THE ROLE OF BLOOD TRANSFUSION IN THE MANAGEMENT OF SICKLE CELL DISEASE in Africa

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ABSTRACT

Blood transfusions are sometimes required, most usually to treat severe anaemia, in patients with sickle cell disease (SCD). There is general lack of appreciation by clinicians, of the sub-optimal or frankly harmful effects, of inappropriate transfusion in SCD. This article discusses the relevant pathophysiology of sickle cell disease and the appropriate indications for blood transfusion. The adverse effects of blood transfusion in SCD are also discussed, particularly the greater susceptibility than usual to alloimmunization, post-transfusion anaemia, transfusion transmissible infection and vascular and iron overload, among others. Various clinical situations are described in which there is need, either merely to restore oxygen-carrying capacity, or reduce the proportion of circulating sickle cells or suppress the production of sickle haemoglobin.
Types of transfusion appropriate to each of these clinical situations are suggested, and general guidelines are recommended for haemotherapy of SCD.

INTRODUCTION
Sickle cell disease (SCD) refers to a group of conditions in which the abnormal sickle haemoglobin (Hb) gene is inherited in a homozygous state, or a compound heterozygous combination together with another abnormal gene whose Hb product does not inhibit polymerization of the sickle Hb under physiologic conditions. The SCD family includes sickle cell anaemia (HbSS), sickle cell HbC disease (HbSC) and sickle cell thalassaemia (SB0 and SB+thal), and other rarer combinations. One characteristic feature of these diseases is that the sickle Hb is usually the dominant component in terms of concentration. This definition of SCD therefore does not include the heterozygous combination of sickle and normal Hb otherwise called sickle carrier or trait (Hb AS), though some subclinical abnormalities have been described in that condition.[1]

PATHOGENESIS
The pathogenesis of sickle cell disease is now known to be multidimensional. There appears to be an intrinsic abnormality of the sickle Hb molecule which causes it even at full oxygenation to be relatively unstable, and to interact with the cell membrane resulting in oxidative damage, and increased rigidity of the membrane.[2] Denatured Hb molecules on the membrane co-cluster with band-3 and promote IgG and complement binding which in turn facilitates macrophage phagocytosis of sickle erythrocytes.[3] The major pathology of the sickle Hb however derives from its decreased solubility when deoxygenated.[4] In hypoxic conditions, sickle deoxyhaemoglobin molecules polymerize and precipitate intracellularly, forming characteristic elongated bundles of crystals. The crystals progressively impinge on the membrane, causing first, increased rigidity, and later irreversible alteration of shape to produce the pathognomonic sickle cell.[5] Polymerization also causes ionic and other metabolic changes which lead to intracellular dehydration and increased viscosity. .Another effect of intracellular polymerization is the lowering of Hb-oxygen affinity, thus promoting the persistence of intracellular hypoxia, further polymerization, and sickling, in a vicious cycle. Yet another important aspect of the pathology of SCD is the increased adhesiveness of sickled cells to vascular endothelium. This factor further aggravates the stasis arising from the loss of red cell deformability, and contributes to the vaso occlusive phenomena associated with SCD.[6] The viscosity and membrane changes described above cause splenic trapping and premature destruction of sickled cells, producing a persistent haemolytic anaemia which is only partially compensated by the increased haemopoietic activity, and expansion of the bone marrow. This leaves the SCD patient with a permanent anaemia even when the patient is in a so-called stable state with relatively few clinical symptoms. In the stable state, sickle cell anaemia patients maintain Hb concentration of only 6-8g/dl. Because of the right shift of the oxygen dissociation curve of sickle haemoglobin, and the consequent enhanced capacity to deliver oxygen, sufficient tissue oxygen perfusion is achieved in the stable state in spite of the reduced red cell mass.[7]

However, the pathological effects of chronic anaemia are evident, such as an expanded bone marrow and the progressive left ventricular hypertrophy and cardiomegaly, and the gradual premature failure of parenchymal organs. The stable state is usually punctuated from time to time by periods of increased sickling and haemolysis, and, or, reduced haemopoietic activity, called 'crisis', in which there may be more severe vaso occlusive manifestations. The pathophysiology of SCD is further complicated by a state of chronic inflammatory tendency resulting from a cytokine-induced activation of circulating platelets and white blood cells when vascular endothelium is activated by sickle red cell adhesion. Finally, reactive thrombocytosis, which is an offshoot of erythroid hyperplasia, aggravates the hyperviscosity, and adds its own dimension of hypercoagulability in SCD.

