

Intraoperative use of recombinant activated factor VII (rFVIIa)

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Recombinant activated factor VII (rFVIIa, Novoseven[®], Novo Nordisk, Denmark) was introduced as a prohemostatic agent in the early 80s: the only indication approved in USA by Food and Drug Administration (FDA) is the spontaneous bleeding in congenital hemophilia patients who developed inhibitors to FVIII and FIX. Recently, EMEA approved the use of rFVIIa in congenital hemophilia patients with inhibitors undergoing surgery, in subjects with congenital FVII deficiency undergoing surgical or invasive procedures, in patients with acquired hemophilia and in case of Glanzmann's thromboasthenia. Out of these approved indications, the off label use of rFVIIa is rapidly expanding, particularly in surgical patients with acquired coagulation disorders in order to manage severe, uncontrolled bleeding nonresponsive to conventional therapeutic measures or to reduce blood loss and transfusion requirements in potentially bleeding surgical procedures (major liver surgery, liver transplantation, major abdominal or obstetric surgery, trauma surgery). This paper reviews the more recent data coming from retrospective or prospective studies performed in different surgical settings: so far, the major point to be addressed is the place for rFVIIa as an adjunctive but sometimes lifesaving treatment to control haemostasis and critical bleeding in surgery and critically ill patients.

Key words: Recombinant factor VII - Procoagulant factors - Bleeding.

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Recombinant factor VIIa (rFVIIa, Novoseven[®], Novo Nordisk) was introduced as a prohemostatic agent in the early 80s: its action is mainly based on the current view of the coagulation system activation (the so called "cell based model" of coagulation), which is considered to proceed *via* the tissue factor (TF)/FVII pathway.^{1, 2} In this model the initiating event leading to the haemostatic plug is the exposure of the TF at the site of injury and the formation of TF-FVII complex anchored at a TF bearing cell. Hemostasis can be divided into 4 major regulatory steps: initiation (the site of injured endothelium as a point of procoagulant enzymatic activity on TF bearing cells), propagation (an enzymatic step able to convert a local signal to a multicomponent reaction and leading to the formation of thrombin: the TF-dependent pathway plays a major role, mainly on the activated platelet surface); termination (down regulation of the procoagulant response, in order to limit the clot formation on the injured endothelial area) and resolution (or fibrinolysis, a process able to restore vascular patency).²

For its clinical use, the only indication approved in USA by Food and Drug Administration (FDA) is the spontaneous bleeding in congenital hemophilia patients who developed inhibitors to FVIII and FIX.³ Recently, European Medicines Agency (EMA) approved for the EC the use of rFVIIa also in the surgery of hemophilia A and B patients with inhibitors; in subjects with congenital FVII deficiency undergoing surgical or invasive procedures; in patients with acquired hemophilia (FVIII or IX autoantibodies); in case of Glanzmann's thromboasthenia.⁴ So far, the recommended dose in these indications ranges from 90 to 180 µg/kg with possible repeated doses every 3-6 h: the reported results are more than good and the safety profile is excellent.^{3,4} In a subset of patients not responding to the conventional doses, mega doses as high as 200-300 mg/kg have successfully been used.⁵ Adverse effects are reported in the range of 1-2%, but, even if uncommon, they include acute myocardial infarction, hepatic artery thrombosis, deep venous thrombosis, stroke and disseminated intravascular coagulation.⁶

Out of these approved indications, the use of rFVIIa is rapidly expanding in so-called off label indications: among them, in patients with acquired coagulation disorders in case of critical bleeding, a severe, uncontrolled bleeding non responsive to conventional therapeutic measures^{7,8} or as a prophylactic measure in subjects with normal coagulation profile undergoing major surgical procedures at risk for severe perioperative bleeding.⁵ According to the many anecdotal reports,⁹ (see also www.criticalbleeding.org, an Italian network chaired by Pasetto and Girardis from Modena University), pilot studies,^{10,11} small¹² or large randomized trials,^{13,14} rFVIIa has extensively been used in the surgical setting (retropubic prostatectomy, major abdominal and vascular surgery, hepatic surgery and liver transplantation, cardiac surgery, orthopedic surgery, obstetric surgery and neurosurgery).^{3,4,5,15} but also in nonsurgical conditions (trauma, intracranial hemorrhage, postpartum hemorrhage, critically ill patients).^{3,4,5,8} Apparent efficacy in serious and otherwise untractable bleeding disorders

has been demonstrated after 1 or 2 standard doses (40-120 µg kg⁻¹), with decreased or stopped bleeding after frustrating, useless and ineffective transfusion of large quantities of whole blood, fresh frozen plasma (FFP), cryoprecipitates and platelets (PLT) concentrates.

