A RETROSPECTIVE STUDY TO COMPARE EPISODIC AND PROPHYLACTIC FACTOR VIII TREATMENT REGIMENS IN SEVERE HAEMOPHILIA A PATIENTS AT PIETERSBURG HOSPITAL

by

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DECLARATION

I declare that ‘’A RETROSPECTIVE STUDY TO COMPARE EPISODIC AND PROPHYLACTIC FACTOR VIII TREATMENT REGIMENS IN SEVERE HAEMOPHILIA A PATIENTS AT PIETERSBURG HOSPITAL’’ hereby submitted to the University of Limpopo, for the degree of Master of Medicine in Paediatrics and Child Health has not previously been submitted by me for a degree at this or any other university; that it is my work in design and in execution, and that all material contained herein has been duly acknowledged.

Dr Tshipeng, JPM 15th July 2022

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ABSTRACT

Introduction. The purpose of this study was to describe and compare episodic and prophylactic treatment regimens with factor VIII in paediatric patients living with severe haemophilia A at Pietersburg Hospital in Limpopo province, South Africa.

Study design. Anonymised patient record data was collected retrospectively from the haemophilia treatment centre in Pietersburg Hospital, the site responsible for treating paediatric patients living with severe haemophilia A in the province.

Objectives. Annualised bleeding rates and factor VIII consumption were analysed and compared between the two groups.

Results. The results of the study showed that compared to the episodic group, participants in the prophylactic group had a substantial reduction in annualised bleeding rates per patient with a median of 4 vs 6 but a higher consumption of factor VIII. The annual median factor VIII consumption was 12000 IU vs 4000 IU per patient for prophylactic and episodic group respectively.

Conclusion. These findings suggest that treatment of paediatric patients living with severe haemophilia A using low-dose prophylaxis could be a better option in developing countries with limited economic resources.

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DEFINITION OF KEY CONCEPTS

Annualised bleeding rate: the ratio of reported bleeding events and number of months in years (Oldenburg, Yan et al. 2020). In this study, it is calculated as the number of reported total bleeds divided by the duration of treatment in years.

Cost-effectiveness: an evaluation that examines the cost of an intervention or treatment to it effectiveness measured by the result outcome (Newton and Stica 2011). In this study, it shall refer to the monetary cost of factor VIII necessary to reduce the annualised bleeding rate.

Effectiveness: The fact or quality of producing an intended outcome (Oxford English Dictionary 2017). In this study, it shall refer to the benefit produced by factor VIII treatment measured by the reduction in the annualised bleeding rate.

Episodic or on-demand treatment: a treatment whereby factor VIII infusion is given to stop an acute bleed resulting from haemophilia (Coppola, Di Capua et al. 2010). In this study, it shall refer to factor VIII being infused to stop acute bleeding in paediatric patients living with severe haemophilia A.

Haemophilia treatment centre: a facility that normally provides medical care to patients living with haemophilia (https://www1.wfh.org accessed on 23/12/2021).

Hemarthrosis: a condition that occurs as a result of bleeding into a joint cavity (Kliegman 2015). In this study, it shall refer to a bleed into a joint cavity, reported by the paediatric patient living with severe haemophilia A or identified by the health care worker during a clinical consultation.

Incidence of the disease refers to how often new cases of the disease occur (Kibel 2017). In this study, it shall refer to the number of new haemophilia A cases per total male births per year.

Inhibitors: antibodies directed against factors that block the clotting activity (Kliegman 2015). In this study, these shall refer to antibodies against factor VIII in patients treated for haemophilia A with a laboratory confirmation.

Prevalence of the disease: the ratio (at a given time) of the number of persons with the disease (all new and old cases) to the number of persons at risk population (Kibel 2017). In this study, it shall refer to the proportion of a population who have haemophilia A in a given time period.

Prophylactic treatment or prophylaxis: a treatment whereby factor VIII infusion is given to prevent bleeding (Coppola, Di Capua et al. 2010). In this study, it shall refer to factor VIII being infused to prevent or reduce the number of bleeds in paediatric patients living with severe haemophilia A.

Target joint: a joint that has had recurrent bleeding episodes. Commonly four bleeds into the same joint for a period of six months will define a target joint (Wu, Luke et al. 2011) . In this study, it refers to a joint that has 3 or more bleeds in 6 months in paediatric patients living with severe haemophilia A.

ABBREVIATIONS AND ACRONYMS

ABR: Annualised Bleeding Rate

aPTT: activated Partial Thromboplastin Time

BU: Bethesda Unit

CDC: Centre for Disease Control and Prevention

CF: Coagulation Factor

DoH: Department of Health

FIX: Factor 9 clotting protein

FVIII: Factor 8 clotting protein

HJHS: Haemophilia Joint Health Score

HK: High Molecular Weight Kininogen

HTC: Haemophilia Treatment Centre

IgG: Immunoglobulins G

INR: International Normalised Ratio

IU: International Unit

MRI: Magnetic Resonance Imaging

OPD: Out-Patient Department

PK: Prekallikrein

PL: Phospholipids

PMREC: Pietersburg Mankweng Research Ethics Committee

PT: Prothrombin time

TF: Tissue Factor

TREC: Turfloop Research Ethics Committee

UL: University of Limpopo

WFH: World Federation of Haemophilia

CHAPTER 1. INTRODUCTION AND BACKGROUND

1.1. Haemophilia overview

Haemophilia is a rare congenital bleeding disorder resulting from a deficiency of factor VIII, IX or XI. Factor VIII deficiency causes haemophilia A while factor IX and XI deficiency cause haemophilia B and C respectively (Srivastava, Santagostino et al. 2020).

Coagulation factors are proteins in the blood that help control the coagulation process or haemostasis.

Factor VIII is synthetised by different tissues in the body such as the liver, kidney, and spleen. After enzymatic modification, factor VIII is released into the circulation and interacts with other factors to activate a cascade of the coagulation process (Lenting, Van Mourik et al. 1998).

Haemophilia is found in all ethnic groups with no geographic or racial predilection (Zimmerman and Valentino 2013).

Haemophilia has been recognised since ancient times. Queen Victoria of England was known to be a carrier of the haemophilia gene and transmitted the gene to her son Leopold, who subsequently passed it to his children who eventually married into the royal families throughout Europe (https://www.arjinfusion.com accessed on 12/04/2022).

Haemophilia was then described in modern time around the 19th century with the use of antihaemophilia proteins, the production of cryoprecipitates, and the manufacturing of factor VIII and IX products. The development of first recombinant products was mentioned in the 1970s and 1980s. This was the beginning of haemophilia home treatment and the prophylactic regimen with better quality of life for paediatric children living with haemophilia (Franchini and Mannucci 2014).

1.1.1. Physiology of haemostasis

Haemostasis is a process that prevents or stops bleeding from a vascular injury. After an injury, the coagulation cascade is triggered resulting in the haemostasis achievement and repair of the damaged vessels (Versteeg, Heemskerk et al. 2013).

There are two types of haemostasis: primary and secondary.

In primary haemostasis, there is the formation of a platelets plug at the site of injury that stops the bleeding.
In secondary haemostasis, coagulation occurs in two ways: the intrinsic and extrinsic pathways.
Both factor VIII and IX contribute to secondary haemostasis via their role in the intrinsic pathway which activates factor X. Factor X converts factor II to factor IIa, which converts fibrinogen to fibrin (Figure 1). Fibrin enmeshes platelets to form a final clot to stop the bleeding.

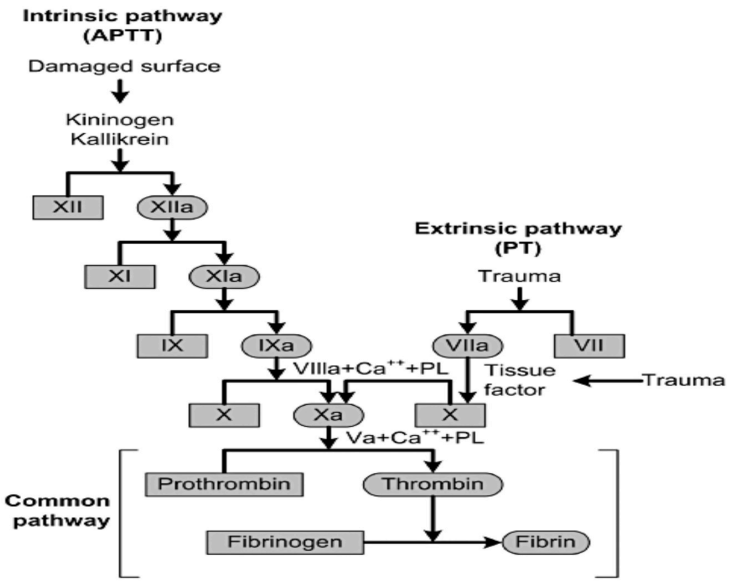

Figure 1. Haemostasis and the coagulation cascade

Source: (Adams and Bird 2009).

