

Transfusion Therapy in Sickle Cell Disease

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Abstract

Background: Blood transfusion is an important therapy in the management of sickle cell disease (SCD); especially in developing countries. Transfusion aids the restoration of the oxygen carrying capacity in patients with SCD and also prevents vaso-occlusion by dilution of the Hbs in circulation. However, there is paucity of information on transfusion as a therapy in the management of SCD.

Aim and objective: This study is aimed at reviewing the available publications on transfusion as a therapy for SCD management.

Materials and methods: Relevant literatures were searched on databases including PubMed, Google Scholar, Scopus, Cochrane and standard texts on haematology and transfusion medicine. The keywords used in the search are sickle cell disease, transfusion, simple and chronic transfusion, complications of transfusion, choice of blood for transfusion and guidelines for blood transfusion. The literatures gathered were reviewed, summarized and presented in this review.

Results: Blood transfusion is a cornerstone in the management of patients with SCD. The management of SCD patients requires a multidisciplinary approach with a great deal of commitment been required from all the experts. Although, many hazards are associated with blood transfusion, it is pertinent that proper care is taken in the handling and administration of blood and blood products.

Conclusion: Transfusion therapy still remains a cornerstone in SCD management and it tends to mitigate the severity and complication associated with SCD disorders. Adequate knowledge and information is needed by experts on the importance of transfusion therapy and its modalities in SCD.

Keywords: Transfusion; Therapy; Sickle cell disease

Introduction

Sickle cell disease (SCD) is a heterogeneous group of disorder, with a highly variable clinical spectrum. It is an autosomal recessive structural hemoglobin disorder [1]. The most prevalent form is sickle cell anemia (HbSS), which is due to inheritance of the sickle cell gene in a homozygous state. Other forms include the compound heterozygous forms in which the sickle beta globin gene is co-inherited with another abnormal hemoglobin gene such as HbC in HbSC, β -thalassemia in HbS β thalassemia among others [1,2].

SCD is the most common genetic disorder in Sub-Sahara Africa. Nigeria bears a high disease burden with an estimated prevalence of 1-3% of its population being affected by the disease. An estimate of 20-30% of her populace carry the sickle cell gene with a normal hemoglobin gene (carrier state) otherwise called the sickle cell trait. The disease burden in Nigeria differs slightly from one geographical region to another. Nwogoh et al. [3] reported the prevalence rate of SCD to be 2.4% and a 23% carrier state in Benin City. Madu et al. [4] reported a prevalence of 3.7% in a multi-center study in Nigeria.

Steady state is the crisis-free period extending from at least 3 weeks since the last clinical event and 3 months since the last blood transfusion to at least one week before the start of a new clinical event [5].

Blood transfusion still remains the major cornerstone of management of SCD; thus, the management of SCD patients requires a multidisciplinary approach including hematologists, orthopedic surgeons, urologists, nephrologist, cardiologists, nurses, psychiatric nurses and social worker [6]. The commitment of the experts, with a lot of other prophylactic and therapeutic measures which includes: appropriate and adequate analgesic, hydration, sedatives, haemopoietic

stem cells transplantation, oxygen, hydroxyurea, folic acid, antioxidant and anti-coagulation as indicated [6].

Blood transfusion is said to restore the oxygen carrying capacity in patients with SCD and may also help to dilute the circulating Hbs, preventing vaso-occlusion [7]. It also suppresses the marrow from further production of sickle cells. There is paucity of information on transfusion as a therapy in SCD; this study is aimed at reviewing the available information on transfusion as a therapy in SCD.

Modalities of Transfusion

There are two major modalities of transfusion in SCD; Top-up (simple) and chronic transfusion.

Top-up (Simple) transfusion

Simple transfusion is a method for acute lower haemoglobin levels in acute sequestration crisis, aplastic crisis and chronic low haemoglobin level in chronic renal failure [7]. Simple transfusion is when a few units of bags of blood are given through small tube (blood given set) usually via the vein. Top up transfusion is frequently been used for SCD patients in need of acute transfusion [8-11]. The aim of top up transfusion is to raise the haematocrit and haemoglobin A (HbA)

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level and also, at the same time dilute the HbS. Hence, increasing the oxygen carrying capacity of blood and also suppress the generation of sickle cell by the bone marrow [12,13]. Its disadvantage is that it could lead to increase blood viscosity that may precipitate crisis [13].

indication for top-up transfusion: The indications for Top-up transfusion includes [7,14-21]:

- a. Acute splenic sequestration.
- b. Aplastic crises.
- c. Chronic hypersplenism.
- d. Chronic renal impairment.

