombotic thrombocytopenic purpura (TPP), hemolytic uremic syndrome (HUS) and myasthenia gravis [5]. TPE or IVIG (Intravenous Immunglobulin) are recommended treatment options in GBS, both have been found to be equally effective and significantly better than the conservative treatment for recovery from the disability [6]. However, in GBS with axonal involvement, TPE has been reported to be of greater potential benefit than IVIG. TPE is more effective when initiated within seven days of disease onset, for controlling symptoms of neuro-immunological disorders [1].

This report briefly described a series of 50 patients who underwent 267 cycles of TPE for various indications. All patients were treated with PE following the ASFA guidelines [4], because they suffered from a disease or condition considered as categories I and III. The ASFA guidelines are based upon stringent review of up-to-date literature, evidenced-based quality analysis and strength of recommendation derived from this evidence [4].

The very focused indication of TPE in the present study was GBS patients (58%), which is almost similar (67.5%) to that reported by Nizar et al. (7). The recommended treatment option for GBS is either PE or intravenous IgG (IVIG) and both has been reported equally effective (5). In initial stage, IVIg was preferred for its ease of administration and familiarity of use. However, PE has proven to be more cost-effective at least in South Asian scenario when compared to IVIg therapy in term of its cost, improvement in technical procedure and extremely safe in experienced hands. It is to be noted that plasma exchange was the first-line therapy in patients with neurological indications such as GBS, while in other indication it was an add-on therapy with other immunosuppressive therapy including steroids and antimetabolites, such as cyclophosphamide/mycophenolate mofetil [7]. In a series of 109 (67.7%) GBS patients reported by Shreedevi et al. [1] and yet another by Gafoor VA et al. reported 203 cases of neurological disorders with GBS were the main indication of TPE and that is similar to our study. They also found that TPE as cost effective alternative to IVIG and is safe in treating various immune mediated neurological disorders [8]. However, in GBS with axonal involvement, TPE has been reported to be of greater potential benefit than IVIG. TPE is most effective when initiated within seven days of disease onset, for controlling symptom of neuro-immunological disorders [1].

The second most common indication was TPP which responded well to TPE procedures. TPE is generally performed daily until the platelet count is >150X10^9/L, and LDH is near normal for 2–3 consecutive days TPE has decreased the overall mortality from >90% to <10% over the period of time [1]. Sidhu et al., have reported that anaphylactic reactions to plasma are very common in TPP cases. They suggested substituting octaplas for FFP or, alternatively, using albumin with slowly increasing amounts of FFP to mitigate the risk of further anaphylactic adverse events [9].

We performed TPE in 4 (8%) patients with post partum HELLP syndrome. All patients responded well to the TPE procedures and TPE in post-partum HELLP is generally performed until platelet counts are >100X 10^9/L or LDH has normalized. Multiple case reports, case series, and one retrospective controlled trial have shown the clinical benefit of TPE in severe post-partum HELLP along with clinically significant improvement in platelet counts and decreases in serum LDH and aspartate aminotransferase levels. TPE is utilized during failure of the patient to improve within 48-72 hr following delivery. Although TPE seems to confer benefit when applied to severe post-partum cases, many studies were done without ADAMTS-13 [a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13] measurements to rule out TTP and may have included patients who had TTP. TPE is considered to be the primary therapy for TTP and should be initiated when there is clinical suspicion of TTP. One study which used ADAMSTS-13 levels to differentiate HELLP from TTP showed recovery in four severe HELLP cases treated with high dose steroids without the use of TPE [10]. There is no role of TPE in ante-partum HELLP as treatment may delay delivery, the definitive treatment for HELLP [4].

Pinching AJ and Peters AK, first described TPE as a form of treatment for MG in 1976 (1). MG treatment modalities include acetylcholinesterase inhibitors, thymectomy, immunosuppressant and either TPE or IVIG. Patients diagnosed with MG either seropositive or negative for the antibodies, responded well to TPE procedure before surgery when compared to any other adjunct therapies. Clinically the effects are observed within 24 hours of TPE and are more effective with immunosuppressants, there are no adequate randomized control trials to prove the effects, but many cases report benefit from plasma exchange over IVIG with improvement in ventilator status. Similar to present study, Kumar R et al., noted tremendous improvement in patients with MG and in those who experience exacerbations in spite of treatment with steroids and oral immunosuppressants [1].