The pathways described in Figure 1 depict the coagulation cascade in the laboratory set-up and can be evaluated with the plasma measurement of PT (Prothrombin

Time) for the extrinsic pathway and aPTT (activated Partial Thromboplastin Time) for the intrinsic pathway.

Figure 2 describes a revised version of the coagulation cascade as it happens in a human cell. In this version, the tissue factor at the wound site will interact with factor VIIa to initiate a series of reactions leading to factor X activating factor Xa, factor IX to be converted in factor IXa and further activate factor X to Xa. This model highlights an amplification in the activation of factor Xa which will convert prothrombin to thrombin to achieve haemostasis with fibrin formation.

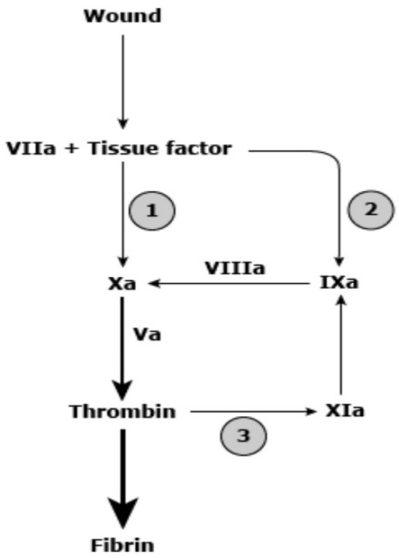

Figure 2. Revised version of the coagulation cascade

Source: https://www.uptodate.com (accessed on 23/11/2021)

1.1.2. Pathophysiology of haemophilia haemostasis

The pathophysiology of haemophilia haemostasis results from a failure of secondary haemostasis due to an interruption of the coagulation mechanisms described above leading to tissue bleeding from minor injuries (Adkison 2007).

1.2. Study background and overview

1.2.1. Problem statement

Paediatric patients attending the haemophilia treatment centre in Pietersburg Hospital are treated according to the treatment guidelines for haemophilia in South Africa with either episodic or prophylactic factor VIII treatment (Mahlangu and Gilham 2008). The outcome of the two treatment regimens on the bleeding rates and factor VIII consumption has not been previously studied.

1.2.2. Aim and objectives of the study

The primary outcome describes and compares bleeding episodes, as determined by the annualised bleeding rate (ABR) and consumption of factor VIII concentrates. The secondary outcomes measure the factor dosage and its cost-analysis.

1.2.3. Significance of the study

This study gives an overview of treatment of paediatric patients living with severe haemophilia A in Limpopo province and will certainly help inform clinical decision making and policy at a provincial and national level.

1.2.4. Dissertation layout

This dissertation is divided into five chapters.

Chapter One is an introduction of the current study. It discusses the aim, objectives, and significance of the study.

Chapter Two exposes the literature sources by other authors that were consulted regarding haemophilia, and its care.

Chapter Three outlines the research design, the selection of the sample, the type of data collection.

Chapter Four shows results findings and their interpretation.

Chapter Five. Concludes the dissertation by discussing the results findings, strengths, and limitations of the current study.

CHAPTER 2. LITERATURE REVIEW

2.1. Incidence and prevalence of haemophilia

The World Federation of Haemophilia (WFH) indicates that 1,125,000 people around the world leave with haemophilia of which 418,000 have severe haemophilia A (Srivastava, Santagostino et al. 2020).

In South Africa, the prevalence of haemophilia A is estimated to about 1 in 10,000 male births. Haemophilia B have a lower prevalence of about1 in 35,000 indicating that it's less common than haemophilia A (Mahlangu, Oldenburg et al. 2018).

2.2. Genetics of haemophilia A

The gene of haemophilia A is located on the X chromosome, making the disease an X-linked disorder.

Figure 3 summarises the genetic inheritance pattern of haemophilia A.

From a healthy father with a carrier mother, on average out of all the children, 50% of daughters will be healthy while the other 50% will be carriers. Of the sons, 50% will be healthy while the other 50% will be affected by the disease.
From a haemophiliac father and a healthy mother, out of all children, the sons cannot inherit the haemophilia gene from their father and all the daughters will inherit the haemophilia gene.

In some rare cases, a person can acquire haemophilia later in life. This is caused by the immune system neutralising its own antibodies against coagulation factors. Acquired haemophilia often resolves with appropriate treatment and is not discussed in this study (Tiede, Collins et al. 2020).

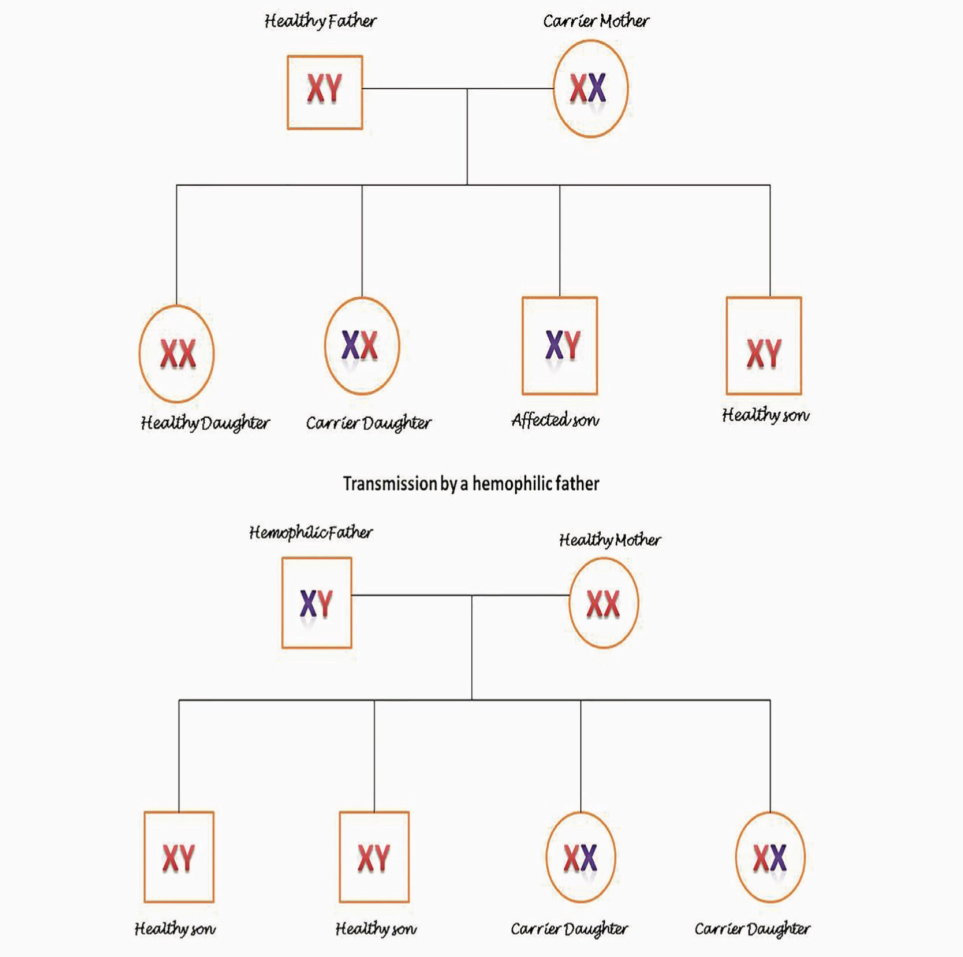

Figure 3. The schematic patterns of haemophilia inheritance

Source: (Mansouritorghabeh 2015)

2.3. Clinical manifestations of haemophilia

Both haemophilia A and B share the same clinical presentation with abnormal bleeding secondary to impaired haemostasis. Clinical manifestations can be grouped according to the age and site of bleeding, disease severity, or complications related to factor VIII infusion.

2.3.1. Age and site of bleeding

Hoot and Shapiro describe the clinical manifestations of haemophilia according to their age and site of bleeding (Hoots and Shapiro 2014) :

Newborns and infants: bleeding may involve the central nervous system (intraventricular haemorrhages), sites of the medical interventions (circumcision, heels sticks, and venepunctures) or extracranial sites (cephalohematoma, caput, or subgaleal haemorrhages).

Children: bleeding involving joints, muscles, bruising, forehead hematomas (''goose-eggs''), frenulum or oral injuries. Musculoskeletal bleeding become more common when children begin walking.

