FUNCTIONAL INDEPENDENCE SCORE OF PEOPLE WITH HEMOPHILIA AND FACTORS AFFECTING IT

Dissertation submitted to

THE TAMILNADU DR. M.G.R MEDICAL UNIVERSITY

CHENNAI

In partial fulfilment of regulations

For award of the degree of

M.D (GENERAL MEDICINE) BRANCH – 1

KILPAUK MEDICAL COLLEGE

CHENNAI 600 010

April 2016

BONAFIDE CERTIFICATE

This is to certify that dissertation named **"FUNCTIONAL INDEPENDENCE SCORE OF PEOPLE WITH HEMOPHILIA AND FACTORS AFFECTING IT"** is a bonafide work performed by **Dr.SIVANESAN.K.R,** post graduate student, Department of Internal Medicine, Kilpauk Medical College, Chennai-10, under my guidance and supervision in fulfilment of regulations of the Tamil Nadu Dr.M.G.R Medical University for the award of M.D. Degree Branch I (General Medicine) during the academic period from 2013 to 2016.

PROF.DR.S.MAYILVAHANAN.M.D
GUIDE FOR THE STUDY
CHIEF UNIT – 1
DEPARMENT OF MEDICINE
GOVT.ROYAPETTAH HOSPITAL
CHENNAI-14

PROF.DR.S.USHA LAKSHMI.M.D.,FMMC.,
PROFESSOR AND HEAD OF DEPARTMENT
DEPARTMENT OF MEDICINE
GOVT.KILPAUK MEDICAL COLLEGE
CHENNAI - 10

PROF.DR.R.NARAYANABABU.M.D.,DCH
THE DEAN
KILPAUK MEDICAL COLLEGE
CHENNAI -10

DECLARATION

I solemnly declare that this dissertation **"FUNCTIONAL INDEPENDENCE SCORE OF PEOPLE WITH HEMOPHILIA AND FACTORS AFFECTING IT"** was prepared by me at Government Kilpauk Medical College, Chennai, under the guidance and supervision of PROF. DR.MAYILVAHANAN.M.D., Professor, Department of Internal Medicine, Government Royapettah Hospital, Chennai.

This dissertation is submitted to The Tamil Nadu Dr. M.G.R.Medical University, Chennai in partial fulfilment of the University regulations for the award of the degree of M.D. Branch I (General Medicine).

Place: Chennai

Date:

(Dr.SIVANESAN.K.R)

ACKNOWLEDGEMENT

At the outset, I would like to thank my beloved Dean, Kilpauk Medical College Prof Dr.R.NARAYANA BABU.M.D.,DCH., for his kind permission to conduct the study in Kilpauk Medical College and also Dr.N.Nazeer Ahmed.M.S(ORTHO).,D.ORTHO., superintendent of Government Royapettah Hospital for giving permission to access haemophilia clinic in the hospital.

I would like to express my special thanks to Professor and Head, Department of General medicine Prof. Dr.S.Ushalakshmi.M.D.,FMMC., Kilpauk medical college for permitting me to conduct this study.

I would like to thank wholeheartedly, Prof. Dr.S.Mayilvahanan M.D., my unit chief for his encouragement and guidance during the study.

I am extremely thankful to Assistant Professors of Medicine, Dr.S.Malathi.M.D., Dr.V.Madhavan.M.D., Dr.S.Gopalakrishnan.M.D., and Dr.S.Kalaichelvi.M.D., for their timely help and guidance.

I would like express my gratitude to the co-operation and constructive criticism shown by my fellow post graduates, colleagues and friends.

Finally, I thank all my patients for their active co-operation in this study, without which this would not have become a reality**.**

CONTENTS

INTRODUCTION

Haemophilia is a group of related bleeding disorders that are inherited. Our country has the second highest burden of haemophilia patients in the world. The pathophysiology of Haemophilia A and Haemophilia B is based on the insufficient generation of thrombin by the factor IXa/factor VIIIa complex through the intrinsic pathway of the coagulation cascade. [1]

Spontaneous hemarthroses are characteristic of severe disease. The most common sites of bleeding are into joints and muscles. Approximately 80 per cent of haemorrhage occurs in the joints, Chronic and recurrent joint bleeds will lead to extensive destruction of articular cartilage, synovial hyperplasia and other reactive changes. This leads to joint deformity, muscle atrophy and soft tissue contractures, eventually leading to functional disability. Severe disability due to chronic hemarthroses is a tragic consequence of haemophilia patients in India. The onus is on the treating physician to prevent this functional disability and hence more light has to be shed into factors leading to joint deformity.

Functional independence scoring in haemophilia is used to measure the disability in haemophilia patients [2]. Identifying the factors having positive or negative influence in functional status of haemophilia patients will help to improve the quality of life in haemophiliacs and also prolong their survival to near normal.

AIM OF THE STUDY

- To assess the functional status of haemophilia patients using FUNCTIONAL INDEPENDENCE SCORING IN HEMOPHILIA (FISH).

- To assess the factors influencing functional status of haemophilia patients.

REVIEW

OF

LITERATURE

HISTORY OF HEMOPHILIA

Haemophilia is a sex linked coagulopathy first recognised by Talmud in the 5th century. It was then referred to as "haemorrhaphilia" (love of bleeding) in 1828. [1]

In 1911, Addis contributed to the history of haemophilia by recognising that the defect is correctable with a small amount of normal plasma but he incorrectly attributed it to the deficiency of prothrombin. With the advent of better protein purification techniques in the 1930s and 1940s, the components of thrombokinase were identified.

In the 19th century several authors recognised the link between bleeding episodes to the delayed blood coagulation. Morawitz developed the classical theory of coagulation that involved 2 reactions –

1. Conversion of prothrombin to thrombin by a tissue substance that he named as thrombokinase.

2. Conversion of fibrinogen to fibrin by thrombin. [3]

The defect in haemophilia is attributed to absence of single gene plasma protein, which is essential for platelet utilisation and thromboplastin generation, was well established by 1947. Pavlovsky[4] identified there are two types of haemophilia. Brinkhous[5] and quick identified haemophilia A is due to factor viii deficiency and haemophilia B is because of factor IX deficiency.

EPIDEMIOLOGY

International incidence of Haemophilia A is found to be 1 in 5000 to 7000 live male births. It occurs in all ethnic groups [6].50 to 60% of patients have severe haemophilia, 25 to 30% have moderate Haemophilia and 15 to 20% have mild haemophilia.

The annual incidence of Haemophilia A has been estimated at approximately 1: 5000 male births. The incidence of Haemophilia B is estimated at approximately 1: 30,000 male births [6].

The incidence of Haemophilia in India is about 1 in 10000 live male births. India is the second largest harbour of haemophilia patients. With the present records available number of Haemophilia patients in India is 11586 while the estimated prevalence is about 50000[7].

Haemophilia B occurs 1 in every 25000 to 30000 male births. As with Haemophilia A, Haemophilia B also occurs in all ethnic groups and geographic distributions.

EPIDEMIOLOGY IN INDIA [14]:

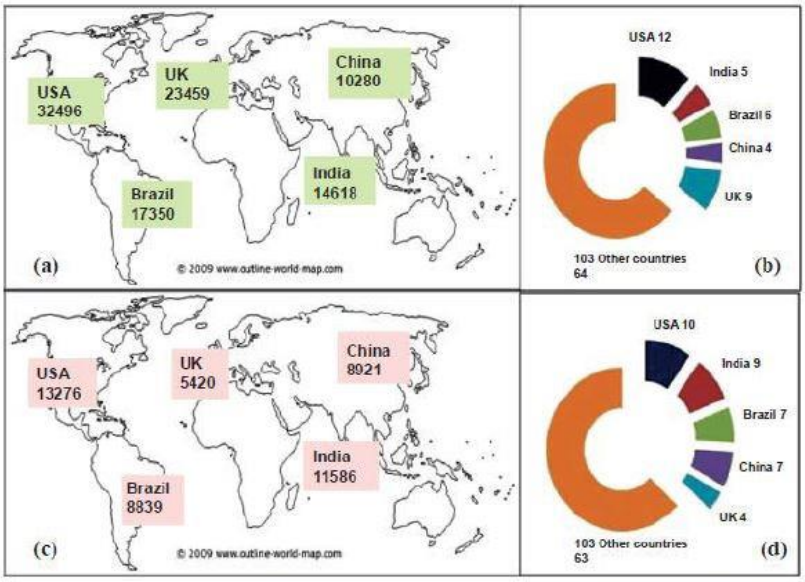


Fig. 3. Global distribution of total reported cases of bleeding disorders **(a)** and haemophilia A **(c)** in five countries reporting the highest number of patients. **(b)** and **(d)** show that nearly 5 and 9% of global patients with bleeding disorders and haemophilia A are from India. (*Source*: Authors' calculation based on data from Ref. 29).

ETIOLOGY

Haemophilia A is a heterogeneous disorder resulting from the reduced levels of functional factor VIII in the peripheral circulation. This can be due to either decreased levels of factor VIII or decreased functionality of factor VIII [1]. Factor VIII must be activated by thrombin for it to be an effective cofactor of factor IXa. Factor IXa has capacity to activate Factor X is exponentially increased in the presence of activated factor VIII - FVIIIa. Thus the clinical manifestations of Haemophilia A and B are not very much different from each other. Together Factor IXa and VIIIa activate factor X which is necessary for effective thrombin formation. In the absence of either factors clot formation is delayed and the clot thus formed is easily friable, dislodged and subjected to fibrinolysis which leads to excessive bleeding.

GENETICS [6]

Haemophilia A and B are X linked recessive disorders. About 30% of Haemophilia A mutations can arise de-novo. The gene for Factor VIII is large with 26 exons and 25 intervening introns. This makes identification of the mutation difficult.

All the sons of affected haemophiliac males are normal while all the daughters are obligatory carriers. Sons of carriers have 50% chance of being affected and the daughters of the carriers have a 50% chance of being carriers themselves. In female carriers, because of lyonization there might be preferential expression of the defective haemophilic allele. Such females who have Haemophilia are called “lyonized carriers”. Other mechanisms for female Haemophilia include homozygosity for the defective Factor VIII allele and hemizygosity for the defective gene.

No single mutation can cause Haemophilia. Hundreds of deletions, point mutations and inversions have been identified.

Analysis of Factor IX mutations show that it occurs due to endogenous processes – deamination of CpG dinucleotides rather than from environmental effects. As with Haemophilia A, no single gene has been attributed to the development of Haemophilia B.

FACTOR VIII gene and HAEMOPHILIA:

Factor VIII gene contains 186 kb with 26 exons, and produces an mRNA transcript of 9kb which is translated into 2351 amino acid polypeptide. The mature protein is divided into homologous domains named A1, A2, B, A3, C1, C3.The most common defect is inversion of 500-600 kb region that results in disruption of F8 region of intron 22. Additional inversion of Intron 1 of Factor VIII contributes to 5% of severe Haemophilia [12]. Point mutations involving CpG dinucleotide are more common.

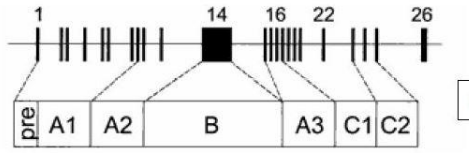


Fig.5:FVIII gene exons

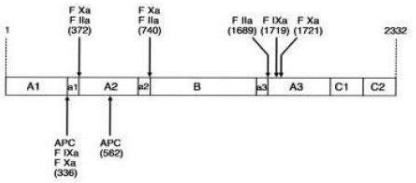
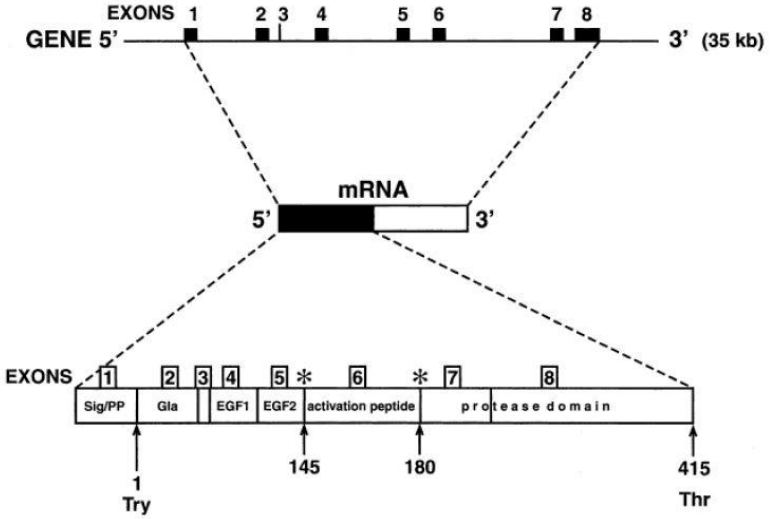


Fig.6:Factor VIII peptide

FACTOR IX GENE AND HEMOPHILIA B [28]:

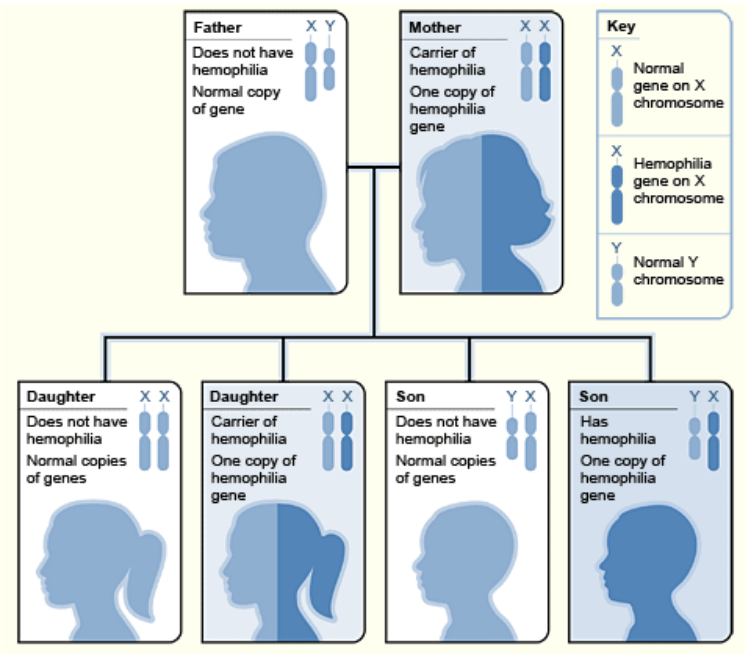
The gene for factor IX is located on the long arm of chromosome X. It is much smaller than the gene for factor VIII measuring only around 33kb.

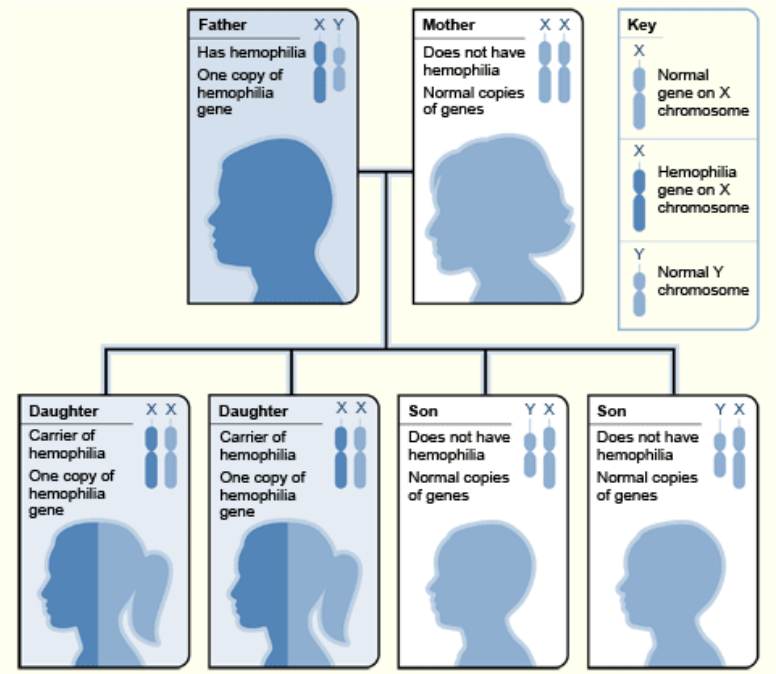
F9 is the gene's official symbol. The *F9* gene is located on the long (q) arm of the X chromosome between positions 27.1 and 27.2.[12]



GENETICS IN HEMOPHILIA

When a carrier woman marries a normal man, there is a 50% chance of the girl Children to be carriers and 50% chance of her son to be a Haemophilic.





