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# ROLE OF ERYTHROCYTAPHERESIS IN SICKLE CELL DISEASE MANAGEMENT: A REVIEW

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**ABSTRACT**

**Objectives:** This article is a literature review illustrating the importance of erythropheresis in patients with sickle cell disease. **Methods:** Several articles published between 2014 and 2020 were compiled, highlighting the indications and side effects of erythropheresis. **Results:** The study reveals that sickle cell disease is the most common genetic disease. Its mode of inheritance is autosomal recessive. It is due to a mutation in the B-globin gene. Erythropheresis, sometimes called red blood cell exchange, is a therapy whose goal is to selectively extract the patient's red blood cells and replace them, to a greater or lesser extent, with those from a donor (exchange transfusion). **Conclusion:** Erythrapheresis remains a major therapeutic option in the management of sickle cell disease by preventing iron overload and reducing hemoglobin S levels.

**KEYWORDS:** sickle cell disease, transfusion, erythrocytapheresis, chelation, iron overload.

## INTRODUCTION

Sickle cell disease (SCD) is the most prevalent inherited genetic disorder, passed down in an autosomal recessive pattern. It is caused by a mutation in the β-globin gene, leading to a structural alteration in hemoglobin, which in turn affects its function.

The disease's pathophysiology starts with the tendency of hemoglobin S molecules to polymerize when oxygen levels are low, forming rigid fibers that deform red blood cells and impair their flexibility. This results in hemolysis and, consequently, anemia.

Moreover, vaso-occlusive crises occur, restricting the flow of oxygen to the affected organs. Additional mechanisms that contribute to the disease's progression include increased red blood cell adhesion to the activated vascular endothelium and vasoconstriction caused by nitric oxide depletion due to excessive hemolysis.[1]

Erythrocytapheresis, or red blood cell exchange, is a therapeutic procedure where the patient's red blood cells are selectively removed and replaced with donor cells. This method allows for more precise control of residual HbS levels, helps prevent hyperviscosity after transfusion, and, over time, reduces the risk of iron overload. The main challenges with this technique include securing venous access, ensuring the availability of red blood cell units, and gaining access to the procedure.

Erythrocytapheresis is also utilized for treating conditions such as polycythemia, genetic hemochromatosis, and both acute and chronic complications of sickle cell disease. This review primarily examines the role of red blood cell exchange in managing sickle cell disease.[2]

### Definition of Erythrocytapheresis

Erythrocytapheresis, also referred to as red blood cell exchange, is a technique used to selectively remove red blood cells from a patient using a cell separator. This procedure allows for efficient, rapid, and automated removal of red blood cells, offering a controlled and effective therapeutic method.

### I. Techniques Employed

There are two primary systems used for erythrocytapheresis, categorized based on whether the separation occurs in a continuous or discontinuous

manner. In both systems, blood components- such as cells and plasma-are separated by centrifugation, either within a centrifuge bowl (discontinuous system) or a rotating ring (continuous system).

The separation typically yields plasma, followed by the leukocyte-platelet layer (known as the buffy coat), and finally, red blood cells. Peristaltic pumps and computer-controlled clamps handle the extraction of red blood cells, reinfusion of remaining blood components, and, if necessary, volume replacement to maintain hemodynamic stability.

**a.** Discontinuous Flow Centrifugation-Based Cell Separators

Systems like MCS-3P® and MCS+® by Haemonetics® (Braintree, MA) use this method. Blood is drawn through one or two peripheral venous lines under normovolemic conditions, with volume compensation automatically handled by the system. The closed, single-use circuit has a volume of approximately 300 mL. A built-in hematology calculator helps determine the blood volume needed to reach a desired hematocrit level, based on the patient's weight, height, sex, and initial hematocrit.

The separation involves repetitive cycles, including: Blood filling and separation, Storage of plasma and buffy coat (in a transfer bag), Extraction of red blood cells after centrifugation stops, Re- integration of plasma and buffy coat into the patient, This system is suitable for collecting up to 600 mL of red blood cells.

**b. Continuous Flow Cell Separators**

In these systems, centrifugation occurs within a rotating ring, enabling continuous separation of blood components. The extracorporeal circuit has a small volume of about 150 mL, which remains stable during operation. Volume compensation is continuously managed by the system.

These systems are generally heavier and less portable, requiring two high-quality venous accesses. However, they offer the advantage of good hemodynamic tolerance and can collect a larger volume of red blood cells in a shorter period. Monitoring is fully automated, with sensors continuously analyzing data such as pressure in the circuit, air detection, and optical measurements. These systems are typically used for collections exceeding 600 mL.

**II. Vascular Access Methods**

The quality of vascular access is critical for the success and duration of the procedure. Required flow rates range from 30 to 60 mL per minute. Puncture is performed under strict aseptic conditions using short catheters or butterfly needles of size 16 or 18. Double-lumen dialysis catheters made of silicone (about 20 cm in length and 11.5 F in diameter) are used, with femoral vein puncture being preferred for short-term treatments.

