Rational Use of Recombinant Factor VIIa in Clinical Practice

T. K. Dutta · S. P. Verma

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Abstract In the United States, the FDA-approved indications for recombinant factor VIIa is for bypassing inhibitors to factors VIII and IX in patients with hemophilia A and B respectively and for treatment of congenital factor VII deficiency. In European countries, rFVIIa is licensed for the above indications as well as for Glanzmann's thrombasthenia. In absence of high-quality data favoring off-label use of this agent and laboratory test to predict response to this agent, and in view of high cost of rFVIIa, off-label use of recombinant factor VIIa should be restricted to only when hemorrhage has not responded to transfusion or other conventional therapy. It appears, two such conditions where recombinant factor VIIa may be beneficial are traumatic and postpartum hemorrhages.

Keywords Recombinant Factor VIIa (rFVIIa) · Hemophilia with inhibitors · Postpartum hemorrhage

Introduction

In recent years, there has been a tremendous increase in the use of recombinant activated factor VII (rFVIIa). This is due to compassionate use of rFVIIa in almost all the bleeding situations to control bleeding even if approved indications are not there. The current worldwide clinical scenario is that the use of rFVIIa has increased more than 100 times than in the previous decade and more than 90 % of these uses are off-label uses. Its apparent safety and

utility in a variety of settings like traumatic bleed, post-operative bleed, postpartum hemorrhage (PPH), spontaneous cerebral hemorrhage, anticoagulant overdose and other conditions, most of which are not supported by clinical trials, has led to its use in less emergent conditions. Today most of the practitioners use this drug in these “off-label” settings. Purpose of this review is to explore the potential benefits, risks and cost effectiveness of rFVIIa on the basis of evaluation of various recent trials and meta-analysis of studies done for various indications.

Recombinant Factor VIIa: Mechanism of Action

Recombinant factor VIIa is produced by transfection of the human factor VII gene into baby hamster kidney cells cultured in bovine albumin. It is commercially available since December 1995. It has an amino acid sequence identical to that of plasma-derived factor VII. As a recombinant product, it is not derived from human or animal plasma, so there is no risk of blood transmitted diseases. Along with the recommended use, off-label use as a general haemostatic agent has been tried in various indications.

The current concept of hemostasis suggests that hemostasis occurs principally on two types of surfaces, the tissue factor (TF) bearing cell and the thrombin-activated platelet. The initiation of hemostasis occurs on the TF-bearing cell surface as a result of the exposure of TF to the vessel wall following an injury. TF is receptor for FVII and activated FVII. Following injury, TF forms a complex with the FVII or FVIIa on the surface of TF bearing cell. This results in limited amount of thrombin generation. Thrombin activates platelets. Thrombin activated platelets expose phospholipids which further support the binding of

T. K. Dutta (✉) · S. P. Verma
Division of Clinical Hematology, Department of Medicine,
Jawaharlal Institute of Postgraduate Medical Education
& Research, Puducherry 605006, India
e-mail: tkduttajipmer@yahoo.co.uk

Fig. 1 Proposed mechanism of action of rFVIIa

the coagulation factors and thereby facilitate the full thrombin burst necessary for effective hemostasis (Fig. 1).

Ordinarily, the activity of FVIIa/TF at the site of injury is needed to initiate coagulation. When administered in doses sufficient to bypass the need for FVIII and FIX, rFVIIa binds to the surface of activated platelets and promotes factor X activation and thrombin generation localized at the site of injury [1]. This activation is independent of TF. The general mechanism of action of rFVIIa to induce hemostasis may be by its capacity to generate a tight fibrin hemostatic plug through increased thrombin generation. A tight fibrin plug aids in resisting the action of local fibrinolytic enzymes triggered by tissue damage which occurs in any trauma.

This formed clot is complex and very strong. In complex situations, there is even a risk of thrombo-embolic complications associated with the use of rFVIIa. However, the risk seems to be very low even in the presence of a disseminated intravascular coagulopathy (DIC). According to the manufacturers' published data, major or minor thrombotic events have occurred in a frequency of about one in 5,500 doses when transfused to patients of hemophilia. Pharmacokinetic properties of rFVIIa are predictable and well characterized. Half-life of rFVIIa is 2.7 h [2].

