ORIGINAL ARTICLE

Pattern, Indications and Gastrointestinal Complications of over-the-counter Traditional Non-Steroidal Anti-Inflammatory Drug Use among Haemophiliacs in Northern Nigeria: A Critical Appraisal of a Small Case Series

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ABSTRACT

Background: coagulation factor VIII (FVIII) is scarce in Nigeria. Therefore, musculo-skeletal bleeding and other painful conditions including dental diseases are neither promptly nor optimally treated, thus encouraging self-medication with traditional non-steroidal anti-inflammatory drugs (tNSAIDs), which are associated with gastrointestinal bleed. Frequency of self-medication with tNSAIDs among Nigerian haemophiliacs is unknown. Hence, pattern of tNSAID-associated gastrointestinal complications has not been documented.

Objective: To determine pattern, indications and gastrointestinal complications of over-the-counter tNSAIDs self-medications among Nigerian haemophiliacs.

Methodology: Retrospective analysis of demographic and clinical data of 17 haemophiliacs who used tNSAIDs on self-medication and subsequently self-reported at hospitals because of intolerable gastrointestinal symptoms as documented in five tertiary hospitals.

Result: Indications for tNSAIDs self-medication showed adults had higher prevalence of chronic arthropathy (42.9%vs.10%), while children had higher prevalence of acute haemarthrosis (30%vs.14.3%) and toothache (30%vs.14.3%). Mean number of days of tNSAIDs consumption was 3.8 (for patients who reported dyspepsia only), 6.9 (for patients who reported dyspepsia and melaena), and 9.4 (for patients who reported dyspepsia, melaena and haematemesis).

Conclusion: tNSAIDs are not safe in haemophiliacs. Risk and severity of tNSAID-induced dyspepsia and gastrointestinal bleed in haemophiliacs correlated with duration of consumption. Government should set-up haemophilia centres with adequate FVIII for optimal and prompt management of musculo-skeletal, dental and other morbidities. Healthcare personnel should intensify counseling against tNSAIDs self-medication, and ensure pain is always promptly and optimally managed according to World Federation of Haemophilia guidelines for safe analgesia in haemophilia.

Key Words: *Haemophilia-A, Musculo-skeletal pain, Toothache, Analgesics, Melaena, Haematemesis*

INTRODUCTION

Hemophilia-A (HA) is an X-linked recessive congenital bleeding disorder caused by quantitative or qualitative deficiency of coagulation factor VIII (FVIII). The deficiency is the result of various types of mutations of the FVIII gene, which is located on the X-chromosome.[1] Low levels of FVIII in the intrinsic pathway leads to impaired production of tenase complex with a resultant reduction in thrombin generation capacity of the intrinsic pathway.[2]

Hence, the clinical severity of HA is largely determined by the residual levels of FVIII, and is thus categorized as severe (FVIII level <1%), moderate (FVIII level 1-5%) or mild (FVIII level 6-40%).[1,2] However, the resultant clinical phenotypes and bleeding rates among haemophiliacs may also be significantly modified by the co-inheritance of prothrombotic genetic polymorphisms or thrombophilic genes.[3,4,5,6,7,8]

Nonetheless, the clinical course of haemophilia is characterized by recurrent bleeding episodes that may occur apparently spontaneously in severe cases, or after provocation by recognizable trauma in non-severe cases.[1,2] The chondrocytes and synovial cells of the joints are known to actively produce tissue factor pathway inhibitor, which attenuates the activity of extrinsic pathway within the joints.[9] Consequently, frequent intra-articular haemorrhages with crippling arthropathy have virtually become pathognomonic clinical features of haemophilia, especially in severely affected patients.[10] Nevertheless, no tissue or organ system is exempted from haemophilic bleeding diathesis, and musculoskeletal bleeding complications are particularly common problems among haemophiliacs.[11]

