Africa Sanguine

2021, Volume 23, Number 1

https://dx.doi.org/10.4314/asan.v23i1.8

Merits and Demerits of Sickle Cell Trait Donor Blood in Tropical Transfusion Medicine: Are There Any Indications for Specific Use of Blood Donated by Carriers of Sickle Cell Trait?

Avantages et inconvénients du sang des donneurs porteurs du trait drépanocytaire en médecine transfusionnelle et en milieu tropical : existe-t-il des indications pour l'utilisation spécifique du sang donné par les porteurs du trait drépanocytaire ?

Ahmed SG[1], Ibrahim UA[2]

1. Department of Haematology, Aminu Kano Teaching Hospital, Kano, Nigeria
2. Department of Paediatrics, Aminu Kano Teaching Hospital, Kano, Nigeria

Corresponding Author:
Dr Sagir G. Ahmed
Email: drsagirahmed@yahoo.com

Key words: Sickle Cell Trait, Blood, Donation, Processing, Storage, Transfusion

ABSTRACT

Haemoglobin-S mutation confers anti-malarial resistance and survival advantage in the tropics. Consequently, a significant and indispensable proportion of tropical blood donors carry sickle cell trait (SCT), which is associated with both merits (advantages) and demerits (disadvantages) in the practice of tropical transfusion medicine. Majority of the literature regarding SCT in blood transfusion highlighted its demerits with little or no reference to its merits, which constitute potentially beneficial qualities and useful applications of SCT blood in tropical transfusion medicine. Hence, the aim of this review is to present an updated, balanced, and comprehensive but concise and critical overview of the literature (using search-terms relevant to SCT in transfusion medicine) for both merits and demerits of SCT donor blood vis-à-vis its potential applications and implications in technical and clinical practice of transfusion medicine in the tropics. The review is presented in a sequential 'stage-by-stage' order from pre-donation procedures to blood donation, processing, storage and transfusion. The review explored the potential adverse effects of pre-donation medications on SCT donor, highlighted SCT-associated technical challenges in blood collection, processing and storage, and elucidated the clinical demerits and implications of SCT blood in sickle cell disease, perinatal, and neonatal transfusions. Moreover, the review expounded the merits of SCT blood vis-à-vis the probability of its low risks for transfusion transmitted malaria and HIV infections, and its potential applications in the evolving concept of 'therapeutically rational transfusion of SCT red cells' in managing severe and/or drug resistant malaria, and possibly haemophilia. In conclusion, the review underscored the need for tropical transfusionists and clinicians to innovate ways of ameliorating or circumventing the demerits and implications of SCT blood, and at the same time explore the feasibility and safety of its potential merits and applications vis-à-vis the practice of blood transfusion in low resource settings in tropical Africa, and by implication in other regions of the world where SCT is prevalent.

RÉSUMÉ

La mutation de l'hémoglobine -S confère une résistance antipaludique et un avantage de survie sous les tropiques. Par conséquent, une proportion importante et indispensable des donneurs de sang tropicaux sont porteurs du trait drépanocytaire (SCT), qui est associé à la fois à des avantages et des inconvénients dans la pratique de la médecine transfusionnelle en milieu tropical. La majorité de la littérature concernant la SCT en transfusion sanguine a souligné ses inconvénients avec peu ou pas de référence à ses avantages, qui constituent des qualités potentiellement bénéfiques et des applications utiles des porteurs du SCT en médecine transfusionnelle. Par conséquent, le but de cette revue est de présenter une vue d'ensemble actualisée, équilibrée et complète mais concise et critique de la littérature ; cette revue a utilisé des termes de recherche pertinents pour la SCT en médecine transfusionnelle pour identifier les avantages et les inconvénients du sang de donneur SCT vis-à

-vis de vis à vis de ses applications potentielles et de ses implications dans la pratique technique et clinique de la médecine transfusionnelle sous les tropiques. L'examen est présenté dans un ordre séquentiel « étape par étape » depuis les procédures préalables au don jusqu'au don de sang, au traitement, au stockage et à la transfusion. La revue a exploré les effets indésirables potentiels des médicaments avant le don sur le donneur SCT, a mis en évidence les défis techniques associés au SCT dans la collecte, le traitement et le stockage du sang, et a élucidé les inconvénients cliniques et les implications du sang SCT dans la drépanocytose, les transfusions périnatales et néonatales. De plus, la revue a exposé les avantages du sang SCT vis-à-vis de la probabilité de ses faibles risques de paludisme transmis par transfusion et d'infections à VIH, et ses applications potentielles dans le concept en évolution de « transfusion rationnelle de globules rouges SCT » dans la prise en charge du paludisme résistant aux médicaments, et peut-être l'hémophilie. En conclusion, l'analyse a souligné la nécessité pour les hémobiologistes et les cliniciens tropicaux d'innover dans les moyens d'améliorer ou de contourner les inconvénients et les implications du sang SCT, et en même temps d'explorer la faisabilité et la sécurité de ses avantages et applications potentiels vis-à-vis de la pratique de la transfusion sanguine dans les milieux à faibles ressources en Afrique tropicale, et par ailleurs dans d'autres régions du monde où la SCT est répandue.

INTRODUCTION

Haemoglobin-S (HbS) is the most classical example of adaptive genetic polymorphism, which is strongly correlated with innate resistance to malaria infection.[1] HbS is a variant of the normal haemoglobin-A (HbA) that arose as a result of GAG>GTG base transition at codon-6 of the β-globin gene on chromosome-11.[1] The GAG>GTG base transition causes the substitution of glutamic acid (polar, hydrophilic amino acid) by valine (neutral, hydrophobic amino acid) at position-6 of the β-globin chain.[1] Consequently, HbS has less anionic potential, slower electrophoretic mobility and reduced deoxygenated solubility that leads to Hb polymerization and red cell sickling.[2] The sickle cell trait (SCT) refers to the heterozygous inheritance of the sickle β-gene.[3] The SCT protects against severe falciparum malaria and confers survival advantage in populations living in malaria endemic countries.[4] This is attained through the process of natural selection[5] and mediated by the phenomenon of balanced polymorphism[6], which is accomplished by immunological and biochemical mechanisms that protect individuals with SCT from malaria.[7] These mechanisms include reduced red cell invasion by the parasite, low intra-red cell parasite proliferation, parasite-induced red cell sickling and phagocytosis, reduced rosetting of parasitized red cells, and enhanced immune response against the malaria parasite.[7] Consequently, the prevalence of SCT in Nigeria and other tropical African countries is up to 25-30% in the general population[4]; and the prevalence SCT will continue to rise through natural selection as long as malaria remains endemic in the tropics.[5]

There are two techniques of collecting blood and blood products from donors viz: whole blood collection and apheresis, the former being the predominant technique especially in the tropics where facilities for apheresis are scarce. Irrespective of blood collection technique, the eligibility of prospective donors must be ascertained by pre-donation assessment of health status.[8,9] The assessment takes the form of verbal interviews and/or questionnaire-based answers to relevant questions on general health, medical history, and social attributes, followed by a general physical examination, which includes the measurements of blood pressure (BP) and body weight (BW).[8,9] Persons within the ages of 18 to 65 years with normal BP and BW, negative test results for HIV, syphilis, hepatitis B and C viruses, and Hb levels of more than 13.5 g/dl for males or 12.5 g/dl for females (except pregnant and lactating women) are acceptable as donors.[8,9] Individuals with SCT are genetically heterozygous for the sickle β-globin gene and their red cells have the HbAS phenotype expressing both HbS (20-40%) and HbA (60-80%).[1,10] The relative abundance of HbA in SCT red cells prevents undue sickling and haemolysis under physiological conditions.[1,10] Thus, carriers of SCT have normal red cell life-span and normal life expectancy.[11] Moreover, SCT carriers are clinically symptomless and haematologically non-anaemic.[11] Therefore, the SCT does not in any way jeopardize or diminish the chances of passing routine pre-donation tests. Consequently, SCT carriers constitute a significant and indispensible proportion of eligible blood donors in tropical African countries such as Nigeria, where up to one quarter or more of blood donors carry the SCT.[12,13] Unfortunately, the SCT blood has certain notable disadvantages and limitations. For example, SCT blood is unsuitable for some blood banking procedures such as leuco-filtration, and is also inappropriate for transfusing hypoxia-susceptible and sickling-prone patients such as foetuses, neonates and sickle cell disease (SCD) patients.[9] Thus, the World Health Organization (WHO) does not consider the SCT as a contraindication for blood donation as long as the donated blood is not subjected to the aforementioned blood banking procedures or used for transfusing the aforementioned categories of patients.[9]

We thus reckon that SCT blood has certain disadvantages (demerits), which constitute significant technical and clinical challenges and implications in the practice of transfusion medicine. Majority of the literature regarding SCT in blood transfusion predominantly highlighted the demerits associated with SCT blood, with little or no reference to the advantages (merits), which constitute potentially beneficial qualities and useful applications of SCT blood in the practice of clinical blood transfusion in the tropics. It is therefore important for the blood transfusion service personnel and clinicians in tropical Africa, and indeed other regions of the world where the SCT is prevalent,

to have a comprehensive and balanced understanding of both proven and potential merits and demerits of SCT in transfusion medicine. Hence, the primary aim of this review

is to present an updated, balanced, and comprehensive but concise and critical overview of the literature (using search terms: sickle cell trait donor, pre-donations procedures, donation, processing, storage, contraindications, transfusion, and relevant sub-terms in Pub Med, Google Scholar, Medline, and other search engines) for both merits and demerits of SCT in transfusion medicine. The secondary aim is to critically highlight the 'pros-and-cons' of SCT blood vis-à-vis its technical and clinical applications and implications in perinatal and neonatal transfusion, sickle cell disease, haemophilia and general transfusion medicine in the tropics. This review is presented in a sequential 'stage-by-stage' order from pre-donation procedures to blood donation, processing, storage and transfusion as outlined in Tables 1 and 2.

