Original Article

**Pattern of blood products transfusions and reactions among multi-transfused haemophilicics in Nigeria: implications on haemophilia care in low resource tropical settings**

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Abstract **Background:** FVIII-concentrate is cornerstone for managing haemophilia-A. Scarcity of FVIII-concentrate compels caregivers in poor countries to adopt less effective therapeutic transfusion strategies with various FVIII-containing blood products including fresh whole blood (FWB), unfrozen fresh plasma (uFP), thawed fresh frozen plasma (tFFP), cryoprecipitate (CP) and stored red cell concentrates (sRCC) for managing haemophilia. This strategy predisposes to sensitizations and immune mediated acute transfusion reactions (IMATRs). Hence in this paper we analyzed the pattern of blood products transfusions and frequencies of IMATRs among multi-transfused haemophilicics in Nigeria.

**Methods:** We determined demographic and clinical data, frequencies of transfusion of each blood product, the prevalence of IMATRs, and the relative frequencies of each type of IMATRs among multi-transfused haemophilicics. Comparisons between patients with and without IMATRs were done using t-test for mean values and Fisher’s exact test for frequencies: p values of < 0.05 were taken as significant.

**Results:** Total of 86 haemophilicics received multiple transfusions of five types of blood products (FWB, uFP, tFFP, sRCC or CP) during study period. The frequencies of
transfusion of individual products were FWB (100%), uFP (65.1%), tFFP (36.0%), CP (32.6%) and sRCC (24.4%). Out of the 86 patients who had multiple transfusions, 61 (70.9%) patients had IMATRs, the commonest types being non-haemolytic febrile and urticarial reactions. Patients with IMATRs had significantly higher prevalence of severe haemophilia (65.6% vs. 24%, \( p < 0.05 \)) and higher mean number of transfusions per patient (21.5 vs. 12.3, \( p < 0.05 \)).

**Conclusion:** Multiple transfusions of FVIII-containing blood products in haemophilia is associated with high risk of IMATRs, which cause harm and impede therapy. Governments in Nigeria and other tropical countries should set up standard haemophilia care centres with adequate supply of FVIII-concentrate. Tropical health personnel can minimize transfusions by regular screening and treatment for tropical parasitic diseases and iron deficiency among haemophiliacs, while intensifying use of pharmacological agents in managing haemophilic bleeding.

**Keywords:** Haemophilia, Nigeria, tropical developing countries, multiple transfusion, transfusion reactions

**Introduction**

Haemophilia-A is an X-linked recessive bleeding disorder due to the deficiency of clotting factor VIII (FVIII). Bleeding episodes in moderate (FVIII level 1–5%) and mild (FVIII level 6–40%) haemophiliaics are usually provoked by recognizable trauma, while bleeding episodes in severe haemophilia (FVIII level <1%) often occur spontaneously.\(^1\)