In 2004, Goodnough *et al.* tried to develop educational guidelines and policy recommendations for rFVIIa use based on a review of the available literature.³ Major issues considered among the off label indications are qualitative and quantitative PLT disorders associated with life threatening bleeding non responsive to PLT transfusion; patients with von Willebrand disease (vWD) and antibodies against vW factor or nonresponsive to conventional therapy; need for rapid reversal of INR in patients on chronic oral anticoagulant therapy when appropriate dosage of FFP (15-20 mL/kg) is considered at risk for fluid overload (an available alternative is prothrombin complex), uncontrollable hemorrhage in trauma patients, in patients admitted to major abdominal surgery, major liver resection, liver transplantation; in severe hepatic failure; in selected critically ill intensive care unit (ICU) patients, including subjects after hematopoietic stem cells transplant.^{3,4,5} The factor common to all the above conditions seems to be the reduced rate of thrombin generation.^{4,5,15,16} This is frequently found in patients with massive transfusion (exceeding more than 1 patient's blood volume within 24 h or blood loss exceeding 500 mL h⁻¹)¹⁷ and large volume resuscitation requirements after surgical and/or traumatic massive untractable blood loss. Hemodilution, severe thrombocytopenia and extensive clotting factors consumption can lead to critical coagulopathy and superimposed, nonsurgical bleeding. Dilutional coagulopathy is usually present after 2 blood volume exchanges with drop of PLT count below 10-15×10⁹ mL⁻¹. Blood levels of coagulation factors below 30%, FV and FX levels absent or below 5-10%, fibrinogen below 50-75 µg dL⁻¹ and PLT count below 50×10⁹ mL⁻¹ are considered critical and process limiting factors:¹⁵ based on its specific mechanism of action, rFVIIa could be easily ineffective if PLT count or FX blood level are extremely low.^{3,4,15,16}

As reported,² rFVIIa acts enhancing thrombin generation at the site of injury by TF-dependent and nondependent mechanisms when given at supraphysiological doses (maximum effect exerted at 10 fold higher concentration than the usual physiological level of FVII).^{16, 18} The TF-dependent mechanism results in FX activation and thrombin generation at the site of vascular injury, where PLT are recruited and activated with subsequent activation of FX to FXa (TF-independent effects).^{16, 18} The localized generation of large quantities of thrombin enhances PLTs adhesion and aggregation, making clots more resistant to fibrinolysis. The supraphysiological dose is responsible for the so called "bypass effect", able to start the thrombin burst, and compensating for a lack of FVIII or FIX. Severe acidosis (pH below 7.2) and extreme hypothermia (core temperature below 33° C), conditions sometimes encountered during extensive surgical procedures complicated by untractable bleeding or trauma, may become process limiting conditions able to reduce or decrease positive rFVIIa effects: the appropriate correction of pH and every efforts spent to maintain core T above 33° C before rFVIIa administration seem to be reasonable guidelines to have maximum procoagulant effects to correct severe hypocoagulation.¹⁶

Intraoperative use

In 2003 O'Connel *et al.* reported a retrospective series of surgical (30 cases) and non surgical (10 cases) patients treated with rFVIIa because of massive bleeding unresponsive to conventional therapy.⁹ Dose range (15-180 mg/kg) and number of doses (median of 2 doses, ranging from 1 to 4) were wide. Eighty percent of the patients had complete or partial cessation of bleeding. Most part of the unsuccessful administrations (6 cases) occurred in liver diseased patients. The so far unpublished series retrospectively collected by the Italian "Critical Bleeding Network" shows very similar figures, with a success rate close to 90% and a survival rate averaging 80% (unpublished

data, courtesy of Prof Pasetto and Prof Girardis, Modena).

