REVIEW ARTICLE

Transfusion Services in Tropical Africa: Challenges and Prospects from the Nigerian Perspective

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ABSTRACT

Background:
The decision to establish voluntary donor based National Blood Transfusion Services (NBTS) in all member states of the World Health Assembly (WHA) was conceived in 1975 as documented in resolution number 28.72 of the WHA. Since the signing and adoption of the resolution, not very much has been done in tropical African countries, including Nigeria. The first NBTS center in Nigeria was set up in the Federal Capital, Abuja, in 2004, which was followed by the establishment of 6 zonal centres across the country. Nonetheless, the NBTS is still unable to provide adequate amount of safe blood and blood products for clinical use in Nigeria. Consequently, the responsibilities of donor recruitment, selection, screening, blood collection, processing, storage, compatibility testing and haemovigilance are essentially relegated to individual hospital blood banks, which are characterized by numerous challenges. This review presents a sequential 'stage-by-stage', (from donor recruitment to compatibility tests) overview of current challenges vis-à-vis efficacy, safety, prospects and solutions within the context of tropical African transfusion medicine from the Nigerian perspectives.

Materials and Methods:
Literature search was conducted using relevant search terms: 'Donor Recruitment, Categories and Selection, Pre-donation screening, Blood collection, Donor Reaction, Blood Processing, Storage, Transfusion, Tropical Transfusion, Nigeria' in various combinations in Pub Med, Google Scholar, Medline, and other search engines.

Results:
Several challenges vis-à-vis effectiveness and efficiency of transfusion service in tropical Africa and Nigeria were found at every stage (from donor recruitment to compatibility tests) of the practice of tropical transfusion medicine in Nigeria. The prospects and possible solutions to the identified challenges are presented in a sequential stage-by-stage format in the discussion section.

Conclusion and Recommendation:
Blood transfusion services in tropical Africa, as typified by the Nigerian setting, are largely hospital-based and are characterised by a myriad of challenges due to combined effects of systemic inadequacies, operational shortfalls, technical deficiencies, endemic transfusion transmissible infections and high prevalence of genetic red cell disorders. These challenges have adverse impact on virtually every stage of tropical transfusion service from donor recruitment up to compatibility testing. Urgent revitalization of centralized national blood transfusion services in Nigeria and across tropical Africa, is hereby recommended.

Keywords: blood transfusion service, tropical Africa, Nigeria, challenges, prospects

INTRODUCTION

The decision to establish a sustainable voluntary-donor-based National Blood Transfusion Service (NBTS) in Nigeria, and indeed all member states of the World Health Assembly (WHA), was conceived in the year 1975 as documented in the WHA resolution number 28.72. [1] However, since the signing and adoption of the WHA resolution in 1975, very little had been done by successive Nigerian governments to achieve the objectives of establishing a NBTS that could be comparable to what is available in the developed countries of the world. Consequently, the Nigerian NBTS has virtually remained as a hospital-based transfusion service provided by individual hospital blood banks. The first federal blood transfusion centre was set up in the federal capital, Abuja, in 2004.[2] The centre initially worked in partnership with non-governmental and international organizations including Safe Blood for Africa Foundation (SBFAF), Center for Disease Control (CDC), President's Emergency Plan for AIDS Relief (PEPFAR), and the World Health Organization (WHO), with the aim of optimizing its services.[2] That was followed by the establishment of several zonal and state blood transfusion service centres across the country.[2] The Nigerian NBTS, which is administratively under the federal ministry of health faces many challenges including voluntary donor inertia coupled with inadequate funding, infrastructure and equipment, all of which militate against the attainment of NBTS objectives of providing adequate and safe blood and blood products.[3,4] Nigeria has the largest population (of over 200 million) in tropical Africa, but for the aforementioned reasons, the NBTS is still unable to provide adequate amount of safe blood and blood products for clinical use across the nation's hospitals. 5] Consequently, the responsibilities of donor recruitment, selection, screening, blood collection, processing, storage, pre-transfusion compatibility tests and haemovigilance are essentially relegated to individual hospital blood banks.[5] The aim of this review is to present a sequential 'stage-by-stage' (from donor recruitment to pre-transfusion compatibility tests) overview of current challenges vis-à-vis efficacy, safety, prospects and solutions within the context of tropical transfusion service from Nigerian perspectives.