Table 1: Demerits of sickle cell trait (SCT) in transfusion

PRE-DONATION STAGE: Pre-donation Haematopoiesis Enhancement Medications
• G-CSF Injections: Neutrophilia, Hyperviscosity, Risk of VOC in SCT Donors
• EPO Injections: Prothrombotic Effects, Risk of VTE in SCT Donors
BLOOD DONATION STAGE: Blood Collection in Bags
• SCT hypercoagulability: Risk of Clotting in SCT Blood Bags
BLOOD PROCESSING STAGE: Leucocyte Depletion Procedures
• SCT Red Cell Sickling, Rigidity: Risk of Filter Clogging During Leuco-filtration
BLOOD STORAGE STAGE: Conventional (aerobic) and Anaerobic Storage at 4°C
• Conventional (aerobic) Storage: SCT Red Cells Associated with Increased in-storage Haemolysis, Reduced Post-Transfusion Survival
• Anaerobic Storage: Risk of Massive Sickling of SCT Red Cells within Blood Bags During Storage
BLOOD TRANSFUSION STAGE: Recipient Exclusions
• SCT Red Cells may Sickle in Potentially Hypoxic Conditions: Unsuitable for Foetuses
• SCT Red Cells may Sickle in Potentially Hypoxic Conditions: Unsuitable for Neonates
• SCT Red Cells Contain About 40% HbS: Unsuitable for Sickle Cell Disease Patients

G-CSF=Granulocyte Colony Stimulating Factor; VOC=Vaso-Occlusive Crisis; EPO=Erythropoietin; VTE=Venous Thrombo-Embolism; HbS=Haemoglobin-S.

Table 2: Merits of sickle cell trait (SCT) in transfusion medicine

PRE-DONATION STAGE: Donor Screening and Risk of Infection
• SCT Donors and Low Risk of Asymptomatic Malaria Parasitemia
• SCT Donors and Low Risk of HIV Infection
BLOOD TRANSFUSION STAGE: Therapeutically Rational Use of SCT Blood
• SCT and Malaria Resistance: Therapeutically Rational Exchange Transfusion for Severe Malaria
• SCT and Hypercoagulability: Therapeutically Rational Additive Transfusion for Severe Haemophilia

DEMERITS OF SICKLE CELL TRAIT IN TRANSFUSION MEDICINE

SCT has been associated with a number of demerits within the ambit of clinical transfusion medicine. The demerits of SCT have been documented at virtually every stage of transfusion medicine ranging from the initial 'pre-donation stage' to the final 'blood transfusion stage' as outlined in Table-1 and pathophysiologically described below.

1. Pre-donation Stage: Pre-donation Haematopoiesis Enhancement Medications

There are two haematopoiesis-enhancing pre-donation medications (granulocyte colony stimulating factor and erythropoietin) that may be administered to eligible donors in clinical transfusion practice as described below.

1a. Granulocyte Colony Stimulating Factor: Neutrophilia, Hyperviscosity, Risk of VOC in SCT Donors

Granulocyte colony stimulating factor (G-CSF) is a cytokine and a haematopoietic growth factor that is naturally produced by monocytes, macrophages, fibroblasts, endothelial cells and marrow stromal cells.[14] However, it is now being commercially produced by recombinant DNA technology.[14] Functionally, G-CSF stimulates the proliferations and maturation of haematopoietic stem cells with a concomitant increase in the production of mature neutrophils (neutrophilia).[15] Moreover, G-CSF can also mobilize marrow haematopoietic stem cells into circulation.[15] Hence, G-CSF is usually administered as a strategy for enhancement and mobilization of haematopoietic stem cells during apheresis.[15] G-SCF mobilized haematopoietic stem cells are cytometrically identified as CD-34 positive mononuclear cells that are selectively harvested by apheresis for the purposes of autologous or allogeneic stem cell transplant procedures.[16] However, there are some concerns and skepticisms regarding the safety of apheresis donations by persons with SCT vis-à-vis the possibility of adverse effect of hypoxia on SCT blood within the extracorporeal apheresis circuit.[17] For this reason, the European committee on blood transfusion guidelines prohibits SCT carriers from donating red cells by apheresis, but the guidelines remain silent about apheresis donation of other blood products by SCT carriers[18], which is allowed or prohibited at the discretion of individual blood bank policies.[17] Nonetheless, a recent study on platelet apheresis donations derived from SCT (HbAS) donors have revealed similar platelet quality in comparison to those derived from non-SCT (HbAA) donors.[17] Moreover, no increase in incidence of adverse reactions was observed among SCT (HbAS) donors in comparison with non-SCT (HbAA) donors.[17]

Despite the safety of platelet apheresis procedure in persons with SCT[17], apheresis must be carried out with caution if it is intended for the purpose of collecting stem cell donation from persons with SCT. This is because G-CSF is usually used as a pre-donation booster and mobilizer for stem cell apheresis[15,16], and unfortunately G-CSF can provoke vaso-occlusive events in SCT carriers.[19] Although SCT carriers are generally asymptomatic, the use of pre-donation G-CSF in a person with SCT has been reported to trigger full-blown vaso-occlusive crisis (VOC).[19] There are at least two possible pathophysiologic mechanisms that can trigger VOC when G-CSF is used in individuals with SCT. First, G-CSF causes neutrophilic leucocytosis, which increases the number of vaso-adherent neutrophils[20] and raises whole blood viscosity[21], both of which are important rheological risk factors for vascular occlusion and pain crisis in sickle cell disorders.[22] Second, G-CSF causes neutrophils activation, which increases the adhesiveness of neutrophils onto the vascular endothelium, thereby increasing the risk of VOC.[23] Nonetheless, some studies have reported that G-CSF is safe for mobilizing hematopoietic stem cells in donors with SCT.[24] These controversies call for caution when considering the use of G-CSF as a pre-donation medication for stem cell apheresis on donors that carry SCT.

1b. Erythropoietin: Prothrombotic Effects, Risk of Venous Thrombo Embolism in SCT Donors

Erythropoietin (EPO) is a member of class-I cytokines and is markedly induced by hypoxia.[25] EPO is mainly produced by peri-tubular fibroblast-like cells in the cortex-medullary border of the kidney, and to a lesser extent by the hepatocytes, bone marrow macrophages, trophoblasts, breast cells, and astrocytes.[25] However, it is now being commercially produced by recombinant DNA technology.[25] Functionally, EPO stimulates the proliferations and maturation of burst-forming and colony-forming erythrocytic progenitors in the bone marrow, thereby increasing and maintaining the red cell mass.[25] Consequently, recombinant human erythropoietin (rhEPO) is commonly used to boost autologous donor red cell mass and facilitate the collection of more units of erythrocyte-rich blood within relatively short intervals of autologous donations.[26] Nevertheless, several studies have previously highlighted increased incidence of thrombotic complications, especially venous thromboembolism (VTE), in patients with various form of chronic anaemias undergoing therapy with Erythropoiesis Stimulating Agents (ESAs), including rhEPO.[27] The pathophysiology of the prothrombotic effects of ESAs is multi-factorial, including polycythemia, hyperviscosity, thrombocytosis, platelet hyperactivity, and activation of blood coagulation cascade.[27] It has therefore been suggested ESAs should be used with caution, especially in patients with background hypercoagulability.[27] Previous studies on the use of rhEPO for autologous donation in Japanese[28] and European[29] donors (among whom SCT would be extremely unlikely) suggested that rhEPO was safe and devoid of any prothrombotic risks. Unfortunately, there is dearth of research on the prothrombotic risk of rhEPO vis-à-vis autologous blood donation in tropical Africa, where up to 25-30% of the general and donor populations carry SCT.[12,13,30] Thus the potential risk of using rhEPO for autologous donation in persons with SCT is unknown.

