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Hemophilia and the evolution of treatment

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Abstract

Objectives: To show the research on Gene Therapy for Hemophilia.
Methods: The methodology to study the objective is to infuse healthy gene into patient's body in two methods: 1. The direct infusion by a Vector which infusing gene carrier into patient's body. The vector carries the clotting factor gene to the patient's cells. Then it is directly communicate. 2. The cells which were transplanted into the patient's body can communicate normal clotting factor. Small amount of clotting factor improves patient's condition.
Findings: The long researches on Gene Therapy tried to production and development of a suitable and safe gene delivery system to long term expression of coagulation factors. Gene Therapy itself is an experimental treatment that involves introducing genetic material into Hemophilia patient cell to produce normal clotting factor. But it has its own limitations with side effects such as liver infection or failure. After the experience of side effects, a unique and novel technology, Adeno-Associated Virus was found. The unique feature in AAV is non-viral delivery system which allows the body to produce missing clotting factor naturally without the damage of the liver when compared with previous studies. In recent clinical trials all 7 patients of Hemophilia A who have received the high dose therapy to correct a defect gene and produce missing clotting factor naturally showed considerable improvement. Likewise in Hemophilia B also 13 patients who have received high dose therapy shown considerable production of missing clotting factor. When we see the results, they add more value to the existing reports.
Improvements: After Gene Therapy all the patients had a growth in missing factor level and they didn't have any type of bleed for 18 months even though they had minor injuries.
Keywords: Factor VIIa/VIII/IX, FEIBA, Chromosomes, Gene Therapy, Inhibitors, Physiotherapy.

1. Introduction

Hemophilia is a lifelong Genetic Bleeding Disorder. A Hemophilia affected patient has one or more of the 10 clotting factors in the blood either missing or deficient. The disease is almost exclusively seen in males while females are asymptomatic carriers. Rarely can it affect females. The main deficient Factors are VIII and IX and 80% of patients belong to Hemophilia A (VIII). To name the condition of bleeding disorder as Haemorrhaphilia, it was first named by Friedrich Hopff, Zurich University student, and his professor Dr. Schonlein, in 1828. Later changed to Haemophilia (Love of Blood). Hemophilia A (Factor VIII) was discovered in 1937 by American researchers A.J. Patek and F.H.L. Taylor. Haemophilia B (Factor IX) was first discovered in 1952. It is called as Christmas disease. It is characterized by spontaneous or trauma related bleeding typically into the large joints or muscles. Untreated or inadequately treated episodes may damage the function of joint, muscle or nerve resulting in progressive deterioration. Mucocutaneous bleeding is not uncommon. Life threating haemorrhages can result spontaneously or from trauma to the head or internal organs. Without proper care and non-availability of factor concentrates, within the first 20 years of life of Hemophilia patient may damage the functioning of limb and joint. This is due to impaired joint mobility, contractures and muscle atrophy. Chronic pain crippling joint deformities can be effectively prevented by adequate care of each episode of bleeding, including replacement of the deficient coagulation factor and very deliberate and persistent physical therapy.

Even though there is availability of factor concentrates and comprehensive care, the risk and threat of Inhibitors which are anti-bodies are present to neutralize the infused factors. 33% of Hemophilia A patients and 6% of Hemophilia B may have Inhibitors against the deficient factor. Such patients don't respond to usual factor replacement therapy. Patients exposed to factor replacement with products that haven't been virus inactivated are prone to acquiring transfusion transmitted viral infections such as human immuno – deficiency virus (HIV),

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Hepatitis B & C viruses. The care of Persons with Hemophilia (PWH) often requires a multidisciplinary team approach to address different aspects of the patient problems. This is the concept of comprehensive care by the doctors of Hemophilia. For every the incidence in general population is 1:5,000 male births and the total registered patients in India was 20,000 and 4,00,000 people overall in the world. If laboratory facilities are available in India the number would be more than 85,000. The comprehensive care of Hemophilia and research work like Gene Therapy are being monitoring by the world federation of Hemophilia and Hemophilia federation of India [1].