Among the possible indications explored in the literature for the use of rFVIIa, there are the cases of major surgical procedures at risk of massive bleeding or life-threatening bleeding situation in Jehovah's witnesses, likely to refuse transfusion of blood and blood products.⁵

The first prospective placebo controlled trial in subjects with preoperative intact coagulation profile undergoing surgery at risk for potential extensive bleeding and able to show a possible reduction of blood loss and transfusion requirements was conducted in patients undergoing retropubic prostatectomy.¹² The patients were randomized to a single dose of rFVIIa (20 or 40 µg kg⁻¹) or placebo. Administration of the higher dosage resulted in 50% reduction of blood loss compared to placebo and no need for blood transfusion (on the contrary, needed in more than 60% of the controls), while the smaller dose (20 µg kg⁻¹) was associated with a smaller but still significant reduction of blood loss (35% less when compared to placebo).¹² Some concerns, however, have to be raised when considering the unusually high blood loss in the placebo group (median blood loss 2.6 L) when compared to the treated patients (range 1 000-1 250 mL).

Liver surgery including major liver resections and liver transplantation (OLT) is one of the most challenging fields of application of rFVIIa^{3-5, 10, 11, 13, 14, 19} OLT are long known to be at high risk of bleeding because of major surgical technical problems and impaired hemostasis associated with the end-stage liver disease (decreased coagulation factors and natural anticoagulants, thrombocytopenia, hyperfibrinolysis, heparin like effect). The use of rFVIIa during OLT as a measure to reduce blood loss and transfusion needs (80 µg kg⁻¹ at the start of operation), was firstly reported by Hendricks *et al.* in 6 adults:¹⁰ the results were compared to matched historical controls. The authors were able to demonstrate a significant reduction in transfusion requirements (both autologous and allogenic) and blood loss (median 3.5 L *vs* 9.8 L) between treated and control groups. Similar

figures were observed in another uncontrolled trial using low dose ($67 \mu\text{g kg}^{-1}$) rFVIIa.²⁰ Rather different results were very recently reported by our group¹¹ in a pilot study conducted in 6 patients with end-stage liver disease undergoing OLT. rFVIIa $20 \mu\text{g kg}^{-1}$ was administered at the start of operation and a second dose of $20 \mu\text{g kg}^{-1}$ was given 30-40 min after reperfusion in the case of significant bleeding. Perioperative blood loss and transfusion requirements recorded in the treatment group were compared with those recorded in 6 patients who underwent OLT the month before without rFVIIa administration (controls). All the patients were successfully transplanted, discharged in good conditions and at least alive 12 months after OLT. The safety profile was excellent and early or late thrombotic complications were absent. Blood loss (L) and transfusion requirement (packed red cells, PRC units) mean values (\pm SD) did not statistically differ between treated and untreated groups: $3.5 \pm 1.3 \text{ L}$ vs $1.8 \pm 1.2 \text{ L}$; and $9 \pm 4 \text{ PRC U}$ vs $7 \pm 2.5 \text{ PRC U}$ respectively. Thus, we were unable to confirm any significant reduction in blood loss and transfusion needs (PRCs, FFP and PLT concentrate units) with rFVIIa administered as some kind of universal prophylaxis. Our preliminary report seems to be quite in agreement with the very recently reported results coming from a large randomized, multicenter study (83 patients),¹⁴ in which $80 \mu\text{g kg}^{-1}$ rFVIIa given at the start of OLT did not change substantially blood loss and PRC transfusions: the only significant reduction was for the FFP requirement. In a larger randomized study (182 patients) comparing the efficacy and safety of 2 different repeated doses of rFVIIa in patients admitted to OLT (60 and $120 \mu\text{g kg}^{-1}$), Lodge *et al.* found that 10% of the patients receiving rFVIIa $60 \mu\text{g kg}^{-1}$ and 7% of the patients receiving $120 \mu\text{g kg}^{-1}$ avoided PRC transfusions whereas all the patients in the placebo group were transfused.¹⁹

Results in major liver surgery seem to be similar. In a large randomized trial (204 patients) Lodge *et al.* used 2 different dosages of rFVIIa during hepatectomies in noncirrhotic patients: blood loss, transfusion require-

ments and the number of transfused patients did not differ in the treated group and in controls.¹³ The thromboembolic events did not differ either. Shao *et al.*, in a study conducted in cirrhotic patients admitted to partial hepatectomy, documented the absence of any significant effect on blood loss and transfusion requirements when 50 or $100 \mu\text{g kg}^{-1}$ rFVIIa or placebo were given as starting bolus before surgery and every second h during surgery.²¹

In spite of the 2 large and well conducted randomized studies,^{14, 19} the definite conclusions on the use of rFVIIa during OLT have yet to be drawn and, probably, they should not be as positive as proposed in a recently published review.⁴ In our opinion the problem of bleeding during OLT, or generally speaking in major liver surgery, is critical, as quoted by Porte and Caldwell²⁰ in the editorial accompanying the articles by Planinsic¹⁴ and Lodge:¹⁹ however, further work has still to be done to find the best way to properly intervene in this specific setting.