MATERIALS AND METHODS

Literature search was conducted using relevant search terms: 'Donor Recruitment, Categories and Selection, Pre-donation screening, Blood collection, Donor Reaction, Blood Processing, Blood Storage, Blood Transfusion, Tropical Transfusion, Nigeria' in various combinations in Pub Med, Google Scholar, Medline, and other search engines. A total of 103 relevant publications were retrieved, which included 92 peer-reviewed journal articles, 8 technical reports, and 3 chapters of edited text book as listed in the reference section.

RESULTS

A number of challenges vis-à-vis efficacy and safety of transfusion medicine in tropical Africa and Nigeria were sequentially found at every stage (from donor recruitment to pre-transfusion compatibility tests) of the practice of tropical transfusion medicine. Prospects and possible solutions to the identified challenges are presented in a sequential stage-by-stage format as discussed below.

DISCUSSION

1. Donor Recruitment: Categorisation and Selection

The official view of the WHO on allogeneic blood donation is that it should in all cases be absolutely voluntary within the context of true altruism.[6] However, in most developing African nations, including Nigeria, voluntary blood donors are scarce due to ignorance, fear and superstitions relating to blood donation.[7] Even the educated Nigerian elites (who are supposed to be more forthcoming) were reported to have frequently dropped off voluntary donor

register simply due to fear of HIV screening and the stigma that might follow any positive result.[8] Consequently, non-voluntary blood donors, notably commercial and family donors, continue to gain prominence on our donor panels.[2] Commercial donors refer to those individuals who give blood in return for payment in one form or the other [9]; most commercial donors had usually 'over-donated' and are thus in poor state of nutrition and their blood had lower haemoglobin concentrations in comparison with that of voluntary and family donors. [10,11] There are three categories of family donors in Nigeria. First, the majority of family donors give blood in replacement of that which has been given to their relatives; such donors are referred to as family replacement donors and they are unaware of the identity of the recipients of their blood.[7] Second, occasionally a person donates blood to 'rescue' a specific related patient with whom the donor shares a rare blood group (e.g. RhD Negative), and such a donor is referred to as family directed donor [12]; but there is need for caution because 'relative-to-relative' transfusion carries a high relative risk of graft-versus-host disease especially if the recipient is immuno-compromised.[13] Third, sometimes a husband donates blood specifically to his wife, and the husband is referred to as 'inter-spousal 'family donor; inter-spousal transfusion should be discouraged as it increases the risk of maternal sensitization by paternal antigens, which may lead to haemolytic disease of the new born in subsequent pregnancies.[14] Only a small fraction of eligible Nigerians participate in autologous blood donation, which should be encouraged because of its zero risks of transfusion transmissible infections (TTIs), allo-sensitisation and immune transfusion reactions, as well as its 'sparing effect' on the utilisation of an inadequate allogeneic donor blood reserve. [7] The overall pattern of blood donation in Nigeria is that of donor blood scarcity, which is perpetuated and sustained by strong voluntary donor inertia [8], poor female gender participation in blood donation,[15] seasonal donor shortfalls due to agrarian activities[16], high rate of donor rejection due to endemic TTIs [17] and high rate of donor deferral due to a myriad of asymptomatic anaemias caused by malnutrition [18,19], endemic tropical parasitic infestations [20] or excessive donations among commercial donors.[10] The perennial voluntary donor scarcity and the prominence of non-voluntary donors on the donation panel can only be remedied by intensifying national donor education campaigns to allay fear and skepticism, and rekindle selflessness and altruism.

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 determined. There is paucity of information regarding how eligibility of prospective donors is determined in Nigerian sub-tertiary hospitals because there is virtual lack of literature emanating from such clinical settings. However, the eligibility of prospective donors in Nigerian tertiary and teaching hospitals is usually determined by pre-donation assessment of health status in line with national blood policy [2] and the WHO guidelines.[21] The assessment is in the form of oral questioning and/or questionnaire screening with respect to general health, as well as medical, sexual, drug and social history, which is followed by simple physical examination and measurements of body weight (BW) and blood pressure (BP).[21] Persons within the ages of 18 to 65 years with normal BW and BP, negative test results for TTIs, 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. [21] Despite the wide age range (18-65 years) for blood donation, blood donor panels in Nigeria are predominated by young persons of the male gender who are

