Mortality of People with Inherited Bleeding Disorders in a Tertiary Academic Centre

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A research report (in the format of a "submissible" paper) submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Haematology.

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Declaration

I Ibrahim Almahdi A. Ganwo declare that this Research Report is my own, unaided work. It is submitted for the degree of Master of Medicine in the branch of Haematology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

……

(Signature of candidate)

…25TH ……day of ……March…….2019…….in Johannesburg……

Dedication

In memory of my late father

Almahdi Milad Ganwo

1924-2013

Abstract

Background. Inherited bleeding disorders (IBDs) are a heterogeneous group of clinical conditions that include abnormalities of blood vessels, coagulation proteins or platelets present at birth. Haemophilia A and B are the major inherited bleeding disorders with the high mortality rate in comparison with the other inherited bleeding disorders. Owing to the availability of virally inactivated plasma-derived clotting factor concentrates (pCFC) and the introduction of combined antiretroviral therapy (cART) for all people with HIV (human immunodeficiency virus) infection, the mortality rate and the leading cause(s) of death in people with IBDs were dramatically changed from bleeding and HIV/AIDS (acquired immunodeficiency syndrome) related deaths to other commonly known causes of mortality such as trauma, cancer and diabetes. There are currently no documented data from South Africa detailing the specific cause(s) of mortality in IBDs.

Objectives. The main aim of this study is to document the cause(s) of death in a cohort of South African people with inherited bleeding disorders from a single tertiary centre and to evaluate the role of co-morbidities in contributing to their mortality.

Methods. The study was a single-centre retrospective cohort study performed at Charlotte-Maxeke Johannesburg Academic Hospital Haemophilia Comprehensive Care Centre (CMJAH-HCCC). Key inclusion criteria were any person with an inherited bleeding disorder with complete hospital records regardless of age. Study procedures included extraction of anonymised data from each patient's file onto a data collection sheet.

Results. Complete data sets were available on 73 people with IBDs who died between 1990 and 2016. The majority of the population was male and Caucasians with a mean age of 38 years. The crude mortality rate for the whole cohort was 10.4% per 100 person-years. The overall mortality rate of people with haemophilia (A and B) was 13.8% while the crude mortality rate of people with Von Willebrand Disease (VWD) was 3.1% with higher mortality rates with type II and type III VWD compared to type I (7.1%, 5.2% vs 2.4% respectively). In this cohort, HIV/AIDS was the leading cause of death (45%) in the 1990s which markedly decreased in the last two decades (<7% in 2000s and <1% 2010s). In the last decade, spontaneous and traumatic bleeding episodes were now the leading causes of death (20%), with intracranial haemorrhage causing 57% of haemorrhagic deaths.

Conclusions. This retrospective study showed a decrease in cause-related mortality in people with IBD in the last three decades. Bleeding is now the leading cause of mortality in this population.

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LIST OF ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
cART	Combined antiretroviral therapy
CEO	Chief Executive Officer
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CMJAH-HCCC	Charlotte Maxeke Johannesburg Academic Hospital-Haemophilia Comprehensive Care Center
FEIBA	Factor eight inhibitor bypassing activity
FFP	Fresh frozen plasma
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IBDs	Inherited bleeding disorders
pCFC	Plasma-derived Clotting factor concentrate
RIBDs	Rare inherited bleeding disorders
VWD	Von Willebrand Disease
VWF	Von Willebrand Factor

A research report in the format of

a “submissible” paper

Introduction:

Inherited bleeding disorders (IBDs) are a heterogeneous group of clinical conditions that encompass abnormalities of blood vessels, coagulation proteins or platelets which are present at birth. They present with a very variable clinical phenotype ranging from mild bleeding diatheses to organ and life-threatening haemorrhage [1]. In South Africa, over 3153 patients with IBDs have been identified. The majority of these have haemophilia A (61%), VWD (20.2%) and haemophilia B (11.6%) with the remainder constituting the rare bleeding diathesis (7.2%) [2]. About half of these patients are located in Gauteng Province with the majority being followed up at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)[3]. However, these percentages are not truly representative of the real prevalence of these disorders, since VWD is the most common IBD, but the least symptomatic and only the minority will follow up at Haemophilia comprehensive care centres.

Haemophilia A and B are X-linked recessive bleeding disorders characterized by a deficiency of coagulation clotting factor VIII and IX respectively and associated with significant bleeding manifestations ranging from mild bleeding to life-threatening haemorrhage[3,4,]. Von Willebrand Disease (VWD) is the most common inherited bleeding disorder characterised by qualitative or quantitative abnormalities of von Willebrand factor (VWF). It is generally classified into Type I and Type III based on the severity of quantitative deficiency of VWF and Type II which is characterised by qualitative deficits in VWF[5]. Inherited blood vessel bleeding disorders and congenital platelet bleeding disorders are uncommon and usually represent <5% of total IBDs and characterised by an inherited deficiency of many other coagulation factors, thrombocytopenia and thrombocytopathies [3,6,7].

