"I would have everie man write what he knowes and no more."—Montaigne

BJA

BRITISH JOURNAL OF ANAESTHESIA

Volume 94, Number 5, May 2005

Editorial

Is recombinant FVIIa the magic bullet in the treatment of major bleeding?

Recombinant activated factor VII (rFVIIa) (NovoSeven®, Novo Nordisk, Bagsvaerd, Denmark) was originally developed to treat bleeding in haemophiliacs with antibodies to factor VIII and IX.[1 2] At present, rFVIIa is approved in the European Union for this indication and also for the treatment of bleeding in FVII deficiency and Glanzmann thrombasthenia refractory to platelet transfusions.

FVIIa normally circulates in minute quantities and binds to tissue factor (TF) expressed by the damaged vascular bed. The TF-FVIIa complex on TF-bearing cells activates FIX and FX. FXa remains in close proximity to TF-bearing cells and activates FV. The FXa–FVa complex on TF-bearing cells rapidly converts small amounts of prothrombin into thrombin.[1 3] This initial small amount of thrombin activates platelets, FVIII, FV and FXI. On the surface of activated platelets, FVIIIa and FIXa gather to activate large quantities of FX which finally (in conjunction with FVa) will result in the large thrombin burst which enables the conversion of fibrinogen to fibrin with initial clot formation. The administration of exogenous rFVIIa accelerates the above mechanism and in haemophiliacs with antibodies to factor VIII and IX, rFVIIa may loosely bind to platelets and activate significant quantities of FX resulting in the thrombin burst necessary for the transformation of fibrinogen to fibrin with local clot formation.

It is tempting to speculate that exogenous rFVIIa, by activating blood coagulation in the close vicinity of TF-bearing cells, may help stop major bleeding in trauma and surgery with absence of general thrombosis. Since the initial spectacular case report in a young Israeli solder,[4] a large number of case reports of successful use of rFVIIa in patients with uncontrolled bleeding including trauma, surgery, warfarin therapy and pregnancy have been published.[2 5–8] The problem with these reports is potential publication bias of positive cases, which, understandably, editors are more likely to publish. Registries of similar patient groups[9] are also susceptible to submission and publication bias of successful cases. Only recently, 'non-responders'[7] and complications[10 11] of rFVIIa treatment have been described in bleeding patients. Faced with a patient with uncontrolled bleeding the clinician is thus left with significant uncertainty as to whether he or she is obliged to use rFVIIa in an 'off-label' or 'out-of-license' indication or whether this could be withheld as there is little published high level scientific evidence nor approval by any health authority in Europe or the US. This dilemma is amplified by the fact that any decision in this scenario is often associated with mortality, morbidity and high cost.

Bleeding is a major cause of mortality and morbidity during the peri- and post-partum period. Several case reports have described dramatic effects in patients suffering from massive bleeding.[2 4 5 7 8] In this issue of the Journal, Ahonen and Jokela describe another series of life-threatening post-partum bleeding in 12 patients treated with rFVIIa.[12] The authors report a partial or good response in 11 of their 12 patients to rFVIIa after a blood loss of between 5 and 15 litres. Despite such partial or good responses, 4 patients had to undergo subsequent arterial embolization.[12] Arterial embolization, however, is not generally available on a 24 h basis in all centres and its efficacy depends on the intervential radiologist's skill. Ideally, a randomized placebo-controlled trial should be performed in patients with massive blood loss associated with delivery. This is unlikely to happen, owing to the rarity of the complication, the difficulty in obtaining informed consent and the highly positive results in already published cases and case series. In the report by Ahonen and Kjokela, rFVIIa was used relatively late and 42% of patients had already had a hysterectomy. A number of centres are now, based on anectodal reports, using rFVIIa immediately before the decision to perform a hysterectomy when arterial embolization is not available. Because of the rapidity of the rFVIIa action, it is possible to wait and observe the rFVIIa effect, if any, before proceeding to hysterectomy.

