

Expert Opinion

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Management of bleeding emergencies: when to use recombinant activated Factor VII

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Recombinant activated Factor VII (rVIIa) was originally released as a clotting factor, with use limited to a select group of patients who had few other treatment options. Due to the apparent ability of rVIIa to stop bleeding, no matter what the underlying cause, there is great interest in use of rVIIa in a wide range of bleeding patients. This article discusses rVIIa and its uses in a variety of patients, especially liver disease and trauma patients, and makes suggestions for appropriate use. Although most of the reports on rVIIa are anecdotes and case series, there is increasing data for clinical trials to help guide usage.

Keywords: bleeding emergencies, haemorrhage, recombinant activated Factor VII, transfusion

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1. Introduction

Recombinant Factor VIIa (rVIIa) was originally released to help haemophiliacs complicated by inhibitors to transfused factors. In the past several years there has been an explosion of publications concerning the use of rVIIa for a variety of situations, leading some to claim that rVIIa is a 'pan haemostatic agent' [1-3]. Temper- ing this enthusiasm is the fact that few randomised, or even prospective, trials of rVIIa exist. This review analyses the use of rVIIa, with the main focus on its use in the treatment of emergency bleeding in both medical and surgical patients.

2. Recombinant Factor VIIa

rVIIa is a recombinant protein, with a molecular weight of 50 kDa, and has the same amino acid sequence as native VIIa. When infused, its half-life is 2 – 3 h [4-6]. The dose recommended for patients with Factor VIII and IX deficiencies complicated by inhibitors is 90 µg/kg [7]. This dose was chosen as it consistently produces a plasma rVIIa level > 10 U/ml, which is thought to be the level necessary for cessation of bleeding. When a lower dose of 35 µg/kg was compared with 90 µg/kg in a randomised trial of haemophiliacs undergoing surgery, bleeding was increased in the 35 µg/kg group [8]. However, in a trial of rVIIa for muscle and soft-tissue bleeding, 35 µg/kg was equivalent to 70 µg/kg [8]. Dosing for other indications is arbitrary, with most reports using the 90-µg/kg dose. It does seem that lower doses are effective for select situations, such as intracerebral haemorrhage and warfarin reversal. There is some evidence of the use of megadoses (300 µg/kg) of rVIIa for young haemophiliacs, which may lead to a rapid haemostatic response without the need for repeat dosing [4,9]. However, these large doses raise the concern about increasing the prothrombotic risk, and have not yet been studied in adults.

The lack of an accepted method of monitoring rVIIa hinders dosing decisions. Normally, routine clotting tests, such as the International Normalized Ratio (INR) and activated partial thromboplastin time (aPTT) will shorten after rVIIa is infused, but this is insufficient to ensure that an effective haemostatic dose has been given.

The use of plasma VIIa levels is controversial, and is not an assay that is widely available. Early work with thrombelastography indicates that it may be useful, but more trials need to be performed [10].

The mechanisms of action of rVIIa remains controversial [5,6,11]. Tissue factor is a membrane-bound protein that is exposed with trauma. Coagulation is initiated when circulating VIIa binds to tissue factor. One theory of rVIIa effect is that the supraphysiological concentrations of rVIIa speeds up the tissue factor–VIIa-mediated reaction, such as activation of Factor X and IX, resulting in more thrombin generation [12]. In a cell-based system, rVIIa can bind to platelets and directly activate Factor X and IX without the need for tissue factor [13]. Finally, recent data indicate that rVIIa can enhance platelet aggregation and adhesion via an increase in thrombin generation [14].

3. Other non-transfusion therapy of bleeding

Many physicians are tempted to use rVIIa for severe bleeding immediately. However, rVIIa is not the only non-transfusion therapy available for bleeding [15,16]. Both desmopressin and antifibrinolytic agents also serve as useful – and less expensive – adjuncts for therapy of the bleeding patient.

