THE CLINICAL PRESENTATION, MAGNITUDE AND RISK FACTORS FOR DEVELOPMENT OF INHIBITORS OF FACTOR VIII AND IX AMONG PATIENTS WITH HEMOPHILIA AT MUHIMBILI NATIONAL HOSPITAL

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By

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A Dissertation/ Thesis Submitted in (partial) Fulfillment of the Requirement for the Degree of Master of Science (Haematology and Blood Transfusion) of

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CERTIFICATION

Undersigned certify that they have read and hereby recommended for acceptance by Muhimbili University of health and Allied Sciences a dissertation entitled **"The clinical presentation, magnitude and risk factors for development of factor VIII and IX among patients with haemophilia at Muhimbili National Hospital"**, in (partial) fulfilment of requirements for the degree of masters of Medicine in Haematology and Blood Transfusion) of Muhimbili university of Health and Allied Sciences.

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(Co-Supervisor)

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Date

DECLARATION AND COPYRIGHT

I, **Oliver Isengwa**, declare that this **dissertation** is my own original work and that it has not been presented and will not be presented to any other university for similar or any other degree award.

Signature…… **Date**……..

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DEDICATION

I dedicate this dissertation first to my mother Mrs. Sabina Isengwa and second to my husband Mr. Valentino Khoja and lastly to my children, Lucy Raya and John Khoja.

ABSTRACT

Background: Inhibitor development continues to be a severe complication worldwide in hemophilia patients on factor replacement therapy. Given the difficulties associated with the treatment of inhibitors in both the developed and the developing world, prediction and prevention of inhibitors following exposure to factor VIII or IX in hemophilia patients has become a management priority.

Objective: To determine the magnitude, clinical presentation and risk factors of factor VIII and IX inhibitors in hemophiliac patients at Muhimbili National Hospital (MNH)

Methodology: A descriptive cross sectional study, involved hemophilia cohort attending MNH. It involved patients in hemophilia registry in MNH which were comprised of 77 patients. Among 77 patients in the registry, only 60 patients had complete details. Forty seven hemophilia A and 13 hemophilia B. Patients were recruited between August 2016 and February 2017. Activated Partial Thromboplastin Time (APTT) was performed to pooled patients plasma with normal activated prothrombin time (23-30 seconds) and hemophiliac patient's plasma. Equal plasmas volume mixing of normal and hemophiliac patient was also done and APTT performed by using automated coagulation analyzer to determine presence of immediate inhibitors. After 2hours at 37 degrees centigrade incubation of normal, hemophiliac patient plasma and a mixture of both, APTT for time dependent factors inhibitors (FVIII) was obtained. The collected data was analyzed using SPSS software version 20.0.

Results: Sixty (60) patients with hemophilia were recruited, 78.3% with hemophilia A and 21.7% hemophilia B. The mean age at diagnosis was 6.6 ± 5.9 years while the mean age at interview being 12.9 ± 7.2 years. Majority of patients were at primary and secondary school by 36.7% and 31.7% respectively. Although hemophilia patients are widely distributed in all regions of Tanzania, 51.7% of patients recruited in the study were residents of Dar es Salaam.

The prevalence of inhibitors was found to be 6.7% in all hemophiliac patients recruited in the study. Among hemophilia A patients, the prevalence of inhibitors was found to be 8.5%. The prevalence of inhibitors was found to be 15.4% in severe hemophilia A. Hemarthrosis was the

frequent clinical feature 45.0%, at the time of diagnosis and 35.0% at the time of interview followed by hematoma 10.0% and 16.7% at diagnosis and interview respectively.

Fifty percent (50%) of hemophilia A patients with inhibitors had a family history of uncontrolled bleeding despite the respective dose of factor eight (FVIII) concentrate which was suggestive of genetic predisposition. 3.6% had <50 doses of factor concentrate develop inhibitors while 40% had been exposed to factor concentrate>50doses developed inhibitors.

Conclusion: The prevalence of hemophilia inhibitors was high in severe hemophilia A attending MNH. The most common symptoms was hemarthrosis followed by hematoma. Majority of hemophilia study population had been exposed to factor concentrates less than 50 doses during the course of illness.

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LIST OF ABBREVIATIONS

APTT	Activated Partial thromboplastin Time
FVIII	Factor VIII
FIX	Factor IX
MNH	Muhimbili National Hospital
MUHAS	Muhimbili University of Health and Allied Sciences
rFVIII	Recombinant factor Eight
FEIBA	Factor eight inhibitor bypassing activity

CHAPTER ONE

1.0 INTRODUCTION

Hemophilia is an X- linked disorder of bleeding that result from deficiency of clotting protein factors. There are two common congenital bleeding disorder, hemophilia A (FVIII deficiency) and hemophilia B (FIX deficiency).

Hemophilia A is affecting 1 in 5000 male live births without ethnic predominance (1), whereas hemophilia B occurs in 1:30,000 male births (3).

The treatment of hemophilia A is factor replacement either by plasma or rFVIII concentrates to achieve hemostasis. Replacement FVIII concentrate is effective unless patient developed alloantibodies/inhibitors towards the infused FVIII concentrates (2).

The development of inhibitory antibodies (inhibitors) to factor concentrates is a serious complication. The incidence of inhibitors varies by disease severity and has been reported to occur in up to 33% of those with severe hemophilia A. Inhibitors are classified into two types, type 1 which is a second order kinetic (disease dependent linear inhibition) and completely inactivate FVIII. Type 2 inhibitors have complex kinetics and incompletely inactivate FVIII. Type 1 is common in severe hemophilia while type 2 is common in inhibitory patients with mild hemophilia or patients without hemophilia who develop an acquired FVIII inhibitors

The risk of inhibitor development can be influenced by both genetic and environmental factors. Currently identified influential genetic modifiers include FVIII genotype and polymorphisms affecting immune responses such as allele 134 of the *IL-10*gene. Additionally, black patients are at greater risk of inhibitor development when compared with white patients, suggesting important racial differences in immune responses or other yet to be identified genetic modifiers. Environmental factors suspected, but not proven, to increase the risk of inhibitor development include recombinant FVIII concentrates, the presence of ongoing inflammation while receiving FVIII concentrates , and exposure to FVIII concentrates while younger than 6 months of age(4)

Autologous (acquired) FVIII inhibitors: have been described in individuals who had previously normal hemostasis. Clinically they present with moderate to severe bleeding. Most affect elderly and in minor cases associated with autoimmune disease (5). Acquired inhibitors/autoantibodies against FVIII in non-hemophiliacs occur in only about one case per million per year(6).

Allogenic factor inhibitors: Patients with congenital hemophilia develop antibodies against infused FVIII concentrates. Alloantibodies to FVIII develop in 20-40% of patients treated with FVIII (4,5).

In 1980s plasma derived factor concentrates were used as a replacement therapy, studies have shown patient suffered from viral hepatitis, though many infected persons did not suffer from acute symptoms, at least 50% developed chronic persistent or chronic active hepatitis that lead to cirrhosis. Many of the older, severely affected hemophilia A patients who were treated before 1985 have antibodies to HIV, indicating infection with the virus. The other disadvantage of plasma derived is that larges volume is required to achieve and to maintain even minimal factor levels.

Recombinant factor VIII concentrate introduced in 1990 with the aim of reducing the chance of transfusion transmitted infections, it is safe and effective compared to plasma derived concentrates (7).

Over the past two decades, different types of viral and non-viral gene delivery systems have been explored for hemophilia gene therapy research with a variety of target cells, particularly hepatocytes, hematopoietic stem cells, skeletal muscle cells, and endothelial cells. Lentiviral and adeno-associated virus (AAV)-based vectors are among the most promising vectors for hemophilia gene therapy (8).

Factor VIII and IX inhibitors often require a change of treatment. Transient inhibitors disappear on their own, other require more factors but not progressive. Most significant inhibitors require bypassing agents such as activated prothrombin complex concentrate (FEIBA) and recombinant activated factor VII (9).