2. How hemophilia occurs

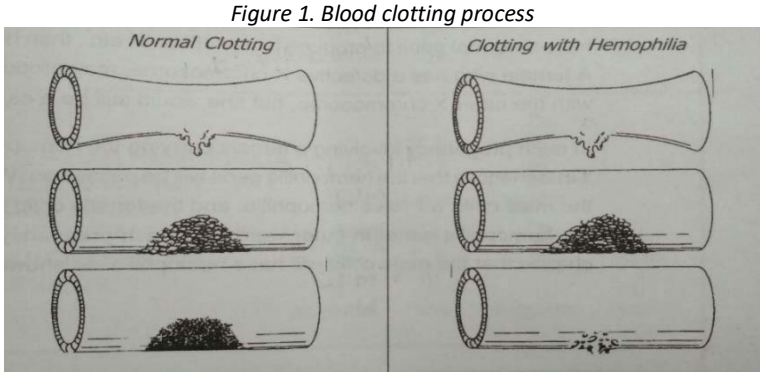
Hemophilia usually is inherited. The clotting factor was produced by X-Chromosome. If a male child gets defective X-Chromosome from mother, he will have Hemophilia. If female receives defective X from father, she will lead normal life with healthy X from mother. But due to one defective X, she would still be a carrier. Without family history also, Hemophilia can occur. This is called Sporadic Hemophilia. Through mutation of the genes 30% of people may be affected with Hemophilia [2].

3. Functioning of blood

Blood travels around inside our body through Blood Vessels. We can consider the blood vessels as pipes carrying blood to all parts of our body. When one of these pipes is damaged, the blood can spill out. At that moment the body must work to the stop the leak and repair the pipe. The first thing the body does is to squeeze the blood vessel tighter so that less blood leaks out. Platelets play an important role in our blood cells. Forming of Platelet Plug will stop the bleeding. It works initially and is effective only for little scratches and cuts and lasts a few hours. For bigger injuries a Fibrin Clot is needed.

The Fibrin Clot is good, strong patch over a hole in blood vessel. Proteins in the blood make the Fibrin Clot. The body then has time to heal the blood vessels. A Fibrin Clot is needed to stop the major bleeds. But the blood in Hemophilics can't make a Fibrin Clot due to lack of clotting factors VIII or IX [3]. The blood clotting process i.e., squeezing of blood vessel and formation of Platelet Plug are common in normal person and Hemophilia person. A permanent Fibrin Clot will not be formed in Hemophilia person as he has no clotting factor when compared with normal person who is shown in Figure 1.

Figure 1. Blood clotting process



4. History of Hemophilia

Symptoms of bleeding first described in the Talmud as early as in the 5th Century. Rabbi Judah - a woman's third son is exempted from circumcision because his two elder brothers had died of bleeding following circumcision.

4.1. 18th century

The first recent descriptions of Hemophilia are from the end of 18th Century. Isaac Zoll (1791): The Salem Gazette, a weekly newspaper in Massachusetts still in existence, published on obituary in 1791, The earliest record of Hemophilia in America, reported that Isaac Zoll, a son of Henry Zoll who had come to America from

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Germany, died of blood loss following an accident with an Axe. The bleeding couldn't be stopped, and 5 of his brothers had died in a similar fashion. All the brothers who died had been from the same mother. The crucial observation suggested that the abnormal bleeding tendency was transmitted through the mother. Consbruch (1793): He provided the first written description of Hemophilia. Otto (1803): He described how only the male lines suffered from Hemorrhagic disposition, nothing that all males in a family were afflicted. He observed that the mother transmitted the disease to her descendants. For the 1st time Otto used the term bleeder in his description of the affected males in this family. It was observed that all described families where males suffered prolonged bleeding following trivial trauma disorder transmitted by unaffected females to a proportion of their sons

4.2. 19th century

In European royal families Haemophilia has featured prominently. Because of this the Hemophilia called as the royal disease. Queen Victoria passed the haemophilia B gene to her son Leopold. Her two daughters are carriers and spread the disease to various royal families across the continent. Empress Alexandra, one of Queen Victoria's granddaughters passed her Hemophilia gene to her son Tsarevich Alexei, son of Nicholas II in Russian Royal family. In Russian royal family, Rasputin was successfully treating Hemophilia of Tsarevich Alexei. Queen of Spain Victoria Eugenie of Battenberg's two sons were Haemophiliacs and died with Hemophilia. She is granddaughter of Queen Victoria [4]. Queen Victoria is the 1st carrier of Hemophiliaand passed the Hemophilia Gene to Royal families in 19th Century. The portrait of Queen Victoria is shown in Figure 2.