Desmopressin is a synthetic analogue of antidiuretic hormone that, when infused, raises the levels of both Factor VIII and von Willebrand proteins several-fold [17]. Desmopressin has been shown to be effective in supporting haemostasis in patients with a wide variety of congenital and acquired bleeding disorders [18–20]. However, prophylactic desmopressin does not reduce blood loss before routine surgery in healthy patients [21,22].

Aminocaproic acid and tranexamic acid function as anti-fibrinolytic agents by blocking the binding of plasmin to fibrinogen [23,24]. These agents are useful in four situations. One is in the presence of excessive fibrinolysis. This most often occurs in liver disease, but may rarely complicate amyloidosis or be associated with congenital defects for fibrinolysis [25–28]. Antifibrinolytic agents are also useful as adjunctive therapy for oral or dental procedures in patients with a bleeding diathesis [29]. Antifibrinolytics can prevent blood loss in a variety of surgeries, including heart bypass, liver transplantation and orthopaedic surgery [30,31]. Finally, in patients with severe thrombocytopenia, the use of anti-fibrinolytic agents may reduce bleeding [32,33].

4. Transfusion therapy

Transfusion of blood products is the crucial therapy used in massive bleeding, and a reasonable attempt needs to be made to correct the patient coagulation defect with blood products before rVIIa use can be considered. In the past, massive transfusion of > 20 units of blood was associated with a high mortality rate [34], but with modern blood banking techniques and improved laboratory testing, this rate has decreased dramatically. Recent studies showed a survival rate of 43 – 70% in patients transfused > 50 units of blood [35–37].

The approach to massive transfusions is to perform five laboratory tests, which reflect the basic parameters essential for both blood volume and haemostasis. The tests are: i) haematocrit; ii) platelet count; iii) prothrombin time (PT-INR); iv) aPTT; and v) fibrinogen level.

Haematocrit goals vary with the clinical situation. For the rapidly-bleeding patient, blood is given until the patient is haemodynamically stable. For patients who are mainly suffering from derangements in coagulation, a lower haematocrit goal may be more appropriate. For a platelet count of < 50 – 75,000/ μ l, a plateletpheresis concentrate or 6 – 8 pack of single-donor platelet concentrate is given to the patient. As the platelets are suspended in plasma, this transfusion will also provide plasma to the patient. For a fibrinogen level of < 100 mg/dl, 10 units of cryoprecipitate should be given. This should raise fibrinogen by 100 mg/dl. For an INR > 3.0, with an abnormal aPTT, 2 – 4 units of fresh frozen plasma should be administered. For an aPTT > 1.5-times the normal, 2 – 4 units of plasma should be administered. If the aPTT is markedly elevated (> 80 s) one should make sure the sample is not contaminated by heparin. If both the PT-INR and aPTT is increased, then the fibrinogen may be low.

The basic five laboratory tests are repeated after administering the blood products. This ensures adequate replacement therapy was given for the abnormal laboratories.

In many situations, the use of both transfusion and non-transfusion therapy is insufficient to halt bleeding or are unable to correct the coagulation defect. It is in these situations that rVIIa may have a clinical role.

5. Use of rVIIa in medical patients

5.1 Haemophiliacs with inhibitors

The availability of specific factor concentrates was a breakthrough for haemophilia therapy, allowing correction of the bleeding defect. Unfortunately, 30% of severe Factor VIII and 5 – 10% of Factor IX-deficient patients will develop inhibitors to the infused factors, rendering these products useless [38]. For a long time, management of these patients was frustrating, as the only blood products shown to decrease bleeding were activated prothrombin complex concentrates (APCCs) [39]. APCCs were more effective than plasma, but carried the risk of thrombosis and virally-transmitted disease [40,41]. The use of rVIIa has allowed patients with inhibitors to undergo complex surgery, and has become a widely accepted choice for inhibitor patients [2,42–44].

5.2 Other Factor deficiencies

Factor VII deficiency is rare (1:500,000), but rVIIa is an effective therapy for these patients [45]. The doses required are less than in inhibitor patients (15 – 30 μ g/kg), and there seems to be benefit in three-times-weekly prophylactic dosing to prevent major haemorrhage [46].

