

# Recombinant factor VIIa (rFVIIa) and its use in severe bleeding in surgery and trauma: a review

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**Abstract** Haemorrhage is a potential complication of any surgical procedure, presenting a major challenge to the surgeon and anaesthetist. In addition, uncontrolled bleeding accounts for at least 40% of the mortality associated with military and civilian trauma. Despite the widespread availability of standard interventions for the control of bleeding in such circumstances, there still remains an urgent need for an effective haemostatic agent that is safe, easy to use, and able to enhance local thrombotic processes without causing generalised arterial or venous thrombosis.

Recombinant factor VIIa (rFVIIa; NovoSeven®) has been successfully used in the management of haemophilia patients with inhibitors for many years. This review will explore its use in the control of surgery- and trauma-associated haemorrhage in patients without pre-existing coagulopathy, and will highlight the growing realisation that rFVIIa may have a major role not only as a treatment for haemophilia, but also as a universal haemostatic agent. This paper will also briefly explore those unanswered questions that should be resolved by future trials aiming to further clarify the safety, efficacy, and optimal dosing strategies of rFVIIa in the surgical and trauma settings.

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## INTRODUCTION: THE NEED FOR AN EFFECTIVE HAEMOSTATIC AGENT IN SURGERY AND TRAUMA

### Incidence of bleeding-related mortality and morbidity

Bleeding is a potential complication of any surgical procedure, and represents a major challenge to the surgeon and the anaesthetist.<sup>1</sup> The larger and more complex the surgery, the greater the potential for unexpected severe bleeding. At present, the standard treatment for significant haemorrhage during surgery or trauma surgery is the rapid control of the source of bleeding by one of the following methods: surgical techniques; packing or tamponading the area of bleed; ligation of major vessels leading to the bleeding area; radiological intervention to thrombose the vessels leading to the bleeding area;<sup>2</sup> and the use of blood-derived products, such as platelets, fresh frozen plasma (FFP), and cryoprecipitate. The action of these products may be enhanced by the use of fibrin sealants<sup>3,4</sup> and other pharmacological agents, such as aprotinin, tranexamic acid, and DDAVP. Despite these interventions, there still remains a need for an agent that will enhance local thrombotic

processes without causing generalised arterial or venous thrombosis. Failure to control massive bleeding will often lead to a combination of hypothermia, acidosis, and coagulopathy, which in turn exert their own negative influences over the clotting process to further exacerbate the problem.

Although mortality is very low for most surgical procedures, ranging from less than 0.1% for most routine surgery to 1–2% for cardiac surgery and 5–8% for elective vascular surgery, this low mortality may be greatly increased when severe bleeding occurs during the operative procedure. Severe, unexpected, and uncontrollable bleeding during the operation can raise the mortality rate from <1% to ≤20%, an observation reflected in most surgical scoring systems that predict outcome, such as POSSUM<sup>5</sup> and TRISS.<sup>6</sup>

After CNS injury, uncontrolled haemorrhage is the most common cause of death in trauma patients. Bleeding accounts for at least 40% of the mortality associated with both military and civilian trauma victims;<sup>7</sup> furthermore, 60% of civilian deaths resulting from uncontrolled bleeding occur after admission to hospital, and are therefore potentially preventable.

### Early intervention

It is well recognised that early intervention is important in reducing mortality and morbidity in trauma victims. Two concepts have influenced the development of pre-hospital and early in-hospital trauma care: the first is the principle of the “Golden Hour” of trauma, which emphasises the importance of early medical intervention in the first hour after trauma has occurred.<sup>8</sup> The second concept is that of the “trimodal distribution of trauma deaths,”<sup>9</sup> a model suggesting that there are three distributions peaks of deaths related to severe trauma. The first mortality peak shows that 50% of trauma deaths occur at the scene. The second peak occurs early in the hospital course (usually within 4 hours of admission), and accounts for a further 30% of deaths. The third and final peak, representing the remaining 20% of deaths, corresponds to those late fatalities that are typically caused by sepsis and multiple organ failure.<sup>8–11</sup> It has been suggested that early intervention may impact on the second, and possibly the third, mortality peaks.<sup>10</sup>

The prognosis in trauma victims is further complicated by post-traumatic coagulopathy. Severe multiple injuries cause massive activation of coagulation, which produces a consumptive coagulopathy and exhaustion of the system. Furthermore, hyperfibrinolysis resulting from activation of the fibrinolytic system may lead to subsequent disruption of newly formed clots. Massive transfusion will result in a dilutional coagulopathy, hypothermia, acidosis, and hypocalcaemia, a combination that will tend to worsen the coagulopathy.<sup>7,10</sup> This severe coagulopathy may lead to death in the ICU, even when control of the major vascular injury has been achieved.<sup>12</sup>

Massive haemorrhage in trauma patients consists of a combination of diffuse coagulopathic bleeding, and bleeding from vessels requiring surgical treatment. In most cases, the surgeon controls the latter type of bleeding during damage-control surgery, which is a surgical strategy designed to cope with the lethal triad of death: hypothermia, acidosis, and coagulopathy.<sup>13</sup> Damage-control surgery also aims to avoid

morbidity resulting from massive transfusion,<sup>14</sup> which often leads to acidosis, hypothermia, and abnormalities of electrolytes and clotting factors, resulting in a clinical picture of refractory coagulopathy and irreversible shock.<sup>15</sup> However, the control of coagulopathic bleeding is often extremely difficult and sometimes impossible to achieve using current therapies.<sup>7</sup>

Trauma-related mortality has been reduced over the last 20–30 years,<sup>10</sup> but a need still remains for an effective haemostatic agent. Such an agent would be required to stop the bleeding without causing thrombosis or other side effects. It should also be easy to use, low volume, have a long shelf-life, require no special storage facilities, and be cost-effective.

