

Role of therapeutic apheresis and phlebotomy techniques in anaesthesia and critical care

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ABSTRACT

Therapeutic transfusion techniques such as apheresis and phlebotomy are frequently used in intensive care units. Use of the apheresis technique for the treatment of various diseases in critically ill patients is growing day by day. There are increasing evidences for using apheresis as a primary therapy or as an adjunct to other therapies for various diseases such as thrombotic thrombocytopenic purpura, haemolytic uremic syndrome, drug toxicities, autoimmune disease, sepsis and fulminant hepatic failure. Apheresis is an invasive procedure. It has significant physiologic consequences, so the care of these patients requires continuous supervision. Phlebotomy is performed as an intervention for some disease management. Its use is nowadays restricted to conditions such as polycythaemia, haemochromatosis and porphyria cutanea tarda. In this review, we have looked at various indications, procedure and complications of apheresis and phlebotomy in critical care unit.

Key words: Apheresis, phlebotomy, plasmapheresis

Access this article online

Website: www.ijaweb.org

DOI: 10.4103/0019-5049.144685

Quick response code



INTRODUCTION

Therapeutic transfusion techniques consist of removal of a blood component from a patient using apheresis technology for removing defective cells or disease mediators. The terminology "Apheresis" stems from Greek verb *apairesos* or Roman *aphairesis* meaning to take away by force or withdraw.^[1] Apheresis (or Haemapheresis) is the collection of blood from a donor or patient followed by separation and removal of a cellular component(s) and/or plasma and return of the remaining blood components to the donor or patient. Cytapheresis is the procedure by which cellular elements of the blood, platelets, leucocytes, lymphocytes, red blood cells (RBC's), are selectively removed from the blood. Plasmapheresis is a process in which plasma is selectively removed. It is used to collect plasma from healthy donor (without any fluid replacement) or to exchange plasma from a patient to remove a constituent (antibody, immune complexes, inflammatory mediator, paraproteins, lipoproteins and toxins, excess cells) which is causing harm.

[Table 1] This allows disease resolution or decrease in morbidity.^[1,2] The procedure was first successfully used for the treatment of Waldenström macroglobulinemia in 1959.^[3,4] Since then, the efficacy of plasmapheresis has been documented in numerous diseases of various organ systems.

Sixty three articles were reviewed using keywords such as, therapeutic apheresis, plasmapheresis and therapeutic plasma exchange (TPE), starting from 1952 till date, accessed through search engines PubMed, Google, Google scholar and Medscape.

Role in intensive care unit

Apheresis therapy like plasma exchange and plasma adsorption is emerging as a therapeutic tool in critical care. Apheresis therapy frequently used in intensive care unit (ICU) patients for thrombotic thrombocytopenic purpura (TTP), haemolytic uraemic syndrome (HUS), autoimmune disease and sepsis. Apheresis therapy is also useful in patients with fulminant hepatic failure for artificial liver support.^[2]

How to cite this article: Bose N, Kanzariya H. Role of therapeutic apheresis and phlebotomy techniques in anaesthesia and critical care. Indian J Anaesth 2014;58:672-8.

Table 1: TPE

Plasmapheresis	TPE
Removal of plasma without fluid replacement This includes the collection of plasma from normal donors	Removal of a large proportion of patient plasma that is replaced with crystalloid, colloid fluids, FFP or occasionally with coagulation factors
TPE – Therapeutic plasma exchange; FFP – Fresh frozen plasma	

Description of apheresis

Apheresis consists of the following:

- Circulating blood components can be removed, either cells (cytapheresis) or plasma solutes (plasmapheresis).
- Circulating substances responsible for certain diseases are removed. Some cells and plasma components are mobilized from their tissue depots and removed.
 - Lymphocytes from the spleen and lymph nodes in chronic lymphocytic leukaemia
 - Low-density lipoproteins (LDLs) in familial hypercholesterolaemia.
- Removal of platelets and lymphocytes.
- Reinfusion of a deficient plasma factor as in TTP.
- Increases clearance of immune complexes by the spleen, in certain autoimmune disorders.

