



World Scientific News

WSN 50 (2016) 250-265

EISSN 2392-2192

Use of apheresis in the treatment of Haematological conditions

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ABSTRACT

Apheresis is a medical technology in which the blood of an individual is passed through an apparatus that separates out one particular blood component and returns the remainder into circulation. In this review, five types of apheresis procedures were studied, which were Erythrocytapheresis, Leucocytapheresis, Plasmapheresis, Photopheresis and Plateletpheresis. The aim of this review was to present the efficacy, safety and use of apheresis procedures in the treatment of diseases associated with abnormal blood components. Erythrocytapheresis used for blood donations and treatment of different diseases such as Polycythemia vera and severe cases of Sickle Cell Anaemia. Leukapheresis is used for separation of white blood cells and also in disease conditions such as Ulcerative colitis. Plasmapheresis is used for separating plasma from whole blood for use in the manufacture of various medications. It is also performed to remove life-threatening antibodies in the blood like in cases of Thrombotic Thrombocytopenic Purpura and Multiple Sclerosis. Photopheresis is mainly used as an immunosuppression therapy in cases of acute and chronic graft-versus-host-disease, cutaneous T-cell Lymphoma and cutaneous Lupus Erythematosus. Plateletpheresis is used to remove platelets from the body of patients or donors for future use. Apheresis enhances the correct use of blood and blood components. It can be a valuable and safe initial treatment for a number of ailments resulting from blood component abnormalities and patients should be brought to light about these procedures before other treatment methods are introduced.

Keywords: Apheresis; Plasmapheresis; Erythrocytapheresis; Plateletpheresis

1. INTRODUCTION

Numerous disease states, including those often encountered in the peri-operative setting, are mediated by excessive, deficient, or abnormal blood components. Appropriate blood usage involves giving the right blood quantity and component when needed. (Sloan *et al.*, 2013). The WHO handbook on the clinical use of blood (2001) defines appropriate use of blood as “the transfusion of safe blood products only to treat a condition leading to significant morbidity or mortality that cannot be prevented or managed effectively by other means .” Blood collection, testing, processing and transfusion are an essential part of the national Health System. Appropriate and rational use of blood products maximizes the effects of transfusion and contributes to avoiding unwanted complications. Moreover early detection and proper care of unavoidable side-effects can minimize patient’s morbidity and mortality. (Koch *et. al.* 2005).

Apheresis is a medical technology in which the blood of a donor or patient is passed through an apparatus that separates out one particular constituent and returns the remainder to the circulation. (Szczepiorkowski *et al.*, 2010). Therapeutic apheresis (TA) provides the means for the removal of blood components that are abnormal or that circulate in excessive amounts and have a defined pathogenetic role, or are thought to have one. Multiple disease processes have been treated with TA at one time or another, but scientific assessment of the therapeutic effects of the procedure has lagged behind application of the technology. (Alvara and Eleftherios, 1997). In developing countries, inappropriate blood usage and poor or lack of apheretic methods have led to wastage of blood products and transfusion complications, some of which have resulted in the sudden death of patients, which could have been avoided. Studies suggest that blood products are often overprescribed in both developed and developing countries. (WHO, 2015).

Evidence also points to clinicians being relatively unaware of the appropriate uses of red cells and associated risks. For instance, a joint study in 2007 reported that some interviewed clinicians found it difficult to state the appropriate haemoglobin (Hb) levels to justify transfusion. Also, all doctors interviewed for that study indicated that they would typically prescribe a minimum of two units of red cells. This is despite national guidelines indicating that red cells should be dispensed one unit at a time, so that the patient’s response can be assessed. (Eureka Strategic Report, 2007). The goal of this review is to present the efficacy, safety, and applicability of therapeutic apheresis in patients with illnesses associated with abnormalities of blood component

1. 1. Apheresis

Apheresis is a medical technology in which the blood of a donor or patient is passed through an apparatus that separates out one particular constituent and returns the remainder to the circulation. It is thus an extracorporeal therapy. (Szczepiorkowski *et al.*, 2010). Depending on the substance that is being removed, different processes are employed in apheresis. If separation by density is required, centrifugation is the most common method. Other methods involve absorption onto beads coated with an absorbent material and filtration. (Koch *et al.*, 2005). Blood taken from a healthy donor can be separated into its component parts during blood donation, where the needed component is collected and the "unused" components are returned to the donor. Fluid replacement is usually not needed in this type of collection. There are large categories of component collections:

Plasmapheresis - blood plasma. Plasmapheresis is useful in collecting fresh frozen plasma (FFP) of a particular ABO group. Commercial uses aside from FFP for this procedure include immunoglobulin products, plasma derivatives, and collection of rare white blood cell and red blood cell antibodies.