often aged less than thirty years [22], which is probably a reflection of the demographic structure of Nigeria as a developing country with a relatively young population in comparison to the developed countries.[23] Moreover, younger people are relatively more educated, and are therefore more amenable to donor recruitment campaigns. [23] Nonetheless, there is the need to boost our donor panels by re-configuring our donor campaign strategy to highlight the fact that healthy middle-aged persons who are not older than 65 years are also eligible to donate.[21] The preponderance of male donors is a reflection of the general low level of blood donation among the female population in Nigeria.[15] Despite the fact that blood donation is acceptable from healthy females that are neither pregnant nor breast-feeding,[21] there is a misconception in the Nigerian population that women are not eligible to donate blood. [15] This misconception must be rectified by re-configuring our donor mobilisation strategy in order to target and sensitise the female sector,[24] which constitutes about half of the Nigerian population [23] towards voluntary blood donation.

2. Pre-donation screening for TTIs

Like other tropical African countries, Nigeria has high prevalence of TTIs and red cell disorders that affect transfusion efficacy and safety as explained below.

2a. Pre-donation screening for routinely tested TTIs: Syphilis, HIV, hepatitis B & C viruses

High prevalence and endemicity of TTIs within the donor populations have compelled blood banks in Nigeria and many other tropical African countries to adopt pre-donation screening and deferral strategy in order to avoid wasteful collection of infected donor blood. [25] This strategy may be at variance with international practice, but it is undoubtedly fiscally prudent and financially rational within the limited health budgets of even the relatively rich tropical countries such as Nigeria.[4]

In Nigeria, prospective donors who have tested negative for HIV, hepatitis B (HBV) and HCV viruses, and syphilis are acceptable as donors.[2] Treponema pallidum survives for only 72-120 hours at the blood banking storage temperature of 4^0C.[26] This limited in-storage viability of T pallidum implies that fresh whole blood, which is commonly transfused into neonates and patients with bleeding disorders,[27] would be associated with higher risk of transmitting syphilis if donors are not properly screened. The three transfusion transmissible viral infections (TTVIs), which include HIV, HBV and HCV), are even more transmissible because they remain viable throughout the period of blood storage. These three TTVIs have comparable epidemiology in terms of their modes of spread including via sexual intercourse, blood-to-blood contacts such as unsterilized invasive procedures (e.g., injections, trado-cultural skin incisions, unhygienic surgical practices) and transfusion of inadequately screened or unscreened blood and blood products. Sexual contact and unsterilized blood-to-blood contact may be largely responsible for the relatively high prevalence of these infections in tropical populations,[28] from which apparently healthy tropical blood donors are derived. Consequently, donor screening studies indicated that up to 15-20% of apparently healthy donors in Nigeria were infected with one or more transfusion transmissible viruses, including hepatitis B virus (HBV), hepatitis C virus (HCV) and human immune deficiency virus (HIV). [29,30] The prevalence rates of individual TTVIs among blood donors in Nigeria are up to 4.1-11.1% for HBV, 1.8-3.6% for HCV, and 1.4-5.2% for HIV.[29,30] Hence, transfusion of inadequately screened or unscreened blood and blood products would certainly increase the risk of acquiring these infections among transfusion dependent patients in Nigeria. The risks of acquiring these infections by even the most transfusion-dependent patients in developed countries have been greatly minimised as a result of

modernisation of blood safety protocols with efficient donor screening procedures, effective viral inactivation techniques and production of recombinant blood products. [31] However, infection risks are particularly high in developing countries and the tropics where the prevalence of blood born infections is high among donor populations, donor screening procedures are inadequate, viral inactivation techniques are virtually absent, and recombinant blood products are scarce. 5,32]