The role of blood transfusion (BTx) in the management of SCD is primarily to improve oxygen carrying capacity particularly in times of crisis or whenever the Hb concentration drops sufficiently to threaten oxygen delivery to vital organs. The rest of this discussion is devoted to the consideration of the adverse effects of BTx in sickle cell disease and the 'when', the 'what', and the 'how' of BTx when it becomes inevitable in SCD.

ADVERSE EFFECTS OF BLOOD TRANSFUSION IN SCD

In spite of its life-saving usefulness, blood transfusion carries grave risks for all recipients, not less SCD patients. Because SCD patients are liable to be transfused repeatedly, the 'usual' hazards of BTx are aggravated while other complications may occur which are peculiar to SCD (Table 1).

Alloimmunization

Alloimmunization to red cell, white cell, platelet and plasma protein antigens is a well-known immunologic adverse effect of BTx which may manifest as acute or delayed local or systemic reaction. Since the frequency of alloimmunization is related to the diversity of antigen exposure, SCD patients who receive multiple transfusions from diverse donors show greater incidence of immunologic reactions. This has been shown in some European and American studies.[9] Experience in Africa, though not widely documented, may not be more favourable, especially as leucocyte-depleted blood is less commonly available. A saving grace however may be the commoner transfusion in Africa, particularly in regions where the population is almost homogeneously black, of donor blood of similar racial origin. SCD patients who develop alloimmunization exhibit the usual manifestation of a haemolytic transfusion reaction which may be acute (AHTR) or delayed (DHTR). However, a peculiar danger of alloimmunization following BTx to SCD patients is that the symptoms of an AHTR may be misinterpreted as those of on-going vaso occlusive crisis and the diagnosis of AHTR may be missed with disastrous consequences. In addition, SCD patients suffer the disadvantage of more frequent allograft rejection in case of bone marrow or other organ transplant.

Post-transfusion anaemia

One adverse reaction to red cell transfusion peculiar to SCD and some other chronic haemolytic conditions is the development of severe post-transfusion anaemia. Red cell transfusion suppresses erythropoiesis; and when a DHTR occurs in a transfused SCD patient, and donor cells are destroyed, the failure of the compensatory production of new autologous red cells due to BM suppression, coupled with the shortened survival of the old cells, leads to a rapid fall in haemoglobin concentration even below pre-transfusion level. Marked reticulocytopenia is observed as evidence of erythropoietic shutdown.

Furthermore, haemolysis of donor cells in HTR in SCD patients may be accompanied by haemolysis of patient's red cells. This is called reactive haemolysis and is explained as a form of "bystander immunocytolysis" phenomenon.[10] The pathogenesis is thought to be as follows. Sickle red cells containing denatured haemoglobin are more susceptible than normal cells to IgG and complement binding.[3] When complement, activated by the antigen-antibody complexes generated in the HTR, is bound by autologous cells which were not originally targets of the HTR, reactive lysis may occur.[11]

Transfusion transmissible infection

Transfusion related infections may arise from transmissible agents particularly HIV and HBV which are common in the same areas where SCD is prevalent. Infections may also arise from bacterial contamination of donor blood within the poor transfusion services of the SCD-endemic regions

SCD patients are relatively immunosuppressed due to hyposplenism, and defective complement activation and opsonization.[12] SCD patients are therefore more likely to suffer more severely from the infective complications of BTx. Some workers have reported higher incidence of hepatitis markers in SCD than in other patients but there was no conclusive proof that the increase was transfusion-related.[13] In a preliminary study in Ilorin, Nigeria, where donor blood was not at the time being screened for Hepatitis C virus (HCV), we failed to observe any difference in the incidence of antibodies to HCV between normal blood donors and multiply transfused SCD patents.[14]

Vascular Overload

Vascular overload is an adverse effect of BTx especially in chronically anaemic patients, including SCD cases. In addition, in SCD patients who already have a high blood viscosity due to the poor deformability and the higher density of the red cells containing sickle Hb, the increased haematocrit from BTx produces a disproportionate increase in blood viscosity.[15] This has the potential to induce or prolong a vaso-occlusive crisis and to blunt the expected increase in oxygen delivery from the transfusion, in spite of improvement in oxygen carrying capacity.