### RECOMBINANT FACTOR VIIa: AN EFFECTIVE HAEMOSTATIC AGENT FOR UNCONTROLLED SURGICAL AND TRAUMA BLEEDS?

Recombinant factor VIIa (rFVIIa; NovoSeven®) has been available for the management of bleeding in haemophilia patients with inhibitor for many years. Earlier reluctance to use it as a haemostatic agent in trauma and surgery resulted, in part, from a lack of understanding of its compartmentalised mode of action, and from its contraindication in hypercoagulopathy. However, as rFVIIa has been used successfully to treat various coagulopathies, and as we now have an increased understanding of its mode of action (MOA), we must consider the possibility that it is a promising adjunctive therapy for controlling haemorrhage in trauma victims and surgery patients who lack pre-existing coagulopathy.<sup>7,16</sup> This notion is supported by a growing number of reports suggesting that rFVIIa may have an indication in uncontrollable haemorrhage following trauma or liver, cardiac, and other types of general surgery.<sup>17,18</sup>

The current paper will review those cases in the literature that describe the use of rFVIIa as a therapy for haemorrhage control in trauma and surgery patients without pre-existing coagulopathies. In examining the MOA of rFVIIa, the paper will also investigate why the drug may be useful in trauma and surgery, and will highlight some unresolved issues and unanswered questions that should be considered in future studies and trials.

### RECOMBINANT FVIIa IN TRAUMA

To date, no placebo-controlled, randomised studies on the use of rFVIIa in trauma patients have been completed. However, such studies are planned and ongoing. In the interim, the literature contains many reports of individual cases in which rFVIIa has been used to manage trauma-associated bleeding. Some of these cases will be discussed.

Kenet and her colleagues<sup>19</sup> reported the first use of rFVIIa as a method of controlling life-threatening bleeding resulting from severe trauma. In this case, a 19-year-old soldier with a high-velocity rifle injury presented with a torn inferior vena cava at the L5 level, with subsequent extensive damage to

the paravertebral muscles at the exit wound. In addition, the patient demonstrated profound hypovolemic shock, ketoacidosis, hypothermia, and disseminated intravascular coagulation (DIC). Surgical attempts to achieve haemostasis failed. Despite receiving packed red cells, FFP, platelets, and cryoprecipitate with tranexamic acid (Table 1), the patient continued to bleed at a rate of 300 ml/min. The authors suggest that a fatal outcome appeared inevitable.

Recombinant FVIIa was administered as a last resort in an attempt to control the bleeding. Following an initial intravenous dose of 60 µg/kg rFVIIa, blood loss slowed to 10–15 ml/min, and a considerable improvement in coagulation tests was observed. A repeat dose of 60 µg/kg rFVIIa administered 1 hour after the initial dose stopped slow residual oozing, and produced normalisation of coagulation tests. Surgeons were then able to identify and ligate a number of small vessel tears. The patient experienced no further blood loss, and his condition remained stable.

This case study implies not only that rFVIIa can be used successfully in the control of severe, life-threatening haemorrhage, but also recommends that the contraindication of rFVIIa use in coagulopathy should be re-evaluated. Following the report of this case study in the literature, rFVIIa has been used worldwide in a number of off-label indications, and has repeatedly demonstrated success in achieving haemostasis in trauma victims or surgery patients when conventional methods have failed.

Following both the case study reported by Kenet et al.<sup>19</sup> and a randomised safety and efficacy study of rFVIIa in hypothermic, coagulopathic swine with liver injuries,<sup>20</sup> Martinowitz and co-workers reported seven massively bleeding, multi-transfused, coagulopathic trauma patients treated with rFVIIa between June 1999 and January 2001.<sup>7</sup> All seven patients were included in the Compassionate Use Program approved by the Israeli Ministry of Health. The series of patients included the 19-year-old male originally reported by Kenet et al. (patient 1),<sup>19</sup> and the remaining six patients presented with a variety of penetrating or blunt injuries (Table 1). All patients experienced uncontrolled bleeding, and were treated with rFVIIa only when conventional surgical techniques (cauterisation, ligation, packing, argon beam [patient 3]) and massive replacement therapy failed to achieve haemostasis (Table 1). Diffuse bleeding stopped within 5–15 minutes following administration of 1–3 doses of rFVIIa, and a significant reduction in blood products was also observed. Doses ranged from 40–120 µg/kg, and a median of 2 doses (range: 1–2.75 doses) was required (Table 1). Laboratory parameters of coagulation also improved. In addition to the haemostatic efficacy achieved with rFVIIa use, the study found no evidence of venous, arterial, or CNS thromboembolic complications. Although three of the seven patients died, the cause of death was considered unrelated to the use of rFVIIa.

Although the data reported by Martinowitz and colleagues<sup>7</sup> are uncontrolled and by no means conclusive, the study strongly indicates that rFVIIa should be considered as an adjunctive haemostatic treatment in those trauma patients where conventional methods have failed. The data also indicate that controlled animal and clinical studies are urgently needed to further investigate the use of rFVIIa in

Table 1 Summary of rFVIIa use in trauma cases

Study	Patient details			Total replacement products required prior to rFVIIa				Time to rFVIIa	Doses of rFVIIa ( $\mu\text{g}/\text{kg}$ )	Outcome
	Patient no.	Age (y)/ Sex	Trauma	PC	FFP	Cryo	PLT			
Kenet et al. (1999) <sup>19</sup>	1	19/M	Penetrating — IVC abdomen, paravertebral muscles. Torn inferior vena cava.	40	20	10	20	4 hours	60, 60	Bleeding stopped rapidly. Coagulation tests normalised. Recovery was uneventful and patient survived.
Martinowitz et al. (2001a) <sup>7</sup>	2*	21/M	Penetrating — liver/chest.	46	26	30	32	14 hours	120	Bleeding stopped rapidly and laboratory values normalised. However, patient died during surgery due to profound shock, hypothermia, and acidosis.
	3	45/M	Penetrating — pelvis, prostate, urinary bladder, hip fracture, renal failure.	70	66	139	107	30 days	120, 60, 60	Bleeding stopped rapidly and laboratory parameters normalised. Patient survived.
	4	17/M	Penetrating — pelvis/chest.	27	19	28	36	9 hours	120	Bleeding stopped quickly. Laboratory values normalised. Patient survived.
	5	21/F	Blunt — massive liver damage.	50	10	—	10	4 hours	40	Bleeding stopped rapidly. However, patient died 4 weeks after injury occurred due to sepsis resulting from liver hypoxia.
	6	75/F	Blunt — hip fracture.	25	20	10	20	7 days	70, 60	Bleeding stopped rapidly. However, patient died 4 weeks after injury occurred due to liver failure resulting from liver hypoxia.
7	42/F	Blunt — pelvic fractures and tears in spleen, diaphragm, and lungs. Intracranial haemorrhage.	20	6	15	12	5 hours	120, 80, 80	Bleeding stopped and laboratory tests normalised rapidly. Patient survived.	
O'Neill et al. (2002) <sup>21</sup>	1	24/F	Penetrating — multiple stab wounds resulting in grade III liver injury and extremity vascular injury.	108	78	18	12†	45 hours	90	All external signs of bleeding ceased immediately. Haemodynamic parameters stabilised. However, patient died 5 weeks after initial presentation due to septic shock and multi-organ failure secondary to <i>Candida</i> infection.

