Editorial

Therapeutic Plasma Exchange in Neurologic Disorders

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Abstract:- Therapeutic Apheresis is removing pathogenic cells/plasma from the patient and returning the normal components to alleviate disease symptoms. It is mainly *Cytapheresis, Therapeutic plasma exchange (*TPE*), RBC exchange, LDL-apheresis, Immunoadsorption etc.* The American Society for Apheresis has given guidelines on the grading recommendation, indication category and use of therapeutic apheresis in clinical practice. TPE involves removal of diseased plasma from the patient and simultaneous replacement by normal plasma or other fluids. Outcome and frequency of TPE depends on the rate of synthesis of the pathogenic substance and its distribution in the body. Life threatening complications are only 0.025 to 0.2% and are associated with the premorbid conditions of the patients rather than the procedure itself. The category I neurologic disorders where TPE is 1st line therapy are Guillain-Barre Syndrome, Myasthenia Gravis, Paraproteinemic demyelinating neuropathies, Chronic inflammatory demylinating polyneuropathy, Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections and Sydenham's chorea.

Key Words:- Therapeutic Apheresis, Guillain-Barre Syndrome, Myasthenia Gravis, Chronic inflammatory demylinating polyneuropathy, Paraproteinemic Demyelinating Neuropathies, Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS), Sydenham's Chorea.

The concept of apheresis dates back to the early 20th century when John Abel coined the term where removal of plasma from immunised horses without exsanguinating them was done in 1914, the scope of its therapeutic applications emerged only in the 1950s.[1] "Apheresis" is derived from the Greek word "Aphairos" or Roman "Aphairesis" which means, "taking away by force or withdraw".[2] Apheresis constitutes a procedure in which the whole blood from the donor/patient is removed and processed to separate the desired component of blood. This component is retained and the remaining blood is returned to the donor/patient.

Applications of Apheresis[1,3]

1. Component collection from donors
2. Therapeutic Apheresis in patients

1. Component collection:

The process of apheresis used for collecting one or more component from a healthy donor with simultaneous return of the remaining components is named according to the component collected viz. plateletpheresis (collection of platelets), leucocytapheresis (collection of leucocytes), erythrocytapheresis (collection of red cells) & plasmapheresis (collection of plasma).

2. Therapeutic Apheresis (TA):[1]

TA is removing pathogenic cells/ plasma from the patient and returning the normal components to alleviate disease symptoms. It may not be the only modality of treatment but often used in conjunction with other forms of treatment. Applications of TA can be subdivided into 2: *Acute Self-limiting diseases* in which apheresis is used to lower the circulating pathogenic substance and *Chronic diseases* in which there is ongoing production of pathogenic substances, so its use is debatable due to the phenomenon of rebound antibody production. TA is mainly of following types:

Cytapheresis: Removal of pathogenic cellular components - e.g. abnormal leukocytes in leukemia (blast crisis, hyperviscosity syndrome); removal of thrombocytes in essential thrombocythaemia.

Therapeutic plasma exchange (TPE): TPE involves removal of diseased plasma from the patient and simultaneous replacement by normal plasma or other fluids such as albumin, electrolytes and colloids.

RBC exchange: A therapeutic procedure in which blood of the patient is passed through a medical device which separates RBCs from other components of blood, the RBCs are removed and replaced with donor RBCs alone and colloid solution.

LDL-apheresis: It removes LDL cholesterol from the blood of patients who have very high cholesterol levels e.g. homozygous familial hypercholesterolemia.

Immunoadsorption (IA): A therapeutic procedure in which plasma of the patient, after separation from the blood, is passed through a medical device which has a capacity to remove immunoglobulins by specifically binding them to the active component (e.g. Staphylococcal protein A) of the device.

Indications of TA

The American Society for Apheresis (ASFA), in conjunction with AABB, has provided guidelines on the use of TA in clinical practice. A systematic review and evidence-based approach has been used in the categorization of indications (Table-1) and grading (Table-2) of therapeutic apheresis.[4]

Table 1 : Indications for TA -ASFA 2013 Categories[4]

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.
III	Optimum role of apheresis therapy is not established. Decision making should be individualized.
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.

Table 2 : Grading Recommendations for TA adopted from Gyatt & co-workers[5]

Recommendation	Description
Grade 1A	Strong recommendation, high-quality evidence
Grade 1B	Strong recommendation, moderate quality evidence
Grade 1C	Strong recommendation, low-quality or very low-quality evidence
Grade 2A	Weak recommendation, high quality evidence
Grade 2B	Weak recommendation, moderate-quality evidence
Grade 2C	Weak recommendation, low-quality or very low-quality evidence

Therapeutic Plasma Exchange (TPE):