Factor XI deficiency is common in certain populations, with the incidence of heterozygous disease as high as 5 – 10% in

Ashkenazi Jews [45,47]. There is a Factor XI concentrate, but use has been marred by an increased incidence of thromboembolic events, and is not available in the US [48]. There are increasing reports of the use of rVIIa for patients with Factor XI deficiencies undergoing surgical procedures [49-51]. Given both the safety and availability issues with Factor XI concentrates, rVIIa is the therapy of choice for severe bleeding.

5.3 Acquired Factor inhibitors

Acquired Factor VIII deficiency due to autoantibodies is the most frequent acquired factor deficiency. This can be seen in patients with autoimmune disease, older patients and postpartum women [52,53]. Patients with acquired Factor VIII inhibitors present with diffuse and severe bleeding. Unlike classic haemophiliacs, these patients will have ecchymoses covering large areas of their body. Patients can bleed from anywhere, but the gastrointestinal tract and skin are the most common sites.

Therapy is twofold, aimed at correcting the haemostatic defect and ridding the patient of the inhibitor. Recombinant VIIa is becoming the treatment of choice for inhibitor patients [4,52,54,55]. For bleeding patients, the dosing is 90 µg/kg repeated every 2 h until the bleeding has stopped. For patients who require surgery or have life-threatening bleeding, the rVIIa should be 'weaned', by decreasing the dose to every 6 h, for several days, after 2 – 3 days of successful every-2-h therapy. rVIIa is safer in these patients than APCC, due to its decreased thrombotic risk [40].

The other key therapy for these patients is immunosuppression to eliminate the inhibitor. Aggressive immunosuppression with the use of multiple agents, such as prednisone, immune globulin, cyclophosphamide and rituximab, can eventually rid most patients of the offending autoantibody [56,57].

Acquired von Willebrand disease (vWD) has been reported to occur in lymphomas, myeloproliferative syndromes, myeloma, monoclonal gammopathies and with the use of certain drugs [58-60]. The most common drug-induced aetiology is administration of hydroxyethyl starch. Rarely, acquired vWD has been reported with valproic acid and ciprofloxacin [61].

The most common presentations are diffuse oozing from surgical sites or gastrointestinal bleeding [62]. As vWD does not often affect routine tests of coagulation, the diagnosis can be overlooked if not specifically sought. Patients with acquired vWD have variable responses to therapy [59,63]. Desmopressin, immune globulin and Humate-P (a factor concentrate containing von Willebrand factor) is effective in many patients with acquired vWD [64-66]. For patients with very strong inhibitors that Factor concentrates cannot overcome, rVIIa is proving useful and is indicated for patients with life-threatening bleeding [67,68].

5.4 Thrombocytopenia and platelet dysfunction

As noted above, *in vitro* data supports the idea that rVIIa can augment platelet function. The strongest clinical evidence for

this is the effectiveness of rVIIa in patients with Glanzmann thrombasthaenia, an inherited disorder of platelet function [69-73]. When rVIIa is used rapidly after the onset of bleeding, it is effective in 77 – 90% of bleeding cases. Use of rVIIa for Glanzmann thrombasthaenia is an approved indication for rVIIa in Europe. Given the role of rVIIa in augmenting and replacing platelet function, it is not surprising that there is increasing interest in its use in thrombocytopenic patients. Multiple case reports of successful use of rVIIa in bleeding thrombocytopenic patients exist [14,69,74,75]. A trial is underway of rVIIa in bleeding thrombocytopenic stem cell transplant patients.

5.5 Intracerebral bleeding

Intracerebral bleeding causes ~ 15% of strokes, but is a devastating event that results in morbidity in ~ 35 – 50% of patients suffering these events. Patients with intracerebral bleeding will often continue to bleed and have expansion of the haematoma hours after the initial event, which leads to further damage. This has led to the concept of ultra-early therapy with rVIIa to control haemostasis [76]. Both the results of a pilot study and a Phase II trial have been published, which indicate that rVIIa is effective in this situation [77]. In a pivotal trial [78], Mayer compared placebo with rVIIa 40, 80 and 160 µg/kg in 399 patients, 1 h after a scan, that demonstrated a spontaneous intracerebral bleed. In the combined rVIIa group, mortality was reduced by 38% (11% absolute reduction) and disability was also reduced. In total, 5% of rVIIa patients experienced thrombotic events, with two patients dying of cerebral infarctions. Further studies are planned to better define the dose and feasibility of rapid therapy, but if these early results are verified, use of rVIIa will become standard therapy for intracerebral bleeding.