Figure 2. Queen Victoria of England 1819-1901

Source: https://en.wikipedia.org/wiki/Haemophilia

5. Inheritance of hemophilia

Hemophilia is an X linked disorder, because the clotting factors are present on the X-Chromosome. It will occur when a defective X-Chromosome gene is inherited. Males have XY Chromosomes while females have two X Chromosomes. A male receives one X-Chromosome from his mother and a Y-Chromosome from his father. Defective gene lies in X-Chromosome only. Hence a direct transfer of Hemophilia from the father to son is not possible. If a female receives only one defective X-Chromosome from father, she doesn't suffer from the disorder. But she will be a carrier of the disease and may transfer the defective X-Chromosome to her male

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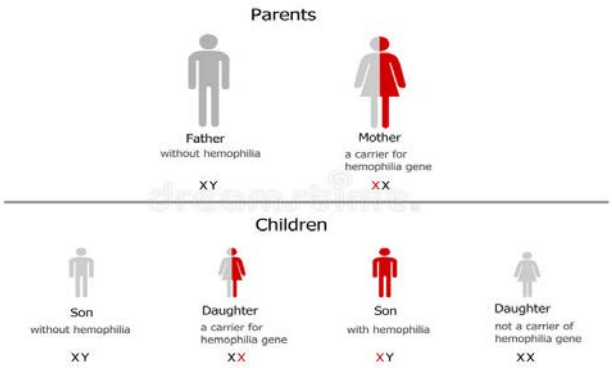
child. Then the male child suffers from Hemophilia. There is no direct transfer of the defective genes from father to son and mother to daughter. The daughter is not affected by Hemophilia but remains the carrier. The affected genes are transferred to her son. Finally we can say that Haemophiliac genes are transferred from grandfather to grandson through the daughter.

If the mother is carrier and father is not Haemophiliac, then there is 50% chance of Hemophilia to their sons and daughters will have 50% chance of being carriers. If the father is Haemophiliac and the mother is not, all sons will be normal, but all daughters will be carriers. Sometimes even when there are no traces of Hemophilia in forefathers, a person may acquire the disease due to mutation in the genes [5]. A mother, carrier of Hemophilia gene passed her defective X to one son and one daughter who became sufferer and carrier respectively and the remaining son and daughter are normal persons which are shown in Figure 3.

Figure 3. Inheritance of Hemophilia



Source: https://www.dreamstime.com/stock-illustration-hemophilia-inheritance-healthy-father-carrier-mother-image 52018482

6. Clinical presentation

The usual age for presentation of symptoms due to Hemophilia is when the child begins to crawl and starts to walk. Falls and bumps cause bruises. Later on, between the age of 2 & 3 years, muscle bleeds and joint swellings occur. In some, the disorder becomes apparent when the person with Hemophilia develops prolonged bleeding after a tooth falls or is extracted, or he has a surgical procedure. Painful swellings after intra muscular injection or vaccination sites are another clinical clue. Prolonged bleeding after the umbilical cord falls is suggestive of fibrinogen or Factor XIII deficiency. If one of these symptoms occur, then it is important to get the child tested for Hemophilia.

The following tests are usually recommended

1. Platelet Count.
2. Platelet Morphology.
3. Bleeding Time (In young children the bleeding time is not usually done).
4. Prothrombin Time.
5. Partial Thrmoboplast in Time.
6. Factor XIII Activity (clot solubility in 5 Molar Urea).

Basing on the outcome of the above tests, a factor assay is done to know the level of the deficient factor. This type of factor assays would be done in a sophisticated laboratory where Hemophilia tests are going on.

6.1. Severity levels in hemophilia

All Hemophilia patients will not have the same levels of factor deficiency. It depends upon the amount of clotting factor he had in his body. This is called deficiency of factor level. The standard factor level is 100% and between 60 and 200% will be considered normal. The level of factor in Hemophilia patient is constant and doesn't change in his life time. Two or more brothers in a family will have the same factor level if they are Haemophiliacs.

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6.1.1. Severe hemophilia

If the factor level is <1% then it is termed as Severe Hemophilia. The main characteristic is spontaneous bleeds into joints, muscles and other tissues, without any injury. May be bleeding twice a week.

6.1.2. Moderate hemophilia

If the factor levels are in between 1-5% are termed as Moderate Hemophilia. Bleeding will occur due to minor injuries, surgeries and tooth extractions. Spontaneous bleed is uncommon. May bleed once in a month.

6.1.3. Mild hemophilia

If the factor levels are>5%then it is termed as Mild Hemophilia. Bleeding is usually associated only with major injuries, surgeries or tooth extractions but there will be no spontaneous bleeds.