Types of apheresis

- Collection of components for transfusion:
 - Platelets - Plateletpheresis
 - Leucocytes - Leucocytapheresis
 - Plasma - Plasmapheresis
 - Peripheral blood stem cells (PBSCs)
- Removal of pathological components, that is, therapeutic apheresis:
 - Therapeutic cytapheresis
 - TPE.

The procedure involved in apheresis is more extensively used to harvest platelets and plasma from healthy donors than as a therapeutic modality. As a therapeutic procedure, it is not curative and does not change the natural course of the disease; however, it can be life-saving in many situations and buys time to affect more definitive therapy. The main emphasis in this article is on various aspects of therapeutic apheresis.

TECHNICAL ASPECT OF APHERESIS

Apheresis instruments separate the blood into components, then selectively remove one component and return the remaining to the patient. By running

this procedure by one or more blood volumes, a significant amount of pathologic components is removed. Anticoagulation of the circuit is required.

Centrifugation apheresis instruments use either a continuous or an intermittent flow method to drive the blood to the separation device. Continuous flow methods draw blood into the extracorporeal circuit, separate blood into components in the centrifugation chamber, channelizes the unwanted portion into a collection bag, and thereafter return the nonpathologic elements back to the patient without interruption. Dual venous access is required for this. Intermittent flow methods have the same steps but with a discrete volume of blood at a time. This takes a longer time but requires only single venous access.^[5]

THERAPEUTIC CYTAPHERESIS

The purpose was to deplete over-abundant or abnormal cellular components.

Common indications are as follows:

- Erythrocytapheresis (the patient's RBCs are removed and replacement with donor red cells if required)
 - Sickle cell disease: Goal of exchanging the sickle red cells for red cells containing haemoglobin A is to interrupt the vicious cycle of stasis, sickling and hypoxia. This procedure has also been used prophylactically in pregnancy with sickle cell disease and prior to general anaesthesia in these patients^[6]
- Hyperparasitaemia: To lower parasite loads in Malaria, Babesiosis.
- Leucocytapheresis
 - Leukaemia with hyperleucocytosis syndrome: Leukostasis results from microvascular obstruction and may lead to endothelial injury, thrombosis and/or haemorrhage. Once total leucocyte count is above 200,000/mm³ in acute myeloid leukaemia and above 300,000/mm³ in chronic myeloid leukaemia, organ dysfunction is likely:
 - Pulmonary dysfunction (hypoxemia, diffuse lung infiltrates)
 - Cerebral dysfunction (confusion, mental status changes, altered level of consciousness).

- Cutaneous T-cell lymphoma (CTCL): In the leukaemic phase, also known as Sezary syndrome, repeated leucocytapheresis reduces circulating malignant cells (sezary cells).^[7,8]
- Extracorporeal photopheresis is also a type of leukopheresis in which the white blood cells are exposed to ultraviolet A light to induce an immunomodulatory effect. It can achieve sustained remission in CTCL.^[9]
- PBSC collection
- Thrombocytapheresis: Acute management of patients with symptomatic thrombocythaemia where a rapid reduction in platelet count is required.
 - Thrombocytosis (platelet count > 450,000-500,000/ul) like polycythaemia vera (PV), essential thrombocythaemia, idiopathic myelofibrosis or unclassified myeloproliferative neoplasm, with an acute and severe thrombotic or haemorrhagic event. Platelets are reduced for symptomatic relief while waiting for cytoreductive therapy to take effect.
 - Useful in those who cannot tolerate drug therapy such as e.g. hydroxyurea or anagrelide.^[10,11]
 - Management of peri-operative thrombohaemorrhagic complications in patients with myeloproliferative neoplasms undergoing splenectomy.^[12]
 - Pregnancy with thrombocythaemia, as drug therapy is contraindicated, and it prevents placental infarction and foetal death.^[13]

