Review

Recombinant activated factor VIIa and hemostasis in critical care: a focus on trauma

Alicia M Mohr[1], John B Holcomb[2], Richard P Dutton[3] and Jacques Duranteau[4]

[1]Assistant Professor of Surgery, Department of Surgery, New Jersey Medical School, Newark, New Jersey, USA
[2]COL, MC, US Army, Chief, Trauma Division, Trauma Consultant for The Surgeon General Commander, US Army Institute of Surgical Research, Fort Sam Houston, Texas, USA
[3]Associate Professor of Anesthesiology, University of Maryland School of Medicine, Baltimore, Maryland, USA
[4]Professor, Departement d'Anesthesie-Reanimation, Hopital de Bicetre, Le Kremlin-Bicetre, France

Corresponding author: Alicia M Mohr, mohr@umdnj.edu

Published online: 7 October 2005
This article is online at http://ccforum.com/supplements/9/S5/S37

Critical Care 2005, **9(Suppl 5):**S37-S42 (DOI 10.1186/cc3784)

Abstract

In this article we describe the current use of recombinant activated factor VII (rFVIIa; NovoSeven®) in trauma patients. Emphasis is placed on current uses as defined by key studies, efficacy data, and safety data. Most published studies in trauma patients are retrospective case studies and reports, although an international, double-blind, randomized, controlled, phase II study has been conducted that reported on the efficacy of rFVIIa in reducing the amount of blood products transfused in blunt trauma patients. That study demonstrated the efficacy and safety profile of this hemostatic agent as compared with placebo as adjunctive therapy in the management of severe bleeding associated with trauma. Further prospective, randomized, and placebo-controlled clinical trials will yield more information on the role of rFVIIa in the management of traumatic bleeding.

Introduction

Trauma mortality has been described to have a trimodal or bimodal distribution [1-4]. Of trauma deaths 50% occur at the scene of injury because of massive head injury or exsanguination [3,4]. There is then a second peak, which represents 30% of the deaths that occur early, half of which are due to uncontrollable hemorrhage [3,4]. A third phase of later deaths, related to multiple organ failure (MOF) associated with prolonged shock, massive transfusion, and infection [5,6], is also seen, although improvements in trauma care have seen figures fall. Life-threatening traumatic hemorrhage that occurs is often due to surgical and coagulopathic bleeding. Successful surgical control of bleeding has been assisted by the evolution and refinement of angioembolization [5,6]. The coagulopathy of trauma has remained problematic and its etiology is multifactorial, involving hypothermia, acidosis, consumption of clotting factors, and dilution [7,8]. If a patient develops the lethal triad of hypothermia, acidosis, and coagulopathy, then surgical control is less likely to be effective alone [9]. Coagulopathy in trauma may also be due to traumatic brain injury, fat embolus syndrome, or pre-existing comorbidities requiring oral anti-coagulation. Attempts to minimize transfusion of blood and blood products have led clinicians to look at alternate means of restoring hemostasis [10].

Use of recombinant activated factor VII in trauma

Recombinant activated factor VII (rFVIIa; NovoSeven®; Novo Nordisk A/S, Bagsværd, Denmark) has been used to control life-threatening traumatic bleeding that has been uncorrected by other means. rFVIIa acts to amplify coagulation at the local site of injury where tissue factor and phospholipids are exposed, accelerating the tissue factor-dependent pathway and generating a thrombin burst along with platelet surface interactions [11,12]. The first published account of the use of rFVIIa in trauma was a case report from Kenet and coworkers [13] published in 1999, documenting the first successful use of rVIIa in a soldier with traumatic coagulopathy following a high velocity gunshot wound to the inferior vena cava. The first case report in the USA was that by O'Neill and coworkers [14] published in 2002, which described the use of rFVIIa in a patient sustaining multiple stab wounds who was transfused with more than 100 units of blood before receiving a single dose of rFVIIa. This patient's coagulopathy did resolve, but she later succumbed to sepsis.

In 2001 Martinowitz and coworkers [15] reported on the use of rFVIIa in experimental grade V liver trauma in coagulopathic swine. In this experimental model, in which liver packing was combined with rFVIIa treatment, post-treatment blood loss was significantly less and the prothrombin time decreased

CABG = coronary artery bypass grafting; ICU = intensive care unit; INR = international normalized ratio; MOF = multiple organ failure; RBC = red blood cell; rFVIIa = recombinant activated factor VII.