External bleeding is the most common and spectacular clinical manifestation of the haemophilic diathesis, but it is usually painless. Conversely, internal bleeding within restricted body compartments often cause pain as a result of local accumulation of blood. Accumulated blood can trigger pain by a combination of factors such as high pressure effect (e.g. headache due to intra-cranial bleed), tissue irritation and inflammation (e.g. musculo-skeletal pain due to acute haemarthrosis, chronic arthropathy, or intra-muscular bleed), tissue compression and necrosis (e.g. compartment syndrome pain due to tense intra-muscular bleed) or luminal obstruction (e.g. ureteric colic due to obstructive intra-luminal clot).[12]

Pain in haemophiliacs may also be associated with poor oral hygiene, dental caries, cavitations and infection especially in children.[12] Therefore, pain is not an uncommon clinical symptom of haemophilia. Non-steroidal anti-inflammatory drugs (NSAIDs) are very effective analgesics because they interfere with prostaglandin metabolism and consequently reduce inflammation and pain.[13] Gastrointestinal haemorrhage, which can manifest as haematemesis, melaena or haematochezia, is not an uncommon clinical problem in haemophiliacs especially in patients with severe disease in whom bleeding may occur spontaneously or be triggered by blunt abdominal trauma, peptic ulcer disease or chronic liver disease with portal hypertension.[14]

Moreover, the risk of haemophilic gastrointestinal haemorrhage can be significantly increased by the use of NSAIDs even among apparently healthy haemophiliacs devoid of the aforementioned co-morbid factors. This is because NSAIDs have two potentially haemorrhagic side effects that are undesirable in the haemophiliacs. Firstly, NSAIDs inhibit the production of gastro-protective prostaglandins and cause gastric mucosal injury, thereby increasing the risks of dyspepsia, gastritis, peptic ulceration and localized gastrointestinal haemorrhage even in normal (non-haemophilic) persons.[15] Secondly, NSAIDs inhibit cyclo-oxygenase, reduce thromboxane-A2 synthesis, and decrease platelet activation and aggregation, thereby jeopardizing primary haemostasis and increasing the risk of systemic haemorrhage even in normal (non-haemophilic) persons.[16]

Hence, the use of NSAIDs in haemophilia would predictably aggravate gastrointestinal and systemic bleeding risks via the dual effects of local gastric mucosal injury and general impairment of primary haemostatic platelet function, both of which are undesirable in the haemophiliac who is already suffering from a pre-existing secondary haemostatic dysfunction due to congenital deficiency of FVIII.[2]

The haemophiliacs would therefore be particularly vulnerable to the haemorrhagic adverse effects of NSAIDs. However, the risks of NSAID-related haemorrhagic side effects are considerably lower with the use of selective cyclo-oxygenase-2 (COX-2) inhibitor NSAIDs (sNSAIDs) in comparison with traditional (non-selective) NSAIDs (tNSAIDs).[17]

In conformity with theoretical expectations, some studies had shown that the use of tNSAIDs in haemophiliacs were associated with significant increase in gastrointestinal and skin bleeding rates.[18,19,20] Nonetheless, some studies had shown that despite theoretical expectations, the use of tNSAIDs in standard doses did not actually increase gastrointestinal or any bleeding rate in haemophiliacs.[21,22] These discrepancies call for more and continuing appraisals on the gastrointestinal complications of tNSAIDs among haemophiliacs especially in tropical countries such as Nigeria, where over-the-counter tNSAIDs are easily accessible by haemophiliacs.

Similar to other low resource countries, scarcity of FVIII concentrate in Nigeria leads to grossly sub-optimal therapy of haemophilic bleeding by merely using fresh whole blood, plasma or cryoprecipitate as the only available therapeutic options.[23,24] Hence, Nigerian haemophiliacs often live with poorly treated acute and/or chronic musculo-skeletal bleeding complications or untreated dental problems (due to fear of provoking surgical bleeding). It is therefore a standard counseling practice among healthcare personnel to advice haemophiliacs (or their parents/guardians) to opt for Paracetamol as the safest (i.e. devoid of haemorrhagic side effects) first-line analgesic to counteract musculoskeletal, dental and other types of pain.[12] Nonetheless, patients may seek relief through the use of NSAIDs when Paracetamol fails to provide adequate relief.