\* Patient no. 1 from this study is the same patient described in the Kenet et al. (1999) case study; † Single donor apheresis platelet units (equivalent to 72 random donor platelet units); rFVIIa, recombinant factor VIIa (NovoSeven<sup>®</sup>); IVC, inferior vena cava; PC, packed cells; FFP, fresh frozen plasma; Cryo, cryoprecipitate; PLT, platelets.

this indication.

The time of rFVIIa administration during trauma-related haemorrhage may also be significant, as implied in a case reported by O'Neill and colleagues.<sup>21</sup> A 24-year-old woman without pre-existing coagulopathy presented to the emergency department with six stab wounds and a right haemothorax. She haemorrhaged massively from both a grade III liver injury and a vascular injury to the right lower leg, necessitating three surgical explorations, two angiographic embolizations, and massive replacement therapy with blood products (Table 1). Despite these conventional treatments, however, the patient continued to demonstrate recurrent episodes of liver haemorrhage, which led to a vicious cycle of transfusion, hypothermia, coagulopathy, and re-bleeding. In the face of such uncontrollable, life-threatening hepatic haemorrhage and a regional blood shortage, a single dose of 90 µg/kg rFVIIa was infused 45 hours after admission. Bleeding stopped almost immediately, and the patient's laboratory values stabilised. In addition, her fluid requirements gradually normalised over the next 24 hours, and she demonstrated no further episodes of recurrent haemorrhage. Surgery undertaken 3 days later (post-injury day 5) to perform an abdominal washout and removal of liver packing was successful, with excellent haemostasis and no re-bleeding.

Unfortunately, the patient's recovery was complicated by multiple nosocomial infections. Although these infections initially appeared to respond to antibiotic therapy, the patient developed *Candida* sepsis several weeks after admission, and antifungal treatment was ineffective. Five weeks after the initial injury, the patient died due to septic shock and multi-organ failure secondary to the *Candida* sepsis.

Although rFVIIa administration in this patient resulted in an almost immediate cessation of bleeding and correction of coagulopathy, the drug may have been given too late. The authors highlight the possibility that early use of rFVIIa in trauma patients is essential to eliminate the need for massive transfusion, which in turn may reduce at least some of the associated short- and long-term morbidity.

## RECOMBINANT FVIIa IN SURGERY

### Management of intra-operative bleeding

In a recently published study, Friederich et al.<sup>22</sup> investigated blood loss and transfusion requirements in 36 patients with normal haemostatic function undergoing retroperic prostatectomy. In this randomised, double-blind, placebo-controlled, single-centre study, patients were randomised to receive either placebo ( $n = 12$ ), or a bolus rFVIIa dose of 20 µg/kg ( $n = 8$ ) or 40 µg/kg ( $n = 16$ ).

Peri-operative administration of rFVIIa was found to produce a significant, dose-dependent reduction in total peri-operative blood loss when compared with placebo. In patients receiving 20 µg/kg and 40 µg/kg rFVIIa, the median total blood losses were 1235 ml and 1089 ml, respectively. In contrast, a median total blood loss of 2688 ml was observed in the placebo group ( $p = 0.001$  for each of the two dose groups compared with placebo). None of the patients receiving the higher dose of rFVIIa required red-cell transfusion,

compared with 7 of 12 (58%) placebo patients. In the lower dose group, 3 of 8 (38%) were transfused. In addition, the duration of the operation in patients receiving rFVIIa was 54 minutes shorter than in placebo patients ( $p = 0.035$  and  $p = 0.014$  for the 20 µg/kg and 40 µg/kg groups versus placebo, respectively), although there was no difference in duration between the two rFVIIa groups. Treatment with rFVIIa during the operative procedure also resulted in a short-lasting reduction of mean prothrombin time (PT) from 12.5 s to 9.7 s. No thromboembolic or other adverse events were encountered. Although the authors suggest that this study is not large enough to draw definite conclusions regarding the safety of rFVIIa, they conclude that the use of rFVIIa appears to be safe and effective in the treatment of patients undergoing surgery associated with significant blood loss, and may show some benefit in reducing transfusion requirements.

### Liver surgery

The literature contains numerous reports demonstrating the efficacy of rFVIIa in controlling intra-operative bleeding during liver surgery, which is known to be associated with a higher level of blood loss than other types of surgery. Furthermore, the liver plays an important role in the maintenance and control of the normal haemostatic balance.<sup>23</sup> The degree of blood loss associated with liver transplants may have important long-term effects on factors such as postoperative infection, mortality, cancer recurrence, and graft survival.<sup>23</sup> In addition, hepatic failure is often associated with a severe coagulopathy that hinders potentially life-saving intervention.<sup>24</sup>

Bernstein and colleagues<sup>25</sup> showed that rFVIIa could effectively correct a prolonged PT in cirrhotic patients. Hendriks et al.<sup>26</sup> later demonstrated that a single dose of rFVIIa (80 µg/kg) could reduce transfusion requirements in cirrhotic patients undergoing orthotopic liver transplant (OLT). Another study by Ejlersen et al.<sup>27</sup> also supported the findings of Bernstein and co-workers<sup>25</sup> by showing that a single injection of rFVIIa (80 µg/kg) could normalise PT within 30 minutes in 10 consecutive patients with alcoholic cirrhosis and bleeding oesophageal varices. Additionally, these authors found that treatment with rFVIIa controlled variceal bleeding successfully.