Older children and adults: bleeds can be found in all the systems including musculoskeletal, central nervous system, gastrointestinal tract, and oral mucosa.

2.3.2. Disease severity

The disease severity of haemophilia is classified according to plasma level of factor VIII into 3 groups : mild, moderate and severe (Castaman and Matino 2019).

- Severe haemophilia: plasma factor VIII $<$1% of normal.
- Moderate haemophilia: plasma factor VIII between 1-5%.
- Mild haemophilia: plasma factor VIII between $>$5% and $<$40%.

2.3.3. Complications of haemophilia

Viral diseases such as human immunodeficiency virus (HIV) and hepatitis C were the common complications in the early 1980 from the infected donors but rigorous screening tests and viral inactivation techniques have made the administration of factor concentrates safer (White 2nd, Blatt et al. 1980).

Other complications are caused by acute bleeding such as intracranial haemorrhage, circumcision, venepuncture bleeding, arthropathy or head trauma (Kulkarni and Soucie 2011). Recurrent joint bleeding results in the development of target joints, and progressive destruction of the large joint, with associated loss of mobility due to the arthropathy and development of contractures.

Factor VIII inhibitors are known to be one of the most challenging complications, while factor IX inhibitors occur very rarely (Kliegman 2015).

2.4. Diagnosis of haemophilia

The diagnosis of haemophilia begins with a thorough patient and family history taking, followed by screening tests such as platelets count and clotting profile (INR and aPTT). The confirmatory test is done by measuring the plasma factor VIII or IX level of activity and/or genetic testing (Jayandharan and Srivastava 2011).

2.4.1. Patient and family history

In all male children, any spontaneous bleeding into a soft tissue, muscle or joint should raise a red flag. With or without a family history of bleeding disorders or trauma, the clinician should conduct a thorough history taking.
Of note, a negative family history cannot be used to exclude the possibility of haemophilia because of new mutation, neonatal deaths, lack of available medical information or when the disease is mild and prior bleeding events were not identified or treated (Jayandharan and Srivastava 2011).

2.4.2. Coagulation assays

Screening tests using coagulation assays in patients with haemophilia will show a normal PT and platelet count with a prolonged aPTT (Figure 1). The confirmatory test will measure the factor VIII or IX plasma level and determine the severity of the disease. The development of inhibitors should be assessed regularly, especially in patients who are still having bleeding events despite factor VIII infusion or where there is a significant family history of inhibitor development, or large factor exposure early on in life (Kliegman 2015).

2.4.3. Genetic diagnosis

Molecular genetic testing where available is useful to identify the mutation in children living with haemophilia but can also predict the risk for the formation of haemophilia inhibitors (Swystun and James 2017).

2.5. Treatment of haemophilia

The treatment of haemophilia has evolved over the last 5 decades. We highlight the successive steps from the past to the future, in the summary below:

2.5.1. The past

In the 1950s and early 1960s, haemophilia could only be treated with blood products (whole blood or fresh plasma). 1970 has seen an increase availability of factor VIII concentrates. This led to more patients accessing treatment with factor VIII at home or at the haemophilia treatment centre (Franchini and Mannucci 2014).

2.5.2. The present

2.5.2.1. Factor VIII treatment

Factor VIII treatment given as prophylaxis is considered as standard care in children living with severe haemophilia A. Episodic treatment is still being used in countries with limited economic resources where the high cost of factor concentrates is among some of the challenges for the implementation of prophylaxis (Srivastava, Santagostino et al. 2020).

2.5.2.1.1. The model of prophylactic treatment and their doses

Prophylaxis in haemophilia consists of regular administration of therapeutic products aimed at maintaining haemostasis to prevent bleeding, especially joint haemorrhages, which would lead to arthropathy and disability.
Prophylaxis has been characterised according to when it is initiated and according to its intensity into (Srivastava, Santagostino et al. 2020):

- Primary prophylaxis: regular continuous prophylaxis started in the absence of documented joint disease, determined by physical examination and/or imaging studies, and before the second clinically evident join bleeds and 3 years of age.

- Secondary prophylaxis: regular continuous prophylaxis initiated after 2 or more joint bleeds but before the onset of joint disease: this is usually at 3 or more years of age.
- Tertiary prophylaxis: regular continuous prophylaxis initiated after the onset of documented joint disease. Tertiary prophylaxis typically applies to prophylaxis commenced in adulthood.

Opinions vary widely between countries and treatment centres but, in general, the trend is towards an early start, that is primary prophylaxis. Several studies on record divide prophylaxis into ‘’high-dose’’, ‘’intermediate-dose’’, and ‘’low-dose’’ categories. High-dose usually requires the administration of factor VIII 25-40 IU/kg every second day or at least three times weekly; intermediate-dose use lower doses administered slightly less frequently of factor VIII 15-25 IU/kg, 2-3 times/week and low-dose use factor VIII 10-15 IU/kg once or twice a week (Ljung 2013).

2.5.2.1.2. Benefits of prophylaxis in the treatment of haemophilia A

There now exists an extensive clinical literature that demonstrates clear benefits of prophylaxis over episodic therapy. Initiated early in life, prophylaxis have been associated with a reduction in the number of bleeding episodes and a significant reduction in joint deterioration and degenerative joint disease. Longer-term benefits include reduction of chronic musculoskeletal pain, functional limitations, and disability, need for orthopaedic surgery, hospitalisation, emergency room visits, and reduced length of hospital stays. All of this leads to greater participation in educational, recreational, and professional activities, with improved quality of life (Hoots and Nugent 2006).

2.5.2.1.3. Barriers and limitations to prophylactic treatment

Barriers and limitations to implement prophylaxis could be related to multiple problems such as difficulty in venous access in children on home infusion, difficulty to travel to the treatment centre for infusion, cost, availability of factor or multiple psychological barriers (Saxena 2013).

Prophylactic treatment is costly and put a lot of financial pressure on the health system, the patient, and his family. These costs may be direct (high price of clotting factors, clinician visits, hospitalisation, laboratory tests, medical and surgical procedures) and indirect (reduced productivity, increased absenteeism, disability or death) (Chen 2016).

2.5.2.1.4. Prophylaxis and development of inhibitors

The main concern in the prophylactic treatment of children with severe haemophilia A is the development of inhibitors antibodies that neutralise infused factor VIII. There is a common consensus that this modality of therapeutic approach is not associated with a higher risk of inhibitor development (Morado, Villar et al. 2005).

2.5.2.1.5. Low-dose prophylactic treatment

Low-dose prophylaxis generally defined as the administration of 10-15 IU/kg once or twice /week for haemophilia A and 10-20 IU/kg once per week for haemophilia B. The superiority of low-dose prophylaxis to On-demand therapy led the World Federation of Haemophilia, in their most recent guidelines, to recommend prophylaxis as standard of care for all regions of the world.
Low-dose prophylaxis have a direct impact on the cost factor and make treatment an affordable option in developing countries. There is a wide variability not only in the types of products used (plasma to recombinant factor concentrates) but also in the doses administered (minimal to very high) for similar indications. Some examples of low-dose models are implemented in China, Algeria, Tunisia, Iran, and other countries (Srivastava, Santagostino et al. 2020).

2.5.2.2. Other treatments

Desmopressin is a synthetic antidiuretic hormone that can be used intravenously, subcutaneously, or intranasally to treat minor bleedings in paediatric patients living with mild haemophilia (Khair 2019).

Tranexamic acid can also be used alone or added to desmopressin to treat minimal bleeding from mucous membranes such as mouth, nose or genitourinary tract (Khair 2019).

Patients with haemophilia who have inhibitors are treated with recombinant factor VII or FEIBA (Franchini and Mannucci 2012).

Monoclonal antibodies such as emicizumab administered subcutaneously have shown promising results when given at least every week or even every two weeks (Mannucci 2020).

2.5.2.5. Supportive care

Haemophilia supportive care includes avoidance of contact sports and the use of protective measures such as helmets and car seatbelts (Kliegman 2015).

Avoidance of nonsteroidal anti-inflammatory drugs that affect platelet function and aspirin is recommended (Schutgens, Van Der Heijden et al. 2016).

2.5.3. The future

The future in the treatment of haemophilia includes anti-tissue factor pathway inhibitors, gene therapy and extended half-life products. The rational of gene therapy is to replace the defective haemophilic gene with a normal and functional gene. This offers the potential for a cure for paediatric patients living with haemophilia (Peyvandi and Garagiola 2019).

2.6. Bleeding rates

Bleeding rates in patients with severe haemophilia A vary from one patient to another. Most patients with severe haemophilia A will experience between 10-15 bleeding episodes per year. Prophylactic treatment has shown to significantly reduce these events and prevent complications (Coppola, Di Capua et al. 2010).

