Introduction

The potential of the blood to coagulate is one of the most ancient facts of scientific knowledge. By the end of the 19th century, it was understood that an inert precursor, Prothrombin, could be activated in the presence of thrombokinase & calcium to produce thrombin & that thrombin was able to convert fibrinogen to fibrin. It was also known that platelets played a part in this process. Before the second World War the prothrombin time was described, heparin was discovered & it was realized that people with haemophilia were deficient in a factor present in the globulin fraction of plasma **(Colvin, 2004).**

After the War Ratnoff and Davie in the USA and Macfarlane in the UK described the "water fall" and "cascade" theories of blood coagulation, which helped to explain the increasingly complex function of the rapidly expanding numbers of discovered coagulation factors. Their presence was often revealed by the existence of patients with specific inherited deficiencies and it became apparent that series of delicate, balanced & dynamic reactions was taking place to secure the formation of a stable blood clot capable of preceding the process of wound healing while maintaining the circulation **(Colvin, 2004).**

Factor VII (formely known as proconvertin) is one of the central proteins in the coagulation cascade. The main role of factor VII (FVII) is to initiate the process of coagulation in conjunction with tissue factor (TFl factor III). Tissue factor is found on the outside of blood vessels normally not exposed to blood stream upon vessel injury, tissue factor is exposed to the blood & circulation, factor VII once bound to TF, FVII is activated to FVIIa by different proteases, among which are thrombin (factor IIa), factor Xa, XIIa & the FVIIa-TF complex itself. The most important substrates for FVIIa-TF are factor X & factor IX. The action of the factor is impeded by tissue factor pathway inhibitors (TFPI) which is released almost immediately after initiation of coagulation. Factor VII is vitamin k dependent; it is produced in the liver. Use of warfarin or similar anti-coagulants decreases hepatic synthesis of FVII. Deficiency is rare & inherits recessively **(Roberts et al., 2004).**

Recombinant human factor VIIa (novo seven) has been introduced for use in uncontrollable bleeding in haemophilia patients (with factor VII or IX deficiency) who have developed inhibitors against replacement coagulation factor. The first report of its use was in an Israeli soldier with uncontrollable bleeding in 1991. It is being increasingly used in uncontrollable bleeding, treatment of haemophilia, factor VII deficiency & glanzman thromboasthenia, treatment of both inherited & acquired coagulopathies as well as

thrombocytopathia or thrombocytopenia, treatment of spontaneous & perioperative intracranial hemorrhage as well as trauma patients. The rationale for its use in hemorrhage is that it will only induce coagulation in those sites where TF is also presents **(Kenet et al., 1999).**

Still, O'Connell et al. report an increased risk of deep vein thrombosis, pulmonary embolism & myocardial infarction in association with the use of rhFVIIa. A 2008 meta-analysis of randomized controlled trials of rhFVIIa in patients without hemophilia showed no additional risk of deep vein thrombosis or pulmonary embolism & the risk of arterial thrombosis to be substantially less the potential to reduce mortality **(Hsia et al., 2008).**

In 2010, a larger study combining the results of 35 trials showed a definite increase in arterial thrombosis, the risk of which was higher in older patients. According to a 2005 study, Recombinant human factor VII improves outcomes in acute intracerebral hemorrhage but a more recent, larger 2008 study by the same group to address these initial findings failed to show any mortality benefit. Factor VII is no longer recommended in the treatment of patients with intracerebral hemorrhage **(Levi et al., 2010).**

Aim of the Work

The aim of the work is to review the role of recombinant activated factor VII in treatment of bleeding, methods of administrations, precautions, contraindications & adverse affects.

Chapter (I):
Anatomy & Pathophysiology of Haemostasis

The blood vessels are the part of the circulatory system that transports blood throughout the body. There are three major types of blood vessels: the arteries, which carry the blood away from the heart; the capillaries, which enable the actual exchange of gases and chemicals between the blood and the tissues; and the veins, which carry blood from the capillaries back toward the heart ***(Gidaspow et al., 1992).***

The arteries and veins have different structures, veins having two layers and arteries having three:

- ***Tunica intima*** (the thinnest layer): a single layer of simple squamous endothelial cells glued by a polysaccharide intercellular matrix, surrounded by a thin layer of subendothelial connective tissue interlaced with a number of circularly arranged elastic bands called the *internal elastic lamina*.
- ***Tunica media*** (the thickest layer): circularly arranged elastic fiber, connective tissue and polysaccharide substances. The second and third layer are separated by another thick elastic band called external elastic lamina. The tunica media may (especially in arteries) be rich in vascular smooth muscle, which controls the caliber of the vessel.