**III.** Anticoagulation of the Extracorporeal Circuit

Calcium citrate solutions (ACD) are commonly used as anticoagulants. Citrate works by chelating ionized calcium, thus preventing coagulation and inhibiting platelet aggregation.

**IV. Substitution Fluids**

Erythrocytapheresis is conducted under normovolemic conditions. Various substitution fluids are used during the procedure:

**a. Hydroxyethyl Starches (HES)**

These are modified polysaccharides derived from plants, commonly used in France. The plasma half-life of HES ranges from 12 to 24 hours, providing sufficient volume expansion during treatment. Allergic reactions to HES are rare, but some interactions with hemostasis may reduce platelet aggregation. Additionally, excessive accumulation of HES can lead to kidney damage or liver overload.

**b. Albumin**

Albumin represents a significant portion (60-80%) of the plasma's oncotic pressure. It is derived from human plasma and undergoes viral inactivation during preparation. Albumin used in apheresis is slightly hypo-oncotic, which allows for isovolemic substitution. Intolerance reactions to albumin are rare, although they may include chills, fever, or diarrhea, depending on the product lot. There are no known fetal or embryonic toxic effects, making it the only colloid suitable for use in pregnant women.

**c. Red Blood Cells**

For transfusion exchanges in sickle cell patients, homologous red blood cell concentrates, which are phenotyped and cross-matched, are used to replace the removed red blood cells. The volume of red blood cells to be transfused is automatically calculated based on the hematocrit calculator, using the patient's weight, height, initial hematocrit, and percentage of hemoglobin S before the procedure.

The aim is to reduce HbS levels to below 30% while maintaining the hematocrit.[3]

**Indications for Erythroapheresis**

Erythrocytapheresis is indicated for both acute and chronic conditions in sickle cell patients. The indications include (table 1):

Occasional and Curative: For conditions such as stroke, acute chest syndrome, splenic sequestration, priapism episodes not responding to Effortil®, vaso-occlusive crises unresponsive to major analgesics, or preparation for surgery.

Occasional and Preventive: In preparation for surgery, travel, or stressful events like exams or school competitions.

Long-term: For severe progressive vasculopathy, chronic

visceral involvement, recurrent severe vaso-occlusive crises unresponsive to hydroxyurea, or abnormal transcranial Doppler findings in children.

In some cases, erythrocytapheresis may be used during pregnancy for certain patients.[4]

**Table 1: Indications for Erythrocytapheresis.[5]**

| | | |
|---|---|---|
| excluding transfusion or exchange transfusion procedures | Exchange transfusion or simple transfusion with two to three units of packed red blood cells, adjusted according to the patient's | Exchange transfusion with a hemoglobin |
| Minor surgery (circumcision, lymph node excision, minor skin | Cholecystectomy in patients with a history of acute chest syndrome. | Thoracotomy |
| nguinal hernia repair, | Laparotomy | Procedure with |
| cholecystectomy in patients without a history of acute chest syndrome and with hemoglobin | Splenectomy | Transplantation |
| Orthopedic surgery in SC sickle cell patients with no prior history | Orthopedics | Neurosurgery |
| Percutaneous aspiration and reinjection of the femoral head | Tonsillectomy | Endovascular angioplasty |
| | Cerebral angiography | Surgery with extracorporeal |
| | Coronary angiography | |
| | Emergency procedure | |
| | Therapeutic abortion, | |
| | voluntary abortion in patients with more than one hospitalization per year for vaso- | |
| | Ophthalmic surgery under general anesthesia | |

**Advantages of Erythrocytapheresis**

The protocols for exchange transfusion are now well-established to prevent long-term complications in both children and adults with sickle cell disease.[6]

Depending on the reason for the exchange, the target hemoglobin S (HbS) level varies:
A level consistently below 30% is recommended after a stroke to reduce the likelihood of early recurrence.

For the prevention of acute chest syndrome recurrence, a hemoglobin S level of less than 50% is often sufficient.

Françoise DRISS published a review in 2014 titled "Transfusional Therapy in Sickle Cell Disease" which highlights that erythrocytapheresis, or red blood cell exchange, allows for volume-for- volume replacement of the removed red blood cells. This method minimizes the risk of iron overload and is well-tolerated due to its isovolemic nature. The technique is capable of handling large volumes of red blood cells, making it highly effective.[4]

In their 2015 literature review, A. Habibia and J.-B. Arlet, in "French Recommendations for the Management of Sickle Cell Disease in Adults: 2015 Update," noted that cell separator-based exchange transfusions are faster, more efficient, and better tolerated in terms of volume (avoiding significant volume fluctuations). These exchanges do not lead to iron overload, making them ideal for long-term management in patients. The exchanged volumes typically match one erythrocyte mass, which corresponds to four to eight packed red blood cell units.[5]