1.1 Literature Review

One of the most serious complications of the treatment of hemophilia A is the development of inhibitors. Former studies mostly considered the prevalence of inhibitor development. Prevalence ranged widely (7%-18%) probably due to the populations studied and the study design.

A cooperative study between the 37 centers of the French Hemophilia Study Group was undertaken to establish the prevalence of inhibitor patients in the French hemophilia population. The prevalence reported in the literature varies widely from 3.6% to 17.5%. Some of the studies are dealing with a small number of patients and inhibitor patients are reported either to the total number of hemophiliacs or to the severely affected ones. Prevalence of inhibitors was found to be 7% in the population of hemophilia A patients and 12.8% in the population of severely affected ones. The prevalence of inhibitors in the population of hemophilia patients was 2% and 4% in the population of severely affected hemophilia B patients. The cooperative study also showed that 47.5% of inhibitors are detected before 10 years of age (10).

A 20yrs survey in Swedish population, patients with hemophilia A showed no significant increase in incidence (21%) in the 1990s, when they were treated mainly with recombinant products, as compared to the 1980s,(17%), when they received intermediate/high-purity plasma-derived concentrates (11).

Black patients with hemophilia A are twice as likely as white patients to produce inhibitors against factor VIII proteins given as replacement therapy. There are six wild-type factor VIII proteins, designated H1 through H6, but only two (H1 and H2) match the recombinant factor VIII products used clinically. H1 and H2 are found in all racial groups and are the only factor VIII proteins found in the white population to date. H3, H4, and H5 have been found only in blacks mismatched factor VIII transfusions contribute to the high incidence of inhibitors among black patients (12).

Mismatched replacement therapy appears to be a risk factor in patients with cross-reactive FVIII. In these patients, the immune system is immunologically tolerant of endogenous factor VIII. Hence, matched exogenous therapeutic factor VIII may be identified as “closer to self” and better tolerated, whereas mismatched factor VIII is identified as “closer to foreign” and more immunogenic. However, the immune systems of patients without cross-reactive factor VIII, which has never had contact with endogenous factor VIII, should recognize all polymorphic variants of factor VIII as being foreign and consider them to be immunogenic (13).

1.1.1 Signs and symptoms of hemophilia and inhibitors

The characteristic phenotype in hemophilia is bleeding, and some bleeds can be life threatening and requiring immediate treatment.

The sites of bleeding are joint bleeding (hemarthrosis), muscle bleeds, mucus membrane bleeds such as mouth, gums, nose and genitourinary tract, intracranial and neck, throat and gastrointestinal bleeds(14).

Most patients with factor VIII and IX inhibitors are identified because they don’t respond to factor therapy.

From World Federation of Hemophilia does not get better after standard treatment with factor concentrates. Inhibitors are suspected when:

- The bleeding is not promptly controlled with the usual dose of factor concentrates.
- Normal treatment seems less and less effective.
- Bleeding is more and more difficult to control.

The dose of rFVIII and rFIX depends on the weight of the patient, percentage of factors levels you want to achieve based on the severity of bleeding. Dosage in Factor VIII units = (Weight in kilograms) x (Factor percentage desired) x .5. Dosage in Factor VIII units = (Weight in kilograms) x (Factor percentage desired) x 1 (13, 15).

1.1.2 Complications of hemophilia

According to the degree of FVIII deficiency, mild, moderate or severe forms are recognized. Although patients with mild hemophilia A usually bleed excessively only after trauma or surgery, those with severe hemophilia experience frequent episodes of spontaneous or excessive bleeding after minor trauma, particularly into joints and muscles (16)**.**

In a study which was done in Pakistan 2010, 229 patients with hemophilia A, 5% of patients diagnosed below the age of 5years, first bleeding episodes were during circumcision accounts about 62%, prolonged bleeding after injury 18.4% and after tooth extraction 5.2%. Arthropathy was the most frequently (76.4%) occurring complication (27)

The most serious and challenging complication of treatment of hemophilia A is the development of inhibitors, which renders FVIII concentrate infusion ineffective and exposes patients to an increased risk of morbidity and mortality (16).

1.1.3 Risk factors for inhibitors development

Genetic: The genetics of the patients, comprising the factor VIII gene mutation and the immune response genes (Major Histocompatibility Complex, the T-cell receptor and cytokines receptors)(17,18)) , FVIII gene mutation (deletions, inversions, non-sense mutations) are more susceptible in developing inhibitors against FVIII. The exclusive presence of H3, H4 FVIII haplotype in black hemophiliacs, distinct from H1, H2 which are found in all race groups that match with FVIII replacement, has been recently proposed as the risk factor in this ethnic group, Inhibitor development should be considered as a complex dynamically interaction between genetic and environmental factors (18).

Immune response: Antibodies develop as a result of a complex multi-factorial interaction between antigen-presenting cells, T- and B-lymphocytes (19).

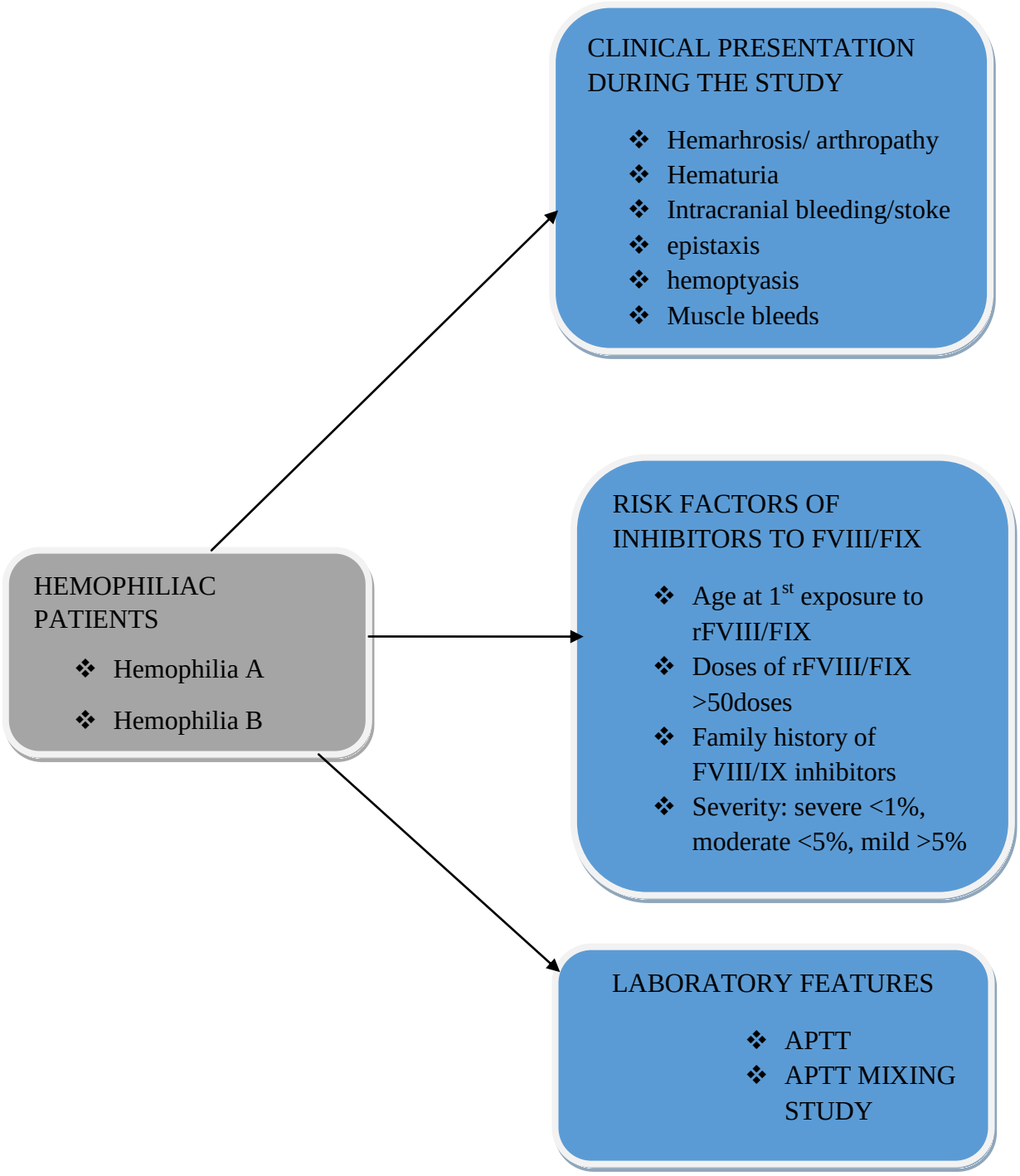
Concurrent infections/ inflammatory states (surgical procedures) have shown to predispose the patient to inhibitor development (19,21).