- ***Tunica adventitia*:** entirely made of connective tissue. It also contains nerves that supply the vessel as well as nutrient capillaries (vasa vasorum) in the larger blood vessels.

Capillaries consist of a layer of endothelium and occasional connective tissue ***(Gidaspow et al., 1992).***

Hemostasis

The term *hemostasis* means prevention of blood loss. Whenever a vessel is severed or ruptured, hemostasis is achieved by several mechanisms: (1) vascular constriction, (2) formation of a platelet plug, (3) formation of a blood clot as a result of blood coagulation, and (4) eventual growth of fibrous tissue into the blood clot to close the hole in the vessel permanently ***(Roberts et al., 2004).***

Vascular Constriction

Immediately after a blood vessel has been cut or ruptured, the trauma to the vessel wall itself causes the smooth muscle in the wall to contract; this instantaneously reduces the flow of blood from the ruptured vessel. The contraction results from (1) local myogenic spasm, (2) local autacoid factors from the traumatized tissues and blood platelets, and (3) nervous reflexes. The nervous reflexes are initiated by pain nerve impulses or other sensory impulses that originate from the traumatized vessel or nearby tissues. However, even more vasoconstriction probably results from

local *myogenic contraction* of the blood vessels initiated by direct damage to the vascular wall. And, for the smaller vessels, the platelets are responsible for much of the vasoconstriction by releasing a vasoconstrictor substance, *thromboxane A2*. The spasm can last for many minutes or even hours, during which time the processes of platelet plugging and blood coagulation can take place ***(Brass, 2003).***

Formation of the Platelet Plug

If the cut in the blood vessel is very small—indeed, many very small vascular holes do develop throughout the body each day—the cut is often sealed by a *platelet plug,* rather than by a blood clot. To understand this, it is important that we first discuss the nature of platelets themselves ***(Brass, 2003).***

Physical and Chemical Characteristics of Platelets

Platelets (also called *thrombocytes*) are minute discs 1 to 4 micrometers in diameter. They are formed in the bone marrow from *megakaryocytes*, which are extremely large cells of the hematopoietic series in the marrow; the megakaryocytes fragment into the minute platelets either in the bone marrow or soon after entering the blood, especially as they squeeze through capillaries. The normal concentration of platelets in the blood is between 150,000 and 300,000 per microliter ***(Tsai, 2003).***

Platelets have many functional characteristics of whole cells, even though they do not have nuclei and cannot

reproduce. In their cytoplasm are such active factors as (1) *actin* and *myosin molecules*, which are contractile proteins similar to those found in muscle cells, and still another contractile protein, *thrombosthenin*, that can cause the platelets to contract; (2) residuals of both the *endoplasmic reticulum* and the *Golgi apparatus* that synthesize various enzymes and especially store large quantities of calcium ions; (3) mitochondria and enzyme systems that are capable of forming *adenosine triphosphate* (ATP) and *adenosine diphosphate* (ADP); (4) enzyme systems that synthesize *prostaglandins*, which are local hormones that cause many vascular and other local tissue reactions; (5) an important protein called *fibrin-stabilizing factor*, which is related to blood coagulation; and (6) a *growth factor* that causes vascular endothelial cells, vascular smooth muscle cells, and fibroblasts to multiply and grow, thus causing cellular growth that eventually helps repair damaged vascular walls ***(Tsai, 2003).***

The cell membrane of the platelets is also important. On its surface is a coat of *glycoproteins* that repulses adherence to normal endothelium and yet causes adherence to *injured* areas of the vessel wall, especially to injured endothelial cells and even more so to any exposed collagen from deep within the vessel wall. In addition, the platelet membrane contains large amounts of *phospholipids* that activate multiple stages in the blood-clotting process ***(Dorsam and Kunapuli, 2004).***