6.2. Sites of bleeding

A person with Hemophilia can bleed into virtually any site. The most common are joints and muscles. All bleeds should be treated early and adequately to avoid complications in later life.

6.2.1. Joint hemorrhage

Bleeding into a joint is a common thing in Hemophilia. The most complicated problem in Hemophilia is joint bleeds. Because for every movement like standing, walking, sitting etc., we have to use joints. The joint is an area where two bones come together for comfortable movement. Bleed can occur into the joint spontaneously or with an injury. After the bleeding into the joint the pressure of blood filling in the gap of two bones and causes pain and swelling and arrest the movement. Immediate treatment like infusion of missing clotting factor, rest, ice, compression and elevation are needed to avoid joint damage. Repeated bleeding into the same joint may lead to damage of joint and will make the particular joint disabled. Repeated bleed into the joint may damage synovium and the joint will become stiff.

Figure 4. Ankle bleed

Source: Personal photo

The synovium is a layer that lubricates and feeds the joint. Synovium contains blood vessels and that's why bleeding into the joints is common for a Hemophilia patient. Joints have two types of cartilage which absorbs shock. When bleeding occurs enzymes from the swollen synovium destroy the cartilage and the bones become stiff and painful. The main symptom of joint bleed is warmth, swelling, pain and stiffness. The target joints are ankle, knee, hip, wrist, elbow and shoulder. Due to Severe level (<1%) of Hemophilia, spontaneous bleeds occur in ankle joint and knee joint and swell up as shown in Figure 4,5.

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Figure 5. Knee Bleed

Source: https://i.pinimg.com/originals/01/76/11/017611fb5508a2a3a319847284eb93c6.jpg

6.2.2. Muscle hemorrhage

Human body is made up of more than 600 muscles. Muscles play an important role in functioning of the body. Bleeding may occur spontaneously or with an injury into the muscles in the arms, legs and thighs. Iliopsoas muscle bleed is very complicated bleed. Due to an injury or spontaneously the bleed can occur. Immediate factor replacement and rest is the treatment for the Iliopsoas bleed. Most bleeds in the muscles can occur spontaneously and internally.Depending upon the pain, for any muscle bleed rest is the primary step and infusing factor concentrate is needed basing on severity of bleeding. The bleed in calf muscle restricts the movement of the muscle and the patient can't walk normally. To confirm the location of the bleed the patient has to test each muscle separately.

6.2.3. Head injury

Intracranial bleed known as bleed in the brain is a serious complication which may take the patient to death. Hemophilia patient can have brain hemorrhage spontaneously or with trauma. We have to observe the symptoms like headache, stiff neck, vomiting sensation, and drowsiness, irritation towards sounds, light etc., and change in behaviour, shivering and weakness of hands and legs and seizures. If the patient has some of the above symptoms, immediately high amount of factor concentrate must be infused and should be kept in specialist doctor's observation. CT scan of the brain should be taken to confirm the bleed and its severity. Treatment must be continued for several days basing on the advice of the specialist doctor. If untreated or inadequate treatment the patient may fall to death. All head injuries must be treated early to avoid being closer to death.

6.2.4. Neck and throat hemorrhages

If the patient had a bleed into the neck or throat, it is also a death causing bleed. The bleeding may quickly get worse. It must be treated properly or otherwise the bleeding in neck or throat blocks the patient's airway due to this he can't breathe properly. Throat bleeding may happen with infection like tonsillitis, cough and common cold.

6.2.5. Gastro – intestinal bleeding

It presents as blood tinged vomiting or dark brown/black or frank bloody stools. Apart from Hemophilia there can be other causes like ulcers, abnormal blood vessels, piles etc., for bloody stools. In the event of severe bleeding the patient must be admitted in the hospital and administer tranexamicacid and factor concentrates. Transfuse blood if required. Treat the under lying cause according to the Endoscopy findings.

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6.2.6. Other bleeds

In addition to joint, muscle, head, neck and throat and GI bleeds the patients may suffer from bleeds in the other parts also. Bleeding from skin cuts, mouth and gums etc., will also happen. Though they are not serious the in time treatment is a must. Due to infection urinary bleed may happen [6].