In a tropical low resource country such as Nigeria, a significant residual risk of TTVIs would persist despite routine pre-donation screening for several reasons. First, a high proportion of our blood donors are commercial donors that carry high risk of TTVIs.[9,33] Second, the routine immunoassay techniques for screening blood donors for HBsAg in Nigeria are basic rapid immuno-chromatographic tests that may not detect low levels of HBsAg in donors with occult HBV infection.[5] Unfortunately, nucleic acid tests for detecting occult HBV infections [34] are not routinely available in Nigeria. Third, the routine serological techniques of screening blood donors for HIV and HCV antibodies in Nigeria also employ rapid immuno-chromatographic kits.[5,35] These rapid kits are relatively cheap but less accurate and more likely to give false negative results than long incubation ELISA technique,[36] which is not consistently used in many Nigerian blood banks because the ELISA technique is expensive and requires standard equipment, skill and training.[35] Fourth, more advanced procedures for the detection of window period infections, such as p24 antigen for HIV,[37] viral core antigen for HCV [38] and nucleic acid tests for both HIV and HCV [39] are not routinely available in Nigeria. Finally, there is a complete absence of viral inactivation technology for the elimination of the residual risks of TTVIs in blood and blood products in Nigeria.[40] All of the aforementioned challenges need to be addressed if Nigeria, and indeed other tropical African nations, are to achieve the prospect of attaining international level of transfusion safety.

2b. Pre-donation screening for non-routinely tested TTIs: Cytomegalovirus, Malaria

These two important TTIs are very common in tropical populations, but they are not routinely tested among blood donors.

2bi Cytomegalovirus (CMV)

Unlike HIV, and hepatitis B & C viruses, CMV is usually not routinely screened in clinical blood transfusion practice in most countries, including Nigeria, despite the fact that CMV is transmissible in blood.[41] In fact, CMV is highly contagious because in addition to blood, it is also spread via various other body fluids such as semen, saliva and excrements.[41] The virus is known to infect both immune-competent and immuno-compromised persons.[42] However, while it often causes clinically severe disease in immuno-compromised persons, it usually causes mild disease in immuno-competent individuals.[4] The virus has a worldwide distribution. The global blood donor seroprevalence of both CMV-IgG (indicating past exposure with less risk of transmission) and CMV-IgM (indicating recent or active infection with greater risk of transmission) was 83.16% as revealed in a recent meta-analytical study. [43] Nonetheless, CMV donor seroprevalence varies from 40–100% in different parts of the world.[43] Developed countries tend to have relatively lower prevalence, while developing countries tend to have higher prevalence because of factors such as poor personal and environmental sanitation.[43] For example, the seroprevalence of CMV in Nigerian blood donors was reported to be 100% in a previous study.[44] Hence, transfusion recipients especially those that are immuno-compromised due to age (e.g., neonates) or diseases (e.g., HIV/AIDS, SCD, cancers) in developing countries are at high risk of acquiring CMV infection. [41,45]

Prevention of transmitting CMV into transfusion recipients is difficult because of the high seroprevalence of CMV among blood donors, especially in the developing countries where it is virtually impossible to produce CMV seronegative blood products. Fortunately, CMV is a highly leuco-cytotropic virus and leuco-depleted blood is considered relatively CMV-safe irrespective of donor sero-status.[46] Therefore, leuco-depletion should have been the best strategy for producing relatively CMV-free blood in the tropics where sero-positivity for CMV antibodies is virtually 100% among donors.[44] Regrettably, tropical transfusion services are under-developed and cannot readily undertake leuco-depletion of donor blood (details in subsequent sections). Hence, the only feasible method of producing CMV-safe blood for vulnerable patients (i.e., neonates and the immuno-compromised) in the tropics is by saline washing of red cells, which will wash-off most of the infected donor leucocytes and presumably reduce, but not abolish the risk of CMV transmission.[47,48]

2bii. Malaria Parasites

Malaria infection is endemic and widely distributed across most tropical countries where the temperature patterns and other climatic factors are conducive for the proliferation of the mosquito vectors. As in many other tropical malaria endemic countries, donor screening for asymptomatic malaria parasites (AMP) and post transfusion haemovigilance of patients are not routinely conducted in Nigeria.[49] Hence, the exact incidence of transfusion transmitted malaria (TTM) among transfused patients in Nigeria is unknown. 50] However, the incidence of TTM is presumably high because the prevalence of AMP among Nigerian donors was reported to range from 6% to as high as 45.8%. [51,52] Suffices to say that TTM is a serious but inadequately quantified (i.e., exact incidence is unknown due to lack of post transfusion haemovigilance) complication of blood transfusion in Nigeria and other malaria endemic countries.[49,50] Nonetheless, the risk of acquiring TTM would certainly be higher among patients with various forms of vulnerabilities and immune incompetence as may be encountered in the elderly, pregnant women, neonates, children, and patients with cancers, HIV/AIDS and Sickle cell disease (SCD).[53] However, a previous study has reported that malaria parasites can survive and maintain their infectivity in blood stored at 4°C for only 18 days.[54] The result of that study would suggest that the risk of malaria infection would be higher in fresh blood. Hence, the conventional use of fresh blood for neonatal transfusion would paradoxically increase the neonate's risk of acquiring TTM in the tropics.[48] Consequently, immuno-compromised patients in general (e.g., the elderly, pregnant women, neonates, children, and patients with cancers, HIV/AIDS and SCD) [53], and patients that require fresh blood in particular (e.g., haemophilia, chronic liver disease) [27] must receive close post-transfusion haemovigilance for early detection and prompt chemotherapy of TTM.

