

Recombinant Factor VIIA

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MJAFI 2009; 65 : 59-61

Key Words : Recombinant factor VII; Hemophilia; Hemorrhage

Introduction

Recombinant activated factor VII (rFVIIa) was originally developed for the treatment of hemophilic patients with inhibitors and then used successfully for treating hemorrhages in patients with acquired hemophilia. In the last few years, along with the improvement in the knowledge of its mechanisms of action, rFVIIa has also been used with benefit as a “universal hemostatic agent” in many other nonhemophilic bleeding situations, including congenital FVII deficiencies, quantitative and qualitative platelet disorders, hepatic failure, liver transplantation, major surgery and trauma [1]. This review briefly analyzes the uses of rFVIIa in treatment and focuses particularly on the newer uses, for which there are only a few randomized, controlled clinical trials. Table 1 summarizes the current approved and “off-label” clinical applications of rFVIIa.

Mechanisms of Action and Pharmacokinetics

Recombinant activated factor VII is an important contributor to the initiation of hemostasis [2]. According to a cell-based model of coagulation, tissue factor (TF) is exposed to circulating blood following injury to the vessel wall and TF-FVIIa complexes are formed on the TF-bearing cells, where they activate factor X (FX) to produce activated FX (FXa), leading to the conversion of prothrombin to thrombin (Fig.1). The limited amount of thrombin formed activates FV, FVIII, and FXI, as well as platelets, which in turn change shape and expose negatively charged phospholipids, such as phosphatidylserine. These activated platelets provide the template for further FX activation and full thrombin generation with a positive feedback on FV, FVIII, and FXI. The extra formation of thrombin results in the activation of thrombin-activatable fibrinolysis inhibitor (TAFI), which protects the fibrin clot from premature lysis by down-regulating fibrinolysis. The direct activation of FIX on activated platelets in the absence of TF,

resulting in improved thrombin generation, may also explain the mechanism of rFVIIa action in acquired coagulopathy following trauma, surgery. Moreover, the binding of rFVIIa to activated platelets may explain why rFVIIa is localized only to the site of bleeding. The rapid decrease of rFVIIa level in vivo means that this drug must be given as frequent bolus injections (every 2-4 hours) or as a continuous infusion [2]. All published studies show that treatment with rFVIIa can be effective at doses between 35 and 120 µg/kg. Effective doses are independent of the inhibitor titer, with the standard recommended dose being 90 µg/kg given as a bolus and repeated after two hours. When more than two doses are necessary to ensure and maintain hemostasis in uncomplicated bleeding episodes, the dose interval may be prolonged to every four hours for 1 to 2 days and then every six hours until discontinuation, depending on the size and severity of the bleed. [1].

Use in Hemophilic Patients

Hemophilia A and B is treatable with highly purified plasma-derived and recombinant DNA- derived factor VIII and factor IX concentrates. However, a well recognized and potentially life-threatening complication

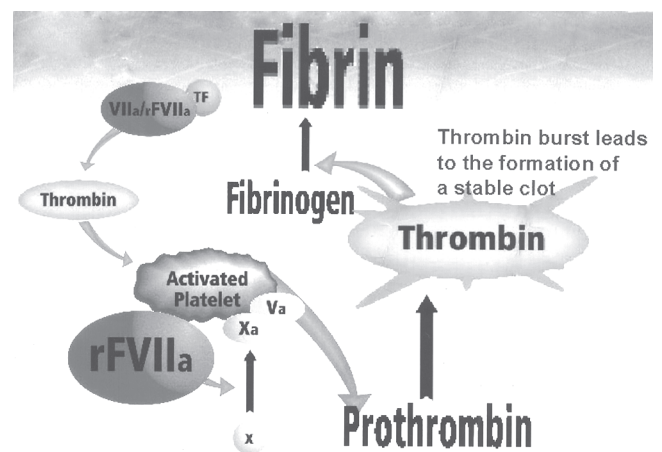


Fig. 1 : Role of rFVIIa in causing thrombin burst

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of hemophilia is the development of neutralizing antibodies against the missing factor. Up to 25 % of patients develop an inhibitor to factor VIII, and 3-5% to factor IX. To date, therapeutic interventions in these situations have included large doses of factor VIII and activated/non-activated prothrombin complex concentrates and porcine FVIII. All these have significant drawbacks including high cost, unpredictability of response, transmission of blood-derived infections, thromboembolic complications and in the case of porcine FVIII, development of anti-porcine antibodies. All these existing therapeutic caveats led to the development of rFVIIa as a potential solution for treating hemophilia patients with inhibitors and in acquired hemophilia [3]. The standard (and approved) intravenous (IV) dose of rFVIIa in hemophilia patients with an inhibitor is 90 µg per kg until hemostasis is achieved; for surgical patients, repeated doses are given every two hours until hemostasis is achieved and less frequently thereafter[4].

