

HEMOPHILIA - AN OVERVIEW

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ABSTRACT

Hemophilia unfortunately a less attracted disease for researchers compared to other life threatening diseases. The prevalence of hemophilia is estimated to be about 1:10,000 birth and that of the severe form of the disease to be about 6% per 1,00,000 population. The most pathetic part of this disease is that even medical personnel are sometimes not familiar with its diagnosis and management. There is obviously a need to establish facilities and treatment options that will help the patient with hemophilia to manage their life with ease. As this is a genetic disorder no complete cure is possible as of now. The only available treatment option is the infusion of factors and some adjuvant therapies depending upon the bleeding conditions. The initiative for the development of new dosage forms, new delivery systems of the existing therapies or new treatment options has to be driven by pharmacy professionals. This article present an overview of hemophilia, in order to drag the attention of medical as well as pharmacy professionals for the benefit of millions of hemophilic patients.

Keywords: Hemophilia, Factor VIII, factor IX, Hemostasis, Thrombin.

WHAT IS HEMOPHILIA?

Hemophilia is a genetic condition that causes people to keep on bleeding for a long time unless treated. People with hemophilia do not bleed faster than anyone else; but will bleed continuously at the normal rate until they are treated. This is because the blood is unable to clot without any therapy.

Internal bleeding is the major concern in hemophilia. Bleeding is common into joints such as knees, ankles and elbows. This may be caused by injury, but in severe hemophilia, can begin spontaneously.

MOST COMMON TYPES OF HEMOPHILIA

Hemophilia-A (Classic hemophilia)

It is otherwise called as the classic hemophilia. It is "X" linked recessive disorder occurred due to the absence or deficiency of clotting factor VIII (FVIII). Hence it affects only males. Females are said to be carriers. Carrier females usually are asymptomatic but can have bleeding symptoms (e.g., are easily bruised or have menorrhagia or excess bleeding after trauma) when they have significant reductions in factor VIII levels, which are caused by the greater (extreme) inactivation of the normal FVIII gene, compared with the hemophilic FVIII gene, during early embryogenesis. The occurrence of hemophilia –A is 1: 5000-10000.^{1, 2, 3, 4}

Hemophilia B (Christmas disease)

It is also an "X" linked recessive disorder occurring due to the absence or deficiency of the clotting factor IX. The inheritance pattern and the symptoms of hemophilia B are same as that of the classic hemophilia. The occurrence of hemophilia –B is 1: 20000-34000^{1, 2, 3, 4}

Hemophilia C

It is an autosomal recessive disorder exhibits bleeding symptoms because of the absence /deficiency of the factor XI. For inheriting the disease both parents must carry the defective gene. Reports are there as exceptions, that people have bleeding problems when only one of their parents has the gene which causes Factor XI Deficiency. Factor XI Deficiency affects males and females in equal numbers. The occurrence of the Hemophilia C is 1:100000

SYMPTOMS

Symptoms for hemophilia A, B and C are summarized in the table .1

HOW BODY WORKS TO STOP BLEEDING

(Hemostasis and blood coagulation)

Blood travels around inside the body through blood vessels. These include Veins, arteries, and capillaries. When any of these is damaged the blood can spill out. Sometimes this happens when the skin is cut or scratched. Other times the blood can leak out of a blood vessel inside the body. In both the cases, body must work to stop the leak and repair the injury. The process of blood clotting (Coagulation), the subsequent dissolution of the clot and the beginning of the repair of the injured tissue, is termed as hemostasis. Blood clotting is considered as an important step in the hemostasis. This is a process that leads to the formation of fibrin clot. During an injury the sequential steps that lead to the formation of clot are:⁷

Step I). Vascular constriction. This limits the flow of blood to the area of injury.



Step II). Platelets become activated by thrombin and aggregate at the site of injury, forming a temporary, loose platelet plug.

Step III). Formation of a strong fibrin clot.

Blood coagulation entails the interaction of a large number of plasma glycoprotein with blood platelets and vascular endothelial cells. Blood clotting (Coagulation) proceeds through three pathways which leads to the fibrin production. (Fig. 1)

- 1 Tissue factor pathway (Extrinsic)
2. Contact activation pathway (intrinsic)
3. Common pathway

Table 1: The comparison of symptoms of different types of hemophilia .^{1, 2, 3,4,5,6}

| Type | Symptoms |
|--------------|--|
| Hemophilia A | Spontaneous bleeding to joints , muscles and soft tissues, Hemarthrosis, Deep-muscle hematomas Intracranial bleeding in the absence of major trauma, Neonatal cephalohematoma or intracranial bleeding, Prolonged oozing or renewed bleeding after initial bleeding stops following tooth extractions, mouth injury, or circumcision, Prolonged bleeding or renewed bleeding following surgery or trauma Unexplained GI bleeding or hematuria, Menorrhagia, especially at menarche, Prolonged nosebleeds, especially recurrent and bilateral, Excessive bruising, especially with firm, subcutaneous hematomas |
| Hemophilia B | Same clinical symptoms as that of hemophilia A |
| Hemophilia C | Mostly same as that of the mild hemophilia. Individuals are not likely to bleed spontaneously, and hemorrhage normally occurs after trauma or surgery. Certain procedures carry an increased risk of bleeding such as, dental extractions, tonsillectomies, surgery in the urinary and genital tracts and nasal surgery. Joint, muscle and soft tissue bleeds are uncommon. |

WHY DO HEMOPHILIACS BLEED?