Iron overload

Other potential hazards of BTx, which may occur in patients with SCD and other chronic haemolytic conditions, include iron overload. Bone marrow iron stores are known not to be depleted in stable SCD even during pregnancy.[16] BTx imposes mandatory intravenous iron intake and with the poor excretory capacity for iron in humans, the more frequent the transfusions the greater the iron load. This is why SCD patients may be susceptible to iron overload from repeated BTx. The measure presently available to combat iron overload is administration of the iron chelator desferrioxamine. The need to give this drug inconveniently by subcutaneous infusion with a mechanical pump device over 8-12 hours every night for 5 to 6 nights per week makes for poor compliance. However, with the recent approval by the US Food and Drug Authority of an oral iron-chelating agent (deferasirox; exjade) developed by Novartis, the problem of iron chelation may become simpler and more acceptable in the resource-poor countries of Africa.

INDICATIONS FOR BLOOD TRANSFUSION IN SCD

It is usually not necessary to transfuse sickle cell anaemia patients with Hb concentration of up to or greater than 5.0g/dl, and in West Africa, where donor blood is usually in short supply, transfusion is generally not given unless the Hb concentration falls below 4.5g/dl or there is clinical evidence of acute congestive cardiac failure.[17] Sickle Cell HbC disease and SB+thal patients usually maintain a higher Hb concentration of 8-11g/dl in the stable state and simple transfusions are rarely required. Special forms of transfusion such as exchange or hypertransfusion may be given to SCD patients for reasons other than the improvement of oxygen carrying capacity. Indications for the simple and special forms of BTx in SCD are listed in Table 2.

TRANSFUSING BLOOD OF THE APPROPRIATE HB PHENOTYPE

It sounds reasonable to prescribe sickle-free blood for transfusion to SCD patients, presumably in order not to increase the total proportion of HbS and the blood viscosity. However, the matter may not be as simple as it sounds since haemoglobin functions within red cells and not as a plasma constituent. Sickle trait red cells containing less than 50% sickle haemoglobin may not be different from normal cells in their internal viscosity or be inferior in oxygen delivery capacity unless polymerization and sickling take place in the sickle trait red cells at the oxygen tensions prevailing in SCD patients' tissues. This has not been shown in any study to be the case. On the contrary, in vitro studies of sickle trait red cells under different conditions have showed them to have rheological properties similar to normal red cells.[18] We have shown in Ilorin, Nigeria, that the filterability of 21-day stored sickle-trait red cells was not significantly different from that of normal red cells, while the filterability of HbSS red cells was greatly impaired and declined markedly with storage.[19] More studies are required to resolve this issue since the requirement for sickle-free blood puts more strain on the transfusion service in the areas of high prevalence of SCD. In Nigeria for instance, 25% of the potential donor population carries the sickle trait gene, and this reduces the potential sickle-free donor pool.[20] There is also the added cost in financial expenditure and man-hours, of determining the sickle status by sickling test or electrophoresis, of blood being considered for transfusion to SCD patients. Nevertheless, until the situation is further clarified, concerning the use of sickle trait donor blood, the recommendation should remain that only sickle-free blood should be given to SCD patients, especially those in critical clinical situation. The idea of transfusing cord blood to patients is another grey area of SCD care. In a pilot study in which umbilical cord red blood cells were transfused into children with severe anaemia in a Kenyan hospital, Hassall *et al* found good efficacy, and zero adverse effects of transfusion.[21] In theory, the higher concentration of foetal red cells in cord blood can be advantageous in diluting a SCD patient's sickle cells, but unless the foetal haemoglobin in cord red cells is transferable intracellularly into the patient's own cells it is doubtful if sickling can be reduced. There is also the potential disadvantage of having too many foetal cells in circulation, which could impair oxygen delivery. More studies are required to clarify the situation.