Erythrocytapheresis - red blood cells. Erythrocytapheresis is the separation of erythrocytes from whole blood. It is most commonly accomplished using the method of centrifugal sedimentation. This process is used for red blood cell diseases such as sickle cell crises or severe malaria. The automated red blood cell collection procedure for donating erythrocytes is referred to as 'Double Reds' or 'Double Red Cell Apheresis'.

Plateletpheresis (thrombapheresis, thrombocytapheresis) - blood platelets. Plateletpheresis is the collection of platelets by apheresis while returning the red blood cells, white blood cells, and component plasma. The yield is normally the equivalent of between six and ten random platelet concentrates. Quality control demands the platelets from apheresis be equal to or greater than 3.0×10^{11} in number and have a pH of equal to or greater than 6.2 in 90% of the products tested and must be used within five days.

Leukapheresis - leukocytes (white blood cells). Leukapheresis is the removal of polymorphonucleotides (PMNs, granulocytes), basophils, eosinophils for transfusion into patients whose PMNs are ineffective or where traditional therapy has failed. There is limited data to suggest the benefit of granulocyte infusion. The complications of this procedure are the difficulty in collection and short shelf life (24 hours at 20 to 24 °C). Since the "buffy coat" layer sits directly atop the red blood cell layer, a sedimenting agent is employed to improve yield while minimizing red blood cell collection. Quality control demands the resultant concentrate be 1.0×10^{10} granulocytes in 75% of the units tested and that the product be irradiated to avoid graft-versus-host disease (inactivate lymphocytes). Irradiation does not affect PMN function. Since there is usually a small amount of red blood cell collected, ABO compatibility should be employed when feasible.

Stem cell harvesting - circulating bone marrow cells are harvested to use in bone marrow transplantation. (Koch *et al.*, 2005).

1. 2. Therapeutic Apheresis

Therapeutic apheresis describes blood processing techniques that selectively remove pathogenic substances or abnormal cells from the bloodstream while simultaneously replacing the needed blood components. (Grima, 2000). The following are different types of therapeutic apheresis ordered based on a patient's specific condition:

- plasmapheresis (or plasma exchange)
- white blood cell depletion
- Photopheresis (lymphocytes)
- red blood cell exchange
- platelet depletion

Similar to the apheresis blood donation process, an automated machine separates blood components, isolates the targeted substance and returns the remaining components to the patient. (Szczepiorkowski *et al.*, 2010).

a. Indications for Therapeutic Apheresis

Therapeutic apheresis (TA) are helpful for patients facing a variety of medical conditions. It can be used to treat patients with blood disorders, kidney problems, metabolic diseases, and neurologic disorders. It is also indicated in patients with autoimmune diseases. In autoimmune conditions, the body's immune system mistakenly attacks its own tissues. (McMaster and Shann, 2003). An anticoagulant is given during the procedure, and some patients may feel tingling around the lips, or a pins and needles feeling in the fingers or toes. It is important to tell the nurse if this happens. Some patients may feel dizzy, lightheaded or cold during the procedure. Some patients feel tired after a procedure, but most are able to continue routine daily activities. The duration of the entire process depends on the type of procedure your doctor has ordered. Usually the procedure takes between 2-3 hours. (Szczepiorowski *et al.*, 2010). Some haematological and oncological indications for therapeutic apheresis are listed in the table below:

Table 1. Indications for therapeutic apheresis in hematology/oncology

Disease	Procedure
Thrombotic thrombocytopenic purpura (TTP)m	TPE
Post-Transfusion Purpura	TPE
HIV-related Hyperviscosity, TTP	TPE
Eaton Lambert Myasthenic Syndrome	TPE
Extreme Leukocytosis/ AML or CML	Leukapheresis
Extreme Thrombocytosis/ CMPD	Plateletpheresis
Cutaneous T cell Lymphoma	Photopheresis
Sickle Cell Disease	Red Cell Exchange
Haemolytic-uremic Syndrome	TPE
Myeloma and Paraproteinemias	TPE
Paraproteinemic Peripheral Neuropathy	TPE
Receipt of ABO-incompatible BMT	TPE
Coagulation Factor Inhibitors	TPE
Immune Thrombocytopenic Purpura	Protein A column
Immune Thrombocytopenic Purpura	TPE
Platelet Refractoriness	Protein A column

