Review Article

Therapeutic Apheresis

Deshpande A. S.[1], Sawant R.[2]

ABSTRACT

The advent of sophisticated blood cell separators has dramatically changed the application of apheresis with increasingly specific blood cells being targeted. This technology is now used in both the donor setting for the collection of blood product and in the therapeutic application for the treatment of many disease processes. Apheresis technology is also extensively used for collecting Peripheral blood stem cells in both allogenic and autologous Bone marrow transplant settings. We hope to see many centres in India carrying out Therapeutic apheresis procedures.

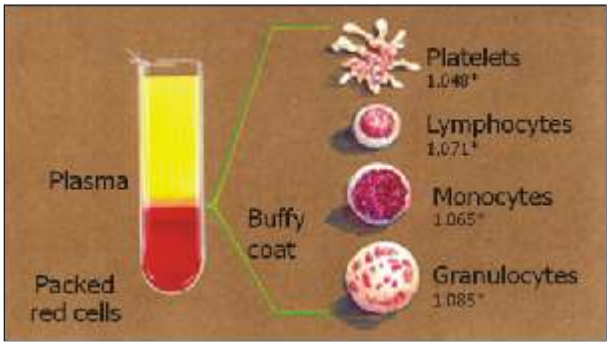
Introduction -

Apheresis has been derived from the Greek word 'Apo' meaning 'away' and 'heresis' meaning 'taking'. It is the process which involves removal of whole blood, separating and collecting any of the blood components extracorporeal while returning remaining blood components to the donor/patient. Hemapheresis is frequently used synonymous with apheresis[1]. The advent of sophisticated blood cell separators ***(Figure 1)*** has dramatically changed the application of apheresis with increasingly specific blood cells being targeted. This technology is now used in both the donor setting for the collection of blood product and in the therapeutic application for the treatment of many disease processes. The technique of apheresis has been developed and improved during second half of the 20th century. In early 1950's, a Harvard biochemist Dr. Edwin Cohn envisioned Cohn centrifuge designed to separate desired blood component i.e. donor plasma, during whole blood donation. In 1970s, the third generation of apheresis instruments came into market which allowed multiple different procedures to be done with more sophistication and precise control[2]. The most widely used apheresis equipment applies the similar principle to that of spinning the blood in a test tube and separation of blood components as per specific gravity[3]. ***(Figure 2)***

[1]Consultant Transfusion Medicine & Haematology,
[2]Consultant Transfusion Medicine
P. D. Hinduja National Hospital & M R C
Mahim, Mumbai-400 016

Address for Correspondence -
Dr. Anand Deshpande
E-mail : dr_adeshpande@yahoo.co.in

Fig. 1



*Average specific gravity of cell type shown

Fig. 2

Depending on the blood components removed the apheresis procedure is called as

Plasmapheresis - where plasma is removed,
Erythrocytapheresis - where RBCs are removed,
Leucocytapheresis - where WBCs are removed,
Thrombocytapheresis / Plateletapheresis - where platelets are removed

Therapeutic apheresis : When the apheresis procedure is carried out for therapeutic purpose it is known as therapeutic apheresis. Basis of therapeutic apheresis is to reduce the load of pathologic substance to levels that will allow clinical improvement. Other beneficial outcomes of therapeutic apheresis include alteration of the antigen to antibody ratio, modification of mediators of inflammation and clearance of immune complexes. In some conditions replacement with normal plasma is intended to supply an essential substance that is absent [4].

The American Society For Apheresis (ASFA) has developed guidelines on the use of therapeutic apheresis in clinical practice. The indications are divided in four categories where category I - being therapeutic apheresis as standard and acceptable first line therapy either as a primary standalone treatment or in conjunction with other modes of treatment. Category II - being 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 - Optimum role of apheresis is not established. Decision making should be individualized. Category IV Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful[5]. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.

Some common diseases for which TA is indicated in the ASFA Guidelines-2013. (Please refer to ASFA guidelines for details).

