Therapeutic applications of red cell exchange in apheresis: A review

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ABSTRACT

Apheresis in India is still in infancy and red cell exchange (RCE) is scarcely used. Few centers are at present doing in India. The superior advantage of erythrocytapheresis compared with phlebotomy and long-term positive role in management of patients with hemoglobinopathies needs to be impressed upon to the clinicians. Patients comfort in hemoglobinopathies like sickle cell disease and thalassemia has improved drastically due to RCE and if used on larger scale, will bring down the cost of the procedure.

Key words: Apheresis, Erythrocytapheresis, Red cell exchange

INTRODUCTION

Apheresis (Greek - apairesos, Roman - aphaireis, “to take away” or “to separate”) is a mode of therapy involving removal of plasma components or cellular components from the blood. The process of apheresis involves removal of whole blood from a patient or donor. An instrument like a centrifuge is used to separate the components of whole blood. One of the separated portions is then withdrawn, and the remaining components are retransfused into the patient or donor.[1,2]

The components that are separated, and withdrawn include:
• Plasma (plasmapheresis)
• Platelets (plateletpheresis)
• Leukocytes (leukocytapheresis)
• Red blood cells (RBC) – erythrocytapheresis, red cell exchange (RCE).[1,3]

Apheresis is becoming a therapy more than the removal of pathogenic compounds, and now involves added approach in defective components too. The procedure is safe even in infants and young children.[1,3]

Historical development and future

It has its origin in a procedure called as “Bloodletting,” a practice originally performed to remove the bad humors from the body, initiated by the Egyptians around 1000 BC and lasted until the end of the 19th century. The procedure was developed in 1914 by John Abcl and gained major acceptance after World War II, due to the increased requirement of plasma. In the last 30 years, apheresis technologies have helped to treat many diseases by removing pathological macromolecules or pathological cells from patient’s blood.

Now, it is believed that, apheresis therapy has many major possibilities in treating diseases like heart disease, diabetes mellitus, cancer and some authors believe that the aging process can also be prevented.[1,3]

Classification: Therapeutic apheresis and donation apheresis.

Donation apheresis includes plateletpheresis, plasmapheresis, red cell apheresis, stem cell apheresis and granulocytapheresis. The process takes a couple of hours.[3]

Therapeutic apheresis is therapeutic plasma exchange, erythrocytapheresis, thrombocytapheresis, leucocytapheresis, extracorporeal photopheresis (ECP), immunoadsorption (IA), selective removal methods, adoptive cytapheresis, and membrane differential filtration.[2,3]

Donor apheresis is, usually, an outpatient procedure lasting usually 2-3 hr. In therapeutic apheresis, certain conditions like RCE for hemoglobinopathies can be treated as a day care procedure whereas it is dependent on patient’s preadmission condition in rest other cases.

The indications of apheresis is divided into four categories by American society for apheresis (ASFA) like first line therapy (Category 1), second line therapy (Category 2), Optimum role not established (Category 3) and evidence suggestive of ineffective or
Complications of apheresis

In general, therapeutic apheresis is a relatively safe procedure. The overall adverse reactions of apheresis even though very minimal are citrate toxicity, allergic reactions, blood volume shifts, platelet reduction, hypovolemia, transfusion transmitted diseases, etc. The overall incidence of death is 0.05%, but many of these deaths were in patients with severe pre-existing conditions in which the apheresis procedure, itself, may not have been the precipitating cause. As with all extracorporeal treatments requiring large bore vascular access, catheter-related trauma, clotting, infection, and bleeding may also occur.\[^{1,3,6}\]

RCE/erythrocytapheresis

RBC exchange has been used over the years for a large number of applications. The procedure involves removal of patient RBCs and replacing with donor packed RBCs. It is an effective but possibly underutilized therapy in the acute and chronic treatment of many disease conditions including hemoglobinopathies like sickle cell disease (SCD) etc. It is frequently used in developed countries since a long time. There are very few centers performing RCEs in India.\[^{1,3,9}\]

RCE and erythrocytapheresis are most often used interchangeably with similar meanings. In an RCE, the patient’s red cells are removed and replaced by exogenous normal red cells, whereas erythrocytapheresis is removal of RBCs alone without replacement.\[^{1,3,10}\]

The use of modern cell separators, increasing safety of RBC concentrates, and the introduction of leukodepletion in blood products have made this treatment modality very effective, comfortable and safe.\[^{14}\]

Methods

RCE can be accomplished by bleeding and infusing red cells manually or more efficiently through the use of an apheresis machine which spins blood to separate the plasma from cells. The machine then can replace the patient’s red cells on an mL for mL basis with normal cells, minimizing fluid shifts and blood pressure variations. In the older patients, veno-venous access and in small children, blood given back via port is, usually, followed. Well-trained technicians are necessary to conduct the procedure. COBE spectra and spectra optia are commonly used RCE separators.\[^{1}\]

Indications of RCE

- Hemoglobinopathies like SCD, thalassemia, etc.
- Protozoal infections of RBCs - malaria, babesiosis
- Some types of poisoning like carbon monoxide, arsenic, etc.
- Incompatible transfusion and hemolytic disease of newborn
- Others such as erythrocytosis, hereditary hemochromatosis, refractory warm autoimmune hemolytic anemias and porphyria, etc.\[^{3,6}\]

Hemoglobinopathies

SCD is a condition identified by the presence of hemoglobin-S (HbS) or sickled RBC that replaces a proportion of normal HbA. Sickled RBC can lead to endothelial dysfunction, microvascular complications, vaso-occlusion, hyper-viscosity and blood clumping leading to severe vaso-occlusive crisis and dysfunction of various organ systems. It also reduces free Hb and nitric oxide scavenging, restoring normal vasodilatation and endothelial function. Transfusion of normal (non-sickle) blood into patients with SCD increases hematocrit (Hct) and simultaneously (by dilution) lowers the fraction of cells that contain HbS. By increasing the Hct, transfusion may also reduce the erythropoietic drive due to anemic hypoxia and thereby, decreased production of sickle hemoglobin will also occur.\[^{10,11}\]

The indications for RCE recommended by ASFA is:

For acute cases: Category I - Stroke, Category II - Acute chest syndrome, Category III - Priapism, multiorgan failure, splenic sequestration.