When a single joint has more than 3 bleeding events for period of 6 month, it is called a target joint. A joint bleed is generally diagnosed clinically by pain, swelling

and/or impairment in joint mobility and can be confirmed on ultrasound (Manco-Johnson, Warren et al. 2021).

2.7. Factor VIII consumption

There is significant variation in the reported factor VIII consumption across the world, with developed countries using more factor than developing countries (Stonebraker, Brooker et al. 2010).

One study conducted in the USA in 2007 and published in the New England Journal of Medicine, showed that children on prophylactic treatment use more than double factor VIII per kilogram per year as compared to those on episodic treatment (Manco-Johnson, Abshire et al. 2007).

The 2020 World Federation of Haemophilia report showed the global mean and median global factor VIII consumption per patient per year according to the gross national income (Figure 4).

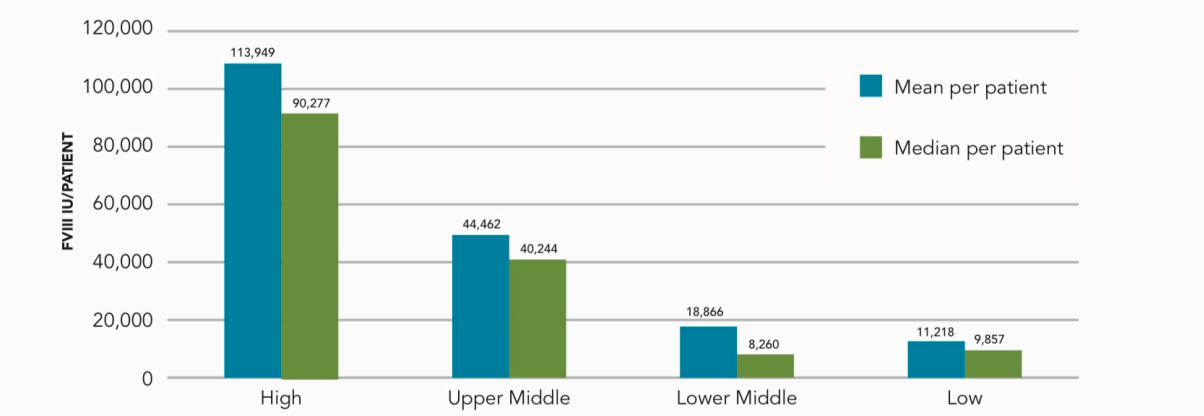

Figure 4. Mean and median global factor VIII per patient

Source: WFH. Report on the annual global survey 2020

2.8. Factor VIII cost in public sector in South Africa

Factor VIII is supplied and delivered to the Department of Health in South Africa by the National Bioproducts Institute NPC under the registered name Haemosolvate®

Factor VIII 500 IU'' at the price of R1674.03 (all prices are inclusive of 15% VAT) as stated in the contract circular Ref: HP10-2021BIO (DoH 2021).

2.9. Treatment cost and treatment cost-effectiveness

Haemophilia treatment cost involves direct and indirect costs.

Direct costs include OPD consultations, emergency room treatment, hospital admission, diagnostic tests and prescriptions, rehabilitation, home care treatment, etcetera. Indirect economic costs include lost school time, lost work time by family and friends, unpaid caregiving services, disability, or premature death (Zhou, Koerper et al. 2015).

The monetary cost of treatment with factor VIII differs from one area to another.
In one study in the USA, published in 2021, the average annual cost of prophylactic treatment with factor VIII was estimated at around $4865 (R75393.47) (Rodriguez-Merchan 2020).

A more recent study estimated the mean annual factor VIII costs at $264,777 (R4286739.60) for patients on prophylactic treatment (Croteau, Cook et al. 2021).

2.10. Age of reported first bleed

The first bleeding event in children living with haemophilia is often reported as delayed in historic studies.

In 2002, results from a French study showed that the median age for reporting the first bleeding event varied with the severity of haemophilia: 5,8 months in severe haemophilia, 9,0 months in moderate haemophilia and 28,6 months in mild haemophilia (Chambost, Gaboulaud et al. 2002).
Early reporting of first bleed in haemophilia should start from the neonatal period in a male neonate with unusual bleeding or a positive family history of the disease. Thereafter, abnormal bruising or bleeding after a procedure should lead the clinician to suspect haemophilia (Bertamino, Riccardi et al. 2017).

2.11. Haemophilia and physical activity

Vigorous physical activity increases the risk of bleeding in paediatric patients living with haemophilia.

One multicentre study conducted in Australia in 2012 showed that certain sports such as swimming and basketball have a lower bleeding risk while wrestling is associated with greater bleeding risk (Broderick, Herbert et al. 2012).

Looking at the association between haemophilia and physical activity, a study conducted in Japan in 2016, suggested that factor VIII should be used prior to any physical activity in order to reduce the risk of bleeding associated with physical activity (Goto, Takedani et al. 2016).

2.12. Development of inhibitors

The development of inhibitors is one of the most challenging complications in the treatment of paediatric children living with haemophilia. These patients do not respond to the conventional treatment with factor VIII infusion due to the development of antibodies against factor VIII or IX. It is estimated that around 25-30% of paediatric patients living with severe haemophilia A will develop inhibitors while only 3-5% of those with haemophilia B will have inhibitors (Franchini and Mannucci 2012).

Haemophiliac inhibitors increase the risk of complications making the treatment of these patients most costly because they require other molecules and treatment rather than factor VIII. Clinicians should have a high threshold to screen for inhibitors in patients who still have bleeding events despite the adequate usage of factor VIII (Srivastava, Santagostino et al. 2020).
The current guidelines recommend the screening for inhibitors in paediatric patients living with haemophilia every year or twice a year in suspected patients. Bethesda titre of $>$ 0.6 BU for Factor VIII and $>$ 0.3 BU for Factor IX is defined as positive (Srivastava, Santagostino et al. 2020).

2.13. Haemophiliac arthropathy

Haemophiliac arthropathy is another major complication in paediatric patients living with severe haemophilia A. These are largely due to lack of treatment (no-availability of factor VIII), delayed implementation of prophylaxis or non-adherence to prophylaxis. There is scanty data available regarding the number of haemophiliac children with chronic arthropathy but it is obvious that most of these patients will have impaired quality of life and will require rehabilitation (Di Minno, Ambrosino et al. 2013).

Children with haemophiliac arthropathy will present with contractures and joint deformity (because of the swelling) with limited range of movements without an acute history of bleeding (Singh, Mehta et al. 2019).

Haemophiliac arthropathy can be prevented by early start of prophylactic treatment in younger patients with haemophilia. A multidisciplinary approach including patient's education, supervised home therapy and physiotherapy (Gualtierotti, Solimeno et al. 2021).

2.14. Haemophilia and mortality

Mortality in haemophilia is caused by acute haemorrhages, mainly intracranial haemorrhage (Santo 2021). Viral diseases are becoming rare with the regular screening of patients (Junaid, Siddique et al. 2017).

Rarely, mortality related to inhibitor development has been mentioned too (Young 2012).

2.15. Treatment of severe haemophilia A. Global perspective

Table 1 gives a global perspective in the treatment of haemophilia A across the world considering the dosage of factor VIII used.

In the USA, a multicentre randomised trial assigned 65 boys with haemophilia A who were under 30 months of age to receive prophylaxis with factor VIII at the dose of 25 IU/kg every other day or episodic therapy only at the time of joint bleeding. Results at six years of age showed that the total bleeding episodes was significantly less in the prophylaxis group (mean 3.3 versus 17.7 per person per year) (Manco-Johnson, Abshire et al. 2007).

In Italy, a trial randomly assigned 45 children with severe haemophilia aged 1- 7 years to receive prophylaxis with factor VIII at the dose of 25 units/kg three times per week or episodic therapy at the time of bleeding. After 7 years of observation, the findings of the study showed that the total bleeding episodes were also significantly less in the prophylaxis arm (mean 38 versus 82 over the entire study period) (Gringeri, Lundin et al. 2011).

In China, a 12 weeks observational study between children on prophylactic and episodic treatment using factor VIII at the dose of 10IU/kg found that there was a reduction in the mean number of joint bleeds from 9.9 to 1.2 in children on prophylaxis (Tang, Wu et al. 2013).

In India, data from one study showed that low doses of 15 IU/kg of factor VIII given 2 times weekly, reduced significantly the ABR to < 3 bleeds / year, a level at which major improvements in long term musculoskeletal outcome in haemophilia can be expected (Abraham, Apte et al. 2017).