TRANSFUSING DONOR BLOOD OF THE APPROPRIATE AGE IN SCD TREATMENT

There is another contentious issue concerning transfusion to SCD patients. How fresh should the blood be? We know that suitably stored red cells have a long shelf life of sometimes up to 42 days. In theory, there should be no absolute indication for fresh blood. However as Hb-oxygen affinity increases gradually with storage of red cells due to a fall in 2-3-DPG, long-stored red cells are unable to efficiently release oxygen to tissues until the 2-3-DPG is restored a few hours after retransfusion. SCD patients like any other patients who have acute cardio-respiratory problems or are very ill, should preferably receive relatively fresh or short-stored blood. This recommendation is appropriate for SCD patients for another reason. Long-stored blood may have a greater proportion of aged cells which will be destroyed within a few hours of transfusion. This may create an additional haemolytic burden for the SCD patient.

PREVENTION OF ALLOIMMUNISATION

One way to reduce the likelihood of alloimmunization in transfusion to SCD patients is to use donor blood of similar ethnic origin. Fortunately, this is what is done in the parts of Africa which have homogenously black population Nevertheless, transfusion to SCD patients, calls for donor and recipient red cell phenotyping beyond the traditional ABO and RhD typing, if the likelihood of alloimmunization is to be minimized. Transfusing whole blood to SCD patients merely to raise oxygen-carrying capacity, as is the practice in many centres in Africa greatly increases the likelihood of alloimmunization. Only red cell concentrates should be transfused for that purpose. Another measure to reduce alloimmunization is to transfuse pre-storage leucocyte-reduced red cells. This increases the cost of transfusion, but more importantly, the large numbers of SCD transfusions and the poorly developed transfusion services of those countries where SCD is most prevalent preclude the wide usage of this technique. In the absence of leuco-reduced blood, washed red cells may be used, but the process of cell-washing is also cumbersome and risky for contamination. The amount of white cells transfused may crudely be reduced by allowing the donor blood to settle upside down and during transfusion, to let only four-fifths of the red cells run in undisturbed while the remaining one-fifth of the red cells and hopefully the overlying buffy coat are discarded. This is the so-called bottom-and-top or B.A.T. technique.

SPECIAL TYPES OF TRANFUSION

Exchange Transfusion

Exchange transfusion is usually done manually in many centres in Africa, as automated equipments are not widely available. Furthermore there are many technical difficulties in the procedure and it is advisable to refer the patient to tertiary health centres where there are experienced personnel and suitable facilities. The exchange may be done by withdrawing and transfusing whole units one after another usually with saline for the first replacement or by exchanging small volumes through a device with multiple-way taps. Free access through a large blood vessel is important and some heparinisation may be required to achieve free-flowing phlebotomy and fast fluid replacement, even with an 18G catheter. Exchange transfusion is done with red cell concentrate of about 0.6 haematocrit in preservative fluid. For adults and older children it is usually necessary to exchange equivalent of half of the patient's estimated blood volume to achieve a 60-70% reduction in HbS concentration. A top-up simple transfusion may be given after a 1:1 volume exchange to temporarily raise the final Hb concentration to about 10-11g/dl for a patient with a stable Hb concentration of 7-8g/dl. This is to compensate for the loss of enhanced oxygen delivery which was previously provided by the sickle cells.

Hypertransfusion

Hypertransfusion programme for SCD is not commonly practiced in West Africa due to the high cost of procuring and processing the large amounts of donor blood required. Indications for hypertransfusion are shown in Table 2.To bring the metabolism of a SCD patient near that of a non-SCD person, it is necessary to keep HbS concentration below 20% permanently. For this, simple transfusion may be required every 4-6 weeks with periodic exchange transfusions.
Unless a hypertransfusion programme is to last for only a short period, desferrioxamine regime must be instituted and iron status closely monitored. Inability to manage the attendant iron overload is another reason why hypertransfusion may be uncommonly practiced in developing countries.