A study by Bérengère Koehl and Florence Missud, published in 2017 in the Journal of Visualized Experiments under the title "Continuous Manual Exchange Transfusion for Patients with Sickle Cell Disease: An Efficient Method to Avoid Iron Overload," demonstrated that after an average of 51 months of erythrocytapheresis, ferritin levels remained stable without the need for iron chelation. In contrast, after an average of 39 months of manual exchange transfusion (MET), ferritin levels increased from 327 µg/L (range: 206-535) to 802 µg/L (range: 146-873) without therapeutic iron chelation.[7]

**Risks of Erythrocytapheresis**

Dr. Katerina Pavenski, MD, FRCPC, in her 2018 review, "GUIDE TO TRANSFUSION PRACTICE CHAPTER 14: THERAPEUTIC APHERESIS," reported that the incidence of adverse effects linked to apheresis is approximately 4-5%, with slightly higher risks during the first procedure. These effects may stem from venous access issues, the replacement fluids used, or the apheresis procedure itself.[8]

Around 1% of adverse effects are related to venous access, including complications such as bleeding, pneumothorax, infections, and thrombosis. Adverse effects from replacement fluids can include transmission of infections and transfusion reactions such as fever, allergic responses, and TRALI.

The risks of red blood cell exchange are similar to those

seen with massive blood transfusions, including febrile reactions, alloimmunization, allergic reactions, citrate toxicity, TRALI, and the transmission of bloodborne pathogens.

Citrate toxicity is the most common adverse effect associated with apheresis. It can lead to hypocalcemia, which is detectable through laboratory tests and may present clinically as paresthesia, nausea, vomiting, chills, muscle cramps, tetany, seizures, and arrhythmias. In patients with renal insufficiency, citrate administration can also cause metabolic alkalosis.

Other complications may include hypotension resulting from anemia, hypovolemia, or vasovagal reactions, volume overload, loss of cells (such as iron deficiency anemia or thrombocytopenia), and electrolyte imbalances (including hypocalcemia or hypomagnesemia)(table 2).

The procedure may also remove pharmacological agents present in the blood, particularly those with a strong affinity for plasma proteins or those with a low volume of distribution.[8]

**Table 2: Adverse effects associated with erythrocytapheresis.[8]**

| category | category | frequency (%) |
|---|---|---|
| Frequent side effects | | < 10 % |
| hypocalcemia | Paresthesia | 1.5-9 |
| Hypovolemia | hypotension | 0.4-4.2 |
| | Muscle cramps | 0.4-2.5 |
| | Headaches | 0.3-5 |
| Anaphylactoid reaction | Urticaria | 0.7-12 |
| | chills | 1.1-8.8 |
| Rare adverse effects | | 1.5 % |
| Cardiac | ischemia, Shock, Myocardial infarction | 0.1-1.5 |
| | Arrhythmia | 0.1-0.7 |
| Pulmonary | Respiratory arrest, Pulmonary edema | 0.2-0.3 |
| | Pulmonary embolism | 0.1 |
| Hematologic | Thrombosis, Hemorrhage | 0.02-0.7 |
| Infectious | Hepatitis | 0.7 |
| | Other infection | 0.3 |
| Neurological | Seizure | 0.03-0.4 |
| | Ischemic stroke | 0.03-0.1 |
| Other | Hyperthermia | 0.7-1 |

**Erythrocytapheresis On Demand or for Prophylaxis**

Blood transfusion is infrequently used to raise hemoglobin levels, as anemia in sickle cell disease is typically chronic and well-tolerated by patients. Additionally, uncomplicated vaso-occlusive bone crises are not an indication for transfusion. The main goal of transfusion in sickle cell disease is to quickly lower the percentage of red blood cells containing hemoglobin S, which helps to stop the detrimental pathophysiological processes. There are various approaches to transfusion: simple transfusion or exchange transfusion (which involves phlebotomy, either manually or via erythrocytapheresis), either as a one-time procedure or a regular program, for curative or preventive purposes, and for primary or secondary prevention.[6]

Indications for Transfusion: Two scenarios can be distinguished:

One-time transfusion (simple or exchange transfusion): This is used to prevent or treat an acute complication.

Chronic transfusion program: In this case, transfusions or exchange transfusions are employed for the primary or secondary prevention of complications. It is important to periodically reevaluate the continuation of this program, taking into account its effectiveness, venous access sites, iron overload, and the emergence of antibodies. Blood transfusions are typically scheduled every 3 to 6 weeks.[6]

## CONCLUSION

Transfusion therapy, despite certain side effects, remains a key component in managing complications in sickle cell patients. Erythrocytapheresis, using a cell separator, is preferred as it is better tolerated, more effective in reducing the HbS level, and, most importantly, helps prevent iron overload during long-term transfusion programs.

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