CLOTTING CASCADE

1. VASCULAR CONSTRICTION

2. PLATELET ACTIVATION

3. EXTRINSIC PATHWAY

4. INTRINSIC PATHWAY

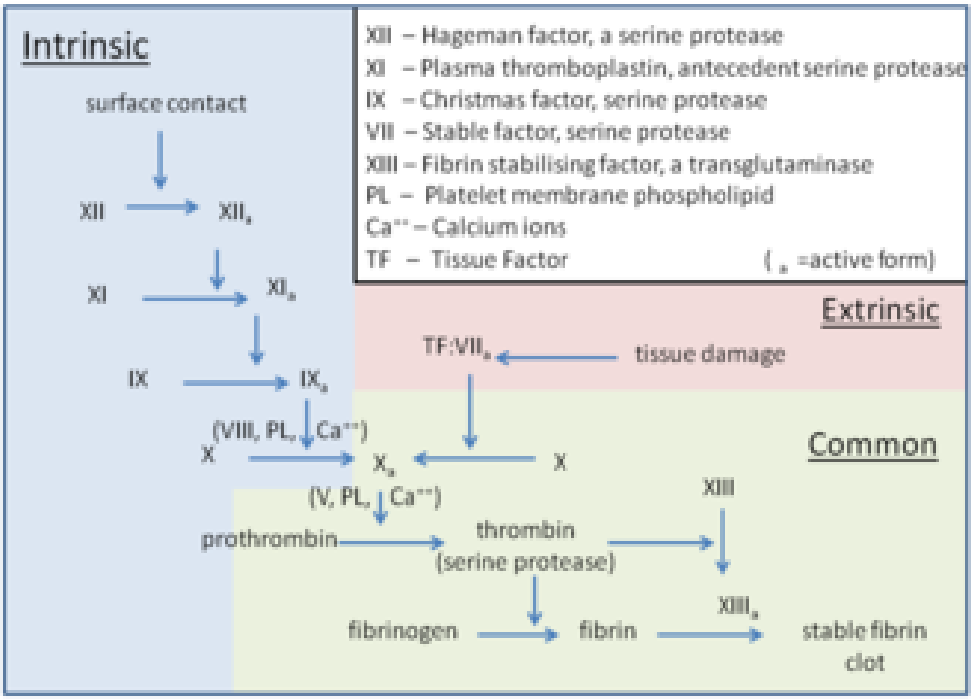
5. FINAL COMMON PATHWAY

6. COFACTORS

7. REGULATORS

8. FIBRINOLYSIS

The three pathways that makeup the classical blood coagulation pathway



VASCULAR CONSTRICTION

After a trauma, the blood vessel immediately constricts causing reduced blood leakage. This occurs due to local myogenic reflex, local autocoid factors released by the vessel wall and the platelets and neurogenic reflex. The neurogenic reflex originates from the pain nerve endings. Of the above mentioned factors, the myogenic reflex is the most powerful. Of the autocoids, the most important vasoconstrictor is the thromboxane A2.

PLATELET ACTIVATION

If the cut vessel is very small, it can be sealed by the platelet plug itself. Many such small leaks keep happening throughout the day.

PLATELET PHYSIOLOGY

The platelets' cell membrane has glycoprotein that repulses attachment to the vessel wall but gets attached to injured endothelium and exposed collagen. In addition platelets contain phospholipids that activate various stages of blood coagulation process. The half-life of platelets is 8 to 12 days.

When the platelets come in contact with collagen they change their characteristics. They tend to swell up and the contractile process within the platelets releases the contents of the granules. These make the platelets even stickier and they tend to bind avidly to each other and to the exposed collagen and Von Willebrand factor. It also releases ADP which forms Thromboxane A2. This further makes the platelets sticky. A platelet plug is formed which is initially loose and then tends to become closely packed. Small leaks are closed by platelet plugs themselves.

The coagulation process is initiated by three factors [1][6]

- Damage to bleed vessel
- Damage to the blood components
- Exposure of blood to damaged endothelial cells or the underlying collage

In each instance, it leads to the formation of the prothrombin activator which converts prothrombin to thrombin and the coagulation continues

The prothrombin activator can be formed by two processes:-

- EXTRINSIC PATHWAY – Begins with the trauma to the vessel wall
- INTRINSIC PATHWAY – Begins in the blood itself

EXTRINSIC PATHWAY[1]:

This is also known as tissue factor pathway. This begins with the exposure of blood to the damaged extra vascular tissue or traumatised vessel wall.

STEPS

1. Release of TISSUE FACTOR: Damaged vessel releases several tissues factors or tissue thromboplastin.
2. FACTOR VII AND TISSUE FACTOR: The lipoprotein tissue factor forms complexes with Factor VII and in the presence of Calcium catalyses the activation of Factor X to Xa.
3. Factor Xa combines with Factor V and in the presence of calcium becomes the PROTHROMBIN ACTIVATOR.
4. Prothrombin activator complex in the presence of calcium converts prothrombin to thrombin and the coagulation continues.

In the prothrombin activator complex, Factor X is the actual protease and Factor V accelerates the protease activity. The formed thrombin further activates Factor V which becomes an additional accelerator of prothrombin activator thereby becoming a positive feedback mechanism.

INTRINSIC PATHWAY[1]

The second pathway for initiating coagulation is the intrinsic pathway which gets activate with damage to the blood components.

1. Trauma to blood causes activation of Factor XII. When Factor XII comes in contact with wet able surfaces like collagen it gets activated to a protease – Factor XIIa. Simultaneously, platelets release platelet factor 3 which in turn contributes to the coagulation cascade.

2. Factor XIIa activates Factor XI to XIa. This reaction needs High molecular weight kininogen and prekallikrein.

3. The activated Factor XI then enzymatically cleaves Factor IX to form the activated Factor IXa.

4. The activated Factor IXa, along with activated factor VIIIa, Platelet factor 3 and platelet phospholipids end in activating Factor X to Xa. Factor VIII is also known as the antihaemophlic factor.

5. This step is the same as in intrinsic pathway. The activated Factor X combines with Factor V to form the prothrombin activator complex.

6. The prothrombin activator causes conversion of prothrombin too thrombin thereby setting the coagulation cascade into motion.

CONVERSION OF PROTHROMIN TO THROMBIN

After the formation of prothrombin activator by either the intrinsic or extrinsic pathway, it causes conversion of prothrombin to thrombin in the presence of ionic calcium. Thrombin causes polymerization of fibrin molecules within 10 to 15 seconds. So, the rate limiting step in coagulation process is the formation of the prothrombin activator and not the steps that happen beyond it. Platelets also play a role in the conversion of prothrombin to thrombin as most of the prothrombin binds to the prothrombin receptors on the surface of the platelets.

PROTHROMBIN AND THROMBIN

Prothrombin is formed by the liver and it needs Vitamin K for formation. The normal plasma concentration is about 15mg/dl. It is constantly being used up in the body for coagulation process. In the presence of liver failure or vitamin K deficiency, prothrombin production is grossly reduced and can result in coagulopathy. Thrombin is the link between vascular injury, coagulation and platelet activation.

CONVERSION OF FIBRINOGEN TO FIBRIN

FIBRINOGEN

Fibrinogen is a high molecular protein, (MW=3, 40,000) with a plasma concentration of 100 to 700mg/dl. It is produced in the liver and so liver disease can result in reduced plasma levels of fibrinogen. Because of its high molecular weight, little, leaks outside the blood vessels. In case of trauma, it leaks out and can cause clotting of tissue fluids just like plasma and blood.

CLOT RETRACTION

Within a few minutes after clot formation, it begins to contract expressing the serum. In this way serum differs from plasma because it cannot clot as the clotting factors have been depleted. The platelet themselves contribute to the process of clot retraction. Clot retraction is affected in case of thrombocytopenia. The platelets bring the fibrin molecules together. The contractile process within the platelets gets activated and this is involved in clot retraction. It also releases procoagulant factors. The contraction is activated by thrombin and accelerated by the calcium released from the endoplasmic reticulum and Golgi apparatus within the platelets. As the clot retracts, the edges of the broken blood vessels are pulled together there by contributing further to complete haemostasis.

COFACTORS

Substances required for the proper functioning of the coagulation cascade:

- CALCIUM
- VITAMIN K

Except for the first two steps of the intrinsic pathway, Calcium ions are needed for the activation and propagation of the entire coagulation cascade. In live, the levels of ionised calcium rarely become low enough to affect the coagulation. But after sampling, blood can be maintained in the liquid state by adding citrate, that binds with the ionised calcium or oxalate, which precipitates the calcium.

Vitamin K is essential for the gamma carboxylation of Factor II, VII, IX and X. This process is essential for the factors to bind to phospholipids and there by participate in the coagulation cascade. In the absence of vitamin K, either due to deficiency or liver disease, PIVKAs (Proteins formed in the absence of Vitamin K) are formed. These are defective proteins and do not participate effectively in the coagulation cascade.

REGULATORS[6]

There are four mechanisms that keep platelet activation and the coagulation cascade in check. Abnormalities can lead to an increased tendency toward thrombosis:

- ***Protein C***

  Thrombin activates protein C into aPC. Activated protein C inhibits factor Va and VIIIa. This causes termination of the role of factor VIIIa in the tenase complex and the role of factor Va in forming the prothrombin activator complex. The net effect on the coagulation cascade is inhibition of further fibrin and there by clot formation.

- ***Antithrombin*** is a serine protease that inhibits factor Xa and thrombin. Antithrombin deficiency can cause thrombotic disorders

- **Tissue factor pathway inhibitor (TFPI)** limits the action of tissue factor (TF) and also inhibits excessive TF-mediated activation of Factor VII and Factor X

- **Plasmin** is produced from the plasminogen, a zymogen produced in the liver. Plasminogen after binding to clots it adopts an open conformation and can be activated to plasmin by a variety of factors, the most important of which is Tissue plasminogen activator. Plasmin deficiency, which is rare in humans, can cause thrombosis.

PRENATAL DIAGNOSIS AND CARRIER DETECTION[11][12]

Prenatal diagnosis can be suggested to woman those who are related to obligate Haemophilia carriers and known Haemophiliacs. Germ line mutations have different implications when it occurs in the grandfather and the mother.

Prenatal diagnosis can be done using cells obtained during amniocentesis done at 16 weeks of gestation. If the foetus is a female little is the concern as carrier females rarely have bleeding manifestations. In case of a male foetus, the diagnosis can be made by DNA analysis of the cells.

Studies identified the causative mutation in 90% of patients with mild and moderate haemophilia A but only 50 to 60% of patients with severe disease[12]. The analysis is performed in the eleventh to twelfth week of gestation either by amniocentesis or chorionic villus sampling.

CLINICAL PRESENTATION[23][24][1]

Clinical presentation of Haemophilia A and B are indistinguishable. Both are very similar in their presentation.

- Severe Haemophilia refers to factor levels less than 1% of normal or less than 0.01u/ml. They present in early infancy with spontaneous haemorrhage.
- Moderate haemophilia has factor levels between 1 to 5% of normal. They present with increased bleeding after a minor trauma and surgery. Spontaneous bleeds are rare.
- Mild haemophilia refers to factor levels of 6 to 30% of normal. These patients bleed secondary to surgery and rarely do they present with spontaneous hemarthroses.

- Most carriers have factor levels greater than 50% and do not have bleeding manifestations. Factor VIII levels should be checked in all Haemophilia carriers.

INTRAPARTUM COMPLICATIONS

A study of the modes of delivery and peri-natal complications in affected male babies shows that the risk of intracranial bleed is less in normal delivery. (<3.8%)[6]. The risk of subgaleal and cephalic hematoma increases with vacuum delivery. Caesarean section does not eliminate the risk of intracranial haemorrhage. Forceps delivery and prolonged labour increase the risk of intracranial bleeds. Seizures are common during the acute intracranial bleed episode.

Psychomotor complications and cerebral palsy can occur as long term complications. In a European study, involving 508 children born with Haemophilia A or B, intracranial bleeds occurred in 18 (3.5%) within the first 28 days of life [8].

CIRCUMCISION AND BLEEDING

50% of undiagnosed haemophiliacs have excessive bleeding during circumcision that can be stopped with factor infusion. Thus, failure to bleed does not eliminate the presence of Haemophilia in that patient.

AGE OF BLEED ONSET

Children with severe haemophilia become symptomatic within the first 2 years of life. In a study, the mean age of first bleed leading to the diagnosis of Haemophilia was at 0.9 years of age, in the absence of any prothrombotic factor coinheritance.

In the presence of prothrombotic factors, the mean age for diagnosis was late and was around 1.6 years of age[5]. Joint bleeds are very common and early diagnosis would help to prevent the joints from hemarthropathy.

The age of diagnosis in mild and moderate Haemophilia is later than that for severe haemophilia.

Mild haemophilia without family history can go undetected for a very long period of time, as about one third of patients have very few bleeding episodes.

- HEMARTHROSES
- HEMATOMAS
- PSEUDO TUMORS
- HEMATURIA
- NEUROLOGICAL COMPLICATIONS
- MUCOUS MEMBRANE BLEEDS
- POST SURGICAL BLEEDS

HEMARTHROSES[1][6]

Hemarthroses is the most common bleeding manifestation in severe haemophiliacs contributing to about 75% of the bleeding episodes[30]. Anatomy of the synovium favours bleeding, it has numerous cells and abundant capillaries that lie beneath the synovial layer. These capillaries are susceptible to damage during mechanical trauma associated with the daily use of joints. The joints involved in decreasing order of frequency are knee, elbow, ankle, shoulder, elbow and hip. Hinge joints are more commonly affected than ball and socket joints.

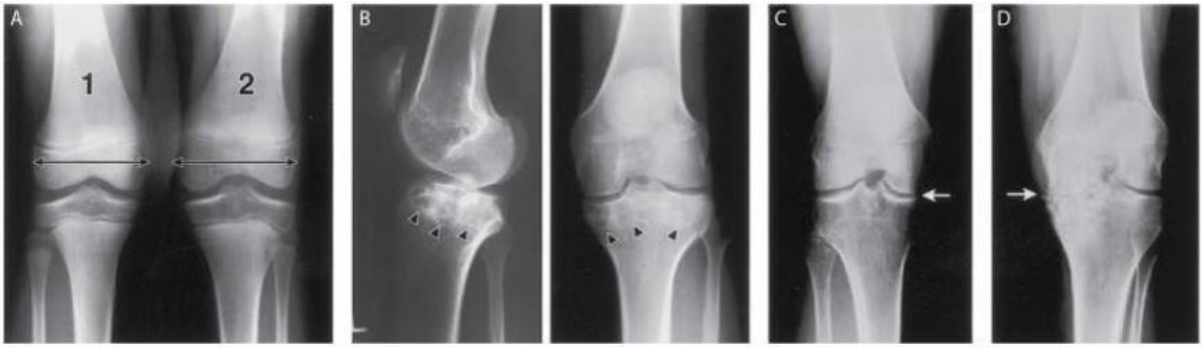
Hemarthroses might produce an aura of discomfort that gradually progresses to cause joint enlargement and excruciating pain. The joint becomes swollen, warm and tender with decreased range of movement. Patient might have a mild fever during the bleed. However, sustained fever indicates an infected joint.

When bleeding stops, the blood is reabsorbed in a couple of days. If the bleed is treated early and the joint is not affected chronically, pain subsides in 6 to 8 hours and disappears in 12 to 18 hours. However, repeated bleeding into the joint causes articular destruction and leads to haemophilic arthropathy. Once chronically affected it may be difficult to distinguish the pain of degenerative arthritis from the pain of bleeding.

The synovium becomes thickened and folded leading to repeated bleeds in the same joint causing the so called target joint. The joints most often involved are the weight bearing joints, knee and ankle. Bleeding into a joint with thickened synovium causes less pain than bleeding into a normal synovium.