The patient with hemophilia is deficient of FVIII/FIX/factor XI. The entire three factors are very much essential in the conversion of FX to its activated form. Deficiency of any of these factors fails to activate the factor X (Fig 2). If this is the case the total contact activation pathway (intrinsic) will be paralyzed. But the tissue factor pathway (extrinsic pathway) is normal in hemophilia patients which does not utilize the help of the above mentioned factors. So naturally one can think that whether this pathway is sufficient for the clot formation. but researches shows that Even though F VIIa-TF complex (Extrinsic pathway) is responsible for initial FXa generation, which provides sufficient thrombin to induce the local aggregation of platelets and the activation of the critical cofactors FV

and F VIII in normal hemostasis, Persistent hemostasis requires the continued production of additional F Xa through the action of F IXa and F VIIIa, since the FXa generation by F VIIa-TF complex is inhibited by TFPI (Tissue factor pathway inhibitor). Thus, hemophilia patients bleed because the Xa generated through the action of F VIIa-TF complex, and dampened by TFPI, is insufficient to sustain hemostasis and must be amplified through the action of F IXa and F VIIIa. And that persistent hemostasis requires the continued production of F Xa through the action of F IXa and F VIIIa.

FACTOR VIII:

Description, Activation, Role in coagulation and half life

It is a cofactor for factor IXa which, in the presence of Ca⁺² and phospholipids forms a complex that converts factor X to the activated form Xa. The non enzymatic protein cofactor which plays an important role in clotting mechanism is secreted from a variety of tissues including spleen, lymph nodes, liver, and kidney as an inactive single chain protein. But liver is considered as the primary source of factor VIII.^{11, 12} within the liver the hepatocytes are the major factor producing cells.

The gene of factor VIII is located at the tip of the long arm of the "X" chromosome, is 186000 base long and the information for the factor VIII is spread among 26 exons, which encode a poly peptide chain of 2351 amino acids. After extensive post translational processing it is released to the blood stream as a set of heterodimeric proteins [having a carboxy terminal-derived light chain (MW: 80,000) in a metal-dependent association with the amino terminal-derived heavy chain (MW: 90,000-200,000)]¹¹ (Fig 3). This intern interacts readily with its carrier protein vWF (von Willebrand's Factor) to form a tight non covalent bond. This complex will circulate in the blood as inactive zymogen and will turn in to active form when the thrombin or activated X (Xa) is available in the blood. the cleave in structure either in the light chain or in the heavy chain by thrombin(Fig. 3) or activated factor X (Xa) converts the inactive form of factor VIII in to its active form (VIIIa).^{8, 9, 11, 12}

In order to activate factor X, FIXa and FVIIIa assemble into a membrane bound complex. Even though the binding of the factor VIII to the membrane surface is inhibited by vWF, the cleavage at the light chain decreases the affinity towards vWF, favors the factor VIIIa binding to the membrane surface and IXa. These cleavages are associated with dramatic changes of the molecular properties of factor VIII, including dissociation of vWF and development of biological activity. Thus the formation of the membrane bound factor VIIIa-factor IXa complex that activates the factor X.^{11, 12}

The plasma concentration of factor VIII is approximately 200 ng/mL and the biological half life is approximately 12hours.^{4, 5, 11, 12}



Figure 1: The role of coagulation factors on blood clotting⁹ (* the "a" with the factor indicates the activated form)