The most commonly observed adverse effect was fall in the arterial blood pressure (n=9, 3.37 %). 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, 0.5 to 1 L normal saline was given IV running. These measures were sufficient to stabilize blood pressure in 7 cases. In 2 patients, institution of pressor amine (dopamine) was needed. The all TPE cycles were completed after restoring normal blood pressure. Strict monitoring of patient’s hydration status and basic vital parameters, elimination of factors contributing complications including the use of vasodilating drugs, are essential for prevention of serious episodes of hypotension. The procedures should be particularly meticulously planned in patients with the history of hypotension before plasmapheresis procedures and with arrhythmias before the institution of therapy [2]. Gafoor et al reported 32.2% episode of hypotension during TPE in a tertiary care hospital in South India [8].

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The side effects most frequently described in literature result from the supply of citrate, which can be used as an anticoagulant within the circuit and filter, being also the constituent of the plasma transfused. Citrate binding of calcium ions leads to a reduction in its serum concentration. Hypocalcaemia decreases the cell irritability threshold and is likely to induce a wide spectrum of tetany or paresthesia symptoms. In most cases, the symptoms are mild, however, it is worth remembering that they can cause discomfort or anxiety and hinder the completion of plasmapheresis [2]. Nausea has been reported during as many as 15% and paresthesia in 9% of exchanges utilizing concentrated citrate solution, such as ACD-A2. Hypocalcemia was the most frequent complication in a Korean study, complicating 11.1% of procedures [5]. 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.

Ara et al. In their study experienced a low incidence of the symptoms of hypocalcemia (paresthesia, tingling) even in patients treated with FFP regular after parenteral replacement of calcium in all procedures [11]. We tried to minimize analytic changes after per-forming PEs. Therefore, we administered prophylactic Ca solution to prevent citrate-induced hypocalcemia.

The likelihood and nature of allergic reactions depend on the materials used to replace discarded plasma. Fresh frozen plasma is most likely to induce allergic reactions ranging from mild episodes responsive to antihistamines to anaphylaxis [12]. 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 [13]. Ara et al. reported allergic reactions during 29 (8.73%) procedures; 9 of them subsided spontaneously; 5 patients needed additional antihistamine; 15 patients received injection hydrocortisone in a single bolus [11]. Gafoor et al reported 2.2% episode of allergic reaction during TPE in a tertiary care hospital in South India [8]. In this study allergic reactions were observed during 4 (1.5%) procedures, where most reactions were limited to rigor or urticaria; 3 of them subsided spontaneously and one patient needed antihistamine.

N Basic-Jukic et al. (5) reported severe anaphylactoid reactions requiring the use of aminophylline, epinephrine and steroids during five (0.1%) treatments. Urticaria, wheezing and hypotension characterized anaphylactoid reactions to replacement fluid. All five reactions occurred in patients treated with FFP. Allergic reactions which were characterized as mild or moderately complicated the course of PE in 1.6% of treatments. A significantly higher incidence of allergic reactions was recorded in patients requiring FFP (9.5%) [5]. We experienced one severe anaphylactoid reaction (0.37%) requiring epinephrine, steroids and artificial ventilation. So the TPE procedure had stopped for that patient. In this case the replacement fluid was 5% albumin.

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 [11]. Careful assessment of the patients and expertise in TPE is essential to optimize therapy and minimize adverse consequences [1].

In summary, PE performed by trained personnel was a safe and effective therapeutic approach for patients hospitalized in intensive care units. The current ASFA guidelines are a very useful tool to identify those situations. The safety of the PE procedures can be increased after performing few medical interventions. First, a careful review of current medications that the patient was taking prior to starting the PE procedures and that could interfere with physiologic compensatory cardiovascular responses to hypovolemia and hypotension must be conducted. Second, prophylactic Ca solution must be administered to prevent citrate-induced hypocalcemia.

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References


