# The rational use of recombinant factor VIIa in the treatment of major intractable bleeding in the trauma patient

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## Abstract

**Background:** The off-label use of recombinant factor VIIa (rFVIIa / Eptacog Alfa/NovoSeven®) in trauma patients with massive haemorrhage has increased since 1999. Some clinicians see its role as a prophylactic drug to prevent major blood loss, while others use it as a rescue drug in life-threatening haemorrhage. There has been much debate regarding its clinical application, effectiveness, thromboembolic potential and cost/benefit ratio. A literature review was done to attempt to clarify some of these issues.
**Methods:** An electronic literature search of Medline and Pubmed databases was conducted applying keywords: NovoSeven, rFVIIa, recombinant FVIIa, Eptacog Alfa, trauma, major blood loss.
**Results:** rFVIIa has been used off-label in a variety of clinical settings either to prevent blood loss, or to treat intractable major haemorrhage. This includes several case reports and cohort studies in the trauma setting. Unfortunately there are only two randomised clinical trials (RCT) available regarding the use of rFVIIa in trauma. These RCTs were small and did not show significant benefit in favour of rFVIIa. There is still not sufficient level 1 evidence to support the routine use of rFVIIa in trauma patients, either prophylactically or as first line treatment for major haemorrhage. It also seems that the drug has a higher potential to cause thromboembolic complications than initially reported. It is very expensive and therefore has an unfavourable cost/benefit ratio. In the absence of good evidence of benefit, expert opinion regards rFVIIa as drug to be used only in life-threatening major haemorrhage where conventional treatment has failed.

## Introduction

Recombinant factor VIIa (rFVIIa / Eptacog Alfa/NovoSeven®) is licensed for use in Haemophilia A and B with inhibitors against coagulation factor VIII or IX. Additional indications include acquired haemophilia, congenital FVII deficiency, and Glanzmann's thrombasthenia refractory to platelet transfusion.[1] It was first used in the early 1980s in these patients.

In 1999, the Lancet published a case report of a soldier who sustained a gunshot wound and developed uncontrollable bleeding as a complication from this trauma. rFVIIa was administered to this soldier, with remarkable haemostatic response. This sparked renewed interest in the use of rFVIIa for off-label indications, including the treatment of uncontrollable bleeding in major trauma.

There are a large number of case reports and cohort studies describing the exceptional haemostatic abilities of rFVIIa in the treatment of major uncontrollable bleeding. Its use has been reported in the peri-operative setting of cardiac surgery (adult and paediatric), liver resection and transplantation, prostate surgery, orthopaedic surgery, and spinal surgery, as well as in major trauma, gastrointestinal and obstetric bleeding, and intracranial haemorrhage. Looking at this evidence, there can be no doubt that it is an effective haemostatic agent. However, is also prohibitively expensive and has been associated with major thrombotic complications.

The first question that must be answered is if rFVIIa has clinically relevant outcomes, compared to traditional medical treatment and blood component replacement, in major haemorrhage in the trauma setting. Secondly, what are the risks involved in using this drug, and which patients are at risk of developing thrombotic complications, and thirdly, is it cost-effective to use rFVIIa?

Thus, as with all interventions and therapies, one needs to have a clear understanding of its indications, pharmacological action, complications and limitations when used for off-label indications like major bleeding associated with trauma.

### Pathophysiology of major bleeding in trauma

Massive intractable bleeding is associated with many injuries, including major vascular trauma, visceral blunt trauma, high velocity penetrating injuries, long bone fractures and injuries to abdominal and thoracic vital organs. In the trauma scenario, there is the added factor of exposure to the elements, which may lead to hypothermia.

Massive intractable blood loss is considered to be present when more than 8 units of pure red blood cells (PRBC) is needed within 24 hours, or more than 4 units of PRBC is required within the first hour of resuscitation in the presence of ongoing uncontrollable bleeding.

In the trauma patient with previous normal coagulation, there is an initial vascular component to major haemorrhage which needs urgent correction. In many cases this involves surgical correction in theatre, which may create the ideal conditions for the second component related to major haemorrhage to develop, due to exposure, inappropriate fluid resuscitation, long operation time and the additional inflammatory response associated with surgery.

The coagulopathic stage is this second component of major blood loss, and develops more insidiously. This medical cause of bleeding is due to a dilutional coagulopathy, a consumptive coagulopathy, and a dysfunctional coagulopathy. The coagulation components (platelets and clotting factors) are diluted due to ongoing blood loss, which is replaced by PRBC, crystalloids or colloid solutions. Where large areas of tissue damage are present, massive amounts of tissue factor (TF) is exposed, and this leads to a consumption of platelets and factors as the system tries to "plug all the holes". Added to this is the overstimulation of the fibrinolytic system by fibrin degradation products, with poor quality fibrin clots forming. Platelets are also primed for activity due to the stress response seen in trauma and surgery which activates the complement and sympathetic systems. On the other hand, the coagulation components may show significant dysfunction due to hypothermia and acidosis, and thus lead to increased blood loss which aggravates the acidosis and hypothermia.[2]

**Pharmacology**

Recombinant factor VIIa is a glycoprotein, manufactured from recombinant techniques in rabbit cells, with a very low infection potential and antigenicity.