The absence of FVIII prophylaxis virtually allows haemophilia to run its natural course in the Nigerian patients. Hence, the incidence of spontaneous and trauma induced haemophilic bleeding is high especially in patients with severe haemophilia, which is strongly associated with very early infant and childhood mortality. The few haemophiliacs that survive and access tertiary hospitals are usually treated as bleeding emergency cases that are inadequately managed with 'on-demand' multiple transfusion therapy using blood products such as fresh whole blood, fresh plasma or cryoprecipitate that are by far haemostatically inferior to FVIII concentrate.[24]

Moreover, surgical procedures for dental, musculo-skeletal and other morbidities are often deferred due to lack of FVIII concentrates for prevention of post-operative bleeding. Consequently, surviving haemophiliacs in Nigeria have to endure recurrent, multiple and painful articular and musculoskeletal haemorrhagic complications or dental problems that compel them to use various types of analgesics including cheap tNSAIDs that are often purchased over-the-counter.

The quickest way (devoid of hospital-based clinical consultations and formalities) of getting rapid access to NSAIDs is by direct 'over-the-counter' purchase from patent medicine stores. However, in comparison to sNSAIDs, tNSAIDs are generally cheaper and more available in local patent medicine stores. Consequently, it is not uncommon in Nigeria for haemophiliacs or their parents (who are oblivious of drug side effects) to purchase tNSAIDs on self-medication for treatment of pain.

To the best of our knowledge, the use and gastrointestinal adverse effects of over-the-counter tNSAIDs among haemophiliacs have not been previously reported from Nigeria. Hence, in this study we retrospectively reviewed the pattern, indications and gastrointestinal complications of over-the-counter oral tNSAIDs self-medication as self-reported by a small number of haemophiliacs accrued from five tertiary hospitals in northern Nigeria.

METHODOLOGY

Clinical Setting, Study Description and Patient Diagnosis

This study is a retrospective analysis of such data accrued from a total of 17 haemophilia patients who purchased and used un-prescribed over-the-counter oral tNSAIDs and subsequently self-reported the self-medication incidents due to intolerable gastrointestinal side effects as documented (between 1996 and 2012) in five northern Nigerian tertiary hospitals. The study hospitals included University of Maiduguri Teaching Hospital (UMTH) Maiduguri, North East Nigeria; State Specialist Hospital (SSH) Maiduguri, North East Nigeria; Federal Medical Centre (FMC) Birnin Kudu, North West Nigeria; Murtala Muhammad Specialist Hospital (MMSH) Kano, North West Nigeria; and Aminu Kano Teaching Hospital (AKTH) Kano, North West Nigeria.

The patients self-reported the incidents at the haematology and/or paediatrics departments of the respective hospitals where they usually received clinical care and blood products transfusion therapy as and when needed. Hence, 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.[25] On the basis of FVIII levels, patients were categorized as severe (FVIII level <1%), moderate (FVIII level 1-5%) or mild (FVIII level 6-40%) haemophiliacs.[25] This study was conducted with the approval of local institutional ethics committees of the five hospitals.

Selection of Patients, Definition of Gastrointestinal Symptoms, and Data Retrieval

Data regarding the age, sex, disease severity and types of tNSAIDs (including the indications for using the drug, the dosage and duration of use) and associated presenting gastrointestinal symptoms in each patient were identified, retrieved and collated.

Three types of symptoms were identified and defined on the basis of clinical history and presentation as documented in patients' clinical records as follows: dyspeptic epigastric pain, haematemesis and melaena. In this study, dyspeptic epigastric pain referred to a painful or burning sensation in the mid-chest and/or epigastric region of the abdomen which may radiate to the back or be associated with epigastric tenderness.[26] Haematemesis referred to any episode of vomiting of coffee-coloured and/or bright red blood, which is generally associated with the upper gastrointestinal bleeding.[27] Melaena referred to any episode of passage of tarry black stool, which is usually due to bleeding from the upper gastrointestinal tract after which the normal red colour of blood is altered by the hind gut flora to tarry black colour.[27]