Environmental and treatment related: Age at start of treatment, higher incidence of inhibitors in patients starting replacement therapy before the age of 6month (16), however some studies showed that exposure to FVIII during neonatal period was not directly associated with higher incidence of inhibitors, Chalmers at al. The risk of inhibitor development was not clearly lower in plasma-derived compared with recombinant factor VIII products (20).

1.1.4 Detection of Inhibitors

Usually suspected from the clinical history or the finding of a prolonged clotting test that does not correct in a 50:50 mix with normal plasma. Circulating inhibitors or anticoagulants that target clotting factors may be either time-dependent e.g. FVIII inhibitors or immediately acting e.g. FIX inhibitors (34). Inhibitors should be suspected when there is a lack of response to FVIII infusion as a result of poor recovery, shortened half-life, or inadequate clinical response. Inhibitor screening should be performed especially at the initial 50 doses of rFVIII or rFIX concentrates infusion. After the patient received up to 150 days of factor replacement, the rate of development inhibitors is substantially reduced (2,22).

1.2 Conceptual Framework



1.3 Problem Statement

Various studies have shown that factor inhibitors are common in severe form of hemophilia A, who receives rFVIII concentrate while less common in hemophilia B patients. And it is as twice as common in black people than in white people. But so far in Tanzania there is no study which already done to determine the presence of FVIII and FIX inhibitors against infused recombinant factor concentrates.

Identifying the presence of FVIII and IX inhibitors among these patients will help to address and change the management plan accordingly as well as to improve the quality of life to patients.

1.4 Rationale

This study target to increase awareness of hemophilia in Tanzania as well as to address major challenge in management of hemophilia. Alloimmunization is the major complication of hemophilia in which the patient develop during treatment with factor concentrates.

Also this study will describe the common clinical presentation of hemophiliac patients attending MNH, and describe the risk factors for development of inhibitors.

1.5 Research Questions

The study aims to answer the following questions among hemophiliac patients attending MNH.

1. What are the presenting clinical features of patients with FVIII and FIX deficiencies at Muhimbili National Hospital?
2. What is the prevalence of FVIII and FIX inhibitors in hemophiliac patients?
3. What are the risk factors for the development of FVIII and FIX inhibitors in hemophiliac patients?

1.6 Objectives

1.6.1Broad objective

To determine the magnitude, clinical presentation and risk factors of factor VIII and IX inhibitors in hemophiliac patients at Muhimbili National Hospital.

1.6.2 Specific objectives

1. To determine the prevalence of factor VIII and IX inhibitors among hemophiliac patients at Muhimbili National Hospital.
2. To describe the clinical presentation of hemophiliac patients at Muhimbili National Hospital.
3. To describe the risk factors of developing factor VIII and IX inhibitors among hemophiliac patients.

CHAPTER TWO

2.0 RESEARCH METHODOLOGY

2.1 Study design

This was a hospital based descriptive cross-sectional study.

2.2 Study site

The study was conducted at the Muhimbili National Hospital (MNH) in Dar-es-salaam Tanzania, which is the main referral hospital in the country, serving four hundred million people living in Dar-es-salaam as well as surrounding regions.

The study involved all hemophilia A and B patients in MNH hemophilia registry which was established since 2010. As MNH receives hemophiliac patients around Dar-es-salaam and other regions of Tanzania, phone calls used to patients residing in Dar-es-salaam. Other patients were tracked in different wards admitted due to various conditions, and who came for follow up in hematology clinics as well as those who came for replacement therapy after minor bleeding. And also involved hemophiliac patients who came for circumcision as an elective surgery in paediatrics surgery wards.

The management of hemophiliac patients in MNH involve factor replacement therapy with recombinant factor VIII or IX concentrates, and is calculated according to the site of hemorrhage, weight of the patient and the desired factor levels (30-100%), in combination with tranexamic acid and analgesia.

2.3 Study population

The study comprised all hemophiliac patients in the hemophilia registry with complete details. The registry contain 77 patients, but only 60 patients had complete details and had factor VIII and IX deficiencies while 17 patients were not tested and had incomplete details. The registry contained the name, hospital identification number, sex, age, type of hemophilia, percentage of factor at diagnosis, address, patient's contacts and complication/presentation the patient had during diagnosis. All patients in the registry were at one point in time used recombinant factor

concentrates due to bleeding episodes that predisposed patients to develop inhibitors, this might be due to lack of prophylactic treatment. Currently we are receiving factor VIII and IX concentrates as donation from World Federation of Hemophilia (WFH).

2.4 Study time

Data were collected between August 2016 and February 2017.

2.5 Inclusion criteria

All hemophilia A and B patients from the hemophilia registry attending at MNH were included in the study.

Consent and assent obtained to participate in the study.

2.6 Exclusion criteria

Patients who had incomplete details in the registry were excluded after initial inclusion.

2.7 Sample size

The hemophiliac cohort at MNH, which contained 60 patients diagnosed with hemophilia in the MNH hemophilia registry. Thirteen patients had hemophilia B and 47 had hemophilia A.

Recruitment of the study subjects

All hemophiliac patients of all ages who had mild to severe form of a disease attended at MNH during the study period.

2.8 Sampling procedure and data collection

Patients were explained about the purpose of the study and asked for consent/assent. Data collection was in the form of a questionnaire. Information regarding socio-demographic characteristics, presence or absence of complaints, episodes of bleeding and frequency, age at diagnosis and clinical presentation and a roughly dosage of factor concentrates the patient received.

Type of hemophilia and percentage of factor at diagnosis was obtained at MNH hemophilia registry which was started 2010.

Patients were examined for the presence of and site of bleeding, severity and deformity. A phlebotomist drew 2mls of venous blood from each study participant. The blood was collected into -citrate-based anticoagulant tubes. APTT and APTT-mixing study were run within 24 hours after collection, performed by chief investigator with the assistance of laboratory technician.

Principle of the test: APTT measures the clotting time of plasma after the activation of contact factors but without added tissue thromboplastin and so indicates the overall efficiency of the intrinsic pathway. To standardize the activation of contact factors, the plasma is first pre incubated for a set period with a contact activator such as kaolin, silica, or ellagic acid. During this phase of the test factor XIIa is produced, which cleaves factor XI to factor XIa, but coagulation does not proceed beyond this in the absence of calcium. After recalcification, factor XIa activates factor IX and coagulation follows. A standardized phospholipid is provided to allow the test to be performed on platelet poor plasma. The test depends not only on the contact factors and on factors VIII and IX, but also on the reactions with factors X, V, prothrombin, and fibrinogen. It is also sensitive to the presence of circulating anticoagulants (inhibitors) and heparin (33)

APTT was performed to pooled patients plasma with normal activated prothrombin time and hemophiliac patient’s plasma. Then equal volume of normal and Haemophiliac plasma were mixed and APTT was performed to determine presence immediate inhibitors. After 2hours at 37 degrees centigrade incubation of normal, haemophiliac patient plasma and a mixture of both, APTT was done for time dependent factors inhibitors, FVIII (23)

Correction Tests Using APTT

Principle

Unexplained prolongation of the APTT can be investigated with simple correction tests by mixing the patient's plasma with normal plasma. Correction indicates a possible factor deficiency, whereas failure to correct suggests the presence of an inhibitor (33)

2.9 Definition of key terms

Factor inhibitors: Prolonged APTT after 2hrs incubation at 37 degrees centigrade which indicates the presence of antibodies against FVIII.