Its pharmacokinetic action is identical to endogenous factor VIIa, i.e. tissue factor (TF) is brought into contact with FVII, which activates the factor. FVIIa binds to platelets to activate them at the site of injury (the major mechanism), and also activates factors IX and X (the minor mechanism) to produce the all important thrombin burst necessary for efficient clotting. Thus, two prerequisite conditions are necessary for rFVIIa to be effective. There should be a sufficient number of functional platelets in the circulation and a sufficient plasma concentration of prothrombin. Previously it was suspected that rFVIIa is less effective in the setting of acidosis and hypothermia, and was one of the main rationales for giving the drug early in resuscitation. However, new evidence in vitro and in animals suggest that the drug is effective under these conditions.[3] It is probable that the decreased clinical effect seen is due to the inhibiting effects of acidosis and hypothermia on platelets and other coagulation factors in vivo, and not to a decreased effect of the drug.

The main difference is that endogenous FVII is present in minute quantities and is in the inactivated form under normal circumstances, whereas recombinant FVII is given in a much higher concentration and is in the activated form, thus greatly enhancing the thrombin burst while its action remains site specific. This explains the clear dose-response relationship as well as the increased incidence of thrombotic complications seen in higher doses.

The half-life of rFVIIa is 2,7 ± 0,5 hours, and clearance is not dose dependent.

The optimal dose of rFVIIa and dosing interval remain unknown, but data from recent reviews of all RCTs suggest that doses between 20 and 90 µg/kg are optimal. This is confirmed by in vitro studies which show that a dose of 100 µg/kg leads to maximum thrombin generation. Previously much larger doses of between 100 and 200 µg/kg were used in the two RCTs conducted in trauma patients.[4]

Available data does not support repeated dosing for haemostatic control, except in traumatic bleeding, although this is based on only two trials, where up to three doses were given.[4]

**Thromboembolic risk**

There is justifiable concern regarding the use of rFVIIa being associated with increased incidence of thromboembolic events. It should be kept in mind that, although the drug works mainly on sites where TF is expressed, it is possible to induce thrombosis at sites distant to the area of bleeding. At higher doses. it is more likely that this will occur. Thus any patient with atherosclerotic disease, vascular injury, hypercoaguable states like pregnancy, DIC, crush injury, central venous or arterial cannulae and septicaemia are at increased risk of developing a thromboembolic event.[5] Many of these conditions may be present in the patient with major trauma.

Before 2005, the incidence of serious adverse events associated with the off-label use of rFVIIa was reported to be less than 1%. This value may have been underestimated because all major RCTs excluded patients with major thromboembolic risk. Since then, as the use of the drug increased and more studies were done, this picture changed significantly, with some cohort studies reporting an incidence of up to 25%. This led the FDA to issue a warning to consumers regarding the thrombotic risk associated with the drug. Over 200 thromboembolic events directly associated with the use of rFVIIa in off-label settings was reported to the FDA at that stage (2005).

DVT and pulmonary embolism, clotting of intravenous central catheters and arterial catheters, as well as stroke and myocardial infarction, have all been associated with rFVIIa. Of the RCTs in the quoted reviews that did specifically report on thromboembolic events, none were sufficiently powered to detect major complications of a thromboembolic nature.[1,6,7] It must be remembered that greater numbers of patients are needed to show an adverse outcome than to show efficacy of a drug.

Thus it seems that the risks associated with rFVIIa use is very real and may be higher than initially suspected, certainly higher than the risks of infection and ARDS associated with blood component replacement therapy, especially in the high-risk patient which may include the heavily injured patient.

**The cost of rFVIIa therapy**

The latest price of a 1,2 mg ampoule of rFVIIa is ± R6 000 in the state sector, and ± R8 000 in the private sector. If the recommended

conservative dose of 20 - 50µg/kg is administered as an initial dose, the cost for a 70 kg patient would amount to R12 000 to R18 000 in the state, and R16 000 to R24 000 in the private sector.

**Efficacy of rFVIIa versus conventional treatment**

17 RCTs have been conducted to determine the efficacy of rFVIIa in various clinical settings. All of these studies have used surrogate outcomes, namely reduction in blood loss and blood transfusion. No study has been done on mortality and long term morbidity. The trials were all placebo controlled, but none specified a conventional treatment protocol regarding replacement of clotting factors and platelets. Thus, we cannot be sure that the drug is more effective than standard conventional therapy. None of these studies were sufficiently powered to detect major thromboembolic complications due to the use of rFVIIa. Only two of these studies used thromboelastography (TEG) as measurement tool, which is the preferred in vivo test for coagulopathy in the clinical setting.