In general, the life expectancy of severe haemophilia patients has been very short, being less than 12 years in Sweden in the period from 1880-1920[8]. After the introduction of pCFC in Sweden from1957-1980, the life expectancy changed from a median 19 years to a median 50 years in severe haemophilia patients. The main cause of death in 56% of those patients was haemorrhage with one third due to intracranial haemorrhage, However about 36% of deaths were not related to haemophilia (non-bleeding deaths)[9,10]. The emergence of HIV between the years 1980 and 2000 increased the mortality rate so that HIV/AIDS was the leading cause of death in about 60% of haemophilia patients in Italy and about 25% in the Netherlands. With changes in replacement

blood products and cART, HIV is no longer the major cause of death [11,12,13].

With all these therapeutic advances, the life expectancy of haemophilia patients is expected to be close to that of the non-haemophilia population. The emerging trend is that deaths in people with haemophilia are due to the same causes seen in the general population including cancer, diabetes mellitus, ischemic heart disease, renal failure, cerebrovascular disease and others but it is not clear whether this is true for patients with IBDs in South Africa.

Objectives

The main aim of this study is to document the cause(s) of death in a cohort of South African people with inherited bleeding disorders in a single tertiary centre and to evaluate the role of co-morbidities in contributing to their mortality.

Methods

Study design and study population

The study was a single-centre retrospective cohort study performed at Charlotte Maxeke Johannesburg Academic Hospital haemophilia Comprehensive Care centre (CMJAH-HCCC). The CMJAH is a tertiary hospital in Johannesburg with specialist units only and receives referrals from all over South Africa and beyond its borders. This study was approved by the University of the Witwatersrand Human Research Ethics Committee with certificate number of M170379. Approval was also sought and granted by the CMJAH management. The study population comprised of patients with IBDs seen at the CMJAH-HCCC who died between 1st of January 1990 and 31st of December 2016. The key inclusion criterion was any person with an inherited bleeding disorder with complete hospital records regardless of age. The exclusion criteria of this study were incomplete hospital records and acquired bleeding disorders

Data collection

After obtaining the permissions from CMJAH CEO and CMJAH-HCCC director to access the site database, all patients who died while attending the CMJAH-HCCC between 1st of January 1990 and 31st December 2016 as recorded in the database were obtained and reviewed. The names from the database were used to locate and identify the patient's hospital files which were located in the centre. A specific data collection sheet was completed for every person with an inherited bleeding disorder who died between 1st of January 1990 and 31st of December 2016 which included demographic data (age of birth, age of death, ethnicity and family history), type of inherited bleeding disorder and severity, co-existing diseases, infection and/or inhibitors, chronic treatment and the leading cause of death. Each case was given a specific study number, and the extracted data were anonymised and analysed.

Statistical Analysis

Crude mortality rate was calculated for the whole cohort and each inherited bleeding disorder including each type of haemophilia by the level of severity. The rates were expressed as the number of deaths among patients who were attending CMJAH-HCCC in each specific category per 100 person-years at risk. The cause-specific mortality was calculated as the percentage of people who died due to a particular cause for the total number of deaths in a specific period. Descriptive stats including mean (SD) for numerical values and percentages for categorical data were used. Statistical analysis was performed using GraphPad Instat (v3.0) from GraphPad.com[14].

Results

Demographic and general characteristics of the participants

According to CMJAH-HCCC database the total number of persons with inherited bleeding disorders were attending the CMJAH-HCCC in the period between 1st of January 1990 to 31st of December 2016 was 701, which included 395 persons with haemophilia A. Of these 295 (74.6%) had severe haemophilia, 42 (10.6%) had moderate haemophilia,57 (14.4%) had the mild type and two persons were carriers. There were 82 persons with haemophilia B - 59 (71.9%) had severe haemophilia, 10 (12%) had the moderate type and 12 (14.6%) had mild haemophilia and one person was a carrier. A further 194 persons had VWD with 161 (83%) having type I, 14 (7.2%) with type II and 19 (9.8%) with type III leaving 30 persons with rare bleeding and congenital platelet disorders - 10 persons with Factor XI deficiency, 4 persons with Factor X deficiency, 2 persons with Factor VII deficiency, 3 persons with Factors V and VIII deficiency, 4 persons with factor V deficiency, 1 person with Factor XIII deficiency , 4 persons with Bernard Soulier Syndrome, 1 person with Platelet Storage Pool disease and one person with May Hegglin Anomaly.

Among 701 persons with inherited bleeding disorders, there were 73 deaths of which 59 (80.8%) had haemophilia A - 47(80%) had severe haemophilia, 7(12%) had the moderate type, and 5(8%) had the mild type. There were 7(9.6%) persons with haemophilia B - 4(57%) had a severe type of haemophilia, 1(14%) had the moderate type, and 1(14%) had the mild type. Also, there were 6 (8.2%) persons with VWD and one person with Factor V deficiency (1.4%). Table 1 shows the general characteristics of people with IBDs who died between 1990 and 2016 and table 2 shows the distribution of the various bleeding disorders in the patients who died during the study period.