Patients who took tNSAIDs concurrently with oral iron-containing haematinics were excluded from this study for two reasons. First, iron pills are independently associated with the risk of gastritis and may cause dyspeptic epigastric pain and upper gastrointestinal bleeding even in haemostatically normal persons.[28] Second, oral iron preparations can cause black discoloration of the stool (pseudo-melaena) even in the absence of gastrointestinal bleeding.[27] Moreover, none of the patients studied in this report had any documented history of recent blunt abdominal trauma, HIV-associated thrombocytopenia, chronic liver disease, portal hypertension, peptic ulcer disease or positive stool test for helminthiasis, any of which could independently predispose to gastrointestinal haemorrhage in haemophiliacs irrespective of tNSAIDs consumption.[14, 29]

Categorization of Patients on the Basis of Symptoms Constellation

Each patient was allocated into one of three discrete 'symptom categories' on the basis of constellation of presenting symptoms: Category-1: Patients with dyspeptic epigastric pain only. Category-2: Patients with dyspeptic epigastric pain and melaena. Category-3: Patients with dyspeptic epigastric pain, melaena and haematemesis.

Statistical Data Analysis

Data accrued from the five tertiary hospitals were collated and analyzed. In order to correlate duration of tNSAID consumption and severity of symptoms, mean values of duration of time (in days) of consumption of tNSAIDs among patients in each symptom category (Categories 1-3) were calculated and compared using the Student *t*-tests with *p*-values of less than 0.05 taken as significant. Statistical analysis was performed using computer software: statistical package for

social science (SPSS) version 15.0 (SPSS Inc., Chicago, IL, USA).

RESULT

A total of 17 haemophilia patients who used oral tNSAIDs on self-medication and subsequently self-reported the incidence due to intolerable gastrointestinal symptoms were retrieved and collated from the five hospitals during the period under review.

Table 1. General demographic, clinical and drug information data as seen among 17 male haemophiliacs who used tNSAIDs

S/N	Patient age, haemophilia severity	Pain indication for using tNSAIDs	Types of tNSAIDs used	Total daily doses	Duration of use	Adverse symptoms of tNSAIDs		
						Dyspeptic epigastric Pain	Melaena	Haematemesis
1	22 years, Moderate	Chronic Arthropathy	Indomethacin	100mg	11 days	(P)	(P)	(P)
2	20 years, Moderate	Chronic Arthropathy	Diclofenac	100mg	10 days	(P)	(P)	(A)
3	19 years, Moderate	Chronic Arthropathy	Piroxicam	20mg	11 days	(P)	(P)	(P)
4	19 years, Moderate	Acute Muscle Bleed	Diflunisal	1g	9 days	(P)	(P)	(A)
5	18 years, Moderate	Toothache	Naproxen	750mg	8 days	(P)	(P)	(A)
6	18 years, Moderate	Acute Muscle Bleed	Ketoprofen	150mg	5 days	(P)	(A)	(A)
7	18 years, Moderate	Acute Haemarthrosis	Ibuprofen	1.2g	5 days	(P)	(A)	(A)
8	15 years, Moderate	Chronic Arthropathy	Diclofenac	75mg	9 days	(P)	(P)	(P)
9	14 years, Moderate	Acute Haemarthrosis	Diclofenac	75mg	4 days	(P)	(A)	(A)
10	14 years, Severe	Acute Muscle Bleed	Diclofenac	75mg	3 days	(P)	(A)	(A)
11	10 years, Severe	Toothache	Ibuprofen	600mg	8 days	(P)	(P)	(P)
12	9 years, Severe	Acute Muscle Bleed	Ibuprofen	600mg	2 days	(P)	(A)	(A)
13	9 years, Severe	Toothache	Ibuprofen	600mg	6 days	(P)	(P)	(A)
14	8 years, Severe	Acute Muscle Bleed	Ibuprofen	600mg	6 days	(P)	(P)	(A)
15	7 years, Severe	Toothache	Ibuprofen	300mg	8 days	(P)	(P)	(P)
16	7 years, Severe	Acute Haemarthrosis	Ibuprofen	300mg	5 days	(P)	(P)	(P)
17	6 years, Severe	Acute Haemarthrosis	Ibuprofen	300mg	4 days	(P)	(P)	(A)