5.6 Liver disease

There is much interest in the use of rVIIa for treating the coagulation defects of liver disease. Patients with severe liver disease have multiple coagulation defects and frequently present to the hospital with severe bleeding [79-82]. The liver is the source of most of the coagulation factors and synthesises the key growth factor for platelets. Most often the bleeding is due to 'mechanical' reasons (gastric ulcer, ruptured varices), but the coagulation defects render the patient more difficult to treat.

Traditionally, the management of patients with liver disease has been with plasma infusions to replace the missing coagulation factors. However, this is very ineffective, rarely corrects factor levels and can lead to fluid overload of the patient, which may increase portal pressures, leading to more bleeding [83]. Abnormal fibrinolysis is an often overlooked cause of bleeding in patients with liver disease [28,84,85]. Bleeding in these patients tends to be characterised by diffuse oozing from sites of minor trauma. Diagnosis is made either clinically or, if available, by demonstrating a shortened euglobulin clot lysis time in the setting of excessive bleeding. In the patient who is bleeding from fibrinolysis, a trial of antifibrinolytic therapy is warranted [17,80,86,87].

Given the difficulties of routine therapies, the use of rVIIa has been studied extensively in liver disease. Doses of rVIIa

5 – 80 µg/kg can shorten the INR into the normal range without causing disseminated intravascular coagulation [88]. A pilot study [45] in patients undergoing laparoscopic liver biopsy used dose ranging (5 – 120 µg/kg). In total, 74% of patients had normal haemostasis within 10 min of dosing, and no patient had bleeding sufficient to require blood transfusion. Shami *et al.* [89] reported that the use of rVIIa 40 µg/kg before intracranial monitor placement allowed successful placement without bleeding or the need for massive plasma infusions. Trials of rVIIa for therapy of variceal bleeding are not as encouraging. Two reports consisting of 18 patients in total showed that rVIIa could stop bleeding in patients presenting with severe variceal bleeding, but 12 of these patients went on to die of their underlying disease [90,91]. Bosch *et al.* [92] randomised 245 patients with cirrhosis and upper gastrointestinal bleeding to either placebo or 8 doses of rVIIa 100 µg/kg given over 32 h. rVIIa had no effect on the ability to control bleeding and prevent rebleeding, transfusions or mortality. Subgroup analysis suggested a positive effect of rVIIa in the subgroup that had more severe cirrhosis and variceal bleeding.

Given the currently available data, the use of rVIIa for patients with liver disease should be limited. A clear indication would be in procedures crucial to transplant, such as intracranial monitor placement. However, trials do not support using rVIIa for variceal or other massive bleeding in the patient with end-stage liver disease because of the poor underlying prognosis.

5.7 Reversal of anticoagulation

As the indications for anticoagulation increase, the need for reverse anticoagulation is also rising, especially as medically fragile patients are being anticoagulated.

Both heparin and low molecular weight heparin can be reversed by protamine [93,94]. Although anecdotes exist of rVIIa reversing the effects of low molecular weight heparin, animal studies have shown no effect of rVIIa on heparin-induced bleeding, and protamine remains the therapy of choice [95-97]. The newer heparinmimetics, fondaparinux and idraparinux, cannot be reversed by protamine. There is volunteer data that one dose of rVIIa can reverse the effects of both of these new agents [98-100]. However, given the long half-lives (20 and 72 h for fondaparinux and idraparinux, respectively), repeat dosing may be necessary [101]. For example, in the idraparinux study, its anticoagulant effect was still present after 7 days and continued to be neutralised by rVIIa.