Table 1

Summary of the current literature published regarding the use of recombinant activated factor VII in trauma

Ref. (year)	Patients (*n*)	Type of study	Type of patients	Dose (μg/kg)	Reported reduction in transfusion requirements	Mortality (deaths; *n*)	Thrombotic complications
[13] (1999)	1	Case report	Penetrating	60, 60	100%	0	None
[12] (2001)	7	Case series	Blunt and penetrating	120–212	100%	3	None
[14] (2002)	1	Case report	Penetrating	90	100%	1	None
[21] (2002)	19	Case series	Blunt and penetrating	129	78%	6	1 DVT
[22] (2002)	18	Case series	Blunt and penetrating	40	83%	5	1 IAT
[17] (2003)	5	Case series	Blunt and penetrating	80–144	60%	2	None
[19] (2003)	21	Case series	Multi-trauma and surgical	30–180	86%	5	None
[20] (2004)	29	Retrospective matched case series	Blunt and penetrating	40	100%	11	None
[32] (2004)	24	Retrospective chart review	Blunt and penetrating	?	100%	9	None
[18] (2004)	81	Retrospective cohort	Blunt and penetrating	48–148	80%	47	None
Unpublished (2004)	277	Prospective phase II	Blunt and penetrating	200, 100, 100	Decreased	69	None

DVT, deep vein thrombosis; IAT, iliac artery thrombosis.

5 min after injection. However, in a later study with a similar experimental model of liver trauma in noncoagulopathic swine, rFVIIa alone, without liver packing, did not reduce blood loss [16]. Thus, an experimental conclusion suggests first that there is a need to establish surgical control of bleeding, which should then be followed by adjunctive use of rFVIIa to aid in the cessation of coagulopathic bleeding. There appeared to be no role for rFVIIa in noncoagulopathic animals.

Treatment with rFVIIa is not currently licensed for use in trauma patients. In 1999 the US Food and Drug Administration approved rFVIIa for the treatment of spontaneous bleeding in patients with hemophilia A or B and in patients with known inhibitors to factor VIII or IX. In the European Union, rFVIIa is also licensed for the treatment of spontaneous and surgical bleeding in hemophilia A and B with known inhibitors to factor VIII and IX, as well as for use in the following indications: acquired hemophilia; patients with congenital factor VII deficiency undergoing surgery or invasive procedures; and patients with Glanzmann's thrombasthenia with antibodies to blood platelets, glycoprotein IIb/IIa, or HLA. Its use in trauma patients has been described, but currently there are no published prospective randomized control trials documenting its benefits. A summary of the current available literature on the use of rFVIIa in trauma is given in Table 1. Most of the published literature is limited to retrospective studies, anecdotal reports, and abstracts (Table 1) [12-14,17-22].

The largest, most recent study is a double-blind, phase II, multicenter, multinational, prospective, randomized controlled trial of rFVIIa in trauma patients conducted during the period 2001-2003. The final results are yet to be published in full, but the results were presented in part at the 6th World Congress on Shock, Inflammation & Sepsis in Munich, Germany (February 2004) and at the 25th International Symposium on Intensive Care and Emergency Medicine in Brussels, Belgium (March 2005) [23-25]. The final results will be published in the *Journal of Trauma* in 2005.

In this study, trauma patients who received 6 units of red blood cells (RBCs) within 12 hours of hospital admission were randomized into the study; both blunt and penetrating injuries were included, but those with major traumatic brain injury were excluded. After being administered a further 2 units of RBCs, patients received either placebo or rFVIIa given in three doses: first 200 μg/kg, followed by 100 μg/kg at 1 hour, and an additional 100 μg/kg at 3 hours. There was no significant difference in mortality between the group treated with rFVIIa and the placebo group (Table 2). In blunt trauma, RBC transfusion was significantly reduced with rFVIIa compared with placebo (estimated reduction by 2.6 RBC units; $P = 0.02$), and the need for massive transfusion (>20 units of RBCs) was reduced (14% versus 33% of patients; $P = 0.03$), representing a relative risk reduction of 58%. In penetrating trauma, similar analyses revealed trends toward reduced RBC transfusion with rFVIIa (estimated reduction of 1.0 RBC units; $P = 0.10$) and massive transfusion (7% versus 19%; $P = 0.08$). Trends toward reductions in mortality and critical complications were observed. Adverse events including thromboembolic events were evenly distributed between treatment groups [23,24].

Table 2

Outcomes measured in a randomized controlled trial of recombinant activated factor VII

	Blunt trauma			Penetrating trauma		
Outcomes	rFVIIa	Placebo	*P*	rFVIIa	Placebo	*P*
Mortality	25%	30%	0.58	24%	28%	0.69
MOF/ARDS	10%	23%	0.07	7%	17%	0.11
ICU-free days	13	8	0.18	24	20	0.26
Ventilation-free days	17	14	0.44	26	22	0.17

Both intensive care unit (ICU)-free and ventilator-free days were measured for 30 days. ARDS, acute respiratory distress syndrome; MOF, multiple organ failure; rFVIIa, activated recombinant factor VII.