3. Blood Collection: Quality, Donor Reactions, Bag Clots, ABO and Hb Phenotypes

Once an eligible donor is identified, the largest vein in the ante-cubital fossa is selected by applying a tourniquet or blood pressure cuff inflated to 40-60 mmHg. [55,56] After meticulous skin cleaning and disinfection, a minimally traumatic ‘single-attempt’ phlebotomy is performed using the 16-gauge needle that is attached to the blood collection bag.[55,56] In order to facilitate and maintain optimal rate of blood flow, the donor is instructed to squeeze a compressible rubber ball or open and close the fist slowly every 10-12 seconds during the period of blood collection.[55,56] After every 30 seconds during the donation, blood is manually mixed with the anticoagulant (citrate-phosphate-dextrose-adenine) in the donation bag until a target volume of 500 mL is collected.[55,56] Normal blood has a specific gravity of about

1.053, hence the target volume of 500 mL would correspond to an average weight of about 500 g (474-579 g),[56] which can easily be measured with manual weighing scales in Nigerian blood banks; regrettably many blood banks in Nigeria don't weigh their blood bags. In Nigeria, and in many other African countries, the blood collection procedure is entirely manual, which is unlike what is obtainable in developed countries where automated electronic blood collection monitors equipped with auto-flow rate-sensing, auto-mixing, auto-weighing, and auto-clamping facilities are available. The risk of clotting increases with the length of donation time. Hence, blood donation procedure should ideally be completed in less than 10 minutes, and a blood unit drawn over a period longer than 15-20 minutes may not be suitable for making haemostatically active blood components such as platelet concentrates, fresh frozen plasma or cryoprecipitate. [56]

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, as well as tissue factor-mediated activation of FVII. [57,58] 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.[59] Third, over-filling of bags and/or under-mixing of blood within the bag can also undoubtedly predispose to clot formation.[60,61] Fourth, inadequate skin cleansing can result in contamination with bacteria, which can proliferate, trigger coagulation and eventually cause clot formation in blood bags.[55,56] High levels of quality control in phlebotomy and blood collection is obviously required to avoid triggering any or all of the aforementioned coagulation activation mechanisms during blood donation.[55,56]

The incidence of clots in donated blood bags is low in developed countries due to a high level of quality control and haemovigilance, and the use of automated blood collection monitors. [56,62] In contradistinction, the incidence of blood clots would be expected to be high in developing countries (including Nigeria) due to a low level of quality control, poor haemovigilance and lack of automated blood collection monitors.[49,63] Indeed, the incidence of clotting in donated blood bags is high in Nigeria, but the problem is poorly studied since clotted blood bags are usually simply returned to the hospital blood bank and substituted with another blood bag, and risk factors and root-cause analysis of clotted blood bags are not adequately studied. Nonetheless, a recent and preliminary study [64] revealed that the incidence of clotting in blood bags in northwest Nigeria was quite high at about 3% (which may in fact be an under-estimation due to inadequate documentation); the high incidence of clotting was attributed to systemic inadequacies such as lack of automation during blood collection, and poor quality control and haemovigilance during manual blood collection.[49,63] The aforementioned study had further demonstrated that non-O blood group (which is associated with natural hypercoagulability) was associated with increased risk of clotting in blood bags [65], while group-O (which is associated with natural hypocoagulability) was associated with reduced risk of clotting in blood bags. [66] Another Nigerian study had demonstrated that donor sickle cell trait (SCT), which is associated with prothrombotic hyperviscosity, is an independent risk factor for clotting in blood bags, and that SCT interacts synergistically with non-O blood groups in escalating the prothrombotic risk of clotting in blood bags in Nigeria.[67] Hence, the coinheritance of SCT and a non-O blood group in Nigerian blood donors is associated with high risk of clotting in blood bags.[67] Frequent clotting and wastage of donated blood in Nigeria would only worsen the pre-existing blood