In a study in Tunisia, fifty-five children received factor VIII at a dose of 30 IU/kg given once, twice, or thrice a week. Results of the study showed a clear reduction in the number of bleeding episodes in all children (Gouider, Jouini et al. 2017).

Table 1. Episodic vs prophylactic treatment studies across the world

Author (Country)	Cohort size	Type of study	Median dose IU/kg		Median ABR	
			Episodic dose per bleed	Prophylactic dose per week	Episodic	Prophylaxis
Manco-Johnson et al. 2007 (USA)	65	Randomised control trial	40	75	17,7	3,3
Gringeri et al. 2011 (Italy)	45	Randomised control trial	25	25	6,2	2,4
Tang et al. 2013 (China)	34	Randomised control trial	20	20	30,9	5,2
Abraham et al. 2017 (India)	26	Prospective study		30		<3
Guider et al. 2017 (Tunisia)	55	Prospective study		30-60		0,5

2.16. Treatment of severe haemophilia A. South African perspective

In South Africa, no study has yet been conducted to compare the outcome of the two modalities of treatment in paediatric patients living with severe haemophilia A.

The South African guidelines advocate the use of either on-demand treatment or prophylactic treatment depending on the patient's circumstances and needs such as possibility of home treatment or easy access to haemophilia treatment centre, acceptability of treatment options offered, financial and social circumstances and adequate peripheral venous access. Dosages from 20-40 IU/kg for minor bleeds and 40-50 IU/kg for major bleeds are recommended for episodic treatment while a prophylactic dose of 25-40 IU/kg 2-3 times a week is used (Mahlangu and Gilham 2008).

Several themes related to haemophilia care such as bleeding rates, factor consumption, and low-dose prophylaxis are currently understood poorly in our setting.

CHAPTER 3. RESEARCH METHODOLOGY

3.1. Research design

The study is a retrospective cohort review of patient's medical records collected from the haemophilia treatment centre in Pietersburg Hospital. It covers a five-year period from January 2017 to December 2021.

3.2. Sampling

Convenience sampling was used, and it included all eligible participants attending the haemophilia treatment centre in Pietersburg Hospital.
Eligibility criteria were: 15 years old of age or less, a plasma factor VIII level of ≤1 IU per decilitre and undetectable levels of factor VIII inhibitors.

Participants were excluded from the study if they had previously defaulted treatment and follow-up, had incomplete information available, were had transferred to another province, developed inhibitors, or died during the duration of the study.

3.3. Data collection

Data was obtained from hospital medical records, and it included demographic and clinical data recorded by the treating physician within the period of the study. It was collected at the first visit and all follow-up visits. At each follow-up visit, the information for the period since the previous clinic visit was recorded.

All participants were provided with a unique patient identifier number to assure anonymity and confidentiality.

Two groups of participants were identified. The prophylactic group with participants on prophylactic treatment and the episodic group with participants on episodic treatment.

Report of bleeding episodes and factor VIII usage were collected from the patient's file at each consultation or by direct counting from the patient's haemophilia diary where available.

Annualised bleeding rate was calculated as the number of reported bleeding episodes divided by the duration of treatment in years.

The factor VIII cost was evaluated as the monetary yearly cost of factor VIII used expressed in South African Rands. Other medical and non-medical costs were not included in the cost evaluation in this study.

A data collection sheet including patient's characteristics was developed and used for the purpose of the study (Annexure D).

3.4. Treatment of severe haemophilia A at Pietersburg Hospital

Haemosolvate® 500IU was the most used factor VIII infusion at the haemophilia treatment centre at Pietersburg Hospital. Participants were treated according the guideline for the treatment of haemophilia in South Africa (Mahlangu and Gilham 2008).

The dose is always rounded up to use complete vials (without discarding any of the product), except for small children. This explains why participants in the study were treated with factor VIII at the dose of 500-1000 IU.

Participants on prophylactic group were treated with factor VIII infusion weekly or twice a week to prevent bleeding episodes while those on episodic group were treated with factor VIII infusion at the time of reported bleeding episodes.

3.5. Data analysis

Data was captured in data collection sheet designed for the study and transferred to an Excel spreadsheet and subsequently to STATA version 11 (Stata Corp, College Station, TX, USA, July 2009) for analysis.

Since the data was not normally distributed, median, and interquartile ranges were used to analyse demographic and clinical data. The Wilcoxon rank- sum test was also used to compare the two groups and the Spearman's rank correlation to assess the relationship between the bleeding events and the age.

3.6. Outcome measures

The primary outcome describes and compares bleeding episodes, as determined by the annualised bleeding rate (ABR) and factor VIII consumption.
Secondary outcomes measure factor VIII dosage and its cost-analysis.

3.7. Laboratory assays

Blood samples were collected quarterly for measurement of plasma factor VIII inhibitor levels and annually to check for hepatitis B and C.

3.8. Informed consent

The study was retrospective using pre-existing data from patient's records. A request for waiver of informed consent using personal health information was sought and obtained from the TREC (Annexure A).

3.9. Reliability, validity, and objectivity

To ensure reliability of the data, the test-retest reliability test was used by administering the same test twice over a certain period to all participants. The researcher also permitted the supervisor a direct access to the study data to verify its accuracy.
For its validity and objectivity, the data was transcribed as accurately as possible without assumptions, manipulations, or substitutions to reach a specific outcome.

3.10. Bias

To minimise selection bias, all participants meeting inclusion criteria were part of the study. Information bias resulting from wrong or inexact recording of individual factors

or missing files was minimised by getting information from two different sources: from the patient's files and the register at the haemophilia treatment centre.

3.11. Anonymity, confidentiality, and privacy

All medical records consulted from the haemophilia treatment centre were given a unique patient identifier number to assure anonymity and confidentiality.

To prevent data security threats from third parties, we made sure that the data was encrypted with a unique password, the computer used to store data remained secure by using an antivirus software and firewall.

Paper documents were stored securely in locked file cabinet which was handled only by the researcher.

To prevent data loss, data was backed up regularly in a separate location with a secure password.

When no longer needed, the data will be erased using an appropriate software for removing all the files or destroyed in case of paper documents.

3.12. Non-maleficence

The risk of harming participants in this study could be the inadvertent disclosure of patient's information. This risk was minimised by anonymising the data, having a protected password file, and to store the paper records in a locked secure cabinet.

3.13. Ethical approval

The Ethical approval was granted by the University of Limpopo research ethics committee (TREC/83/2021:PG) and the collection of data was approved by the Pietersburg/Mankweng Research Ethics Committee (PMREC 25 AUGUST UL 2021/D).

CHAPTER 4. RESULTS AND INTERPRETATION

4.1. Enrolment period

The enrolment period was from January 2017 to December 2021. Of the 37 patients who were identified through the database, 11 were excluded: 8 developed inhibitors, 1 died, 1 had incomplete data and 1 moved to another province. Of the remaining 26 patients, 18 were on episodic treatment (69.23%), 6 were on prophylactic treatment (23.07%) and 2 (7.69%) had bimodal treatment whereby either one of the two regimens was used at some time during the period of the study.
All data were collected between 1st September and 31st December 2021.

4.2. Baseline characteristics of all participants

All patients in the cohort were of African ethnicity (100%).

Participants on the prophylactic group were younger compared to those on the episodic group with a median (IQR) 8 (2-14) years and 9 (1-15) years respectively.

There was no major difference in the median weight (IQR) between the two groups with a median of 29.3 kg (12.0-57.3) for the prophylactic group and a median of 28 kg (11-56) for the episodic group.

The median annual hospital visit (IQR) was the same for the two groups with 2 (1-4) and 2 (1-5) for the prophylactic and episodic groups respectively.