In the presence of fever, leukocytosis and other systemic manifestations the probability of an infected hemarthroses should be considered. Rapid diagnosis is a must as infection in such joint progresses rapidly causing loss of joint space and architecture. The joint should be aspirated under strict aseptic techniques and factor replacement should be given. Chronic haemophilic arthropathy is painful with weight bearing but the pain subsides or disappears once the joints become ankylosed. Muscle atrophy around the joint can lead to increased inability and increased bleeding from the loss of cushioning effect provided by the muscles. Patients with factor VIII or IX deficiency with levels greater than 20% of normal rarely develop haemophilic arthropathy even if they have experienced previous bleeds[6].

Radiographic stages of haemophilic joint[6]



Stage 0 – Normal joint

Stage 1 – fluid in the joint

Stage 2 – Osteoporosis and epiphyseal overgrowth – Fig A

Stage 3 – Subchondral bone cysts – Fig B (arrowheads)

Stage 4 – Prominent bone cysts with marked narrowing of joint space – Fig C (arrows)

Stage 5 – Joint obliteration with epiphyseal overgrowth

HEMATOMAS

Hematomas can occur in the subcutaneous plane or into the muscle[6]. They are very characteristic of clotting factor deficiencies. Hematomas, with bleeding into the muscles occur most commonly in the quadriceps, iliopsoas and forearm.

RETROPERITONEAL HEMATOMA

Retroperitoneal hematomas can dissect through the diaphragm into the chest and neck and compromise the airways. They might cause ureteral obstruction and compromise renal function. An abdominal hematoma can rupture and drain into the colon which is very rare and most often fatal.

Iliopsoas bleeds tend to be large and compromise neurovascular structures causing compartment syndrome. These bleeds can be localised with ultrasound and require larger doses of factor VIII[30].

Patients with Haemophilia can develop hematoma of the bowel wall and present as appendicitis, intestinal obstruction or intussusception. The diagnosis of "pseudo appendicitis" can be made with CT scan.

PSEUDOTUMOR[30]

Pseudotumor is also known as blood cysts. There are three types of Pseudotumor[6],

Type 1: Simple cyst; confined by the tendinous attachment within the fascial muscle.

Type 2: Simple cyst that compromises the vascular supply to the adjacent bone and periosteum resulting in bone resorption and cyst formation

Type 3: Subperiosteal bleeding resulting in separation of the periosteum from the bone cortex.

Pseudotumors contain either a serosanguinous fluid or brownish material surrounded by a fibrous membrane. They cause pain only when the collection is rapid or when they compress nearby neurological structures. Pseudotumors tend to expand over years together and can become multiloculated. They can reach a stage where they become inoperable. Sinus tract formation from a pseudotumor is a risk for increased infections.

Most common sites for pseudotumor formation are in the lower limb but they can occur at other sites too. Small joints of the hands can be involved in younger patients.

MRI and CT help in diagnosis. Needle biopsy of the pseudotumor should be avoided for fear of bleeding and infection. The only definitive treatment is complete excision. If incompletely removed the pseudotumor tends to reform.

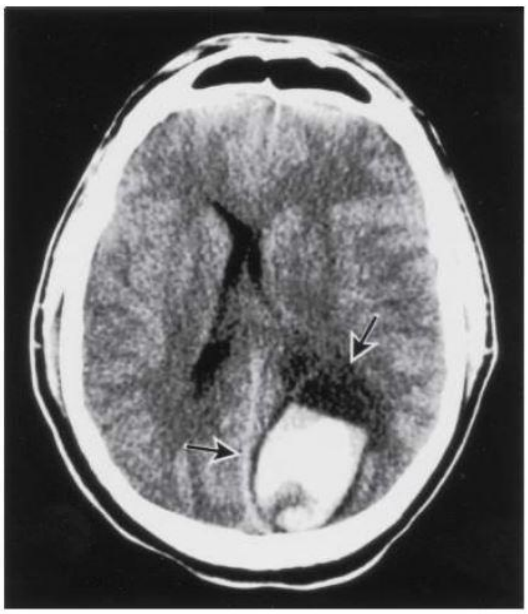
HEMATURIA

Haematuria is frequently seen in severe haemophiliacs. Bleeding can occur from anywhere along the genitourinary tract from the renal pelvis till the bladder. Patients can experience colicky pain if clots obstruct the ureter.
Bleedings tends to last from days to weeks depending on the severity of the bleed.

NEUROLOGICAL COMPLICATIONS[6]

Intracranial bleed is the most severe of all complications. The bleed can occur spontaneously but most commonly occurs after a trivial trauma. Symptoms might occur soon after the bleed or it might be delayed. Suspicion of an ICH should arise when a haemophilia patient complains of severe headache. Treatment should be started immediately when there is a suspicion of intracranial bleed without waiting for imaging studies.

Bleeding into the spinal cord is very rare and can result in paraplegia[31]. Epidural bleeding compressing the cord is more common. Muscle hematomas in the periphery can result in peripheral nerve compression. Femoral nerve compression by iliopsoas bleed is most common and can result in sensory loss over the anterior and lateral thigh, weakness and atrophy of the quadriceps. Ulnar nerve is the next most commonly involved peripheral nerve.



Source: Lichtman MA, Beutler E, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT: *Williams Hematology*, 7th Edition: http://www.accessmedicine.com

MUCOUS MEMBRANE BLEEDS

Mucous membrane bleeds in the form of epistaxis and haemoptysis is common in haemophiliacs. Peptic ulcer disease is more common in Haemophilia A when compared to the general population. Occult blood loss in urine or stools might contribute to the iron deficiency seen in these patients and was recorded so in a study conducted in the university of Florida.

POST SURGICAL BLEED

Severe haemophilic patients need to be treated with factor preoperatively and post operatively. Mild or moderately affected patients are at times diagnosed only after bleeding occurs from the surgical site. Wound healing is poor in such patients. Appropriate Factor VIII replacement can prevent intra operative and postoperative bleeding.

Dental extraction is the most common surgical procedure done on haemophilia patients. Loss of permanent teeth causes more bleeding than loss of deciduous teeth.

COMPLICATIONS IN HAEMOPHILIA

There are three major complications that can occur in haemophiliacs,

- Joint destruction and abnormalities due to hemarthroses
- Blood borne infection transmission
- Development of Inhibitor antibodies

HEMOPHLIC ARTHROPATHY[1]

There are several factors that contribute to the development of arthropathy. The most important among them would be the deposition of iron in the synovium and the development of synovial fibrosis that leads to contracture formation. The patient has extreme pain and limitation of the range of movement.

Primary prophylactic treatment with factor VIII or IX dramatically reduced the incidence of arthropathy and increased the quality of life. A randomized control trial comparing three times per week prophylactic dosing against the on-demand dosing showed that prophylactic dosing was superior to on-demand dosing schedule.

The relative risk of MRI detected joint damage with episodic therapy as compared with prophylaxis was 6.1 (95% CI 1.5-24)[34]. Orthopaedic complications still remain a major issue as on-demand treatment is still the treatment method followed in India.

The completed Joint Outcome Study in the United States has demonstrated that prophylaxis with Factor VIII at 25-35 units per kilogram body weight every other day is superior to intensive on-demand (e.g., 40 units/kg initially, then 25 units/kg at 24 and 72 hours) factor replacement therapy in preventing joint disease in previously pristine joints at age six years. The 80 per cent lower incidence of pristine joints in the on-demand arm was confirmed by validated physical exam and radiographic scoring as well as by

follow-up magnetic resonance imaging of ankles, knees, and elbows in the 66 children randomly assigned between the two arms of the study.

INFECTION

The incidence of infection has dramatically reduced with the advent of recombinant products and use of intensive donor screening and virucidal techniques. Patients treated with older factor VIII or IX concentrates are at higher risk of developing Hepatitis B, C and D or HIV infection. Co-infection with HCV and HIV has a bad prognosis as far as the liver derangement is concerned. These people tend to respond poorly to treatment. Since the mid 1980s, no HIV infection has been reported with the use of anti-haemophilic factor with advanced virucidal techniques.

Other rare infections that can be transmitted through the use of anti-haemophilic factors are parvo B19, Creutz feldt Jacob disease and the new variant of CJD. CJD and nvCJD are transmissible spongiform encephalopathies.

DEVELOPMENT OF INHIBITORS

The most important complication of Haemophilia is the development of inhibitors to factor VIII or IX.

HAEMOPHILIA A AND INHIBITORS

The development of inhibitors is more common with Haemophilia A than B. The severe Haemophilia A phenotype is most commonly due to a null mutation. A null mutation refers to the complete absence of the protein thereby predisposing to the development of inhibitors. In severe disease 30%, moderate disease 3% and in mild disease 0.3% tend to develop inhibitors[32].

Genetic and environmental factors play a role. The presence of a first degree relative with Inhibitors increases the risk of inhibitor development three fold in the patient.

Established Risk Factors	Possible [a]
Type (hemophilia A > hemophilia B)	Age at first exposure
Severity (severe > mild/moderate)	Type of factor concentrate (plasma-derived vs recombinant factor VIII)
Underlying mutation (e.g., intron 22)	Method of infusion (continuous vs bolus)
Race (African/Latino > Caucasian)	Prophylaxis vs on-demand
Family history	

Mutations that play an important role in inhibitor formation include, inversion of intron 22, large deletions affecting more than one domain and nonsense mutations involving the light chain.

Inhibitor development is seen more in patients exposed to continuous factor infusions as seen during surgeries[1].

Normally when factor VIII is secreted, it is non-covalently bound to vWF via the light chain. Upon thrombin activation, factor VIIIa dissociates from VWF and via the C2 domain, which is no longer bound by VWF, binds to phosphatidylserine on the platelet membrane. Inhibitors interrupt this process through a number of different mechanisms.

With the development of inhibitors, the frequency of bleed does not increase but the patient tends to respond poorly to treatment and develop damaged joints that bleed more frequently.

Any Haemophilia patient who fails to respond to treatment should be evaluated promptly for the development of inhibitors.

The diagnosis is made by using the Bethesda assay. It was developed in 1975 and it depends on the ability of the patient's plasma to inactivate factor VIII in the normal plasma. The result is expressed in Bethesda units[28].

HAEMOPHILIA B AND INHIBITORS

The incidence of inhibitors in Haemophilia B is less than that in Haemophilia A[1]. The other differences include the possibility of anaphylactic reaction on infusing factor IX concentrates, lesser response to immune tolerance therapy and increased incidence of nephrosis with immune tolerance therapy.

Similar to Haemophilia A, inhibitors should be suspected when treatment failure happens. Treatment is similar to that of Haemophilia A with inhibitors[26].

DIAGNOSIS AND DETECTION OF CARRIERS

Diagnosis begins with review of family history especially on the maternal side. The mother can be identified as a carrier when a family history of bleeding is present. One third of patients have a negative family history. Hence, the lack of family history does not rule out haemophilia.

REASONS FOR NO FAMILY HISTORY

- The patient might have spontaneous mutations involving factor VIII gene. 25 to 33 % of cases have spontaneous mutations.
- Neonatal deaths or the passage of the trait through successive female carriers might give a negative family history.

Symptomatic haemophilia is well documented in female. The possible reasons include,

- Unequal and early inactivation of the X chromosome
- Mating between an affected male and a carrier female produces homozygous disease in one half of the female offspring.
- An abnormal karyotype as in Turner's syndrome

SCREENING TESTS

Three initial tests should be performed in patients presenting with unknown bleeding disorder.

1. Platelet count
2. Prothrombin time
3. Activated partial thromboplastin time

PROLONGED PT AND OR aPTT

A normal PT, Platelet count and a prolonged aPTT are characteristic of Haemophilia A and Haemophilia B. The test is abnormal in those with factor levels less than 30%. In mild diseases the aPTT may be normal. So, in case of a mild undiagnosed bleeding disorder with normal lab values factor assays should be done.

Other disorders that prolong the aPTT but not the PT include acquired inhibitors to factor VIII and IX. A similar pattern is also seen in patients with antiphospholipid antibodies but they tend to thrombose rather than bleed.

In the absence of inhibitor which does not occur in patients not treated with the factor, the elevated aPTT should be correctable with normal plasma.

SPECIFIC ASSAYS

Specific assays for factor deficiency that result in isolated prolonged aPTT are done in the order of statistical significance – VIII, IX and XI.

There are two methods to perform the assay for factor VIII – one stage method and two stage method.

The one stage method is preferred as it easier and cheaper. But there are chances of false negatives if only the one stage method was used for diagnosis. Chromogenic substrate assay is another method for identifying factor VIII levels. The above test depends on the Factor VIII mediated activation of factor X.

Other methods that have developed include, immunoradiometric methods and enzyme linked immunoabsorbent assay.

DISTINCTION FROM VON WILLEBRAND DISEASE

Ristocetin cofactor assay is the most sensitive test to identify Von Willebrand disease. It is difficult to perform. Von Willebrand is an acute phase reactant and its level increases in times of stress like pregnancy, fever and hormone replacement. In type 2N Von Willebrand disease, there is a defect in the binding site for factor VIII and bleeding results from the low levels of factor VIII. Type 2N Von Willebrand is a diagnostic difficulty. It is one differential diagnosis of mild Haemophilia. Type 2N Von Willebrand disease should be suspected in any female with a low level of Factor VIII.

DIFFERENTIAL DIAGNOSIS

- Von Willebrand disease
- Platelet disorders – eg. Glanzman thrombasthenia
- Clotting factor deficiency – V,VII,X or XI
- Acquired haemophilia

Haemophilia is diagnosed with the presence of a positive family history, prolonged bleeding, hemarthroses and spontaneous soft tissue bleeds. The last two features differentiate it from von Willebrand disease in which hemarthroses and soft tissue bleeds are generally rare except in case of severe type 3 disease.

The main differentiating factors are a prolonged bleeding time, reduced von Willebrand antigen assay and abnormal ristocetin induced platelet aggregation. vWd – Normandy variant is difficult to distinguish from Haemophilia A. In the Normandy variant, vWd levels are normal but factor VIII levels are low. Factor VIII is produced normally but there is a failure in the incorporation of factor VIII into the von Willebrand factor.

Differentiating Haemophilia A and B is impossible from history and physical examination. Factor assay is a must. Similarly, factor assays are needed to differentiate between Haemophilia and deficiency of other clotting factors.

Acquired Haemophilia is seen in autoimmune syndromes, in which inhibitors to Factor VIII develop spontaneously.

TREATMENT

Treatment of Haemophilia includes

- Preventive measures
- Treatment with factor replacement either as on-demand or prophylaxis
- Treatment of complications

PREVENTIVE CARE

Circumcision

Approximately 40% of undiagnosed haemophiliacs bleed in association with circumcision[1]. For this reason, male babies born to female carriers should be deferred from the procedure. Whether circumcision can be carried on in this group is still a controversy. Fibrin glue can be used. It reduces the bleeding and the high cost involved in the treatment of haemophilia.

Immunisation

The routine immunizations given intramuscularly in normal people can be used. Pressure and ice packs must be applied for three to five minutes at the injection site in haemophiliacs. Intramuscular injections are contraindicated in Haemophilia. Hepatitis B vaccine should be given to all infants affected with Haemophilia. Inactivated polio vaccine should also be given.

Dental Care

Proper dental care should be advocated. The patients should be taught about the importance of routine cleaning and maintenance of oral hygiene. Early and proper toothbrush training should be given to the children.

Counselling and Education

Genetic and Psychosocial counselling should be given to the patient as well as the family members. About 30% of the cases have no family history and in that case proper education about the disease and its complications is very important. Normal socialization and development should be encouraged.

Exercise and Athletic participation

A regular exercise regimen should be introduced into the life of haemophiliacs. Most of the Haemophilia patients, for fear of bleed, tend to become sedentary and end up with obesity which further increases the risk of bleeds in the weight bearing joints. With the advent of prophylaxis all over the world, The World federation for Haemophilia advocates regular exercise regimen. Proper communication between the parent, patient and staff is very important.

REPLACEMENT THERAPY

The cornerstone to the management of Haemophilia is the factor transfusion. The dosing is standard but the length of the treatment; choice of product depends on individual decision.