Disease Name	TA Modality	Disease Condition	Category	Grade
Acute inflammatory demyelinating Polyneuropathy (Gullain Barre Syndrome)	TPE	Post IVIG	I III	IA 2C
ANCA associated rapidly progressive Glomerulonephritis (Granulomatosis with polyangiitis; Wegener's Granulomatosis)	TPE TPE TPE	Dialysis dependence DAH Dialysis independence	I I III	IA IC 2C
Chronic inflammatory demyelinating Polyradiculoneuropathy	TPE		I	IB
Cryoglobulinemia	TPE	Symptomatic/severe	I	2A
Focal segmental glomerulosclerosis	TPE	Recurrent in transplanted Kidney	I	IB
Hemolytic uremic syndrome, atypical	TPE	Complement gene mutations	II	2C
Hyperviscosity in monoclonal Gammopathies	TPE	Symptomatic	I	IB
Myasthenia gravis	TPE TPE	Moderate-severe Pre-thymectomy	I I	IB IC
Renal transplantation, ABO incompatible	TPE	Desensitization, live donor	I	IB
Thrombotic thrombocytopenic Purpura	TPE		I	IA
Malaria	RBC exchange	severe	II	2B
Polycythemia vera and erythrocytosis	Erythrocy Tapheresis	Polycythemia Vera	I	IB
Sickle cell disease	RBC exchange RBC exchange	Acute stroke Acute chest Syndrome, severe	I II	IC IC

DAH : diffuse alveolar hemorrhage

Therapeutic plasma exchange -

Therapeutic plasma exchange is the most commonly performed therapeutic apheresis procedure. The first therapeutic plasmapheresis procedure was done by Schwab & Fahey in 1960[2]. It is also interesting to note the changing pattern of indications for Therapeutic plasma exchange between 1981 and 1997 as reported by Clarke et al. In 1981, five most common indications were Myasthenia Gravis (MG), Systemic Lupus Erythematosus (SLE), Thrombotic Thrombocytopenic Purpura (TTP). Gullian-Barre Syndrome (GBS) and Hyperviscosity. In 1997, they were TTP, MG, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Hyperviscosity and GBS in that order[6].

TPE involves removal of large volumes (usually 2 -5 liters) of plasma and replacement with an appropriate fluid substitute. In this procedure cellular blood components are separated from the plasma and returned with the replacement fluid, thus restoring intravascular volume.

The theoretical basis for TPE is to reduce the patient's load of a pathogenic substance that will allow improvement e.g.

- Specific antibody (Myaesthenia Gravis)
- Immunoglobulins (Hyperviscosity syndrome)
- Immune complexes (SLE)

Or replacement of deficient plasma factor as Von Willebrand factor cleaving protease (TTP). Other possible outcome of TPE could be non-specific Immunomodulatory effect like removal of inflammatory mediators[7].

When a TPE procedure is planned, a goal of therapy should be established. It could depend upon objective outcome or predetermined duration for the therapy, whichever is achieved first. The catheters used in the procedure are generally large lumen, double bore catheters placed in the subclavian, femoral or internal jugular vein. In TPE, exchange is usually limited to 1.5 plasma volumes or approximately 40-60 ml plasma exchanged per Kg body weight and standard being every 24-48 hours. The efficiency with which material is removed can be estimated by calculating patient's plasma volume and using the following graph. ***(Figure 3)***

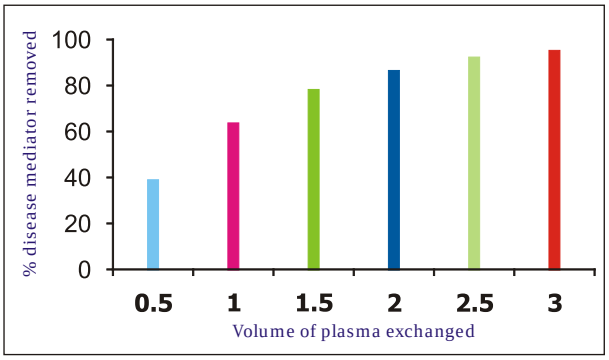


Fig. 3

Plasma removed during TPE should be discarded properly and cannot be used for manufacture of plasma derivatives. During 1.5 volume plasma exchange, 75-80 % of fibrinogen, C3 are removed which come back to normal within 3 4 days[8]. The coagulation proteins are less affected, 10% or more decrease occurs in platelet counts with 2-4 days needed to return to pre-exchange levels.