Table 1: **Demographic and general characteristics of the participants that died during the study period**

Characteristic	Sub-category	N=73/ %(n)
Age, mean (SD)		38.1 (16.3) years
Ethnicity	White	71.2 (52)
	African	20.6 (15)
	Coloured	1.4 (1)
	Unknown	6.8 (5)
Haemophilia	Yes/No	62.5/37.5 (30/18)
Family History		
n=48		
HCV (n=68)	Pos/neg	55.9 / 44.1 (38/30)
HIV	Pos/neg	46.6/ 53.4 (34/39)
Chronic treatment	Cyclokapron	6.8 (5)
	Desmopressin	1.4 (1)
	FEIBA*	10.9 (8)
	FFP**	1.4 (1)
	Haemosolvate	67.2 (49)
	Haemosolvex	6.8 (5)
	None	5.5(4)

*FEIBA: Factor eight inhibitor bypassing activity, **FFP: Fresh frozen plasma.

Table 2: Distribution of the various bleeding disorders in the patients who died during the study period.

Diagnosis	Subtypes	% (n)
Haemophilia A	Total	80.8 (59)
	Mild	8.4 (5)
	Moderate	11.9 (7)
	Severe	79.7 (47)
	With inhibitors	12.1 (7)
	Without inhibitors	88.1 (52)
	Carrier	1.6 (1)
Haemophilia B	Total	9.6 (7)
	Mild	14.3 (1)
	Moderate	14.3 (1)
	Severe	57.1 (4)
	With inhibitors	0
	Without inhibitors	6 (100)
	Carrier	14.3 (1)
VWD	Total	8.2 (6)
	Type I	66.7(4)
	Type II	16.7(1)
	Type III	16.7(1)
Others *		1.4 (1)

*__Others__: Includes rare blood vessel bleeding disorders and congenital platelet disorders.

Cause-specific mortality of people with IBDs

Table 3 shows the primary causes of death between 1990 and 2016 divided into three calendar periods (1990-1999, 2000-2009 and 2010-2016). In general, the most common cause of death (14 persons -19.1%) was due to haemorrhagic episodes, with intracranial haemorrhage constituting 57% (8/14) of these episodes followed by 12 persons (16.4%) who died due to HIV/AIDS-related causes. The proportion of people who died of HIV/AIDS decreased during the last two calendar periods (2000-2009 and 2010-2016) in comparison to the period between 1990-1999 (6.6% and 0%) in the last two calendar periods and (45%) in the first period. Haemorrhagic episodes became the most common cause of death in the last two calendar periods (2000-2009 and 2010-2016) (26.6% and 19%) and an account of (9%) in the first calendar period. Other causes of death stayed constant during the three periods of study.

Table 3: The main causes of death of people with IBDs in the period between 1990 and 2016.

Main cause of death	**1990-1999 N (%) *n*=22**	**2000-2009 N (%) *n*=30**	**2010-2016 N (%) *n*=21**	**Total N (%) *n*=73**
Haemorrhages	2(9)	8(26.6)	4(19)	14(19.1)
HIV/AIDS related causes*	10(45)	2(6.6)	0(0)	12(16.4)
HCV/HBV related causes†	0(0)	1(3.3)	1(4.7)	2(2.7)
Cancer other than Hepatocellular carcinoma	1(4.5)	0(0)	3(14)	4(5.4)
Infections	4(18.8)	4(13.3)	2(9.5)	10(13.6)
Cardiovascular disease	2(9)	1(3.3)	1(4.7)	4(5.4)
Pulmonary embolism	0(0)	1(3.3)	0(0)	1(1.4)
Trauma/MVA	1(4.5)	2(6.7)	1(4.7)	4(5.4)
Others‡	10(45)	12(40)	9(42)	23(31.5)

*HIV/AIDS-related causes included Kaposi sarcoma and opportunistic infections. † HCV/HBV related causes included chronic liver disease, liver cirrhosis and hepatocellular carcinoma. ‡Other causes include suicide, stroke, sudden death and unknown causes.

Mortality rates of people with IBDs

Crude mortality rates were calculated for the whole cohort population and each inherited bleeding disorder including each type of haemophilia with the level of severity. The rate was expressed as the rate per 100 person-years at risk. Table 4 shows the mortality rates for all groups of patients with IBDs.

Table 4: The mortality rate for people with inherited bleeding disorders

Type of IBD		Mortality rate per 100 person-years (death events/People at risk) %(n/N)
1-Total population with IBDs		10.4(73/701)
2- Haemophilia	Total	13.8(66/477)
Haemophilia A	Total	14.9(59/395)
	Severe	15.9(47/295)
	-With inhibitors	20.5(7/34)
	-Without inhibitors	16(43/268)
	Moderate	16.6(7/42)
	Mild	9.6(5/52)
	Carrier	50(1/2)
Haemophilia B	Total	8.5(7/82)
	Severe	6.7(4/59)
	Moderate	18.1(2/11)
	Mild	0
	Carrier	100(1/1)
3- VWD	Total	3.1(6/194)
	Type I	2.4(4/161)
	Type II	7.1(1/14)
	Type III	5.2(1/19)
4- Rare bleeding	Total	3.33(1/30)
disorders	Factor V	25(1/4)

The overall mortality rate of people with haemophilia (A and B) was higher in people with more severe sub-types and less in people with the mild type. The mortality of the carriers of haemophilia is not genuinely accurate since most of the carriers are asymptomatic and attending the clinic only if they had other diseases associated with increased risk of bleeding, only two people were carriers for Haemophilia (A and B) and both of them died due to cancer. The mortality rate for severe Haemophilia A with inhibitors was 20.5% vs 16% for those without inhibitors. There were no death events reported for people with severe Haemophilia B with inhibitors.