Guidelines for replacement have been established but the minimum factor level required for haemostasis has not been established. For minor bleeds it's enough if the factor level is raised to 25 to 30% of normal. In case of major bleeds the factor levels should be raised to 50% of normal and in life threatening bleeds and surgery the factor levels should be maintained at 100%. Each unit of Factor VIII per kg of body weight tends to increase the factor level by 2%. Therefore, 1750 units of factor VIII will raise the factor level by 50% of normal. The decrease in factor level post transfusion depends on the pharmacokinetics of the factor.

Half-life of factor VIII is 8 to 12 hours. Half of the initial dose is repeated every eight hours to maintain the desired factor level[40][1].

Factor VIII can be derived from the plasma or can be recombinant – derived from cell lines genetically engineered to express large amounts of factor VIII. Solvent treated fresh frozen plasma can be given in the absence of factor.

1st GENERATION RECOMBINANT FACTOR VIII

These recombinant factors are derived from the cell cultures of transfected hamster derived cell lines and need no further purification. The human albumin, added for stabilization purposes, contributes to the risk of viral contamination.

2nd GENERATION RECOMBINANT FACTOR VIII

This recombinant factor does not contain albumin. Instead, sucrose is added for stabilization.

3rd GENERATION RECOMBINANT FACTOR VIII

These have no added albumin or added protein at the end of preparation.

LONGER HALF LIFE PREPARATIONS

Factor VIII with longer half-life is desirable as it would decrease the frequency of dosing intervals in Haemophilia patients.

- The two strategies under study for prolonging the half-life of factor VIII are – fusion with the Fc portion of immunoglobulin.
- Reconstitution with pegylated liposomes

INVESTIGATIONAL STRATEGIES

A potentially exciting advance is to develop a product that would bind both Factor X and IXa, thereby bringing the two substrates together and bypassing the cofactor function of Factor VIII. This interesting idea is still under study.

The choice of product depends on the purity, safety and cost. Purity and viral safety are utmost important to both, the treating physician and the patient. Ultrapure products are preferred in HIV coinfected Haemophiliacs as they stabilize the CD4 counts.

FACTOR IX PRODUCTS

In the 1970s and 80s, Prothrombin complex concentrate was used. It was produced by the co-purification of Vitamin K dependant cofactors. This co-purification resulted in the activation of Factor VII to VIIa resulting in an increase in thrombotic complications. PCCs are no longer preferred because of the increased thrombosis risk. Instead, purified human derived or recombinant factors are used.

PURIFIED FACTOR IX

Chromatographic partitioning and monoclonal antibody affinity purification are the techniques used to purify Factor IX. They are further subjected to viral inactivation processes.

RECOMBINANT FACTOR IX

It is genetically engineered by inserting the gene for factor IX into a Chinese hamster ovary cell line. It has no added albumin and is safe in the treatment of patients with previously treated and untreated Haemophilia B. Half-life of recombinant factor is about 16 to 17 hours.

LONGER ACTING PRODUCTS

Factor with longer half-life are preferred as it would reduce the dosing intervals. As with Factor VIII, binding of factor IX to Fc portion of immunoglobulin increases the half-life about 3 to 5 fold. There are other studies investigating the use of Factor IX fused to Pegylated liposomes or albumin.

DOSING

Early treatment of bleeding episodes with appropriate dose of factor will reduce the duration of bleed and prevent further complications. It also reduced the tendency to re-bleed.

Several plasma products are available for raising factor levels. The major disadvantage of plasma is that large volumes need to be infused for maintaining very low factor levels. It is very difficult to achieve haemostasis with plasma infusion. Cryoprecipitate can be used. It contains 80 units of factor in 10ml. The disadvantages are the dosing of factor VIII can only be estimated and the cryoprecipitate has to be stored in a frozen state.

In case of Haemophilia B, in older days, PCC was used. PCC contains vitamin K dependant factors including protein C and protein S. A few of the factors like VII IX and X become activated and increased incidence of thrombotic events has been reported including DIC.

Table 115–4. Doses of Factor VIII for Treatment of Hemorrhagea

Site of Hemorrhage	Desired Factor VIII Level (% of Normal)	Factor VIII Dose[b] (U/kg Body Weight)	Frequency of Dose[c] (every no. of Hours)	Duration (Days)
Hemarthroses	30–50	~25	12–24	1–2
Superficial intramuscular hematoma	30–50	~25	12–24	1–2
Gastrointestinal tract	~50	~25	12	7–10
Epistaxis	30–50	~25	12	Until resolved
Oral mucosa	30–50	~25	12	Until resolved
Hematuria	30–100	~25–50	12	Until resolved
Central nervous system	50–100	50	12	At least 7–10 days
Retropharyngeal	50–100	50	12	At least 7–10 days
Retroperitoneal	50–100	50	12	At least 7–10 days

To achieve 100% factor level, that is, 1u/ml, 3500 units of factor VIII is required. However, the site and the severity of bleed determines the dosing in a particular patient. Factor VIII can be given as infusion. After a loading dose, about 150 to 200 units per hour can be given as infusion. Factor levels can be monitored regularly using venous sampling[40].

The dose calculation for factor IX is different from that of Factor VIII as the intravascular recovery of factor IX is only 50%. This is probably due to the binding of Factor IX to collagen type IV in the vessel wall. The dose of factor IX can be estimated by assuming that 1 U of factor IX per kilogram body weight increases circulating factor IX by 1 per cent of normal or 0.01 U/ml. Thus, to achieve 100 percentage of normal (using only highly purified factor IX products) in a severely affected patient, 100 U of factor IX per kilogram body weight should be given as a bolus, followed by half this amount every 12 to 18 hours.

Prophylactic therapy can be attempted in Haemophilia B and the dosing is 20 to 40 units/kg twice a week[39].

HAEMOPHILIA A AND INHIBITORS

The most important complication of Haemophilia is the development of inhibitors against factor VIII.

Risk Factors

1. Disease severity

2. Exposure to factor concentrates

3. Method of purification of Factor VIII concentrates

4. Genetic factors

The inhibitors against factor VIII are antibodies that belong to the IgG4 subclass. Most commonly these antibodies are directed against the A2 and C domain of Factor VIII. Early diagnosis of factor VIII inhibitors is important.
The diagnosis is most often made when a patient does not respond to Factor VIII infusions. The inhibitors are detected using a common assay called the Bethesda assay. A mild modification of this is the Nijmegen assay.

HIGH RESPONDERS

High responders are defined as patients whose inhibitor titre is higher than 10 Bethesda units (BU) at baseline or whose initial inhibitor titre is less than 10 BU but rises to greater than 10 BU after administration of factor VIII[32].
Major bleeding episodes in high responders with initial inhibitor levels
<10BU can be treated with high doses of either human factor VIII or porcine Factor VIII. This high will overcome the inhibitors. Though factor eight bypass activity can be used, it is not as reliable as factor VIII and the effects cannot be monitored by a reliable blood investigation.

In major bleeds factor VIII is given in a dose of 10,000 to 15,000 units stat followed by 1000 units per hour infusion with frequent monitoring of factor VIII levels[32][35].

In high responders with inhibitor less than 10BU, who experience minor bleeds, the preferred treatment would be factor eight inhibitor bypass activity or Recombinant factor VIIa. The dose of Recombinant factor VIIa is 90 to 120mcg/kg that can be repeated at two to three hour intervals[35].

Patients with inhibitors >10BU rarely respond to high levels of factor VIII. In this case the treatment of choice would be either recombinant factor VIIa or factor VIII inhibitor bypass activity for both minor and major bleeds.

LOW RESPONDERS

Low-responder patients are arbitrarily defined as patients whose inhibitor titre is less than 10 BU even after challenge with factor VIII. For major bleeds high dose of factor VIII is recommended. In case of minor bleed, recombinant factor VIIa or FEIBA is preferred as most low responders become high responders when challenged with repeated doses of factor VIII[35].

IMMUNE TOLERANCE INDUCTION

The most promising approach to the eradication of inhibitors is the immune tolerance induction. This involves the daily expose of these patients to factor VIII. Both low dose and high dose regimens have been tried. Bleeds that happen during the immune tolerance period are treated with factor VIII inhibitor bypass activity[1][32].

Other immunosuppressive drugs, including cyclosporine and rituximab have been tried to eradicate the factor VIII inhibitors. However, these seem more promising in cases of acquired antibodies, in which case the antibodies are autoantibodies rather than alloantibodies as seen in Haemophilia patients.

IMMUNE TOLERANCE PROTOCOL	DOSE	RESPONSE
High dose regimen	100 U/kg factor VIII two times per day until antibody reaches 1 BU/ml, then 150 U/kg factor VIII per day until factor VIII half-life is normal	In 16 of 21 patients, titre fell to <1 BU/ml
Low dose regimen	50U FVIII/kg/day	9 out of 12 responded
Netherlands protocol	25U FVIII/kg/day	11 out of 18 responded

OTHER TREATMENT OPTIONS IN HEMOPIHLIA A

DESMOPRESSIN

Desmopressin is effective in mild to moderate haemophilia. Severe Haemophiliacs do not respond. The dose is 0.3mcg/kg body weight and the factor level increases 30 to 60 min after infusion. A concentrated nasal spray can be used at a dose of 150mcg in each nostril[26]. Tachyphylaxis can happen with repeated administration of desmopressin.

ANTIFIBRINOLYTIC THERAPY

Anti-fibrinolytics like epsilon aminocaproic acid and tranexamic acid can be used as adjuvant in cases of mucosal bleeds. They are contraindicated in the presence of haematuria. The dose of EACA is 4 to 5gms stat followed by 1gm/hr. Tranexamic acid can be given as 1g every fourth hourly [26][1].

FIBRIN GLUE

Fibrin glue is also known as fibrin tissue adhesive. It contains a mixture of fibrinogen, thrombin and factor XIII and can be applied topically to the injury site. It is most commonly used as an adjunctive to dental procedures.

LIVER TRANSPLANTATION AND GENE THERAPY

Liver transplantation has been done successfully in patients with Haemophilia and has resulted in complete cure in haemophilic patients. Gene therapy is under study and so far the results have been poor with the level of factor rise being very less and the level remained elevated only for a month.

FACTOR IX AND INHIBITORS

When the inhibitor titre is less than 10BU, it can be overcome with high doses of factor IX. In case of acute bleeds in patients with inhibitor levels 5 to10 BU/ml should be treated with same factors used to bypass the activity of factor VIII inhibitor. Recombinant factor VIIa can be used in the dose of 90 to120 mcg/kg ever 2 to 3 hrs[26]. Induction of immune tolerance can be tried with daily dosing of purified factor IX.

MATERIALS

AND

METHODS

MATERIALS AND METHODS

This study was done at Government Royapettah Hospital, Chennai for a period of eight months from December 2014 to September 2015. The study was performed after procuring informed written consent from all the participants involved. Clearance was obtained from the Ethical Committee of the Government Kilpauk Medical College & Hospital Chennai.

STUDY DESIGN

The study design is a cross sectional study.

POPULATION

The study population included 58 patients who attended the Haemophilia OP at Government Royapettah Hospital and in-patients in the same hospital.

INCLUSION CRITERIA

1. Patients diagnosed as Haemophilia including
2. Factor VIII deficiency including inhibitors
3. Factor IX deficiency
4. Von Willebrand disease

EXCLUSION CRITERIA

1. New born babies with haemophilia
2. Patients with acute bleed
3. Bleeding disorders other than haemophilia

METHODOLOGY

All patients, diagnosed and registered in the Haemophilia clinic were taken as the study population. The sample size was set to be 58.

A detailed history regarding the onset and progression of the disease, family history, maternal carrier status, treatment history and the presence of complications were taken.

After obtaining consent joint status assessment was done using Functional Independence Scoring in Haemophiliacs (FISH) scoring system.

The observations were statistically analysed using SPSS 20.0 software and results were interpreted.

FUNCTIONAL INDEPENDENCE SCORE IN HEMOPHILIA (FISH)[2]

The Functional Independence Score in haemophilia (FISH) is a performance-based assessment tool to objectively measure an individual's functional ability. It is intended to measure what the person with disability *actually does*. It can also be used to evaluate change in functional independence over time. It is relatively safe to perform this test.

The advantage is that it can be used with persons of different linguistic abilities, as it is an objective, performance-based instrument. It includes the assessment of 8 activities: eating, grooming, dressing, chair transfer, squatting, walking, step climbing, and running. Each activity is graded according to the amount of assistance required to perform it.

LEVELS OF FUNCTION AND THEIR SCORES

4- The subject is able to perform the activity without any difficulty.

3- The subject is able to perform the activity without aids or assistance, but with slight discomfort.

2- The subject needs partial assistance/ aids/ modified instruments/ modified environment to perform the activity.

1- The subject is unable to perform the activity, or needs complete assistance.

EATING AND GROOMING

(A) EATING

This activity assesses the subject's ability to gather food from the plate and take it to the mouth. Important aspects observed in this activity was posture, elbow movement, cascade grasp (if using hands to eat) and the use of aids and adaptations.

Score 4

- ❖ Has no difficulty in performing the activity.

Score 3

- ❖ Has to lean over unnaturally to reach his food due to limitation of flexion of the elbow.
- ❖ Has to take several breaks in between due to pain. The subject is not to be asked if he has pain, but is to be observed to see if he has any discomfort.
- ❖ Has no difficulty in performing the activity with prosthesis, using implements commonly used in his community.

Score 2

- ❖ Uses implements that are not commonly used in his community e.g. spoon or a fork in a community where other members use their hands.
- ❖ Uses modified utensils/implements to feed himself.
- ❖ Has difficulty feeding him using prosthesis, or uses implements that are not commonly used in his community.
- ❖ Is a right-handed individual, but has to eat with his left hand due to problems with the right upper limb.

Score 1

- ❖ Is unable to feed himself.

(B) GROOMING

Grooming includes oral care, hair grooming, washing hands and face. It does not include the subject's ability to sit on the stool / floor / the surface on which the individual does the grooming.

Score 4

- ❖ The subject has no difficult in grooming.
- ❖ The child needs assistance only to apply the toothpaste on the brush.

Score 3

- ❖ Adopts abnormal postures to comb the back of his head/ shave/ wash his face.
- ❖ Experiences pain or discomfort while grooming (as assessed by the observer).
- ❖ Takes an unnaturally long time to perform the activity.

Score 2

- ❖ Is not able to comb hair in all areas of the head -the back /side of the head
- ❖ Requires any modified instrument.
- ❖ Is a right-handed individual, but uses the left hand for grooming, due to problems with the right upper limb

Score 1

- ❖ Is unable to do the activity because of problems with reach.

BATHING

This activity assesses the ability to wash, soap, and dry different parts of the body – including the perianal region, and feet. It is essential to assess the reach on both sides of the body, using both hands.

Score 4

- ❖ Has no difficulty in bathing.

Score 3

- ❖ Adopts unusual postures while bathing e.g. Places feet on a stool to apply soap.
- ❖ is in discomfort while performing the activity

Score 2

- ❖ The subject requires a shower instead of water from a bucket in a community where the other members use water from a bucket (modified environment); but if others in the community too use the shower, score 4.
- ❖ The bathtub or bathroom has to be modified (modified environment.)
- ❖ The subject sits on a stool for his bath (modified environment.)
- ❖ The subject has to use instruments to reach any part of the body (except the back).
- ❖ The subject requires occasional help to bathe and dry the feet, perineum, or any other part of the body, except the back.

Score 1

- ❖ The subject requires a bed bath, or is unable to perform most of the activity of bathing/ drying.

DRESSING

This activity assesses the ability to get dressed - wearing a shirt /T-shirt/ vest/ trouser/ dhoti /. This activity does not include ironing clothes or taking clothes from a cupboard.

Score 4

- ❖ Is able to get dressed without discomfort and without assistance.

Score 3

- ❖ experiences discomfort during the activity
- ❖ Takes momentary support from the wall/ table to steady him while donning his trousers.
- ❖ Uses adaptive manoeuvres to don the shirt due to discomfort.

Score 2

- ❖ Requires help to wear the trouser.
- ❖ Sits to put on his trousers (aid).
- ❖ Requires considerable amount of support from the wall/ table while donning trousers.
- ❖ Requires complete help in <50% of the activity, e.g. – partial assistance in donning the trouser, but no help required in putting on the shirt.

Score 1

- ❖ Requires help in >50% of the activity.

CHAIR TRANSFER

Chair with armrests of an appropriate height was placed in front of the subject. The subject was asked to oppose his palms, get up from the chair, and then sit down.