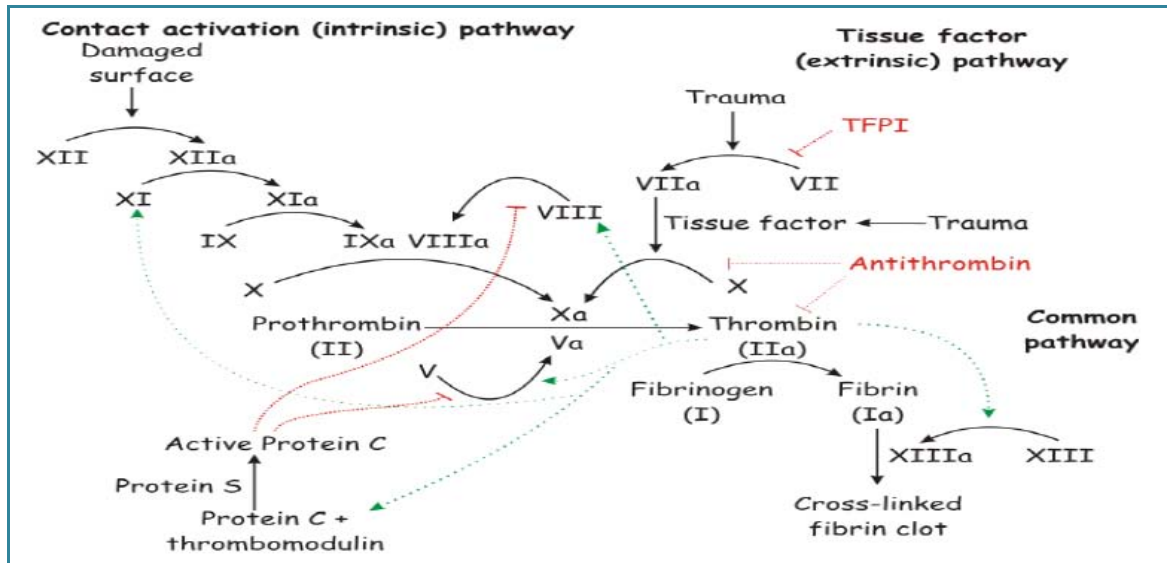


Figure 2: Schematic representation of why the hemophilia patients bleed than the normal individuals⁷

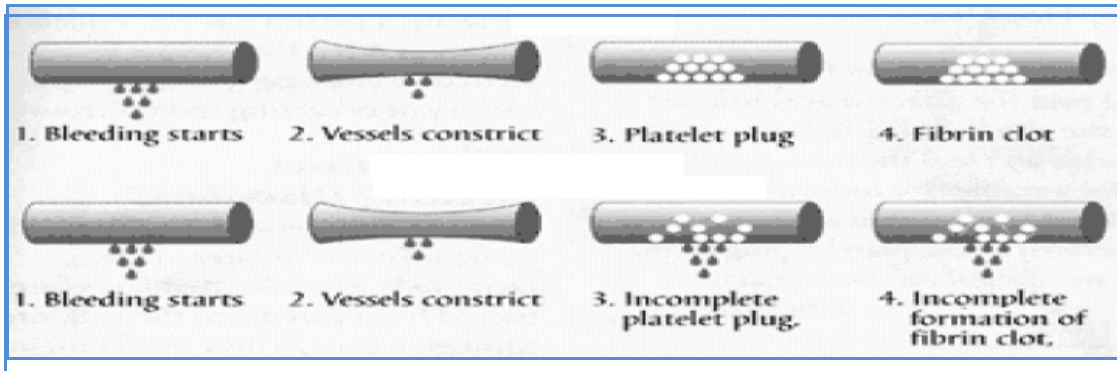


Figure 3: The domain structure of precursor FVIII and the site of thrombin cleavage the region A1&A2 - the heavy chain, A3-C2 - the light chain. B - Connecting region.¹²

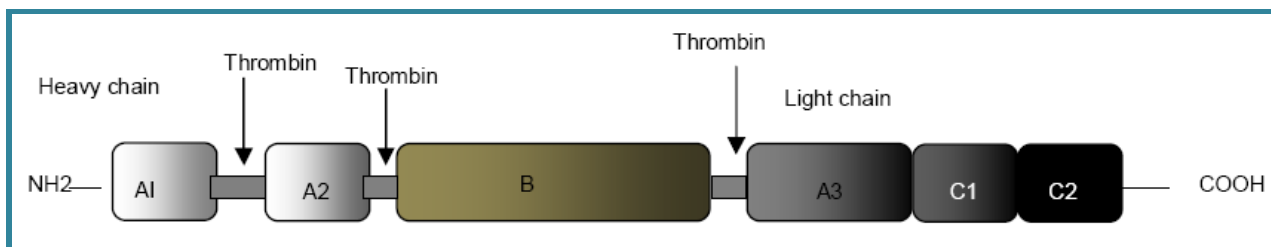


Figure 4: The domain structure of factor IX¹³ where: GLA=region containing γ -carboxyglutamic acid residues, EGF=region containing sequences homologous to human epidermal growth factor, AP=activation peptide released upon conversion of the zymogen to the active serine protease, and Catalytic domain=region containing the serine protease catalytic triad. Arrows indicate the sites which are proteolytically cleaved by factor XIa during activation of the zymogen.