Platelet Refractoriness	TPE
Aplastic Anaemia/ Pure Red Cell Aplasia	TPE
Autoimmune Haemolytic Anaemia	TPE
Haemolytic Disease of the Newborn	TPE
Non-haematologic Cancer	Protein A column
Graft-versus-Host-Disease	Photopheresis
Paraneoplastic syndromes with neurologic manifestations	TPE

Abbreviations: AML = acute myelogenous leukemia; CML = chronic myelogenous leukemia; CMPD = chronic myeloproliferative disease; BMT = bone marrow transplant; TPE = therapeutic plasma exchange. (Alvara and Eleftherios, 1997).

b. Fluid replacement during apheresis

When an apheresis system is used for therapy, the system is removing relatively small amounts of fluid (not more than 10.5 ml/kg body weight). That fluid must be replaced to maintain intravascular volume, red cell mass or hemostasis. (Smith *et al.*, 2003). Fluids such as albumin, crystalloid or blood components are used. If a crystalloid like normal saline (NS) is used, the infusion amount should be triple what is removed as the 3:1 ratio of normal saline for plasma is needed to keep up oncotic pressure. Some institutions use normal serum albumin, but it is costly and can be difficult to find. Some advocate using fresh frozen plasma (FFP) or a similar blood product, but there are dangers including citrate toxicity (from the anticoagulant), ABO incompatibility, infection, and cellular antigens. (Grima, 2000).

1. 3. Erythrocytapheresis

Erythrocytapheresis is an apheresis procedure by which erythrocytes (red blood cells) are separated from whole blood. It is an extracorporeal blood separation method whereby whole blood is extracted from a donor or patient, the red blood cells are separated, and the remaining blood is returned to circulation. (Ullrich *et al.*, 2007). For the separation of erythrocytes, whole blood is passed through an apparatus that isolates the red blood cells from the remaining components. In erythrocytapheresis, centrifugation is the most commonly used red blood cell fractionation method. This is because the hematocrit, or the percentage of blood volume taken up by red blood cells, is present in the highest percentage of all blood cell components in the solid portion of blood. Therefore, since erythrocytes have the highest specific weight in comparison to other solids in blood, they can easily be separated using centrifugation. Whole blood is spun down in a spinning bowl centrifuge and the bottom layer, concentrated with erythrocytes, sediments to the bottom. These are separated and the rest of the blood can be re-transfused. (Diehl and Frey, 1998). Erythrocytapheresis can also be used for blood donations. The procedure is commonly done using automated red blood cell collection which involves the removal of two units of red blood cells. This includes either two standard units of red blood cells or one unit plus of red blood cells and another of either plasma or platelets. The advantage to the donor is the use of smaller needles and saline

compensation, as well as more convenient donating schedules (the no-donation period following apheresis is twice as long as that for a single unit). The advantage to the blood bankers is the on-line separation into standardized RBC masses with the subsequent reduction in testing, data entry and staffing. This process is commonly referred to as 'Double Reds' or 'Double Red Cell Apheresis'. (Kim *et al.*, 1994).

a. Clinical application of therapeutic erythrocytapheresis (TEA)

Therapeutic erythrocytapheresis (TEA) has been used in different diseases such as polycythemia vera (PV), secondary erythrocytosis or hemochromatosis as a process of the less cumbersome but more expensive phlebotomy. Therapeutic erythrocytapheresis is preferred in emergency conditions such as thrombocytosis or in conditions such as porphyria cutanea tarda (PCT) or erythropoietic porphyria when plasma exchange (PEX) is often combined with TEA to reduce extracellular levels of uroporphyrin which contribute to plasma hyperviscosity. TEA is often combined with drug therapy used to mobilize and reduce iron stores in hemochromatosis. Benefits from this combination may be more long lasting than expected. Nonetheless for TEA, there is no standard protocol and, clinical experience with this therapy remains highly anecdotal. Therapeutic red cell-exchange (TREC) has been used with much interest over the years, starting with the management of hemolytic disease of the newborn and later used to correct severe anemia in thalassemia patients thereby preventing iron overload.