Table 2. Baseline characteristics of patients on prophylactic treatment

Year	Median (IQR) age	Median (IQR) weight	Median (IQR) factor dosage / week	Median (IQR) factor dosage / kg (IU)	Median (IQR) factor usage / year (IU)	Median (IQR) ABR	No of visits / year
Year 2017 (N=6)	6.5 (2-11)	30.7 (29.3-30.7)	750 (500-1000)	22.8 (17.0-31.3)	6000 (1000-18000)	2.5 (0-10)	1 (1-3)
Year 2018 (N=5)	8 (3-12)	32.0 (25.2-48)	1000 (500-1000)	24.6 (17.0-39.6)	15000 (4000-23000)	4 (2-22)	2 (1-4)
Year 2019 (N=5)	8 (4-13)	29.3 (12.0-48.0)	500 (500-1000)	20.8 (17.0-26.7)	12000 (12000-26000)	5 (0-23)	2 (1-4)
Year 2020 (N=5)	7 (5-13)	21.1 (19.1-27.0)	500 (500-1000)	23.6 (18.5-26.1)	8000 (4000-30000)	1 (0-30)	2 (1-4)
Year 2021 (N=4)	7.5 (6-14)	23.9 (22.4-57.3)	500 (500-1000)	21.0 (17.4-22.3)	13500 (11000-19000)	4.5 (1-19)	3 (1-4)
Overall median	8 (2-14)	29.3 (12.0-57.3)	500 (500-1000)	20.8 (17.0-39.6)	12000 (1000-30000)	4 (0-30)	2 (1-4)

Table 3. Baseline characteristics of patients on episodic treatment

Year	Median (IQR) age	Median (IQR) weight	Median (IQR) factor dosage / bleed	Median (IQR) factor dosage / kg (IU)	Median (IQR) factor usage / year (IU)	Median (IQR) ABR	No of visits / year
Year 2017 (N=6)	9 (1-11)	30 (20.0-48.0)	500 (500-1000)	26 (12.75-28.9)	1750 (1000-4000)	6 (4-6)	2 (1-2)
Year 2018 (N=8)	10 (2-12)	32 (17.3-56)	750 (500-1000)	21 (12.75-33.33)	4000 (1500-18000)	5 (4-18)	2 (1-4)
Year 2019 (N=13)	9 (1-13)	28 (35-43)	750 (500-1000)	29 (12.75-55.86)	4000 (0-12000)	6 (0-9)	2 (1-4)
Year 2020 (N=15)	9 (1-14)	25 (12-48)	500 (500-1000)	29 (16.66-52.91)	8000 (0-20000)	9 (0-27)	2 (1-3)
Year 2021 (N=19)	10 (2-15)	25 (11-56)	500 (500-1000)	25 (16.39-45.45)	7500 (1500-24000)	10 (4-24)	2 (1-5)
Overall median	9 (1-15)	28 (11-56)	500 (500-1000)	26 (11.11-45.4)	4000 (0-24000)	6 (0-27)	2 (1-5)

4.3. Primary outcome data

4.3.1. Bleeding rates

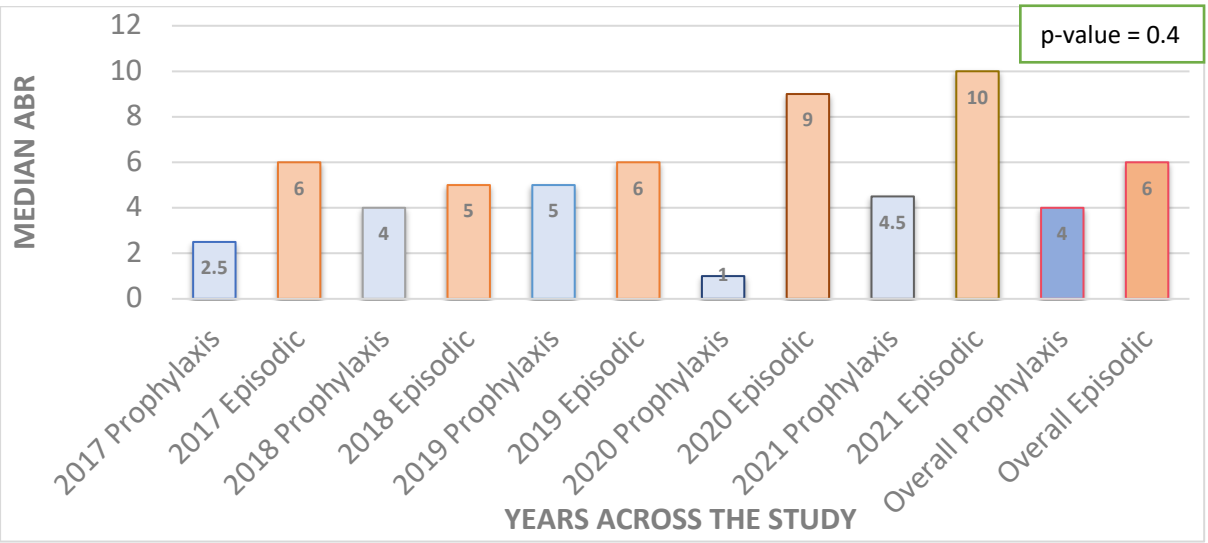

Figure 5. Median annualised bleeding rate per patient across the years of the study

The prophylactic group had almost half as few bleeding episodes compared to the episodic group (median 4 vs 6).

4.3.2. Factor VIII consumption

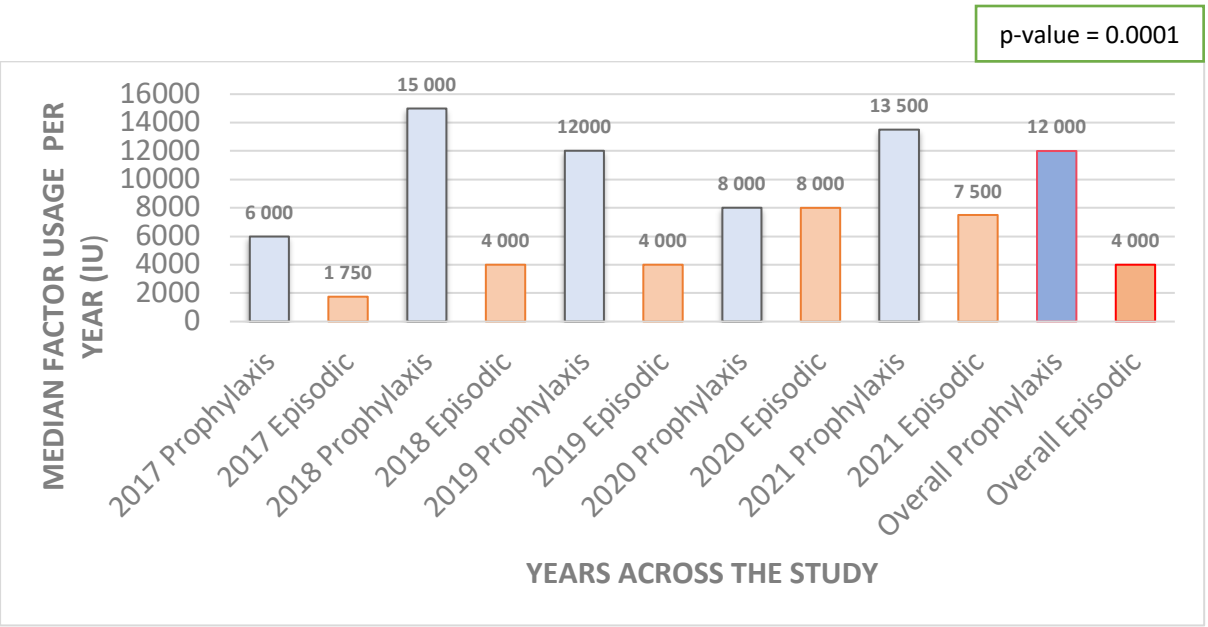

Figure 6. Median annual factor VIII consumption per patient across the years of the study

The prophylactic group used more than the double factor VIII compared to the episodic group (12000 vs 4000).

4.4. Secondary analyses

4.4.1. Factor VIII dosage

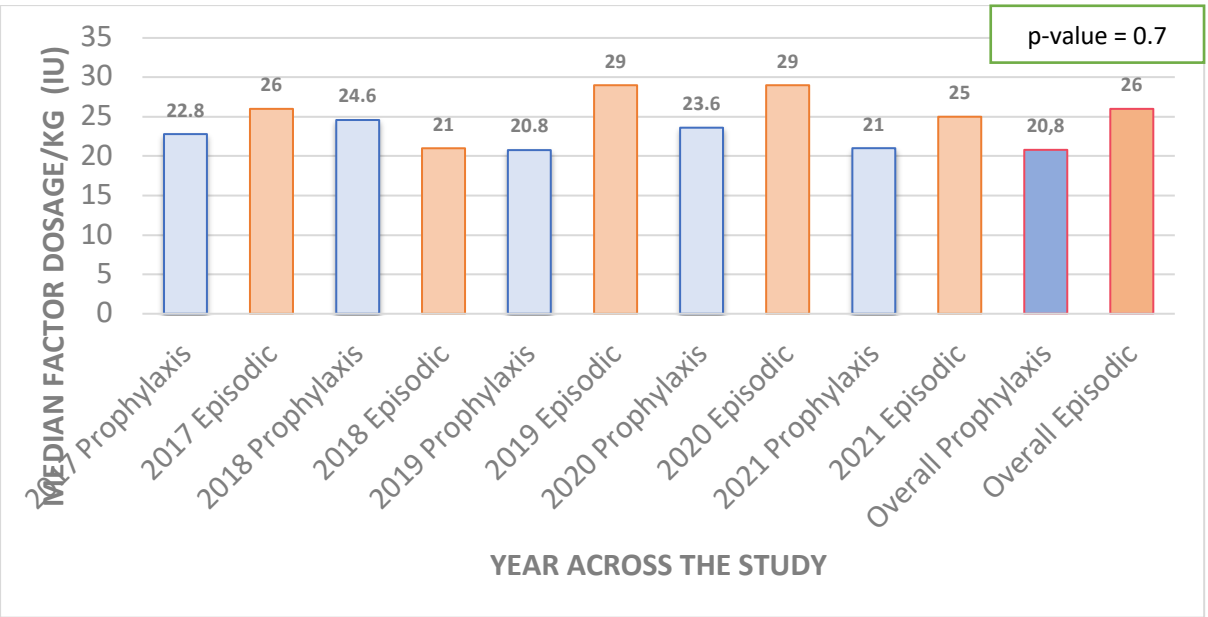

Figure 7. Factor VIII dosage per patient across the years of the study

There was not a significant difference in factor VIII dosage between the two groups (20.8 vs 26).