The outcomes have been disappointing. One study in intracranial haemorrhage patients showed benefit in that clot sizes were reduced, but at a cost of a higher stroke rate in the rFVIIa treatment arm. Two other small, underpowered pilot studies (spinal surgery and pelvic fractures) showed slight benefit in using rFVIIa. The other studies showed no significant difference between rFVIIa treatment and conventional treatment in reducing blood loss and/or blood transfusion.[1,6,7]

As far as the trauma patient is concerned, two concurrent RCTs were published in 2005.[4] One study was done in penetrating trauma (n=134), and the other in patients with blunt trauma (n=143). Patients who showed massive intractable bleeding after 48 hours were randomised into conventional treatment and rFVIIa treatment groups. The primary end-point was a reduction in units transfused. No statistical difference was observed between the two regimens in the penetrating study, but there was a statistically significant benefit to using rFVIIa in blunt trauma. However, when patients who died within 48 hours were included into the randomisation, this significant difference disappeared. The CONTROL study in trauma patients (Phase III trial), initiated in 2005, promised to clarify a number of issues regarding rFVIIa treatment. Unfortunately, it was discovered that the study was not sufficiently powered to justify continuation, and was discontinued.

All expert reviews on the use of rFVIIa, as well as a recent Cochrane database review (Stanworth et al, 2007), are of the opinion that there is not sufficient level 1 evidence to support the routine use of rFVIIa, either prophylactically or therapeutically. Large adequately powered clinical trials that prove the benefit of rFVIIa in reducing rates of clinically important end-points with acceptable risk are needed before its routine use can be justified.[1,6,7]

**Recommendations**

The Canadian NAC rFVIIa Medical Task Force has developed recommendations on the off-label use of rFVIIa for massive bleeding. These recommendations are in concordance with the majority of expert opinion.[1,6,7]

In short, the following principles must be followed:

- rFVIIa should only be used under the direction of a physician experienced in its use, and ideally in consultation with a haematologist.
- Because of the paucity of published evidence, the potential for harm in some clinical situations and the lack of cost/benefit data, rFVIIa should be used only if there is a sound rationale for the product's use, the risks of administration are clearly understood by the administering physician, and the product is administered properly.

According to expert opinion, there is only one indication for all cases of massive intractable bleeding where rFVIIa treatment is justified, including trauma. It is indicated where conventional treatment has failed and there is ongoing blood loss that is life-threatening.

The accepted standard of conventional therapy is defined as follows:

1. Sequential TEG analysis and Fibrinogen levels are the preferred clinical measuring tools for detection of the aetiology of the coagulopathy in the clinical setting.
2. Maintain a platelet count > 50 X $10^9$/l in most cases of trauma, with the exception of traumatic brain injury where a level > 100 X $10^9$/l is required.
3. FFP / FDP at a dose of 15 ml/kg if indicated, guided by TEG results.
4. Cryoprecipitate (1 unit/5 – 10 kg) should be administered to maintain fibrinogen > 1 g/l.
5. Maintain a haematocrit above 0,24 to optimise haemostasis.
6. Correct acidosis to a level above pH of 7,1.
7. Treat hypothermia and maintain body temperature > 35°C.
8. Calcium chloride replacement if the ionised calcium level is below the reference value.
9. If TEG indicates increased fibrinolysis, give an anti-fibrinolytic drug like tranexamic acid or aminocaproic acid.

The recommended initial dose is 20 – 50 µg/ kg and should be rounded to the nearest vial to avoid wastage. A second dose may be repeated if no response is seen within 30 minutes. A third dose may be given up to 2 hours later with ongoing blood loss. Three doses should not be exceeded. Higher doses appear not to have additional benefit, but may increase thromboembolic events.

rFVIIa should not be mixed with infusion solutions and should be administered intravenously over 2 – 5 minutes. Reconstituted solution should be used within 3 hours.[7]

**Summary**

There can be no doubt that rFVIIa is an effective haemostatic agent, especially if utilised for registered indications. In major intractable bleeding due to trauma, it is at least as effective as conventional therapy in achieving haemostasis, but only in ideal haemostatic

conditions, i.e.in a patient with sufficient levels of clotting factors, platelets and red blood cells, who is not hypothermic and acidotic. Thus, to administer rFVIIa to a trauma patient who has suffered major haemorrhage without applying conventional therapy is probably futile, a waste of resources and, additionally, exposes the patient to serious adverse events.

There are a few proponents of the prophylactic use of rFVIIa as part of the initial empiric treatment protocol for all major trauma cases. The rationale behind this reasoning is that it prevents major blood loss, and thus the secondary coagulopathy, from developing.[8] This approach is based on case reports and small retrospective studies and is not supported by level 1 evidence. It makes more economic and clinical sense to apply conventional treatment early to prevent the secondary coagulopathy from developing.

Taking into account the lack of level 1 evidence of benefit, the possible major thromboembolic complications that it may cause, and its cost, rFVIIa remains a drug that should only be used in trauma patients with life-threatening bleeding where conventional measures have failed to achieve haemostasis.

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