shortage and makes it more difficult to offset the high transfusion demand for maternal and childhood anaemia [68], as well as anaemias resulting from separate or combined onslaught of poverty, malnutrition, haemoglobinopathies, and endemic tropical diseases such as malaria, schistosomiasis, tuberculosis and HIV/AIDS.[69-71]

Every effort must be made to minimise the risk of clotting in blood bags. Available literature on clots in blood bags in Nigeria has linked high prevalence of clotting to non-modifiable risk factors (i.e., donor non-O blood groups and SCT) on the one hand [64,67], and modifiable risk factors (i.e., poorly controlled manual blood collection technique) on the one hand. [49,63] Nonetheless, it is conceivable that the clotting risk associated with the 'non-modifiable' factors can be effectively mitigated or neutralized by improving or eliminating the 'modifiable' risk factors by applying stricter quality control and haemovigilance during manual blood collection or by introduction of automated blood collection monitors. Interestingly, hydration studies have suggested that SCT-associated hyperviscosity, whether during exercise or at rest (as is the case during blood donation), can simply be preemptively ameliorated by optimum oral hydration with water.[72] Accordingly, some authors recommend that blood banks in Nigeria should consider the possible application of a pre-donation hydration strategy for SCT-positive donors with aim of reducing SCT-associated hyperviscosity and its synergistic prothrombotic effect on the non-O blood groups; this strategy would hopefully mitigate the risk of clotting in blood units derived from by donors with SCT and non-O blood groups.[67] In another interesting and pleasant coincidence, we note that pre-donation hydration strategy would also provide an additional benefit of minimizing the risk of donation associated vaso-vagal syncopal reactions.[73] It is therefore plausible to further recommend pre-donation hydration across-board for all donors irrespective of ABO groups and Hb phenotypes so as to mitigate the occurrence of vaso-vagal attacks, which had been reported to be the most frequent adverse reactions encountered among Nigerian donors.[74] The rationale behind this recommendation is the fact that vaso-vagal reactions are strongly inimical to donor return and retention,[75] which is very undesirable in a country such as Nigeria where the current blood donor base is narrow, precarious and overstretched by high demand.[5,7]

4. Blood Processing: Leucocyte Filtration, SCT Red Cell Sickling, Rigidity, Filter Clogging

The concept of blood component therapy is only sparingly applicable in the tropical clinical settings, wherein cell separators for apheresis are rarely available. Hence, the only option for producing blood components is to use the cold centrifuge, which is also not routinely available even within the tertiary hospitals in Nigeria. Consequently, patients with various types of thrombocytopenia and/or deficiencies of coagulation factors are usually transfused with fresh whole blood, which has high 'volume-to-efficacy' ratio and may lead to undesirable volume overload.[27] Leucocyte depletion of whole blood is also not usually feasible in tropical African settings where neither the equipment nor the skill are readily available. Even in places where the facilities are available, donor SCT status would create a significant impediment. This is because donors with SCT are genetically heterozygous for the sickle β-globin gene, their red cells contain both Hb A and Hb S. But the relative quantities of the haemoglobins (Hb A and Hb S) are asymmetrically distributed (i.e. Hb A≒ 60%; Hb S≒ 40%) within the red cells of persons with SCT.[76] Thus the relative abundance of Hb A (~ 60%) prevents clinically significant polymerization and sickling under physiological conditions. Nonetheless, 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.[77,78] However, the filterability of SCT blood can be greatly improved by increasing the oxygen saturation level (thereby inhibiting HbS polymerization) within the SCT blood bag.[78] Thus SCT represents the most common cause of leuco-filtration failure (which is economically wasteful) in developed countries.[79] Even if SCT blood units 'manage' to pass through the leucocyte filter, they often have unduly prolonged filtration time and high post-filtration residual leucocyte counts.[80] In view of the tendency of SCT donor red cells to sickle under suboptimal aerobic circumstances, WHO guidelines recommend that whole blood donated by persons with SCT should not be subjected to leuco-filtration, and should also not be used in transfusing three categories of hypoxia-susceptible and sickling-prone patients, viz: foetuses, neonates and SCD patients.[21] The fact that SCT donor blood is technically 'unfilterable' by standard method is a major challenge for tropical African blood banks where about one-quarter to one-third of the donor population carry the SCT.[81,82] 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 and prospective recipients of haematopoietic stem cell transplant.[83] Therefore, any tropical African transfusion centres and blood banks that intends to conduct leuco-depletion should either completely exclude SCT donor blood or adopt Stroncek's method [78], 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.