There is scientific evidence that rFVIIa may be efficacious in experimental trauma. Treatment with rFVIIA (180 $\mu g\ kg^{-1}$) after grade V liver injury decreased blood loss by nearly 50% in pigs.[13] Even in pigs with coagulopathy, with grade V liver injury, blood loss was reduced by ~50% in rFVIIa (180 and 720 $\mu g\ kg^{-1}$) treated animals.[14] Interestingly, rFVIIa (180 and 720 $\mu g\ kg^{-1}$) treatment before puncturing a 2 mm hole into the aorta did not decrease the initial blood loss but diminished significantly re-bleeding during resuscitation, and rFVIIa treated animals

tolerated a higher blood pressure before re-bleeding.[15] Patients suffering from major trauma may also benefit from rFVIIa according to a recently completed prospective randomized double-blind placebo-controlled multi-centre study. In total, 301 patients with blunt or penetrating trauma requiring transfusion of 8 units of red blood cells were recruited.[16] In this trial, three doses of rFVIIa were given: 200 $\mu g\ kg^{-1}$ at study entry, 100 $\mu g\ kg^{-1}$ at 1 h and another 100 $\mu g\ kg^{-1}$ at 3 h. In blunt trauma red blood cell transfusions and the incidence of acute respiratory distress syndrome (ARDS) were reduced and the incidence of multi-organ failure tended to be reduced in patients with penetrating trauma.[16] Mortality, however, was equal in the two groups.

So far, only two prospective randomized double-blind placebo-controlled studies evaluating the efficacy of rFVIIa in reducing blood loss and red blood cell transfusion needs in surgery have been published.[17 18] In 36 patients undergoing open radical prostatectomy, relatively low doses of 20 $\mu g\ kg^{-1}$ and 40 $\mu g\ kg^{-1}$ of rFVIIa decreased perioperative blood loss by more than 50% and allogeneic blood transfusions were equally reduced.[17] In contrast, in 204 non-cirrhotic patients undergoing partial hepatectomy rFVIIa at doses of 20 $\mu g\ kg^{-1}$ or 80 $\mu g\ kg^{-1}$ did not decrease perioperative blood loss and allogeneic blood transfusions.[18] The study by Raobaikady and colleagues[19] published in this issue of the Journal is important since it represents only the third prospective randomized double-blind placebo-controlled study in this setting. The authors randomized 48 patients undergoing major pelvic-acetabular surgery to rFVIIa (90 $\mu g\ kg^{-1}$) or placebo. The primary outcome variable was the total volume of perioperative blood loss. In contrast to the study by Friederich and colleagues,[17] no reduction in perioperative blood loss or allogeneic blood transfusion was observed.[19] The only difference was a slightly reduced postoperative blood loss (240 ml *vs* 370 ml) in the rFVIIa-treated patients. Why were these results so different, despite the fact that pre-defined transfusion guidelines were used in both studies? First, assessment of perioperative blood loss is notoriously fraught with difficulties and imprecision. In addition, and more importantly, the timing of the rFVIIa dosing was different. In the study by Friederich and colleagues[17] the rFVIIa was given during the operation, just prior to the main blood loss, whereas in the studies by Raobaikady and colleagues[19] and Lodge and colleagues,[18] rFVIIa was administered at skin incision. Given the rather short half life of rFVIIa of approximately 2 h in bleeding patients, dosing at skin incision might have been somewhat early in operations with an average duration of 3 and 4 h.[18 19] Alternatively, local blood coagulation could already be maximally stimulated in patients undergoing orthopaedic surgery without the addition of exogenous rFVIIa, such that rFVIIa treatment cannot improve local blood coagulation any further, at least not in patients without compromised blood coagulation. For now, rFVIIa is not indicated for routine use prior to high bleeding risk elective surgery.

More recently, another 'off-label' use of rFVIIa has been reported in patients with acute intracerebral haemorrhage but without an underlying coagulopathy.[20] The further increase in the volume of the intracranial bleeding was diminished by rFVIIa (40, 80 and 160 $\mu g\ kg^{-1}$) treatment by ~50% and the neurological outcome at 3 months was improved. Mortality tended to be lower in rFVIIa-treated patients. However, thromboembolic events tended to be more frequent in rFVIIa-treated patients. This is not a surprise as these are patients with a normal coagulation system who may have artherosclerotic plaques exposing TF-bearing cells to the blood.[21] This may well be the basis for rFVIIa-activated local blood coagulation and eventual thrombosis.