The direct thrombin inhibitors – argatroban, bivalirudin, lepirudin and ximelagatran – do not have a specific reversal agent. Both animal and human data suggests that APCCs are more effective reversal agents than rVIIa and, if available, should be used in seriously bleeding patients receiving direct thrombin inhibitors [102-105]. The most effective dosing of APCCs in these studies was 25 – 50 units/kg.

Administration of rVIIa, even small doses (5 µg/kg), to patients on warfarin will result in a rapid reversal of the INR [106-109]. Despite reports of the use of rVIIa in patients with warfarin-induced bleeding, including intracerebral bleeding, it remains uncertain how reliable this rapid INR reversal reflects

restoration of normal haemostasis [107,110-112]. Given that vitamin K, plasma and prothrombin complex concentrates can effectively reverse warfarin [113,114], use of rVIIa should be limited to patients on warfarin suffering intracerebral bleeding, for which immediate reversal is required and prothrombin complex concentrates are not available. A large trial is underway to better define the role of rVIIa in warfarin reversal [75].

6. Surgical bleeding

6.1 Planned operations

There is conflicting data on whether planned use of rVIIa before surgery can prevent blood loss. Friederich *et al.* [115] showed that both rVIIa 20 and 40 µg/kg can lessen blood loss and transfusion requirements in 36 patients undergoing prostatectomy. The placebo arm were transfused 1.5 ± 4 units of blood versus 0.6 ± 4 in the 20 µg/kg arm and none in the 40 µg/kg arm. In contrast, Lodge *et al.* [116] compared a dose of 20 or 80 µg/kg versus placebo in 204 non-cirrhotic patients undergoing hepatectomy, and showed no benefit in blood loss or transfusion requirements. Also, a small randomised trial of 48 patients with traumatic pelvic fractures showed no prophylactic benefit of rVIIa 90 µg/kg [117]. Both of these trials demonstrated no increase in thrombotic events.

6.2 Cardiac surgery

Cardiac bypass results in very complex and poorly defined defects in all aspects of haemostasis that result in massive bleeding in some patients [118,119]. Several reports note that, for patients with massive chest tube output after cardiac surgery, the use of rVIIa led to a major reduction in bleeding and prevention of reoperation [120-123]. The possible increase in complications is of concern. Ravio [122] reported on 16 patients receiving rVIIa for excessive bleeding after cardiac surgery. Although rVIIa was effective in stopping bleeding in 82% of patients, four patients had thromboembolic complications and another three had multi-organ system failure. A case control study of 51 patients who received rVIIa showed a reduction in blood loss, with an increase in renal insufficiency and a need for intensive care [124]. Although the use of rVIIa may be considered for the cardiac surgery patient with massive bleeding, the possible increase in complications in this high-risk population is of concern and randomised trials are needed.

6.3 Hepatic surgery

The advent of liver transplantation has significantly impacted the survival of patients with severe liver disease. As expected, due to their underlying liver disease, patients may often require large amounts of blood during the procedure. Massive transfusions of red cells and plasma are not unusual in very ill patients or complicated surgeries [125,126]. Given this blood loss, liver transplantation surgery is an appealing area for use of rVIIa. Multiple case reports and small series exist about the use of rVIIa in liver transplants [127-131]. rVIIa shortens the INR preoperative and corrects some coagulation parameters, but the effect on blood loss has

been inconsistent in these reports. Randomised clinical trials are needed to better define the role of rVIIa in liver transplantation.

7. Trauma

The area with most intense focus for rVIIa use is in trauma patients. The coagulation defects that occur in trauma patients are complex in origin, the most common reasons being dilution of haemostatic factors by fluid or blood resuscitation, hypothermia, tissue damage from trauma and effects of underlying diseases [55,132].

There are multiple reports concerning the use of rVIIa in trauma bleeding [132-135]. It is clear that transfusion requirements are decreased after administration of rVIIa, but large clinical trials are needed to see if this translates into improved survival. There are preliminary results available from a randomised trial in 297 patients that compared placebo with rVIIa 200 µg/kg followed by a 100 µg/kg dose after 1 and 3 h in massively bleeding trauma patients [136]. rVIIa decreased transfusion needs in blunt, but not penetrating, trauma patients. Also of interest was the observation that multi-organ system failure and acute respiratory distress syndrome seemed to be decreased in the rVIIa group. A larger trial is underway to better define rVIIa use in this population.