Use of rFVIIa in Platelet Disorders

In inherited thrombocytopenia, rFVIIa was reported to enhance local fibrin deposition and to partially restore platelet aggregates in Glanzmann thrombasthenia and Bernard-Soulier syndrome [3]. In these patients first the coagulopathy is corrected with platelets, fresh frozen plasma (FFP) and cryoprecipitate. Subsequently desmopressin is administered and rFVIIa is given at a dose of 50-100 µg/kg, which is titrated with the clinical response [4].

Use of rFVIIa in Liver Disorders

The coagulopathy of liver disease is due to decreased synthesis of vitamin K-dependent coagulation factors (particularly FVII, protein C and protein S), increased

fibrinolysis, and thrombocytopenia. Traditional therapies include vitamin K, FFP, desmopressin and platelets. Trials of rFVIIa in doses of 100 µg/kg have been successful [3].

Use of rFVIIa in Trauma and Surgery

rFVIIa has been successfully used in moribund trauma patients in whom standard procedures failed to correct bleeding. Successful use of rFVIIa to control bleeding in a 19 year old Israeli soldier with a high velocity bullet injury has been reported, when standard measures failed to restore hemostasis, administration of 60mcg/ kg rFVIIa substantially reduced bleeding and a second dose after one hour resulted in complete cessation of bleeding [5]. There are some reports demonstrating the efficacy of rFVIIa in controlling intraoperative bleeding during liver surgery and in pulmonary hemorrhage [1]. A standard protocol used in trauma is shown in Fig. 2 [6].

Use of rFVIIa for Reversal of Anticoagulant Therapy

rFVIIa has also been employed in the reversal of warfarin therapy in cases in which the administration of vitamin K alone was found to be insufficient in doses between 20 and 90 µg per kg [4].

rFVIIa in Intracerebral Hemorrhage

The volume of bleeding into the brain is an important predictor of neurological and clinical outcomes after 30 days and it has been well documented that such bleeding continues over the early hours following symptom onset. The incorporation of rFVIIa dose reduces the rate of formation of hematoma. [7].

Use of rFVIIa in Other Conditions

There are reports on the use of rFVIIa for type III von Willebrand disease, congenital factor VII deficiency (20µg/kg with FFP- two hourly till hemostasis is achieved), factor XI and IX deficiency and in patients with extensive burns or uremia having bleeding [1].

Safety of rFVIIa

The mechanism of rFVIIa in initiating hemostasis has led to concerns that besides acting locally at the site of vessel injury, more widespread coagulation could be possible if tissue factor is in contact with plasma, e.g., when tissue factor is upregulated on the surface of circulating monocytes in the setting of gram negative septicemia/ endotoxemia resulting in disseminated intravascular coagulation (DIC). Tissue factor is expressed within the lipid core of atherosclerotic plaques and is exposed at the sites of plaque fissure which can lead to myocardial infarction. rFVIIa should not be used in patients with a known hypersensitivity to mouse, hamster or bovine proteins.

Table 1

Approved and potential clinical applications of recombinant activated factor VII

Hemophilia and clotting defects

- Hemophilia with inhibitors
- Acquired hemophilia
- Congenital factor VII deficiency
- Glanzmann thrombasthenia
- Other platelet disorders (qualitative and quantitative)
- Other coagulation factor defects (factor XI and von Willebrand disease)

Emergency bleeds

- Intracerebral hemorrhage
- Upper gastrointestinal bleeds
- Trauma

Oral anticoagulant-induced hemorrhage surgery

- Liver resection
- Orthotopic liver transplantation
- Neurosurgery
- Cardiac surgery

