Complications Of Therapeutic Plasma Exchange In Neurological Disorders : A Retrospective Study Of 112 Procedures

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Type of Publication: Original Research Paper
Conflicts of Interest: Nil

ABSTRACT

Background- 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. In this procedure, patient’s blood is passed through apheresis machine, where plasma and red blood are separated and filtered plasma is removed and discarded and red blood cells are reinfused along with replacement fluid such as plasma or albumin in to the patient. In our study, complications related to TPE procedures are studied.

Material and Method -The present study was conducted in the Department of Transfusion Medicine, M. Y. hospital, Indore. In this study, 24 cases were included who have undergone 112 procedures of Therapeutic plasma exchange between 2018 to 2019.

Result- In this study, Total 112 procedures were done on 24 patients. Neurological indications included Guillain-Barre’ syndrome (n =09), transverse myelitis (n =06), chronic inflammatory demyelinating polyneuropathy (n =04), neuromyelitis optica (n = 02), HTLV induced myeloneuropathy (n = 01), acute disseminated encephalomyelitis (n =01) and polymyositis (n =01). Male to female ratio is 14/10. In our study, total 5.35% complications were reported during and after the procedures, in which 4.46% complications were during the use of albumin as replacement fluid while 0.89% complications were during the use of FFP as replacement fluid. Allergic reactions are the common side effects with both the replacement fluid. Adverse reactions detected in 06(5.35%) cases out of 112 TPE. Common complications were allergic reactions, fever, vomiting, tachycardia and anxiety . Allergic reactions were observed during 2 procedures (1.78%). Both of the TPE cycles were completed successfully. 1(0.89%) patients complained of vomiting. During 1(0.89%) procedures, fever detected. Patients also reported symptoms like restlessness, anxiety and tachycardia. The complaints were mild and subsided spontaneously.

Conclusion- Most of the complications of TPE are mild. TPE is a relatively safe method of treatment even as first line therapy for certain disorders when performed with all precautions.

Keywords: Therapeutic plasma exchange, Complications.

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. TPE was first employed in 1952 in patients with multiple myeloma to control hyperviscosity[1]. 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-Barre syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP)[2,3]. TPE is
associated with complication also which may be related to blood access, replacement fluids, the procedure itself, transfusion of blood products or to the use of anticoagulants. The incidence of severe, life-threatening complications is estimated at 0.025 to 4.75% of procedures \(^4,5\). The common adverse effects are 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% \(^6,7\). Although thousands of procedures are carried out each year, there are only a few reports on complications of PE \(^8-17\).

**Material and Method** - The present study was conducted in the Department of Transfusion Medicine, M. Y. hospital, Indore. In this study, 24 cases were included who have undergone 112 procedures of Therapeutic plasma exchange between 2018 to 2019. All the patients were properly analyzed for detailed clinical history, personal (drug intake and adjuvant therapy received like IV immunoglobulins and corticosteroid) and past history, indications and need of TPE as front line or second line therapy. Patients not willing to undergo the procedure were excluded. The result and complications of each procedure were recorded. TPE was done through a central venous access in all the patients. Continuous flow cell separator spectra Optia and intermittent flow cell separator Haemonetics MCS 300Plus were used for the procedure. For a single patient, TPE was done every alternate day. Human albumin, normal saline and fresh frozen plasma were used as replacement fluid and acid citrate-dextrose solution was used as anticoagulant during procedure. Around 1 -1.5 volume plasma was exchanged depending on patients’ heights, weights, genders and hematocrit values.

Central venous catheter was inserted through the jugular vein in all patients. All procedures were performed by senior apheresis technicians under direct supervision of faculty of Transfusion Medicine. All the basic investigations like complete blood count, prothrombin time, serum electrolytes, serum calcium levels were done a day before the procedure was performed. Patients relatives were explained about the risk and complications of procedures in detail and written informed consent was taken before the beginning of the procedure. The patients were continuously monitored for the vital signs and for the complications throughout the procedure. the beginning and at the end of each procedure.

Patient’s total blood volume was calculated as per Nadler’s formula \(^18\). A 10 ml of calcium gluconate was given during the procedure to prevent citrate toxicity in patients with low calcium levels \(^19\). Depending on the amount of plasma exchanged, the duration of procedure varied from 1 to 3 hours. One plasma volume is exchanged with 3 units of FFP. Albumin is the choice of replacement fluid alternate to FFP but of high cost. The dose was 250 ml albumin in 500 ml of normal saline infusion.