7. Evolution of treatment

7.1. Past

Treatment for Hemophilia patient in 19th century was infusion of fresh blood only as there were no blood banks to store the blood. After that usage of venoms of particular snakes in diluted method were used to clot the blood of Hemophilia patient. Plasma was given for joints and muscle bleeds in 1926, in America and found some useful results. The globulin in plasma which decreases clotting time in patients with Hemophilia was found in 1937 which was published in a paper by Arthur Patek. In the early 1960s fresh frozen plasma was transfused to Hemophilia patients. Due to less quantity of plasma in each FFP bag the huge volumes of FFP had to be administered to control the bleed. Preparation of Cryoprecipitate in blood banks is an important breakthrough in 1965. It has large amount of Factor VIII in a smaller volume also. It could be controlled serious bleedings also. Factor concentrates for VIII and IX are available in the form of lyophilized powder in the 1970s for the treatment of Hemophilia. Patients had stored the vials at home and self-infused whenever there is a bleed. But due to lack of sophisticated screening of blood in 1980s HIV/AIDS were transmitted to Hemophilia patients through the use of blood products and thousands of patients had died. Due to infected factor products prepared from the blood donors, Hepatitis C virus (HCV) infection was also transmitted.

7.2. Present

After affected by HIV/AIDS and HCV the total Hemophilia community was in a dilemma to use plasma derived factor concentrates as there is no sophisticated blood screening facilities to detect HIV and HCV virus. Inventions were going on to prepare virus free factor concentrates and saw the good results in preparing recombinant factors and also mechanism for sophisticated blood screening. In 1992 Food and Drug Administration (FDA) had approved the 1st recombinant Factor VIII. After overcoming from the nightmare of HIV virus, the Hemophilia patients fearlessly infused factor concentrates and started prophylaxis treatment i.e., infusion of factor concentrates for twice or thrice a week. From 1995 the prophylaxis treatment became more common and the Hemophilia patients lived with less pain and without joint damages. The recombinant factor IX was approved by FDA in 1997. Though the prophylaxis treatment was very useful, some Hemophilia patients had developed Inhibitors which are anti-bodies to infused factor concentrates. Again the research went on to face the challenges of Inhibitors to factor concentrates. As a result Bypassing Agent came into existence from 1997 and became helpful to Inhibitors patients to stop bleeds and joint damages. Now the 4th Generation new recombinant products were produced. Preparation without human or animal plasma derivatives is the special property of the recombinant product. With these new recombinant products there had a chance of decreasing the regular infusion rate and also lowering the development of Inhibitors.

7.3. Future

7.3.1. Gene therapy

The future treatment of Hemophilia patients lies on Gene Therapy. The researches ‘are going on Gene Therapy in America and Britain. In Gene Therapy healthy genes of Factor VIII/IX were injected into the patient’s liver through a vector. As a result the new healthy gene started to work to produce clotting factor naturally. The gene of Hemophilia A is larger and needs separate and accurate research [7].

7.3.2. Gene therapy for hemophilia B

The trials of Gene Therapy for Hemophilia B were going on and were successful up-to some extent. Some patients who were under the trail of Gene Therapy shown some development after infusing healthy gene of Hemophilia B into patients liver through a vector. The bleed frequency had eliminated after Gene Therapy [8].

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7.3.3. Gene therapy for hemophilia A

Barts Health NHS Trust had made their efforts in gene therapy for haemophilia A and found some fruitful results. They infused healthy gene of Factor VIII into the patient's liver through a vector and observed a drastic change in the patient's level of Factor VIII with normal or near normal levels after one year of the Gene Therapy. In this study the Adeno-Associated virus was used to transfer the missing DNA to the liver cells for the making of Factor VIII. This was done by a single injection. The Gene Therapy will only work for the patients who are above 18. There is one problem in using of Gene Therapy is that this method is unlikely to work in patient with anti-bodies [9].

8. Factor replacement therapy

8.1. Fresh whole blood

When no other product is available, Fresh Whole Blood may have to be used. If it has to be used, then Screened donors should be used to donate blood. 1 IU of Factor VIII/IX will be present in about 2 ml of whole blood. There is a significant risk of transmission of HIV, Hepatitis B & C and other known and unknown viruses with the use of any of these products.

8.2. Fresh frozen plasma

The developing countries depend upon Fresh Frozen Plasma for replacement therapies. It contains all clotting factors in near normal quantities. Hence both Factor VIII and IX patients can use FFP. If Plasma is used within 6 hours of bleeding from a donor, it is considered to be Fresh Plasma and contains all clotting factors in near normal quantities. If this plasma is frozen and stored at or below -30℃, then it is called Fresh Frozen Plasma. Each bag of Fresh Frozen Plasma should be between 100-200 ml (and 100-200 IU of Factor VIII/IX). The dose to be infused will depend upon the Factor level to be achieved.