b. Erythrocytapheresis and Sickle Cell Anaemia

In a study on the clinical applications of therapeutic erythrocytapheresis, Valbonesi and Bruni (2000) performed exchange transfusions utilizing the technique of automated erythrocytapheresis. In an attempt to determine guidelines for the use of erythrocytapheresis, they studied the use of this procedure in three distinct clinical situations in nine patients with sickle cell disease. Patients with dangerous complications of sickle cell disease such as acute respiratory distress and priapism responded well to erythrocytapheresis, showing marked improvement within 24-48 hours. Patients with prolonged painful vasoocclusive crises showed only variable improvement after erythrocytapheresis therapy, insufficient to justify exposing the patient to the risks of the procedure. Patients treated to decrease the frequency of painful crises demonstrated no prolongation in symptom-free intervals between crises. They therefore reached a conclusion that erythrocytapheresis has its main value in the management of acute, dangerous complications of sickle cell disease.

1. 4. Leukapheresis

Leukapheresis is a laboratory procedure in which white blood cells are separated from a sample of blood. It is a specific type of apheresis. Leukapheresis may be performed to decrease a very high white blood cell count, to obtain autologous (the patient's own) blood cells for later transplant back into the patient, or to obtain cells for research purposes. In the case of hematological malignancies such as acute leukemias, white blood cell counts may be high enough to cause hemostasis and "sludging" in the capillaries. This can affect retinal vasculature leading to vision changes, pulmonary vasculature leading to shortness of breath from decreased efficiency in oxygen exchange, as well as other organ systems such as the brain which would become clinically apparent with neurological deterioration of a patient from cerebrovascular compromise. (Loftus, 2004).

Leukapheresis may also be performed to obtain the patient's own blood cells for later transplant. White blood cells may be removed to protect them from damage before high-dose chemotherapy, then transfused back into the patient, in the treatment of advanced breast cancer. Another novel use of cells obtained through leukapheresis is to stimulate a patient's immune system to target prostate cancer cells. (Oxelmark, 2007). Alternatively, only granulocytes, macrophages and monocytes can be removed, leaving the lymphocyte count largely unchanged. This is used as a treatment for autoimmune diseases such as ulcerative colitis and rheumatoid arthritis, where these cells play an active part in the inflammation process. (Schwella *et al.*, 2003).

a. Leukocyte Apheresis in the Management of Ulcerative Colitis

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) with a relapsing and remitting course. It affects many individuals worldwide with deleterious effects on the quality of life. Many medications, including anti-inflammatory drugs, immunosuppressive drugs like corticosteroids, and biological agents, are used to induce and maintain remission without curing the disease and with many side effects. (Present, 2000). The pathogenesis of UC is ill-understood, and seems to result from a complex interplay between susceptibility genes, environmental factors, and the immune system. Many inflammatory cytokines, such as tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , IL-6, IL-8, and others are involved. The sources of these cytokines are the activated peripheral blood granulocytes which get mobilized first, then infiltrate the colonic mucosa and interact with lymphocytes to orchestrate the inflammatory response and initiate disease activity and/or relapse. Therefore, removal of these activated granulocytes by extracorporeal cytopheresis systems, *i.e.*, leukocytapheresis and granulocytapheresis may be a logical therapeutic maneuver, (Papadakis, 2000).

Cytapheresis is an extracorporeal removal of specific cells from the blood using special filters or columns. Due to its ability to remove white blood cells, cytopheresis has been used as a therapeutic modality in many diseases, such as leukaemia, in which sensitized white cells have a pathogenic effect. (Tibble, 2000). Leukocytapheresis and granulocytapheresis were mainly used in Japan, but over the last decade, they have also attracted much attention in Europe and North America. (Tibble, 2000).

1. 5. Plasmapheresis

It is an extracorporeal therapy (a medical procedure performed outside the body). The method is also used during plasma donation: blood is removed from the body, blood cells and plasma are separated, the blood cells are returned while the plasma is collected and frozen to preserve it for eventual use in the manufacture of a variety of medications. (Yazdi *et al.*, 2012). The procedure is used to treat a variety of disorders, including those of the immune system, such as Goodpasture's syndrome, myasthenia gravis, Guillain-Barré syndrome and lupus. (Bacocchi *et al.*, 2000).