2.10 Data management and statistical analysis

All questionnaires were checked for completeness by the investigator. The collected data were checked for quality and coding was done prior to entering data into the computer (SPSS ver. 20.0) statistical program.

Data analysis included calculation of means and standard deviations for numerical data. Medians and inter-quartile ranges were used in laboratory tests (APTT mixing study) which was not normally distributed.

The investigator performed descriptive statistics for socio-demographic characteristic. The risk factors and clinical presentations of Hemophilia inhibitors which are categorical data were summarized by frequencies and percentages.

The chi-squared test were used for assessing the risks for development of FVIII/FIX inhibitors as categorical variables. A p value < 0.05 was considered statistically significant.

2.11 Ethical consideration and confidentiality

Ethical clearance was sought from the Research and Publications Committee of MUHAS. The permission to conduct this study was sought from authorities of MNH. A formal written informed consent, in Swahili and assent was sought from the participants. Non-consenting patients and those not eligible for the study were attended in keeping with normal standard and care without bias. As the study entails collecting venous blood, aseptic technique was employed to avoid contaminations. Patient's information were kept confidential and information collected on questionnaires was entered into computer using patients' identification numbers to maintain confidentiality.

Patients who founded with inhibitors were treated with bypassing agent (FEIBA).

CHAPTER THREE

3.0 RESULTS

A total of 60 patients in the hemophilia registry were recruited between August 2016 and February 2017, all were receiving factor concentrate since the diagnosis was made.

3.1 Socio-demographic characteristics of the study population.

Of total 60 patients, 5(8.3%) were below 1year of age, 28(46.7%) aged between 2 to 12 years, 23(38.3%) aged 13-23 years while 4(6.7%) were between 24-34 years, figure 1.

Primary and secondary educations were the highest level of education with the highest frequency across the study participants 22(36.7%) and 19(31.7%) respectively as shown in table 1.

The mean age at diagnosis was 6.6(±5.9), majority being below 10 years of age. Youngest being 4months and oldest 21years. The mean age at the interview was 11.9 (±7.2) with the youngest being 1year and the oldest 32 years as in table 2

The median age at diagnosis was 6.0(3, 9) years, majority being below 10 years of age.

The median age at first exposure to factor concentrates and at the interview was 1.0 (1.0, 1.0) and 11.0(6.2, 17.0) year as shown in table 2

Majority of patients are the residents of Dar-es-salaam (DSM) which accounts 31 (51.7%) which is followed by Zanzibar 5(8.3%) as shown in figure 2.

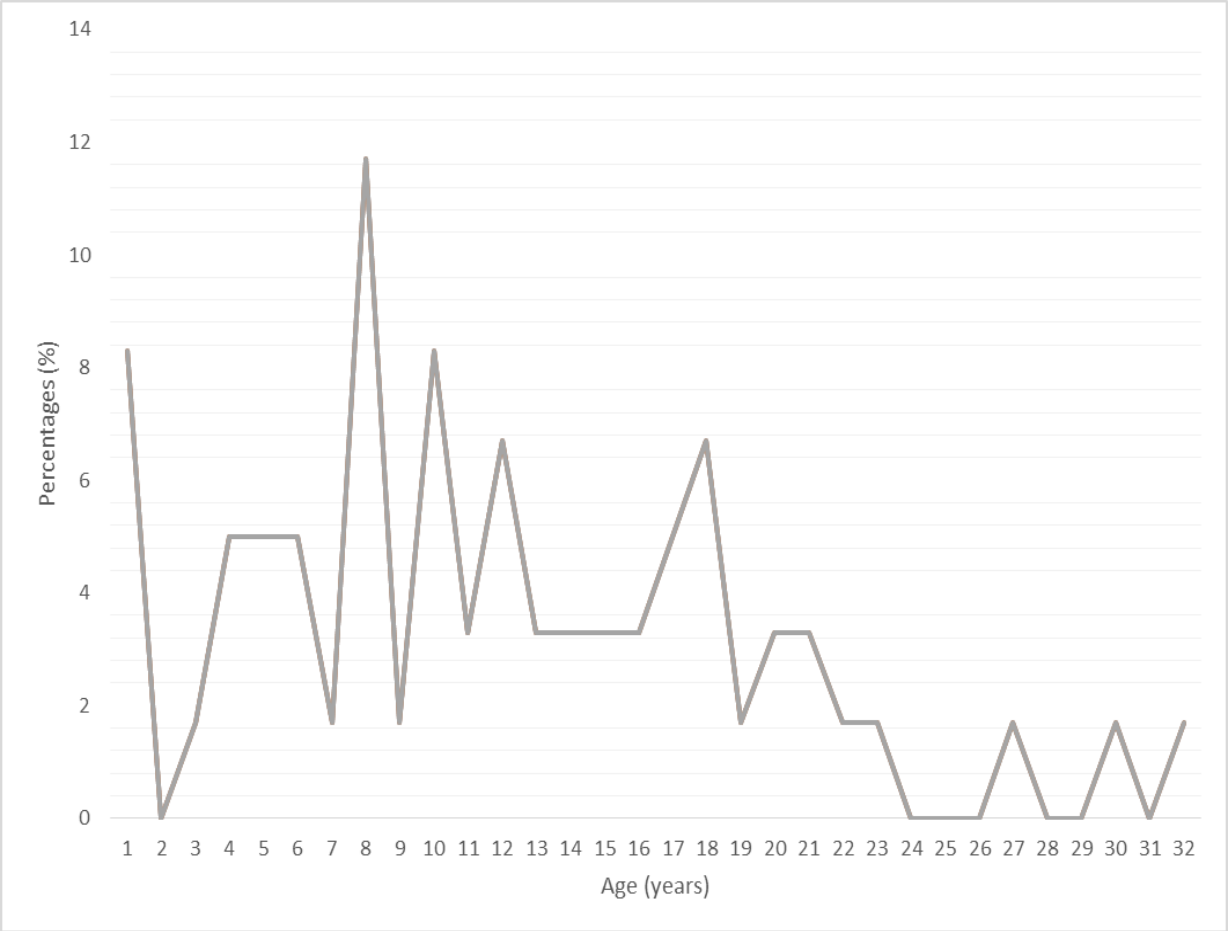


Figure 1: Age distribution of hemophiliac patients during the study period

Table 1: Socio-demographic characteristics of hemophilia patients

Variable	Category	N (%)
Age group	<1 year	5(8.3)
	2-12 years	28(46.7)
	13-23 years	23(38.3)
	24-34 years	4(6.7)
Level of education	Non-formal	17 (28.3)
	Primary	22 (36.7)
	Secondary	19 (31.7)
	University/ College	2 (3.3)

Table 2: Age (years) at diagnosis, 1st exposure to FVIII/FIX concentration and at the time of study interview

Statistic	Diagnosis	1st exposure to FVIII/FIX concentrates	Time of study interview
Median Age (years)	6.0	1.0	11.0
IQR	3.0,9.0	1.0,1.0	6.2,17.0