Anticoagulation -

During plasmapheresis, like in every extracorporeal procedure, coagulation in activated by circulating the blood outside the endogenous blood stream, harboring the risk that the system could be halted by thrombosis.[9] To avoid excessive activation of the coagulation system anticoagulants are required. Unfractionated heparin (UFH) and citrate are the most commonly used anticoagulants for apheresis techniques. Recently a report has been published where they have used low molecular weight (LMW) heparins (body weight adjusted) for anticoagulation in plasmapheresis therapies.[10]

Replacement fluids -

In therapeutic procedures, large volumes of patient's plasma are retained extracorporeal. The fluid must be replaced to maintain appropriate intravascular volume and oncotic pressure. Available solutions include crystalloids, albumin, plasma and HES. The advantages and disadvantages are as follows.[7] ***(Table 1)***

Table 1 : Comparison of replacement fluids

Replacement Solution	Advantages	Disadvantages
Crystalloids	low cost Hypoallergenic No viral risk	2 -3 volumes required Hypo-oncotic No coagulation factors No immunoglobulins
Albumin	Iso-oncotic No contaminating "inflammatory mediators" No viral risk	High cost No coagulation factors No Immunoglobulins
Hydroxyethyl starch	Moderate cost Iso-oncotic No contaminating "inflammatory mediators"	No coagulation factor Long term residual levels of HES Contraindicated with renal failure Possible coagulopathy
Plasma	Maintains normal level of: • Immunoglobulins • Complements • Antithrombin • Other proteins	Viral transmission risk Citrate load ABO incompatibility risk Allergic reactions Sensitization

Complications -

Therapeutic apheresis is accepted as a safe procedure, overall incidence of mostly reversible adverse effects being 4.75%[11]. In this same study, the percentage of adverse events with TPE (plasma replacement) is reported as 7.8% and TPE (without plasma replacement) as 3.55%.

Sarkar et al have reported Adverse Events with TPE as 1.23%[12]. It has been reported that mortality associated with TPE in cases of TTP and HUS is higher as these patients are acutely ill[13] ***(Table 2)***

Table 2 : Complications of TPE

Vascular Access	Procedural	Replacement Fluid
Hematoma Thrombosis/Sclerosis	Vasovagal episodes hypotension	Allergic Reactions Anaphylaxis
Arterial Perforation	Hypervolemia	Electrolyte imbalance
Sepsis at catheter site	Mechanical hemolysis	Blood borne infections
Infiltration	Air embolism	Hypoproteinemia
Other catheter related Complications	Citrate toxicity, sp. alkalosis, hypocalcemia	Coagulation factor depletion-bleeding
	Chills, rigors, nausea	Ig Depletion-bacterial Sepsis

Plasma has been primarily used as a replacement fluid for TTP and HUS cases. Cryosupernatant plasma has been used in these cases also.

Some of the clinically important conditions where TPE was carried out[5] in our setup

Myasthenia Gravis -

Myasthenia gravis (MG) is an autoimmune disease characterized by weakness and fatigability with repetitive physical activity, which usually improves with rest. Common presentation includes ptosis and diplopia with more severe cases having facial, bulbar, and limb muscle involvement. The disease is more prevalent in 20-40 year old women. The causative antibody is usually directed against the acetylcholine receptor (anti-AChR) on the postsynaptic surface of the motor end plate.

Current management/treatment : With modern treatment regimens the mortality from MG has greatly decreased from 30% to less than 5%. The four major treatment approaches include cholinesterase inhibitors, thymectomy (anti-MUSK antibody positive patients respond less often than anti-AChR positive patients), immunosuppression, and either TPE or IVIG

Rationale for therapeutic apheresis : TPE is used principally to remove circulating auto-antibodies. TPE is especially used 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 hours but may take a week. The benefits will likely subside after 2-4 weeks, if immunosuppressive therapies are not initiated to keep antibody levels low.

Acute Inflammatory Demyelinating Polyneuropathy (Guillain-Barre Syndrome) :

Acute Inflammatory Demyelinating Polyneuropathy (AIDP : Guillain-Barre Syndrome (GBS) is an acute progressive paralyzing illness affecting both motor and sensory peripheral nerves. Typically the disease begins with symmetrical muscle weakness and paresthesias that spread proximally. Weakness progresses over a period of 12 hours to 28 days before the nadir is reached and may involve respiratory and oropharyngeal muscles in more severe cases. Thus, mechanical ventilation is required for approximately 25% of patients. Autonomic dysfunction can cause variability in blood pressure and heart rate. Spontaneous recovery may occur, however up to 75% of patients develop long-term neurologic deficits. Mortality is estimated at 5%.

Current management/treatment : Since spontaneous recovery is anticipated in most patients, supportive care is the mainstay of treatment in ambulatory patients with AIDP. Severely affected patients may require intensive care, mechanical ventilation and assistance through the paralysis and necessary rehabilitation over several months to a year or more. Corticosteroids when used alone show minimal, if any, therapeutic effect. TPE was the first therapeutic modality to impact the disease favourably and several major randomized controlled clinical trials have confirmed its efficacy.