The special vulnerability of haemophilic joints to recurrent bleeding is due to the role of synovial cells and chondrocytes as producers of the tissue factor pathway inhibitor,\(^2\) which makes severe haemophiliaics susceptible to frequent intra-articular haemorrhages with crippling arthropathy as a pathognomonic clinical feature of the disease.\(^3\) Nonetheless, no tissue or organ system is exempted from haemophilic bleeding diathesis.\(^4\) In developed countries, FVIII concentrate is the cornerstone for prophylactic and therapeutic management of haemophilia-A. In contrast, lack of FVIII concentrates is the single most important cause of poor haemophilia care in low resource tropical African countries such as Nigeria.\(^5\) The only possible conceivable ‘advantage’ of the scarcity of FVIII concentrates in tropical developing countries is the low incidence of FVIII inhibitors among local populations of haemophilia patients.\(^6\) This is because the risk of developing FVIII inhibitors is partly related to the intensity of patient exposure to FVIII concentrates.\(^7\) However, the virtual absence of FVIII concentrates compels haemophilia care givers in resource limited tropical countries to adopt less effective and non-specific therapeutic transfusion strategies in the management of haemophilic bleeding diathesis. These strategies include the transfusion of various non-specific FVIII-containing blood components such as fresh whole blood (FWB), unfrozen fresh plasma (uFP), thawed fresh frozen plasma (tFFP), and cryoprecipitate (CP). The choice of blood products is determined by patient’s clinical presentation with respect to whether or not active bleeding is associated with significant anaemia. Thawed FFP or CP may suffice for patients with active bleeding without significant anaemia, but these blood products are often not readily available in most Nigerian blood banks. Fresh whole blood is the most suitable blood product for actively bleeding patients with significant anaemia. In the absence of FWB, patients with active bleeding and anaemia can be managed with stored red cell concentrate (sRCC) (which is poor in FVIII) in conjunction with tFFP or CP as supplementary sources for FVIII. Like in many other tropical African countries, donor blood supply is inadequate in Nigeria.\(^8\) Therefore, more often than not relatives of haemophiliacs are required to donate FWB, which is either transfused as a whole (for patients with active bleeding and significant anaemia), or the plasma is harvested and transfused as uFP (for patients with active bleeding but without significant anaemia). Multiple transfusions of various blood products carry the inherent risks of infections,
sensitization and reactions. Hence haemophiliacs in Nigeria are frequently multi-transfused and inadvertently sensitized against multiple antigenic epitopes located on donor red cells, white cells, platelets and plasma proteins. On the one hand, multi-transfused patients often produce alloantibodies against donor blood antigens that can cause various forms of immune mediated acute transfusion reactions (IMATRs). On the other hand, some donors also have high titre of preformed antibodies in their plasma that can react with various antigens in recipient blood wherein they are also capable of causing a variety of IMATRs. Therefore, IMATRs in multi-transfused patients may occur due to alloantibodies in patient plasma or due to passively transfused antibodies in donor plasma. Irrespective of the source of the antibodies, IMATRs are particularly undesirable in haemophiliacs because they prevent optimal delivery of transfusion therapy and hence create a sense of dissatisfaction among the patients and their parents as well as among the blood bank personnel and clinicians. In this paper we evaluated the spectrum and clinical significance of IMATRs among haemophiliacs who received multiple transfusions (i.e. two or more transfusions) with FWB, uFP, tFFP, CP or sRCC in Nigeria. The main objectives of this paper are to determine the pattern of blood products transfusions, identify and estimate the relative frequencies of individual types of reactions among Nigerian haemophiliacs, analyze their clinical implications and proffer possible solutions within the context of haemophilia and its treatment in a low resource tropical setting.