A multi-national, double-blind, placebo-controlled study evaluating the haemostatic efficacy and safety of rFVIIa in non-cirrhotic patients undergoing partial hepatectomy due to cancer/metastasis or benign tumour was reported in 2002 by Lodge and colleagues.<sup>28</sup> A total of 204 patients were randomised to receive a pre-operative injection of either placebo or rFVIIa (20 µg/kg or 80 µg/kg). If the anticipated surgery time exceeded 6 hours, a second dose of rFVIIa was administered 5 hours after surgery began. A reduction in both red blood cell transfusion requirements and intra-operative blood loss was observed in the 185 patients receiving rFVIIa, and this effect was more pronounced in those patients receiving the higher dose. The incidence of thromboembolic and other adverse events was similar between all three groups. However, the effects of rFVIIa in this particular study are not as marked as those observed in some of the earlier reports.

A number of reports have investigated the effects of

rFVIIa on parameters of coagulation and fibrinolysis during and after OLT.<sup>29,30</sup> Such studies have found that rFVIIa does not have any effect on fibrinolytic potential, and suggest that rFVIIa treatment in OLT appears to work by enhancing thrombin generation in a localised and time-limited manner, without activation of systemic coagulation. Lisman et al.<sup>29</sup> also showed that clotting times are significantly reduced following administration of rFVIIa, a finding confirmed by Hendriks and colleagues.<sup>31</sup>

#### *Cardiothoracic surgery*

Aggarwal and co-workers<sup>32</sup> reported a study in which rFVIIa was used to treat intractable bleeding in a series of eight surgical patients, six of whom underwent cardiac procedures (coronary artery bypass graft [CABG], mitral valve repair [MVR], type I aortic dissection, repair of ventricle rupture, post-CABG tamponade, or post-CABG bleeding). During the operative procedure, all patients developed coagulopathy and DIC with massive haemorrhage, necessitating aggressive blood-product support. Patients were therefore given a standard bolus dose of 90 µg/kg rFVIIa, which stopped the bleeding immediately in all but one patient (type I aortic dissection), who continued to demonstrate oozing from the incision. A second bolus dose of 90 µg/kg rFVIIa achieved haemostatic efficacy in this patient. There was no evidence of thrombosis in any patient following rFVIIa infusion, and the authors concluded that this agent is safe and effective in achieving haemostasis in surgical or trauma patients experiencing massive haemorrhage. In addition, they suggest that rFVIIa offers an important advance in the therapeutic options for such patients, with early treatment leading to the potential benefits of decreased transfusion requirements and associated reductions in morbidity and mortality.<sup>32</sup>

#### **Management of postoperative bleeding**

A number of case reports have demonstrated that rFVIIa may be effective in controlling severe postoperative bleeding. Svartholm et al.<sup>33</sup> reported the case of a 50-year-old woman with severe gallstone-induced pancreatitis who developed necrosis and a pseudocyst of the pancreas after initial treatment. An attempt to drain the pseudocyst endoscopically produced massive haemorrhage from the splenic artery, and despite immediate laparotomy and repeated packing, the patient continued to bleed. Approximately 11 hours after the start of bleeding, following a second laparotomy and massive administration of blood products (19 l of packed cells, 4.5 l of FFP, 300 g of platelets), a dose of 120 µg/kg rFVIIa was administered. Bleeding slowed considerably, and a second dose of 120 µg/kg rFVIIa given 5 hours later stopped the bleeding entirely. Re-operation successfully took place 3 days later.

The efficacy of rFVIIa in controlling intractable post-surgical bleeding has also been demonstrated by Ng and colleagues.<sup>34</sup> A female patient with end-stage renal failure presented with cardiac ischaemia and cardiomyopathy, and she was administered low molecular weight heparin (LMWH) and aspirin for a period of one week. As the patient's vascular access for haemodialysis had been compromised due to repeated arteriovenous fistula (AVF) thrombosis and development of pseudoaneurysm, the decision was

made to proceed with plans to re-create a new AVF for dialysis. This procedure was performed one week after admission, and one day after discontinuation of treatment with LMWH and aspirin.

Following the operation, continuous slow oozing from the site of the AVF was observed for the first 36 hours. The bleeding was reduced following transfusion of two units of packed cells, six units of FFP, and local measures of compression and superficial stitching. However, removal of the pressure bandage one day later for the purpose of wound inspection resulted in massive bleeding that could not be controlled by local measures. Urgent surgical re-exploration was performed, but suturing and application of thrombin powder also failed to produce haemostasis. Further transfusions of FFP, cryoprecipitate, platelets, and tranexamic acid were also ineffective.

Recombinant FVIIa was then administered as a slow bolus infusion of 120 µg/kg in order to control the haemorrhage. Bleeding stopped soon after the infusion, but a second dose was given 6 hours later to ensure adequate haemostasis. Laboratory parameters also improved, and the patient was discharged one week later with a functional AVF.

This case report highlights the efficacy of rFVIIa in securing haemostasis in patients with post-surgical bleeding following the use of LMWH. The pharmacological activity of LMWH accumulates in individuals with end-stage renal failure, ensuring that such patients remain anticoagulated for a longer period than would otherwise be expected following discontinuation of therapy. Concomitant use of aspirin also increases the potential for bleeding. However, a single dose of rFVIIa (120 µg/kg) was sufficient to achieve haemostasis in the patient reported by Ng et al.,<sup>34</sup> with a second dose administered as a precautionary measure. This study suggests not only that rFVIIa is effective in controlling haemorrhage in patients treated with LMWH, but also that such observations ensure that the agent gains further credibility as a potential universal haemostatic agent.