8.3. Cryoprecipitate

This is manufactured from stored plasma after thawing at 4° centigrade over a period 12-20 hours or may be instantly. The yield varies from 60-80 units and it requires storage at -20℃. It contains Factor VIII, VonWille Brand Factor, Fibrinogen and Factor XIII.

8.4. Anti-haemophilic factor

The dosage of Factor VIII is calculated on the basis of patient's body weight and type of bleed. The desired factor level is measured in percentage. Factor VIII lasts for 10-12 hours and Factor IX lasts for 24 hours in the patient's body. Basing on the severity of the bleed the doses may be continued. One or Two doses are usually necessary. At present plasma derived and recombinant factors are available in our country. To control the bleed, Anti Hemophilic Factor must be infused which was available in the form of lyophalized powder in a vial with distilled water as shown in the Figure 6.

Figure 6. Anti Hemophilic Factor VIII

Source: http://www.thecardiologyadvisor.com/novoeight/drug/34534/

8.5. Tranexamic acid tablets

It helps to prevent bleeding by inhibiting the breakdown of the clot i.e., formed and is particularly useful when bleeding occurs from the Mucous membranes. Eg. Mouth and Nose [10].

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9. Patients with inhibitors

In a human body anti bodies protecting the immune system and fight with foreign bodies that are harmful to the body. The anti-bodies are called Inhibitors. Anti-bodies are part of the body's natural defence system attacking foreign substances that enter the body. They are valuable for taking care from viruses and bacteria. Patient with Hemophilia A or B can develop anti-bodies known as Inhibitors which prevent their Factor VIII/IX treatment from working to form a clot to stop bleeding. The Inhibitors in the patient's body view the infused clotting factor as foreign substance and attack it and stop it from clotting the blood. Inhibitors usually develop in young children. Approximately 20-33% Hemophilia A patients is affected by Inhibitors at some point in their lives. Approximately 1-6% with Hemophilia B develops Inhibitors. After infusing clotting factor for a bleed, patient with Hemophilia feel better from bleeding tendency, but the Inhibitor patient won't get relief from the pain even after infusing clotting factor. Because the Inhibitors in his body neutralize the factor concentrates. Inhibitor patients should be tested for inhibitors regularly to know the change in Inhibitor levels [11]. To get rid of Inhibitors the patient has to go for Immune Tolerance Induction (ITI) which is infusion of factor twice or thrice a week in a specialized medical supervision. But it is too expensive and also takes long time. At present FEIBA (Factor Eight Inhibitor Bypass Activity) and Factor VII are being used instead of Factor concentrates. Inhibitors would be measured in Bethesda Units (B.U). <5 BU would be classified as low responders and >5 BU would be classified as high responders. For low responders i.e., <5 BU factor concentrates must be infused 2-5 times the normal to neutralize the Inhibitors [11].

10. Role of physiotherapy In Hemophilia treatment

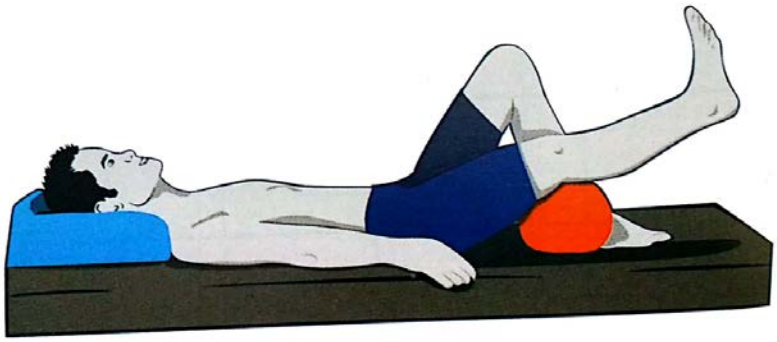
Physiotherapy plays a vital role in treatment of Hemophilia other than factor replacement. The goal of physiotherapy is:

1. Relief from pain.
2. Restoring muscle power and control.
3. Restoring range of joint movement.
4. Preventing further injury to a target joint [12].