Thus, the platelet is an active structure. It has a halflife in the blood of 8 to 12 days, so that over several weeks its functional processes run out. Then it is eliminated from the circulation mainly by the tissue macrophage system. More than one half of the platelets are removed by macrophages in the spleen, where the blood passes through a latticework of tight trabeculae ***(Solum, 1999).***

Platelets contribute to vascular homeostasis in multiple ways. In the arterial circulation they are the first responders to breaks in vascular integrity, adhering to exposed vWF, recruiting passing platelets to form a platelet plug, and releasing vasoconstrictors to reduce blood loss. Factor XIII and platelet factor 4, both released from platelet granules during activation, protect the nascent clot from fibrinolysis. By contrast, in the venous circulation, the platelet's role is more ancillary, providing a surface replete with receptors for coagulation factors and a source of negatively charged phospholipids to optimize the kinetics of the soluble coagulation cascade. Adhesive ligands and growth factors, released from platelet granules, promote clot consolidation and wound healing, respectively ***(Roberts et al., 2004).***

Mechanism of the Platelet Plug

Platelet repair of vascular openings is based on several important functions of the platelet itself. When platelets come in contact with a damaged vascular surface, especially

with collagen fibers in the vascular wall, the platelets themselves immediately change their own characteristics drastically. They begin to swell; they assume irregular forms with numerous irradiating pseudopods protruding from their surfaces; their contractile proteins contract forcefully and cause the release of granules that contain multiple active factors; they become sticky so that they adhere to collagen in the tissues and to a protein called *von Willebrand factor* that leaks into the traumatized tissue from the plasma; they secrete large quantities of ADP; and their enzymes form *thromboxane A2*. The ADP and thromboxane in turn act on nearby platelets to activate them as well, and the stickiness of these additional platelets causes them to adhere to the original activated platelets ***(Geddis and Kaushansky, 2004).***

Therefore, at the site of any opening in a blood vessel wall, the damaged vascular wall activates successively increasing numbers of platelets that themselves attract more and more additional platelets, thus forming a *platelet plug.* This is at first a loose plug, but it is usually successful in blocking blood loss if the vascular opening is small. Then, during the subsequent process of blood coagulation, *fibrin threads* form. These attach tightly to the platelets, thus constructing san unyielding plug ***(Caprini et al., 2004).***

Formation of Blood Clot

The third mechanism for hemostasis is formation of the blood clot. The clot begins to develop in 15 to 20 seconds if the trauma to the vascular wall has been severe, and in 1 to 2 minutes if the trauma has been minor. Activator substances from the traumatized vascular wall, from platelets, and from blood proteins adhering to the traumatized vascular wall initiate the clotting process ***(Kahn and Ginsberg, 2004).***

Within 3 to 6 minutes after rupture of a vessel, if the vessel opening is not too large, the entire opening or broken end of the vessel is filled with clot. After 20 minutes to an hour, the clot retracts; this closes the vessel still further. Platelets also play an important role in this clot retraction ***(Koreth et al., 2004).***

Fibrous Organization or Dissolution of the Blood Clot

Once a blood clot has formed, it can follow one of two courses: (1) It can become invaded by *fibroblasts*, which subsequently form connective tissue all through the clot, or (2) it can dissolve. The usual course for a clot that forms in a small hole of a vessel wall is invasion by fibroblasts, beginning within a few hours after the clot is formed (which is promoted at least partially by *growth factor* secreted by platelets). This continues to complete organization of the clot into fibrous tissue within about 1 to 2 weeks ***(Levi, 2014).***

Conversely, when excess blood has leaked into the tissues and tissue clots have occurred where they are not needed, special substances within the clot itself usually become activated. These function as enzymes to dissolve the clot ***(Levi, 2004).***

Mechanism of Blood Coagulation

More than 50 important substances that cause or affect blood coagulation have been found in the blood and in the tissues-some that promote coagulation, called *procoagulants*, and others that inhibit coagulation, called *anticoagulants*. Whether blood will coagulate depends on the balance between these two groups of substances. In the blood stream, the anticoagulants normally predominate, so that the blood does not coagulate while it is circulating in the blood vessels. But when a vessel is ruptured, procoagulants from the area of tissue damage become "activated" and override the anticoagulants, and then a clot does develop ***(Saenko et al., 2003).***