Score 4

- ❖ Has no difficulty in performing the above activity.

Score 3

- ❖ Leans excessively forward in order to get up.
- ❖ Sits with one or both knee joints slightly extended, but does not require support to get up.
- ❖ uses momentary support of the arm rest while getting up

Score 2

- ❖ Requires a lot of support from the armrest to get up.
- ❖ Requires the use of crutches to get up.

Score 1

- ❖ Is not able to get up from the chair.

SQUATTING

This assesses the ability to squat on the floor and rise to an erect posture. The subject was asked to stand by the wall ,and to oppose his palms (as in a prayer/ Namaste position).

This is a provocative test. Hence we asked the patient first, if he feels able to perform the activity. If they said it is not possible for them to squat, the test was stopped, and the subject scored appropriately.

Score 4

- ❖ Has no difficulty in performing the activity.

Score 3

- ❖ Is able to squat to a height of 8-12 inches (6-10 for children).
- ❖ Is able to squat to a height of 8 inches, with one leg in extension (6inches for children).
- ❖ Is able to squat to a height of 8-12 inches (6-10 for children) using momentary support from the side/floor

Score 2

- ❖ Is able to squat to a height of 8-12 inches (6-10 for children) with maximum support from a chair/grab-rail.

Score 1

- ❖ is not able to squat to a height of 12 inches with support from the side

WALKING PATTERN

Walking was assessed over a distance of 10 meters. There has to be a good heel to toe pattern in the gait, with steps of relatively equal length and cadence. Heel strike should be with knee in full extension. The knee should bend adequately during stance and swing phase. There should not be an obvious limp.

Score 4

- ❖ Has an apparently normal gait.

Score 3

- ❖ Has a stiff knee gait/ limp. If stance phase in a limb is reduced due to pain

Score 2

- ❖ Uses a cane/walking stick.
- ❖ Uses a knee/ankle brace

Score 1

- ❖ Is unable to walk 10 meters.

STAIR CLIMBING

The subject was placed in front of a flight of stairs side rails and asked to climb at least 14 steps, each of approximately 8 inches in height. This is a provocative test therefore subjects were not forced to perform. If they felt they are not able to do, scoring was given accordingly

Score 4

- ❖ Is able to climb up/down the stairs without a limp or aid with an alternating stepping pattern. He should be able to climb up/down the steps in less than 9 seconds .

Score 3

- ❖ Has a limp/discomfort while climbing the steps. If he uses the rails for occasional minimal support – he should be able to climb up/down the steps within 14 seconds (in either direction).
- ❖ Climbs up or down the stairs, taking one step at a time.

Score 2

- ❖ Takes more than 14 seconds to climb up/down the stairs using the aid of the rails or crutches/ assistance of a helper (in either direction).

Score 1

- ❖ Is unable to climb 14 steps.

RUNNING

Running was assessed over a distance of 25 meters for children, and 50 meters for adults. Subjects were not forced to perform this provocative test.

Score 4

- ❖ Has no difficulty/discomfort while running.

Score 3

- ❖ Has pain/discomfort while running.
- ❖ Is able to run only part of the distance.

Score 2

- ❖ is not able to run, but is able to walk briskly

Score 1

- ❖ is not able to walk briskly

STATISTICAL

REPORTS

DESCRIPTIVE STATISTICS FOR FISH SCORE

TABLE 1

FISH	MINIMUM	MAXIMUM	MEAN	STD. DEVIATION
Eating/grooming	1	4	3.88	0.462
Bathing	1	4	3.59	0.838
Dressing	1	4	3.59	0.838
Chair	1	4	3.47	1.012
Squatting	1	4	2.71	1.257
Walking	1	4	3.34	0.983
Stairs	1	4	2.97	1.108
Running	1	4	2.60	1.363
Total fish score	8	32	26.00	6.551

Lowest mean score was for squatting, running and then stair climbing

Mean FISH score was 26, lowest was 8 and maximum of 32.

AGE DISTRIBUTION

TABLE 2

PARAMETER	N	MINIMUM	MAXIMUM	MEAN	S.D
Age in years	58	4	85	28.24	16.770

From the analysis the minimum age of the study population was 4years and maximum age was 85, with a mean age of 28.24.

AGE OF DIAGNOSIS OF DISEASE

TABLE 3

MINIMUM	MAXIMUM	MEAN	S.D
0	38	5.50	8.844

Minimum age of diagnosis was at birth and the maximum age was 38 years, with a mean age of 5.5 years.

TABLE 4

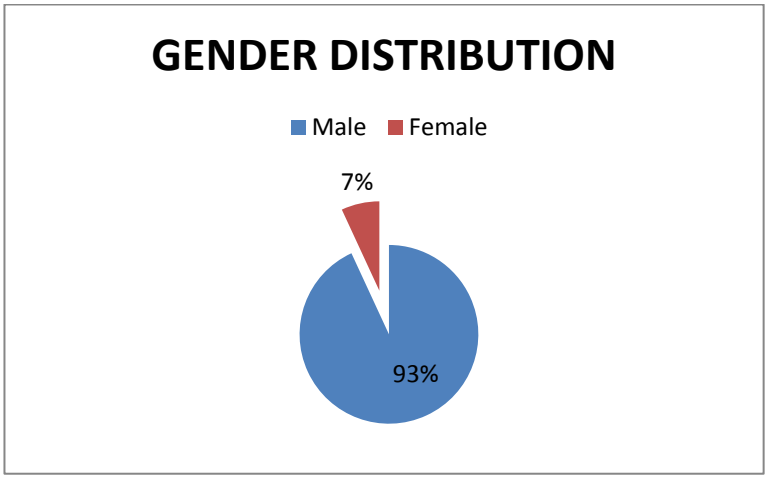
FISH	Age in years	Duration of disease(yrs)
Total fish score	-.678(**)	-.562(**)

From this table it is pointed out that, there is a significant negative correlation between age and duration of disease and FISH score, i.e., as the age and duration of disease increases, the FISH score is reduced.

GENDER

TABLE 5

SEX	FREQUENCY	PERCENT
Male	54	93.1
Female	4	6.9



Majority – 93% of the study population were males, as it is an X linked disorder. 7 % were females and these patients had Von Willebrand disease.

DISEASE (HEMOPHILIA)

TABLE 6

DISEASE (HEMOPHILIA)	FREQUENCY	PERCENT
A	44	75.9
B	10	17.2
Von Willebrand	4	6.9

75% are hemophilia A patients. 17% are hemophilia B and only 7% von willebrand disease.

TABLE 7

FISH	DISEASE	N	MEAN	S.D	P VALUE
Total fish score	A	44	25.95	6.390	0.183
	B	10	24.10	7.724	
	Von Willebrand	4	31.25	1.500	

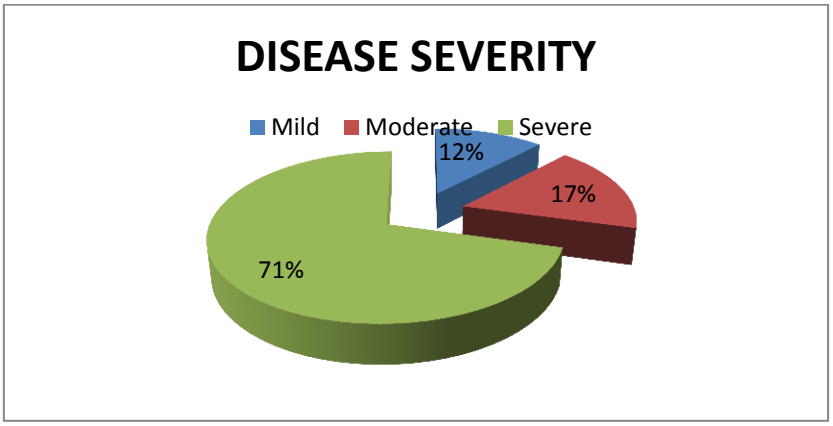
** imply Significant at 1 level (Highly Significant)
* imply Significant at 5 level (Significant)
No star imply no statistical significance

Type of disease did not significantly influence the FISH score.

SEVERITY

TABLE 8

SEVERITY	FREQUENCY	PERCENT
Mild	7	12.1
Moderate	10	17.2
Severe	41	70.7



Majority -71% of them are severe hemophiliacs. 17% belong to mild and moderate group.

TABLE 9

FISH	SEVERITY	N	MEAN	STD. DEVIATION	P VALUE
Total fish score	Mild	7	24.86	9.155	0.195
	Moderate	10	29.40	3.688	
	Severe	41	25.37	6.480	

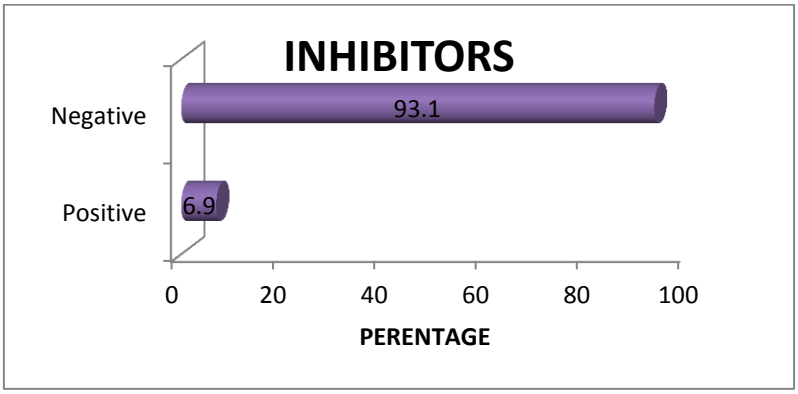
** imply Significant at 1 level (Highly Significant)
* imply Significant at 5 level (Significant)
No star imply no statistical significance

Severity of the disease did not significantly alter the FISH score.

INHIBITOR STATUS

TABLE 10

INHIBITOR	FREQUENCY	PERCENT
Positive	4	6.9
Negative	54	93.1



7% are inhibitor positive. 94% are negative for inhibitor status.

TABLE 11

FISH	INHIBITOR STATUS	N	MEAN	STD. DEVIATION	P VALUE
Total fish score	Positive	4	20.75	9.845	0.097
	Negative	54	26.39	6.199	

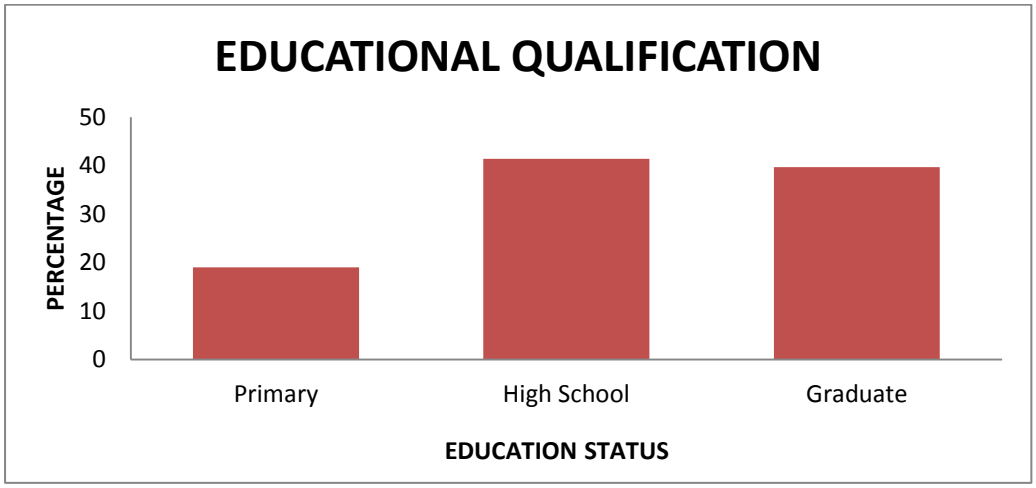
** imply Significant at 1 level (Highly Significant)
* imply Significant at 5 level (Significant)
No star imply no statistical significance

Total FISH score was not significantly affected by inhibitor status.

EDUCATIONAL QUALIFICATION

TABLE 12

EDUCATIONAL QUALIFICATION	FREQUENCY	PERCENT
Primary	11	19
High School	24	41.4
Graduate	23	39.7

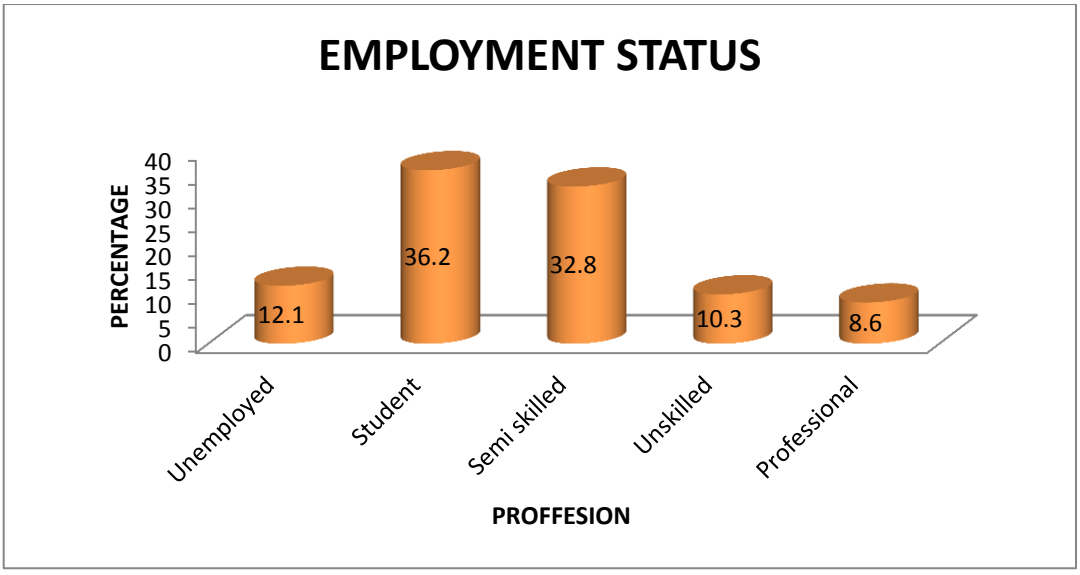


This table shows majority of the population had high school education or graduates.19% stopped with primary school.

OCCUPATION

TABLE 13

OCCUPATION	FREQUENCY	PERCENT
Unemployed	7	12.1
Student	21	36.2
Semi skilled	19	32.8
Unskilled	6	10.3
Professional	5	8.6



Most of the patients were students, followed by semi skilled workers.

12% patients were unemployed.

TABLE 14

EMPLOYMENT STATUS	N	MEAN	STD. DEVIATION	P Value
Unemployed[a]	7	18.14	7.988	<0.01**
Student[c]	21	31.76	.625	
Semi skilled[a]	19	22.11	5.065	
Unskilled[b]	6	26.50	5.505	
Professional[b]	5	27.00	2.121	

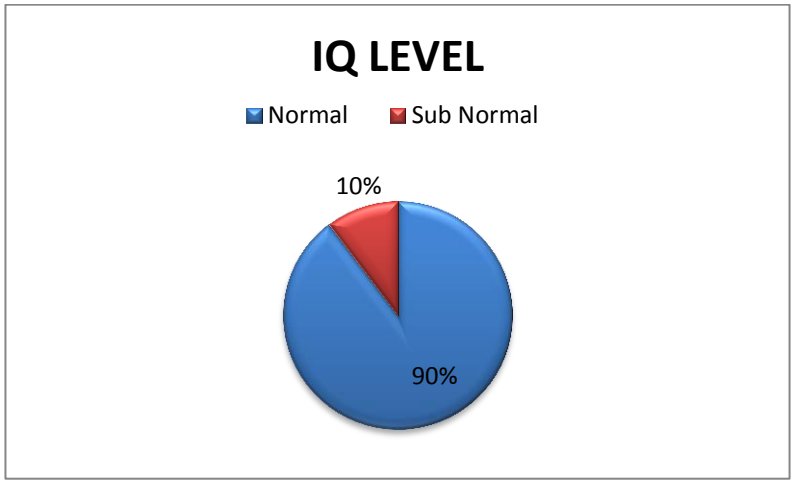
** imply Significant at 1 level (Highly Significant)
* imply Significant at 5 level (Significant)
No star imply no statistical significance

Mean FISH score was lowest in unemployed group and highest in students at level 1 significance using ANOVA and POST HOC DUNCAN TESTS.