(P): Present; (A): Absent

Table 1 showed the general demographic, clinical and drug information data of the 17 patients, which revealed that the 17 patients included 10 children and 7 adults male haemophiliacs within the age range of 6-22 years with various painful conditions including acute and chronic musculo-skeletal complications and toothache for which they used 7 types of tNSAIDs including Diclofenac, Indomethacin, Piroxicam, Ibuprofen, Ketoprofen, Naproxen and Diflusinal at the stated dosages.

Table 2 showed the comparison of clinical parameters and pattern of tNSAIDs utilization between adults and children with haemophilia. Pattern of disease severity showed that in comparison with children, adult patients had higher prevalence of moderate haemophilia (100% vs. 20%, p=0.002) and lower prevalence of severe haemophilia (0% vs. 80%, p=0.000). The indications for tNSAIDs showed that in comparison with children, adult patients had higher prevalence of chronic arthropathy (42.9% vs. 10%, p=0.002), lower prevalence of acute haemarthrosis (14.3% vs. 30%, p=0.003), lower prevalence of toothache (14.3% vs. 30%, p=0.003) and a comparable prevalence of acute muscle bleed (28.6% vs. 30%, p=0.07).

Table 3 showed the correlation between duration of tNSAID use and symptom categories. The mean number of days of tNSAIDs consumption rose from 3.8 days for category-1 patients to 6.9 days for category-2 patients and 9.4 days for category-3 patients. The inter-category differences between the three mean values were statistically significant: (3.8 vs. 6.9, p=0.03); (6.9 vs. 9.4, p=0.03).

DISCUSSION

Nigeria has the largest population in Africa and presumably carries the heaviest burden of persons living with haemophilia in the continent. However, 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 coupled with very high and early childhood mortality resulting from poor management.[23,30] Consequently, this study was based on a relatively small sample size, despite a fairly extended period of review and the use of a multicentre approach.

Haemophilia in developing countries is characterized by lack of prophylaxis, inadequate management, poor prognosis, early mortality and low survival rate into adulthood.[23,31] This is partly responsible for the relatively low proportion of adults in our study cohort. Moreover, all of the adult patients in this study had the moderate (non-severe) type of haemophilia, which has better long-term prognosis and was most probably a contributory factor to their survival into adulthood.

The predominance of chronic arthropathy as the indication for using tNSAIDs among our adult patients is consistent with the fact that the incidence of chronic haemophilic arthropathy is more common in adult haemophiliacs than in children as reported in previous studies.[32] Thus chronic arthropathy has been reported to be the main musculo-skeletal morbidity in the adults and ageing haemophiliacs as the cumulative episodes of recurrent acute haemarthrosis, inflammation and joint damage increase with age in an

almost linear fashion in both severe and moderate haemophilia.[32]

Conversely, the overwhelming majority of our haemophilic children had severe haemophilia that is clinically characterized by high bleeding rates with frequent occurrence of acute haemarthrosis and acute muscle bleeding, which were indeed the predominant indications for the use tNSAIDs among children in this study.[11] However, while toothache was a minor indication for tNSAIDs use among adult patients, it was a major indication for the use of tNSAIDs among children in this study. Toothache was the indication for tNSAIDs use in about one third of the haemophilic children studied in this report. This finding is consistent with the fact that children by nature are prone to excessive consumption of sugary food items upon which oral bacteria thrive and produce lactic acid.[33] In the presence of poor oral hygiene, lactic acid dissolves the enamel

Table 2. Comparison of clinical parameters and pattern of drug utilization among 17 adults and children with haemophilia who used tNSAIDs