REDUCING TRANSFUSION REQUIREMENTS IN SCD

SCD remains an incurable inherited disorder. Bone marrow or haemopoietic stem cell transplantation which could be curative is still quite hazardous and could cause death in a severe but otherwise not-immediately-fatal disease. Suitable bone marrow donors are not easy to come by, and the procedure is extremely care-intensive and expensive. In this emerging age of cord blood or peripheral blood stem cell transplantation it may sound naïve but plausible to speculate that peripheral stem cells previously unknowingly transfused during the many transfusions in a SCD patient may have successfully engrafted. If that ever happened, it may offer one explanation for the occasional anecdotal reports of spontaneous remissions of SCD. This phenomenon merits further investigation. Gene therapy, another potentially curative measure is still in experimental stage. We are therefore, left with management rather than cure of SCD. Apart from aplastic crisis, which is known to be caused by parvovirus B19 infection,[21] the causes of other types of crisis are not known. However, associated or aggravating factors such as malaria infection, septicaemia, dehydration and stress may be controlled. Vaccination against pneumococcal infection should be given where available or long-term prophylactic penicillin instituted. Other general causes of anaemia such as iron and folate deficiency and malnutrition may be prevented by supplementation. Among the anti-sickling agents, hydroxyurea, a chemotherapeutic agent that promotes HbF formation offers some hope to SCD patients.[22] This drug is not yet in routine use everywhere, and is to be used with caution in children. There are also unconfirmed reports of some African traditional edible plants that have antisickling properties. Zanthoxylum zanthoxyloides (FAGARA), Cajanus cajan and Niprisan* (proprietary name) are examples. These agents require further investigation and development.

CONCLUSION

From the foregoing, it is clear that blood transfusion in SCD in not as simple as it sounds. It is more hazardous in SCD patients than in other conditions. It may do less good than expected, or worse, more harm than good. On the other hand, it must be accepted that blood transfusion cannot always be avoided in SCD. A conservative approach is recommended and the guidelines suggested in Table 3 should be found useful.

Table 1: Adverse effects of Blood Transfusion

TYPE	SUBTYPE	SPECIAL EFFECTS IN SCD
Alloimmunization	Acute haemolytic reaction Delayed haemolytic reaction Post transfusion purpura Febrile reaction Anaphylaxis TRALI	Higher incidence and greater severity of AHTR and DHTR. Future allograft rejection
Post-transfusion anaemia	Reactive haemolysis	Commoner in SCD
Transfusion-related infection	Transmissible agents Contaminated blood. Post-op infection	Higher incidence and greater severity in SCD
Hyperviscosity	Vascular overload	Disproportionate increase in blood viscosity Aggravation of vaso-occlusion. Suboptimal improvement in oxygen delivery
Iron overload	Iron overload	Common in hypertransfusion regime

Table 2: Indications for Blood Transfusion In SCD

Improvement in oxygen carrying capacity (Simple Tx)	Reduction of proportion of sickle cells (Exchange Tx)	Suppression of production of sickle cells (Hyper Tx)
Hyper haemolytic crisis Aplastic crisis Sequestration crisis Peri-operative transfusion Other causes of blood loss	Cerebro-vascular episode Acute chest syndrome Priapism Peripartum sickle crisis Hepatic failure	Previous history of stroke CNS disease End-stage renal disease Chronic sickle lung Pregnancy Severe obstetric complications

Table 3: Recommended Guidelines for Blood Transfusion In SCD

1.	Avoid blood transfusion if at all possible.
2.	Introduce measures to reduce blood transfusion requirement.
3.	Consider transfusion only when Hb <5.0g/dl in uncomplicated cases.
4.	Transfuse to restore Hb. concentration to patient's pre-crisis stable level only (except for exchange or hyper-transfusion).
5.	Transfuse donor blood of similar ethnic origin or same previous donor where possible.
6.	Transfuse only red cell concentrate to correct anaemia.
7.	Transfuse only sickle-free red cells where possible.
8.	Always do recipient antibody screen prior to transfusion.
9.	Do full phenotyping of donor and recipient blood, and exclude corresponding antigen in donor blood for any recipient with atypical antibody.
10.	Always do full crossmatch, including the anti-human globulin technique.
11.	Transfuse fairly fresh or short-stored red cells.
12.	Transfuse leucocyte-reduced or buffy coat poor blood or washed cells where possible.
13.	Transfuse slowly, with diuretic cover where clinically indicated.
14.	Monitor blood transfusion very closely.

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