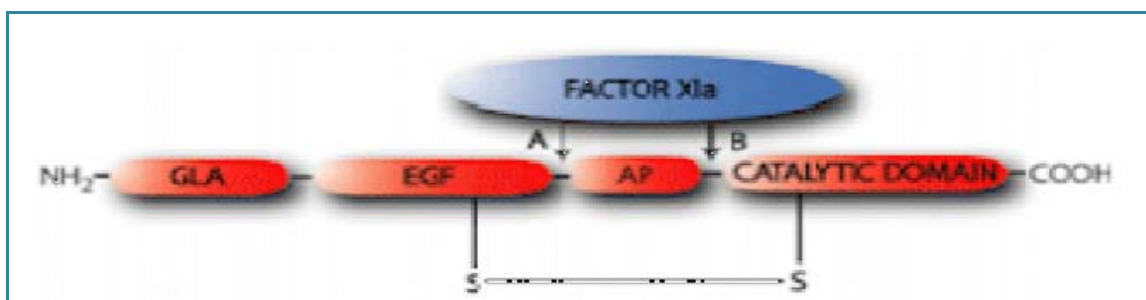


Figure 5: The domain structure of factor XI¹³ R1 - R4 correspond to four tandem amino acid sequence repeats (which ultimately comprise the heavy chain of factor XIa) during proteolytic activation by factor XIIa, the "CATALYTIC DOMAIN", which comprises the light chain of factor XIa, is cleaved from the heavy chain region. The heavy and light chains of factor XIa remain associated through a disulfide bond.