The crude mortality rate of people with VWD was 3.1 % with more higher mortality rates of type II and type III in comparison with type I (7.1%, 5.2% vs 2.4%). All four patients with type I VWD died from non-bleeding causes while the other two types are associated with more significant bleeding manifestations.

Only a few people were diagnosed with rare inherited bleeding disorders and congenital platelet disorders, and only one person diagnosed with a moderate Factor V deficiency died due to uncontrolled bleeding.

Discussion

This study is a retrospective cohort analysis performed to provide an evaluation of the mortality rate and the leading causes of death of people with inherited bleeding disorders attending CMJAH-HCC, which is one of the largest haemophilia comprehensive care centres in South Africa and cares for over 1000 patients with IBDs registered in its data base. In the current study, 701 people diagnosed with an IBD attending CMJAH-HCC in the period between 1st of January 1990 and 31 December 2016 were examined, and 73 death events were identified (59 with haemophilia A, 7 with haemophilia B, 6 with VWD and 1 with Factor V deficiency).

In this study, the most common cause of death was bleeding (57% due to intracranial haemorrhage) and HIV/AIDS-related causes which accounted for 19.1% and 16.4% respectively While in the period between 1990-1999, HIV/AIDS was the leading cause of death in about 45% which dropped sharply in the following two decades to <1% in period between 2010-2016. Haemorrhagic episodes during the same period did not fall as much - only 9% in the period from 1990-1999 and 26.6% and 19% during 2000-2009 and 2010 -2016 respectively. Other causes of death stayed similar during the three calendar periods of study.

The decrease of HIV/AIDS-related mortality is most likely attributed to two main factors; the first factor is the availability of virally inactivated plasma-derived clotting factor concentrates and the second factor the introduction of combined antiretroviral therapy for all people with HIV infection. Also, patients became more aware of HIV transmission and preventive measures to avoid infection. These results are similar to the Italian cohort study which showed HIV/AIDS was the leading cause of death in about 60% in the 1990s and dropped up to 23% in 2000s. In the Netherlands, there is only reporting of HIV/AIDS-related mortality of only 25% in the 1990s, see figure (1-a) [11,12].

Interestingly, despite the high incidence of HCV infection of this cohort study about (55%), HCV related mortality was very low in last two calendar periods (3.3% and 4.7%) and (<1%) in the 1990s. These results are much less than what has been reported in the Italian and Dutch cohort studies in the same decade, see figure (1-b)[11,12].

In this cohort study, the mortality rates were measured for the whole cohort and each type of IBD. As expected the people severe haemophilia were associated with higher mortality rates than the milder types (15.9% and 6.7% for severe haemophilia A and haemophilia B vs 9.6% and <1% for mild haemophilia A and haemophilia B). The mortality of the carries of haemophilia is not genuinely accurate, the majority of the carriers are asymptomatic under normal conditions, only attending CMJAH-HCC during pregnancy, planning for surgery, having other diseases and/or associated with an increased risk of bleeding [13], only two people were carriers for haemophilia A and haemophilia B and both of them died due to cancer.

The development of inhibitors is more common in severe haemophiliacs, in particular, Haemophilia A. In our patient population, the incidence of inhibitors was 11.5% for severe Haemophilia A and 6.7% for severe Haemophilia B with no evidence of the development of inhibitors in the moderate and mild haemophilia types[3]. In this cohort, the mortality rate appears not to be affected by the development of inhibitors as the mortality rate for severe Haemophilia A with inhibitors was 20.5% vs 16% for those without inhibitors. There are no death events reported for people with severe Haemophilia B with inhibitors. These results are consistent with the British cohort study which showed there is no significant difference in mortality rates between severe haemophiliacs with or without inhibitors [15]. In contrast to these results, the United State cohort study showed that the risk of death is significantly higher among patients with severe haemophilia A with inhibitors than those without inhibitors (42% vs 12%, $p<0.0001$), however, this study was