TPE is a procedure in which the plasma is separated from the blood, discarded in total, and replaced with a substitution fluid such as albumin or plasma from healthy donors. This is performed to remove toxins or auto-antibodies that have accumulated in plasma. Outcome of TPE depends on the rate of synthesis of the pathogenic substance and its distribution in the body which also dictates the frequency of TPE. The ASFA indication categories for the therapeutic apheresis in neurologic disorders are given in Table-3. The volume of plasma to be exchanged is usually based on the estimated plasma volume of the patient. One volume Plasma Exchange (PV) ≥ 40 ml plasma exchanged/ kg body weight of the patient.[4] Rate of exchange is about 2 L/hour, but depends on the body weight, vascular access and other vital parameters of the patient. When more than 1.5 times plasma volume is exchanged in one sitting and albumin is used as replacement fluid there may be a decrease in various blood components such as the procoagulant factors. Usually albumin and saline are used as replacement solution. Fresh frozen plasma (FFP) is primarily used only when there is a need to replace coagulation factors and other immuno-

Table 3 : ASFA Indication Categories for TA in Neurologic Disorders[6]

Disorder	TA Modality	Disease Condition	Indication Category	Grade
Acute disseminated encephalomyelitis	TPE	--	II	2C
Acute inflammatory demyelinating polyneuropathy (Guillain-Barre Syndrome)	TPE	Post IVIG	I III	1A 2C
Chronic focal encephalitis (Rasmussen encephalitis)	TPE IA	-- --	III III	2C 2C
Chronic inflammatory demyelinating polyneuropathy	TPE	--	I	1B
Lambert-Eaton myasthenic syndrome	TPE	--	II	2C
Multiple sclerosis	TPE IA TPE	Acute CNS inflammatory demyelinating disease Acute CNS inflammatory demyelinating disease Chronic progressive	II III III	1B 2C 2B
Myasthenia gravis	TPE TPE	Moderate-severe Pre-thymectomy	I I	1B 1C
Neuromyelitis optica (Devic's syndrome)	TPE TPE	Acute Maintenance	II III	1B 1C
Paraneoplastic neurologic syndromes	TPE IA	-- --	III III	2C 2C
Paraproteinemic demyelinating polyneuropahties	TPE TPE TPE IA	IgG/IgA IgM Multiple myeloma IgG/IgA/IgM	I I III III	1B 1C 2C 2C
PANDAS: Sydenham chorea	TPE TPE	PANDAS exacerbation Sydenham's chorea	I I	1B 1B
Phytanic acid storage disease (Refsum's disease)	TPE	TPE LDL apheresis	II II	2C 2C
Stiff-person syndrome	TPE	--	III	2C

PANDAS-Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection; TPE- Therapeutic plasma exchange; IA- Immunoadsorbtion.

globulins. The main risks in using FFP are the possibility of disease transmission, allergic reactions and citrate overload. The frequency of TPE procedures can be disease specific and relates to the type of antibody present and the rate at which it equilibrates (redistributes or rebounds). Larger molecular weight proteins (IgM) that reside mostly in the intravascular compartment are more easily removed. IgG, has a larger extravascular distribution, so less efficiently removed, requiring multiple procedures. The type of vascular access device needed will depend on patient condition and length of time TPE is needed. Types of access can be peripheral veins femoral or central venous catheter; implanted ports[3]; graft/fistula or radial artery cannulation

Anticoagulation in Apheresis - ACD-A, Heparin, Combinations of ACD-A and Heparin

Complications - Apheresis procedures are relatively safe and the complications are relatively reversible. They include limb paraesthesias, muscle crumps, urticaria, dizziness, nausea and vomiting. Central venous access related complications include air embolism, pneumothorax, hematoma, venous thrombosis and sepsis. Life threatening complications are only 0.025 to 0.2% and are associated with the premorbid conditions of the patients rather than the procedure itself. TPE related complications are because of use of plasma, anticoagulants and the experience of the team performing the procedure.

Patient Monitoring

Pre procedure- Informed written consent, CBC, electrolytes, coagulation studies (PT/aPTT) and disease specific indicators (baseline).

During the procedure- Monitoring for comfort & vital signs.

Post procedure-follow up consultation, vitals and laboratory assessment for disease markers.

Acute Inflammatory Demyelinating polyneuro-pathy (AIDP) (Guillain-Barre Syndrome[GBS])[7]

Incidence	Condition	Procedure	Recommendation	Category
1-2/100,000/yr	After IVIG	TPE	Grade 1A	I
		TPE	Grade 2C	III

AIDP is an acute progressive paralyzing illness affecting both motor and sensory peripheral nerves. Presence of antibodies against four gangliosides GMI, GD1a, GT1a, and GQ1b suggests an autoimmune pathogenesis.

Current Management

Since spontaneous recovery is anticipated in most patients, supportive care is the mainstay of treatment in ambulatory patients with AIDP. Clinical trials have confirmed that TPE was the first therapeutic modality to impact the disease favourably. TPE, IVIG and TPE followed by IVIG in severe AIDP are equally effective.

Rationale for TA

As AIDP is autoimmune damage to the peripheral nerve myelin, TPE can accelerate motor recovery, decrease time on the ventilator, and speedy attainment of other clinical milestones.

Chronic Inflammatory Demylinating Polyneuropathy (CIDP)[8]

Incidence	Procedure	Recommendation	Category
1–2/100,000	TPE	Grade 1B	I

CIDP is characterized by proximal and distal symmetrical muscle weakness, with or without numbness, that progresses and relapses.