Materials and Methods
There are no organized haemophilia care centres in Nigeria and FVIII concentrates is not usually available for prophylaxis or treatment. Consequently, the incidence of spontaneous and trauma induced haemophilic bleeding would be high especially in patients with severe disease. Moreover, regular long-term clinical follow-up is poor due to ignorance, poverty, logistic difficulties and disease mortality, which is expectedly high in low resource settings. Therefore, the few haemophiliacs who access tertiary hospitals usually present as emergency cases for ‘on-demand’ multiple transfusion therapy with less effective blood products such as FWB, uFP, tFFP, CP or sRCC, all of which have higher antigenic load than FVIII concentrates. The aforementioned situations make it very difficult to conduct prospective studies on haemophilia in developing countries. Hence, the hospital-based researchers in developing nations often have to be contented with scant and scattered retrospective data that were collected during previous bleeding emergencies. Therefore, this is a retrospective cohort study of data accrued from haemophilia patients who were transfused with various blood products at different time intervals in five northern Nigerian tertiary hospitals, including the University of Maiduguri Teaching Hospital, Maiduguri, north east Nigeria (1997–2007); State Specialist Hospital, Maiduguri, north east Nigeria (1997–2007); Federal Medical Centre Birnin Kudu, north west Nigeria (2004–2008); Murtala Muhammad Specialist Hospital, Kano, north west Nigeria (2008–2010); and Aminu Kano Teaching Hospital, Kano, north west Nigeria (2008–2012). The patients studied in this report were registered cases of haemophilia-A that were previously diagnosed on the basis of characteristic clinical profiles with low FVIII levels as assayed by automated coagulometers or by the one-stage manual assay technique. Patients were categorized as severe (FVIII level <1%), moderate (FVIII level 1–5%) or mild (FVIII level 6–40%) haemophiliacs. This study was conducted with the approval of local institutional ethics committees. The clinical and blood product transfusion records of haemophilia patients who had multiple transfusions (i.e. two or more transfusions) with FWB, uFP, tFFP, CP or sRCC were studied. However, patients who were transfused only once were not included in this study. Data regarding the age, sex, disease severity, and types of blood products transfused in each patient were retrieved and
collated. The each type of IMATR is identified and collated. Cases of IMATRs were identified on the basis of clinical features of the reactions and associated laboratory findings as documented in patients’ clinical notes, blood bank records and outcome of routine investigations for transfusion reactions.\textsuperscript{(13)} Uninvestigated cases of clinically suggested cases of IMATRs were excluded from this report. In this study, non-haemolytic febrile transfusion reaction (NHFTR) refers to febrile reaction of $\geq 1\text{C}$ rise in pre-transfusion temperature, chills and rigors, which may be associated with respiratory and haemodynamic instability in severe cases; urticarial transfusion reaction (UTR) refers to multiple itchy circumscribed pruritic skin reaction, which may be associated with angiooedema and anaphylaxis in severe cases; Transfusion related acute lung injury (TRALI) refers to respiratory reaction with fever, chills and respiratory distress, which may be associated with cyanosis, hypoxemia and pulmonary oedema in severe cases; and immediate haemolytic transfusion reaction (IHTR) due to donor haemolysins refers to haemolytic reaction corroborated by laboratory evidence of recipient red cell haemolysis in the presence of high titre haemolysins in donor plasma.\textsuperscript{(13)} The number of transfused patients with and without IMATRs were determined separately. Patients with and without IMATRs were compared with respect to age, disease severity, and number of transfusions per patients. The number and relative frequencies of each type of IMATR as seen among affected patients were also determined.

Data accrued from the five tertiary health institutions were collated and analyzed. Values of studied parameters were compared between patients with IMATRs and those without IMATRs using the $t$-test for mean values and the Fisher’s exact test for frequencies, with $p$ values of less than 0.05 taken as significant. Statistical analysis was performed using computer software SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

**Results**

A total number of 86 male haemophiliacs (aged 4–11 years) received multiple transfusions of five types of blood products (FWB, uFP, tFFP, CP or sRCC) during the period under review in the five health institutions. The pattern and frequency of transfusion of each type of blood products are shown in Table 1.

<table>
<thead>
<tr>
<th>Blood products*</th>
<th>Number of patients transfused (%)</th>
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<tbody>
<tr>
<td>FWB</td>
<td>86(100)</td>
</tr>
<tr>
<td>uFP</td>
<td>56(65.1)</td>
</tr>
<tr>
<td>tFFP</td>
<td>31(36.0)</td>
</tr>
<tr>
<td>CP</td>
<td>28 (32.6)</td>
</tr>
<tr>
<td>sRCC</td>
<td>21 (24.4)</td>
</tr>
</tbody>
</table>

* Every patient was transfused with more than one type of blood product.

The pattern and relative frequencies of each type of IMATR among the 61 affected patients are shown in Table 2.

<table>
<thead>
<tr>
<th>Type of reaction</th>
<th>Number of episodes (%)</th>
</tr>
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<tbody>
<tr>
<td>NHFTR</td>
<td>162 (72)</td>
</tr>
<tr>
<td>UTR</td>
<td>54 (24)</td>
</tr>
<tr>
<td>IHTR (due to donor haemolysins)</td>
<td>7 (3.1)</td>
</tr>
<tr>
<td>TRALI</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>All types of reactions</td>
<td>225 (100)</td>
</tr>
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</table>

The distribution of age, disease severity and number transfusions per patient among multi-transfused patients with and without IMATR is shown are Table 3.