Curiously, although hypothermia has a detrimental effect on blood coagulation, this does not seem to affect the function of rVIIa. Meng *et al.* [137] showed no decreased in rVIIa effect on thrombin generation *in vitro* at 33°C, and this finding is supported by clinical data [132,134,137]. In contrast, low pH does seem to have a negative effect. The Meng data demonstrated that the effect of rVIIa was reduced by 90% when the pH was lowered from 7.4 to 7.0. This is also supported by clinical data showing that trauma patients who did not respond to rVIIa were more likely to have pH < 7.2 compared with responders [132].

Until data from larger trials are available, it does seem that uncontrolled bleeding from trauma (and perhaps any surgical setting) is a reasonable indication for use of rVIIa [132]. Before rVIIa (recommended dose 90 µg/kg) is used, one should:

- determine that the patient has a survivable injury;
- attempt to correct coagulation defects with, use of blood products: red cells to get haematocrit > 30%; fresh frozen plasma (15 – 30 ml/kg) to get aPTT < 1.8-times the normal; platelet transfusions to get platelet count above 50,000/µl; and 10 units of cryoprecipitate to get fibrinogen > 100 mg/dl;
- attempt to repair large vessel bleeding;
- attempt to raise the pH above 7.2;
- use a dose of 90 µg/kg.

8. Other haemorrhage

There is a plethora of case reports about the successful use of rVIIa for a larger variety of bleeding problems [42,138-144]. However, the true success rate and the long-term outcome for these types of patients is unknown. A recent pessimistic report [145]

noted that, although rVIIa may control bleeding, patients often went on to die of their underlying disease – similar to what has been noted in patients with end-stage liver disease. In patients from the author's institution, with massive bleeding from complications of an untreatable underlying process, such as recalcitrant gut graft versus host disease, rVIIa was effective at slowing blood loss, but not influencing the overall course.

9. Complications

Surprisingly, despite the multiple pro-coagulation effects on rVIIa on haemostasis, thrombotic complications are rare. In 700,000 doses given to haemophiliacs, only 16 thrombotic complications were seen [4]. Even in the trauma setting, in which disseminated intravascular coagulation is a concern, the report rate of thrombosis is very low; in the clinical trial setting it was not different to control patients [136]. However, when used in older patients, especially those with vascular risk factors, the risk of arterial thrombosis seems to increase. For example, in the Mayer trial [78] the thrombosis rate was 5% in the older patient population. In patients undergoing cardiac surgery, the complication rates in several studies has been reported to be higher [146]. Until more safety data are available, the risk-benefit ratio should be considered before using rVIIa in patients with a history of vascular disease, such as strokes or myocardial infarction.

10. Cost of therapy

A major concern has been the extraordinary costs associated with rVIIa therapy in certain patient populations. Although the cost of rVIIa to purchasers varies, a reasonable assumption is a cost of US \$1 per µg [147]. A single dose in an average 70 kg person would be \$6300. To put this in perspective, the cost of a full replacement dose of Factor VIII would be \$2 – 3500, for Factor XI, \$4 – 7000 and for APCC, \$7 – 10,000/dose. As patients with Factor inhibitors may require multiple doses, their costs can be substantial. For other uses of rVIIa, only a single dose is required, but this is still costly and emphasises the need for clinical trials to better define these non-approved indications.

11. Expert opinion

rVIIa seems to be a very promising agent for controlling bleeding in patients. Clinical trials are needed to define the appropriate role of this agent, but from the data amassed so far it is clear rVIIa is useful for:

- patients with Factor IX and VIII deficiency and inhibitors;
- patients with Factor VII and XI deficiency;
- patients with Glanzmann thrombasthaenia;
- patients with acquired VIII and vWD;
- uncontrolled surgical bleeding;
- preprocedural management in patients with end-stage liver disease;
- trauma.

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