Rationale for therapeutic apheresis : The favoured etiology of AIDP is autoimmune-mediated damage to the peripheral nerve myelin. The results of several controlled trials comparing TPE to supportive care alone indicate TPE treatment can accelerate motor recovery, decrease time on the ventilator, and speed attainment of other clinical milestones.

Thrombotic Thrombocytopenic Purpura (TTP) :

TTP is a systemic thrombotic illness affecting mostly small vessels. When initially described, TTP was defined by a pentad of clinical findings: thrombocytopenia, MAHA (fragmented red cells on blood smear and elevated LDH), mental status changes, renal failure and fever. In current practice, however, the clinical findings of unexplained thrombocytopenia and MAHA are sufficient to diagnose TTP. More recently TTP was shown to be associated with a severe (<5%) deficiency of plasma ADAMTS13 (A disintegrin and metalloproteinase with a thrombospondin type I motif, member 13) enzyme activity, which is responsible for maintaining normal distribution of VWF multimers by cleaving ultra large multimers released from the endothelium.

Current management/treatment : TPE has decreased the overall mortality of idiopathic TTP from uniformly fatal to <10%. TPE should be initiated emergently once TTP is recognized. If TPE is not immediately available, plasma infusions may be given until TPE can be initiated. Both plasma and cryoprecipitate poor plasma (less VWF) have been used as replacement fluid for TPE, with similar results in patient outcome.

Rationale for therapeutic apheresis : TPE with plasma replacement has significantly improved patients' clinical outcomes. No other intervention has had as significant impact on the treatment of acquired idiopathic TTP. One hypothesis is that TPE removes the anti-ADAMTS 13 autoantibody, while restoring ADAMTS 13 protease activity. However, the clinical course does not always correlate with plasma ADAMTS 13 activity or ADAMTS 13 inhibitor and / or levels.

Hemolytic Uremic Syndrome, Atypical -

HUS is characterised by a triad of Coombs negative microangiopathic haemolytic anemia, thrombocytopenia and acute kidney injury. The typical form of HUS follows a diarrheal (D+) prodrome and is associated with O157 : H7 E.coli infections. Atypical form of HUS (a-HUS), formerly referred to as D-HUS, are non-infection related and account for about 10% of cases. New insights indicate that a-HUS is caused by uncontrolled activation of the alternative complement system. Complement-mediated thrombotic microangiopathy can manifest similar to HUS, but may have a chronic, progressive course, punctuated by catastrophic events such as retinal thrombosis, stroke, or acute kidney injury. Other reported complications of a-HUS include liver involvement, pancreatitis, diarrhea, pulmonary haemorrhage, and peripheral thrombosis.

Current management/treatment : Because treatment response is similar in patients with or without an identified genetic mutation, all patients diagnosed with a-HUS should be treated immediately. TPE has been first line treatment for a-HUS, although without prospective trials.

Rationale for therapeutic apheresis : The rationale is that it can effectively remove the autoantibody or mutated circulating complement regulators while replacing absent or defective complement regulators. Despite conflicting reports of the effectiveness, the European group as well as others recommend TPE over plasma infusion because of potential therapeutic benefits of TPE without risk of volume overload, development of hyperproteinemia, or refractoriness to regular plasma infusion in a disease with the high risk of rapid progression to ESRD.

Renal Transplantation, ABO incompatible -

Due to a relative shortage of compatible organs for transplantation, ABO incompatible (ABOi) living donors are being increasingly used. Major incompatibility refers to the presence of natural antibodies in the recipient against the donor's A or/and B blood group antigen. These antibodies may cause hyperacute / acute humoral rejection of the organ due to endothelial damage (A and B antigens are expressed on vascular endothelium).

Rationale for therapeutic apheresis : While there are no controlled clinical trials on using TPE to facilitate ABOi renal transplantation, an abundance of supportive evidence exists. Given that both hyperacute rejection, and acute AMR are definitive risks in ABOi renal transplants, TPE has been used as the key therapeutic modality to reduce anti-A or anti-B antibody titres in the per-transplant period with the goal of preventing rejection and facilitating graft survival.