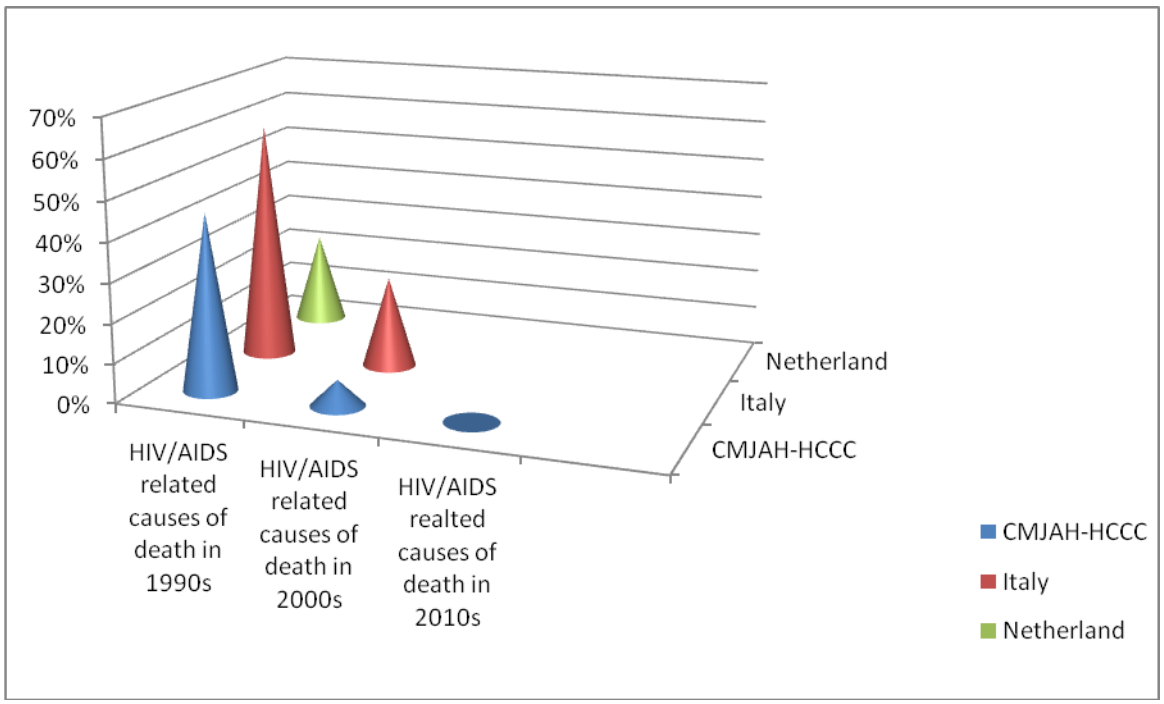

Fig.(1-a): HIV/AIDS related causes of death at CMJAH-HCCC in three calendar periods in comparison with the Italian and Dutch cohorts

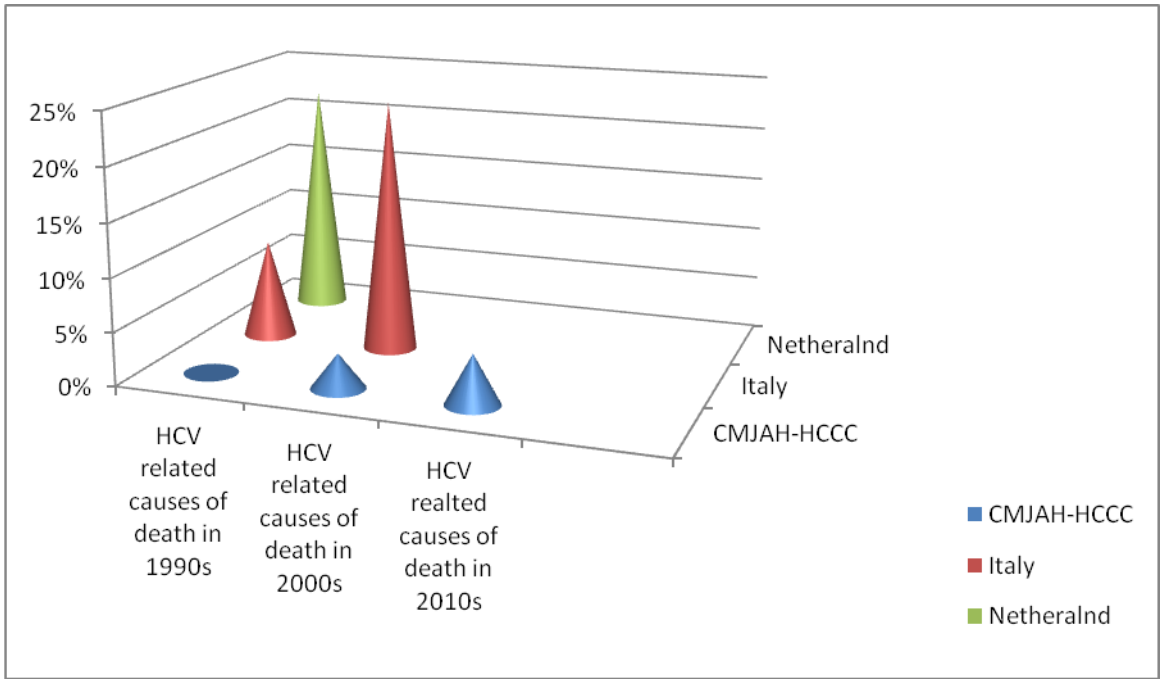

Fig.(1-b): HCV related causes of death at CMJAH-HCCC in three calendar periods in comparison with the Italian and Dutch cohorts.

performed only on persons with severe haemophilia A and those underwent successful tolerisation were considered as non-inhibitor patients [16].