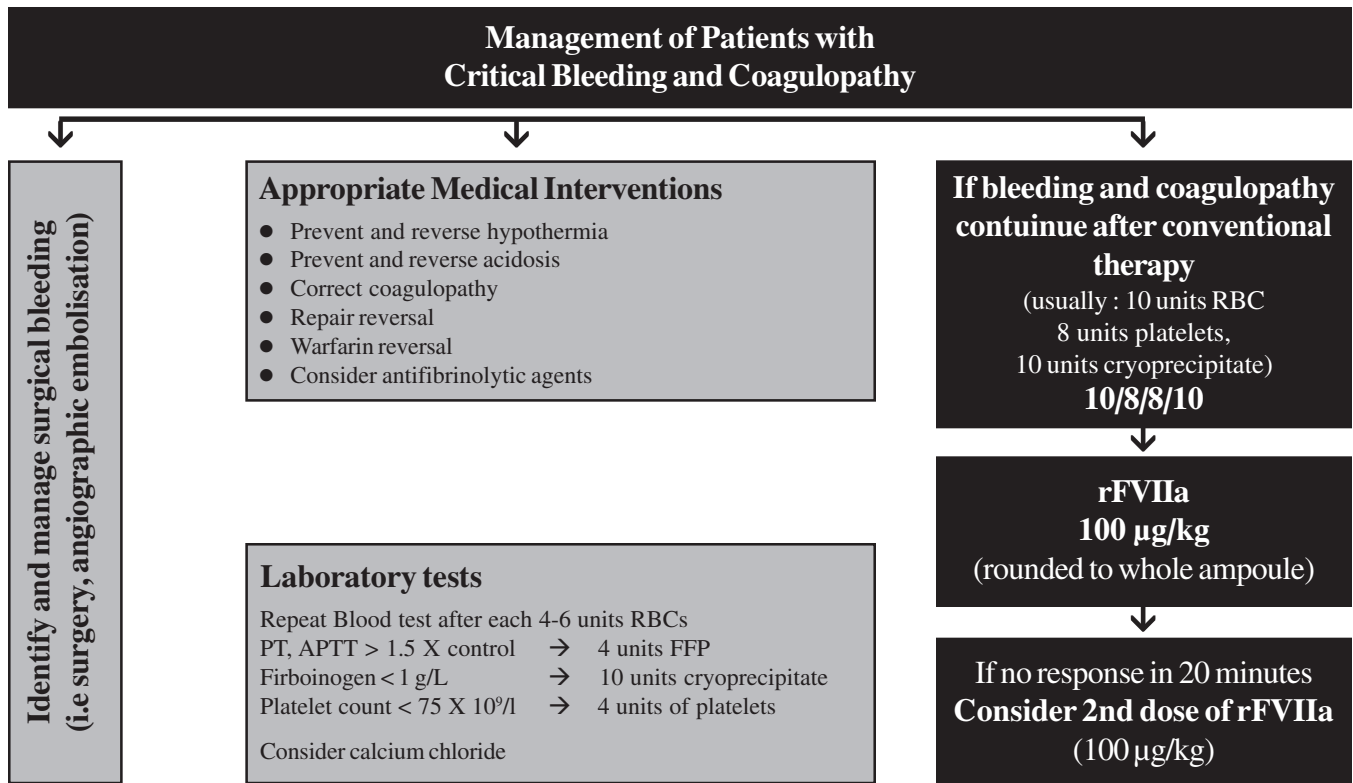


Fig. 2: rFVIIa protocol recommended in moribund trauma patients [6]

Of the more than 1,70,000 standard doses of rFVIIa given after its approval (almost all to patients with hemophilia and inhibitors), only rare (<1:11,300) thrombotic events have been reported. This thromboembolic phenomenon is the primary concern which includes cerebral and pulmonary thromboembolism. Due to the thrombotic potential of rFVIIa, it is felt that it should not be combined with activated protein C and should be used in patients with life-threatening bleeding or cases with no identifiable surgical source and failure to respond to blood component therapy. Use of activated factor concentrates should be used with caution in patients with known hypercoagulability (e.g. history of thrombotic complications, established thrombotic disorders like factor V Leiden, antiphospholipid syndrome, etc.) or those having excessive bleeding in the setting of DIC or other states of generalized activation of the hemostatic system (e.g., after cardiac surgery) based on the potential for development of localized or systemic intravascular thrombosis [4].

The cost/benefit ratio associated with the use of rFVIIa is currently not fully known. Although the drug itself is expensive (about Rs. 3,00,000 per 100 mcg/kg dose), more rapid correction of traumatic coagulopathy will substantially reduce transfusion requirements and

may impact ventilator days and the need for dialysis. It is possible that an initial timely therapy with rFVIIa will ultimately reduce the economic burden associated with transfusion therapy, organ system support and critical care [1].

Conflicts of Interest

None identified

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