IQ

TABLE 15

IQ	FREQUENCY	PERCENT
Normal	52	89.7
Sub Normal	6	10.3
Total	58	100



90% patients were having normal IQ and 10% were having sub normal IQ.

TABLE 16

FISH	IQ	N	MEAN	S.D	P VALUE
Total fish score	Normal	52	26.58	5.886	0.047*
	Sub Normal	6	21	10.119	

** imply Significant at 1 level (Highly Significant)
* imply Significant at 5 level (Significant)
No star imply no statistical significance

From this table, FISH scoring was significantly low (level 5) in patients with sub normal IQ.

MONTHLY INCOME(RS)

TABLE 17

MONTHLY INCOME(RS)	FREQUENCY	PERCENT
No income	28	48.3
Below 10000	15	25.9
10000-20000	10	17.2
Above 20000	5	8.6

48% patients are in the no income group. Only 9% are in the high income group.

TABLE 18

INCOME GROUP	N	MEAN	S.D	P VALUE
No income[b]	28	28.36[b]	7.109	0.018*
Below 10000[ab]	15	25.73[ab]	3.845	
10000-20000[a]	10	22.10[a]	5.685	
Above 20000[a]	5	21.40[a]	6.504	

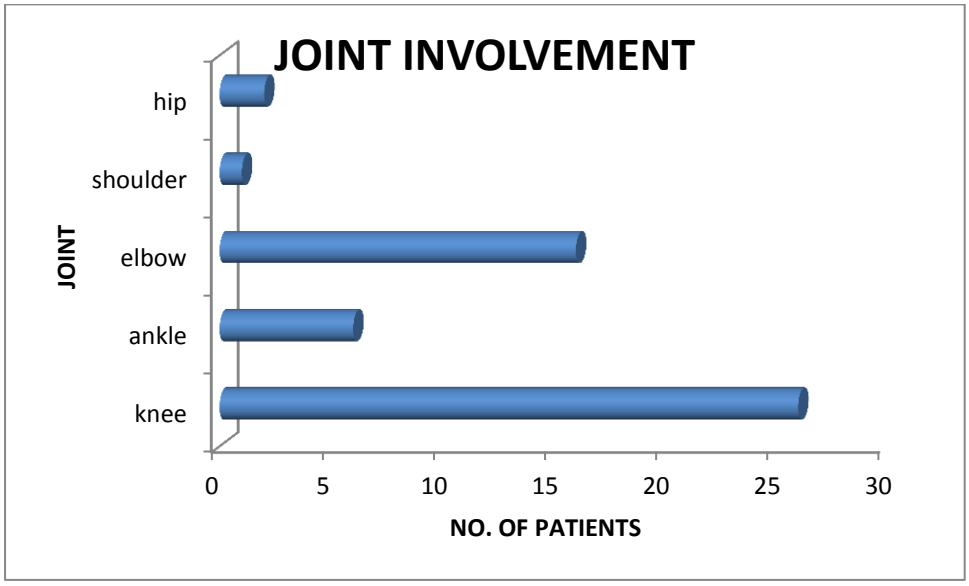
** imply Significant at 1 level (Highly Significant)
* imply Significant at 5 level (Significant)
No star imply no statistical significance

Total fish score was significantly (level 5) low in high income groups compared to others using ANOVA and POST HOC DUNCAN TESTS.

FREQUENTLY INVOLVED JOINT

TABLE 19

JOINT	FREQUENCY
knee	26
elbow	16
ankle	6
hip	2
shoulder	1

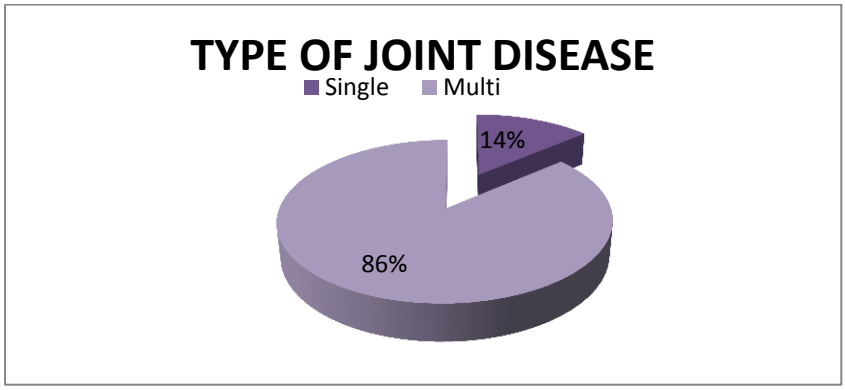


Majority of patients had knee joint involvement, followed by elbow and ankle joints.

JOINT DISEASE

TABLE 20

TYPE	FREQUENCY	PERCENT
Single	8	13.7
Multi	50	86.2



86% of patients had multi joint disease, i.e., arthropathy involving more than one joint.The arthropathy occurs due to iron deposition and fibrosis of the synovium. Repeated hemarthrosis can accelerate the arthropathy process thereby affecting the patients' quality of life.

SINGLE VS MULTI JOINT DISEASE

FISH SCORE was significantly lower (level 5) in patients with MULTI JOINT DISEASE.

FISH SCORE was significantly lower (level 5) in patients with MULTI JOINT DISEASE using TWO TAILED T TEST.

TABLE 21

JOINT DISEASE	N	MEAN	S.D	P VALUE
Single	8	30.13	3.834	0.027*
Multi	45	24.60	6.638	

** imply Significant at 1 level (Highly Significant)
* imply Significant at 5 level (Significant)
No star imply no statistical significance

AVERAGE BLEED

TABLE 22

PARAMETER	MIN	MAX	MEAN	S.D
Avg. Bleed per month	0	6	1.41	1.364
Avg. Bleed per year	0	150	15.84	21.683

Maximum bleed per month was 6 with a mean of 1.4 episodes. Mean bleed per year per patient was 16 episodes.

CO MORBIDITIES

TABLE 23

CO MORBIDITIES	FREQUENCY	PERCENT
Present	7	12.1
Absent	51	87.9

12% of hemophiliacs had co morbidities like HIV, HBSAG, diabetes or hypertension.

TABLE 24

CO MORBID	N	MEAN	S.D	P VALUE
Present	7	19.00	7.616	0.002**
Absent	51	26.96	5.845	

** imply Significant at 1 level (Highly Significant)
* imply Significant at 5 level (Significant)
No star imply no statistical significance

FISH score was significantly lower in patients with co morbidities like HIV/HBSAG assessed using TWO TAILED T TEST.

SURGERY

TABLE 25

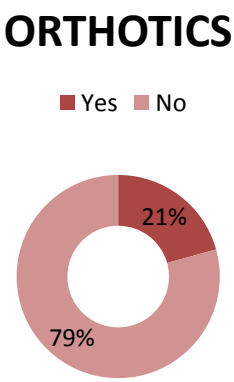
SURGERY	FREQUENCY	PERCENT
Yes	17	29.3
No	41	70.7

29% Patients had previous surgical history.

USING ORTHOTICS

TABLE 26

USING ORTHOTICS	FREQUENCY	PERCENT
Yes	12	20.7
No	46	79.3



20% of the study population are using orthotics for support and walking.

TABLE 27

FISH	Using orthotics	N	Mean	Std. Deviation	P VALUE
Total fish score	Yes	12	16.50	5.334	<0.01**
	No	46	28.48	4.130	

** imply Significant at 1 level (Highly Significant)
* imply Significant at 5 level (Significant)
No star imply no statistical significance

FISH score was significantly low in patients using orthotic support.

PROPHYLAXIS

TABLE 28

PROPHYLAXIS	FREQUENCY	PERCENT
Yes	2	3.4
No	56	96.6

Majority of our patients are not on prophylaxis treatment. Only 2 patients are using prophylactic factor administration.

TABLE 29

PROPHYLAXIS	N	MEAN	STD. DEVIATION	P VALUE
Yes	2	26.00	1.414	1.000
No	56	26.00	6.666	

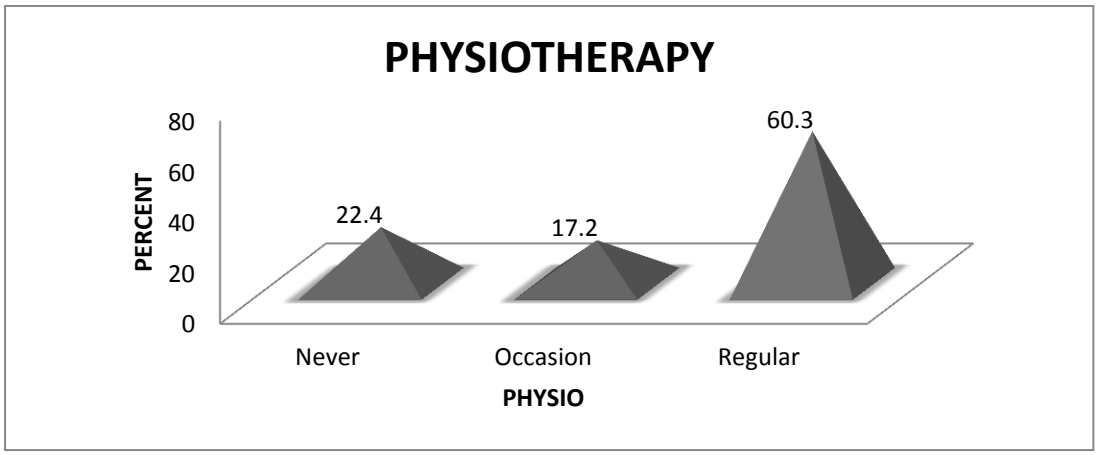
** imply Significant at 1 level (Highly Significant)
* imply Significant at 5 level (Significant)
No star imply no statistical significance

Prophylaxis use did not significantly affect fish score probably because less no. Of patients were under prophylaxis

PHYSIOTHERAPY

TABLE 30

PHYSIOTHERAPY	FREQUENCY	PERCENT
Never	13	22.4
Occasion	10	17.2
Regular	35	60.3



60% are doing regualr physiotherapy, and the remaining are occasionally doing or never done physiotherapy.

TABLE 31

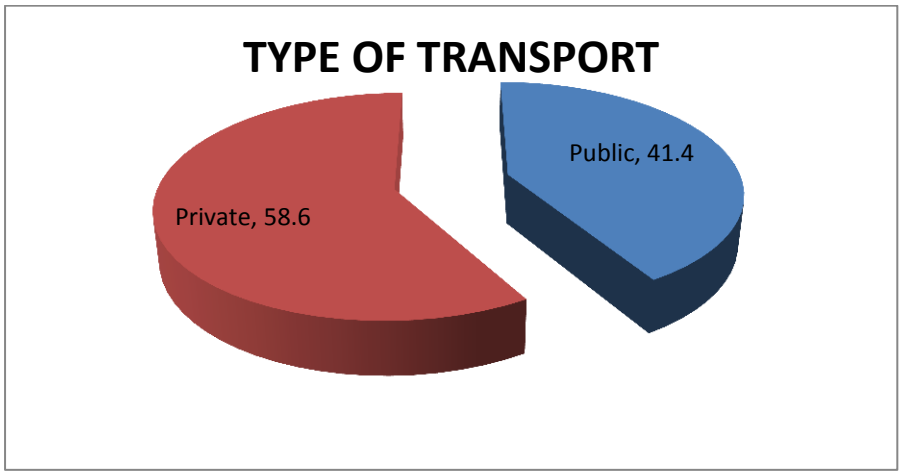
FISH	PHYSIO	N	Mean	S.D	P VALUE
Total fish score	Never	13	29.46	6.319	0.073
	Occasion	10	26.30	7.646	
	Regular	35	24.63	5.986	

Regular physiotherapy is not significantly improving FISH score.

MODE OF TRANSPORT

TABLE 32

MODE OF RANSPORT	FREQUENCY	PERCENT
Public	24	41.4
Private	34	58.6



58 % are using their own transport for medical treatment, and the remaining are using public transport like BUS and TRAIN for treatment.

TABLE 33

Mode of transport(vehicle)	N	Mean	Std. Deviation	P VALUE
Public	24	25.38	6.819	0.546
Private	34	26.44	6.421	

** imply Significant at 1 level (Highly Significant)
* imply Significant at 5 level (Significant)
No star imply no statistical significance

Mode of transportation for treatment did not significantly affect FISH scoring

DISTANCE TRAVELLED FOR TREATMENT

TABLE 34

MINIMUM	MAXIMUM	MEAN	S.D
1	300	33.50	63.710

Minimum distance travelled for treatment is 1km and a maximum was 300km, with a mean distance of 33.50 km.

TABLE 35

FISH	DISTANCE	N	Mean	S.D	P VALUE
Total fish score	Below 10	20	24.30	7.706	0.358
	11-20	24	27.04	5.737	
	Above 20	14	26.64	6.021	

** imply Significant at 1 level (Highly Significant)
* imply Significant at 5 level (Significant)
No star imply no statistical significance

Distance travelled did not significantly influence FISH score

COST OF TREATMENT

TABLE 36

COST	FREQUENCY	PERCENT
Free	47	81
Subsidised	10	17.2
Paid	1	1.7

TABLE 37

COST	N	Mean	S.D	P VALUE
Free	47	26.40	6.024	0.122
Subsidised	10	25.40	8.140	
Paid	1	13.00	.	

** imply Significant at 1 level (Highly Significant)
* imply Significant at 5 level (Significant)
No star imply no statistical significance

Type of treatment did not significantly influence FISH scoring

DISCUSSION

Analysis of FISH score shows that lowest scores are for squatting , followed by running and stair climbing. Mean FISH score was 26, the results are comparable to a Mexican study done by Alberto Tlacuilo et al[45], where the mean FISH of Mexican haemophiliacs was 25.8. Since squatting was most difficult to perform, we should give early toilet training to haemophilia children and advice them to use western style lavatories to avoid stress on knee joint.

Demographic and clinical characteristics of our study population are, Oldest patient was 85 years and the mean age of study population was 28 years, whereas a similar study conducted by A.kar et al in Kolkata haemophilia society, INDIA had a mean age of to be 19.2 years.[44].

Mean age of diagnosing haemophilia in our centre was 5.5 years, which was comparatively late than western population[47]. Age also seems to be an important factor in determining joint function, as we can see, as the age goes up, the FISH score becomes significantly lower.

Tables 5 and 6 shows that 93% were males , this group majority were hemohilia A and 7 % were females. All females had von willebrand disease. But the type of disease did not significantly influence joint function.

70% of our patients are having severe disease i.e., factor levels <1%, but the severity of their disease did not affect the joint function, probably because arthropathy is a chronic problem due to repeated joint trauma, rather than the

factor levels in the serum.7% were inhibitor positive but it did not significantly affect the FISH score.

All our patients had basic primary education, and none of them were uneducated. But 19% patients stopped with primary school and 40% with high school, whereas 40% were graduates.

Tables 13 and 14 shows that majority of our study population were students or employed as per their educational standards, only 12% were unemployed.

Table 17 shows that 48% population were in the no income group , probably because most of our patients were students , hence they did not have stable income source, comparable to a similar study in Kolkata[44].

Our study had 10% patients with sub normal I Q levels, and they were significantly having low FISH score, which shows that I Q is an important determinant of joint health.

Most commonly involved joint in our study was knee joint followed by elbow and ankle joints similar to Buzzard et al[48], because these joints lack edequate muscle cover and are not able to withstand rotatory and angular stress. We also found that 86% of our patients had multi joint disease i.e., arthropathy of more than one joint and it significantly lowered their FISH score.

Mean bleeding episodes is 16 episodes per year. We expected that as the bleeding episodes increase FISH score to come down but in our study the result was not significant.

7 patients had associated HIV or HBSAG infection and these patients had significantly lower Functional status compared to the rest of the population.

20 % of the population are using orthotic support and their FISH score was significantly low compared to others.

Only 2 of patients were on prophylaxis treatment compared to the western population where majority of severe haemophiliacs take prophylaxis [47], these western studies have shown that prophylactic treatment prevents hemophilic arthropathy

48% of patients were on regular physiotherapy but that did no significantly improve their FISH score, this result was similar to A.Kar et al[44], which may be because the patients were doing exercise to reduce the effect of impairment rather than for strengthening their joints. More studies are required to probe into what type of exercise the patients are actually doing.