In comparison with patients without IMATRs, patients with IMATRs had significantly higher proportion of severe disease (65.6% vs. 24%, $p < 0.05$) and higher mean number of transfusions per patient (21.5 vs. 12.3, $p < 0.05$); however, mean ages did not significantly differ between the two groups (8.2 vs. 7.3, $p > 0.05$). All of the IMATRs found in this study were of mild to moderate clinical severity.
Table 3: Age, disease severity and number of transfusions per patient among 86 haemophiliacs with and without IMATRs

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Haemophiliacs with IMATRS (n=61)</th>
<th>Haemophiliacs without IMATRS (n=25)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (mean ± SD)</td>
<td>7.3 ± 1.5</td>
<td>8.2 ± 2.1</td>
<td>p &gt; 0.05</td>
</tr>
<tr>
<td>Number (%) of patients with severe haemophilia</td>
<td>40 (65.6)</td>
<td>6 (24)</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Number (%) of patients with non-severe haemophilia</td>
<td>21 (34.4)</td>
<td>19 (76)</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Number of transfusions per patient (mean ± SD)</td>
<td>21.5 ± 4</td>
<td>12.3 ± 3</td>
<td>p &lt; 0.05</td>
</tr>
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</table>

Discussion
The Nigerian National Blood Transfusion Service is still rudimentary, hence individual hospital blood banks are continuously faced with the difficult task of donor procurement and production and storage of blood products for the clinical needs of their patients. The pattern of blood product utilizations among haemophiliacs in this study revealed that FWB was the most frequently transfused blood product. There are at least two possible reasons for this finding. First, production of FWB is technically very simple, which requires neither product separation nor sub-zero deep-freezing storage facility. Second, many haemophiliacs in Nigeria also suffer from chronic anaemia as a result of the combined effect of poverty, malnutrition, and frequent haemophiliic bleeding, as well as comorbid endemic tropical parasitic infections that aggravate blood loss and increase the risk of iron deficiency within the haemophilic population. Hence the ease of production of FWB and its dual advantage as a product that can simultaneously treat active bleeding as well as anaemia makes it the most frequently used blood product in the management of haemophiliacs in this study. Unfortunately, FWB is also the most antigenic of all blood products since it has the full complement of both cell-associated and plasma-associated antigens that can sensitize recipients and subsequently trigger IMATRs. The second most frequently used blood product is uFP because it can easily be manually harvested from FWB. However, clinical experience has shown that uFP for emergency use is usually hurriedly harvested and is often significantly ‘contaminated’ with red cells, leucocytes and platelets, which make uFP almost as antigenic as FWB. Only about one third of our subjects were transfused with tFFP or CP because the production of FFP and CP requires relatively more sophisticated blood banking procedures (e.g. product separation and sub-zero freezing) as compared with the relatively simpler production procedures for FWB and uFP. Although sRCC is the most readily available product in our blood banks, only about one quarter of our patients were transfused with it. This is because of the common knowledge that sRCCs contain low levels of labile factors including FVIII. Hence sRCCs were usually transfused in conjunction with tFFP or CP that serve as supplementary sources of FVIII.