It is well established that SCT confers upon its carriers a significant state of prothrombotic hypercoagulability[31], which results in elevated risk of VTE among apparently healthy carriers of the trait.[32] SCT-associated hypercoagulability has been pathophysiologically attributed to the effects of sub-clinical red cell sickling[33], which increases red cell rigidity[34], raises blood viscosity[34], scrambles red cell membrane phospholipids[35], releases procoagulant phospholipids[36], and ultimately increases the activation rate of clotting factors.[33,36] Moreover, SCT has also been associated with increased expression of monocyte-derived tissue factor, which undesirably aggravates the background hypercoagulability due to sub-clinical red cell sickling.[33] Therefore, SCT is inherently prothrombotic. Accordingly, we envisage that rhEPO-associated hypercoagulability may act synergistically with SCT-associated hypercoagulability and predispose person with SCT to high risk of thrombosis. This potentially prothrombotic synergy between rhEPO and SCT calls for cautious and judicious considerations whenever the use of rhEPO is contemplated for autologous donors who carry SCT.

2. Blood Donation and Collection Stage: SCT hypercoagulability, Risk of Clotting in Blood Bags

Clotting in blood bags has undesirable economic and clinical consequences in Nigeria, and indeed other low-resource tropical countries, where health budgets are typically inadequate (37), voluntary blood donors are usually scarce[38,39], and unmet transfusion needs are often high.[40] There are four possible trigger mechanisms (root causes) for coagulation activation and clot formation in blood bags during blood donation. First, an untidy and unduly traumatic venepuncture can cause significant vascular endothelial injury with exposure of sub-endothelial microfibrils and collagen, which can trigger contact activation of platelets and FXII.[41] Second, slow blood flow (e.g. due to poor vein selection) within the anticoagulant-free plastic tubing can also lead to contact activation of blood coagulation.[42] Third, over-filling of bags and/or under-mixing of blood within collection bags can also predispose to clot formation.[43] And fourth, inadequate skin cleansing of venepuncture site can result in contamination with bacteria, which can proliferate, trigger coagulation and eventually cause clot formation in blood bags.[8] High level of quality control in phlebotomy and blood collection is obviously required to avoid triggering any or all of the four aforementioned root causes of coagulation activation and clotting during blood donation.[8]

Quality control, haemovigilance and root-cause analysis for clotted blood bags are generally inadequate or lacking in Nigeria and many

other developing tropical countries, as clotted blood bags are more often than not simply discarded without further investigations.[39,44] Nonetheless, a recent study on clotted bags in Nigeria revealed that the incidence of clotting in blood bags was estimated to be high at about 3%, but the actual incidence maybe much higher due to under-reporting and under-documentation of clots in blood bags.[45] Another study from Nigeria revealed that irrespective of the root causes or trigger mechanisms for clotting within blood bags, donor SCT was associated with relatively higher risk of clotting in blood bags.[46] This phenomenon was interpreted to be a manifestation of the innate hyperviscosity and hypercoagulability of SCT blood.[31-36] There is therefore a need for Nigeria and other tropical countries with high prevalence of SCT among their general and donor populations[12,13,30] to assess the actual extent to which SCT contributes to clotting and wastage of donated blood vis-à-vis the feasibility of preemptive pre-donation hydration. This is because optimal oral hydration has been shown to reduce blood viscosity in persons with SCT, both at rest and during exercise.[47] Hence, pre-donation oral hydration (for SCT donors) may predictably minimize hyperviscosity, reduce hypercoagulability and attenuate the risk of clotting in blood collected from donors with SCT. Although a recent study has identified SCT as a risk factor for clotting in blood bags in Nigeria[46], we believe that the clotting risk associated with SCT is perpetuated by the prevailing poor quality control within the Nigerian blood transfusion service.[44], as is usually the case in other developing tropical countries.[39] Hence, there is the need for tropical countries to improve quality control in blood donation and collection procedures in order to minimizing the incidence of clotting and wastage of donated blood irrespective of donor haemoglobin phenotypes.

3. Blood Processing Stage: Leucocyte Filtration, Red Cell Sickling, Rigidity, Filter Clogging

Because people with SCT are genetically heterozygous for the sickle β-globin gene, their red cells contain both HbA and HbS.[1] But the relative quantities of the haemoglobins (HbA and HbS) are disproportionately distributed (i.e. HbA:~ 60%; HbS:~ 40%) within the red cells of persons with SCT.[10] Thus the relative abundance of HbA (~ 60%) prevents clinically significant polymerization, sickling and haemolysis under physiological conditions.[10] Nonetheless, relative to HbAA red cells, SCT red cells are inherently stiffer and more viscous[34], which may be a manifestation of subclinical Hb polymerization and sickling. Moreover, sickling of SCT red cells may occur in the relatively hypoxic environment within donated blood bags, a situation that is thought to be responsible for the high incidence of filter-clogging during leuco-depletion of whole blood units donated by persons with SCT.[48,49] However, the filterability of SCT blood can be improved by increasing the oxygen saturation level (thereby inhibiting HbS polymerization) within the SCT blood bag.[49] Therefore, SCT represents the most common cause of leuco-filtration failure.[50] Moreover, SCT blood units that 'manage' to pass through the leucocyte filter often have unduly prolonged filtration time and high post-filtration residual leucocyte counts.[51] Consequently, WHO guidelines recommend that whole blood donated by persons with SCT should not be subjected to leuco-filtration.[9] This is a major challenge for tropical blood banks where up to one quarter or more of blood donors carry the SCT.[12,13] And yet SCT blood cannot be easily and satisfactorily filtered to produce leucocyte depleted red cell concentrates, which may be essential in the prevention and/or management of immune sensitization and febrile reactions among chronically transfused patients.[52] Therefore, a pertinent clinical research question remains to be answered. Should the tropical transfusion centres and blood banks adopt Stroncek's method[49], which is an effective but potentially costly method of facilitating leuco-filtration of SCT blood by increasing oxygen saturation levels within whole blood bags donated by SCT carriers?

4. Blood Storage Stage: Conventional (Aerobic) and Anaerobic Storage at 4°C

Liquid blood can be stored at 4°C by two methods: conventional (aerobic) and anaerobic methods. The former method is the standard method in current practice of blood transfusion, while the later method is still under experimental exploration. Each one of these two methods of storage has potential problems with respect to SCT red cells as described below.

4a. Conventional (Aerobic) Storage: SCT Red Cells Associated with Increased in-storage Haemolysis, Reduced Post Transfusion Survival

As earlier mentioned, haemo-rheological studies had suggested that SCT is associated with subtle HbS polymerization and red cell sickling in-vivo[34,46], while leuco-filtration studies had suggested that subtle HbS polymerization and red cell sickling of SCT red cells also occur in-vitro within donated blood bags during conventional (aerobic) storage at 4°C.[48-50] HbS polymerization and red cell sickling cause oxidation-induced damage to both lipid and protein components of the red cell membrane[53], which would invariably compromise membrane integrity, reduce stability of SCT red cells during storage, and presumably decrease post transfusion survival of stored SCT red cells. Quite expectedly, a study on human and transgenic murine models of SCT had shown that in comparison to HbAA red cells, SCT red cells were associated with accelerated in-storage haemolysis, rapid post transfusion clearance, and reduced post transfusion recovery.[54] Therefore, a important clinical research question remains to be answered. Should the tropical transfusion centres and blood banks review the duration of storage shelf-life of blood donated by persons with SCT? This can only be adequately answered after a rigorous and large scale study on the impact of SCT on storage changes and post transfusion recovery of red cells donated by persons with SCT.