The efficacy of plasmapheresis lies in the elimination of pathologic intravascular components (*e.g.* immunoglobulins, immune complexes, and hormones) or the replacement of abnormal or deficient proteins. Thus, plasmapheresis can only logically be used when the pathologic cause of disease seems amenable to these mechanisms. In fact, the use of plasmapheresis for treatment of autoimmune diseases such as lupus nephritis or rheumatoid arthritis has proven to be of no benefit, likely because the immune insult is localized in

peripheral tissues outside of the intravascular space. Over 100 disease states have been successfully managed with plasmapheresis using guidelines established by the American Society for Apheresis. (Sloan *et al.*, 2013). Plasma exchange is performed to remove antibodies in the blood that threaten the body's healthy tissues. Another example of a disease where plasma exchange is beneficial is thrombotic thrombocytopenic purpura (TTP). For this type of blood disorder, therapeutic apheresis (plasma exchange) removes the offending agent and is replaced with donated plasma. (Szczepiorkowski *et al.*, 2010).

a. Plasmapheresis and Multiple Sclerosis

Khatri *et al.*, (1985) studied 54 patients with chronic-progressive multiple sclerosis (MS) who, in addition to receiving oral low-dose cyclophosphamide and prednisone, were randomized to receive either true plasmapheresis or sham plasmapheresis for 20 weeks. This study showed that patients in the true-PP arm were more likely to improve (14/26 at 5 months and 11/26 at 12 months) than were those in the sham-PP arm (8/29 at 5 months and 5/29 at 11 months). A recent report by Rodriguez *et al.* (1993) suggests that in certain individuals with acute fulminant multiple sclerosis, plasmapheresis may be of benefit, without the use of concomitant immunosuppressive therapy. The exact role of plasmapheresis in the care and treatment of patients with multiple sclerosis remains unclear. While selected Multiple Sclerosis patients may benefit from this therapy, they are also likely to be on concomitant immunosuppressant drug treatments, so that the true effect of plasmapheresis is difficult to determine. Therapeutic plasmapheresis may have a role in selected cases of fulminant Multiple Sclerosis, and a double-blind NIH-funded trial is currently under way. Based on these studies, plasmapheresis for the treatment of Multiple Sclerosis must be considered promising, based on some Class I evidence.

b. Plasmapheresis in Autoimmune Disorders

An important use of plasmapheresis is in the therapy of autoimmune disorders, where the rapid removal of disease-causing autoantibodies from the circulation is required in addition to other medical therapy. It is important to note that plasma exchange therapy in and of itself is useful to temper the disease process, while simultaneous medical and immunosuppressive therapy is required for long-term management. Plasma exchange offers the quickest short-term answer to removing harmful autoantibodies; however, the production of autoantibodies by the immune system must also be suppressed, usually by the use of medications such as prednisone, cyclophosphamide, cyclosporine, mycophenolate mofetil, rituximab, or a mixture of these.

c. Plasmapheresis and Solid Organ Transplantation

Humoral rejection of transplanted organs remains a major source of postoperative morbidity and mortality and is frequently associated with antibodies directed against ABO blood group antigens or human leukocyte antigen. Nonetheless, the significant shortage of organs available for transplantation has resulted in increasing use of ABO-incompatible donor organs. According to the Organ Procurement and Transplantation Network, 0.5 percent of all solid-organ transplants occurred in the setting of ABO incompatibility between January 2009 and May 2012. Transplantation of ABO-incompatible organs is associated with an increased risk of hyperacute rejection because of the presence of preformed recipient anti-A or anti-B

antibodies. In addition to immunosuppressive therapy, peri-operative plasmapheresis to remove offending anti-ABO antibodies has been shown to improve clinical outcomes after renal and cardiac transplantation, although definitive randomized controlled trials have not been performed. Results after ABO-incompatible liver transplantation have been varied as a result of the emergent nature of these procedures and differences in immunosuppressive regimens. (Rydberg, 2001).