Recurrent exposure to multiple donor antigens is thought to be responsible for the high prevalence of IMATRs that were seen in up to 70.9% of haemophiliacs in this study. This is consistent with our data, which revealed that in comparison with haemophiliacs who did not have IMATRs, haemophiliacs with IMATRs had higher prevalence of severe disease (which implied higher bleeding rate) with a commensurate higher mean number of transfusions per patient (which implied greater antigenic exposure and sensitization). IMATRs are particularly undesirable in haemophiliacs because they impede therapy by decreasing the ability of sensitized patients to tolerate the transfusion of optimal doses of non-specific FVIII-containing blood products (F WB, uFP, tFFP, CP or sRCC), which are usually administered in relatively large volumes because of their lower efficacy in comparison with FVIII concentrates. Four
types of IMATRs were identified in this study in which TRALI was the least frequent. TRALI is basically mediated by passively transfused anti-leucocyte antibodies that are usually present in multiparous female donors that were sensitized by previous pregnancies. Agglutinated recipient leucocytes become trapped in the lungs where they release cytokines, trigger inflammation and cause respiratory distress. TRALI is relatively uncommon even in developed countries and the risk is being further reduced by barring females with anti-leucocyte antibodies from blood donation. However, the rarity of TRALI as found in this study is most likely due to the scarcity of female donors in Nigeria as is usually the case in many other tropical developing countries. The frequency of donor haemolysin mediated IMATR among our patients was about three times that of TRALI. Haemolysins are immune IgG antibodies that are produced by group-O individuals in response to immunization resulting from previous incompatible transfusions, pregnancies or vaccines that are contaminated with A or B-like antigens. Group-O donors who have immune anti-A or anti-B haemolysins are referred to as dangerous universal donors. For this reason, the concept of universal donor and the practice of indiscriminate transfusion of group-O blood to non-O recipients should be strongly discouraged. The tendency to give group-O blood to non-O recipients is greater in areas of chronic donor blood shortage as is usually the case in Nigeria where group-O blood is considered extremely valuable since it could theoretically be given to any patient especially under emergency situations such as a severe haemophilic bleeding. Unfortunately, haemolysin screening is not routinely conducted in Nigerian blood banks despite clear evidence in the literature confirming the presence of haemolysins in some group-O donors in the local populations. The cases in this study clearly highlighted the need for regular screening of all group-O donors for high titre haemolysins and if found positive, such blood should not be used in transfusing group-A or B patients including haemophiliacs. NHFTRs and UTRs were the most frequent IMATRs in this study. While NHFTR is usually mediated by recipient antibodies formed against donor leucocytes, UTR is usually mediated by recipient antibodies formed against donor plasma proteins. The risk of recipient sensitization against donor leucocyte and plasma protein antigens increases with multiple transfusions. The high frequency of NHFTR and UTR in this study is consistent with previous studies that revealed positive correlation between multiple transfusions and the incidence of both NHFTR and UTR in Nigerian patients with sickle cell anaemia and other types of chronic anaemia. Non-severe NHFTRs can be managed by administering antipyretics, and once haemolysis and bacterial contamination of the donor blood unit are ruled out, the transfusion may continue at slow speed. Likewise, non-severe UTRs can be managed by administering anti-histamines, after which transfusion may resume at slow speed. Therefore, non-severe cases of NHFTRs and UTRs should not invariably lead to discontinuation of transfusion unless clinical evaluation dictates otherwise. However, clinical experience has shown that even mild cases of NHFTR and UTR often lead to premature termination of transfusion. Premature termination of transfusion causes delay in patient’s clinical progress and increases the burden of responsibility on patient’s relatives in the task of sourcing another blood donor, which can be extremely difficult especially if the patient has a rare blood group. Both NHFTR and UTR tend to recur in affected patients. However, recurrence of UTRs in subsequent transfusions can be prevented by the use of pre-transfusion anti-histamines, while the recurrence of NHFTRs in subsequent transfusions can be prevented by pre-transfusion antipyretics in conjunction with the use of leucocyte depleted blood products or bed-side micro-aggregate filters. Unfortunately neither leucocyte depleted blood products nor micro-aggregate filter are
readily available in tropical African countries. Although transfusion with washed red cell concentrates (in which both leucocytes and plasma proteins are washed off) is effective in the prevention of both NHFTRs and UTRs,\(^{(10,13,28)}\) however, this is not a feasible option for haemophiliacs scheduled for FWB transfusion because the therapeutically active anti-haemophilic factor (FVIII) is contained within the plasma compartment of the blood unit.