Our experience : We have carried out 438 Therapeutic plasma exchange procedures in both adult and pediatric patients. First of these procedures was carried out in our institute in January 1992. In all the procedures ACD was used as the anticoagulant. In neurologic cases like GBS and MG crystalloid and colloids were used as replacement fluid while carrying out TPE whereas in TTP & Hemolytic-Uremic- syndrome (HUS) Fresh Frozen Plasma (FFP) was used as replacement fluid. Goal of therapy was significant clinical improvement in case of neurologic disorders and platelet count more than

hundred thousand in case of TTP and HUS. An average of five procedures per patient were required for clinical benefit. Clinical outcome was satisfactory.

Other important application of TA is - **Therapeutic red cell exchange -**

Removal of red cells for therapeutic purposes is referred to as Erythrocytapheresis, use of automated equipment to exchange patient red cells is also referred to as red cell exchange. It can be performed by manual exchange transfusion or with automated blood processing instrument[14]. According to ASFA, red cell exchange is indicated (category I & II) for treatment of severe manifestations of the protozoal infections-Plasmodium falciparum and Babesia microti and for the management of Sickle Cell Disease (SCD)[5]. In Malaria therapeutic red cell exchange is indicated when Parasitic index >30% without complications, Parasitic >10% with complications, Parasitic >10% with failure to respond to antimalarials after 12-24 hours, Parasitic >10% in elderly patients and patients with poor prognostic factors[15]. In malaria due to Plasmodium falciparum life threatening complications are in part related to the degree of parasitemia. Red cell exchange has been used for the removal of parasites from circulation of patient with high rate of parasitemia and renal dysfunction.

TREX in Malaria

Rationale for therapeutic apheresis

RBC exchange transfusion (with whole blood or red cell replacement) in severely ill patients with hyperparasitemia (i.e., 30%) appears to improve blood rheological properties, capillary perfusion and microcirculatory flow[16]. Whole blood exchange may also, theoretically, reduce pathogenic humoral mediators such as parasite and host toxins, hemolytic metabolites and cytokines. The CDC recommends exchange transfusion be strongly considered for persons with a parasite density >10% or if complications such as cerebral malaria, acute respiratory distress syndrome, or renal complications exist. The recommended goal is a parasite density below 1%. Quinidine administration should not be delayed and can be given concurrently. Automated apheresis instruments calculate the amount of RBCs required to achieve the desired post-procedure hematocrit, fraction of red cells remaining and, by inference, the estimated final parasite load. A single two-volume RBC exchange can reduce the fraction of remaining patient red cells to roughly 10-15% of the original[17]. The risks include circulatory overload, transfusion reactions, blood-borne infection (especially in developing countries), hypocalcemia, RBC allosensitization and possible need for central venous access. Usually one or two treatments are required.

Replacement fluid : RBCs (consider leukoreduced), fresh frozen plasma

Duration and discontinuation/number of procedure: Treatment is discontinued after achieving significant clinical improvement and/or <1% residual parasitemia.

TREX in Sickle Cell Disease (SCD)

RBC exchange transfusion is recommended for treatment of several severe complications of SCD including stroke, severe acute lung syndrome, and acute multi-organ failure syndrome. Complications, for which exchange transfusion has been recommended but remains more controversial, include priapism, retinal infarction, and hepatopathy. It has also been used in complicated pregnancies and before surgery to reduce or prevent sickle-related complications. In most cases, the goal is to keep the percentage of HbS <30% and the total hematocrit 30% to suppress HbS production.

Advantages of exchange transfusion include improved control of blood volume and viscosity during transfusion and a decreased risk of developing transfusion-related hemochromatosis.

Rationale for therapeutic apheresis

In severe anemia, simple transfusion is the best transfusion method to improve oxygen-carrying capacity of blood by increasing RBC mass. However, in acute ischemic stroke, ACS, acute hepatic crisis, or acute life-or organ-threatening

complications, RBC exchange is preferred as the HbS concentration is reduced rapidly by replacing RBCs containing HbS with normal RBCs without causing hyperviscosity or volume overload (18). Additionally, beneficial effects on blood viscosity, elasticity, and relaxation time, and reduction of adhesion molecule level like sVCAM-1 has been documented after RBC exchange.

Frequency : One procedure to achieve target HbS level

Replacement fluid: HbS negative leukoreduced RBCs and, if available, antigen-matched for at least C, E, and K.

Our experience : We have carried out 08 TREX procedures, in 2 paediatric patients with malaria, 2 with sickle cell disease (SCD) & one adult patient with SCD. The first procedure was carried out in January 2001.The procedure time ranged from 52 to 90 minutes and 97 to 117 minutes in adult patient. Group specific cross-match compatible packed red blood cells were used as replacement fluid. In cases of malaria the infestation rate dropped from 75 % to 18 % and 67% to 08 % after the TREX. In the adult patient with SCD, Hb S levels dropped to <20% after each procedure and in pediatric patients HbS levels dropped five fold in both cases post procedure. All the above patients were clinically benefitted by the TREX procedures and these procedures were tolerated well even by paediatric patients.