4b. Anaerobic Storage: Potential Risk of Massive Sickling of SCT Red Cells within Blood Bags During Storage

Stored red blood cells are continuously subjected to oxidative stress and membrane injury by reactive oxygen species during conventional (aerobic) liquid storage at 4°C.[55] Studies have shown that removal of oxygen from blood bags during storage (i.e. anaerobic storage) eliminates the adverse contribution of oxygen to the development of red cell storage lesions.[55] Consequently, anaerobic storage of red cells has many potential advantages over conventional storage with respect to mitigation of oxidative red cell damage[56], thus allowing for extended storage with good post transfusion red cell viability[57], which could be further augmented by the addition of metabolite precursors in the storage solutions.[58] However, these studies[55-58] were conducted on Caucasian donor red cells, and cannot therefore be deemed to be safely applicable to donor red cells derived from tropical Africa and other regions with high prevalence of SCT among donor populations.[12,13] This is because SCT red cells contain about 40% HbS[10], which may potentially polymerize and induce red cell sickling within the relatively hypoxic confinement of blood bags. For example, some studies have shown that SCT blood stored under conventional (aerobic) conditions has poor filterability during leuco-depletion procedures[48-50], which suggest that some degree of HbS polymerization and red cell sickling occur (due to relative hypoxia in blood bags) even during conventional aerobic storage. It is therefore easy to envisage that anaerobic storage might potentially trigger more intense and massive HbS polymerization and sickling of SCT red cells. It should be appreciated that deoxygenation and sickling cause significant damage to the membranes of HbS-containing red cells.[53,59] Hence, we infer that the deoxygenation process associated with anaerobic storage of SCT red cells may lead to extensive and/or irreversible sickling, which may adversely affect the post transfusion viability of transfused SCT cells and/or obstruct the microvasculature of the recipient circulation.[60] Obviously, further studies are required to determine the feasibility and safety of storing SCT red cells under anaerobic conditions.[60] Meanwhile, if anaerobic storage of blood is contemplated in the tropics and other areas with high prevalence of SCT, donor Hb phenotyping should be routinely carried out in order to identify SCT donors and avoid subjecting their red cells to anaerobic storage.[61]

5. Blood Transfusion Stage: Recipient Exclusions

Blood donated by persons with SCT can be safely transfused into the vast majority of patients with normal cardiopulmonary functions devoid of significant hypoxia. However, the WHO has explicitly declared that SCT blood is inappropriate for transfusing three categories of hypoxia-susceptible and sickling-prone patients viz: foetuses, neonates and SCD patients as described below.

5a. SCT Red Cells may Sickle in Potentially Hypoxic Conditions: Unsuitable for Foetuses.

Foetal anaemia is a serious complication of pregnancy. Foetal anaemia may be caused by genetic or infectious factors, but it is commonly due to foeto-maternal blood group incompatibility resulting in maternal sensitization and cross-placental transfer of maternal allo-immune IgG, which is followed by haemolysis of foetal red cells.[62] Severe foetal anaemia is associated with high incidence of perinatal morbidity and mortality.[62] Fortunately, intrauterine transfusion (IUT) therapy is considered a most successful management of foetal anaemia.[62] However, IUT is not devoid of potentially serious complications. For example, fetal distress during or after the IUT procedure can occur due to local cord accidents such as spasm, rupture, excessive bleeding, or tamponade from a hematoma[62], all of which can independently or concertedly cause severe post-placental foetal hypoxia.[63] The high risk of foetal hypoxia makes the use SCT donor red cells unsuitable for IUT. This is because hypoxia may trigger polymerization of HbS and sickling of transfused SCT red cells, a situation that would aggravate the adverse outcome of any hypoxia-inducing mishap during or after IUT. Hence the outright recommendation of the WHO, which stipulates that SCT red cells should not be used for IUT.[9] Regrettably, the sophisticated equipments and monitoring techniques that are required for successful IUT are currently unavailable in the vast majority of tropical developing countries. Nonetheless, it should be kept in the mind of the tropical perinatologists and transfusionists that SCT red cells are contraindicated for IUT.[9]

5b. SCT Red Cells may Sickle in Potentially Hypoxic Conditions: Unsuitable for Neonates

Developing tropical countries are characterized by high population growth rates. For example, Nigeria, which has the largest population in tropical Africa, also has one of the highest birth rates in the world.[40] Consequently, Nigeria carries a heavy burden of neonatal anaemia, jaundice and transfusion due to high prevalence of sepsis, prematurity, and G6PD enzyme deficiency.[64] There are two techniques for neonatal blood transfusion in clinical practice, viz: additive transfusion for simple anaemia or exchange transfusion for anaemia complicated by severe jaundice.[64] Irrespective of the type of transfusion, blood obtained from SCT donors has two important disadvantages that makes it unsuitable for neonatal transfusion. First, HbS in stored SCT red cells polymerizes and prevents optimal leuco-filtration[48-51,65], whereas adequate leuco-filtration is an important requirement for preventing the transmission of cytomegalovirus infection into neonates.[66] Second, SCT red cells may sickle under hypoxic conditions and are thus not suitable for patients with hypoxia and cardiopulmonary insufficiency[67], whereas apnea, bradycardia, oxygen desaturation, and hypoxia are not uncommon in newborns especially in premature neonates.[68] The potential risk of using SCT

solitary case-report of a neonate who was massively transfused with SCT red cells, which resulted in massive splenic infarct, multiple haemorrhagic renal infarcts, and acute renal failure.[69] It is therefore not surprising that the WHO recommends that SCT red cells should not be used for neonatal transfusion.[9] Accordingly, the standard of care for best practice for neonatal transfusion requires selective use of HbAA red cells.[70]

5c. SCT Red Cells Contain About 40% HbS: Unsuitable for Sickle Cell Disease

With the largest tropical back population of over 200 million, SCT frequency of 25-30% and SCD prevalence of 2-3%, Nigeria carries the heaviest burden of both SCT and SCD in the world.[30] As a chronic haemolytic disorder, the management of SCD is transfusion intensive.[71] In similarity with neonatal transfusion, there are basically two types of transfusion techniques for SCD patients, viz: additive transfusion for simple anaemia or exchange with hyper-transfusion for serious complications such acute chest syndrome, stroke or priapism.[71] Irrespective of the type of transfusion, SCT red cells are not recommended for transfusing patients with SCD for three clinically relevant reasons. First, SCT blood is intrinsically hyper-viscous[34,47], and it would obviously aggravate the pre-existing haemo-rheological abnormalities in the blood of patients with SCD.[72] Second, SCT blood is inherently hypercoagulable[31-33,35,36], and it would undoubtedly add to the pre-existing hypercoagulability of SCD.[73] Third, SCT red cells may contain about 40% HbS[10], which would increase the pre-existing burden of HbS in patients with SCD, thereby diminishing the therapeutic efficacy of exchange transfusion in reducing the quantity of HbS in the blood of patients with SCD.[71] It is therefore easy to appreciate why the WHO recommends that SCT red cells should not be used for patients with SCD.[9] Hence, the standard of care for best practice for SCD transfusion requires selective use of HbAA red cells.[74]

MERITS OF SICKLE CELL TRAIT IN TRANSFUSION MEDICINE

Inspite of the aforementioned demerits, SCT has nonetheless been associated with a limited number of merits and beneficial qualities within the ambit of clinical transfusion medicine, especially at the 'pre-donation stage' and the 'blood transfusion stage' as outlined in Table 2 and described below.

1. Pre-donation Stage: Donor Screening and Risk of Infection

High prevalence of endemic transfusion transmissible infections has compelled tropical blood banks in Nigeria and other African countries to adopt pre-donation screening and deferral strategy in order to avoid wasteful collection of infected donor blood.[8] This strategy may be at variance with international practice, but it is undoubtedly fiscally prudent and financially rational within the limited health budgets of tropical countries.[37] Although SCT has traditionally been associated with resistance against malaria[75-78], recent studies have also associated SCT with resistance against HIV.[79-84] Thus SCT donors may have lower risk of having malaria and HIV infections, which would translate into a lower incidence of pre-donation deferrals among prospective donors with SCT. Moreover, recipients of SCT donor blood would also be at lower risks of acquiring transfusion transmitted malaria (TTM) and transfusion transmitted HIV (TTHIV) infections as expatiated below.