10.1. Aims of physiotherapy

Resuming routine life at the earliest is an essential part of life today, and Haemophiliacs are not exception to this rule. Joint movement and joint function are closely associated and are imperative to leading a productive life. Hence achieving maximum joint movement is of paramount importance in patients. The recurring bleeds may damage target joints and muscles which may lead to arthritis. Infusion of clotting factor may stop the bleeding but not restore the mobility of the joints and muscles function. At the time of bleed the movement will be restricted. But after controlling of the bleed, physiotherapy is needed to strengthen joints and muscles and prevent further injury to a target joint.

Figure 7. Physiotherapy in Hemophilia



Source: Changing Hemophilia book by Novo Nordisk

An expert physiotherapist may know the parts of the body and functioning of each part of the body. Physiotherapist knows incorrect posture and damage of joints. Physiotherapist can suggest the patient Rest, Ice, Compression and Elevation, (R. I. C. E) apart from factor concentrate. When the patient is in continuous infusion

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he may lead healthy life with healthy joints and muscles. This is possible in children and teenagers only. For elder people joint damages may occur. Musculoskeletal is an attempt to reduce prolonged bleeding and recurrent bleeding episodes in persons with Hemophilia by improving physiotherapy and musculoskeletal resources for them. It is also a very inexpensive way to treat and prevent joint/muscle bleeds in Hemophilia [12]. To strengthen the weak knee joint and quadriceps, physiotherapy is needed. Lying straight and put a bottle wrapped in a towel, lift the foot up and straighten the knee and lower slowly. Relax, and then repeat 10-15 times as shown in the Figure 7.

11. Psychological problems in hemophilia

A Hemophilia patient and his family need to be strong psychologically as they have to live with the disease which is incurable. As the treatment is too expensive it will be a financial burden to them. Psychological support is an essential ingredient of any successful medical management. Since Hemophilia is an illness with an early onset, many patients are children or adolescents. There is a tendency among health professional to discuss issues related to illness or treatment only with the parents, partly to spare the child distress and partly in the belief that the children are not capable of grasping these matters. However many children understand a great deal and often wish to know more. Including them in discussions can reduce resentments and restrictions and improve adherence to instructions. The following are the main problems they are facing.

11.1. Glass with care

People with this disease should be treated as a glass with care by the parents. They shouldn't be left alone.

11.2. Loneliness

They cannot move and play freely like others. They are not supposed to play outdoor games. Due to confine to bed at the time of bleeds, some inferiority complex may develop.

11.3. Education

Due to frequent and spontaneous bleeds they are unable to attend schools and colleges regularly. Because of this they are facing failures in studies. During the exams they need a SCRIBE to write the examinations, as they will bleed into hand and fingers. Due to tension in the exams they will get bleeds in brain also.

11.4. Employment

It is very difficult to get an employment basing on their marks, grade and this disease. They may not attend interviews at the stipulated time due to bleeds.

11.5. Marriage

It is very difficult to get a better half who understands the disease and the patient completely on the sympathetic grounds. When the blood test report of Hemophilia is about to come, the doctor/social worker had to prepare them for bad news. Encourage them to express fears, concerns and doubts and give an overview of the treatment plan in simple language in a stepwise manner with pauses in between. Make it clear that the treatment is available for them at any time. End with a hopeful statement that is not excessively optimistic. These steps are equally useful in dealing with family. It may be necessary to give a little extra time to the mother who in addition to coping with child's illness may suffer blame/guilt at being the carrier. The role of a social worker in helping the management of chronic illness is being increasingly recognized. Family visits help in providing psychological support, aid in assessment of problems faced in day to day living and continuity of care. In area with high prevalence, family members can be encouraged to setup self-help groups that meet regularly on their own and decide their own agenda. The physician could be a resource person for them [13].

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12. Prevention of hemophilia

The management of Hemophilia in the developing countries is an ever challenging job. Without proper management Hemophilia adversely affects every aspect of life for the person with Hemophilia and for his family. Advanced treatments are being introduced and the patients are unable to meet the expenses of Hemophilia treatment. Though there is invention of new medical treatments, there is a gap between patient and treatment. Only 25% of the patients are getting adequate treatment. In developing countries like India, where factor concentrates are hardly affordable for replacement therapy, Carrier Detection and Prenatal Diagnosis remains the key step for the prevention of the birth of babies with Hemophilia. This will also reduce the Hemophilia burden on the society.

