

RECOMBINANT ACTIVATED FACTOR VII IS IT A UNIVERSAL HAEMOSTATIC AGENT?

Asoka Gunaratne*

Consultant Anaesthetist, Teaching Hospital Karapitiya, Galle

*Corresponding author: E-mail : asoka.gunaratne@yahoo.com

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Process of coagulation

The newer time based model of coagulation could better explain the process of initiation, amplification, propagation and stabilization. This cannot be well explained by the historical intrinsic and the extrinsic pathways. The model also highlights the importance of platelets in the chain of reactions in coagulation. As depicted in **figure 1** the reactions in the historic extrinsic pathway are coined in **initiation**. Tissue factor (TF) is considered to be the principle initiator. TF is a membrane bound lipoprotein expressed on cells in the sub endothelium (TF bearing cells). Tissue injury disrupts the endothelial cell barrier that normally separates TF-bearing cells from the circulating blood. Once exposed to the blood, TF serves as a high affinity receptor for FVII. Activated FVII is found in the circulation at concentrations roughly corresponding to 1% of total FVII protein mass. FVII alone shows very little proteolytic activity. This complex activate factor X which convert prothrombin to thrombin, the primary thrombin burst.

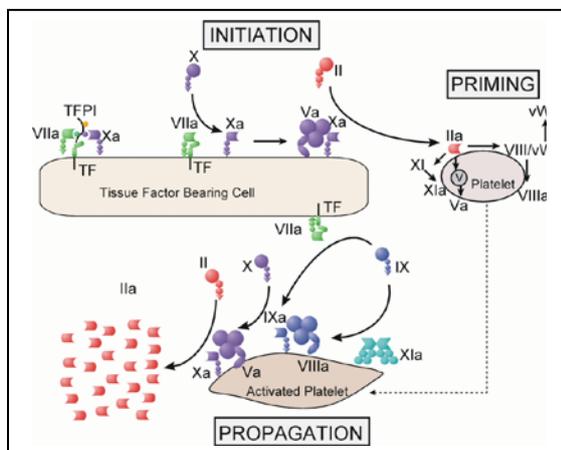


Figure 1

The platelets at the site of damaged endothelium get attached to the sub endothelium via the Von Willebrand's factor. This causes platelet activation (**figure 2**).

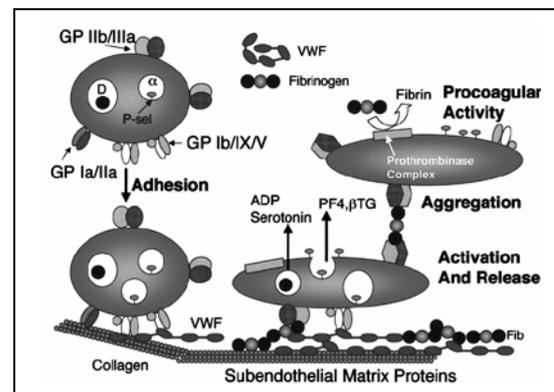


Figure 2

The thrombin generated in the primary thrombin burst also act on the platelets to activate them at the site of injury (figure 1). The activated platelets change their morphology, release their granular contents including factor V and aggregate. Activated platelets also provide a procoagulant surface for clotting factors. All the factors in the historical intrinsic pathway get activated on the activated platelet surface. This chain of reaction leads to a huge secondary thrombin burst (**figure 1**). This **amplification** process play an important part at this juncture because the quantity of thrombin generated in initiation is not sufficient to convert fibrinogen in to fibrin. **Propagation** occurs due to production of large amounts of factor Xa mainly through activation by factor IXa. Thrombin acts in a

positive feed back loop to activate other factors. **Stabilization** mediated by factor XIII occurs when thrombin reaches a peak level.

Functions of thrombin

- Cleave fibrinogen to fibrin
- Activate platelets
- Activate factors V, VIII and XI in a positive feed back loop
- Stabilize the clot by the activation of factor XIII and thrombin activatable fibrinolytic inhibitor (TAFI)
- Activate protein C

Haemophilia and coagulation

Haemophilia is a condition in which factor VIII is deficient (haemophilia A) or factor IX is deficient (haemophilia B). Though the primary thrombin burst could take place in the absence of factor VIII or IX the secondary thrombin burst is absent (**figure 3**). It has already been mentioned that the primary thrombin burst is insufficient to convert fibrinogen to fibrin. As a result these patients form a loose clot which dissolves quickly by the fibrinolytic system.