Transfusion to dilute the circulating sickle red blood cells (Chronic transfusion)

Chronic transfusion is a kind of transfusion where an individual is transfused at 2-3 units within 3-4 weeks [7] with the therapeutic aim of reducing sickle haemoglobin [7,22]. Chronic transfusion can be further divided into the conservative transfusion therapy which is aimed at maintaining the Hb level at 10 to 11 g/dL with 50% reduction in HbSS (hypertransfusion) or the aggressive form (exchange blood transfusion) aimed at reducing sickle Hb level to less than 30% [23]. Exchange blood transfusion can either be automated or partial exchange transfusion [7]. It has the advantage of rapid removal of sickle cell from the circulation, prevention of hyperviscosity, prevention of haemosiderosis, volume overload compare to hypertransfusion [24]; it also has the advantage of providing immunologic component at site of infection in patients with overwhelming infection [25].

Studies have showed that chronic transfusion has effectively help to prevent complication associated with Sickle cell anemia [7,26-31].

Indication for chronic transfusion [32-40]:

- a. Cerebrovascular disease (first stroke prevention)
- b. Repeat stroke prevention
- c. Cerebral blood flow greater than 2 m/sec highly predictive of stroke using Transcranial Doppler (TCD) ultrasonography
- d. Recurrent episode of acute chest syndrome unresponsive to hydroxyurea
- e. Recurrent bone pain crisis of more than three or more hospital admission and unresponsive to hydroxyurea therapy
- f. Severe sickle cell disease with no HLA matching donor
- g. Pregnant women with bad obstetric history and recurrent bone pain crisis
- h. Chronic lungs disease
- i. Chronic vital failure
- j. Chronic leg ulcer

Guidelines for chronic Transfusion [22,24,41]:

- a. Initiation of chronic transfusion regimen in patients should be individualized
- b. In clear terms, the decision to hyper transfuse should be well explained to the patients as well as their relatives
- c. A well drafted therapeutic plan, easily comprehensible by all staff should be drafted

- d. An active blood bank with proper pre transfusion services
- e. Pretransfusion laboratory investigations should include: Extended phenotyping and transfusion transmissible infections
- f. Therapeutic goals such as the final haematocrit and the target sickle haemoglobin level should be set before each transfusion.

Choice of blood for transfusion and monitoring

The objective of chronic transfusion is lowering of HbSS level and it's effective if donor blood is confined to the normal AA genotype. Although, AS-genotype may be adequate thus improving blood flow but it complicate the monitoring of HbSS. Fresh blood should be advocated for since it stays longer in the recipients' circulation and reduce the frequency and duration of transfusion [42]. Chronic transfusion is usually monitored by HbS level, the post transfusion Hb is a secondary consideration. Abrupt changes in haematocrit level may complicate renal function and excessive transfusion may cause cerebral haemorrhage [43].

Complications of blood transfusion

Blood transfusion therapy despite being a major component in the management of SCD, also has its own draw backs. The knowledge of the limitation is very important to arm physicians with the necessary skill to ameliorate and curtail these complications. Complications of blood transmission are numerous and may be categorized either as: immunologic or non-immunologic, acute or chronic, early (occurring within 24 hours) or delayed (up to 4 weeks or longer).

Febrile non-hemolytic transfusion reaction (FNHTR): The most frequent hazard of transfusion is the febrile non-hemolytic transfusion reaction (FNHTR) [44,45]. This is as a result of the immunological exposure of an all immunized recipient to foreign antigen or donor white cells platelet, which leads to release of pyrogens. Furthermore, it could be attributed to leakage of cytokines from inflammatory cells in stored blood. FNHTR can also be found in multiparous women. It began within 30 minutes to an hour of commencement of transfusion, symptom include fever, chills, headache and itching.