VWD is the most common IBD and type I comprises the majority of the population. Type I VWD is very mild and rarely associated with life-threatening bleeding episodes. Type III VWD is rare but associated with severe and fatal bleeding events. Type II is not common, and its severity is dependent on its sub-type[3,5]. In this cohort study, the mortality was consistent with the expectations, since all people with type I VWD died from non-bleeding causes. The mortality rate was higher for type III and type II VWDs in comparison to type I VWD (7.1%, 5.2% vs 2.4%).

In this cohort study, the prevalence of rare inherited bleeding disorders and congenital platelet disorders was <5%, therefore, the mortality rate will not be truly accurate due to a small number of people at risk. There is only one person diagnosed with a moderate Factor V deficiency who died due to uncontrolled bleeding.

Study Limitations

The major limitation of this study is its retrospective design and a few people with IBDs who were excluded because of loss of follow up or incomplete hospital records. This was a single centre experience which may not reflect that of the country or regional mortality.

Conclusion

This retrospective study of the mortality rate and the leading causes of death of people with inherited bleeding disorders (IBDs) who were attending Charlotte-Maxeke Johannesburg Academic Hospital Haemophilia Comprehensive Care Centre (CMJAH-HCCC) showed a drop in the HIV-related deaths over the last three decades. Deaths from other causes did not change.

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Appendix A

Approved research protocol

RESEARCH PROTOCOL

RESEARCH TITLE: Mortality of People With Inherited Bleeding Disorders in a Tertiary Academic Centre

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1-Background

Inherited bleeding disorders (IBDs) are a heterogeneous group of clinical conditions that encompass abnormalities of blood vessels, coagulation proteins or platelets present at birth. The phenotypic presentation of IBDs is very variable ranging from mild bleeding diathesis to organ and life-threatening haemorrhage (1).

The latest World Federation of Haemophilia (WFH) annual survey of 2015 published in October 2016 indicates that the total number of people with IBD in 191 countries (approximately 91% of the world population) is 304,362. The majority of these (187,183) have haemophilia, 74,819 have von Willebrand disease (VWD) and 42,360 have other rare IBDs (2).

In South Africa, there are over 2500 patients with IBDs identified the majority of which are haemophilia A (1300) and Von Willebrand Disease (600). About half of these patients are located in Gauteng Province with the majority being followed up at the Charlotte Maxeke Johannesburg Academic Hospital(3).

Haemophilia A

Haemophilia A is an inherited X-linked recessive bleeding disorder characterized by a deficiency of coagulation clotting factor VIII. It affects about 1 in 10,000 live births with similar prevalence in all ethnic groups and populations around the world. It is a disease of males. However, females also can be affected if they are symptomatic carriers. Factor VIII deficiency occurs as a result of a heterogeneous number of genetic lesions which include deletions (large and small), inversions, insertions, point mutations and splice in the factor 8 gene (4).

Haemophilia B

Haemophilia B is an inherited X-linked recessive congenital bleeding disorder characterized by a deficiency of coagulation clotting factor IX. It affects about 1 in 25,000 live births with similar prevalence in all ethnic groups. Factor IX deficiency occurs as a result of some genetic mutations of FIX gene, the vast majority of which are missense mutations(3,4).

Von Willebrand Disease (VWD)

VWD is the most common inherited bleeding disorder characterised by qualitative or quantitative abnormalities of von Willebrand factor (VWF) with an estimated frequency of 1 in 100 live births. VWD is generally classified into Type I and Type III based on the severity of quantitative deficiency of VWF and Type II which is characterised by qualitative deficits in VWF. Generally, Type I and

Type II inherited in an autosomal dominant manner and Type III is inherited in an autosomal recessive manner(3,5).

Other rare inherited bleeding disorders (ribs)

RIBDs are characterised by an inherited deficiency of many other coagulation factors which include deficiency of fibrinogen, prothrombin, factor V, combined factor V and factor VIII, factor VII, factor X, factor XI, factor XIII and Vit K-dependent coagulation factors. Generally, ribs are inherited in an autosomal recessive manner with the prevalence of less than 1 in 500,000 live births(6).

Congenital platelet disorders

Generally, congenital platelet disorders are classified into two main groups, namely, thrombocytopenias and thrombocytopathies.

Inherited thrombocytopenia includes inherited thrombocytopenia with reduced platelet size such as Wiskott-Aldrich syndrome, inherited thrombocytopenia with normal platelet size such as congenital amegakaryocytic thrombocytopenia and inherited thrombocytopenia with increased platelet size such as May-Hagglin Anomaly(7).

Inherited thrombocytopathies include disorders of platelet adhesion such Bernard-Soulier syndrome, disorders of platelet signalling transduction such Cyclooxygenase deficiency and disorders of platelet aggregation such Glanzmann thrombasthenia(7).

The majority of patients with IBDs followed-up at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). The surrounding hospitals usually refer to Charlotte-Maxeke Johannesburg Academic Hospital Haemophilia Comprehensive Care Centre (CMJAH-HCCC). This centre provides comprehensive management for all patients diagnosed with inherited and acquired bleeding disorders. The CMJAH-HCCC looks after over 1000 patients with IBDs registered in its database. Haemophilia A and Haemophilia B represent more than 66% of those patients, VWD patients represented about 22% and RIBDs and inherited platelet disorders represent less than 12%(8).