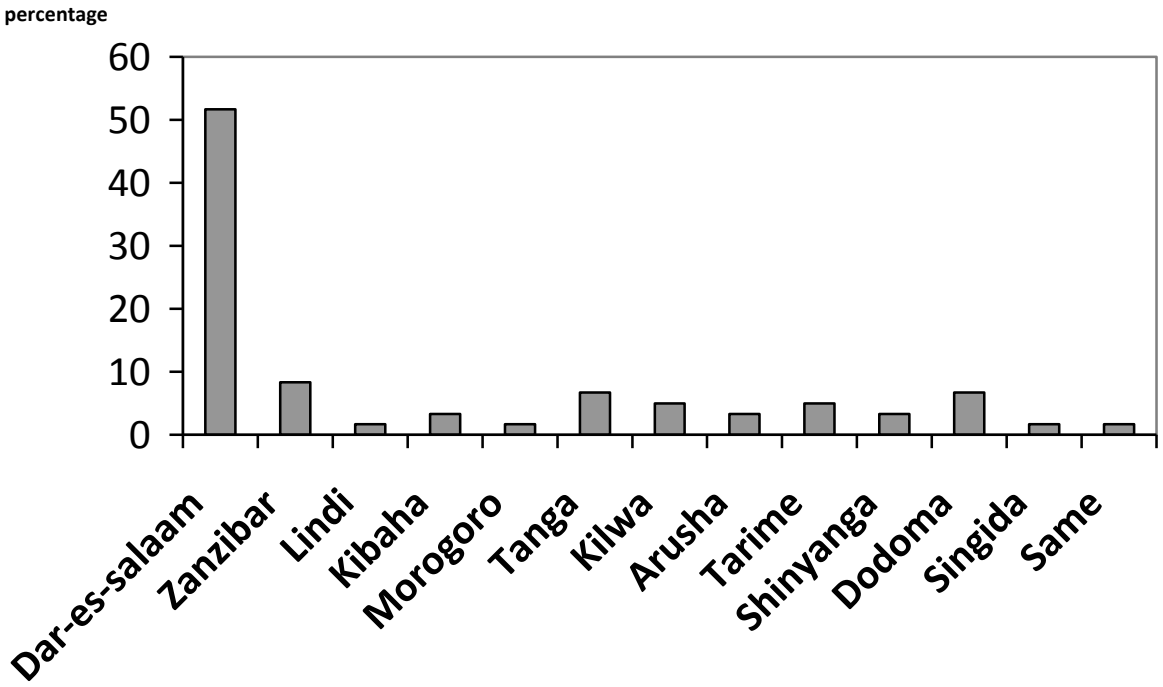


Figure 2: Distribution of hemophiliac patients according to place of residence

3.2 Prevalence of factor eight and nine inhibitors

The prevalence of FVIII and FIX inhibitors was varying among hemophiliac patients based on the severity of the disease.

Presence of inhibitors was detected in 4 patients with hemophilia A. There were no inhibitors in hemophilia B patients.

The prevalence of inhibitors was 6.7% (4 patients) of all hemophilia patients recruited in the study. All four patients had severe hemophilia A, which constitute 8.5% of patients with hemophilia A and 15.4% patients with severe hemophilia A, as shown in figure 3.

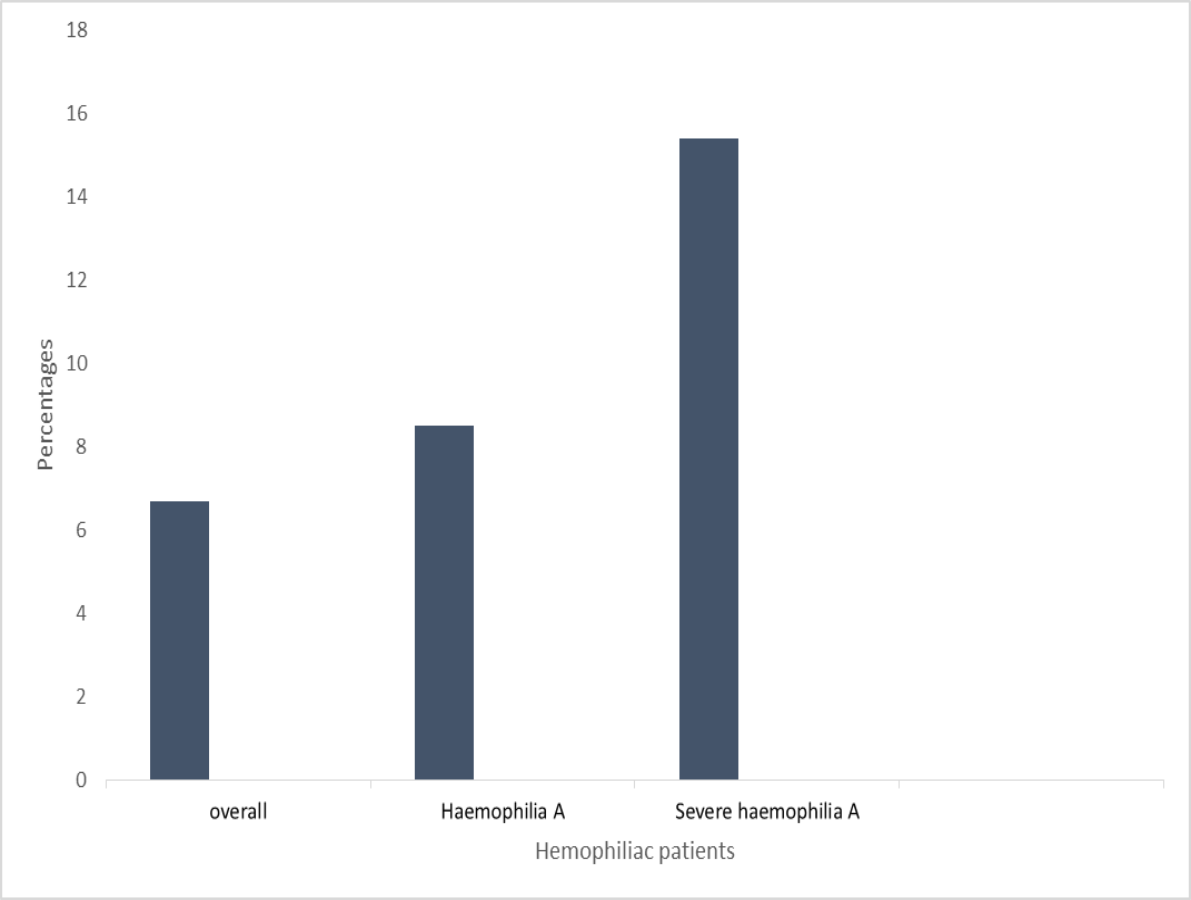


Figure 3: Prevalence of inhibitors among hemophiliac cases

3.2.1 Immediate APTT, APTT-mixing study before and after 2hrs incubation at 37C

The mean APTT level before mixing/dilution with a normal control plasma seems to be high 59.8 ± 11.3 seconds in the study group, which was corrected 29.9 ± 2.9 (the reference range of 23-30seconds) after been mixed with the normal plasma. After 2hrs incubation the mean APTT was again high 55.1 ± 10.1 seconds but also corrected 28.2 ± 6.4 seconds after mixed with the normal plasma as shown in table 5 below.

Table 3: Immediate APTT, APTT-mixing study before and after 2hrs incubation at 37C

Statistic	Immediate APTT	Immediate APTT- mixing study	APTT after 2hrs incubation	APTT-mixing study after 2hrs incubation at 37C
Mean Time (seconds)	59.77	29.85	55.05	28.15
SD	11.478	2.881	10.134	6.393
Minimum	36	23	32	22
Maximum	88	38	79	63

3.3 Clinical presentation of hemophilia patients

Hemarthrosis was the most frequent complaint across study participants which was found in 27(45.0%) at diagnosis and 21(35.0%) during interview. Hematoma was the second most common complaint and was found in 12(20.0) at diagnosis and 10(16.7) during interview. Hematoma was caused by intramuscular injections among the study participants. For patients who had no complain during interview, they were called for interview or came for follow up clinic during the study period. One patient had intracranial bleeding at diagnosis as shown in table 4.