12.1. Carrier detection

In Hemophilia males are suffers and females are carriers. To prevent the Hemophilia in future, we have to make carrier detection test for females who are in Hemophilia family. There are two ways to test women to see if she is a carrier of Hemophilia. The 1st way is to test the factor level in her blood and the 2nd way is DNA test. Women who carry the Hemophilia gene may have a level i.e., lower than normal. Some carriers may have levels low enough to cause bleeding problems. The blood tests for factor level can tell if a woman is a carrier 80% to 90% of the time. The tests may not be accurate and we also look at the family history of Hemophilia. To know the correct result about carrier detection DNA test must be performed .All daughters of a Haemophiliac father, mothers of Haemophiliac son are obligatory carriers whereas mothers of one Haemophiliac son without family history and all daughters of a carrier are possible carriers [14].

12.2. Prenatal diagnosis

Haemophiliacs have to infuse factors to control the bleed. But the factors are most expensive and not easily available. So to avoid upcoming generations suffering from Hemophilia, the prenatal diagnosis is important. Prenatal diagnosis is nothing but the test of fetus for Hemophilia in between 10-12 weeks. There is a risk of miscarriage associated with Chronic Villus Sampling (CVS). However rarely it can be occurred. But before going to the test the couple must have genetic counselling thoroughly and final consequences of the test. If the foetus is detected with Hemophilia it will be better terminated or abort [15].

12.3. Other preventive steps

Avoid marriages with close relations. Disclose the disorder of Hemophilia to his partner before marriage. After marriage the couple may opt not having their own child and choosing to adopt a child.

13. Service organizations for the Hemophilia patients

13.1. World federation of hemophilia

The World Federation of Hemophilia (WFH) was established at Montreal, Quebec, Canada in 1963 by Frank Schnabel, a Montreal businessman born with severe Hemophilia A. His vision, as he stated, was to improve treatment and care for the hundreds of thousands of haemophiliacs worldwide. As a mark of his service to Hemophilia community, his birthday was celebrated as World Hemophilia Day on 17thApril every year. Hemophilia Societies in 134 countries were affiliated to WFH. From 1963to till date the WFH had been working with the societies across the globe to provide best available treatment to Hemophilia patients [16].

13.2. Hemophilia federation of India

Today India had made a lot of progress in Hemophilia treatment. But 35 years ago even doctors at major hospital wouldn't touch Haemophiliac patients. They became silent when they saw Hemophilia patients. Because there is no suitable treatment available in India. In 1975 a Hemophilia A patient Mr. Ashok B Verma met with an accident and fractured his leg. At that time when the options in India for his treatment were exhausted he set his sights for treatment abroad. After 5 years he could meet a prominent Haematologist professor Mannucci in Italy. After verifying the condition of his leg, the doctor was forced to amputate his leg up to mid-thigh. After his treatment he realised that there is no treatment in India and he received treatment in Italy for

Hemophilia. So he wanted to provide some service through a society and he started Hemophilia Federation of India in 1983 in New Delhi. At present 82 Chapters across India are affiliated to Hemophilia Federation of India. Visakhapatnam Chapter is also affiliated to HFI and working for the welfare of Hemophilia community. As a mark of the services of late Mr. Ashok B Verma, his birthday was celebrated as Founder's Day on 28th November every year. HFI was affiliated to WFH.

14. Conclusion

As a person of Hemophilia, I, K. Aravind Nikhil have been continuously suffering from last 21 years with bleeds, pain, stress and mental agony. From the last 15 years I have been suffering from Inhibitors also. I have faced regular spontaneous bleeds into my joints and muscles and for 5 times I sustained from life threading IC bleeds and forego crucial public examinations also. Even then I have been living with Hemophilia and my ray of hope is that the Gene Therapy would bring the sunshine in the lives of persons with Hemophilia. In our country there are so many undiagnosed Hemophilia patients due to lack of education, public awareness, and diagnostic facilities. I feel that in coming future the central and state governments would look into this matter and create awareness about Hemophilia and provide laboratory facilities for every district to identify the patients with bleeding disorders. Once if they were identified then the treatment plan could be implemented and could save the lives of patients. Treatment plan includes establishing the Hemophilia Treatment Centers, which provides Factor Replacement Therapy including FIEBA and Factor VIIa, Physiotherapy etc. With a long term vision the Governments have to eradicate the growth of Hemophilia by establishing more laboratories in every district that can do the Carrier Detection which can diagnose whether the female is a carrier of Hemophilia or not and Prenatal Diagnosis whether the baby is affected from Hemophilia or not. As a part of social responsibility, the corporate sector has to allot some funds for the welfare of Hemophilia patients under CSR cell. The Governments have to provide reservations to Hemophilia patients in education and employment.

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