Mortality, causes of deaths and impacts of the management on mortality of haemophilia patients

Since haemophilia was described as an inherited bleeding disorder 1600s, the reduced life expectancy and high mortality have been its characteristic feature. In general, the life expectancy of severe haemophilia patients has been very short. It was less than 12 years in Sweden in the period between 1880-1920 (9).

After the introduction of plasma-derived clotting factor concentrates (pCFC), the mortality of haemophilia patients markedly decreased in countries which could access pCFCs. In Sweden for example, between 1957-1980, the life expectancy changed from 19 years to 50 years in severe haemophilia patients. The main cause of death in 56% of those patients was haemorrhage with one third due to intracranial haemorrhage, However in this study, about 36% of deaths were are not related to haemophilia (non-bleeding deaths)(10,11).

Although derived plasma factor concentrates decreased the mortality rate, the blood-borne viral infections increased the mortality rate in the period between 1980 to 2000. In 1980s HIV infection appeared as a significant complication of the use of plasma-derived clotting factors. Also, approximately 80%of haemophilia patients who received plasma-derived clotting factor concentrates (pCFC) before 1992 became infected with Hepatitis C virus (HCV) in Netherland (12). Figures in other parts of the world were similar or worse. In the period between 1985-2000, HIV/AIDS was the leading cause of death in about 60% of haemophilia patients in Italy and about 25% in the Netherlands while HCV infection accounted for 8% and about 15% respectively in the same countries (13,14).

With the introduction of recombinant DNA technology and novel screening techniques, the plasma-derived clotting products became free of HIV and HCV. Subsequently, recombinant clotting coagulation factor concentrates (rCFC) became available with much fewer risks of blood-borne viral infections (15). Recently, the introduction of CFC with extended half-lives such as recombinant factor VIII Fc fusion protein have enabled an improved therapeutic approach for haemophilia including prolonged haemostatic protection with less frequent dosing. (16).

Replacement therapy is however associated with the development of neutralizing antibodies against CFC, called inhibitors. These inhibitors are immunoglobulin G (IgG) antibodies which neutralise replacement CFC activity. However, the development of bypassing agents such as FEIBA and recombinant factor VII decreased the risk of bleeding. There is no significant change in mortality rates between severe haemophiliacs with or without inhibitors (17).

With all these therapeutic advances, the life expectancy of haemophilia patients is expected to be close to that of the non-haemophilia population. The emerging trend is that deaths in people with haemophilia are due to similar causes are seen in the general population including cancer,

diabetes mellitus, ischemic heart disease (myocardial infarction and cardiac arrest), renal failure, cerebrovascular disease and others. There is currently no documentation of the reasons for death in PWH in South Africa.

2- Study Rationale

Data around the world is emerging that deaths in patients with IBD are changing from bleeding related deaths to other commonly known causes of mortality such as trauma, cancer and diabetes. There is currently no documented data in South Africa detailing the specific cause(s) of mortality in IBDs.

3- The aim of the study

This study aims to document the mortality and cause(s) of death in a cohort of South African people with inherited bleeding disorders in a single tertiary centre and to evaluate the role of co-morbidities in contributing to their mortality

4- Objectives

A- To document the cause(s) of death in a cohort of South African people with inherited bleeding disorders in a single tertiary centre.

B- To evaluate the role of co-morbidities in contributing to the mortality of people with IBD.

C- To compare the mortality of people with inherited bleeding disorders in our centre to those reported in developed world centres.

5- Methods

5.1 Study design

A single centre retrospective cohort study.

5.2 Study population

- Cases

The study cases will be people with inherited bleeding disorders seen at the Charlotte-Maxeke Johannesburg Academic Hospital Haemophilia Comprehensive Care Centre (CMJAH-HCCC) who died between 1st of January 1990 to 31st of December 2016 who meet the following inclusion criteria

1- Diagnosed with any inherited bleeding disorders
2- Patient with complete data set in the hospital record
3-All age groups
4- Including patients with or without inhibitors
5- Including patients with or without transfusion-transmitted infection

5.3 Exclusion

- Acquired bleeding disorders
- Those with incomplete hospital records.

5.4 Control population

- There is no control arm for this study due to the challenges in establishing mortality in our hospital populations.

5.5- Hospital record review, data collection and identification

- Permission from the relevant custodians will be obtained before the start of the study. Permission has been requested from CMJAH CEO to review the hospital records. Permission has been obtained from the CMJAH-HCCC director to access the site database.
- All patients who have died attending the CMJAH-HCCC at recorded in the database. This database will be accessed and reviewed.
- Names from the database will be used to locate and identify the patient's hospital files which are kept in the centre.
- Using the data sheet, specific information will be extracted from the hospital files as indicated in the attached data collection sheet.

- Each case will be given a study number.
- The extracted data will be anonymized and archived before analysis.