Parameters	**Children (< 18 Years) [N=10]**	**Adults (≥ 18 Years) [N=7]**	**P-values**
Age (Years)			
Mean ± SD	9.9 ± 2.4	19.1 ± 0.8	0.004
Disease severity	No. of Patients	No. of Patients	
Severe haemophilia	(%)	(%)	0.000
Moderate haemophilia	8(80)	0(0)	0.002
Mild haemophilia	2(20)	7(100)	0.000
	0(0)	0(0)	
Indications for tNSAIDs			
Acute haemarthrosis	3(30)	1(14.3)	0.003
Acute muscle bleed	3(30)	2(28.6)	0.07
Chronic arthropathy	1(10)	3(42.9)	0.002
Toothache	3(30)	1(14.3)	0.003
Types of tNSAIDs used			
Diclofenac	3(30)	1(14.3)	0.003
Indomethacin	0(0)	1(14.3)	0.000
Piroxicam	0(0)	1(14.3)	0.000
Ibuprofen	7(70)	1(14.3)	0.001
Ketoprofen	0(0)	1(14.3)	0.000
Naproxen	0(0)	1(14.3)	0.000
Diflusinal	0(0)	1(14.3)	0.000
Symptom categories			
Category-1 (Epigastric pain only)	3(30)	2(28.6)	0.07
Category-2 (Epigastric pain and melaena)	4(40)	3(42.9)	0.08
Category-3 (Epigastric pain, melaena and haematemesis)	3(30)	2(28.6)	0.07

Table3. Mean duration of tNSAID use and categories of gastro-intestinal symptoms

Symptoms Categories	Symptoms constellations	Duration of use of tNSAID (days) Mean ± SD
CATEGORY-1 (n=5)	Epigastric pain only	3.8 ± 0.7
CATEGORY-2 (n=7)	Epigastric pain and melaena	6.9±1.4
CATEGORY-3 (n=5)	Epigastric pain, melaena and haematemesis	9.4±1.1

and is thus a major contributor to the development of dental caries, cavitations and infections, all of which are strongly associated with the development of severe toothache. [34-37]

Unless the distressed haemophiliac with agonizing toothache is promptly offered the required dental procedure, the aching tooth will continue to compel the patients to access cheap and locally available over-the-counter tNSAIDs in spite of the potential risks of gastrointestinal haemorrhage.

The array of seven tNSAIDS (Diclofenac, Indomethacin, Piroxicam, Ibuprofen, Ketoprofen, Naproxen, Diflusinal) used by the haemophilia patients in this study portrayed a pattern that was reflective of low cost and local availability of the drugs in street side medicine stores. Moreover, the daily dosages used by all the patients in this study (as shown in Table1) were standard dosages in consistency with the ages of the patients.[38] While utilization of the seven tNSAIDs were equally spread among the adult patients, only Diclofenac and Ibuprofen were used by older and younger children respectively as the remaining five tNSAIDs are generally not recommended for children.[38] However, Ibuprofen was the most frequently used drug because of its suitability for children and greater dosage flexibility, and is commonly available in oral suspensions, which allows for easier administration across a wide range of ages among the children.

We reckon that the risk of developing dyspepsia and gastrointestinal haemorrhage at standard dosages of tNSAIDs may vary with individual tNSAIDs.[38,39] For example, previous studies suggested that Piroxicam and Ketoprofen were associated with highest risks, while Diclofenac, Indomethacin and Naproxen were associated with intermediate risks, and Ibuprofen was associated with lowest risk of gastrointestinal haemorrhage in normal (non-haemophilic) individuals.[38,39] However, because of their underlying haemostatic defect, haemophiliacs would be more sensitive to the gastrointestinal side effects of any type of tNSAIDs in general.

Our results have shown that the risk of dyspepsia and gastrointestinal haemorrhage at standard dosages of tNSAIDs among haemophiliacs was time-dependent. This is because haemophiliacs who took tNSAIDs for an average duration of 3.8 days experienced painful dyspepsia only. However, those who used the drugs for a longer average period of 6.9 days had a dual constellation of painful dyspepsia and melaena. Moreover, those who

used the drugs for the longest average period of 9.4 days had a triple constellation of painful dyspepsia, melaena and haematemesis, suggestive of severe gastrointestinal haemorrhage. Therefore, the symptom-time trend depicted by our results had shown that both risk and severity of tNSAID-induced dyspepsia and gastrointestinal haemorrhage in haemophiliacs were directly correlated with the duration of drug intake.