All research workers in the field of blood coagulation agree that clotting takes place in three essential steps: (1) In response to rupture of the vessel or damage to the blood itself, a complex cascade of chemical reactions occurs in the blood involving more than a dozen blood coagulation factors. The net result is formation of a complex of activated substances collectively called *prothrombin activator* (2) The

prothrombin activator catalyzes conversion of *prothrombin* into *thrombin* (3) The thrombin acts as an enzyme to convert *fibrinogen* into *fibrin fibers* that enmesh platelets, blood cells, and plasma to form the clot ***(Brass, 2003).***

Conversion of Prothrombin to Thrombin **Prothrombin and Thrombin.**

Prothrombin is a plasma protein, an alpha2 globulin, having a molecular weight of 68,700. It is present in normal plasma in a concentration of about 15 mg/dl. It is an unstable protein that can split easily into smaller compounds, one of which is *thrombin*, which has a molecular weight of 33,700, almost exactly one half that of prothrombin ***(Toh and Dennis, 2003).***

Prothrombin is formed continually by the liver, and it is continually being used throughout the body for blood clotting. If the liver fails to produce prothrombin, in a day or so prothrombin concentration in the plasma falls too low to provide normal blood coagulation. Vitamin K is required by the liver for normal formation of prothrombin as well as for formation of a few other clotting factors. Therefore, either lack of vitamin K or the presence of liver disease that prevents normal prothrombin formation can decrease the prothrombin level so low that a bleeding tendency results ***(Toh and Dennis, 2003).***

First, prothrombin activator is formed as a result of rupture of a blood vessel or as a result of damage to special substances in the blood. Second, the prothrombin activator, in the presence of sufficient amounts of ionic Ca++, causes conversion of prothrombin to thrombin. Third, the thrombin causes polymerization of fibrinogen molecules into fibrin fibers within another 10 to 15 seconds. Thus, the rate-limiting factor in causing blood coagulation is usually the formation of prothrombin activator and not the subsequent reactions beyond that point, because these terminal steps normally occur rapidly to form the clot itself ***(Brass, 2003).***

Platelets also play an important role in the conversion of prothrombin to thrombin because much of the prothrombin first attaches to prothrombin receptors on the platelets already bound to the damaged tissue ***(Solum, 1999).***

Conversion of Fibrinogen to Fibrin-Formation of the Clot

Fibrinogen.

Fibrinogen is a high-molecular-weight protein (MW = 340,000) that occurs in the plasma in quantities of 100 to 700 mg/dl. Fibrinogen is formed in the liver, and liver disease can decrease the concentration of circulating fibrinogen, as it does the concentration of prothrombin. Because of its large molecular size, little fibrinogen normally leaks from the blood vessels into the interstitial fluids, and because

fibrinogen is one of the essential factors in the coagulation process, interstitial fluids ordinarily do not coagulate. Yet, when the permeability of the capillaries becomes pathologically increased, fibrinogen does then leak into the tissue fluids in sufficient quantities to allow clotting of these fluids in much the same way that plasma and whole blood can clot **(Moake, 2002)**

Action of Thrombin on Fibrinogen to Form Fibrin.

Thrombin is a protein *enzyme* with weak proteolytic capabilities. It acts on fibrinogen to remove four low-molecular weight peptides from each molecule of fibrinogen, forming one molecule of *fibrin monomer* that has the automatic capability to polymerize with other fibrin monomer molecules to form fibrin fibers. Therefore, many fibrin monomer molecules polymerize within seconds into *long fibrin fibers* that constitute the *reticulum* of the blood clot ***(Lindsberg and Kaste, 2003).***

In the early stages of polymerization, the fibrin monomer molecules are held together by weak noncovalent hydrogen bonding, and the newly forming fibers are not cross-linked with one another; therefore, the resultant clot is weak and can be broken apart with ease. But another process occurs during the next few minutes that greatly strengthens the fibrin reticulum ***(Roberts et al., 2004).***