For chronic cases: Category II - Stroke prophylaxis, pre-operative management, Category III - vaso-occlusive crisis.\[^{3,7}\]

The target HbS level of below 30% may require repeated exchanges. A single volume exchange will replace ~65% of the patient’s cells; a double volume exchange will replace ~85%. The aim is to exchange 0.5-1 blood volume in each exchange. The calculated amount of blood to be exchanged is approximately 50-60 mL/kg of body weight for an average adult. In the exchange transfusion protocol used for pediatric patients, the volume of 10 mL/kg of blood is phlebotomized, and 15 mL/kg of blood infused immediately. Major advantage of RCE in SCD has been its iron neutrality since the removed Hbs has just as much iron as the administered Hba. Treatment of patients with bone marrow necrosis and multi-organ failure is mainly supportive.\[^{12,14}\]

In hemoglobinopathies like thalassemia, abnormal patients RBC’s are replaced with donor RBC’s to improve oxygen delivery and manage clinical condition more efficiently than a simple top up transfusions.\[^{13}\]

Parasitic infections: Malaria and babesiosis

Mosquito-borne illness caused by infection of RBCs with Plasmodium protozoa. In the malaria, RCE offers a rapid approach to treating acute, severe cases of malaria. It is used as an adjunct with anti-malarial drugs since 1974. It helps by reducing both parasitemia and could buy time for anti-malarials to work. It is expected to increase the oxygen-carrying capacity of the blood along with a reduction of parasitic load, removal of toxic substances, to aid in increasing the effectiveness of anti-malarials and also a reduction of microcirculatory sludging.\[^{15,47}\]

The most commonly reported indications for RCE in malaria is hyper parasitemia (>5-70% infected erythrocytes). There have been several studies showing RCE as an adjunct therapy in several Plasmodium falciparum malaria to be very beneficial, but still controversy exists over its efficacy. WHO guidelines to provide RCE are: as an adjunct therapy-level of parasitemia of >10% with or without disease, or failure to improve after 24 hr of the anti-malarial chemotherapy.\[^{9}\]

Tick-borne, malaria-like illness caused by infection of RBCs with Babesia protozoa. It is characterized by flu like syndrome, headache, chills, sweats, myalgia and arthralgia. RCE is often cited as the first line of therapy in babesiosis. Although clinical trials are lacking, several case reports and case series suggest that, given the absence of exo-erythrocytic phase of infection, RCE combined with antibiotic therapy, can be beneficial in severe cases of babesiosis with >5% parasitemia.\[^{3,6,8}\]
Carbon monoxide and other poisonings

Carbon monoxide is the most common cause of fatal poisoning worldwide. Nitrobenzene poisoning is a rare but fatal condition. It causes methemoglobinemia ($\text{Fe}^2+\text{O}$) and reduces oxygen carrying capacity of RBCs. RCE can also be used in poisonings like Carbon monoxide, nitrobenzene, arsenic and sodium hypochlorite, etc. [3,6,19,20]

Hemolytic disease of newborn

Hemolytic disease of the newborn is characterized by presence of IgG antibodies in maternal circulation, which causes hemolysis in the fetus by crossing the placenta and sensitizing RBC for destruction by macrophages in the fetal spleen with consequent hyperbilirubinemia. RCE removes circulating bilirubin, antibodies in plasma and antibody-coated sensitized RBCs, replacing them with RBCs compatible with maternal serum or neonates’ serum and providing albumin with new bilirubin site. Few studies recommend the use of reconstituted blood (O cells suspended in AB plasma) instead of whole blood, irrespective of neonates and mothers blood group. It can also be used in removal RBC in ABO incompatible post-transplant or post-transfusions. [1,8,23]

Red cell depletion in erythrocytosis

Erythrocytosis conditions are commonly polycythemia, hereditary hemochromatosis, etc. Compared to phlebotomy, RCE is known to be superior as it reduces the risk of volemic imbalances (also plasma containing thrombocytes, coagulation factors and proteins) and is an efficient, safe and well-tolerated method. Amount of iron removed can be increased by 2-3 folds for each procedure by using erythrocytapheresis for selective withdrawal of red cells. Rapid normalization of iron and organ damage prevention goals are achieved sooner with this procedure. The main problems noticed were the cost, and is negated by the reduced risk of thromboembolism and a clear decrease in viscosity, which makes the cost effectiveness balance sufficiently positive. [2,3]

CONCLUSION

The cost of erythrocytapheresis is still high in our country. If it is widely used, the cost per procedure is going to get lower due to more efficient use of equipment. In addition, collected blood is being used for transfusion purposes collected from conditions like hemochromatosis in parts of United States, Canada and France. Treatment costs will also be no higher as fewer procedures will be required to attain the target haemoglobin. [2,3]

Looking at all the happening in RCE field, it is more likely that in future erythrocytapheresis programs will be more often initiated as a primary prophylactic intervention.

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