Table 4: Clinical presentation at diagnosis and during interview

Variable	Presentation at diagnosis N (%)	Presentation at interview N (%)
Hemarthrosis	27(45.0)	21(35.0)
Hematoma	12(20.0)	10(16.7)
Epistaxis	10(16.7)	6(10.0)
GI bleeding	5(8.3)	1(1.7)
Hematuria	0(0)	1(1.7)
CNS bleeding	1(1.7)	1(1.7)
Bleeding post circumcision	4(6.7)	0(0)
Asymptomatic	0(0)	20(33.3)

3.4 Risk factors for factor eight and nine inhibitors

All 4 patients with inhibitors had severe hemophilia A. Inhibitors was found in 8.5% of all hemophilia A patients, p=0.36. Fifteen point four percent of patients who has severe hemophilia A had inhibitors, p= 0.61.

Family history of uncontrolled bleeding which was suggestive of presence of inhibitors was found in 2 (50%) patients with inhibitors while the other two patients with inhibitors had no family history of uncontrolled bleeding and this was found to be statistically significant as shown in table 5 below.

Majority of the study participants were exposed to factor concentrates less than 50 doses 53(96.4%) and didn't developed inhibitors, only 2(3.6%) developed inhibitors. Two patients who had inhibitors were exposed to factor eight concentrates more than 50 doses while the rest 3(60%) had no inhibitors and were exposed to FVIII concentrates more than 50 doses, P=0.032.

All patients who had inhibitors, 4 (6.9%) had 1st exposure to rFVIII concentrate >6months of age while 54 (93.1%) with no inhibitors had 1st exposure >6months of age. Only 2 (100) had been using rFVIII concentrate < 6months of age and had no inhibitors, P=0.701.

Table 5: Comparison of risk factors of FVIII and FIX inhibitors in a study group

VARIABLE	INHIBITORS		P-value
	YES N(%)	NO N(%)	
Type of hemophilia			
Hemophilia A	4 (8.5)	43 (91.5)	
Hemophilia, B	0 (0.0)	13 (100)	0.36*
Severity			
Mild	0 (0.0)	8 (100)	
Moderate	0 (0.0)	26 (100)	
Severe	4 (15.4)	22 (84.6)	0.61
Family history of uncontrolled bleeding			
YES	2 (100)	0 (0)	
NO	2 (3.4)	56 (96.6)	0.003*
Duration of exposure to factor concentrates			
<50doses	2 (3.6)	53 (96.4)	
>50doses	2(40)	3 (60)	0.032*
Age at 1st exposure to Factor concentrate			
<6 months	0 (0)	2 (100)	
>6 months	4 (6.9)	54 (93.1)	0.701

Test statistic was Pearson chi square, unless otherwise stated *Fisher exact test

CHAPTER FOUR

4.0 DISCUSSION

Development of FVIII and FIX inhibitors are the major complication among hemophilia patients on treatment with recombinant factor concentrates. Early screening, identification of the presence of inhibitors and treatment would potentially improve quality of life and reduce the burden of care to hemophiliac patients.

This study recruited hemophilia patients in Muhimbili hemophilia registry with mild to severe forms, attending Muhimbili National Hospital (MNH) which offers hematology services all over the country. This study is a hospital based in tertiary care setting.

Majority of hemophilia patients recruited in the study were of younger age, 46.7% aged 2-12years. The mean age was found to be 11.9 ± 7.2 years during the interview, which is approximately half of the study which was done in Poland, the mean age was 26.6 ± 4.3 years (24)

The mean age of the first exposure of factor concentrates in Poland was 2.6 ± 2.1 years, in this study mean age at diagnosis and first exposure to factor concentrates was 6.6 ± 5.9 and 6.7 ± 5.4 years respectively this explains the late diagnosis and treatment with factor concentrates (23).

In another study which involved 7 centers from the central and western regions of Saudi Arabia from May 2008 to December 2011, most patients (74.9%) were diagnosed with hemophilia before their first birthday while in this study very few patients (8.3%) were diagnosed before 1 year of age (31)

Prevalence of inhibitors was found to be 6.7% of all hemophiliac patients recruited in this study, which is within the range of cooperative study between the 37 centers of the French Hemophilia Study Group which ranges from 3.6% to 17.5%. And 8.5% in patients with hemophilia A and 15.4% in severe hemophilia A. this prevalence is higher compared to

French hemophilia study group which was 7% in the population of hemophilia A patients and 12.8% in the population of severely affected ones (8)

The prevalence of inhibitors in severe hemophilia A in this study was 15.4% which is approximately the same compared to the study which was done in Hispanic population with severe hemophilia , the prevalence was 15.8% (3.6% for the high titer inhibitors and 12.2% for the low titer inhibitors according to Bethesda assays) (25)

The prevalence in severe hemophilia A was low compared to the study which was done May 1998 to September 30, 2011 in United States on impacts of inhibitors of hemophilia A mortality, 7,386 males with severe hemophilia A were recruited and the prevalence was 1287 (17%), (29)

An elevated APTT is a major key feature in diagnosis of FVIII and FIX deficiency. In this study most of patients had an elevated APTT with the mean of 59.7 ± 11.4 seconds. But after dilution with a normal plasma seems to be corrected 29.8 ± 2.8 seconds with the maximum time of 38 seconds.

The mean APTT-mixing after 2 hours incubation at 37 degrees centigrade was 28.1 ± 6.3 seconds, this is because of the few number of patients (4patients with inhibitors) who had uncorrected APTT-mixing after 2 hours of incubation. The maximum APTT was high (63seconds) and this is for the time dependent inhibitors (FVIII inhibitors). However there is a limited papers which elaborate screening for factor inhibitors in hemophilia patients using APTT-mixing study, majority of papers used Bethesda and Nijmegen (Modified Bethesda) for diagnosis and quantification of inhibitors.

Hemarthrosis was the most frequent complaint across study participants both at diagnosis and during interview 27(45.0%) and 21(35.0%) respectively followed by hematoma 12(20.0) and 10(16.7) at diagnosis and during interview respectively, this might be because majority of the study participants have severe hemophilia A, (51.1%). Hematoma was caused by intramuscular injections. For patients who had no complain during interview, they were called

for interview or came for follow up clinic during the study period. One patient had intracranial bleeding at diagnosis 1.7%.

In a study which was done in Pakistan, arthropathy was found in 76.4% among hemophilia A patients which is high compared to an index study and the CNS complication was found to be 4.4% (27).

In another study by Aznar et al in Spain observed that 30% of patients had established hemophiliac arthropathy. A study carried out by Zafar T et al (2006) in Rawalpindi also showed joint involvement in (75.2%) of hemophilic patients.

Among 4 patients with inhibitors 50.0% had hemarthrosis and 25.0% had hematoma and 25.0% had no complain.

All patients with inhibitors were hemophilia A, which is more common type of hemophilia to develop inhibitors and it is most common in severe hemophilia A. in this study majority of study participants were hemophilia A (78.3%), while hemophilia B was 21.7%. 51.1% of study participants had severe hemophilia A.

In the study done in Marashtra, India, the proportion of hemophilia A and B patients registered and 77% were hemophilia A while 19% were hemophilia B, giving a ratio of 4.2:1.(26)

In the study done in central and western regions of Saudi Arabia, most patients with hemophilia A had the severe form (126 patients; 85.7%). A large proportion of the patients with severe disease were diagnosed during infancy (96 patients; 79.3%; $P=0.003$) (30).

The percentage of hemophilia A is high due to the large number of patients in the study group compared to this study (51.1%).

Among 4 patients with hemophilia A inhibitors, 50% had a family history of unresponsiveness to the prescribed dose of FVIII concentrate, which were suggestive of genetic risk factor. FVIII gene mutation (deletions, inversions, non-sense mutations) are more susceptible in developing inhibitors against FVIII. In severe hemophilia A sibling-pair study (in Malmo

International Brother Pair Study) inhibitor concordance among 269 sibling pairs have demonstrated high familial inhibitors of 72%, (15, 31)

In the study done in78 patients of Federal Region IV South Hemophilia Treatment Centers, 29% had missense mutation (A2, C1 and C2domains), 33% H1+H2 and 21% H3+H4, followed by inversions (intron 22) by 18% with 19% H1+H2 and 16%H3+H4. But unfortunately the genetic tests were not gone among study participants (28)

In this study, only 3.6% of participants had factor eight inhibitors and were exposed to FVIII concentrate <50 doses,

In this study majority of participants were exposed to factor concentrate after 6months, the mean age was 6.7 ± 5.4, but there are conflicting data regarding age at first treatment as a risk factor for inhibitor formation. Two small cohort studies found an inverse correlation between the age (<6 months) of first exposure and inhibitor formation but they were not controlled for risk factors for inhibitor formation. (32)

CHAPTER FIVE

5.0 CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

The prevalence inhibitors was 6.7% in all hemophilia patients recruited in the study, 8.5% in patients with hemophilia A and 15.4% in severe hemophilia A.