1a. SCT Donors and Low Risk of Asymptomatic Malaria Parasitemia

SCT red cell is naturally endowed with the ability to resist initiation and propagation of the erythrocytic phase of malaria infection via five layers of protective mechanisms. First, SCT red cells are innately resistant to invasion by P. falciparum.[7,75] Second, if the parasites manage to successfully invade the SCT red cells, the invasion triggers red cell sickling and/or eryptosis, which lead to phagocytic clearance of the infected SCT red cells along with the invading parasites.[7,75] Third, if the infected SCT red cells escape phagocytosis, the intra-erythrocytic growth of the invading parasites is significantly repressed by translocation of host micro-RNAs into the parasite genome.[76] Fourth, survival of the repressed parasites is retarded by the ambient inhospitable conditions (dehydration, osmotic shrinkage, low intracellular potassium, and HbS polymerization) within the cytoplasm of the infected SCT red blood cells.[7] And fifth, any residual surviving parasites are eventually and effectively cleared by the host anti-malarial immune response, which is particularly more developed in persons with SCT (than in persons with HbAA).[7] Therefore, SCT polymorphism is naturally designed to resist P. falciparum, and has been shown to offer a wide spectrum of protect against all clinical stages of malaria infection ranging from asymptomatic malaria to clinically non-severe and severe malaria.[7,77,78] Interestingly, a recent study from Nigeria has specifically demonstrated that in comparison to blood donors with HbAA, donors with SCT were associated with low risk of asymptomatic malarial parasitemia.[78] The finding of that study implied that SCT blood carries low risk of TTM infection.[78] Hence, donor SCT phenotype is an important but surreptitious mitigator of the risk of TTM infection in Nigeria and by implication, in other malaria endemic tropical countries.[78]

1b. SCT Donors and Low Risk of HIV Infection

Recent studies suggest that sickle β-globin gene (in SCD patients and in SCT carriers) may be associated with protection against acquisition and progression of HIV infection.[79] A possible mechanism of the protection could exist within the genome of persons with sickle β-globin gene, which probably facilitates the production of TRIM5α leucocyte membrane protein.[79] This protein prevents HIV pre-integration complex from arriving at the nucleus, thus interfering

with reverse transcription[80,81], which may explain the lower (than the expected) rate of HIV infection among individuals with sickle β-globin gene.[79] Additional possible mechanisms for HIV resistance in patients with SCD include up-regulation of haeme oxygenase-1, hypoxia related to anaemia, higher expression of inflammatory cytokines and inhibition of HIV transcription in the presence of deregulated iron metabolism[79,82], as well as lower CD4+ T-cell expression of CCR5 and CCR7 chemokine receptors for HIV.[83] Interestingly, in similarity with SCD, SCT is also associated with resistance against HIV infection. A recent cohort study of Nigerian children with HIV infection had shown that in comparison with normal HbAA phenotype, SCT confers relative protection against acquisition of HIV infection.[84] Moreover, HIV viral RNA load was significantly lower in the HIV infected children with SCT as compared to their counterparts with normal HbAA phenotype.[84] On the basis of the aforementioned studies, we presume that donors with SCT phenotype would be at lower risk of having HIV infection, which implies that (in comparison to HbAA donor blood) SCT donor blood would be associated with lower risk of TTHIV infection. Hence, donor SCT maybe an important but surreptitious mitigator of the risk of TTHIV infection in tropical Africa, where a significant proportion of blood donors carry the SCT.[12,13] This meritorious attribute of SCT would be particularly desirable in sub-Saharan Africa, where the risk of TTHIV infection is high due to inadequacy of standardized serological tests for detecting donor HIV infection, which is exacerbated by lack of nucleic acid tests for detecting serologically negative HIV infected donors during the window period.[85]

2. Blood Transfusion Stage: Therapeutically Rational Use of SCT Blood

Anti-malarial resistance and hypercoagulability form the pathophysiologic basis for the potentially useful applications of SCT blood within the context of 'therapeutically rational application of SCT blood' in managing severe malaria and possibly haemophilic bleeding, as described below.

2a. SCT and Malaria Resistance: Therapeutically Rational Exchange Transfusion for Severe Malaria

Exchange blood transfusion (EBT) has been used as an adjunct treatment modality for reducing parasite load, decreasing blood viscosity, and increasing microvascular perfusion in patients with severe malaria.[86] However, the role of EBT vis-à-vis its benefits on patients' clinical outcome remains controversial.[86] Therapeutically rational exchange (TREX) transfusion using malaria resistant SCT red cells is an attractive theoretical model that may augment the benefits of red cell exchange in the management of severe malaria, which is often seen among HbAA individuals and other vulnerable persons in the tropics.[87,88] TREX with SCT red cells would presumably be particularly valuable and life-saving for high-risk cases such as non-immune and immune-compromised patients[89], as well as for patients with drug resistant malaria, which is unfortunately becoming increasingly prevalent in malaria endemic African countries inspite of the current use of Artemisinin based combination therapy as recommended by WHO.[90]

The concept of TREX with SCT red cells in managing severe malaria was prompted by the natural ability of SCT red cells to resist P. falciparum invasion and proliferation.[7] Nonetheless, other red cell associated polymorphisms such as the ABO blood groups are also important in anti-malarial resistance.[91] Accordingly, the proponents of TREX with SCT red cells recommended the use of SCT donor red cells alone[87], or in combination with other malaria resistant red cell phenotypes (such as blood group-O phenotype)[88] in the management of severe P. falciparum infections. Nigeria is malaria endemic[30], and it has the largest global genetic pool of SCT carriers[30] with a commensurate high prevalence of SCT among its blood donors.[12,13] Thus, Nigeria was (by default) considered to be a prototype country for evaluating the feasibility and effectiveness of TREX with SCT red cells in the management of severe malaria.[88] In view of the potential thrombotic complications of SCT red cells[32], the proponents of TREX with SCT red cells had reckoned that prudence and caution are required for patients who are pregnant[92], or taking birth-control hormones[93], or have a personal or family history of deep vein thrombosis or other thrombotic events.[88] Moreover, we believe there are two additional haemostatic safety issues that need to be cautiously considered with respect to the use of SCT red cells for TREX in severe malaria. First, severe malaria by itself is potentially prothrombotic[94], hence patients with severe malaria may be more susceptible to the thrombotic challenge posed by transfused SCT red cells. Second, patients with severe malaria are more likely to have non-O blood groups[95], and coincidentally, non-O blood groups are also independently associated prothrombotic tendencies.[96] There is therefore a need for standardized expert guidelines regarding indications, precautions and contraindications for TREX with SCT red cells vis-à-vis the separate and/or combined prothrombotic effects of SCT red cells, pregnancy, oral contraceptive use, non-O blood groups, and/or family history of thrombotic events in patients with severe malaria.

2b. SCT and Hypercoagulability: Therapeutically Rational Additive Transfusion for Severe Haemophilia

Haemophilia-A is an X-linked recessive disorder associated with deficiency of coagulation FVIII and lifelong bleeding diathesis.[97] Severe haemophilia is characterized by musculoskeletal complications due to recurrent spontaneous bleeding into muscles and joints.[97] However, it is known that the coinheritance of thrombophilic (prothrombotic) genes, e.g. Factor-V Leiden (FVL) gene, often reduces spontaneous bleeding rates and complications in European patients with severe haemophilia.[98] The sickle β-globin gene occurs with high frequencies in tropical Africa and other

malaria endemic regions, where it causes variable degrees of clinical (symptomatic) and subclinical (asymptomatic) red cell sickling in persons with SCD and SCT respectively.[1] In similarity with FVL gene, the sickle β-globin gene is prothrombotic as mentioned in previous sections.[31-33,35,36] Hence, the coinheritance of the sickle β-globin gene should presumably improve bleeding phenotypes of haemophiliacs. But only a few studies have suggested possible benefits of sickle β-globin gene on haemophilic bleeding. To the best of our knowledge, there are only three notable but very small studies in the literature regarding coinheritance of haemophilia-A and the sickle β-globin gene.[99-101] First, a case report from India suggested that SCD was associated with reduction in bleeding complications in severe haemophilia.[99] Second, a small retrospective study from Nigeria suggested that SCT was associated with reduction in bleeding rates in severe haemophilia.[100] And third, a case report from Maroc implied that SCT could possibly delay the onset of spontaneous haemorrhagic manifestations of severe haemophilia.[101] Regrettably in low resource tropical countries, FVIII concentrate and cryoprecipitate are scarce[102,103], hence 'fresh whole blood' is still commonly used to treat haemophilic bleeding in the tropics.[104] In view of the aforementioned potentially favourable effects of sickle β-globin gene on haemophilic bleeding[99-101], there are two clinically pertinent issues that need to be resolved with respect to SCT and haemophilia in tropical countries. First, there is need for large and controlled studies to determine the actual impact (if any) of the sickle β-globin gene on haemophilic bleeding and complications. Second, there is need to determine whether or not 'fresh whole SCT blood' can be safely and effectively used for 'therapeutically rational additive transfusion' in treating intractable bleeding in severe haemophiliacs (who have HbAA phenotype) in the absence of FVIII concentrate and cryoprecipitate, as is usually and regrettably the case in low resource tropical African clinical settings.[102,103] It must however be appreciated that although transfusion of SCT blood is considered safe for non-hypoxic older children and adults, a precautionary recommendation of the WHO[9] dictates that transfusion of SCT blood should be generally avoided in all neonates (which by implication include haemophilic neonates), as earlier elucidated in sections 5, 5a, 5b and 5c of this review.