Recombinant VIIa is a drug that is easy and quick to mix and administer. It is generally well tolerated with thrombosis being the primary adverse effect of concern to clinicians. Although initially thromboses were rare since the drug was used in patients with severe coagulopathies, more recently more thromboses have been reported as the drug was used prophylactically in surgery or in patients without a coagulopathy such as in cerebral bleeding referred to above. Aledort calculated that the risk of rFVIIa-related thrombosis is 25 per 10^5 infusions.[11] In published placebo-controlled studies, however, the risk of thrombosis was not statistically different between patient and control groups.

So, where do we stand in May 2005? Are we obliged to give rFVIIa to patients with major bleeding to avoid accusation of substandard treatment or is rFVIIa treatment not indicated, owing to the lack of high level scientific evidence, lack of approval by any health authority, the potential of serious side-effects and its high cost? No definitive answers can be given at present. However, the following issues should be on the research agenda in the near future for this interesting drug. First, the clinical scenario, outside congenital bleeding disorders, where rFVIIa is beneficial needs to be defined. In terms of trauma, the trauma trial discussed above,[16] once published in a peer-reviewed journal, may provide further information. Second, the optimal timing and dose, which are largely unknown, need to be ascertained. Third, the most appropriate co-treatment with conventional blood products,[22] the minimum levels of coagulation factors and platelets required and also the minimum pH and temperature for the optimal efficacy of rFVIIa need to be determined. Fourth, laboratory monitoring of the efficacy of rFVIIa treatment will be helpful. The effect on prothrombin time is particularly marked but this does not always translate to clinically improved blood coagulation. Similarly measurement of the level of factor VII in plasma does not correlate with clinical efficacy. Two promising monitoring techniques are thrombelastography[13] and the endogenous thrombin potential measured in platelet rich plasma.[23]

Last but not least, we should keep in mind that the current treatment guidelines for the severely bleeding patient of the Committee on Trauma of the American College of Surgeons in their ATLS® program (www.facs.org) simply aim at 'stop the bleeding'.[24] This may be achieved using different strategies, be it a proper surgical source control, embolization, the use of coagulation enhancing drugs or any combination thereof.

In conclusion, rFVIIa is certainly a highly potent substance capable of locally promoting blood coagulation under certain circumstances. However, its clinical efficacy outside the setting of congenital coagulation disorders remains to be defined. Whilst nobody should be accused of providing substandard care when opting not to give rFVIIa for major bleeding, a trial of rFVIIa when conventional surgical, interventional and blood product support measures have failed is certainly worth a try.

Declaration of interest

Donat R. Spahn has served on an Executive Advisory Board for Novo Nordisk and is currently on the NovoSeven® European Trauma Advisory Board. Dr Michael Makris has attended meetings sponsored by Novo Nordisk and is a recipient of a British Society for Haemostasis and Thrombosis Novo Nordisk grant.