The common clinical presentation is hemarthrosis 35.0% at interview and 45.0% at diagnosis followed by hematoma 16.7% and 10.0% at interview and at diagnosis respectively.

Among 4 hemophilia a patients with inhibitors, 2 patients had family history of uncontrolled bleeding/inhibitors. Two patients among 4 who had inhibitors were exposed to less than 50 doses of rFVIII concentrates.

5.2 Recommendations

Screening test (APTT mixing study) should be done to all patients with hemophilia or to those who suspected to have inhibitors so that to plan the management options.

5.3 Study limitations

This study being a hospital based and used small study sample size, as a results majority of study population had severe hemophilia which might have overestimated the prevalence of inhibitors among the hemophiliac study population.

Bethesda assay is important in quantifying inhibitory titer present in patients with factor inhibitors which will help in the management plan and follow up of patients.

In this study, it was not possible to measure the quantity of inhibitory antibodies (Bethesda Assay) in 60 patient’s primary due to financial constraints.

REFERENCES

1. Viel KR, Ameri A, Abshire TC, Iyer R V, Watts RG, Lutcher C, et al. Inhibitors of factor VIII in black patients with hemophilia. N Engl J Med [Internet]. 2009;360(16):1618–27.
2. Witmer C, Young G. Factor VIII inhibitors in hemophilia A: rationale and latest evidence. Ther Adv Hematol [Internet]. 2012;4(1):59–72. Available from: http://tah.sagepub.com/lookup/doi/10.1177/2040620712464509
3. Buchanan GR. Hemophilia. Pediatr Clin North Am. 1980;27(2):309–26.
4. Kempton CL, Soucie JM, Abshire TC. Incidence of inhibitors in a cohort of 838 males with hemophilia A previously treated with factor VIII concentrates. J Thromb Haemost. 2006;4(12):2576–81.
5. Verbruggen B. Diagnosis and quantification of factor VIII inhibitors. Haemophilia. 2010;16(102):20–4.
6. Ma AD, Carrizosa D. Acquired factor VIII inhibitors: pathophysiology and treatment. Hematology Am Soc Hematol Educ Program. 2006;432–7.
7. Posthouwer D, Plug I, Van Der Bom JG, Fischer K, Rosendaal FR, Mauser-Bunschoten EP. Hepatitis C and health-related quality of life among patients with hemophilia. Haematologica. 2005;90(6).
8. Chuah MK, Evens H, Vandendriessche T. Gene therapy for hemophilia. Journal of Thrombosis and Haemostasis. 2013. p. 99–110.
9. Ananyeva NM, Lee TK, Jain N, Shima M, Saenko EL. Inhibitors in hemophilia A: Advances in elucidation of inhibitory mechanisms and in inhibitor management with bypassing agents. Seminars in Thrombosis and Hemostasis. 2009. p. 735–51.
10. Sultan Y. Prevalence of inhibitors in a population of 3435 hemophilia patients in France. Thromb Haemost. 1992;67(6):600–2.

11. Knobe KE, Sjörin E, Tengborn LI, Petrini P, Ljung RCR. Inhibitors in the Swedish population with severe haemophilia A and B: a 20-year survey. Acta Paediatr. 2002;91(8):910–4.

12. Viel KR, Ameri A, Abshire TC, Iyer R V, Watts RG, Lutcher C, et al. Inhibitors of factor VIII in black patients with hemophilia. N Engl J Med. 2009;360(16):1618–27.

13. Santos A, Annichino-Bizzacchi JM, Ozelo MC. Inhibitors of Factor VIII in Hemophilia [8]. N Engl J Med. 2009;361(3):309–10.

14. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, et al. Guidelines for the management of hemophilia. Haemophilia. 2013;19(1).

15. Srivastava A. Dose and response in haemophilia--optimization of factor replacement therapy. Br J Haematol. 2004;127(1):12–25.

16. Franchini M, Mannucci PM. Hemophilia A in the third millennium. Blood Rev. 2013;27(4):179–84.

17. Oldenburg J, Brackmann HH, Schwaab R. Risk factors for inhibitor development in hemophilia A. Haematologica. 2000. p. 7–14.

18. Astermark J. Why do inhibitors develop? Principles of and factors influencing the risk for inhibitor development in haemophilia. Haemophilia. 2006. p. 52–60.

19. Coppola a, Santoro C, Tagliaferri a, Franchini M, DI Minno G. Understanding inhibitor development in haemophilia A: towards clinical prediction and prevention strategies. Haemophilia. 2010;16 Suppl 1:13–9.

20. Gouw SC, Van Der Bom JG, Auerswald G, Ettinghausen CE, Tedgård U, Van Den Berg HM. Recombinant versus plasma-derived factor VIII products and the development of inhibitors in previously untreated patients with severe hemophilia A: The CANAL cohort study. Blood. 2007;109(11):4693–7.

21. Chambost H. Assessing risk factors: Prevention of inhibitors in haemophilia. Haemophilia. 2010. p. 10–5.

22. Kempton CL, White GC. How we treat a hemophilia A patient with a factor VIII inhibitor. Blood. 2009;113(1):11–7.

23. Kasper C. Diagnosis and management of inhibitors to factors VIII and IX. An introductory discussion for physicians. Treat Hemoph. 2004;(34):1–12.

24. Windyga J, Lopaciuk S, Stefanska E, Juszynski A, Wozniak D, Strzelecki O, et al. Haemophilia in Poland. Haemophilia. 2006;12(1):52–7.

25 S.J Carpenter,R.Presley et al. Increased prevalence of inhibitors in Hispanic patients with severe haemophilia A enrolled in the Universal Data Collection database. Haemophilia (2012), 1–6

26. Kar A, Potnis-Lele M. Descriptive epidemiology of haemophilia in Maharashtra, India. Haemophilia. 2001;7(6):561–7.

27. Shahida Mohsin et al Clinical Manifestations and Complications of Haemophilia A in Pakistan 2010; 6(3): 168-171

28 Kevin R. Viel, Afshin Amer, Thomas C. Abshire et al Inhibitors of Factor VIII in Black Patients with Hemophilia 2009; 360:1618-1627

29. Christopher E. Walsh , J. Michael Soucie et al, Impact of Inhibitors on Hemophilia A Mortality in the United States 2015; 90:400-405

30. T. Owaidah, A.Momen, H. Alzahrani et al. The prevalence of factor VIII and IX inhibitors among Saudi patients with hemophilia: Results from the Saudi national hemophilia screening program 2017,96:e5456

31. D. Michelle, G.Rivard, C. Hay et al. Inhibitors in haemophilia:clinical aspect, 2004:10:140-145

32. Lorenzo, Vander Bom et al, Incidence of factor VIII inhibitors n severe haemophiia: The importance of patient age,200;113,600-603

33. Paul Monagle (ed.), Haemostasis: Methods and Protocols, Methods in Molecular Biology, vol. 992, DOI 10.1007/978-1-62703-339-8_8, © Springer Science+Business Media New York 2013

34. Lossing TS, Kasper CK, Feinstein DI. Detection of factor VIII inhibitors with the partial thromboplastin time. Blood 1977; 49:793-797.