Activity of rFVIIa is decreased in presence of decreased levels of other coagulation factors and co-factors, thrombocytopenia and acidosis. However, its activity is maintained at lower temperature when overall haemostatic function of body is impaired.

Clinical Uses

Hemophilia with Inhibitors

On treatment with factor concentrates, patient may develop inhibitory IgG antibodies to FVIII or FIX (alloantibody) in hemophilia A or B respectively. Inhibitor formation occurs in up to 36 % of patients with severe hemophilia A [3] and

3–5 % of patients with hemophilia B. Inhibitor formation is currently one of the most significant complications affecting patients with hemophilia. Inhibitors bind FVIII/IX and prevent its hemostatic action and render factor VIII/IX replacement ineffective in treatment of bleeding episodes in surgical and nonsurgical settings. Treatment includes agents "Bypassing" the deficient factor [4]. Recombinant factor VIIa is the preferred bypassing agent. Standard doses are 90–120 mcg/kg given every 2–3 h till effective hemostasis is achieved. It is effective in 92 % of treated bleeds after a mean of 2.2 injections [5]. Target joints are more difficult to treat. It is reasonable to use up to 270 mcg/kg for treatment of target joint bleeds. It has been shown to be effective and well tolerated in majority of these patients with no evidence of an anamnestic response or antibody formation against factor VII. Still dosing levels, intervals, duration of treatment and method of administration are subject to considerable variation at different medical centers. The issue of continuous versus bolus infusion is still not solved although few studies have shown bolus dose better than continuous infusion.

Glanzmann's Thrombasthenia

It is a rare inherited autosomal recessive bleeding disorder due to defect in glycoprotein GP IIb–IIIa present on platelets which results in absent or defective fibrinogen binding. Acute bleeding in patients of Glanzmann's thrombasthenia can be treated by rFVIIa. Repeated platelet transfusions can induce anti-glycoprotein GP IIb–IIIa or anti-HLA alloimmunisation. This can be a real challenge in surgical setting or in acute nonsurgical bleeding. rFVIIa as the first line therapy in patients with Glanzmann's thrombasthenia or with anti-GP IIb–IIIa iso-antibodies, who were scheduled for surgery, had excellent clinical efficacy in a study of three patients [6]. Several other studies have shown the efficacy of rFVIIa in Glanzmann's thrombasthenia. The current recommended dose of rFVIIa in Glanzmann's thrombasthenia is 90 mcg/kg every 2 h until hemostasis occurs.

Factor VII Deficiency

FVII deficiency is a rare (1 in 500,000 live births) inherited coagulation disorder, historically treated with FFP, prothrombin complex concentrates or plasma derived FVII concentrates. One study [7] used rFVIIa successfully for treating bleeding episodes in their FVII deficient patients. Twenty-seven spontaneous bleeding episodes, seven major and 13 minor surgical interventions were treated using a mean dose of 22–26 mcg/kg. Excellent hemostasis could be achieved in all patients. Other studies have also

Table 1 Approved indications for rFVIIa

United States Food and Drug Administration (FDA) approved indications

- Treatment or prevention of bleeding in patients with hemophilia A or B who have inhibitors to factors VIII or IX, respectively
- Treatment or prevention of bleeding episodes in patients with acquired hemophilia
- Treatment or prevention of bleeding episodes in patients with congenital factor VII deficiency

European approved indications

- Bypassing inhibitors to factors VIII and IX in patients with hemophilia A and B
- Treatment of congenital factor VII deficiency
- Glanzmann's thrombasthenia

supported the role of rFVIIa in FVII deficiency. The recommended dose of rFVIIa in factor VII deficiency is 15–30 mcg/kg every 4–6 h until hemostasis is achieved. Table 1 summarizes approved indications for rFVIIa.