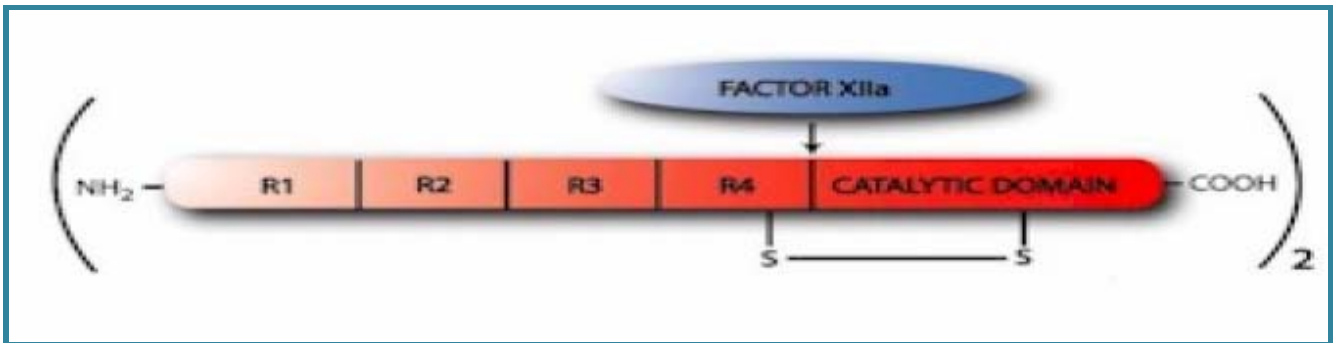


Figure 6: The inheritance pattern of hemophilia A and B

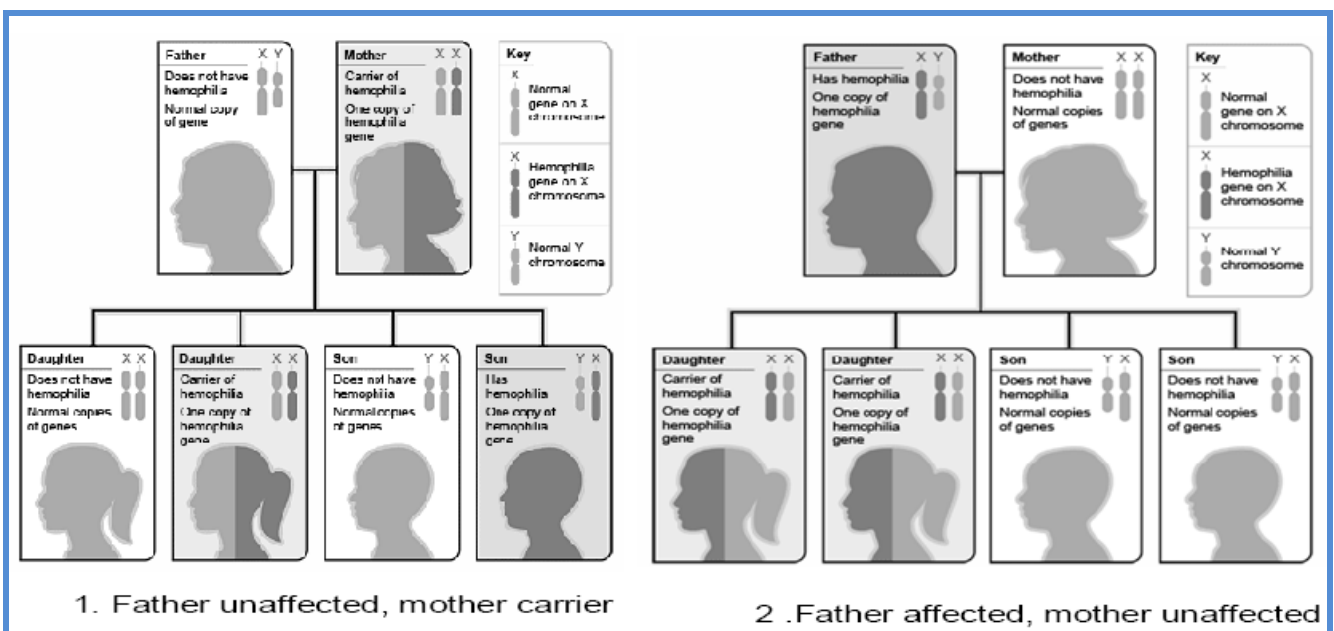
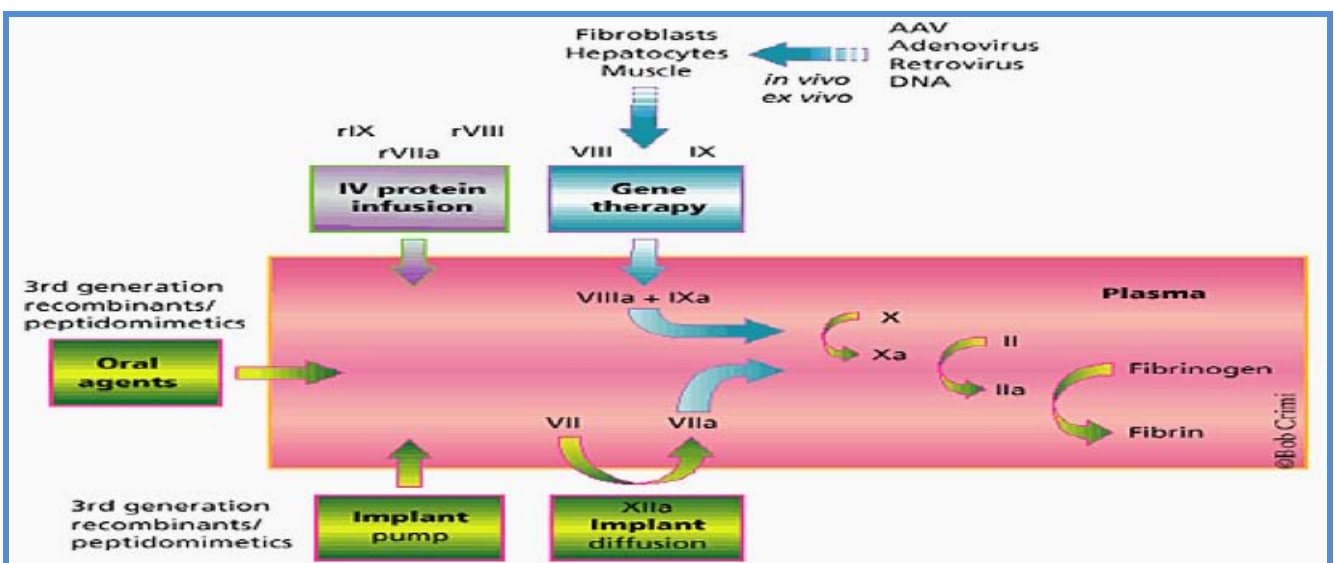


Figure 7: The possible future developments for the treatment of hemophilia



Von willebrand's factor (vWF)

vWF is a glycoprotein (MW 260,000 to >10,000,000) synthesized from endothelial cells and stored in intracellular organelles or secreted constitutively. The gene for the vWF is located on the chromosome 12. The vWF has dual role in hemostasis. a) It promotes platelet adhesion to thrombogenic surfaces as well as platelet to platelet cohesion during thrombus formation. b) It is the carrier for FVIII. The half life of the FVIII is considerably decreased in the absence of vWF because of the rapid degradation reaction. (Normal half life 12 hr) the plasma concentration of vWF is approximately 10 mcg/mL.¹²

FACTOR IX (FIX)

Description, Activation, Role in the coagulation and half life

FIX, a vitamin K-dependent single-chain glycoprotein (MW 55000), is synthesized by the hepatocytes as a precursor protein. It undergoes extensive posttranslational modification to become the fully gamma-carboxylated mature zymogen that is secreted into the blood.^{3, 5, 9}

Single-chain plasma FIX has the Gla domain (12 gamma-carboxyglutamic acid residues) at its amino terminal end (Fig .4). The Gla domain is responsible for Ca²⁺ binding, which is necessary for the binding of FIX to phospholipid membrane. The Gla region is followed by (1) two epidermal growth factor regions, (2) the activation peptide, which is removed when the single-chain zymogen FIX is converted to activated factor IX (FIXa), and (3) the catalytic domain, which contains the enzymatic activity.¹³

During the hemorrhage TF (Tissue Factor) becomes available, factor IX complexes with FVIIa or XIa and get activated. Following activation, the single-chain FIX becomes a 2-chain molecule, in which the two chains are linked by a disulfide bond attaching the catalytic region to the Gla domain. Activated factor VIII is the specific cofactor for the full expression of FIXa activity. Platelets not only provide the lipid surface on which solid-phase reactions occur, but they also possess a binding site for FIXa that promotes complex formation with FVIIIa and Ca²⁺.