Current management

Corticosteroids, TPE, and IVIG yield similar treatment outcomes. Therapies should be initiated early to prevent permanent disability. Maintenance therapy, including continuing steroids, periodic TPE, or repeated infusion of IVIG, is usually required because discontinuation of therapy may be followed by relapse.

Rationale for TA

The presumed etiology is autoimmune (humoral and cell-mediated) attack on the peripheral nerves. Therapies are aimed at modulation of the abnormal immune response.

Volume treated: 1–1.5 TPV	Frequency: 2–3/week until improvement, then taper
Replacement fluid: Albumin	as tolerated

Duration and discontinuation/number of procedures

TPE provides short-term benefit but rapid deterioration may necessitate maintenance treatment with TPE and/or other immuno-modulating therapies.

Myasthenia Gravis (MG)[9]

Incidence	Condition	Procedure	Recommendation	Category
1/100,000	Moderate–severe	TPE	Grade 1B	I
	Pre thymectomy	TPE	Grade 1C	I

MG is an autoimmune disease characterized by weakness and fatigability with repetitive physical activity, usually improves with rest. The antibody is usually directed against the acetylcholine receptor (anti-AChR) on the postsynaptic surface of the motor end plate. Approximately 50% of anti-AChR seronegative disease is due to antibodies to the muscle specific receptor tyrosine kinase (MusK).

Current management

The four major treatment approaches include cholinesterase inhibitors, thymectomy, immunosuppression, and either TPE or IVIG.

Rationale for TA

TPE is used principally to remove circulating autoantibodies, especially in myasthenic crisis, perioperatively for thymectomy, or as an adjunct to other therapies to maintain optimal clinical status. TPE works rapidly; clinical effect can be apparent within 24 hrs. TPE may be more effective than IVIG in patients with MusK related MG.

Volume treated: 1–1.5 TPV	Frequency: Daily or every other day	Replacement fluid: Albumin

Duration and discontinuation/number of procedures

Typical induction regimen consists of processing 225 ml/kg of plasma over a period of up to two weeks.

Paraproteinemic Demyelinating Neuropathies[10,11]

Incidence	Condition	Procedure	Recommendation	Category
MGUS: up to 3% of general population >50 yrs; Multiple myeloma 4–6/100,000/yr	IgG/IgA	TPE	Grade 1B	I
	IgM	TPE	Grade 1C	I
	Multiple myeloma IgG/IgA/IgM	TPE	Grade 2C	III
		IA	Grade 2C	III

Coexistence of neuropathy and monoclonal gammopathy is a common clinical problem. Polyneuropathy can present as acute, subacute or chronic process with initial sensory symptoms, associated with and/or caused by the presence of monoclonal proteins.

Current management

Combination therapy with low dose cyclophosphamide and prednisone improves clinical outcome irrespective of antibody class. IVIG has also shown clinical benefit.

Rationale for TA

The rationale for TPE is removal of antibodies. It is suggested that TPE is probably more effective for IgA and IgG MGUS-associated polyneuropathy, and not for IgM-MGUS. Patients with CIDP and MGUS respond well to TPE.

Volume treated: 1–1.5 TPV	Frequency Every other day	Replacement fluid: Albumin/plasma

Duration and discontinuation/number of procedures

5–6 treatments over the course of 10–14 days followed by tapering off TPE.

Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections (PANDAS); Sydenham's Chorea (SC)[12]

Incidence	Condition	Procedure	Recommendation	Category
Unknown for PANDAS and SC; 1.5–2.5% and 6.6–24% of school-aged children have OCD and tic disorders	PANDAS, exacerbation	TPE	Grade 1B	I
	SC	TPE	Grade 1B	I

PANDAS and SC are paediatric post-infectious autoimmune neuropsychiatric disorders, which typically follow Group-A beta-haemolytic streptococcus (GABHS) infection. GABHS infection has been associated with childhood-onset neuropsychiatric disorders in genetically susceptible individuals, such as SC, PANDAS, OCD, tic disorder, Tourette's syndrome, etc. SC occurs in about 10–20% of patients with acute rheumatic fever, typically 4–8 weeks after GABHS pharyngitis. The major clinical manifestations include chorea, hypotonia and emotional lability. In PANDAS, exacerbations of neuropsychiatric symptoms are temporarily associated with streptococcal infection but are not associated with rheumatic fever.

Current management

In severely symptomatic patients with PANDAS or SC, immunomodulatory therapies, such as IVIG or TPE, have been shown to be effective in reducing symptom severity or shorten the course.

Rationale for TA

Because of the possible role of antineuronal antibodies in the pathogenesis, antibody removal by TPE may be effective. More than 80% of the patients who received IVIG or TPE improved. The TPE group appeared to have

greater OCD and tic symptom relief than did the IVIG group.

Volume treated:	Frequency:	Replacement fluid:
1–1.5 TPV	Daily or every other day	Albumin

Duration and discontinuation/number of procedures:

Five procedures over 7 to 14 days.

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