Off-Label Uses

Recombinant FVIIa is being used as a “general hemostatic agent” to enhance hemostasis in patients with bleeding who may or may not have an underlying coagulation defect. During its early development, rFVIIa was demonstrated to have haemostatic effect in conditions like thrombocytopenia, platelet function abnormalities and warfarin over-anticoagulation. Literature concerning off-label use of rFVIIa is expanding rapidly. One database based retrospective study has shown a 140-fold increase in use between 2000 and 2008 and 97 % of these uses have been off-label [8]. Most of these clinical situations (Table 2) were adult and pediatric cardiac surgery, brain and body trauma and intracranial hemorrhage.

Traumatic Bleeding

One of the first off-label uses of rFVIIa in trauma patients was in an Israeli soldier who suffered extensive bleeding following a gunshot wound to the abdomen in the year 1999. This patient underwent extensive abdominal surgery to control bleeding and required multiple transfusions of red cells, plasma, cryoprecipitate, and platelets resulting in hemodilution, hypothermia, and a severe coagulopathy characterized by thrombocytopenia and deranged coagulation profile. In an attempt to control hemorrhage, the patient

was given 60 µg/kg of body weight of rFVIIa on two occasions with subsequent dramatic control of the hemorrhage. This triggered an interest in the use of high-dose rFVIIa therapy in patients with a wide range of bleeding conditions which could not be managed by conventional therapy [9].

In a series, seven critically ill trauma patients with severe hemorrhage were treated with rFVIIa. Dose administered ranged between 40 and 120 mcg/kg to arrest bleeding; four patients survived while three non-survivals were most likely due to the very unsalvageable nature of injury [10].

Two randomized, multi-center controlled trials of the use of rFVIIa for this indication are available. One trial enrolled 143 bleeding patients with severe blunt trauma and the other enrolled 134 bleeding patients with penetrating trauma [11]. Six units of blood were given to these patients within 4 h of admission before enrolment to the study. Patients assigned to receive rFVIIa received three doses of drug (200, 100 and 100 mcg/kg). The first dose was given after the eighth unit of red cells and the two subsequent doses were given 1 and 3 h later. There was a statistically significant reduction in red blood cell transfusion and need for massive (>20 unit) transfusion in blunt trauma patients. There was a similar trend in the penetrating trauma group. There were no differences in adverse events, such as thrombo-embolism or mortality, between the treatment groups in either study. These studies have been however criticized on several counts and interpreted as showing no benefit, since overall mortality was the same.

In another study, a retrospective analysis was done to find the patient group likely to benefit from treatment with rFVIIa. Logistic regression analysis of 380 injured patients who received this agent as an adjunct for bleeding control indicated that systolic blood pressure >90 mm Hg, platelet count >100 000/µl, and a blood pH ≥ 7.2 were associated with significantly improved survival for this group of patients [12].

Perioperative Blood Loss

Following surgery, patients may develop a coagulopathy with uncontrollable microvascular bleeding. Basic management includes controlling hypothermia and acidosis,

Table 2 Common conditions where off-label use of rFVIIa is practiced

Traumatic bleeding
Peri-operative blood loss
Postpartum hemorrhage
Spontaneous intracerebral hemorrhage
Bleeding in liver diseases
Anticoagulant associated bleeding

and blood component transfusion. Recombinant FVIIa has generally been used when conventional therapy failed. First randomized controlled trial of rFVIIa on perioperative bleeding was done to see its effect to prevent or reduce bleeding in patients undergoing retropubic prostatectomy. [13] Blood loss and perioperative need for transfusions were reduced at intravenous bolus doses of 20–40 mcg/kg.

A randomized placebo controlled dose escalation trial evaluated safety and efficacy of rFVIIa in 68 patients who had post cardiac surgery bleeding [14]. Two treated groups were there receiving 40 and 80 mcg/kg rFVIIa respectively. Significantly, fewer patients in both groups underwent reoperation or required allogeneic transfusion as a result of bleeding. However critical serious events (deaths, cerebral infarction, thromboembolic events) were observed more in rFVIIa treated groups, although not statistically significant.