The complex of FIXa, FVIIIa, Ca²⁺, and activated platelet (phospholipid surface) reaches its maximum potential to activate FX to FXa. This activator complex, which contains FIXa, is termed the intrinsic tenase complex ultimately lead to thrombin generation.

FIX is present in a concentration of 4-5 µg/mL with a half-life of approximately 18-24 hours.⁵

FACTOR XI

Description, Activation, Role in coagulation and half life

Factor XI (FXI) is produced by the liver and circulates as a homo-dimer in its inactive form (zymogen). It is a 160,000-d protein composed of a disulfide-linked dimer

with identical polypeptide chains (Fig .V). The gene controlling the production of plasma FXI is on the distal end of the long arm of chromosome 4.

This is activated by factor XIIa (FXIIa), thrombin, or it is auto catalyzed. FXIa complexes with high-molecular-weight kininogen, which then aids in the binding of FXIa to negatively, charged surfaces. FXIa remains on the surface and activates factor IX in plasma.

The plasma half-life of FXI is approximately 52 hours. FXI circulates at a concentration of approximately 5 mcg/mL.⁵

POSSIBLE REASONS FOR HEMOPHILIA

Inheritance

The gene for factor VIII and IX are both located on the "X" chromosome. [Female (XX) male (XY)]. Hemophilia is therefore said to be an "X" linked hereditary disorder. This results in males being affected by the disease while females are carriers. While affected males with no functioning factor VIII gene or IX gene have very low to no factor in blood, carrier females have at least one (out of two) functioning X chromosomes with a normal factor VIII or IX gene that provide about 50% factor levels. Carrier females who have excessive lyonisation (inactivation) of the normal X chromosome can have very low levels of factors and symptoms of bleeding. The inheritance pattern of both hemophilia A and B can be summarized as shown in the Fig .6.

Factor XI deficiency is usually an inherited condition, caused by a gene alteration. It is an autosomal recessive disorder, meaning that both parents must carry the affected gene in order to pass it to their children. However, some people have bleeding symptoms when it is known that only one of their parents was a carrier. In some cases, factor XI deficiency can occur spontaneously in people with no known family history.

Mutation

These include point mutations, inversions, deletions, and unidentified mutations which constitute 46%, 42%, 8%, 4%, respectively. It is of course also possible for a human to acquire it spontaneously (de novo), rather than inheriting it, because of a new mutation in one of their parents' gametes. Spontaneous mutations account for about 1/3 of all hemophilia.

DIAGNOSIS

The diagnosis of hemophilia cannot be made on clinical findings. A coagulation disorder is suspected in individuals with any of the symptoms specified in Table 1.

Tests available for the diagnosis

As most of the bleeding disorders having more or less clinical similarities it is important to identify exact situation to proceed with a more accurate therapy.



- 1) Basic screening tests for hemophilia
 - a) Bleeding time
 - b) Prothrombin time (PT)
 - c) Platelet count
 - d) Activated partial thromboplastin time (APTT)

2) Correction studies with factor deficient plasma

3) Factor assays

Individuals with a history of a lifelong bleeding tendency should have specific coagulation factor assays performed even if all the coagulation screening tests are in the normal range. The level of factors VIII, IX and XI depending upon the severity is summarized in Table .2 and Table .3

Table 2: Severity of hemophilia A&B depending upon the factor level present in the plasma

| Type | Factor level (VIII/IX) |
|----------|------------------------|
| Severe | < 1% |
| Moderate | 1-5% |
| Mild | 5-30% |
| Normal | 50-150% |

Table 3: Severity of Hemophilia C depending upon the factor level

| Type | Factor level (XI) |
|------------------------------------|------------------------------|
| Mild –Moderate Bleeding | 0-15% of normal factor level |
| Problems only after surgery/trauma | 15-70% of normal level |
| Normal | 60-140 % |

- 4) Molecular genetic testing
 - a) Sequence analysis
 - b) targeted sequence analysis
 - b) Deletion and duplication analysis
- 5) Linkage analysis (Mutation analysis)
 - a) Tracking an unidentified mutation
 - b) Identifying the origin of a de novo mutation
- 6) Carrier detection
 - a) Factor assay
 - b) DNA analysis
 - C) Phenotype analysis
 - d) Genotyping
- 7) Prenatal diagnosis (this is done if the fetus is suspected to have hemophilia)
 - a) CVS (chorionic villous sampling)
 - b) Amniocentesis

PRESENT TREATMENT OPTIONS

I. Factor concentrates

Infusions of factor concentrates are the most effective therapy available for hemophilia. There is no substitute for this therapy as it contains the corresponding factors in required quantity to stop the bleeding. Mainly there are two types of factor concentrates,

1) Plasma derived factor concentrates

Plasma derived virus inactivated factor VIII, IX and XI concentrates are available in the market. Each vial usually has 250- 1000 IU of factor activity. Bleeding episodes are controlled rapidly after intravenous infusions of factor concentrates. Some marketed products of plasma derived factors are shown in the Table 4. Fast, effective treatment of bleeding episodes prevents pain, disability, and chronic joint disease.