APPENDICES

Appendix I: Questionnaire

Study No |__|__|

Today's Date (DD-MM-YY)……|__|__|-|__|__|-|__|__|DATE TODAY

SOCIO-DEMOGRAPHIC CHARACTERISTICS (Registration station)	
Hospital ID…… |__|__|__|__|__|__|__|HID	
Name……..|_____| **NAME**	
Sex ……(F/M) |__| SEX	
Date of birth…… .|__|__|-|__|__|-|__|__| DOB	
MARITAL STATUS(mark with an X, on appropriate box)	
Single |__|	Cohabiting |__|
Married |__|	Widow |__|
Divorced |__|	Others |__|
LEVEL OF EDUCATION (mark with an X, on appropriate box)	
Informal/None |__|	University |__|
Primary School |__|	Other |__|
Secondary School |__|	

CLINICAL PRESENTATION AT INTERVIEW	
Hemarthrosis |__|	Intracranial bleeding |__|
Hemaptyasis |__|	Epistaxis |__|
Muscle bleeding/hematoma |__|	No complain |__|
Hematuria |__|	Other sites |__| specify……
RISK FACTORS FOR FVIII AND FIX INHIBITORS	
Type of hemophilia……..A/B |__|	
Factor level…….|__|%	
Family history of FVIII/FIX inhibitors (Mark with an X, on appropriate box)	
Family member with hemophilia |__|	
History of uncontrolled bleeding to the family member with hemophilia |__|	
Duration of exposure to recombinant factor concentrates:	
<50doses |__|	>50doses |__|
Age at first exposure to rFVIII/rFIX concentrates |__| Months	
LABORATORY INVESTIGATIONS	
APTT (immediate)…….|__| sec	
APTT-MIXING STUDY (immediate)……|__| sec	
APTT (after 2hour incubation)…… |__| sec	
APTT-MIXING STUDY (after 2hours incubation)…… |__| sec	
Interpretation	
Corrected |__|	
Not corrected |__|	

Appendix II: Consent Form (English Version)

Consent to participate in the study of the clinical presentations, magnitude and risk factors for development of inhibitors of factor VIII and IX among patients with hemophilia at Muhimbili National Hospital.

Dear Sir/Madam,

Greetings!

My Name is Dr. Oliver Isengwa, a resident doctor in the Department of Haematology and Blood Transfusion at MUHAS. I am conducting a study regarding the presence of inhibitors among haemophiliac patients attending at MNH. I am requesting your participation.

Purpose of the study

The aim of this study is to determine the prevalence of factor inhibitors among haemophiliac patients, risk factors for development of factor inhibitors and the clinical presentations in haemophiliac patients attending at MNH.

How to participate

Patients who will be ready to participate will sign a consent form to approve his/her willingness.

Short interview will be done and blood sample for investigation will be taken.

Confidentiality

Information obtained from you will be confidential and will help in improving the care of haemophiliac patients.

Costs

You will not be required to pay anything for your participation.

Voluntary participation & rights to withdraw

Your participation is voluntary and you have the right to withdraw from participating in our study at any time. Whatever your decision may be, it will not affect in any way your rights to care and treatment.

Risks

Blood sample will be drawn from your arm. We don't expect any complications from drawing blood although you will feel some pain when the needle pierces your skin and mild bleeding (on the arm) which will be controlled by compression to the injection site and replacement therapy as per protocol. The skin on your arm will be thoroughly cleaned prior to the procedure so as to prevent infections.

Benefits

Your participation in this study will help you know whether or not you have factor inhibitors against the infused recombinant factor concentrate, and whether it is associated with other risk factors as well as the way forward regarding the treatment.

You will as well get the benefit of getting appropriate treatment as per need.

We hope that the information from this research will be useful in contributing to improve the quality of care in haemophiliac patients.

Contact Persons

If you have any inquiries about this study, please do not hesitate to contact:

Dr. Oliver Isengwa
Principal Investigator
Muhimbili University of Health and Allied Sciences (MUHAS)
Department of Haematology and Blood Transfusion
P.O. Box 65001 Dar es Salaam.
Tel. 0659208589

OR in case of any information about your rights as a participant in this study please contact:

Professor. Said Aboud
The Chairman
Senate Research and Publication Committee Research and Publication Committee
Muhimbili University of Health and Allied Sciences (MUHAS)
P.O. Box 65001
Dar es Salaam
Tel. 2151489

I will be grateful if you willingly agree to participate in this study.

I _____

Have understood the above information and my questions have been answered by the investigator to my satisfaction. I willingly agree to take part in this research.

Name of the participant: _____

Signature of the participant: _____Date _____

Signature of Investigator _____ Date: _____

Appendix III: Consent Form (Swahili Version)

Habari! Mimi ni Dk Oliver Isengwa ni Daktari katika shahada ya Uzamili katika Chuo Kikuu Cha Sayansi Za Tiba cha Muhimbili. Nafanya utafiti kuhusu mwili kupigana na dawa za himofilia kwa wagonjwa wa himofilia katika hospitali ya Muhimbili.

Ninaomba ushirikiano wako.

Nia ya utafiti

Lengo la utafiti huu ni kujua wagonjwa wangapi miili yao inapigana na dawa za himofilia tunazowapa, dalili za mwili kupigana na dawa za himofilia pamoja na mambo/vitu vinavyochangia mwili wa mgonjwa wa hemofilia kupigana na dawa. Utafiti huu utafanywa miongoni mwa wagonjwa wote wa himofilia wanaofika hospitali ya Muhimbili.

Jinsi ya kushiriki

Mgonjwa ambaye yuko tayari kushiriki ataweka sahihi yake , ili kuonyesha utayari. Yatafuata maswali machache ya Utangulizi, kasha kipimo cha damu vitachukuliwa

Usiri

Taarifa za mgonjwa hazitatangazwa kwa yeyote zaidi ya mtafiti**,** matokeo ya utafiti kwa ujumla yatasaidia kuboresha huduma kwa wagonjwa wa himofilia.

Gharama

Hutatakiwa kulipa gharama yoyote kwa kushiriki kwako.

Utayari wakushiriki au kujitoa

Kushiriki kwako ni hiyari na waweza kujitoa. Lakini haitakunyima haki ya kupata tiba zingine

Athari

Damu kwa ajili ya vipimo itatolewa kwenye mkono. Hatutegemei athari yoyote damu itakapovutwa, isipokuwa waweza kusikia maumivu kidogo, bomba lenye sindano ndogo litatumika ili kupunguza kutoka damu nyingi baada ya kipimo. Ili kuepuka kusababisha maambukizi, mara zote ngozi yako itasafishwa vema na dawa kabla ya kuchomwa sindano yoyote.

Faida

Kushiriki kwako katika utafiti kutakusaidia kujua iwapo mwili wako unapigana na dawa za himofilia zinazotolewa, na pia kubadilishiwa dawa kulingana na tatizo hilo.

Ni tumaini letu kuwa utafiti huu utasidia kuboresha huduma kwa wagonjwa wenye himofilia hapa Muhimbili na kwingineko.

Nitakushukuru kwa kushiriki kwako utafiti huu. Aksante.

Iwapo utakuwa na swali lolote kuhusu utafiti huu wasiliana na;

Dkt. Oliver Isengwa,

Chuo kikuu Cha Afya Na Sayansi za Tiba Muhimbili; Idara ya Tiba

S.L.P 65001 Dar es Salaam,

Simu 0659208589

AU endapo utakuwa na swali lolote kuhusu haki zako kama mshiriki katika utafiti huu wasiliana na:

Prof: Said Aboud,

Mwenyekitii wa Kamati ya Tafiti na Matoleo Chuoni,

Chuo Kikuu Cha Afya na Sayansi Shirikishi Muhimbili,

S.L.P 65001,

Dar es Salaam.

Simu 2151489.

Mimi……nimeelezwa/ nimesoma yaliyomo katika fomu hii na nimeelewa maana yake. Nakubali kushiriki katika utafiti huu.

Sahihi…….. (Mshiriki) Tarehe……..

Sahihi……. (Mtafiti) Tarehe……..