D. R. Spahn*
M. A. Tucci
Department of Anaesthesiology
University Hospital Lausanne (CHUV)
CH-1011 Lausanne
Switzerland

M. Makris
Sheffield Haemophilia and Thrombosis Centre
Royal Hallamshire Hospital
Sheffield
UK

**Corresponding author. E-mail: donat.spahn@chuv.hospvd.ch*

References

1 Roberts HR, Monroe DM, Escobar MA. Current concepts of hemostasis: implications for therapy. *Anesthesiology* 2004; **100**: 722–30
2 Ghorashian S, Hunt BJ. 'Off-license' use of recombinant activated factor VII. *Blood Rev* 2004; **18**: 245–59
3 Bombeli T, Spahn DR. Updates in perioperative coagulation: physiology and management of thromboembolism and haemorrhage. *Br J Anaesth* 2004; **93**: 275–87
4 Kenet G, Walden R, Eldad A, Martinowitz U. Treatment of traumatic bleeding with recombinant factor VIIa. *Lancet* 1999; **354**: 1879
5 Goodnough LT, Lublin DM, Zhang L, Despotis G, Eby C. Transfusion medicine service policies for recombinant factor VIIa administration. *Transfusion* 2004; **44**: 1325–31
6 Grounds M. Recombinant factor VIIa (rFVIIa) and its use in severe bleeding in surgery and trauma: a review. *Blood Rev* 2003; **17**: S11–21
7 Dutton RP, McCunn M, Hyder M, *et al*. Factor VIIa for correction of traumatic coagulopathy. *J Trauma* 2004; **57**: 709–19
8 Eikelboom JW, Bird R, Blythe D, *et al*. Recombinant activated factor VII for the treatment of life-threatening haemorrhage. *Blood Coagul Fibrinolysis* 2003; **14**: 713–17
9 Kessler C. Haemostasis.com: clinical experiences in the investigational use of rFVIIa in the management of severe haemorrhage. *Br J Haematol* 2004; **127**: 230
10 Siegel LJ, Gerigk L, Tuettenberg J, Dempfle CE, Scharf J, Fiedler F. Cerebral sinus thrombosis in a trauma patient after recombinant activated factor VII infusion. *Anesthesiology* 2004; **100**: 441–3
11 Aledort LM. Comparative thrombotic event incidence after infusion of recombinant factor VIIa versus factor VIII inhibitor bypass activity. *J Thromb Haemost* 2004; **2**: 1700–8
12 Ahonen J, Jokela R. Recombinant factor VIIa for life-threatening post-partum haemorrhage. *Br J Anaesth* 2005; **94**: 592–5
13 Martinowitz U, Holcomb JB, Pusateri AE, *et al*. Intravenous rFVIIa administered for hemorrhage control in hypothermic coagulopathic swine with grade V liver injuries. *J Trauma* 2001; **50**: 721–9
14 Schreiber MA, Holcomb JB, Hedner U, Brundage SI, Macaitis JM, Hoots K. The effect of recombinant factor VIIa on coagulopathic pigs with grade V liver injuries. *J Trauma* 2002; **53**: 252–7; discussion 257–9
15 Sondeen JL, Pusateri AE, Hedner U, Yantis LD, Holcomb JB. Recombinant factor VIIa increases the pressure at which rebleeding occurs in porcine uncontrolled aortic hemorrhage model. *Shock* 2004; **22**: 163–8
16 Rossaint R, Boffard KD, Warren BL, *et al*. Decreased transfusion utilization using recombinant factor VIIa as an adjunct in trauma. *Intensive Care Med* 2004; **30** (Suppl. 1): S199
17 Friederich PW, Henny CP, Messelink EJ, *et al*. Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: a double-blind placebo-controlled randomised trial. *Lancet* 2003; **361**: 201–5
18 Lodge JP, Jonas S, Oussoultzoglou E, *et al*. Recombinant coagulation factor VIIa in major liver resection: a randomized, placebo-controlled, double-blind clinical trial. *Anesthesiology* 2005; **102**: 269–75
19 Raobaikady R, Redman J, Ball JAS, Maloney G, Grounds RM. Use of activated recombinant coagulation factor VII in patients undergoing reconstruction surgery for traumatic fracture of pelvis and acetabulum: a double blind, randomized, placebo-controlled trial. *Br J Anaesth* 2005; **94**: 586–91
20 Mayer SA, Brun NC, Begtrup K, *et al*. Recombinant activated factor VIIa for acute intracerebral hemorrhage. *N Engl J Med* 2005; **352**: 777–85
21 Charo IF, Taubman MB. Chemokines in the pathogenesis of vascular disease. *Circ Res* 2004; **95**: 858–66
22 Hardy JF, De Moerloose P, Samama M. Massive transfusion and coagulopathy: pathophysiology and implications for clinical management. *Can J Anaesth* 2004; **51**: 293–310
23 Gerotziafas GT, Chakroun T, Depasse F, Arzoglou P, Samama MM, Elalamy I. The role of platelets and recombinant factor VIIa on thrombin generation, platelet activation and clot formation. *Thromb Haemost* 2004; **91**: 977–85
24 American College of Surgeons Committee on Trauma: Advanced Trauma Life Support® for Doctors, 2004

doi:10.1093/bja/aei103