The findings of this study have highlighted the haemorrhagic risks associated with the use of over-the-counter tNSAIDs by haemophiliacs in Nigeria. However, the use of these non-prescribed tNSAIDs was clearly dictated by musculo-skeletal pains or toothaches. The definitive solution to the problems of painful musculo-skeletal complications is the provision of adequate and effective therapeutic and prophylactic management of haemophilic bleeding diathesis with FVIII concentrate, which unfortunately is scarce in Nigeria. Likewise, the definitive surgical solution to toothache in haemophilic children depends on availability of FVIII concentrate and anti-fibrinolytic agents; again, FVIII concentrate is a limiting factor in this context.

However, healthcare providers can prevent the risky use of tNSAIDs among haemophiliacs by intensive counseling against self-medication with tNSAIDs, coupled with the implementation of the World Federation of Haemophilia (WFH) recommendations and guidelines on the choice and application of safe analgesics. The WFH guidelines and other expert reviews on general care and management of pain in haemophilia recommend the use of sNSAIDs and dissuade the use of tNSAIDs.[40,41,42] On the basis of pain severity, the general recommendation revolves around a step wise sequential use of Paracetamol, sNSAIDs, and narcotics as may be dictated by pain severity in management of musculo-skeletal complications among haemophiliacs.[40-42]

The rationale behind the stepwise choice of these analgesics for the haemophiliacs is three-fold. First, Paracetamol is a centrally active COX-3 inhibitor analgesic with little or no anti-inflammatory action and is devoid of undesirable gastric mucosal irritation and anti-platelet side effects of tNSAIDs.[43] Second, sNSAIDs have comparable analgesic effect to tNSAIDs but with less gastrointestinal bleeding risk, which can be further reduced with concomitant use of proton pump inhibitors.[17] Third, narcotics are centrally active analgesics that are strong enough to counteract the severest of pains and yet they are devoid of both anti-inflammatory and anti-platelet effects of tNSAIDs.[44]

Nonetheless, even the WFH and other expert guidelines for analgesia in haemophilia must be applied judiciously for the shortest possible time in order to avoid the hepatotoxic effect of paracetamol, nephrotoxic and cardiovascular complications of sNSAIDs and the addictive potentials of narcotics. [45,46,4748]

As a limitation of this study, we were unable to perform a robust multi-variate analysis to determine the risk associated with each of the seven tNSAIDs used by our hemophiliacs (who are nevertheless expected to be more sensitive to tNSAIDs than normal

individuals) due to the smallness of our sample size.

CONCLUSION

tNSAIDs are not safe in haemophilia. Toothaches and acute musculo-skeletal complications were the main indications for self-medications with tNSAID use among haemophilic children, while chronic musculo-skeletal complications were the main indications among adult haemophiliacs. The array of tNSAIDs used by the patients in this study depicted a pattern that was reflective of low cost and over-the-counter availability of the individual drugs in local medicine stores. The risk and severity of tNSAID-induced dyspepsia and gastrointestinal haemorrhage in haemophiliacs were directly correlated with the duration of drug intake. There is urgent need for governmental interventions in setting up standard haemophilia care centres with adequate supply of FVIII concentrates for regular use in prophylaxis and treatment of haemophilic bleeding diathesis, and for provision of haemostatic cover for prompt dental and other essential surgical procedures. In this way, the healthcare providers can provide optimum management, prevent musculo-skeletal complications and safely conduct dental (and indeed other surgical) procedures, all of which will ultimately minimize unnecessary pain and suffering among paediatric and adult haemophilia patients in Nigeria.

In the meantime, haemophilia healthcare providers in Nigeria can prevent the risky use of tNSAIDs among haemophiliacs by intensive counseling (against self-medication with tNSAIDs) and careful implementation of the WFH and expert guidelines on the choice and application of safe analgesics protocol for the management of pain in haemophilia.

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