#### *Cardiac surgery*

Cardiac surgery is often associated with profuse haemorrhage. Excessive bleeding (>2 L after surgery) is encountered in 5–7% of patients, and may require re-operation in 3.6–4.2% of patients if conventional methods fail to arrest the bleed.<sup>35</sup> The current literature contains several reports in which rFVIIa has been used in an attempt to control postoperative bleeding in patients undergoing such procedures.

A pilot study investigated the role of rFVIIa in the treatment of 5 patients (aged 2.5–73.0 years) undergoing open-heart surgery for valvular heart disease.<sup>36</sup> Two patients experienced severe postoperative haemorrhage, and the remaining three patients exhibited considerable intra-operative bleeding. All haemorrhages failed to respond to conventional blood-component therapy, and each patient was given a single dose of 30 µg/kg rFVIIa. Treatment with rFVIIa achieved satisfactory haemostasis in all cases, producing an overall decline in mean blood loss from 4,170 ml (650–8000 ml) to 262.5 ml (220–334 ml). The two patients experiencing postoperative bleeding underwent two surgical operations, and a mean blood loss of 600 ml/h was observed following both procedures. Recombinant FVIIa was given after the sec-

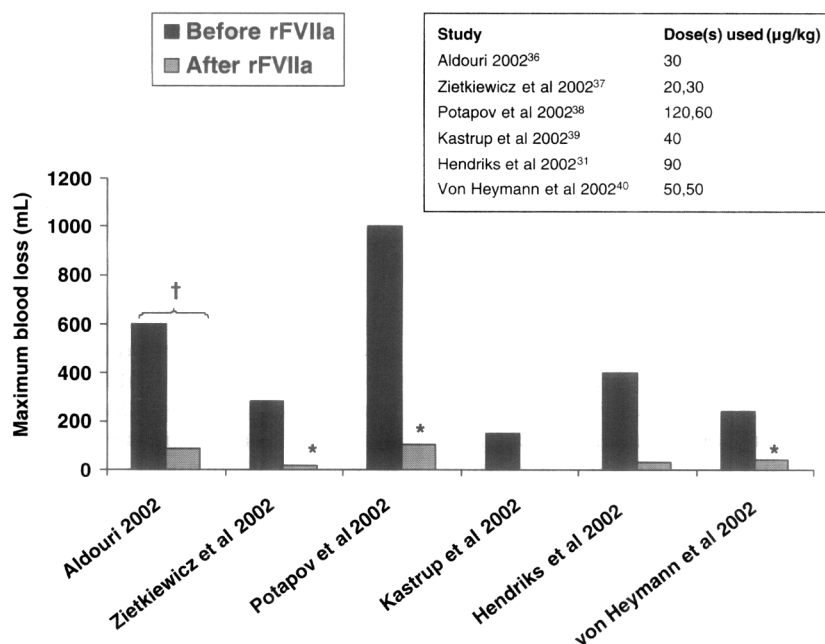


Fig. 1. Maximum postoperative blood loss per hour before and after administration of recombinant factor VIIa (rFVIIa) in cardiac surgery. \* 2 doses of rFVIIa required. † Mean blood loss based on 2 patients with postoperative bleeding.

ond procedure in both cases, reducing mean blood loss to 85 ml/h (Fig. 1). Furthermore, a mean intra-operative blood loss of 5800 ml was observed among the three patients that experienced haemorrhage during surgery. Following administration of rFVIIa, mean blood loss fell to 140 ml in the first hour after the procedure. No significant adverse events were observed.

Bleeding is the most frequent complication following implantation of a mechanical cardiac assist device. Two reports by Zietkiewicz et al.<sup>37</sup> and Potapov et al.<sup>38</sup> describe the successful use of rFVIIa in two patients experiencing severe haemorrhage following the implantation of a ventricular assist device. Zietkiewicz et al.<sup>37</sup> report the case of a 34-year-old male patient who had previously undergone repeated cardiac surgery. He presented with severe left ventricular dysfunction and haemostatic disturbances, and soon developed cardiogenic shock. Following implantation of a left ventricular assist device in order to unload the heart and prevent multi-organ failure, the patient began to bleed heavily. Intra-operative blood losses of 2500 ml were followed by postoperative drainage exceeding 150 ml/h for 6 hours, and massive epistaxis and excessive oozing from the surgical wound led to additional blood losses of 800 ml. As the bleeding failed to respond to conventional therapy, 20 µg/kg rFVIIa was given. After 30 minutes, bleeding and oozing were significantly reduced (drainage: 25 ml/h), and laboratory parameters also showed considerable improvement. A second dose of 30 µg/kg rFVIIa administered 4 hours after the initial dose produced further reductions in bleeding and oozing, with hourly drainage falling to below 15 ml (Fig. 1). No further bleeding episodes were encountered, and no significant side effects were observed. Seven days later, the patient developed a tension pneumothorax, leading to right ventricular failure, and he eventually died

despite lung-protective ventilatory strategy. Upon removal, the left ventricular assist device was found to be free of thrombin and platelet aggregates.

In another study, a 57-year-old woman with acute myocarditis and profound cardiogenic shock underwent implantation of a biventricular assist device, resulting in heavy, diffuse bleeding.<sup>38</sup> The patient received a total of 30 units of packed red cells, 56 units of FFP, and 4 pooled platelet concentrates. Despite acceptable coagulation parameters found in routine laboratory investigation, she continued to bleed at a rate of 1 l/h. Twelve hours after surgery, 120 µg/kg rFVIIa was administered. Blood loss decreased immediately to 500 ml/h, and some clot formation occurred. Two hours after the initial administration, a second dose of 60 µg/kg rFVIIa was given, along with 2 platelet concentrates. Blood loss fell to 300 ml/h, and then to 100 ml/h (Fig. 1). Following chest closure, the patient was transferred to the ICU, and bleeding remained below 100 ml/h for the next 4 hours before stopping entirely. No thromboembolic events were encountered.