CONCLUSION AND RECOMMENDATIONS

The high prevalence of SCT in tropical donor populations signifies the indispensability of SCT donor blood in the practice of tropical blood transfusion. Nonetheless, the SCT donor blood has well recognized technical and clinical demerits and implications in transfusion medicine. Inspite of its demerits and implications, SCT has some potential merits and applications that have neither been adequately explored nor standardized. Hence, the onus lies on tropical transfusionists and clinicians to innovate ways of ameliorating or circumventing the demerits and implications of SCT blood, and at the same time explore the feasibility and safety of its potential merits and applications vis-à-vis the practice of blood transfusion in low resource settings in tropical Africa, and by implication in other regions of the world where SCT is prevalent.

REFERENCES

1. Flint J, Harding RM, Boyce AJ, Clegg JB. The population genetics of the haemoglobinopathies. Bailliere's Clin Haematol 1993;6:215-22.DOI:10.1016/S0950-3536(05)80071-X.
2. Kaul DK, Fabry ME, Nagel RI. The pathophysiology of vascular obstruction in the sickle cell syndromes. Blood Rev 1996;10:29-44. DOI:10.1016/S0268-960X(96) 90018-1.
3. Pecker LH, Naik RP. The current state of sickle cell trait: implications for reproductive and genetic counseling. Blood 2018;132:2331-8. DOI:10.1182/blood-2018-06-848705.
4. Fleming AF, Storey J, Molineaux L, Iroko EA, Attai ED. Abnormal haemoglobins in the Sudan savanna of Nigeria: I. Prevalence of haemoglobins and relationships between sickle cell trait, malaria and survival. Ann Trop Med Parasitol 1979;73:161-72. DOI:10.1080/00034983.1979.11687243.
5. Elguero E, Délicat-Loembet LM, Rougeron V, Arnathau C, Roche B, Becquart P. Malaria continues to select for sickle cell trait in Central Africa. Proc Natl Acad Sci 2015;112: 7051-4. DOI:10.1073/pnas.1505665112.
6. Olatunji PO. Malaria and the sickle gene: polymorphism balance in favour of eradication. Ann Health Res 2018;4:88-96. DOI:10.30442/ahr.0402-1-12.
7. Gong L, Parikh S, Rosenthal PJ, Greenhouse B. Biochemical and immunological mechanisms by which sickle cell trait protects against malaria. Malar J 2013;12:317. DOI:10.1186/1475-2875-12-317.
8. Salawu L, Murainah HA. Pre-donation screening of intending blood donors for antibodies to infectious agents in a Nigerian tertiary health institution: a pilot study. Afr J Med Med Sci 2006;35:453-6.
9. https://apps.who.int/iris/bitstream/handle/10665/76724/9789241548519_eng.pdf. [Accessed April 1, 2021].
10. Ahmed SG, Ibrahim UA. Haemoglobin-S in sickle cell trait with papillary necrosis. Br J Haematol 2006;135:415-6. DOI:10.1111/j.1365-2141.2006.06318.x.
11. Barbedo MMR, McCurdy PR. Red cell life span in sickle cell trait. Acta Haematol 1974;15:339-42. DOI:10.1159/000208316.
12. Ahmed SG, Hassan AW, Ibrahim UA. The frequency and clinical significance of structural haemoglobin variants in donor blood at university of Maiduguri teaching hospital. Niger J Surg Res 2000;2:127-30. DOI:10.4314/njsr.v2i3.12199.
13. Garba N, Danladi SB, Abubakar HB, Ahmad SG, Gwarzo MY. Distribution of haemoglobin variants, ABO and Rh blood groups in blood donors attending Aminu Kano Teaching Hospital, Nigeria. Clin Med J 2016;2:20-24. http:// www.aiscience.org/journal/cmj.
14. Kubota N, Orita T, Hattori K, Oheda M, Ochi N, Yamazaki T. Structural characterization of natural and recombinant human granulocyte colony-stimulating factors. *J Biochem* 1990;107:486-92. DOI:10.1093/oxfordjournals.jbchem.a123072.
15. Bendall LJ, Bradstock KF. G-CSF: from granulopoietic stimulant to bone marrow stem cell mobilizing agent. Cytokine & Growth Factor Rev 2014;25:355-67. DOI:10.1016/j.cytogfr.2014.07.011.
16. Lemos NE, Farias MG, Kubaski F, Scotti L, Onsten TGH, Brondani LA, et al. Quantification of peripheral blood $CD34^+$ cells prior to stem cell harvesting by leukapheresis: a single center experience. Hematol Transfus Cell Ther 2018;40:213-8. DOI:10.1016/j.htct.2018.01.002.
17. Barbosa SAT, Brunetta DM, Filho SLAP, Primo GAS, Santos FJC, Carlos LMB, et al. A new insight into apheresis platelet donation by sickle cell trait carriers: evidences of safety and quality. Hematol Med Oncol 2019;4:1-4. DOI:10.15761/ HMO.1000179.