Some reports demonstrated the efficacy of rFVIIa in controlling intra-operative bleeding during liver surgery, which is known to be associated with a higher degree of blood loss as compared to other types of surgery. One study has demonstrated that a single dose of rFVIIa (80 mcg/kg) could reduce transfusion requirements in cirrhotic patients undergoing orthotopic liver transplant [15]. Controlled trials have shown rFVIIa to be of no benefit in reducing transfusion in liver resection or transplantation.

A meta-analysis of seven randomized controlled trials of the safety and efficacy of rFVIIa in major surgical procedures concluded that treatment with rFVIIa was associated with reduced requirement of packed red cell transfusion, without any significant difference in thromboembolic complications or mortality rates [16]. Significant treatment benefit was only seen in patients receiving a dose of at least 50 mcg/kg body weight.

Postpartum Hemorrhage

Severe bleeding remains a leading cause of morbidity and mortality in obstetrics. The first-line standard treatment of massive PPH includes medical measures directed at improving uterine tone, replacement of lost intravascular volume, blood and coagulation factors, and surgical or invasive procedures. A case series study of ten patients with major PPH from India showed that there was good response to doses ranging from 20 to 80 µg/kg of rFVIIa in all the cases, after failure of usual medical management of PPH [17]. In a review, a critical analysis of the published literature on the use of rFVIIa in severe PPH was done [18]. Overall, a total of 272 PPH women were collected among the largest case series and/or international registries. Data suggested that, at a median dose of 81.5 mcg/kg, rFVIIa is effective in stopping or reducing bleeding in

85 % of the cases. There has been recently an unpublished report from India of its benefit in preventing hysterectomy in a study of five patients. However, there have been no randomized controlled trials on this aspect.

Spontaneous Intracerebral Hemorrhage (ICH)

ICH is a serious medical emergency. The volume of bleed into the brain is a strong predictor of clinical and neurological outcomes after 30 days. Bleeding in ICH continues over the early hours following symptom onset. Among patients who undergo computed tomography (CT) within 3 h after the onset of ICH, one-third have an increase in the volume of the hematoma related to subsequent bleeding. Recently one study was done by Mayer et al. including 399 patients of ICH who underwent CT scan within 3 h of stroke and received placebo (96 patients) or 40 mcg/kg (108 patients), 80 mcg/kg (92 patients) and 160 mcg/kg (103 patients) doses of rFVIIa within 1 h of the baseline scan [19]. The mean increase in hematoma volume was 29 % in the placebo group, as compared to 16, 14, and 11 % respectively in the three treatment groups ($p = 0.01$). Growth in the volume of ICH was reduced by 3.3, 4.5, and 5.8 ml respectively in the three treatment groups, as compared to that in the placebo group ($p = 0.01$). Mortality at 90 days was 29 % for patients who received placebo, as compared to 18 % in the three rFVIIa groups combined ($p = 0.02$). Serious thromboembolic adverse events, mainly myocardial or cerebral infarction, occurred in 7 % of rFVIIa-treated patients as compared to 2 % of those given placebo and this was not statistically significant. Study reported encouraging results—showed that early administration of rFVIIa is associated with reduced haematoma growth at 24 h and improved clinical outcome at 90 days with marginal risk of thromboembolic phenomena.

However, recently published results of a phase three randomized trial including 841 patients of ICH by the same group concluded that haemostatic therapy with rFVIIa reduced growth of the haematoma but did not improve survival or functional outcome after ICH [20]. Study also showed increased risk of thromboembolism, particularly arterial, in rFVIIa treated group.

Bleeding in Liver Diseases

Two major facts make us think about the use of rFVIIa in hepatic coagulopathy patients. Firstly factor VII has the shortest half life of all the procoagulant factors synthesized in liver and secondly in many cases the volume of plasma required to maintain coagulation factors at hemostatic levels is not tolerated well in patients with significant liver disease. Given the paucity of the published data and lack of

randomized trials, there is not enough evidence to support the use of recombinant activated factor VII in liver disorders with bleeding; and randomized, controlled clinical trials are needed to better define the role of recombinant activated factor VII in such situation.