As it is vital to obtain a balance between the dangers of bleeding and thrombosis in patients with implanted mechanical assist devices, the case studies reported by Zietkiewicz et al.<sup>37</sup> and Potapov et al.<sup>38</sup> are important, as they demonstrate both the efficacy of rFVIIa in achieving postoperative haemostasis and its apparent lack of thromboembolic complications in such patients. The use of rFVIIa during implantation of a device may also shorten the operating time and reduce the amount of transfusion products required during the procedure.<sup>38</sup>

Recombinant FVIIa has also been used in valve replacement surgery. In one case study, a 26-year-old man with osteogenesis imperfecta and severe aortic valve regurgitation underwent aortic valve replacement.<sup>39</sup> No transfusion was

required during surgery. However, after admission to the ICU, an average blood loss of 150 ml/h from the mediastinal chest drain over a period of 6 hours necessitated transfusion of 3 units of packed red cells, 4 units of FFP, and 2 units of platelets. When blood loss from the drain exceeded 1000 ml, 40 µg/kg rFVIIa was administered. Bleeding stopped immediately (Fig. 1) and no further blood products were required. On the second day after surgery, the patient was discharged from the ICU in a stable clinical condition.

In a further case study, a 65-year-old man underwent cardiac surgery due to severe mitral and tricuspid regurgitation.<sup>35</sup> During surgery to repair the mitral and tricuspid valves, the patient received 2 units of packed red cells, and oozing was treated with 3 units of FFP and 5 units of platelet concentrates. Postoperative blood loss via chest drains approached 750 ml/h, and declined to 400 ml/h following a re-thoracotomy. However, despite a second re-thoracotomy and treatment with conventional blood-replacement products, haemostasis could not be achieved. Approximately 21 hours after the first operation, a single dose of 90 µg/kg rFVIIa was administered, resulting in a prompt reduction in blood loss to 350 ml over the next 12 hours (Fig. 1). The only blood products transfused after this time were 2 units of FFP.

Finally, von Heymann et al.<sup>40</sup> report the successful use of rFVIIa in a 65-year-old male patient undergoing CAVBG surgery. Upon transfer to the ICU, immediate blood losses of >250 ml/h from the pleural and mediastinal chest drainage tubes were observed, and a re-sternotomy was performed 2 hours after the initial operation to cauterise bleeding sites. However, bleeding continued at a rate of 100–240 ml/h despite continuous transfusion of blood products, and on the first postoperative day the rate of blood loss increased to 220–229 ml/h. A total of 9 units of red blood cells, 6 units of FFP, and 1 unit of platelets had been transfused by this time. As further surgical revision was considered inappropriate, a dose of 50 µg/kg rFVIIa was administered as a rescue medication. Two hours later, a second 50 µg/kg dose was given. Blood losses decreased to 40 ml/h following the second dose (Fig. 1), and the chest was closed on the same evening. No thromboembolic side effects were noted, and the patient was discharged from the ICU in a stable clinical condition 10 days after the initial surgery.

Although the cases outlined above encourage the investigation and use of rFVIIa in the treatment of bleeding following cardiac surgery, Dietrich and Spannagl<sup>41</sup> urge caution. Their published response to the Hendriks et al.<sup>35</sup> study of rFVIIa use in a 65-year-old patient undergoing valve repair surgery is perhaps applicable to many studies in which rFVIIa is used in cardiac procedures. They claim that rFVIIa treatment in such cases is not only controversial but may also cause thrombotic adverse events. Monocyte activation during and after cardiopulmonary bypass results in a hypercoagulable state, as the monocytes provide the main source of tissue factor (TF) activation. As a result, the bleeding site may not be the only source of TF expression in cardiac patients. Therefore, Dietrich and Spannagl<sup>41</sup> claim that despite the local MOA of rFVIIa, its addition to such a hypercoagulable situation may increase the propensity of not only local but also universal TF activation, potentially leading to

thrombotic complications. These authors also point out that as rFVIIa is approved only for the treatment of haemophilic patients with inhibitors, it should be demonstrated that the coagulation defect present in haemophiliacs is comparable to that causing intractable bleeding following cardiac surgery.

Despite the concerns raised by Dietrich and Spannagl,<sup>41</sup> the current literature suggests that rFVIIa use is not associated with an increased risk of thromboembolic events. In support of this, a report by Roberts<sup>42</sup> reviewed clinical experience with rFVIIa between 1988 and May 2001. During this time, more than 180,000 standard doses (90 µg/kg) were administered to patients with haemophilia or other coagulation disorders, and even to healthy patients without any clinical evidence of a bleeding disorder. Only 17 patients experienced thrombotic events; of these, 11 patients had an arterial thrombotic event, and 6 demonstrated a venous thrombosis. A total of four patients died due to thromboembolic complications. Of the 17 patients, 3 demonstrated thrombotic symptoms either before or more than 10 days after rFVIIa administration, suggesting that the events were unlikely to be related to rFVIIa use. A further 6 patients were aged 70 years or older (range: 70–91 years), and suffered from one or more age-associated conditions, such as diabetes, atherosclerosis, and hypertension, all of which are risk factors for thrombosis in individuals with a normal coagulation system. It was concluded that the reported incidence of rFVIIa-associated thromboembolic events is very low, and that in the majority of cases, thrombotic events appear to be caused by improvements in the haemostatic system rather than a direct effect of the agent itself.<sup>42</sup>

However, Dietrich and Spannagl's recommendation that controlled trials should be performed to elucidate the MOA and safety of rFVIIa in cardiac surgery and other trauma/surgical indications should not be dismissed.<sup>41</sup> Indeed, the encouraging reports discussed in this review suggest that such trials are clearly warranted.

#### MODE OF ACTION OF rFVIIa

The exact MOA of rFVIIa remains to be established. Traditional theories based on its effect in haemophilia patients suggest that it provides local thrombin generation by enhancing TF/FVIIa assembly at the injury site, thereby augmenting the TF-dependent pathway of haemostasis. The TF/FVIIa complex then initiates the coagulation cascade by activating factors X and IX.