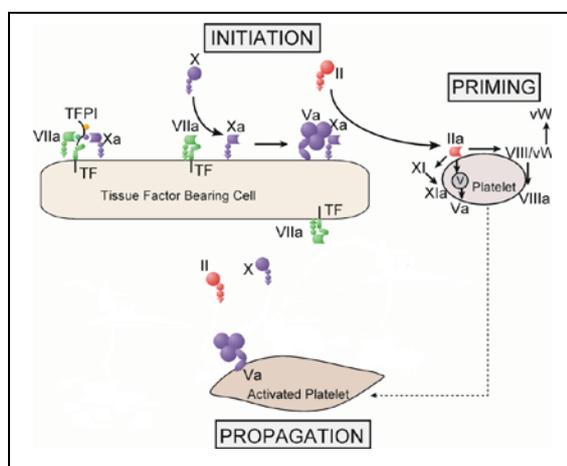


Figure 3

Haemophilia was treated traditionally with replacement of factors VIII or IX concentrates. However some of these patients (up to 36%)¹ developed antibodies or inhibitors to these factors. This incidence of inhibitor development may be 50% in children.² Such patients were treated with supraphysiological doses of factor concentrate (immune tolerance therapy) with the hope that some amount of factors will still remain in circulation available for coagulation after the majority of it binds with the inhibitors.¹

rFVIIa for the treatment of haemophilia

The Food and Drug Administration (FDA) approved rFVIIa in March 1999 for the treatment of bleeding episodes in patients with haemophilia A or B or who have developed inhibitors to factors VII or IX. It is also used in factor VII deficiency and Glanzmann thrombasthenia in some countries.³

Mode of action of recombinant activated factor VII (rFVIIa)

FVIIa binds loosely to the activated platelet. However given in supra-physiological doses rFVIIa can bind to the activated platelet and convert FX to Xa on the platelet surface.¹ This reaction which is independent of factors V, VIII, IX and XI can produce a thrombin burst sufficient enough to convert fibrinogen to fibrin (**figure 4**). As rFVIIa act at the site of vascular injury where TF is exposed and activated platelets are found, its action is primarily at sites of tissue damage. Given intravenously rFVIIa has a half life of approximately 2.5 hours.⁴

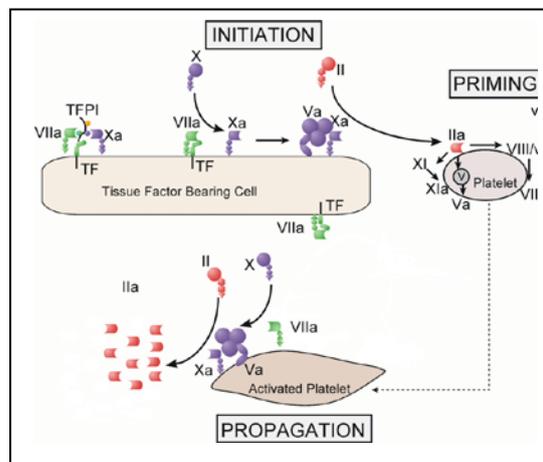


Figure 4

Off-label uses of rFVIIa

As evidenced by published literature rFVIIa has been successfully use in a variety of bleeding disorders and coagulopathies for which it has not been adequately studied.⁵ Some of the stated advantages of rFVIIa, as opposed to other haemostatic treatments (FFP, platelet concentrate, packed cells and cryoprecipitate), include a belief that since rFVIIa is not active unless it binds with TF, it will not induce systemic coagulation. Second, the activity of rFVII is not altered by the presence of clotting

inhibitors. Third, there is no risk of transmission of infection since rFVIIa is not a human derived blood product. Potential off-label uses include the following.

- Variety of congenital and acquired platelet disorders
- To reverse per oral anticoagulant or antiplatelet therapy
- Coagulopathy due to liver disease
- Diffuse bleeding triggered by surgery and trauma
- D.I.C.
- As a rescue intervention in patients with intractable bleeding despite other therapeutic measures
- As prophylaxis for small bleeds at dangerous sites (e.g. liver / epidural haematoma)

It has been recommended that the patient has a fibrinogen level > 0.5g/dl and a platelet count > 50,000 before the use of rFVIIa. However the bulk of the evidence of off-label uses is in the form of case reports and case series. Therefore the appropriate dose for each indication, the dosing interval, whether or not to combine with other haemostatic agents (e.g. aminocaproic acid, tranexamic acid), optimal timing for use, need for repeat doses, etc. is not clear.

Monitoring

Laboratory coagulation parameters (e.g. PT, aPTT) may be monitored together with monitoring for clinical signs of a haemostatic response. However, there is no evidence correlating achievement of haemostasis and an effect of rFVIIa on these coagulation parameters.

Dose

The recommended dose and dosing interval for rFVIIa are available for FDA approved indications (e.g. haemophilia A or B with inhibitors prior to surgery or during active bleeding). It ranges from 90-120 mcg /kg /dose every 2 – 4 hours.¹ At this time, there is no

sufficient evidence to suggest a particular dose for off-label indications. Additionally, from the available data, there is not a clear dose response relationship for achieving haemostasis. However, one group has recommended 50-100 mcg /kg in individuals weighing 50-100 kg. While another group has recommended a dose of 20-40 mcg/kg for anticoagulation reversal and doses of 40-90 mcg/kg for other appropriate scenarios.

Safety

rFVIIa may contain traces of foreign proteins from the manufacturing process. There is a potential for a harmful antibody response in some persons.³ Inhibitors can develop against FVII. However, there are no reported cases of inhibitors developed against rFVIIa.³ Thromboembolic events (TE) correspond to 2 events /10,000. In more than 800,000 doses given TE reported were around 1%.

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