Treatment: Discontinue the transfusion exclude other causes of fever, underlying disease in the patient, administer antipyretic, antihistamine leucodepleted red cell, premedication with antipyretic and transfusion should go slowly in subsequent transfusion [22].

Acute haemolytic transfusion reaction (AHTR): It is a serious life threatening complication of transfusion. It is due to incompatible blood components attributed to clinical errors. This results in immune response and activation of complement system leading to intravascular hemolysis. Furthermore, there is a massive release of inflammatory cytokines (cytokine storm). Also, there is a release of an anaphylatoxins both chemicals causes hypotension and acute renal failure. Moreover, the severe intravascular hemolysis triggers disseminated intravascular coagulopathy. AHTR is an emergency which is usually noted few minutes of starting the transfusion. Patients complains of heat and pains at the infusion site, loin pain, restlessness, fever, tachycardia, hypotension and bleeding [46].

Treatment: Transfusion should be stopped immediately. Replace plasma volume with crystalloid, manage complications, and investigate for AHTR, checking blood compatibility by repeating recipient's pre- and post-transfusion blood samples on donor blood unit. Check for haemolysis, direct anti-globin test on pre- and post-transfusion sample, fibrin degradation product, D-dimer to rule out DIC and electrolyte, urea and creatinine, to rule out acute kidney injury [46].

Urticarias: These are attributed to allergens which the recipients have been previously sensitized with. The allergens are found in donor blood. Symptoms include: rashes, pruritus within minutes of transfusion. If patients are unresponsive to antihistamines, stop transfusion. Anaphylaxis is a severe form of allergy that is associated with immunoglobulin-A deficient recipients. Transfusion should be stopped immediately and patient is given adrenaline, chlorpheniramine/promethazine, and hydrocortisone [22].

Delayed Haemolytic Transfusion Reactions: This is a serious complication and constituted 14-44% of patients with antibodies [47,48]. The symptoms include myalgia, severe bone pain, dark urine/hemoglobinuria, increased anemia, and often reticulocytopenia and sometimes might mimic painful bone crisis. Delayed haemolytic reaction that occurs in aluminized individuals with low antibody titre often missed during investigation. Implicated antibodies include non-D Rh (E, C, and c), kell, duffy, and kidd antibodies [49,50]. With re-exposure to the antigen, secondary immune responses develop with antibody production manifesting about 7 to 10 days later with jaundice, fever, worsening anemia. Hemolysis is usually extravascular; antibody's screening and identification are very important for life threatening conditions or subsequent transfusion, the least incompatible blood is advocated for.

Recipient alloimmunization: It is a fatal complication that follows multiple transfusions. It reduces the outcome of successful transfusion. To mitigate this complication, extended red cell typing to identify significant blood group antigens including Rh, Kell, Kidd and duffy is very important [41,51,52]. For already alloimmunized patients, antigen or least incompatible blood unit should be transfused.

Iron overload: Each unit of blood used in transfusion contains about 225 mg of iron. With the vigorous use and duration of chronic transfusion, there is increased tendency of iron deposition in the tissues (liver and heart). Attempts to mitigate this problem include: reducing the rate of iron accumulation by modifying transfusion method by voraciously reducing the target HbS level [52-54]. Automated red cell exchange may also be advocated for the use of chelating agent [55,56].

Conclusion

Transfusion is an important component in the management of SCD particularly in developing countries with the aim of reducing the Hbs level and increasing the Hb level thereby, lessening the likelihood of SCD crisis and complication. The numerous hazards associated with this modality of treatment have made it unpopular and unrealistic. Therefore, a balance must be struck between its merit and demerits. The decision of transfusion is determined by several factors; the availability of resources for extending grouping, facilities for exchange transfusion, availability of effective chelating agent, other option of therapy such as hydroxyurea and failure to respond to hydroxyurea. All these factors contribute immensely to the reduction in transfusion therapy in sickle cell. Despite other disease modifying therapy in SCD, haemopoietic stem cell transplantation (HSCT) is the only potential curative form for now. Further efforts should be directed at educating and boosting the knowledge of specialists involved in the management of SCD patient on transfusion therapy as it remains the cornerstone strategic management especially in our environment.

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