A more recent cell-based model of haemostasis, however, offers an alternative MOA. According to this theory, high-dose rFVIIa enhances haemostasis in haemophiliacs by binding to activated platelets with low affinity, and activating FX independently of TF. The FXa produced in this way is sufficient to partially restore platelet-surface thrombin generation in haemophiliacs, leading to the subsequent production of fibrin.<sup>43</sup> Presumably, rFVIIa works in the same way in trauma and surgery patients, augmenting the normal coagulation process to produce a faster and more pronounced thrombin burst. In surgery and trauma, rFVIIa therefore has two potential sites of action: at the injury site, by binding to

exposed TF to initiate the coagulation process; and on the surface of activated platelets, to produce thrombin independently of TF. These MOAs suggest that the effects of rFVIIa are localised to the site of injury in a time-limited manner, without systemic activation of the coagulation process.<sup>18,44</sup> Thrombotic potential is therefore reduced.

Furthermore, when compared with normal clots, those produced by rFVIIa have a different type of architecture that is stronger and far more resistant to degradation by fibrinolytic enzymes. One of the reasons why rFVIIa-associated 'super-clots' show an increased resistance to fibrinolysis is the activation of thrombin-activatable fibrinolysis inhibitor (TAFI), which only occurs in the presence of a high thrombin concentration.<sup>7</sup> The ability of rFVIIa to produce such 'super-clots' has the potential to impact significantly on the treatment of trauma victims and surgical patients.

## UNRESOLVED ISSUES

This review has shown that rFVIIa is being used successfully in a growing number of different clinical situations involving surgery and trauma. However, there are a number of questions that remain unanswered.

### Does rFVIIa work in the presence of the lethal triad of death?

The lethal trauma triad of death in bleeding patients — i.e. acidosis, hypothermia, and coagulopathy — forms the underlying basis upon which the philosophy of damage-control surgery has been built.<sup>45</sup> Virtually every aspect of the normal coagulation cascade is affected in the cold, acidotic, exsanguinating trauma patient,<sup>46</sup> making major surgery highly dangerous.

Severely bleeding patients face a high risk of developing hypothermia, which adversely affects coagulation as it causes platelet dysfunction, alteration of coagulation enzyme kinetics, disruption of fibrinolytic equilibrium, and prolongation of clotting time. Hypothermia therefore perturbs the normal haemostatic response to injury, and affects multiple organ systems and physiological processes.<sup>47</sup>

Acidosis is a pathophysiological state associated with serious morbidities and mortality.<sup>48</sup> Haemorrhagic shock can lead to intracellular derangements of oxygen and substrate utilisation, and hypoperfusion may be associated with consumptive coagulopathy. Acidosis lasting longer than 150 minutes will significantly increase activated partial thromboplastin time (APTT) and decrease the activity of FV.

Both severe hypothermia and severe acidosis have been found to be strong predictors of death in trauma patients if conventional reparative surgery is undertaken.<sup>49</sup> Consequently, a need exists for a haemostatic agent that is effective in such situations, and rFVIIa may be an important candidate for this role. Lynn et al.<sup>46</sup> suggest that rFVIIa may be successful in moribund trauma patients in whom standard procedures have failed to correct bleeding. Additionally, several cases discussed in this review have successfully used rFVIIa in patients exhibiting one or more components of the lethal triad, e.g. Kenet et al.<sup>19</sup> (acidosis, hypothermia, DIC); Martinowitz et al.<sup>7</sup> (coagulopathy); Aggarwal et al.<sup>32</sup>

(coagulopathy, DIC). Further study is clearly needed to determine whether rFVIIa should be used — and whether it is successful — in the presence of the lethal triad.

### When is the optimal time to administer rFVIIa?

Several workers suggest that early use of rFVIIa is essential for the successful control of bleeding.<sup>7,32</sup> Martinowitz et al.<sup>7</sup> postulate that rFVIIa should be administered as early as possible, before the occurrence of metabolic complications, severe coagulopathic defects, prolonged hypoxia, and damage from multiple transfusions — in other words, before the lethal trauma triad has time to become established. This is supported by the O'Neill et al.<sup>21</sup> case study of a young woman with multiple stab wounds and a right haemothorax. Conventional therapies failed to control the bleeding, and administration of rFVIIa did not occur until 45 hours after initial presentation. Although rFVIIa successfully and rapidly controlled the haemorrhage, the patient later died. Future studies should therefore attempt to determine the optimal time of rFVIIa administration.

### What is the optimal dose of rFVIIa?

The studies discussed in this review use a wide range of doses, with varying degrees of efficacy (Figs. 2a,b). Further studies are clearly needed to determine optimal dosing regimens in trauma and surgery patients. Reports in the literature suggest that most clinicians use doses of up to 90 µg/kg, which is the recommended dose for haemophilia patients, but many administer doses smaller than this. To date, very few clinicians have used larger doses.

How often should doses be repeated? The agent has a half-life of only two hours, and so it may be reasonable to suggest that the dose should be repeated if blood loss following the first dose initially decreases, but then rises again. Further studies are also urgently required to clarify the exact MOA of rFVIIa in non-haemophilic trauma and surgery patients. Although case studies discussed in this review found no postoperative increase in thrombotic events, controlled trials are needed to clarify and characterise the adverse event profile of rFVIIa.

### Should rFVIIa be used in the presence of DIC?

Another unresolved issue is that of rFVIIa use in the presence of DIC. Although DIC remains a contraindication of rFVIIa use, Kenet et al.<sup>19</sup> suggest that this should be re-evaluated. Other workers also support this view, as rFVIIa has shown efficacy in treating DIC in several cases.<sup>32</sup>

### What will the cost of rFVIIa treatment be in trauma and surgery patients?

Although the cost of this agent is currently very high, any cost-benefit analyses should take into account not only the cost in terms of the potential loss of life, but also the actual cost of any haemostatic agents (platelets, FFP, cryoprecipitate, DDAVP, fibrin glue, aprotinin, tranexamic acid) that may be used in these severe bleeding cases. Such studies should also consider the cost of prolonged ICU care in those cases where the bleeding is not rapidly controlled.