Our patients travelled upto maximum 300km for treatment and mean was 33km and most used their own vehicle for coming to hospital. Their travel was not significantly affecting the FISH score. In the study conducted by A.Kar et al in Kolkata[44] where they compared cost of treatment with disability was also

significant. Opening of more treatment centres and starting home based self-administration of factors would help patients to avoid long travel for treatment.

Table 36 shows that more than 80% of the haemophilia patients are taking free treatment from the state, which is a good indicator how health care has improved in the state of Tamil Nadu.

CONCLUSION

- In this study we have documented the widespread prevalence of haemophilic arthropathy, which is a preventable disability.
- The study explored the risk factors for disability with the objective of identifying some modifiable risk factors that could be used in future.
- Traditionally joint status is measure using radiological and clinical scores measuring range of movement of individual joints, but these scores involves exposure to radiation, cumbersome use of goniometer yet do not adequately assess the functional ability of patients. Hence we have used FISH scoring system, which is a reliable, inexpensive and easily administered even by paramedical workers and takes only 12 minutes per patient.
- Patients can also be followed up to see if their functional status comes down over a period of time.
- Squatting was the most affected movement in our patients.
- Most of the patients travelled a long distance for treatment, therefore opening of more treatment centres and home therapy may be sought for.
- Majority of our patients are taking on demand treatment. Global studies have shown that prophylactic treatment has reduced the incidence of chronic arthropathy. More Indian studies are needed in this aspect to see the impact on Indian population.

LIMITATIONS OF THE STUDY

The test used some provocative movements which could not be done by some patients. Only the functional limitations of our patients were assessed but this could not identify early arthropathy changes, where functions are not limited. Larger multicentre trials with more number of subjects are required. The functional assessment should be coupled with radiological and goniometric measurement for better joint status assessment.

BIBLIOGRAPHY

1. Hoffman text book of haematology
2. Poonnoose PM, Thomas R, Bhattacharjee S, Shyamkumar NK, Manigandan C, Srivastava A. Functional Independence Score in Haemophilia (FISH): A new performance based instrument to measure disability. *Haemophilia* 2005; 11:598-602.
3. Morawitz P: Die Chemie der Blutgerinnung. *Ergeb Physiol* 4:307, 1905
4. Pavlovsky A: Contribution to the pathogenesis of hemophilia. *Blood* 2:185, 1947
5. Brinkhous KM: A study of the clotting defect in hemophilia. The delayed formation of thrombin. *Am J Med Sci* 198:509, 1939
6. Williams text book of haematology
7. Epidemiology and social costs of haemophilia in India review article J MED RES July 2014
8. Clinical features and manifestations of Haemophilia A – up-to-date
9. A ten years cohort study. J Assoc Physicians India 2005; 53 :1021- Mohanty D, Colah RB, Gorakshakar AC, Patel RZ, Master 117
10. DC, Mahanta J, et al. Prevalence of β-thalassemia and other haemoglobinopathies in six cities in India: a multicentre study. J Community Genet 2013; 4 : 33-42. Chatterjee N, Mishra A, Soni R, Kulkarni H, Mamtani M,Shrivasatava M. Bayesian estimates of the prevalence of β-thalassemia trait in voluntary blood donors of central India: a survey. Hemoglobin 2010;34 : 548-60.Christianson A, Modell
11. Medical genetics in developing countries. Annu Rev Genomics Hum Genet 2004; 5 : 219-65.Genome-based Research and Population Health.
12. Report of an expert workshop held at the Rockefeller Foundation Study and Conference Centre; 2005 April 14-20; Bellagio, Italy. Available from: http://www.phgfoundation.org/file/2205, accessed on November 22, 2012.
13. UNICEFIndiastatistics.http://www.unicef.org/infobycountry/india_statistics.html, accessed on October 15, 2012.
14. Census of India 2011, Office of the Registrar General and Census Commissioner, India, Controller of Publications, New Delhi. Available

from: http://www.censusindia.gov.in/2011-provresults/ prov_results_paper1_india.html, accessed on October 12, 2012.
15. http://www.censusindia.gov.in/2011-Common/srs.html,accessed on October 12, 2012.
16. Rural Health Mission PIP: 2012-13 Mission Flexipool. Government of Maharashtra. Available from: http://www.nrhm.maharashtra.gov.in/partb.pdf, accessed on May 9, 2013.
17. Skinner MW. WFH: closing the global gap - achieving optimal care.Haemophilia 2012; (Suppl 4) : 1-12. Lee CA. Historical introduction. In: Lee C, Berntorp E, Hoots K, editors
18. Textbook of hemophilia. 2nd ed. West Sussex: Wiley-Blackwell;2010. p. 1-6. van den Berg HM, Fischer K.
19. Phenotypic - genotypic relationship. In: Lee C, Berntorp E, Hoots K, editors. Textbook of hemophilia, 2nd ed. West Sussex: Wiley-Blackwell; 2010. p. 33-7.Mannucci PM, Tuddenham EG.
20. The hemophilias - from royal genes to gene therapy. N Engl J Med 2001; 344: 1773-9. Bowen DJ.
21. Haemophilia A and haemophilia B: molecular insights. Mol Pathol 2002; 55: 127-44. Berntorp E, Shapiro AD
22. . Modern haemophilia care. Lancet 2012; 379 : 1447-56.Philipp C.
23. The aging patient with hemophilia: complications, comorbidities, and management issues. Hematology Am Soc Hematol Educ Program 2010; 2010 : 191-6. Cohen JS, Biesecker BB.
24. Quality of life in rare genetic conditions: a systematic review of the literature. Am J Med Genet A 2010;152A : 1136-56. Dharmarajan S, Phadnis S, Gund P, Kar A.
25. Out-of-pocket and catastrophic expenditure on treatment of haemophilia by Indian families. Haemophilia 2014; 20 : 382-7.Haldane JB.
26. Hay CR, Baglin TP, Collins PW, Hill FG, Keeling DM: The diagnosis and management of factor VIII and IX inhibitors: A guideline from the UK Haemophilia Centre Doctors' Organization (UKHCDO). Br J Haematol 2000; 111:78.
27. Gene deletions in patients with haemophilia B and anti-factor IX antibodies. Nature 1983; 303 : 181-2. World Federation of Haemophilia (WFH).

28. Kasper CK, Aledort L, Aronson D, et al: Proceedings: A more uniform measurement of factor VIII inhibitors. Thromb Diath Haemorrh 1975; 34:612.
29. Dharmarajan S, Phadnis S, Gund P, Kar A. Treatment decisions and usage of clotting factor concentrate by a cohort of Indian haemophilia patients. Haemophilia 2012; 18 : e27-9.Haemophilia Federation (India). Available from: http://www.hemophilia.in/, accessed on October 12, 2012.
30. Gilbert MS: Musculoskeletal complications of haemophilia: The joint. Haemophilia 6:34, 2000. [PMID: 10982265]
31. Hanley JP, Ludlam CA: Central and peripheral nervous system bleeding, in Hemophilia, edited by CD Forbes, L Aledort, R Madhok, p 87. Chapman & Hall, London, 1997.
32. Astermark J, Oldenburg J, Escobar M, White 2nd GC, Berntorp E: The Malmo International Brother Study (MIBS). Genetic defects and inhibitor development in siblings with severe hemophilia A. Haematologica 2005; 90:924..
33. Gill F: The natural history of factor VIII inhibitors in patients with hemophilia A. In: Hoyer LW, ed. Factor VIII Inhibitors: Proceedings of an International Symposium Held in Farmington, Connecticut, Berlin, Heidelberg: Springer; November 3–5, 1983:19.1984
34. Steven MM, Yogarajah S, Madhok SD, et al: Hemophilic arthritis. Q J Med 1986; 58:181
35. Astermark J: Treatment of the bleeding inhibitor patient. Semin Thromb Hemost 2003; 29:77..
36. Joint range-of-motion limitations among young males with hemophilia:prevalence and risk factors J. Michael Soucie, Christy Cianfrini et al.
37. Physical Functioning in Boys with Hemophilia in the U.S.Paul E. Monahan, MD, Judith R. et al.
38. Kreuth III: European consensus proposals for treatment of haemophilia with coagulation factor concentrates P. GIANGRANDE, R. SEITZ et al.
39. Guidelines for the management of haemophilia A. SRIVASTAVA,* A. K. BREWER et al.
40. Factors affecting the Haemophilia Joint Health Score in children with severe haemophilia M. BLADEN, E. MAIN et al.

41. Motor performance and disability in Dutch children with haemophilia: a comparison with their healthy peers M. A. G. C. SCHOENMAKERS et al.
42. Pain and functional limitations in patients with severe haemophilia F. R. VAN GENDEREN et al.
43. Long-term major joint outcomes in young adults with haemophilia: interim data from the HGDS Y. SU, W.-Y. WONG et al.
44. Disability in Indian patients with haemophilia A. KAR,* R. MIRKAZEMI et al.
45. Functional Independence Score in haemophilia: A Cross-Sectional Study Assessment of Mexican Children Alberto Tlacuilo-Parra, MD, MSc, Justo Villela-Rodriguez et al.
46. Guideline on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders.
47. Joint range-of-motion limitations among young males with haemophilia: prevalence and risk factors. Michael Soucie, Christy Cianfrini et al.
48. Buzzard BM. Physiotherapy for prevention and treatment of chronic haemophilic synovitis. Clin Orthop Relat Res 1997; 343: 42–6.

ANNEXURES

																													SELF CARE			TRANSFERS		LOCOMOTION				
S.NO	NAME	AGE	SEX	ADDRESS	EDUCATION	I.Q	OCCUPATION	MONTHL	DISEAS	SEVERITY	AGE	DURATI	INHIBITO	MORBIDIT	PES OF BLE	FREQUEN	SINGLE/	AVG. BLEED	AVG.	BLOOD	FACTO	SURGE	ORTHO	PROHP	PHYSIO	DISTAN	MODE	COST	BATIN	BATHI	DRESSI	CHAIR	SQUATT	WALKI	STAIRS	RUNNIN	TOTAL
1	vijay	31	m	chennai	high schoo	normal	semi skilled	6000	A	mild	12	20	negative	no	joint and	left ankle	single	1	6	yes	8	yes	no	no	ocassi	25	privat	subsidi	3	3	3	4	4	4	4	4	29
2	abishek	14	m	chennai	high schoo	normal	student	0	A	moderate	10	4	negative	no	joint and	right	single	1	3	no	4	yes	no	no	never	25	privat	free	4	4	4	4	3	4	4	4	31
3	yuvaraj	22	m	chennai	graduate	normal	student	0	B	severe	1	21	negative	no	joint	left hip	multi	0	1	yes	7	no	no	no	never	20	public	free	4	4	4	4	4	4	4	4	32
4	kalyanara	18	m	chennai	graduate	normal	student	0	A	mild	13	5	negative	no	joint and	right	multi	0	1	yes	5	yes	no	no	regula	40	public	subsidi	4	4	4	4	4	4	4	4	32
5	dhanasek ar	36	m	chennai	graduate	normal	professional	10000	A	severe	0	36	negative	no	joint	both knee	multi	1	12	yes	20	yes	no	no	regula r	1	privat e	free	4	4	4	4	3	4	3	2	28
6	rajesh	33	m	chennai	graduate	normal	professional	15000	B	severe	2	31	negative	no	joint and	left ankle	multi	0	5	yes	15	yes	no	no	ocassi	25	privat	free	4	4	4	4	3	4	4	3	30
7	subramani	57	m	chennai	graduate	normal	semi skilled	15000	A	severe	3	50	negative	hyperte	joint	right	multi	2	10	yes	20	no	yes	no	regula	15	privat	free	4	2	3	2	1	2	2	1	17
8	purushoth	32	m	chennai	high schoo	normal	unskilled	6000	A	severe	1	32	negative	HBSAG	joint and	right	multi	1	12	yes	10	yes	no	no	regula	20	public	free	4	4	4	4	1	4	3	2	26
9	venkatra man	16	m	chennai	high schoo	normal	student	0	A	severe	1	18	positive	no	joint	right elbow	multi	2	12	no	15	no	no	no	regula r	7	privat e	free	4	4	4	4	4	4	4	4	32
10	rakesh kumar	15	m	chennai	high schoo	normal	student	0	A	severe	2	13	negative	no	joint	left elbow	single	1	8	yes	14	no	no	no	never	5	privat e	free	4	4	4	4	4	4	4	4	32
11	baskaran	36	m	chennai	graduate	normal	semi skilled	10000	A	severe	20	16	negative	no	joint and	left	multi	1	12	yes	8	no	no	no	regula	15	privat	free	4	4	4	4	1	4	3	2	26
12	kumaran	22	m	chennai	high schoo	normal	semi skilled	0	A	severe	1	21	negative	no	joint	right ankle	multi	2	25	no	20	yes	no	no	regula r	15	privat e	free	4	4	4	4	2	4	3	1	26
13	suresh	31	m	chennai	graduate	normal	professional	15000	A	severe	1	30	negative	HIV	joint	left knee	multi	3	30	yes	20	yes	no	yes	regula r	10	privat e	free	4	4	4	4	3	4	3	1	27
14	umar	12	m	chennai	mary sch	normal	student	0	A	severe	1	12	negative	no	joint and	right	single	0	5	yes	12	no	no	no	ocassi	17	privat	free	4	4	4	4	4	4	4	4	32
15	sasikumar	18	m	chennai	graduate	normal	student	0	B	moderate	1	18	negative	no	joint and	left	single	0	5	yes	14	no	no	no	ocassi	25	public	free	4	4	4	4	4	4	4	4	32
16	nirmal	20	m	chennai	graduate	normal	student	0	A	severe	1	20	negative	no	joint and	left	multi	2	15	yes	15	no	no	no	regula	20	public	free	4	4	4	4	2	4	4	4	30
17	selvam	33	m	chennai	graduate	normal	semi skilled	10000	A	severe	0	33	negative	no	joint and	left	multi	2	25	yes	14	no	no	no	regula	5	public	free	4	4	4	4	1	4	3	1	25
18	karmegam	46	m	chennai	high schoo	normal	unemployed	0	A	severe	1	40	negative	no	joint	right	multi	0	2	yes	20	no	no	no	ocassi	15	privat	free	4	4	4	4	3	3	2	4	28
19	vignesh	18	m	chennai	graduate	normal	student	0	A	moderate	6	12	negative	no	joint and	left	single	2	22	no	6	no	no	no	regula	35	public	free	4	4	4	4	4	4	4	4	32
20	vedhesh	1	m	chennai																																	
21	siciliya	11	f	chennai	mary sch	normal	student	0	Willeb	mild	3	8	negative	no	gum bleed			0	2	yes	1	no	no	no	never	20	privat e	free	4	4	4	4	4	4	4	4	32
22	anthony	14	m	chennai	high schoo	normal	student	0	A	severe	2	12	negative	no	joint and	left	multi	6	40	yes	12	no	no	no	never	12	public	free	4	4	4	4	4	4	4	4	32
23	prithvi	1	m	chennai					A	mild			negative	no	muscle	arms		7	26																		
24	s.balaji	4	m	chennai	mary sch	normal	student	0	B	severe	1	3	negative	no	mucosal	gums		0	0	yes	3	no	no	no	never	15	privat e	free	4	4	4	4	4	4	4	4	32
25	sriram	27	m	chennai	graduate	normal	semi skilled	10000	A	severe	3	25	negative	no	joint and	right	multi	1	3	yes	25	yes	yes	no	regula	25	public	free	4	3	3	4	2	3	3	3	23
26	amaly	15	f	irunelve	high schoo	normal	student	0	Willeb	severe	1	14	negative	no	mucosal	gums		0	0	yes	14	no	no	no	never	300	public	free	4	4	4	4	4	4	4	4	32
27	senthil velan	40	m	allakuric	mary sch	sub norma	unemployed	0	B	mild	30	10	negative	no	joint	both knee	multi	3	40	yes	5	no	yes	no	never	300	public	free	4	1	1	1	1	1	1	1	11
28	s.pranav	8	m	chennai	mary sch	normal	student	0	A	moderate	1	2	negative	no	muscle	gums		0	0	yes	7	no	no	no	never	20	privat	free	4	4	4	4	4	4	4	4	32
29	srinivasan	7	m	chennai	mary sch	normal	student	0	A	mild	1	7	negative	no	joint	right elbow	multi	4	50	no	7	no	no	no	never	6	privat e	free	4	4	4	4	4	4	4	4	32
30	anirudh	12	m	chennai	mary sch	normal	student	0	A	severe	1	12	negative	no	joint	right	multi	1	5	no	12	no	no	no	regula	12	privat	subsidi	4	4	4	3	3	4	4	4	30
31	prakash	44	m	chennai	high schoo	normal	self employe	50000	A	severe	2	42	negative	diabete	joint	both	multi	1	20	yes	25	yes	yes	no	regula	10	privat	subsidi	3	1	1	1	1	1	1	1	10
32	madhan	25	m	chennai	high schoo	normal	semi skilled	12000	A	severe	7	18	negative	no	joint	right	multi	0	3	yes	15	no	no	no	regula	15	privat	subsidi	4	4	4	4	3	4	4	3	30
33	kalpana	33	f	chennai	high schoo	sub norma	unskilled	5000	Willeb	moderate	21	8	negative	no	joint	right knee	multi	0	3	yes	5	no	no	no	regula r	20	public	free	4	4	4	4	4	3	3	3	29
34	sundaresa	67	m	chennai	high schoo	normal	semi skilled	15000	B	mild	35	32	negative	no	joint	right	multi	0	3	yes	10	yes	yes	no	ocassi	20	privat	subsidi	4	2	2	1	1	1	1	1	13
35	yuvaraj	7	m	chennai	mary sch	normal	student	0	A	moderate	2	6	negative	no	joint	both knee	multi	2	20	yes	7	no	no	no	regula r	15	public	free	4	4	4	4	4	4	4	4	32
36	govindan	36	m	chennai	high schoo	sub norma	unemployed	0	A	severe	31	8	negative	no	joint	both knee	multi	1	6	yes	5	no	no	no	regula r	6	privat e	free	4	2	2	2	2	3	2	1	18
37	santhana	85	m	chennai	graduate	normal	unemployed	0	A	severe	5	80	negative	no	joint and	urethra	multi	1	10	yes	20	yes	yes	no	ocassi	6	privat	paid	4	2	2	1	1	1	1	1	13
38	srishan	9	m	chennai	mary sch	normal	student	0	A	severe	1	7	negative	no	joint and	right	multi	4	12	no	7	no	no	no	never	7	privat	subsidi	4	4	4	4	4	4	4	4	32
39	mahavir	68	m	chennai	high schoo	normal	unemployed	0	B	severe	38	30	negative	no	mucosal	urethra	single	0	2	no	10	no	yes	no	never	6	privat	subsidi	4	3	3	3	3	3	1	1	21
40	rajkumar	23	m	chennai	high schoo	normal	unskilled	10000	A	severe	2	20	negative	no	joint and	right	multi	2	14	yes	18	no	no	no	regula	15	privat	free	4	4	4	4	4	4	4	4	32
41	manoj	19	m	chennai	high schoo	sub norma	unskilled	10000	A	severe	1	18	negative	no	joint	right elbow	multi	1	6	yes	15	no	no	no	regula r	8	public	free	4	4	4	4	4	4	4	4	32