6- Ethical considerations

Clearance from the University of the Witwatersrand Human Research Ethics Committee will be requested before the initiation of the study. As this is a retrospective study, individual informed consent is not required. Once data has been extracted from the hospital records, it will be anonymized and coded before analysis.

7- Study Budget

This is a retrospective study with no funding required for study execution. Publication cost required in an open access journal is approximately R 20 000.

8- Study Timeline

MONTH 2017	March-May 2017	May -July 2017	August-September 2017	October-November 2017	December 2017
PROTOCOL					
ETHICS					
EXECUTION					
ANALYSIS					
WRITE UP					
PUBLICATION					

9- Conflict of interest

No conflict of interest is foreseen with the investigators in this study.

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11. APPENDIX A: Data collection sheet

DATA COLLECTION SHEET		
A. Baseline Data		
A1	Age	
A2	Sex	
A3	Ethnicity	
A4	Family history	
B. Diagnosis		
B1	Type of IBD	
B2	Subtype of IBD	
B3	Severity	
B4	Date of diagnosis	
B5	Cause of diagnosis	
B6	Any untreated bleed before diagnosis?	
C. Co-existing diseases, infections and inhibitors		

DATA COLLECTION SHEET		
C1	HIV infection	
C2	HCV infection	
C3	HBV infection	
C4	Presence of inhibitors for haemophilia patients	
C5	Others	
D. Treatment since diagnosis		
D1	Factor VIII/Haemosolvate	
D2	Factor IX/Haemosolvex	
D3	Desmopressin	
D4	NovoSeven	
D5	FEIBA	
D6	Fresh Frozen Plasma	
D7	Others	
E. The main cause of death		

DATA COLLECTION SHEET		
E1	Bleeding • Type of bleeding • Site of bleeding • Amount of blood loss • treatment	
E2	HIV/AIDS • CD 4 count • Viral load • AIDS-related complications • Treatment	
E3	Hepatitis C • Liver function • HCV viral load • Cirrhosis • Hepacelluar carcinoma • Treatment	
E4	Malignancy other than HCC. • Type • Site • treatment	
E5	Ischemic heart disease / MI or cardiac arrest • diagnosis	

DATA COLLECTION SHEET		
	• treatment	
E6	Other causes	

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PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

Haemophilia Comprehensive Care Centre
Charlotte Maxeke Johannesburg Academic Hospital

+27 11 488 3295/4736 +27 86 602 6416 Private Bag x 39, Johannesburg, 2000

23 February 2017

Ms Gladys Bogoshi
CEO: Charlotte Maxeke Johannesburg Academic Hospital
Jubilee Road
Parktown

Dear Ms Bogoshi,

REQUEST TO CONDUCT A STUDY

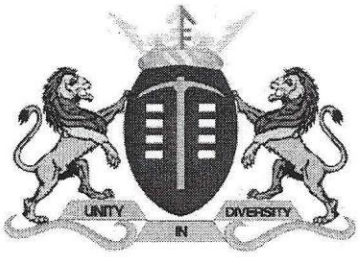
REGISTRAR NAME : Dr Ibrahim Ganwo
SUPERVISOR : Prof J Mahlangu
DEPARTMENT : Haematology
PROTOCOL : Mortality of People with Inherited Bleeding Disorders In a Tertiary Academic Centre
STUDY POPULATION : Patient attending the CMJAH haemophilia clinic

I hereby request your permission to conduct the above named study at the Haemophilia Clinic of the Charlotte Maxeke Johannesburg Academic Hospital. Please find herewith the study protocol proposal. I am awaiting approval from the Wits Human Research Ethics Committee.

Please do not hesitate to contact me if you need further information

Your sincerely

Dr Ibrahim Ganwo
Haematology Registrar
E-mail: ghnaow@gmail.com



GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Mr. J. Maepa
Office of the Clinical Director
Tell: (011) 488-3365
Email:johannes.maepa@gauteng.gov.za
27 February 2017

Dear Dr Ibrahim Ganwo

STUDY TITLE: Mortality of People with Inherited Bleeding Disorder in a Tertiary Academic Centre.

Permission to conduct the above mentioned study is provisionally approved. Your study can only commence once Ethics approval is obtained. Please forward a copy of your ethics clearance as soon as the study is approved by the Ethics committee for the CEO's to give you the final approval to conduct the study.

Supported/~~not supported~~

Dr M.I. Mofokeng
Clinical Director
DATE: 27/02/2017

Approved/not approved

Ms G. Bogoshi
Chief Executive Officer
Date: 28.02.2017

Appendix B

Ethics Clearance Certificate

R14/49 Dr Ibrahim Ganwo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170379

NAME: (Principal Investigator)	Dr Ibrahim Ganwo
DEPARTMENT:	Molecular Medicine and Haematology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Mortality of People with Inherited Bleeding Disorders in a Tertiary Academic Centre
DATE CONSIDERED:	31/03/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Johnny Mahlangu

APPROVED BY: _____

Prof P Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 03/04/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in March and will therefore be due in the month of March each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

_____ _____

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix C

Turn-it-in Report

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ORIGINALITY REPORT

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