2) Recombinant factors

Plasma derived products are more susceptible to viral infections (HIV, hepatitis) Hence Recombinant factors are now well used in foreign countries some marketed products summarized in Table 4. (Not marketed in India) it contains only the corresponding factors.

II. Cryoprecipitate

It is prepared from the pooled blood and contains factor VIII, von willebrand factor, fibrinogen and factor XIII. It should have at least 80 IU of factor VIII activity and should be used as a replacement therapy in factor VIII deficiency.

III. Fresh frozen plasma (FFP)

If the plasma obtained from the donor within 6 hours, it can be considered as fresh plasma and contain the entire clotting factor in near normal quantities. If this plasma is frozen at or below – 30°C then it is called as FFP.

IV. Fresh whole blood

When no other products are available, fresh whole blood can be used as it contains all the clotting factors. Since wet products are not virus inactivated, at present there is a significance risk of transmission of HIV/ AIDS, hepatitis B and C. So screened donor has to be used to donate blood. The infusion should be continued until the bleeding stops.

V. Adjuvant therapies

Tranexamic acid

It is an anti fibrinolytic drug that competitively inhibits the activation of plasminogen to plasmin, a molecule responsible for the degradation of fibrin. Tranexamic acid is a synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect by blocking lysine-binding sites on plasminogen molecules. This inhibits the interaction of plasminogen and the heavy chain of plasmin with lysine residues on the surface of fibrin. Although plasmin can still form, it cannot bind to and degrade fibrin.



Table 4: Marketed factor concentrates (VIII, IX and XI)¹⁴

| Type | Plasma derived Factor | Recombinant Factor | Manufacturer |
|--------------|---|--|---|
| Hemophilia A | Biostate-CSL Hemofil M Humate Wilate | | CSL Baxter CSL Behring Octapharma |
| | | Helixate FS Kogenate FS Recombinate ReFacto Advate | Bayer Bayer Baxter Wyeth Baxter |
| Hemophilia B | Mono FIX-VF Immunine Mononine | | Baxter Aventis Behring CSL Behring |
| | | BeneFix | Wyeth |
| Hemophilia C | Factor XI Concentrate | | Bio Products Limited by BPL |

Tranexamic acid is mainly used to control mucosal bleedings. It is contraindicated to upper hematuria, due to the risk of formation of blood clots in the ureter and hydronephrosis.

Desmopressin (DDAVP)

It is a synthetic analog of the anti diuretic hormone vasopressin (1-deaminocys-8D arginini-vasopressin). It is useful in mild hemophilias who have a base line of factor FVIII >10% as it releases the stored FVIII from endothelial cells. It increases the factor level 2-10 times. Intra nasal sprays are also available. Some literatures reveal that it is also useful in the treatment of patient having low level of FXI.

Fibrin sealant

It is made by mixing fibrinogen and thrombin which mimics the last step in the blood coagulation cascade. A semi rigid to rigid fibrin clot consolidates and adhere to the application site and acts as a fluid tight sealing agent able to stop the bleeding. It is available as sprays and can be used on open wounds or for surgical homeostasis.

Factor eight inhibitor by pass activity (FEIBA)

FEIBA is an activated prothrombin complex concentrate available as FEIBA –TM-4 prepared from pooled human plasma, contains small amount of activated factors II, VII, IX and X. It has been used to treat joint, muscle, and soft tissue bleeding in patients with both high and low responder inhibitor titer.

Recombinant activated factor VIIa

rFVIIa is licensed by the US Food and Drug Administration for the treatment of bleeding in individuals with hemophilia A and B with acquired inhibitors. rFVIIa is produced in vitro in baby hamster kidney cells that are transferred with F7. Tissue factor-dependent and tissue factor-independent enhancement of thrombin generation have been suggested to play a role.^{14,15} Factor VIIa alone,

in the absence of tissue factor, can generate factor IXa and factor Xa on the surface of activated platelets, which, in turn, induces the coagulation cascade to form thrombin.^{16,17,18} In a recent study that evaluated rFVIIa in patients with acute intracerebral hemorrhage, the mortality was relatively reduced by 38% at 3 months when rFVIIa was administered within 4 hours of the hemorrhage.

Anti spasmodic analgesics

For the management of pain during the bleeding episode analgesic like Paracetamol, Dextropropoxyphene, Buscopan, Codeine, Buprenorphine, Tramadol can be used. New generation COX -2 inhibitors are also recommended.