42	kishore	40	m	chennai	graduate	normal	professional	30000	B	mild	1	40	negative	no	joint	both knee	multi	1	5	yes	15	no	no	no	regular	5	private	free	4	3	3	3	3	4	2	3	25
43	nithya	18	f	chennai	graduate	normal	student	0	Willeb	moderate	1	17	negative	no	mucosal	gums		0	5	yes	0	no	no	no	never	6	private	free	4	4	4	4	4	4	4	4	32
44	wilson	29	m	chennai	graduate	normal	semi skilled	15000	A	severe	3	26	negative	no	joint	both ankle	multi	1	15	yes	4	yes	yes	no	regular	20	public	free	3	3	3	1	1	3	2	1	17
45	annavarad	33	m	chennai	graduate	normal	professional	50000	A	severe	6	33	negative	no	joint	both	multi	0	0	yes	0	no	no	no	regula	8	privat	subsidi	4	4	4	2	2	4	3	2	25
46	adwaith	5	m	chennai	mary sch	normal	student	0	A	severe	1	5	negative	no	joint and	right	single	3	20	no	0	yes	no	no	ocassi	15	privat	free	4	4	4	4	4	4	4	4	32
47	govindan	48	m	allakurichi	high scho	sub norma	unemployed	0	A	moderate	5	40	negative	no	joint and	right hip	multi	0	2	yes	10	no	no	no	regula	250	public	free	4	4	4	4	3	3	3	3	28
48	senthilku	43	m	navalur	graduate	normal	semi skilled	12000	B	severe	8	35	negative	no	joint and	both	multi	1	12	yes	15	yes	no	no	regula	100	public	free	4	4	4	2	2	3	2	2	21
49	antony	13	m	chennai	high schoo	normal	student	0	A	severe	1	12	negative	no	joint	both	multi	1	8	yes	10	yes	no	no	ocassi	8	privat	subsidi	4	4	4	4	4	4	4	4	32
50	vijayarane	38	m	chennai	graduate	normal	semi skilled	25000	A	severe	1	35	negative	no	joint and	right	multi	3	25	yes	23	no	no	yes	regula	16	privat	free	3	4	4	4	3	3	3	1	25
51	vijay	21	m	chennai	high schoo	normal	semi skilled	10000	A	severe	3	18	negative	no	joint and	left knee	multi	2	24	no	0	no	no	no	regula	150	public	free	4	4	4	4	4	4	2	2	28
52	adhikesav	33	m	chennai	graduate	normal	skilled	20000	A	severe	1	33	negative	no	joint and	left ankle	multi	5	150	yes	3	no	yes	no	regula	15	public	free	4	3	3	3	2	3	2	1	21
53	thamim	21	m	cheepu	high schoo	normal	semi skilled	15000	B	moderate	4	17	negative	HBSAG	joint and	right	multi	4	50	yes	3	no	no	no	regula	80	public	free	4	4	4	4	2	3	2	1	24
54	yuvaraj	25	m	chennai	mary sch	sub norma	unemployed	0	A	severe	1	25	positive	HBSAG	joint and	righ	multi	2	24	yes	8	no	yes	no	regula	6	public	free	1	1	1	1	1	1	1	1	8
55	jayachand	57	m	chennai	high schoo	normal	unskilled	10000	A	severe	7	50	negative	no	joint and	both	multi	1	12	yes	10	yes	no	no	regula	4	privat	free	4	4	4	3	1	2	1	1	20
56	periyasam	19	m	erambak	diploma	normal	unskilled	10000	A	severe	1	18	negative	no	joint and	right	multi	2	21	yes	6	no	no	no	regula	2	public	free	4	3	2	4	1	3	2	1	20
57	sankar	50	m	chennai	graduate	normal	skilled	25000	A	severe	5	40	negative	no	joint and	both	multi	2	24	yes	1	no	no	no	regula	10	privat	free	4	4	4	4	1	3	3	1	22
58	dharmakri	33	m	chennai	graduate	normal	skilled	20000	A	severe	1	33	positive	HBSAG	joint and	both	multi	2	24	yes	6	no	no	no	regula	16	privat	free	4	4	4	4	1	1	2	1	21
59	karthik	22	m	chennai	high schoo	normal	semi skilled	10000	A	severe	3	18	negative	no	joint and	both	multi	2	24	yes	5	no	yes	no	ocassi	17	public	free	4	4	4	4	1	3	1	1	22
60	purushoth	26	m	chennai	high schoo	normal	semi skilled	5000	A	moderate	1	25	positive	no	joint and	right	multi	2	24	yes	3	no	yes	no	regula	37	public	free	4	4	4	4	1	2	2	1	22

PROFORMA

NAME

AGE

SEX

ADDRESS

PHONE NO.

EDUCATION

GENERAL I.Q

OCCUPATION

TYPE – PROFESSIONAL

SEMI SKILLED

UNSKILLED(MANUAL WORKER)

SPECIAL SKILLS

MONTHLY INCOME

DISEASE

SEVERITY

AGE AT DIAGNOSIS

YEARS LIVED WITH DISEASE

TRANSIENT INHIBITOR

BLOOD PRODUCT ADMINISTERED – YES/NO

HOW MANY YEARS BLOOD PRODUCTS WERE TAKEN

PURIFIED FACTOR ADMINITRETED SINCE WHEN

INHIBITOR STATUS

DURATION AS INHIBITOR

CO MORBIDITIES – DIABETES

HYPERTENSION

HIV

HBSAG/HCV

TYPE OF BLEEDS EXPERIENCED – JOINT

MUSCLE

MUCOSAL

JOINTS FREQUENTLY INVOLVED

SINGLE/MULTI JOINT DISEASE

UNDERGONE ANY JOINT SURGERY – YES/NO

USING ORTHOTICS FOR SUPPORT – YES/NO

TAKING PROPHYLACTIC TREATMENT – YES/NO

AVERAGE JOINT BLEED EXPERIENCED PER MONTH

AVERAGE JOINT BLEED EXPERIENCED PER YEAR

PHYSIOTHERAPY – DOING REGULARLY

DOING OCCASIONALY

NEVER DONE

DISTANCE TRAVELLED FOR TREATMENT

MODE OF TRANSPORTATION FOR TREATMENT

TYPE OF TREATMENT – PAYING FULL COST

SUBSIDIZED TREATMENT

FREE OF COST

FUNCTIONAL INDEPENDENCE SCORE IN HEMOPHILIA (FISH)

Performance based instrument

Patient Name:	Patient Code:
	Today (dd/mm/yyyy): ___/___/___.
A.Self Care	
1. Eating and grooming	○ 1 ○ 2 ○ 3 ○ 4
2. Bathing	○ 1 ○ 2 ○ 3 ○ 4
3. Dressing	○ 1 ○ 2 ○ 3 ○ 4
B. Transfers	
4. Chair	○ 1 ○ 2 ○ 3 ○ 4
5. Squatting	○ 1 ○ 2 ○ 3 ○ 4
C. Locomotion	
6. Walking	○ 1 ○ 2 ○ 3 ○ 4
7. Stairs (12 - 14 steps)	○ 1 ○ 2 ○ 3 ○ 4
8. Running	○ 1 ○ 2 ○ 3 ○ 4
Total Score	

Scores range from 1 - 4 depending on the degree of independence (see scoring key)

Comments:

INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10

Protocol ID No.08/12/2014 Dt. 20-01-2015

CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "Functional Independence score of people with Hemophilia in Govt.Royapettah Hospital & Factors Affecting Fish"- For Project Work- submitted by Dr.K.R.Sivanesan, MD (General Medicine). PG Student, KMC, Chennai-10.

The Proposal is APPROVED.

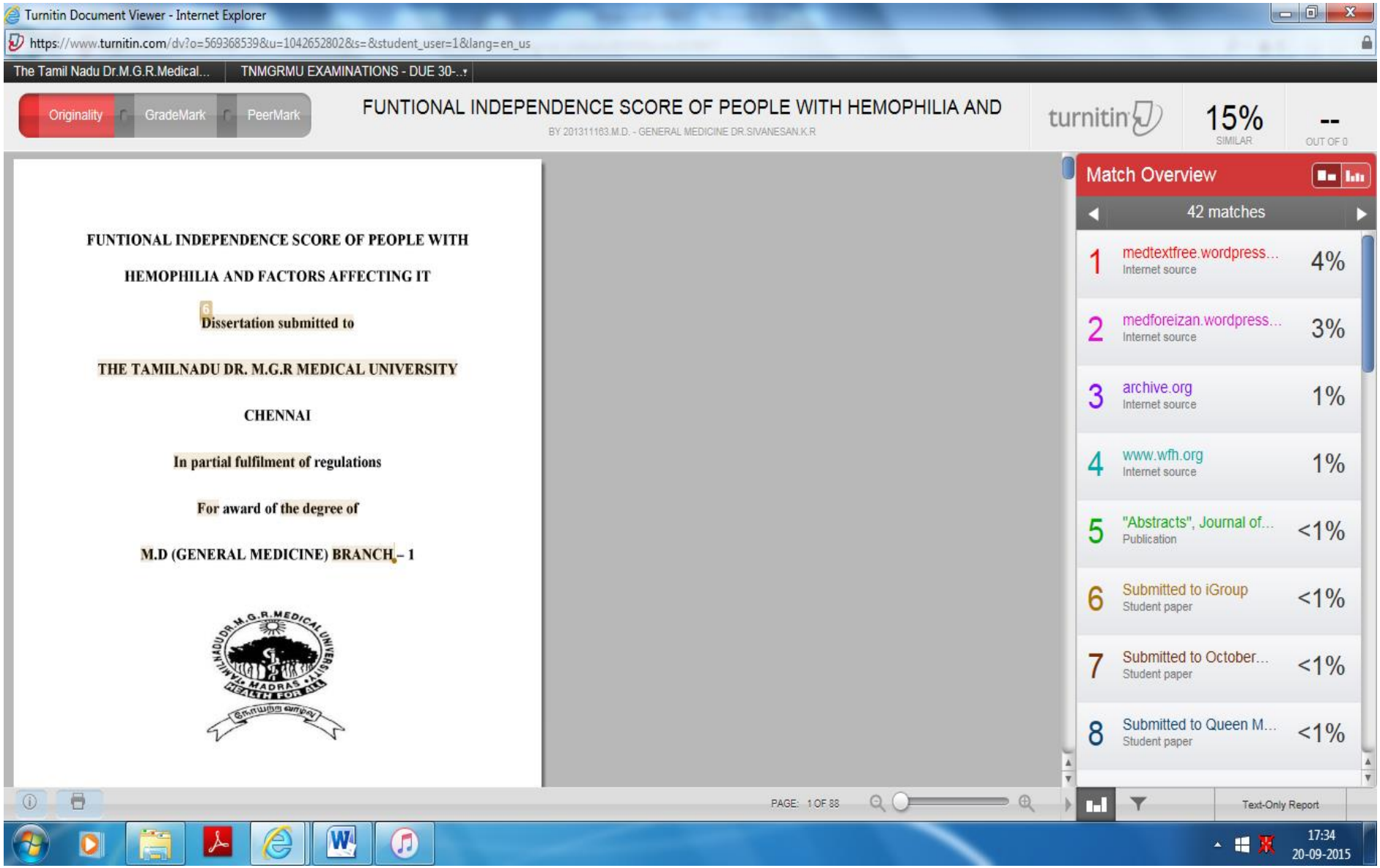
The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

20/1/15

CHAIRMAN,
Ethical Committee
Govt.Kilpauk Medical College,Chennai

GOVT. KILPAUK MEDICAL COLLEGE * Kilpauk, Chennai-10. * 20 JAN 2015

19/1/2015


Turnitin Document Viewer - Internet Explorer
https://www.turnitin.com/dv?o=569368539&u=1042652802&s=&student_user=1&lang=en_us
The Tamil Nadu Dr.M.G.R.Medical...
TNMGRMU EXAMINATIONS - DUE 30-...
Originality
GradeMark
PeerMark
FUNTIONAL INDEPENDENCE SCORE OF PEOPLE WITH HEMOPHILIA AND
BY 201311163.M.D. - GENERAL MEDICINE DR.SIVANESAN.K.R
turnitin
15%
SIMILAR
--
OUT OF 0
FUNTIONAL INDEPENDENCE SCORE OF PEOPLE WITH
HEMOPHILIA AND FACTORS AFFECTING IT
Dissertation submitted to
THE TAMILNADU DR. M.G.R MEDICAL UNIVERSITY
CHENNAI
In partial fulfilment of regulations
For award of the degree of
M.D (GENERAL MEDICINE) BRANCH – 1
Match Overview
42 matches
1 medtextfree.wordpress... Internet source 4%
2 medforeizan.wordpress... Internet source 3%
3 archive.org Internet source 1%
4 www.wfh.org Internet source 1%
5 "Abstracts", Journal of... Publication <1%
6 Submitted to iGroup Student paper <1%
7 Submitted to October... Student paper <1%
8 Submitted to Queen M... Student paper <1%
PAGE: 1 OF 88
Text-Only Report
17:34
20-09-2015