**Result**

**Table no. 1 - Indications and number of procedures of Therapeutic Plasma Exchange**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>DIAGNOSIS</th>
<th>No. of cases</th>
<th>No. of procedures</th>
<th>Gender (M/F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GBS</td>
<td>09</td>
<td>42</td>
<td>4/5</td>
</tr>
<tr>
<td>2</td>
<td>LETM</td>
<td>06</td>
<td>31</td>
<td>3/3</td>
</tr>
<tr>
<td>3</td>
<td>CIDP</td>
<td>04</td>
<td>18</td>
<td>3/1</td>
</tr>
</tbody>
</table>
In this study, (Table no. 1) Total 112 procedures were done on 24 patients. Neurological indications included Guillain-Barre’ syndrome (n = 09), transverse myelitis (n = 06), chronic inflammatory demyelinating polyneuropathy (n = 04), neuromyelitis optica (n = 02), HTLV induced myeloneuropathy (n = 01), acute disseminated encephalomyelitis (n = 01) and polymyositis (n = 01). Male to female ratio is 14/10.

Table no. 2 - Complications related to TPE.

<table>
<thead>
<tr>
<th>Complications</th>
<th>Albumin</th>
<th>FFP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic reactions</td>
<td>01 (0.89%)</td>
<td>01 (0.89%)</td>
<td>02 (1.78%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>00</td>
<td>00</td>
<td>00</td>
</tr>
<tr>
<td>Hypotension</td>
<td>00</td>
<td>00</td>
<td>00</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>00</td>
<td>00</td>
<td>00</td>
</tr>
<tr>
<td>Chills</td>
<td>00</td>
<td>00</td>
<td>00</td>
</tr>
<tr>
<td>Vomiting</td>
<td>01 (0.89%)</td>
<td>00</td>
<td>01 (0.89%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>00</td>
<td>00</td>
<td>00</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>00</td>
<td>00</td>
<td>00</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>00</td>
<td>00</td>
<td>00</td>
</tr>
<tr>
<td>Fever</td>
<td>01 (0.89%)</td>
<td>00</td>
<td>01 (0.89%)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>01 (0.89%)</td>
<td>00</td>
<td>01 (0.89%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>01 (0.89%)</td>
<td>00</td>
<td>01 (0.89%)</td>
</tr>
</tbody>
</table>
In our study, (Table no.2) total 5.35% complications were reported during and after the procedures, in which 4.46% complications were during the use of albumin as replacement fluid while 0.89% complications were during the use of FFP as replacement fluid. Allergic reactions are the common side effects with both the replacement fluid.

<table>
<thead>
<tr>
<th>Total</th>
<th>05 (4.46%)</th>
<th>01 (0.89%)</th>
<th>06 (5.35%)</th>
</tr>
</thead>
</table>

Table 3 – Combination of replacement fluid used during TPE procedures.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Combination of replacement fluid used</th>
<th>No. of Procedures</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FFP and normal saline</td>
<td>103</td>
<td>91.96%</td>
</tr>
<tr>
<td>2</td>
<td>Human albumin and normal saline</td>
<td>8</td>
<td>7.15%</td>
</tr>
<tr>
<td>3</td>
<td>FFP, human albumin and normal saline</td>
<td>1</td>
<td>0.89%</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>112</td>
<td>100%</td>
</tr>
</tbody>
</table>

The number and frequency of TPE procedure depended upon the clinical status of patient. FFP and normal saline were used in 103(91.96%) patients as replacement fluid. Human albumin and normal saline were used as replacement fluid in 8(7.15%) patients and FFP, human albumin and normal saline were used in 1(0.89%) of the patients.

Overall response rate (complete plus partial response) was 20(83.3%) cases. There was no response in 4(16.66%) of the cases. There was 2 (8.3%) mortality related to TPE procedure. Adverse reactions detected in 06(5.35%) cases out of 112 TPE. Common complications were allergic reactions, fever, vomiting, tachycardia and anxiety. Allergic reactions were observed during 2 procedures (1.78%). Itching, rash or urticaria were also noted. 1 of them subsided spontaneously. 1 patient needed additional antihistamine. Both of the TPE cycles were completed successfully. 1(0.89%) patients complained of vomiting, for which injecton ondansetron IV was given. During 1(0.89%) procedures, body temperature was increased. Fever subsided after using paracetamol. We have given injectable 10% calcium gluconate prophylactically to avoid hypocalcemia. Patients also reported symptoms like anxiety 1(0.89%) and tachycardia 1(0.89%). The complaints were mild and subsided spontaneously.

**Discussion** - There is significant reduction in morbidity and mortality of patients with various diseases with the help of therapeutic plasma exchange. The low risk to benefit ratio encouraged its use in many different conditions, with mostly excellent therapeutic results[20-23]. 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[24,25].