Therapeutic plasma exchange

A wide variety of diseases seen in different medical specialties can be treated with TPE and it can be used as a first line of treatment in some diseases (example: TTP or as an adjunct to other therapies (example: Goodpasture syndrome). TPE removes the pathogenic substances such as antibodies, immune complexes, monoclonal proteins, cryoglobulins, lipoproteins, protein-bound toxins and cytokines. Additional evidence suggests that TPE may have an immunomodulatory effect beyond the removal of immunoglobulins (Igs).^[14,15] In TPE, two plasma volumes can be exchanged within 3 h and levels of intravascular solutes can be lowered by 50-60% with each exchange. Due to the dilution of the plasma, the substance cannot be removed completely. Treating

volumes beyond 1.5 plasma volumes removes smaller amounts of pathologic substance while prolonging the procedure and exposing the patient to more replacement fluid and anticoagulant.

The theoretical efficacy of TPE is shown in Table 2.^[2] Role of plasmapheresis in various disease conditions/syndromes are enlisted along with the factors to be removed in each:

- Anti-glomerular basement membrane (anti-GBM) disease^[16] - Anti GBM antibody
- Guillain-Barre syndrome (GBS) - Antimyelin antibody^[17]
- Hyperviscosity syndrome - IgM
- Cryoglobulinemia - Cryoglobulins
- Microangiopathic thrombocytopenia (TTP/HUS) - Von Willebrand factor multimers/anti-endothelial cell antigen^[18-20]
- Homozygous familial hypercholesterolaemia - LDL cholesterol^[21]
- Myasthenia gravis (MG) crisis - Ach receptor antibody
- Coagulation factor inhibitors - Factor VIII inhibitor
- Haemolytic disease of newborn - IgM
- Overdose of certain drugs - e.g. digitalis (digitalis antibody)
- Poisoning involving protein-bound toxins - e.g. *Amanita phalloides*

In hyperviscosity syndrome, due to monoclonal gammopathies, TPE is particularly effective as IgM is largely distributed in the intravascular compartment. Reduction in viscosity can be achieved even with the exchange of as little as 500-1000 ml of plasma by manual bag techniques, which relieves both haemorrhagic and ischemic symptoms.

Therapeutic plasma exchange is a therapy of choice for TTP, if not available temporarily, plasma infusion can be given till transfer to an appropriate facility. Results with TPE are better due to two-fold action of TPE: Removal of IgM autoantibody which acts as a specific protease inhibitor and replacement of

Table 2: Plasma exchange: Theoretical efficiency

Number of plasma volume exchanged	Percentage of the original plasma remaining
0.5	60
1.0	35
1.5	20
2.0	12

deficient factors.^[18-20]

In familial hypercholesterolaemia, chronic TPE can reduce total plasma LDL levels and lead to regression of atherosclerotic changes in blood vessels and promotes resorption of xanthomas and atheromas.^[21] LDL levels are reduced to more than 50%. VLDL and triglyceride levels are also reduced, but HDL is spared. In Refsum's disease, removal of phytanic acid by TPE helps prevent or reverse the neurological manifestations.^[22] In cold agglutinin-induced autoimmune haemolytic anaemia (AIHA), TPE is useful in a reduction of haemolysis as antibody titres falls. In warm antibody (IgG) AIHA, TPE is used as an adjunct to therapy with intravenous Ig (IVIG) and/or cyclophosphamide in refractory cases. In haemophiliacs, development of both auto and allo-antibodies is a major therapeutic challenge. These patients have to undergo surgery after achieving adequate factor VIII levels which are difficult due to the presence of coagulation factor inhibitors. TPE has an important role in removing these. In ABO incompatible marrow transplants, the alloantibodies to RBCs can be removed by TPE.^[23] In Rh-negative pregnant women, maternal IgG antibodies to the foetus can lead to destruction of foetal red cells. TPE can help remove these antibodies.