5. Blood Storage: Impact of SCT and G6PD deficiency

The SCT and G6PD deficiency are among the most classical examples of adaptive genetic polymorphisms that are strongly correlated with innate resistance to malaria infection, which confers survival advantage in the tropics. Consequently, high proportions of blood donors in tropical Africa carry these genetic polymorphisms. Unfortunately, both polymorphisms have adverse effect on donor blood stability during storage.

5a. SCT Donor Blood: 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.

5ai. Conventional (Aerobic) Storage: SCT Red Cells are Associated with Increased in-storage Haemolysis, Reduced Post Transfusion Survival

As earlier noted, leuco-filtration studies had suggested that subtle Hb S polymerization and red cell sickling of SCT red cells also occur in-vitro within donated blood bags during conventional (aerobic) storage at 4°C.[77,78,84] Hb S polymerization and red cell sickling cause oxidation-induced damage to both lipid and protein components of the red cell membrane[85], 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 Hb AA red cells, SCT red cells were associated with accelerated in-storage haemolysis, rapid post transfusion clearance, and reduced post transfusion recovery.[86] Therefore, an important clinical research question remains to be answered. Should the tropical African 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.

5aii. Anaerobic Storage: 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. [87] 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. [87] Consequently, anaerobic storage of red cells has many potential advantages over conventional (aerobic) storage with respect to mitigation of oxidative red cell damage[88], thus allowing for extended storage with good post transfusion red cell viability [89], which could be further augmented by the addition of metabolite precursors in the storage solutions.[90] However, these studies [87-90] 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.[81,82] And it is noteworthy and abundantly clear that some degree of Hb S polymerization and sickling of SCT red cells occur even during conventional aerobic storage.[77-80] It is therefore easy to envisage that anaerobic storage might potentially trigger more intense and massive Hb S polymerization and sickling of SCT red cells. It should be appreciated that deoxygenation and sickling cause significant damage to the membranes of Hb S-containing red cells. [85,91] 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.[92] Obviously, further studies are required to determine the feasibility and safety of storing SCT red cells under anaerobic conditions.[92] Meanwhile, if anaerobic storage of blood is contemplated in the tropical Africa 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.[93]

5b. G6PD Deficient Donor Blood: Conventional Storage at 4°C

There are two abnormal G6PD variants in Africa: G6PD-A and G6PD-A (minus). [94] G6PD-A is enzymatically non-deficient and is thus clinically insignificant, whereas G6PD-A (minus) is enzymatically deficient and is thus clinically significant in the aetiology of haemolytic anaemia.[94] In tropical countries such as Nigeria, the prevalence of G6PD deficiency is as high as 20% in males (symptomatic hemizygotes), while among the females up to 32% are asymptomatic heterozygotes (carriers) and 4% are symptomatic homozygotes.[94] The high prevalence of G6PD deficiency in the tropics is due to the fact that the heterozygous state, through the process of balanced polymorphism, offers protection against severe falciparum malaria.[95] Consequently, up to 13-20% of apparently healthy male blood donors in Nigeria are G6PD deficient.[96] Nonetheless, most tropical African countries, including Nigeria, do not routinely screen blood donors for G6PD deficiency in spite of WHO recommendations that countries where the deficiency is prevalent should routinely screen their donor populations. [21]

Donors who are G6PD deficient may not be symptomatic at the time of donation.[96] But G6PD deficient donor red cells may undergo haemolysis when they encounter drugs, infections or oxidative stress in recipient patients. In order to mitigate the potential adverse effects of G6PD deficient

donor red cells, the WHO and experts made the following recommendation; viz: individuals with G6PD deficiency with history of haemolysis should be not be accepted as donors, while individuals with G6PD deficiency without history of haemolysis can be accepted as donors, but their red cells should not be used for intrauterine and neonatal transfusion or for transfusing any patient with G6PD deficiency or other haemolytic diseases such as SCD irrespective of age.[21,97]