Aspirin should be avoided because it increases the bleeding by inhibiting the platelet aggregation.

Corticosteroids

Prednisone is a corticosteroid drug with predominantly glucocorticoid and low mineralocorticoid activity, making it useful for the treatment of a wide range of inflammatory and auto-immune conditions. It is highly recommended for the treatment of macroscopic upper hematuria.

Calcium alginate

It is a polysaccharide that can be extracted from brown seaweed made in to fibers for swab. When this material is in contact with biological fluids, calcium alginate exchanges its calcium ion with sodium ion and gels.

PROBLEM WITH THE PRESENT THERAPY

Factor concentrates – Cost:

Factor concentrates includes infusion of factor concentrate (VIII & IX and XI) according to the severity of the bleeding. Administration should be continued till the symptoms subside. The half life of factor VIII is 12 hours



and for factor IX is 20 hrs. This increases the frequency of factor administration. The cost of 1 unit of factor is 6 rupees (1 unit /kg body wt), will produce a 2% rise in factor VIII activity and 1% rise in the factor IX activity. For controlling a normal bleed (mild) in a patient with 50 kg body weight, infusion containing at least 500 IU to raise the level 20% is needed. This will cause Rs 3000/- for factor VIII and Rs 6000 /- for FIX. Most of the bleeding episodes requires 50-80% rise to control the bleeding. This makes the cost of the therapy still higher. The available recombinant factors are costlier than plasma derived products.

Greater chance of viral infections

The repeated infusion of the blood products increases the risk of transmission of the most serious blood born disease HIV/AIDS, and hepatitis –B to hemophilic patients.

Development of inhibitors

Another threat of the present therapy is that the continuous administration of factor concentrates develops inhibitors (They are antibodies that neutralize the factor and can either be alloantibodies against exogenous or auto antibodies). The majority of inhibitors are IgG antibodies, more specifically of the IgG4 subclass. 10-20% of people with FVIII deficiency and 2-3% of people with FIX deficiency develops persistent inhibitors. The antibody attaches to the factor VIII or IX and neutralizes—or inhibits—its ability to stop bleeding. The treatment of hemophilic bleeding in a person with an inhibitor can be a challenging experience. When there is a large amount of antibody in the system, as reflected in a high Bethesda titer (The presence of an inhibitor is usually confirmed using a specific blood test called the Bethesda inhibitor assay. The amount of antibody can be measured using this test, and is reported as a number of Bethesda units, or a Bethesda titer. Therefore, the higher the number of Bethesda units or Bethesda titer the more inhibitor is present). Specific treatment with factor VIII or IX is usually not possible in this case because the inhibitor neutralizes even large factor doses.

PREVENTION

The transmittance of the hemophilia to the next generation can be prevented by the following methods.

- 1) Prenatal intrauterine diagnosis with termination of pregnancy as an option
- 2) Pre implantation genetic diagnostic testing (PGD)
- 3) IVF with egg/sperm donation

THERAPIES UNDER INVESTIGATION

Longer acting factor concentrates

A longer-acting factor VIII concentrate has recently been approved by the FDA for clinical trials. The hope is that one infusion a week rather than three to four infusions a week will provide prophylaxis against spontaneous bleeding.¹⁹

A preparation in which recombinant factor IX is fused to a portion of the immunoglobulin Fc protein shows prolonged survival and efficacy in animal models.²⁹ Clinical trials are planned but have not yet been initiated.

Gene therapy

Scientists at The Children's Hospital of Philadelphia conducted an experimental protocol involving dogs with a genetic defect predisposing them to develop hemophilia B. Functional genes capable of producing the clotting Factor IX were attached to an adeno-associated virus vector and injected into the leg muscles of the animals. The theory was that the genetically modified virus would carry the missing gene to muscle cells, which in turn would take up the gene and begin producing the clotting factor and releasing it into the blood stream.²¹

Sustained therapeutic expression of factors VIII and IX has been achieved in preclinical studies using a wide range of gene transfer technologies targeted at different tissues. This achievement has led to six different phase I/II clinical trials that resulted in limited efficacy but minimal toxicity. Recombinant adeno-associated viral vectors appear most promising for hemophilia gene therapy.²²

Attempts are being made to learn more about the immunology of inhibitors and ways to prevent them or improve the success rate of immune tolerance.²³

FUTURE

Gene therapy, oral delivery of factor concentrates, long acting infusions, controlled release implants, prolonged release of other adjuvant therapy drugs are the areas to be concentrated for making the life of hemophilic patients easier. A schematic representation is given in the Figure 7.

CONCLUSION

Hemophilia is a bleeding disorder, very hard to live with. As the number of patients reported with hemophilia is comparatively less than other major diseases like cancer, cardiac diseases, and diabetics it seems to be less concentrated area by researchers. As technologies develop, the days are not far away when hemophilia is treated with ease and even complete cure possible.

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