Perioperative plasmapheresis and immunosuppression decrease the amount of circulating antibody and have been shown to significantly decrease acute rejection in seropositive patients undergoing renal transplantation. Promising results have also been suggested for seropositive patients undergoing lung transplantation. (Sloan *et al*, 2013).

d. Plasmapheresis and Myasthenia Gravis

Myasthenia gravis is an autoimmune disease characterized by bulbar weakness, respiratory failure, and marked sensitivity to neuromuscular blocking agents. Over 80 percent of patients with myasthenia gravis have identifiable antiacetylcholine receptor antibodies. The onset of action of common immunosuppressant agents is delayed, limiting their effectiveness in the acute treatment of myasthenic crisis. Plasmapheresis rapidly reverses weakness associated with myasthenic crisis by eliminating these autoantibodies and is considered by the American Society for Apheresis to be first-line therapy in conjunction with corticosteroids and respiratory support for both seropositive and seronegative myasthenic patients. Plasmapheresis improves early outcomes (1 week) in patients with moderate to severe myasthenia, but this beneficial effect often disappears by day 15. Therefore, the utility of plasmapheresis is limited to the acute treatment of severe myasthenic weakness, and concomitant medical therapy should be instituted. (Welsby *et al.*, 2010).

e. Complications of plasmapheresis therapy

There is a risk of infection from the intravenous manipulations, but this has proven to be minimal. Probably the greatest risk to patients are the procedures necessary to ensure adequate venous access, in particular the placement of the central venous catheters, which are associated with a low but definite risk of pneumothorax, thrombosis, and infection. Deaths from plasmapheresis have been reported, but have generally been related to preexisting illness. (Rodnitzky and Goeken, 1999). Aside from placing the catheter, the procedure itself has complications. When patient blood is outside of the body passing through the plasmapheresis machine, the blood has a tendency to clot. To reduce this tendency, is one common protocol, sodium citrate is infused while the blood is running through the circuit. Citrate binds to calcium in the blood, calcium being essential for blood to clot. Citrate is very effective in preventing blood from clotting; however, its use can lead to life-threateningly low calcium levels. This can be detected using the Chvostek's sign or Trousseau's sign. To prevent this complication, calcium is infused intravenously while the patient is undergoing the plasmapheresis; in addition, calcium supplementation by mouth may also be given. (Newsom-Davis and Murray, 2011).

Other complications include:

- Hypotension
- Potential exposure to blood products, with risk of transfusion reactions or transfusion transmitted diseases

- Suppression of the patient's immune system
- Bleeding or hematoma from needle placement. (Rodnitzky and Goeken, 1999).

f. Extracorporeal Photopheresis

Extracorporeal photopheresis (ecp) is a cell-based immunomodulatory therapy that involves collecting leukocytes from peripheral blood. These cells are exposed to a photosensitizing agent, 8-methoxypsoralen, and are then treated with ultraviolet (uv) radiation, after which they are re-infused. This procedure, which results in cross-linking of pyrimidine bases in DNA, produces massive apoptosis of the treated cells. The procedure was developed in 1987 by Dr. Richard Edelson for use in treating cutaneous T-cell lymphoma. More than 500,000 extracorporeal photopheresis treatments have been performed worldwide. The incidence of reported side effects is extremely low at less than 0.003%. Significantly, the incidence of infections related to the procedure in this patient population is very, very low. Many of the complications are related to vascular access. It would be preferable to use peripheral veins, but patients with chronic graft-versus-host-disease frequently have poor veins, and alternative access must therefore be used. When central venous catheters are used, complications such as infection, clotting in the catheters, deep venous thrombosis, and vessel stenosis can occur. (Marques and Tuncer, 2006).

g. Photopheresis in Graft Versus Host Disease (GVHD)

Acute GVHD

From case reports and small uncontrolled series, extracorporeal photopheresis in acute GVHD can be seen to have been used almost exclusively in patients in whom conventional immunosuppressive therapy failed. A phase II study by Greinix, Knobler and Worel (2006) involving 38 patients reported complete remission in 86%, 55%, and 30% of patients with grades 2, 3, and 4 acute GVHD respectively. The best results were obtained in 82%, 61%, and 61% of patients with skin, liver, and gut acute GVHD respectively. The experience in children is much more limited, but suggests that similar results can be obtained (Kanold, Merlin and Halle, 2007).