Although it has been reported that G6PD deficient red cells remain fairly stable during storage [98], some studies have suggested that G6PD deficient red cells are vulnerable to excessive storage-induced biochemical changes and depletion of antioxidant mechanisms, which increases their susceptibility to post-transfusion haemolysis in transfused recipients.[97] In addition, some studies have also shown that stored G6PD deficient red cells are more susceptible to potassium leakage,[99] which may increase the risks of post transfusion hyperkalaemia. There is therefore the need to identify G6PD deficient donor blood in order to follow expert recommendations regarding its clinical application. We reckon that the proportion of G6PD deficient blood donors in the tropics may be indispensible. But transfusion experts in tropical African need to at least review the duration of storage shelf-life of G6PD deficient blood in order to minimise the severity of in-storage changes, potassium leakage and post-transfusion haemolysis of the deficient rd cells.

6. Compatibility Testing

In order to ensure maximum safety of blood transfusion, compatibility between donor red cells and recipient serum must be ensured through the following protocols.[100]

6a. ABO and D groups of donor and recipient

These must be accurately determined for both donor and recipient. This procedure is usually not a problem even in the remotest tropical African blood banks.

6b. Extended red cell phenotyping of donor and recipient

A part from ABO and D antigens, other antigens that are capable of causing immune sensitizations and reactions such as C, E, c, e, K, k, Fya, Fyb, Jka, Jkb, M, N, S, s, P1, Le-a, and Le-b should be determined by using appropriate anti-sera. This procedure is not routinely available even in tertiary tropical African blood banks.

6c. Antibody screening and identification in recipient serum

Standard cell panels should consist of extensively phenotyped group-O red cells that have all the ‘locally’ implicated transfusion reaction-causing antigens such as D, C, E, c, e, K, k, Fya, Fyb, Jka, Jkb, M, N, S, s, P1, Le-a, and Le-b. Moreover, the panels must have cells that are homozygous as well as cells that are heterozygous for the phenotyped antigens; this is necessary in order to demonstrate ‘dosage effect’ during antibody identification procedure. Unfortunately, this procedure is also not routinely available even in tertiary tropical African blood banks.

6d. Cross-Matching

The recipient serum should be cross-matched with donor red cells that are selected on the basis of the results obtained at 6a-6c above, viz:

1. Selected donor red cells must be ABO and D antigen compatible with recipient.
2. Selected donor red cells should as far as possible have similar extended phenotypes with recipient red cells.
3. Selected donor red cells must lack any antigen that corresponds to any alloantibody found in recipient serum.
4. If for any reason the use of group-O donor blood is contemplated for recipient with non-O group, the selected donor serum must be screened negative for high titre of anti-A/B haemolysins. If donor haemolysin screening is not feasible, the risk of recipient red cell haemolysis can be

mitigated by transfusing washed cells or a limited number of red cell concentrates.
5. Finally, donor red cells must be cross-matched against recipient serum at least by direct agglutination test in normal or low ionic saline, and by indirect Coombs agglutination test.

Regrettably, most tropical African blood banks cannot routinely perform extended phenotyping and antibody identification due to virtual absence of the requisite cell panels and anti-sera. This deficiency is responsible for a rising tide of alloantibodies among multi-transfused patients in Nigeria [101-103]. It is the responsibility of local transfusion experts to devise a workable protocol for sustainable production and utilization of cell panels in Nigeria and other tropical African countries. Suffices to say that simply purchasing cell panels from overseas may not be optimal due to inter-racial variations in global frequencies of red cell antigens.

CONCLUSION AND RECOMMENDATION

Blood transfusion services in tropical Africa as typified by the Nigerian setting are largely hospital-based and are characterised by a myriad of challenges due to systemic inadequacies, operational shortfalls, technical deficiencies, and high prevalence of endemic TTIs and genetic red cell disorders. These challenges have adverse effects on virtually every stage of transfusion service from donor recruitment up to compatibility testing. Urgent revitalization of the centralized national blood transfusion service, as the only permanent solution to the aforementioned battery of challenges, is hereby recommended.

Conflict of Interest: None

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