Nevertheless, haemophilia healthcare personnel working in low resource tropical areas with little or no access to FVIII concentrates can still minimize the use of multiple blood products transfusions in the management of haemophiliacs from at least two perspectives. First, tropical healthcare workers should incorporate regular screening and treatment protocol for common pro-haemorrhagic parasitic diseases and iron deficiency into the standard of care for management of haemophilia as recommended by previous studies based on tropical clinical experience.\(^{(14-16)}\) If this protocol is well implemented, it would minimize the need for multiple blood products transfusion by reducing gastrointestinal and urinary bleeding rates and scaling down the prevalence of iron deficiency anaemia among haemophiliacs living in the tropics.\(^{(29)}\) However, while anti-parasitic therapy may not pose any bleeding risk, iron supplements should be given to iron deficient haemophiliacs with caution. This is because one of the side effects of iron therapy is erosive gastritis and gastric bleeding, which are commonly associated with iron pills, but not with liquid iron preparations.\(^{(30)}\) In view of this risk, we recommend that iron-deficient haemophiliacs, irrespective of their ages, should preferably be treated with liquid iron preparations.\(^{(30)}\) Second, a previous study has identified the lack of adequate use of pharmacological agents such as desmopressin and the anti-fibrinolytic agents (epsilon amino caproic acid and tranexamic acid) as a major limitation in the management of haemophilia in tropical developing countries.\(^{(5)}\) Desmopressin raises vWF and FVIII levels, while anti-fibrinolytic agents inhibit fibrin clot degradation, and have all been shown to be useful in controlling haemophilic bleeding especially in patients with mild and moderate haemophilia.\(^{(31,32)}\) Tranexamic acid in particular has been widely and successfully used alone or in combination with other anti-haemophilic agents in the prevention and management of various haemophilic bleedings due to accidental or surgical trauma in haemophiliacs.\(^{(32)}\) The only exception to the use of anti-fibrinolytic agents is urinary tract bleeding because of the possible risk of obstructive uropathy that may occur as a result of fibrin clot formation in the urinary tract.\(^{(32)}\) We therefore recommend that haemophilia health care givers in the tropics should intensify the use of these pharmacological agents (since they are cheaper than FVIII concentrates) as a way of minimizing multiple blood product exposure and the risk of sensitization and reactions in the management of haemophilic bleeding diathesis.

However, the only true and lasting solution to the problem of multiple transfusions of FWB and other multi-antigenic FVIII-containing blood products for haemophilia patients is regular provision and availability of FVIII concentrates. In similarity with other developing countries, the exact prevalence and incidence of haemophilia in Nigeria are currently unknown due to under-diagnosis, under-documentation and under-reporting of cases\(^{(33)}\) coupled with very high and early childhood mortality resulting from poor management.\(^{(5)}\) Nonetheless, Nigeria has the largest population in Africa and presumably carries the heaviest burden of persons living with haemophilia in Africa. Unfortunately, local clinical experience in Nigeria and other tropical African countries has proven that adequate provision of FVIII concentrates is certainly beyond the financial capability of the average haemophilia patients or their parents.\(^{(5)}\) It is therefore the responsibility of governments to set up standard haemophilia treatment centres and provide adequate supply of FVIII concentrates therein.

In conclusion, multiple transfusions of blood products other than FVIII concentrates in the
management of haemophilia is relatively inefficacious and is associated with high risk of IMATRs, which constitute serious therapeutic impediments among haemophiliacs in Nigeria and by implication in other poor tropical African countries. There is therefore urgent need for governmental interventions in setting up standard haemophilia care centres with adequate supply of FVIII concentrates for regular prophylaxis and treatment of haemophilic bleeding diathesis. Meanwhile, haemophilia health care providers in the tropics can minimize transfusion of multiple blood products by developing local guidelines that would ensure regular screening and treatment for common pro-haemorrhagic parasitic diseases and iron deficiency as well as intensifying iron supplementation and use of pharmacological agents in the standard of care for haemophilia patients.

**Conflict of Interest:** None.

**Ethical clearance:** Obtained.

**Informed consent form:** Obtained

### References