Chronic GVHD

The experience with extracorporeal photopheresis in chronic GVHD is more extensive, but also consists mainly of case reports and small uncontrolled series (Suchin *et al.*, 1999). The protocols are variable, but usually consist of 2 or 3 treatments every 1 or 2 weeks initially (Pavletic *et al.*, 2006). Once the regimen starts to show a benefit, the extracorporeal photopheresis can be tapered to 2 treatments every 3-4 weeks. However, once a treatment is proving to be efficacious, then the usual practice is to start by reducing immunosuppressive agents, especially steroids. If there is no response in 3 or 4 months, then the procedure should be stopped. In sclerodermatous skin changes, the improvement occurs very gradually, and 6–12 months of treatment may be required before tapering is used, (Greinix *et al.*, 2006). Foss *et al.*, (2005) reported on a prospective study of extracorporeal photopheresis in extensive steroid-resistant chronic GVHD that enrolled 25 patients. The extracorporeal photopheresis was administered for 2 consecutive days every 2 weeks in 17 patients and weekly in 8 patients until the best response or stable disease was obtained. The median duration of therapy was 9

months. Improvement in skin or visceral chronic GVHD (or both) was reported in 71% of the overall cohort and in 61% of high-risk patients. Flowers *et al.*, (2008) reported on a multicentre prospective phase II randomized study of extracorporeal photopheresis for the treatment of chronic GVHD. It was conducted in 23 transplant centres in North and South America, Europe, and Australia. The 95 enrolled patients were randomized either to extracorporeal photopheresis plus standard therapy or to standard therapy alone. The patients randomized to extracorporeal photopheresis received 12 weeks of extracorporeal photopheresis treatments. The schedule was 3 treatments during week 1 and then 2 treatments on consecutive days each week during weeks 2 through 12. Cutaneous disease was assessed by a blinded trained observer using the Total Skin Score, which grades 10 body regions on a scale from 0 to 5 (0 = normal; 1 = discoloured or alopecia; 2 = lichenoid plaques thickened, able to move and pinch; 4 = hidebound, unable to move or pinch; 5 = grades 3 or 4, with overlying erythema; maximum score: 50). Quality of life was measured using the median Targeted Symptom Assessment, which patients were asked to complete at baseline and at variable periods thereafter. This assessment revealed a significant improvement in favour of extracorporeal photopheresis. The conclusion reached was that extracorporeal photopheresis had a steroid-sparing effect in the treatment of chronic GVHD.

a. Photopheresis in Cutaneous T-cell Lymphoma (CTCL)

Crovetti *et al.*, (2000) recounted their five-year experience with extra corporal photopheresis in the treatment of cutaneous T-cell lymphoma. 33 CTCL patients were recruited for ECP since June 1994, using two different regimens: two procedures on two consecutive days at four-week intervals for six months, or at two-week intervals for three months with progressive tapering in the second three-month period for the more severe forms. Six patients received ECP with IFN-alpha. ECP was done using the photopheresis UVAR system and UVAR XTS and always with 8-MOP liquid formulation injected directly into the buffy coat bag. Lymphocytes in peripheral blood were immunophenotypically characterized for each patient and every ECP session. In the end all patients tolerated ECP well, without significant side effects. Thirty patients were clinically evaluable. A favourable clinical response was obtained in 80.9% of patients (complete response 33%, partial response 47.6%) and in 66% of patients in the Sézary's syndrome phase (complete response 33.3%, partial response 33.3%). There have been no changes in the peripheral lymphocyte immunophenotype during the follow-up. In 19/30 patients the CD95 antigen, correlated with cellular apoptosis, was expressed and was frequently associated with a good clinical response. They concluded that ECP achieved favourable clinical responses in 73% of patients, in monotherapy or in combination with IFN-alpha, without significant side effects.

b. Photopheresis and Cutaneous Lupus Erythematosus (LE)

Morruzzi *et al.*, (2009) treated one patient with subacute LE having a contraindication to antimalarials and to thalidomide and three patients with chronic LE (lupus panniculitis, lupus tumidus and disseminated discoid LE) refractory to treatment with hydroxychloroquine, chloroquine, thalidomide and dapsone, and also, in some cases, to oral and intravenous corticosteroids, methotrexate, colchicine, acitretine, sulfasalazine, mycophenolate mofetil and intravenous immunoglobulin. Treatment consisted of two 4-hour sessions fortnightly. Only antimalarials were continued during photopheresis.