4.4.2. Factor VIII cost analysis

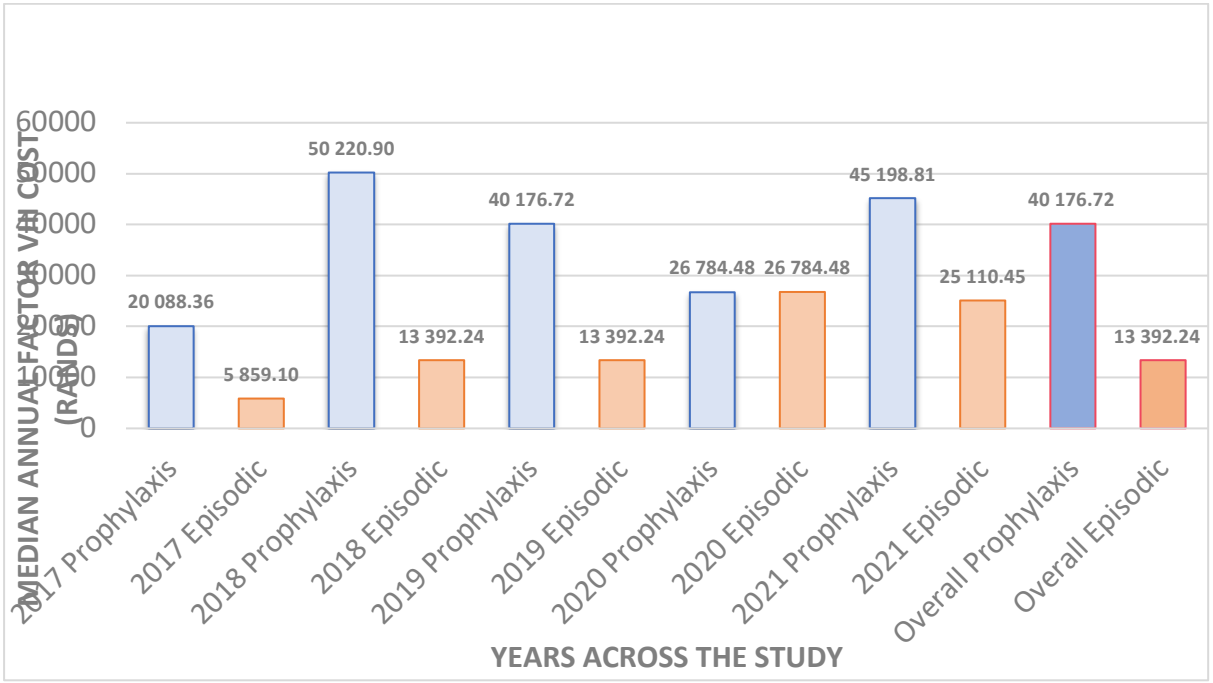

Figure 8. Factor VIII cost per patient across the years of the study

Prophylactic treatment markedly reduces the number of bleeding events but at increased cost. At the time of our analysis, the cost of a vial of 500 IU factor VIII was R1674.03.

The median yearly cost of prophylactic treatment per patient was R40176.72 for the prophylactic group and R13392.24 for the episodic group.

4.4.3. Correlational analysis

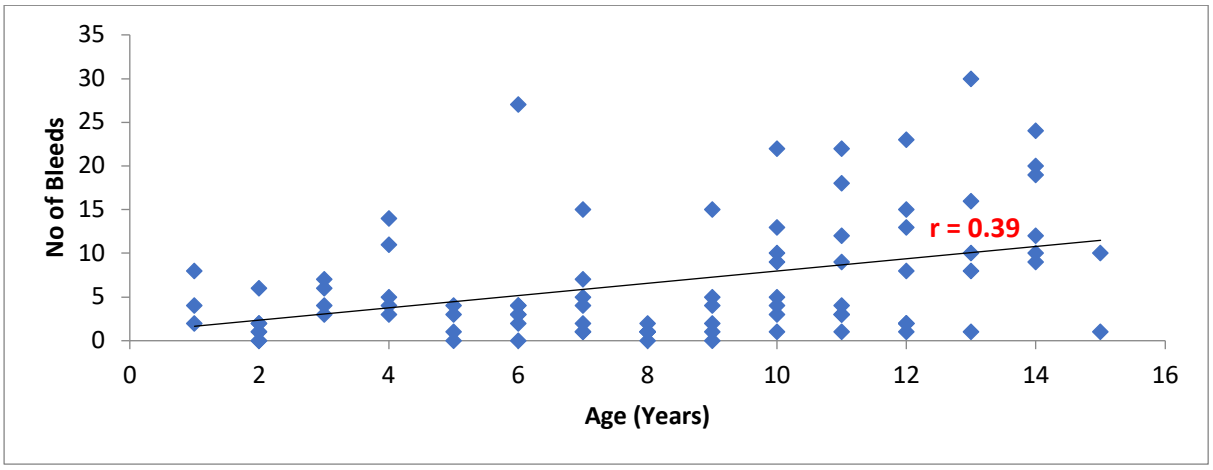

Figure 9. Correlation analysis

Figure 9 shows that there is a relationship between the age of the patient and the number of bleeding episodes. Younger participants reported fewer bleeding episodes than the older ones. However, this figure also highlights the presence of some outliers with abnormally higher reported bleeding episodes.

CHAPTER 5. DISCUSSION

5.1. Treatment by indication

Prophylactic treatment has not been widely used in the treatment of children with severe haemophilia A in the Limpopo province from 2017 to 2021. In this study, only 23% of the participants were on prophylaxis and another 8% had received prophylaxis at some time during the period under study.

Given that it is the intention of the treaters at the haemophilia treatment centre to use low dose prophylaxis in children with severe haemophilia A, when possible, these figures indicate that there are challenges with its implementation. The most likely reason for the non-implementation would be the slow adoption of home-based therapy.

5.2. Bleeding rates and factor VIII dosage

One of the important findings of this study is that low to intermediate dose prophylaxis with factor VIII infusion of 17-39.6 IU per kilogram per week is effective to reduce significant bleeding episodes. This shows that low-dose prophylaxis can be a better option for paediatric patients living with severe haemophilia in countries with limited economic resources.

It is notable that following the introduction of a clinical record template at the haemophilia treatment centre in 2020 (Annexure C), the difference between the median ABR for participants on prophylactic group versus episodic group is even greater than for the overall study period. It is the opinion of the researcher that this is due to the under-reporting of bleeds in the clinical records prior to 2020.

We also found that the p-value is relatively high in this study. This could be related to the fact that the study date was not equally distributed and that the sample size was small. However, compared with results reported by other studies (Table 1.), even with a small sample size, the results are similar and clinically significant.

5.3. Low-dose prophylaxis and cost-effectiveness

In this study the cost-effectiveness of low-dose prophylaxis considered only the monetary cost of factor VIII relative to the reduction of annualised bleeding rates. Other medical direct (health care service, clinician visit, laboratory tests, hospitalisation, physiotherapy, etcetera) and indirect costs (school absenteeism, transportation to healthcare facilities, disability, etcetera) were not considered.

The findings of the study found that low-dose prophylaxis cost R40 176.72 per patient per year vs R13 392.24 for episodic treatment. ABR was 6 and 4 for the episodic and prophylactic groups respectively.

The assessment of cost-effectiveness is broad; this study has paved the way for future studies with improved standardisation of cost-utility analyses which may include both direct and indirect costs.