Therapeutic plasma exchange is used in the treatment of neuro-immunological diseases such as GBS, chronic inflammatory demyelinating polyneuropathy (CIDP), MG and Lambert-Eaton syndrome. Antibodies responsible for these diseases are effectively removed by TPE and help in the amelioration of the disease.^[17,24] The efficacy of plasmapheresis or administration of IVIG appears to be equal in GBS, AIDP and CIDP.^[25,26] In MG, plasmapheresis is reserved for myasthenic crisis and refractory cases.

In Goodpasture syndrome, early institution of TPE and cyclophosphamide is very effective.^[16] Plasmapheresis causes removal of anti-GBM antibodies after diagnosis by renal biopsy or detection of anti-GBM antibodies.^[27] Systemic lupus erythematosus with nephritis does not respond well by adding TPE to cyclophosphamide.^[28] TPE has been beneficial in rapidly progressive glomerulonephritis with dialysis dependent renal failure.^[29]

The disease/disorders treated with TPE that have been

categorized by the American Society for Apheresis are enlisted in Appendix 1.^[30]

PROCEDURE CONSIDERATIONS

Replacement fluid

In most cell collection and cell depletion procedures, no replacement fluid beyond the anticoagulant and saline priming solution is required. But in plasma exchange, 1-1.5 plasma volumes are typically removed, and replacement of intravascular volume is necessary. The main goal of replacement fluid is to maintain intravascular volume, maintenance of colloid oncotic pressure and electrolyte balance and restoration of deficient factors. The solutions used are 5% serum albumin, plasma, starches and crystalloids.

Vascular access

Vascular access through peripheral vein is the preferred route as it is associated with fewer infectious, haemorrhagic and thrombotic complications. When frequent procedures over a prolonged period are required, a double lumen central venous catheter designed for apheresis or haemodialysis should be inserted.

COMPLICATIONS

The rate of complication is variable, and ranges from 4% to 36% but most of the events are mild and easily treatable. Estimated mortality is 3 in 10,000 procedures, and most reported deaths have been due to cardiac and respiratory causes in critically ill patients.^[31] The most common adverse effect of apheresis is symptomatic hypocalcaemia due to infusion calcium chelating citrate ions in the anticoagulants. Hypotension occurs in 0.5-2.9% cases.^[32] Citrate toxicity occurs in approximately 0.8-1.2% cases.^[33]

Complications related to vascular access account for about 1% and include haematoma, pneumothorax, bleeding, thrombosis and infection. Haemostatic alterations and bleeding may occur in patients with baseline coagulopathy or severe thrombocytopenia. Furthermore, there is depletion of coagulation factors during large volume plasma exchanges, wherein depletion of approximately 25-45% can occur.^[34] There is also depletion of platelets and fibrinogen.

Other effects

Additional substances removed include inhibitors of coagulation^[32] and the pseudocholinesterase necessary for the metabolism of some drugs.^[35] Removal of inhibitors of coagulation could predispose patients to thrombosis. Prolongation of actions of neuromuscular blocking drugs has been seen due to reduced activity of the enzymes after TPE. It can also remove drugs which are highly protein bound. Hence, caution is advised if patient is on life-saving drugs.

PHLEBOTOMY

Phlebotomy (also known as bloodletting) means the removal of blood from the body. Therapeutic phlebotomy is the treatment of choice for blood disorders in which the removal of RBCs or serum iron is the most efficient method of managing disease symptoms and complications. Currently, therapeutic phlebotomy is approved for three main indications: Haemochromatosis, polycythaemia and porphyria cutanea tarda.