Excessive Warfarin Associated Bleeding

A case series of 13 patients with critically prolonged INR and bleeding complications due to warfarin showed that they were treated successively and rapidly in all patients, regardless of rFVIIa dose (range, 15–90 µg/kg of body weight) [21]. Indications for use of rFVIIa were an INR >10 in high-risk persons ($n = 5$), clinical hemorrhage ($n = 4$), and diagnostic or therapeutic procedures ($n = 4$). Study concluded that safe, rapid, and effective administration of rFVIIa corrects critically prolonged INRs and can avert or reverse bleeding associated with warfarin anticoagulation. However, it may be a costly affair because warfarin associated bleeding can be treated easily with FFP and vitamin K supplementation.

Meta-analysis and Systematic Review

While there is overwhelming evidence that rVIIa has hemostatic effect in various bleeding conditions, appropriate settings, guidelines for use, risk of complications, appropriate dose and monitoring are still to be answered. These issues were explored to some extent in two recent meta-analysis (Table 3).

2008 meta-analysis of 22 randomized controlled trials of rFVIIa in 3,184 patients without hemophilia showed that those receiving rFVIIa were less likely to require additional transfusions compared to those receiving placebo [22]. However, use of rFVIIa did not significantly decrease mortality nor did it increase the incidence of thromboembolic events.

2011 systemic review of 16 randomized controlled trials and 26 comparative observational studies and 22 non-comparative observational studies reached at a conclusion that for five indications—intracranial hemorrhage, cardiac surgery, trauma, liver transplantation and prostatectomy

there was no evidence that rVIIa changed overall survival [23]. In two of these five indications i.e., intracranial hemorrhage and cardiac surgery, there was rather evidence for an increased risk of thromboembolism.

Issues of Dosing and Laboratory Monitoring

Optimal dose and dosing regimen is still not well defined for rFVIIa in various clinical conditions [24]. Dosing is purely empirical since there is no laboratory test which correlates well with the clinical efficacy of rFVIIa. Functioning of rFVIIa requires platelets and other coagulation factors and deficiency of these two have been shown to affect the degree of thrombin generation at a given level of rFVIIa [25]. A test could be devised involving both these parameters which probably may give an accurate estimate of rFVIIa activity and probability to achieve effective haemostasis.

Safety Issues

Initial use of rFVIIa was supposed to incite the significant risk of thrombosis. Later on, its use in hemophiliacs with inhibitors showed good safety records even if used in doses of 346 mcg/kg. Pre-existing risk factors for thrombosis have also been found to be contributory. Overall reported incidence of thromboembolic events with use of rVIIa has ranged from 1–2 % [26] to up to 9.8 % [19].

Most of these complications have been associated with off-label use of rFVIIa. In a recent review of adverse outcomes reported to USFDA, unlabelled indications accounted for 90 % of the reports. Reported events were arterial thrombosis, thromboembolic cerebrovascular accidents, acute myocardial infarction, pulmonary embolism and venous thrombosis. Thromboembolic events were the probable cause of death in 36 out of total 50 deaths [27].

Cost Issues

Cost benefit ratio associated with use of rVIIa is not fully known. The drug is expensive and costs around 10,000\$ per 100 mcg/kg dose in USA. In Indian setting, single

Table 3 Summary of results of recent meta-analysis for off-label uses of rFVIIa

Meta-analysis	Results
Hsia et al. [22].	<ul style="list-style-type: none"> - Less need for additional transfusion - No mortality benefit - No increase in risk of thrombosis
Yank et al. [23].	<ul style="list-style-type: none"> - No overall survival benefit for five indications (cardiac surgery, intracranial hemorrhage, body trauma, liver transplantation and prostatectomy) - Increased risk of thromboembolism in cardiac surgery and intracranial hemorrhage

therapeutic dose of Novoseven will cost about 200,000 rupees. No proven survival benefit has been shown in randomized trials and meta-analysis which are available for off-label indications. Thus, considering the cost factor and serious adverse effects, the use of rFVIIa should be made cautiously in non-approved situations.

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