5.4. Bleeding rates and age

The study found a positive correlation between the annualised bleeding rates and the age of the patients (r=0.39). This is possibly due to the presence of target joints in older patients. The correlation graph also highlighted the presence of some outliers mentioned in paragraph 5.5.1.4

5.5. Strengths and limitations of the study

5.5.1. Strengths of the study

This study has not been previously done in Limpopo province. It provides a baseline overview of the care of paediatric patients with haemophilia, and outlines their current treatment, as well as the costs thereof. It will certainly help to inform clinical decision making.

It also provides healthcare workers and policy makers a realistic overview of paediatric patient living with haemophilia care in the province. These findings can be extrapolated to other parts of the country who are treating children with the same medical condition for support and improvement of care.

5.5.1. Limitations of the study

5.5.1.1. Retrospective study

The study was a retrospective review and thus incomplete data, and loss of clinical data was expected. The researcher relied on observational data which could be inaccurately captured or subjected to biases. The documentation of bleeding rate is dependent on patient's recording and reporting of bleeding episodes and is thus subject to patient recall.

5.5.1.2. Data collection

The study revealed that the clinical record lacked certain information, such as accurately enumerating bleeding episodes and treatment between visits. In early 2020, a new template to guide the collection of clinical information was introduced at the haemophilia treatment centre (Annexure E). Thereafter it proved easier to collect accurate and meaningful data from the clinical record retrospectively.

However, the presence of poor quality of data prior to 2020 was not grounds for the rejection of the results, but careful attention was required when collecting, analysing, and interpreting the data.

5.5.1.3. Sample size and follow-up period

The study was done at a tertiary centre with a small study population and the duration of follow-up was also relatively short. However, the small sample size is acceptable as the condition is known as a rare disease worldwide.
A multicentre study with a large sample size and long follow-up is required to validate the results of the current study. Certainly, this report has created a platform for such larger studies.

5.5.1.4. Falsely reported bleeding events

The number of bleeds in this study are reported in the patient's file and have sometimes been transcribed from the patient-held record. In some cases, these numbers may be inaccurate.
This limitation was highlighted by the discovery of two outliers with high numbers of reported bleeding events. This prompted a more careful review of their clinical notes.

- One patient had a target joint with chronic arthropathy and tended to over-diagnose and over-treat bleeding episodes in the affected joint.

- Another of the patients reported more bleeding events than usual because of his involvement in playing football. According to the notes, he also wrongly counted episodes of pain related to knee arthropathy as a bleeding event.

5.5.1.5. Covid-19 and patients with haemophilia

The coronavirus disease 2019 (Covid-19) pandemic impacted negatively on the health system, healthcare workers and patients. Minimal information is available regarding Covid-19 patients with haemophilia; however, the study noted a decrease in the number of visits to the haemophilia treatment centre in 2020 and 2021.

5.6. Conclusion

This study demonstrates that low-dose prophylaxis is more beneficial than episodic treatment in preventing or reducing bleeding events in children with severe haemophilia A. The cost is higher, but the outcome is significantly better.

Low-dose prophylaxis could be an effective alternative for many developing countries with limited financial resources including South Africa where factor VIII accessibility and availability are challenging.

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ANNEXURES

Annexure A. Ethics clearance certificate

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Department of Research Administration and Development
Private Bag X1106, Sovenga, 0727, South Africa
Tel: (015) 268 3935, Fax: (015) 268 2306, Email:anastasia.ngobe@ul.ac.za

TURFLOOP RESEARCH ETHICS COMMITTEE

ETHICS CLEARANCE CERTIFICATE

MEETING: **11 May 2021**

PROJECT NUMBER: **TREC/83/2021: PG**

PROJECT:

Title: A Retrospective study to compare Episodic and Prophylactic factor VIII Treatment regimens in Severe Haemophilia Patients at Pietersburg Hospital

Researcher: JP Tshipeng
Supervisor: Dr CJ Sutton
Co-Supervisor/s: N/A
School: Medicine
Degree: Master of Medicine in Paediatrics and Child Health

PROF P MASOKO
CHAIRPERSON: TURFLOOP RESEARCH ETHICS COMMITTEE
The Turfloop Research Ethics Committee (TREC) is registered with the National Health Research Ethics Council, Registration Number: **REC-0310111-031**

Note:

i) **This Ethics Clearance Certificate will be valid for one (1) year, as from the abovementioned date. Application for annual renewal (or annual review) need to be received by TREC one month before lapse of this period.**

ii) **Should any departure be contemplated from the research procedure as approved, the researcher(s) must re-submit the protocol to the committee, together with the Application for Amendment form.**

iii) **PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.**

Finding solutions for Africa

Annexure B. Permission to conduct research in departmental facilities

LIMPOPO
PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

Department of Health

Ref : LP_2021-06-012
Enquires : Ms PF Mahlokwane
Tel : 015-293 6028
Email : Phoebe.Mahlokwane@dhsd.limpopo.gov.za

Jean Paul Mulang Tshipeng

PERMISSION TO CONDUCT RESEARCH IN DEPARTMENTAL FACILITIES

Your Study Topic as indicated below;

A retrospective study to compare episodic and prophylactic Factor viii treatment regimens in severe haemophilia patients at Pietersburg hospital

1. Permission to conduct research study as per your research proposal is hereby Granted.
2. Kindly note the following:
    a. Present this letter of permission to the institution supervisor/s a week before the study is conducted.
    b. In the course of your study, there should be no action that disrupts the routine services, or incur any cost on the Department.
    c. After completion of study, it is mandatory that the findings should be submitted to the Department to serve as a resource.
    d. The researcher should be prepared to assist in the interpretation and implementation of the study recommendation where possible.
    e. The approval is only valid for a 1-year period.
    f. If the proposal has been amended, a new approval should be sought from the Department of Health
    g. Kindly note that, the Department can withdraw the approval at any time.

    Your cooperation will be highly appreciated

PP **Head of Department** **Date** 15/07/2021

Private Bag X9302 Polokwane
Fidel Castro Ruz House, 18 College Street. Polokwane 0700. Tel: 015 293 6000/12. Fax: 015 293 6211.
Website: http/www.limpopo.gov.za

Annexure C. PMREC clearance letter

LIMPOPO
PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

DEPARTMENT OF HEALTH
PIETERSBURG/MANKWENG RESEARCH ETHICS COMMITTEE (PMREC)

ENQUIRIES: DR MA POOPEDI **DATE: 25 AUGUST 2021**

MANAGER: CLINICAL RESEARCH

ANANIASPOOPEDI@GMAIL.COM

REFERENCE	:	**PMREC 25 AUGUST UL 2021/D**
DATE	:	**25 AUGUST 2021**
RESEARCHER	:	**DR JPM TSHIPENG**
		(PRINCIPAL INVESTIGATOR)
RESEARCH	:	**POST-GRADUATE RESEARCH**
DEPARTMENT	:	**PAEDIATRICS AND CHILDHEALTH**
		(UNIVERSITY OF LIMPOPO)

Protocol Title: A retrospective study to compare episodic and prophylactic factor VIII treatment regimens in severe haemophilia patients at Pietersburg Hospital.

Candidate	:	**DR JPM TSHIPENG**
APPROVAL STATUS	:	**APPROVED**

SIGNED:

DR FO Ooko
Chairperson: Pietersburg/Mankweng Complex Research Ethics Committee
School of Medicine
University of Limpopo
REC 300408-006

Annexure D. Data collection tool

A. DEMOGRAPHIC DATA

Participant number	
Race	
Date of Birth / Age	
Date of data collection	

B. CLINICAL DATA

Year:	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Treatment Regimen (Episodic or prophylactic)												
Date of reported 1st bleeding event												
Factor VIII levels at diagnosis (severity)												
Weight (kg)												
No of total bleeds												
Total factor used (prescribed)												
Factor dosage (IU/kg)												

Adapted from Manco-Johnson et al. 2007

Annexure E. Haemophilia Treatment Centre Consultation sheet

Haemophilia Treatment Centre Consultation Sheet Date:_____

Name:_____ Weight:_____

File Number:_____ Height:_____

Date of Birth:_____ BP:_____

Diagnosis:_____

Previous visit date:_____

Total bleeds (including joint bleeds) since previous visit:_____

Joint bleeds since previous visit:_____

Total factor concentrate used since previous visit:_____

Treatment Regimen since previous visit: Episodic [ ] Prophylactic [ ]

Dose of prophylaxis: _____

Dose of episodic Rx: _____

Date of Last Lab tests:_____ (please transcribe)

Last inhibitor level:_____ Date:_____

Lab tests this visit? Yes [ ] No [ ] Sticker>

HJHS done? Yes [ ] No [ ]

Summary of visit (assessment/plan/next review): *[Write clinical notes overleaf]*

_____

| Sign/Name: |