18. European Committee on Blood Transfusion. Guide to the preparation, use and quality assurance of blood components, 19th Edn. European Directorate for the Quality of Medicines & Health Care of the Council of Europe, 2017.
19. Kasi PM, Patnaik MM, Peethambaram PP. Safety of Pegfilgrastim (Neulasta) in patients with sickle cell trait/anemia. Case Rep Hematol 2013;146938. DOI:10.1155/2013/146938.
20. Turhan A, Weiss LA, Mohandas N, et al. Primary role for adherent leukocytes in sickle cell vascular occlusion: A new paradigm. Proc Natl Acad Sci USA 2002;99:3047-51.
21. Ho CH. White blood cell and platelet counts could affect whole blood viscosity. J Chin Med Assoc 2004;67:394-7.
22. Connes P, Alexy T, Detterich J, Romana M, Hardy-Dessources MD, Ballas SK. The role of blood rheology in sickle cell disease. Blood Rev 2016;30:111-8
23. Hoglund M, Hakansson L, Venge P. Effects of in-vivo administration of G-CSF on neutrophil functions in healthy volunteers. Eur J Haematol 1997;58:195-202.
24. De Santis GC, Prado Jr BD, Dotoli GM, Simões BP, Covas DT. Mobilizing hematopoietic progenitor cells in donors with sickle cell trait is safe. Hematol Transfus Cell Ther 2019;41:101-2. DOI:10.1016/j.htct.2018.04.003.
25. Jelkmann W. Molecular biology of erythropoietin. Intern Med 2004;43:649-59.
26. Goodnough LT, Rudnick S, Price TH, et al. Increased preoperative collection of autologous blood with recombinant human erythropoietin therapy . N Engl J Med 1989;321:1163-8.
27. Lippi G, Franchini M, Favaloro EJ. Thrombotic complications of erythropoiesis-stimulating agents. Semin Thromb Hemost 2010;36:537-49. DOI:10.1055/s-0030-1255448.
28. Hasegawa Y, Takamatsu J, Iwase T, et al. Effects of recombinant human erythropoietin on thrombosis and fibrinolysis in autologous transfusion for hip surgery. Arch Orth Traum Surg 1999;119:384-387. DOI:10.1007/s004020050434.
29. Biesma DH, Bronkhorst PJ, De Groot PG, Van de Wiel A, Kraaijenhagen RJ, Marx JJ. The effect of recombinant human erythropoietin on hemostasis, fibrinolysis, and blood rheology in autologous blood donors. J Lab Clin Med 1994;124:42-7. DOI:10.5555/uri:pii:0022214394901538.
30. Galadanci N, Wudil BJ, Balogun TM, Ogunrinde GO, Akinsulie A, Hasan-Hanga F, et al. Current sickle cell disease management practices in Nigeria. Int Health 2014;6:23-28. DOI:10.1093/inthealth/iht022.
31. Lawrie AS, Pizzey A, Trompeter S, Meiselman, H, Mohandas, N, Dumanski JP, et al. Procoagulant activity in patients with sickle cell trait. Blood Coagul Fibrinol 2012;23:268-70. DOI:10.1097/MBC.0b013e32835187f8.
32. Folsom AR, Tang W, Roetker NS, Kshirsangar AV, Derebail AK, Lutsey PL, et al. Prospective study of sickle cell trait and venous thromboembolism incidence. J Thromb Haemost 2015;13:2-9. DOI:10.1111/jth.12787.
33. Westerman MP, Green D, Gilman-Sachs A, Beaman K, Freels S, Boggio L, et al. Coagulation changes in individuals with sickle cell trait. Am J Hematol 2002;69:89-156.
34. Zheng Y, Mark A. Cachia MA, Ge J, Xu Z, Wang C, et al. Mechanical differences of sickle cell trait and normal red blood cells. Lab Chip 2015;15:3138-46. DOI:10.1039/c5lc00543d.
35. Tait JF, Gibson D. Measurement of membrane phospholipid asymmetry in normal and sickle cell erythrocytes by means of annexin-V binding. J Lab Clin Med 1994;123:741-8.
36. Westerman MP, Cole ER, Wu K. The effect of spicules obtained from sickle red cells on clotting activity. Br J Haematol 1984;56:557-62.
37. Hafez R. Nigeria health financing system assessment. World Bank Report, 2018. DOI:10.1596/30174.
38. Ahmed SG, Ibrahim UA, Hassan AW. Adequacy and pattern of blood donations in northeast Nigeria: the implications for blood safety. Ann Trop Med Parasitol 2007;101:725-31. DOI:10.1179/136485907X241442.
39. Roberts DJ, Field S, Delaney M, Bates I. Problems and approaches for blood transfusion in the developing countries. Hematol Oncol Clin North Am 2016;30:477-95. DOI:10.1016/j.hoc.2015.11.011.
40. National Population Commission. Nigeria Demographic and Health Survey 2018. Abuja, Nigeria. Available at: https://www.dhsprogram.com. [Accessed: April 1, 2021].
41. Naudin C, Burillo E, Blankenberg S, Butler L, Renné T. Factor XII contact activation. Semin Thromb Hemost 2017;43:814-26. DOI:10.1055/s-0036-1598003.
42. Shastry S, Das S. Root-cause analysis for clot in blood bag. Asian J Transfus Sci 2016;10:3-4. DOI:10.4103/0973-6247.175385.
43. Arora D, Dara RC, Raina V, Rawat G, Tiwari AK. CAPA analysis of clotted red cell unit detected during leukodepletion process: importance of quality check on blood collection monitors. Asian J Transfus Sci 2015;9:217-8. DOI:10.4103/0973-6247.162732.
44. Aneke JC, Ezeama N, Okocha CE, Onyeyili AN, Ona CE, Ibeh NC, et al. Knowledge, attitude and practice of haemovigilance among healthcare professionals in a Nigerian Tertiary Hospital. Egypt J Haematol 2017;42:108-16. DOI:10.4103/ejh.ejh_25_17.
45. Ibrahim Z, Kani KM, Habib A, Ibrahim UA, Ahmed SG. Clots in blood bags in northwest Nigeria: incidence, correlation with donor ABO blood groups, and implications on blood transfusion in a low resource tropical setting. Trop J Health Sci 2020;27:1-7.
46. Habib A, Ibrahim Z, Kani KM, Ibrahim UA, Ahmed SG. Sickle cell trait and the risk of clotting in donated blood bags in north west Nigeria: Is this a call for predonation hydration? Afr Sanguine 2021, 23(1): In Press.
47. Tripette J, Loko G, Samb A, Gogh BD, Sewade E, Seck D, et al. Effects of hydration and dehydration on blood rheology in sickle cell trait carriers during exercise. Am J Physiol Heart Circ Physiol 2010;299:H908-H914. DOI:10.1152/ajpheart.00298.2010.
48. Beard MJ, Cardigan R, Seghatchian J, Krailadsiri P, Williamson LM. Variables determining blockage of WBC-depleting filters by Hb sickle cell trait donations. Transfusion 2004;44:422-30. DOI:10.1111/j.1537-2995.2003.00669.x.
49. Stroncek DF, Byrne KM, Noguchi CT, Schechter AN, Leitman SF. Increasing hemoglobin oxygen saturation levels in sickle trait donor whole blood prevents hemoglobin-S polymerization and allows effective white blood cell reduction by filtration. Transfusion 2004;44:1293-9. DOI:10.1111/j.0041-1132.2004.04086.x.
50. Schuetz AN, Hillyer KL, Roback JD, Hillyer CD. Leuko-reduction filtration of blood with sickle cell trait. Transfus Med Rev 2004;18:168-76. DOI:10.1016/j.tmrv.2004.03.002.
51. Amar KO, Bourdonné O, Bruneau S, Sellami F, Richard P. Assessment of leuco-reduction of sickle cell trait blood: quality of the filtered product. Blood Transfus 2014;12:s193-8. DOI:10.2450/2012.0084-12.
52. Bianchi M, Vaglio S, Pupella S, Marano G, Facco G, Liumbruno GM, et al. Leucoreduction of blood components: an effective way to increase blood safety? Blood Transfus 2016;14:214-27. DOI 10.2450/2015.0154-15.
53. Kuypers FA. Hemoglobin-S polymerization and red cell membrane changes. Hematol Oncol Clin 2014;28:155-79. DOI:10.1016/j.hoc.2013.12.002.
54. Osei-Hwedieh DO, Kanias T, Croix CS, Jessup M, Xiong Z, Sinchar D, et al. Sickle cell trait increases red blood cell storage hemolysis and post-transfusion clearance in mice. EBioMedicine 2016;11:239-48. DOI:10.1016/j.ebiom.2016.08.006.
55. Yoshida T, Shevkoplyas SS. Anaerobic storage of red blood cells. Blood Transfus 2010; 8:220-36. DOI: 10.2450/2010.0022-10.
56. Burns JM, Yoshida T, Dumont LJ, Yang X, Piety NZ, Shevkoplyas SS. Deterioration of red blood cell mechanical properties is reduced in anaerobic storage. Blood Transfus 2016;14:80-8. DOI:10.2450/2015.0241-15.
57. Yoshida T, Au Buchon JP, Tryzelaar L, Foster KY, Bitensky MW. Extended storage of red blood cells under anaerobic conditions. Vox Sang 2007; 92:22-31. DOI:10.1111/j.1423-0410.2006.00860.x.
58. Dumont LJ, Yoshida T, Au Buchon JP. Anaerobic storage of red blood cells in a novel additive solution improves in vivo recovery. Transfusion 2009;49:458-64. DOI:10.1111/j.1537-2995.2008.02038.x.
59. Merciris P, Hardy-Dessources MD, Giraud F. Deoxygenation of sickle cells stimulates Syk tyrosine kinase and inhibits a membrane tyrosine phosphatase. Blood 2001;98:3121-7. DOI:10.1182/blood.v98.10.3121.
60. Ahmed SG. Anaerobic storage of red blood cells: the need for caution regarding donor red cells with sickle cell trait (letter). Blood Transfus 2011; 9:347. DOI:10.2450/2011.0110-10.
61. Yoshida T, Shevkoplyas SS. Anaerobic storage of red blood cells: the need for caution regarding donor red cells with sickle cell trait (reply). Blood Transfus 2011;9:348. DOI:10.2450/2011.0033-11.
62. Lindenburg ITM, van Kamp IL, Oepkes D. Intrauterine blood transfusion: current indications and associated risks. Fetal Diagn Ther 2014;36:263-71. DOI:10.1159/000362812
63. Hutter D, Kingdom J, Jaeggi E. Causes and mechanisms of intrauterine hypoxia and its impact on the fetal cardiovascular system: a review. Int J Pediatr 2010; Article ID 401323, 9 pages. DOI:10.1155/2010/401323.
64. Olusanya BO, Osibanjo FB, Mabogunje CA, Slusher TM, Olowe SA. The burden and management of neonatal jaundice in Nigeria: a scoping review of the literature. Niger J Clin Pract 2016;19:1-7. DOI:10.4103/1119-3077.173703.
65. Stroncek DF, Rainer T, Sharon V, et al. Sickle Hb polymerization in RBC components from donors with sickle trait prevents effective WBC reduction by filtration. Transfusion 2002; 42:1466-72.
66. Girelli G, Antoncecchi S, Casadei AM, et al. Recommendations for transfusion therapy in neonatology. Blood Transfus 2015;13:484-97. DOI:10.2450/2015.0113-15.
67. Contreras M, Hewitt PE. Clinical blood transfusion. In: Hoffbrand AV, Lewis SM, Tuddenham EGD, editors. Postgraduate haematology. London: Arnold; 2001. p.215-34.
68. Zhao J, Gonzalez F, Mu D. Apnea of prematurity: from cause to treatment. Eur J Pediatr 2011;170:1097-1105. DOI:10.1007/s00431-011-1409-6.
69. Novak RW, Brown RE. Multiple renal and splenic infarctions in a neonate following transfusion with sickle trait blood. Clin Paediatr 1982;21:239-41. DOI:10.1177/000992288202100409.
70. Ahmed SG, Ibrahim UA. Donor blood selection criteria for neonatal red cell transfusion: general and tropical perspectives. Trop J Health Sci 2018;25:1-10.
71. Adewoyin AS, Obieche JC, Hypertransfusion therapy in sickle cell disease in Nigeria. Adv Hematol 2014; Article ID:923593, 8 pages. DOI:10.1155/2014/923593.
72. Connes P, Alexy T, Detterich J, Romana M, Hardy-Dessources MD, Ballas SK. The role of blood rheology in sickle cell disease. Blood Rev 2016;30:111-8. DOI:10.1016/j.blre.2015.08.005.
73. Faes C, Sparkenbaugh EM, Pawlinski R. Hypercoagulable state in sickle cell disease. Clin Hemorheol Microcirc 2018;68:301-18. DOI:10.3233/CH-189013.
74. Diaku-Akinwumi IN, Abubakar SB, Adegoke SA, et al. Blood transfusion services for patients with sickle cell disease in Nigeria. Int Health 2016;8:330-5. DOI:10.1093/inthealth/ihw014.
75. Föller M, Bobbala D, Koka S, Huber SM, Gulbins E, Lang F. Suicide for survival-death of infected erythrocytes as a host mechanism to survive malaria. Cell Physiol Biochem 2009;24:133-40. DOI:10.1159/000233238.
76. La Monte G, Philip N, Reardon J, Lacsina JR, Majoros W, Chapman L, et al. Translocation of sickle cell erythrocyte micro-RNAs into Plasmodium falciparum inhibits parasite translation and contributes to malaria resistance. Cell Host & Microbe 2012;12:187-99. DOI:10.1016/j.chom.2012.06.007.
77. Danquah I, Ziniel P, Eggelte TA, Ehrhardt S, Mockenhaupt FP: Influence of haemoglobins 'S' and 'C' on predominantly asymptomatic Plasmodium infections in northern Ghana. Trans R Soc Trop Med Hyg 2010;104:713-9. DOI:10.1016/j.trstmh.2010.08.001.
78. Kani KM, Ibrahim Z, Habeeb A, Ibrahim UA, Ahmed SG. Haemoglobin phenotypes and the risk of asymptomatic malaria parasitemia among blood donors in northwest Nigeria: Clinical implications in the practice of tropical transfusion medicine. Afr J Clin Exper Microbiol 2021; 22:179-186. DOI:10.4314/ajcem.v22i2.10.
79. Oleske JM, Spiegel HML, Makani J, Scolpino A, Singh S, Shah K, et al. Potential protective effect of sickle cell gene allele on HIV infection. Acad J Ped Neonatol 2017;2: 555600. DOI:10.19080/AJPN.2017.02.555600.
80. Richardson MW, Guo L, Xin F, Yang X, Riley JL. Stabilized human TRIM5α protects human T cells from HIV-1 infection. Mol Ther 2014; 22:1084-95.
81. Javanbakht H, An P, Gold B, Petersen DC, O'Huigin C, et al. Effects of human TRIM5α polymorphisms on antiretroviral function and susceptibility to human immunodeficiency virus infection. Virology 2006;354:15-27.
82. Nouraie M, Nekhai S, Gordeuk VR. Sickle cell disease is associated with decreased HIV but higher HBV and HCV comorbidities in US hospital discharge records: a cross-sectional study. Sex Transm Infect 2012;88:528-33.