We are strongly convinced²² (and in this hypothesis we are now heavily supported by the data coming from studies of Planinsic, Lodge and Shao) that rFVIIa should not be recommended per se as a universal prophylaxis to reduce transfusion requirements during OLT, during major liver resections, or, generally speaking, in major surgical procedures at risk for excessive periperioperative bleeding. This is particularly true in clinical settings in which good surgical technique and expertise in the perioperative management and pharmacological manipulation of coagulation are available.²³ Cost effectiveness of rFVIIa in our opinion has to be challenged against the results recently reported in liver transplantation and partial hepatectomies. As a matter of fact, in spite of the high doses used in Lodge's study in OLT,¹⁹ the only significant result was that 7% to 10% of the treated patients were able to avoid RBC transfusion: however, not different were FFP or other blood products needs, when compared to the controls, negating in our opinion a substantial effect.

According to the reported experiences in liver surgery, we think the surgical use of

rFVIIa should be redefined in very selected subgroups of patients in a randomized fashion, which is, at the moment and according to the available data, ethical. OLT candidates at known risk of surgical or nonsurgical bleeding could be subjects admitted to split liver transplants, retransplantation to be performed years after the first procedure, patients with previous abdominal surgery or suffering for frequent spontaneous bacterial peritonitis, candidates with renal failure. In patients admitted to major liver resection or major abdominal surgery, bleeding risks have to be clearly defined according to the type and site of operation and to comorbidities. In such a setting, rFVIIa could be administered as a sort of pre-emptive therapy in a subset of patients not yet bleeding, but at substantial potential risk because of the presence of specific factors: this approach substantially differs from administering a useless and expensive prophylaxis just because a patient is undergoing a so called potentially bleeding procedure. The randomization, which again seems to be ethical in this specific setting, should give us a chance to redefine at least some of the many off label indications proposed for rFVIIa, making us able to eventually recognise less emotional surgical indications.

Last but not least, in case of critical bleeding and severe hemorrhagic shock, proper timing of administration seems crucial to avoid last ditch or futile use of rFVIIa. Severe acidosis, frequently associated with critical hypoperfusion during hemorrhagic shock, may predict failure of rFVIIa administration.²⁴ Very recently, Stein *et al.*²⁴ identified revised trauma score (RTS) below 4.09, severely altered preadministration coagulation profile (PT longer than 17.6 s) and severe metabolic acidosis as predictors of futile administration of rFVIIa in severely traumatized, hemorrhagic patients. Since these variables should be considered potential counter-indications to the proper use of rFVIIa, earlier but more rationale administration may increase the rate of positive clinical response, thus making this expensive but extraordinarily effective haemostatic drug extremely cost-effective.²⁴

As stated by Key²⁵ in a recent editorial ded-

icated to the approved and off label rFVIIa indications, the decision on when and where to use for patients with uncontrolled bleeding continues to be challenging, it has to be made by individual physicians, assisted by their hospital pharmacotherapeutic or transfusion committees, with appropriate and dedicated coagulation monitoring assistance available.^{15, 23}

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Riassunto

Utilizzo intraoperatorio del fattore VII attivato ricombinante

Il presente lavoro propone una revisione dell'attuale utilizzo del fattore VII ricombinante attivato (Novoseven®, Novo Nordisk, Denmark) in campo chirurgico. Il rFVIIa è un procoagulante approvato per il trattamento del sanguinamento nei pazienti portatori di emofilia A e B con inibitori del fattore VIII e IX: oggi, invece, viene sempre più utilizzato in indicazioni "off label" in caso di sanguinamento intrattabile (critical bleeding) in contesti chirurgici (chirurgia epatica e del trapianto epatico, chirurgia addominale maggiore), traumatologici, ostetrici e recentemente anche in pazienti critici in terapia intensiva. Punto fondamentale (e non ancora risolto) è la necessità di trovare un razionale per un uso appropriato di questo potentissimo proemostatico in indicazioni non ancora approvate ma potenzialmente salvavita.

Parole chiave: Fattore VII ricombinante - Fattori procoagulanti - Sanguinamento critico.

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