In their results, they found that photopheresis had a positive effect on all four patients. They also noticed complete remission in two patients and interruption of progression followed by partial remission in the other two after a mean delay of two to three months of treatment. All treatments other than antimalarials were stopped. They concluded that photopheresis appears to be an effective treatment option in patients with cutaneous LE and that despite its high cost, it should nevertheless remain an exceptional therapeutic option restricted to patients with cutaneous LE resistant to standard therapy.

c. Plateletpheresis

Platelets can be prepared or collected from whole blood after several stages of processing or through the apheresis (plateletpheresis) using cell separators. Plateletpheresis is a method used to remove platelets from the body either from random volunteer donors, patient's family members or HLA matched donors.

In a study on effects of plateletpheresis on blood coagulation parameters in healthy donors at National Blood Centre, Kuala Lumpur, Malaysia, Siti *et al.*, (2013) found that regular plateletpheresis donors develop sustained decreases in platelet count. It was found that the donors should be screened with at least complete blood count before the procedure to ensure that the platelet does not fall below the normal limit. This is similar to the findings of Koch *et al.* (2005). There was significant reduction of platelet count among plateletpheresis donors, perhaps beside collection of platelets; it might also be due to adhesion of platelet to tubing or centrifuge bowl. About 25-50% of circulating platelets might be lost during single plateletpheresis but this is usually normalized by the spleen, therefore significant thrombocytopenia is not observed in plateletpheresis donors (Simon *et al.*, 2002). Hence, the clinical findings of thrombocytopenia are unusual. The reduction in platelet count after plateletpheresis is shown to cause activation of thrombopoiesis to replenish the platelet in the peripheral blood. The activation of the thrombopoiesis will induce temporary increase in serum thrombopoietin level after platelet collection (Dettke *et al.*, 1998).

2. SUMMARY

The benefits of the correct use of blood and blood products cannot be overemphasized. Appropriate blood usage and therapeutic apheresis complement each other. In the past, when the usefulness and/or side effects of individual blood products were not fully known, whole blood was transfused from one individual to the other, irrespective of the fact that a particular component, e.g. plasma, could be pathogenic. Although the main aim of the transfusion, replacing blood, was met, other side effects came into play like circulatory overload, where an individual has too much of a particular cell type or component in his/her circulation.

In recent times, appropriate blood usage entails giving the right blood to the right patient and at the right time and place. It avoids unnecessary and inappropriate transfusions, prevents "wrong blood into patient" incidents which are nearly always caused by human error and may cause fatal reactions due to ABO incompatibility. Data from the UK Serious Hazards of Transfusion (SHOT) initiative show that about 1 in 13,000 blood units are administered to the wrong patient and there are occasional fatal outcomes. (WHO, 2015). Blood is scarce, therefore WHO recommends for the safe and rational use of blood and its products to reduce unnecessary and unsafe transfusions and to improve patients' safety, thereby reducing the

risks of adverse events such as errors, transfusion reactions and the transmission of infections from the blood unit to the recipient.

Therapeutic apheresis has its main purpose to be the removal of a component of blood that is contributing to a diseased state. It is a medical procedure for the clinical treatment of autoimmune diseases and blood disorders. It is more like a general term for treatments that remove harmful proteins, chemicals or cells in the blood that contribute to disease. Just as blood components differ in their nature and functions, so does therapeutic apheresis. In the course of this review, cases have been seen where therapeutic apheresis is very effective and is used as first-line therapy such as in the use of Plasmapheresis for the treatment of Thrombotic Thrombocytopenic Purpura (TTP) and Myasthenia gravis and also in the use of Erythrocytapheresis for sickle cell patients, where patients with dangerous complications showed rapid improvement within 24-48 hours, (Valbonesi and Bruni, 2000).

In conclusion therapeutic apheresis provides a means to rapidly alter the composition of blood components. It can be a valuable and safe initial treatment for a number of ailments resulting from or associated with quantitative and/or qualitative abnormalities of blood cells or plasma. Adverse effects with current techniques are infrequent and usually mild. Appropriate use of blood and blood components should promote safe and effective patient outcomes. In certain clinical circumstances, blood component therapy can save lives, restore normal life expectancy and improve quality of life. However, it is clear that such therapy has limitations and that the decision to transfuse be made with great care. Blood component therapy should only be given when the expected benefits to the patient are likely to outweigh the potential hazards.

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(Received 14 June 2016; accepted 28 June 2016)