83. Kelly S, Jacobs ES, Stone M, Keating SM, Lee T-H, Chafets D, et al. Influence of sickle cell disease on susceptibility to HIV infection. PLoS ONE 2020;15: e0218880. DOI:10.1371/journal.pone.0218880.
84. David AN, Jinadu MY, Wapmuk AE, Gbajabiamila TA, Okwuzu JO, Herbertson EC, et al. Prevalence and impact of sickle cell trait on the clinical and laboratory parameters of HIV infected children in Lagos, Nigeria Pan Afr Med J 2018;31:113. DOI:10.11604/pamj.2018.31.113.15097.
85. Osaro E, Mohammed N, Zama I, et al. Prevalence of p24 antigen among a cohort of HIV antibody negative blood donors in Sokoto, North Western Nigeria-the question of safety of blood transfusion in Nigeria. Pan Afr Med J 2014;18. DOI:10.11604/pamj.2014.18.174.3449.
86. Barman H. Exchange transfusion in complicated pediatric malaria: A critical appraisal. Indian J Crit Care Med 2015;19:214-9. DOI:10.4103/0972-5229.154554.
87. Jajosky RP, Jajosky AN, Jajosky PG. To prevent or ameliorate severe Plasmodium falciparum malaria, why not evaluate the impact of exchange transfusions of sickle cell trait red blood cells? Transfus Apher Sci 2018;57:63-4. DOI:10.1016/j.transci.2017.11.032.
88. Jajosky RP, Jajosky AN, Jajosky PG. Dual-gene malaria-resistance: Therapeutically-rational exchange (T-REX) of group-O sickle trait and group-O C-trait red blood cells can be evaluated in Benin and Nigeria. Transfus Apher Sci 2020;59:102733. DOI:10.1016/j.transci.2020.102733.
89. van Genderen PJJ, Hesselink DA, Bezemer JM, Wismans PJ, Overbosch D. Efficacy and safety of exchange transfusion as an adjunct therapy for severe Plasmodium falciparum malaria in non-immune travelers: a 10-year single-center experience with a standardized treatment protocol. Transfusion 2010;50:787-94. DOI:10.1111/j.1537-2995.2009.02488.x.
90. Uwimana A, Legrand E, Stokes BH, Ndikumana JL, Warsame M, Umulisa N, et al. Emergence and clonal expansion of in-vitro artemisinin-resistant Plasmodium Falciparum kelch13 R561H mutant parasites in Rwanda. Nature Med 2020;1-7. DOI:10.1038/s41591-020-1005-2.
91. Rowe JA, Handel IG, Thera MA, et al. Blood group-O protects against severe Plasmodium falciparum malaria through the mechanism of reduced rosetting. Proc Natl Acad Sci 2007;104: 17471-6.
92. Devis P, Knuttinen MG. Deep venous thrombosis in pregnancy: incidence, pathogenesis and endovascular management. Cardiovasc Diagn Ther 2017;7:S309-S319. DOI:10.21037/cdt.2017.10.08.
93. Austin H, Lally C, Benson JM, Whitsett C, Hooper WC, Key NS. Hormonal contraception, sickle cell trait, and risk for venous thromboembolism among African American women. Am J Obstet Gynecol 2009;200:620.e1-620.e3. DOI:10.1016/j.ajog.2009.01.038.
94. O'Sullivan JM, Preston RJ, O'Regan N, et al. Emerging roles for hemostatic dysfunction in malaria pathogenesis. Blood 2016;127:2281-8. DOI:10.1182/blood-2015-11-636464.
95. Rout R, Dhangadamajhi G, Ghadei M, et al. Blood group phenotypes A and B are risk factors for cerebral malaria in Odisha, India. Trans R Soc Trop Med Hyg 2012;106: 538-43. DOI:10.1016/j.trstmh.2012.05.014.
96. Dentali F, Sironi AP, Ageno W, et al. Non-O blood type is the commonest genetic risk factor for VTE: results from a meta analysis of the literature. Semin Thromb Hemost 2012;38:535-48. DOI: 10.1055/s-0032-1315758.
97. Ibrahim UA, Ahmed SG. Pathophysiology of bleeding diathesis in haemophilia-A: A sequential and critical appraisal of non-FVIII related haemostatic dysfunctions and their therapeutic implications. Egypt J Med Hum Genet 2018;19:285-95. DOI:10.1016/j.ejmhg.2018.01.003.
98. Franchini M, Lippi G. Factor V Leiden and hemophilia. Thromb Res 2010;125:119-23. DOI:10.1016/j.thromres.2009.11.003.
99. Dhiman P, Chaudhary R, Sudha K. Sickle cell-β thalassemia with concomitant hemophilia A: a rare presentation. Blood Res 2015;50:264-7. DOI:10.5045/br.2015.50.4.264.
100. Ahmed SG, Ibrahim UA, Kagu MB, Abjah UA. Does sickle cell trait reduce the frequency of spontaneous bleeds in severe haemophilia? J Haemo Pract 2016;3:50-4. DOI:10.17225/jhp00083.
101. El Maataoui H, Fahi A, Oukkache B. Sickle cell trait and haemophilia: a rare association. Pan Afr Med J 2018;29:92. DOI:10.11604/pamj.2018.29.92.14551.
102. Ghosh K, Ghosh K. Management of haemophilia in developing countries: challenges and options. Indian J Hematol Blood Transfus 2016;32:347-55. DOI:10.1007/s12288-015-0562-x.
103. Okoye HC, Korubo KI, Nwogoh B, et al. Challenges in the management of bleeding disorders in Nigeria. Niger J Clin Pract 2018;21:468-72. DOI:10.4103/njcp.njcp_319_17.
104. Ahmed SG, Kagu MB, Ibrahim UA. Pattern of blood products transfusions and reactions among multi-transfused haemophiliacs in Nigeria: implications on haemophilia care in low resource tropical settings. Sudan Med J 2018;54:29-38. DOI:10.12816/0046389.

92.