Polycythaemia

Polycythaemia is a disorder where too many red cells are produced in bone marrow, which increase the blood volume and viscosity. There is also increase in platelet and white cell production. Patient with polycythaemia tends to develop thrombotic events such as cerebrovascular, cardiovascular accidents and arterial and venous thromboembolism. In primary polycythaemia (PV), one of the major goals of treatment is to reduce these thrombotic events. PV study group prospective trial suggests that patients treated with phlebotomy had a lower incidence of haematological malignancies and solid tumours. Some studies showed that patients maintained at a target haematocrit of <45% had a significantly lower rate of cardiovascular morbidity and major thrombosis.^[36,37]

Phlebotomy can be performed in hypoxic conditions such as chronic lung diseases and cyanotic heart disease. Patients with hypoxic pulmonary disease who have hyperviscosity symptoms or a haematocrit >56% should have phlebotomy to reduce this to 50-52%,^[38-40] AHA recommends performing therapeutic phlebotomy for symptomatic patients of cyanotic congenital heart disease like Eisenmenger's syndrome or tetralogy of Fallot with haemoglobin >20 g/dl and haematocrit >65%.^[41]

Haemochromatosis

Phlebotomy does not improve haemochromatosis clinically, but prevents complications in symptomatic patients or those who have already developed end-organ damage, with a serum ferritin > 300 µg/L for men or post-menopausal women and >200 µg/L for pregnant females.^[42] Phlebotomy sessions are continued until the serum ferritin concentration drops to <50 ng/ml and transferrin saturation is <50%.^[43]

Porphyria cutanea tarda

Porphyria cutanea tarda is caused by uroporphyrinogen decarboxylase deficiency leading to the accumulation of uroporphyrinogen. Therapeutic phlebotomy is the treatment of choice with hydroxychloroquine as a good alternative.^[44] Phlebotomy sessions are repeated every 2 weeks until the haemoglobin level is below 20 ng/ml.^[45] Some studies showed potential for erythrocyte apheresis as a replacement for standard phlebotomy.^[46]

Therapeutic transfusion techniques such as therapeutic cytapheresis, plasmapheresis and phlebotomy are an integral part of ICU procedures, which require intensive monitoring and supervision. There are numerous conditions where this procedure is performed, but decisions should be individualised for optimum use of resources.

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Source of Support: Nil, Conflict of Interest: None declared

APPENDIX

Appendix 1: Disease conditions enlisted as Category 1-4

Category 1

Apheresis as primary therapy or first line adjunct to other therapy.

Examples:

- Thrombotic thrombocytopenic purpura
- Haemolytic uraemic syndrome-atypical
- Acute inflammatory demyelinating polyradiculopathy (Guillain- Barre syndrome)
- Anti-neutrophil cytoplasmic antibodies-associated rapidly progressive glomerulonephritis/vasculitis (Wegener granulomatosis)
- Antiglomerular basement membrane disease (Goodpasture syndrome)
- Chronic inflammatory demyelinating polyradiculopathy
- Paraproteinemic demyelinating polyneuropathies (IgG, IgM, IgA)
- Paediatric autoimmune neuropsychiatric disorders associated with Streptococcal infections (PANDAS)
- Renal transplantation, Ab-mediated rejection
- Myasthenia gravis
- Polycythaemia vera
- Sickle cell disease with acute stroke

Category 2

Apheresis is used as second-line therapy for some disease conditions.

Examples:

- ABO-incompatible haematopoietic stem cell transplantation
- ABO-incompatible solid organ transplantation (heart, kidney)
- Cold agglutinin autoimmune haemolytic anaemia
- Catastrophic antiphospholipid Ab syndrome
- Chronic focal encephalitis (Rasmussen encephalitis)
- Multiple sclerosis
- Phytanic acid storage disease (Refsum disease)
- Red blood cell alloimmunization in pregnancy
- Renal transplantation desensitization

Category 3

This includes diseases for which adequate role of apheresis is not established, and treatment with apheresis is individualized.

Examples:

ABO-incompatible liver transplantation, aplastic anaemia, warm agglutinin autoimmune haemolytic anaemia, hypertriglyceridemic pancreatitis, multiple myeloma, sepsis with multiorgan failure, thyroid storm

Category 4

This category includes diseases in which apheresis is ineffective or harmful.

Examples:

Dialysis dependent Goodpasture syndrome, scleroderma, amyloidosis, amyotrophic lateral sclerosis, polymyositis, psoriasis