In both adult and child studies, the incidence of TPE complications reported in the literature are different. In 2003, Norda et al[26] reported the registration study of TPE in Sweden. The incidence of TPE complications in 20,485 adults was 4.3% of all procedures. Mokrzycki et al[27] summarized 9 large-scale TPE studies published before 2011. The incidence of complications in adults was 5% to 12% of all procedures, and most of them were<10%. However, the incidence of TPE complications in children was 2.2% to 11.0% of all procedures.[32-37] The incidence of severe, life-threatening complications is estimated at 0.025–4.75% of procedures[38].

The present study showed that the incidence of TPE complications was 5.35% of all procedures, which is comparable to other studies. The occurrence of TPE complications is influenced by several factors,
including anticoagulant methods, types and volumes of replacement fluid, vascular access, diseases, and ways of plasma separation.

Basic-Jukic et al reported complications in 509 adult patients with 4857 TPE cases, including abnormal sensation (2.7%), hemopta at the puncture site (2.4%), coagulation (1.7%), and allergic reaction (1.6%). Shemin et al[40] reported complications in 174 adult patients with 1727 TPE, including fever (7.7%), urticaria (7.4%), and hypocalcaemia (7.37%). Brunetta et al[42] reported 215 cases of TPE in children, including hypotension (6%), pain or paraesthesia (6%), transfusion reaction (6%), and facial oedema (1%).

In this study, common complications were allergic reactions, fever, vomiting, tachycardia and anxiety. Allergic reactions were observed during 2 procedures (1.78%). Itching, rash or urticaria was noticed. 1 of them subsided spontaneously. 1 patient needed additional antihistamine. Fresh frozen plasma is most likely to induce allergic reactions ranging from mild episodes responsive to antihistamines to anaphylaxis.[43] Both of the TPE cycles in which allergic reactions were noticed were completed successfully. 1(0.89%) patients complained of vomiting. Injection ondansetron IV was given. During 1(0.89%) procedure, body temperature was increased. Fever subsided after using paracetamol. We have given injectable 10% calcium gluconate prophylactically to avoid hypocalcemia. Patients also reported symptoms like anxiety 1(0.89%) and tachycardia 1(0.89%). The complaints were of mild and subsided spontaneously.

Previous studies showed that FFP had significantly higher rates of adverse reactions than patients receiving other exchange fluids, such as 5% albumin.[40] On contrary to other studies, in present study we found that allergic reaction are more common with 5% albumin as compared to FFP. We believe that FFP is more complementary to normal body fluids and immune components than albumin. The retrospective design and single center analysis may be the limitations of the present study. Selectivity bias of TPE inclusion criteria and disease type may also affect its limitation.

Several investigators have reported deaths associated with PE treatment.[52,53] The incidence of death associated with PE has been estimated to 0.05%.[54]

In our study mortality rate is 8.3% which is slightly higher than previously reported studies. The reason for this mortality is that the respiratory muscles were involved at the time of admission in hospital. Nowadays severe adverse effects are reducing day by day which may be related to increased awareness of side effects and the staff being more aware to prevent progression into severe side effects.

Abnormalities of heart rates may be present including bradycardia, extrasystoles, atrial fibrillation, and tachycardia, which are brief and usually self limited, although fatal cardiac arrest has occurred.[44]. The exact cause of cardiac rhythm disturbances is unclear, but chelation of calcium ion by citrate probably plays a role since.[45]. In this study, there was 1 (0.89%) case reported with tachycardia and 1 (0.89%) case with anxiety. Other than this, there was no episode of clinically significant change in the heart rate requiring medical treatment. However, the risk of this complication depends on the underlying illness. Patients with Guillain-Barré syndrome and associated autonomic nervous system dysfunction frequently experience cardiac arrhythmias irrespective of the form of treatment.[46].

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.[47] Nausea has been reported during as many as 15% and paresthesia in 9% of exchanges utilizing concentrated citrate solution such as ACD-A47. Other study reports vary on the occurrence of these symptoms.[48,49]. But in present study we have not reported incidence of symptoms related to hypocalcemia (parasthesia, tingling). These symptoms may not be happened because we have given injectable 10% calcium gluconate prophylactically.

Basic-Jukic et al[50] report bleeding in 0.06% of procedures where Rossi et al[51] report on hemorrhage in 0.2% of treatments. In present study, there was no bleeding episode may be because of FFP used as a replacement fluid in most of the procedure and TPE procedures were done in alternate day basis. FFP as replacement fluid prevent depletion of coagulation factors.
Conclusion- Most of the complications of TPE are mild. Mode of venous access, the frequency of exchange, the replacement fluid to be used, the need for adjunctive therapy, and the nature of the underlying illness are the few critical factors which should be carefully assessed during the procedures to minimize complication. So, we concluded that TPE is a relatively safe method of treatment even as first line therapy for certain disorders when performed with all precautions.

Reference-