Future : Apart from two main indications of Therapeutic apheresis other applications include Immunoadsorption apheresis in which an affinity column is used along with the apheresis cell separator. This has been used for specific extraction of low density lipoprotein and other materials including immune complexes and ABO issoagglutinins. Apheresis has also been used for photopheresis mainly applicable in cutaneous T cell lymphoma. Apheresis technology is also extensively used for collecting Peripheral blood stem cells in both allogenic and autologous Bone marrow transplant settings. We hope to see many centres in India carrying out Therapeutic apheresis procedures.

References :

1. Gilcher R. Rossi's Principles of Transfusion Medicine. 4th ed. Simon T, Synder E, Stowell C, Strauss R, Solheim B, Petrides M, editor. West Sussex: Blackwell Publishing Ltd; 2009, p. 617-628.
2. McLeod BC. Therapeutic apheresis: history, clinical application, and lingering uncertainties. Transfusion 2010; 50 : 1413-1426.
3. Culotta E. Modern Blood Banking and Transfusion Practices. 3rd ed. Harmening DM, editor. New Delhi : Jaypee Brothers; 1998, p. 334-350.
4. Brecher M, editor. Technical Manual. 15th ed. Maryland: Blackwell Publishing Ltd; 2005, p. 139-161.
5. Schwartz J, Winters J, Padmanabhan A, Balogun R, Delaney M, Linenberger M, et al. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis : the sixth special issue. J Clin Apheresis 2013; 28 : 145-284.
6. Clark WF, Rock G, Buskard N, Shumak K, LeBlond P, Anderson D et al. Therapeutic Plasma Exchange: An Update from the Canadian Apheresis Group. Ann Itrn Me 1999; 131 : 453-462.
7. Mollison PL, editor. Blood Transfusion in Clinical Medicine. 9th ed.: Blackwell Scientific Publications; 1993, p. 39-40.
8. Orlin J, Berkman E. Partial plasma exchange using albumin replacement : removal and recovery of normal plasma constituents. Blood 1980; 56 : 1055-1059.
9. Heimark RL, Kurachi K, Fujikawa K, Davie E. Surface activation of blood coagulation, fibrinolysis and kinin formation. Nature 1980; 286 : 456-460.
10. Schinzel H, Berghoff K, Beuermann I, Sauer O, Von Mach M, Weilemann L. Anticoagulation with low-molecular-weight heparin (dalteparin) in plasmapheresis therapy : initial experience. Transfusion 2006; 46 : 624-629.
11. McLeod BC, Sniecinski I, Ciavarella D, Owen H, Price T, Randels M et al. Frequency of immediate adverse effects associated with therapeutic apheresis. Transfusion 1999; 39 : 282-289.
12. Philip J, Sarkar R, Pathak A. Adverse events associated with apheresis procedures : Incidence and relative frequency. Asian J Transfusion Sci 2013; 7 : 37-41.

13. Rizvi MA, Vesely S, George J, Chandler L, Duvall D, Smith J et al. Complications of plasma exchange in 71 consecutive patients treated for clinically suspected thrombotic thrombocytopenic purpura-hemolytic-uremic syndrome. Transfusion 2000; 40 : 896-901.
14. Kernoff LM, Botha M, Jacobs P. Exchange transfusion in sickle cell disease using a continuous-flow blood cell separator. Transfusion 1977; 17 : 269-271.
15. Severe falciparum malaria. World Health Organization, Communicable Diseases Cluster. Trans R Soc Trop Med Hyg 2000; 94 : 1-90.
16. Harris P, Price S, Senthuran S, Cochupanachimootil J, Norton R. Automated erythrocytapheresis for severe falciparum malaria. Intern Med J 2011; 41 : 60-63.
17. Deshpande A, Kalgutkar S, Udani S. Red cell exchange using cell separator (therapeutic erythrocytapheresis) in two children with acute severe malaria. J Assoc Physicians India 2003; 51 : 925-926.
18. Danielson CFM. The Role of Red Blood Cell Exchange Transfusion in the Treatment and Prevention of Complications of Sickle Cell Disease. Ther Apher Dial 2002; 6 : 24-31.