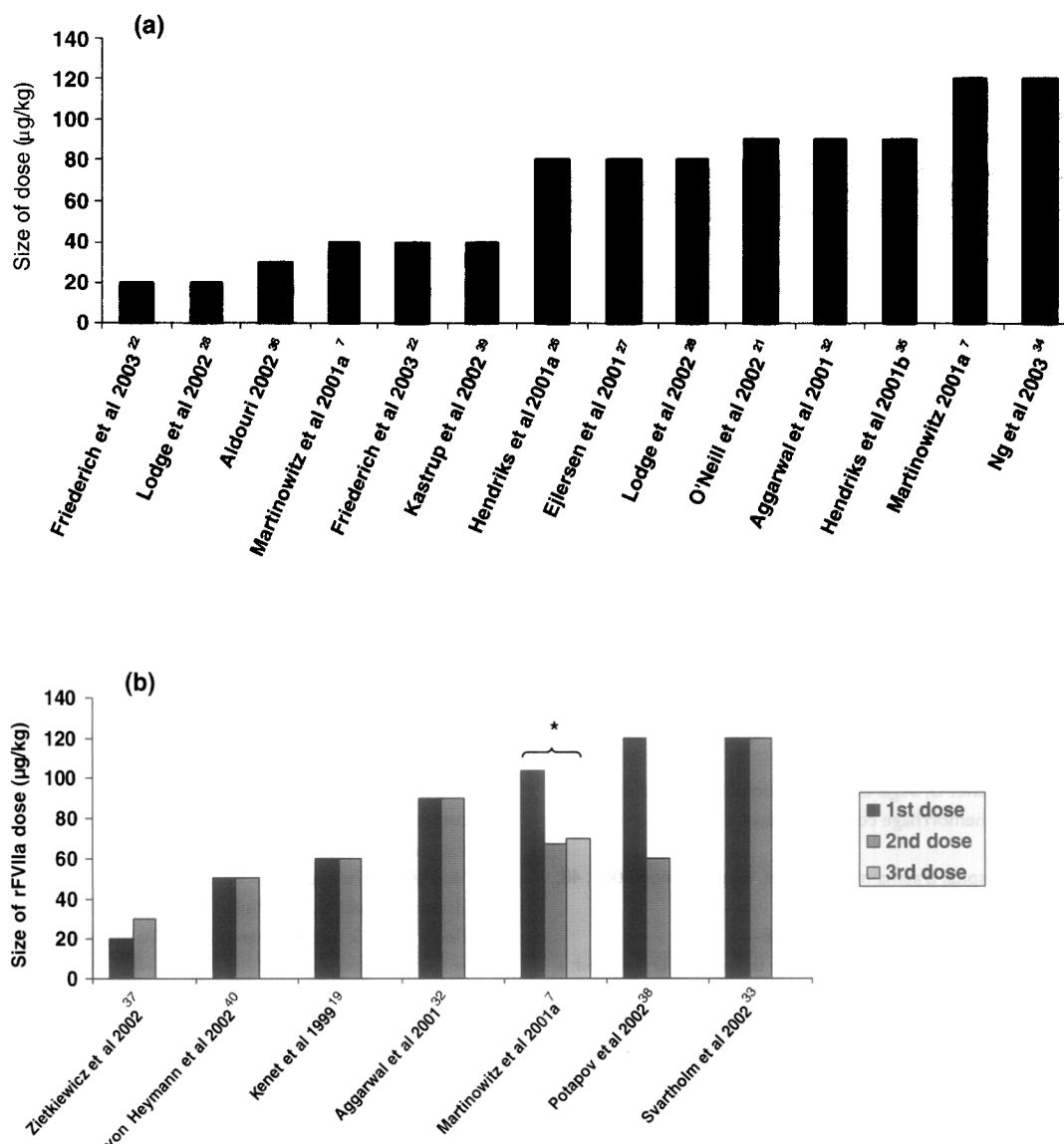


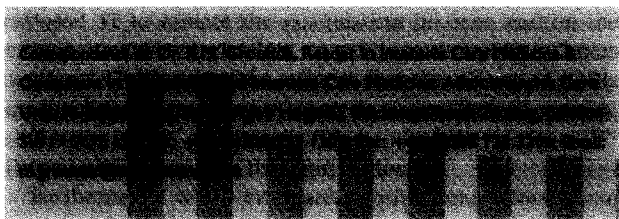
Fig. 2. (a) Size of recombinant factor VIIa (rFVIIa) dose in trauma and surgery cases: single doses. (b) Size of recombinant factor VIIa (rFVIIa) dose in trauma and surgery cases: repeated doses. \* Mean values taken from 3 patients.

## CONCLUSIONS

The studies reviewed here suggest that rFVIIa may have a role in the control of trauma- or surgery-associated haemorrhage that cannot be managed by conventional means, leading to associated reductions in transfusion-related morbidity and mortality. These data add to the growing realisation that rFVIIa may have a major role to play not only as a treatment for haemophilia with inhibitors, but also as a universal haemostatic agent.<sup>36</sup> It is certainly being used increasingly in a number of trauma and surgery settings, and its apparent efficacy supports and justifies additional controlled trials that should further clarify its role, efficacy, and safety.

There still remain, however, a number of unanswered questions, among them the important issue of whether rFVIIa should be used in the presence of the lethal trauma

triad. It is also important to remember that although rFVIIa has shown success in reducing haemorrhage in trauma and surgery, blood loss is also dependent on a number of other factors, including the type of operation, patient age and characteristics, surgical skill, and postoperative care. However, rFVIIa shows considerable promise, particularly when surgical haemostasis is difficult to achieve or when conventional therapies are unsuccessful. This does not mean, however, that rFVIIa should be administered to every trauma and surgery patient; optimal patient selection is vital. Controlled trials are needed to clarify unresolved issues, and to determine optimal dosing regimens, optimal time of administration, criteria for patient selection, adverse event profile, and specific MOA. Preliminary pre-clinical and clinical studies are currently underway.



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