Although not statistically significant, there was also a trend toward a reduced incidence of MOF and acute respiratory distress syndrome. Furthermore, intensive care unit (ICU)-free and ventilator-free days were more pronounced in the treated blunt trauma group (Table 2).

To date, in the USA the largest series is that reported by Dutton and colleagues [18], with more than 80 patients studied, including a previous study of five patients [17]. In their series the indications for use of rFVIIa included acute post-traumatic hemorrhage, severe traumatic brain injury, septic coagulopathy, and factor deficiencies. Most of the successful anecdotal studies report on the use of rFVIIa in similar patients, but often these patients have been found to be unresponsive to conventional coagulant therapy before rFVIIa use. Coagulopathy was reversed in 61 out of 81 cases (75%), with 42% of patients surviving to hospital discharge [18]. Although all patients in the study were found to have an initial clinical improvement in coagulation, 24% developed irreversible hemorrhagic shock, re-developed coagulopathy, received an average of 54 units of RBCs, and died within a few days of admission. Those patients who responded received an average of 33 units of RBCs during their hospital stay. The patients included in this study received FVIIa relatively late in their clinical course, after an average transfusion of 20 units of RBCs. Interestingly, patients with a sustained hemostatic response were treated earlier than were patients who did not respond (15 versus 26 units of RBCs; $P = 0.002$). In this study, 59 patients received rFVIIa within 24 hours of admission. The average time from admission to dosage was 5.5 days in the remaining 22 patients (range 1–37 days). One of the current theories is that rFVIIa works better when it is used earlier, because there has been less dilution of platelets and fibrinogen earlier in the course.

In 2002 Martinowitz and coworkers [21] reported on the use of rFVIIa in 19 trauma patients, including patients from previous reports [12,13]. Using one to three doses of rFVIIa, cessation of hemorrhage was documented in 79% of patients, transfusion requirements decreased, and 13/19 (68%) patients survived. In 2003, Eikelboom and coworkers [19] reported a case series of 21 patients treated with rFVIIa for life-threatening hemorrhage. Only three patients in this study had a traumatic injury as the cause of hemorrhage. Bleeding was noted to stop in 18 of the 21 patients. At the American Association for the Surgery of Trauma meeting in September 2004, Harrison and coworkers [20] presented a retrospectively matched case series of 29 patients treated with a lower dose of 40 μg/kg rFVIIa and demonstrated a significant decrease in the number of packed RBCs transfused, with no difference in mortality.

At the Eastern Association for the Surgery of Trauma meeting held in January 2002, Sifri and coworkers [22] presented retrospective data on the first 18 patients to receive rFVIIa at the University of Medicine and Dentistry of New Jersey-University Hospital. Five patients received rFVIIa for coagulopathy and 13 for active hemorrhage. All patients received a low dose (<50 μg/kg) of rFVIIa within the first 10 hours after injury [22]. Bleeding was controlled in 83% of patients, and there was a reduction in the transfusion requirements following the use of rFVIIa [22]. There was one possible drug-related thrombotic complication noted in a patient with underlying atherosclerotic disease of his iliac arteries who underwent angiography for a pelvic fracture that developed iliac artery thrombosis.

Based on the anecdotal data summarized above, Dutton and colleagues are also administering rFVIIa earlier in each patient's clinical course and are studying the clinical markers that might indicate futility of rFVIIa use. Their studies have found that the most significant factor in determining whether rFVIIa use will be futile is a patient's pH [18]. *In vitro* testing of rFVIIa has demonstrated that decreasing the pH from 7.4 to 7.0 reduced the activity of rFVIIa by over 90% [26]. Temperature was not found to adversely affect the activity of rFVIIa [26]. In addition, at the University of Maryland three independent predictors of futility of rFVIIa administration were found to be a Revised Trauma Score less than 4.1, prothrombin time greater than 17.6 s, and lactate greater than 13 mg/dl [27].

Dutton and colleagues [18] used rFVIIa in nine patients with severe traumatic hemorrhage and coagulopathy from use of warfarin. Five of the nine patients died, four from their traumatic brain injury and one from MOF. In 2002, a report of 13 patients with an elevated international normalized ratio (INR) secondary to warfarin use underwent treatment with rFVIIa either for a critically prolonged INR of 10 or greater or bleeding complications [28]. All patients were noted to exhibit correction of coagulation parameters, and bleeding complications were treated. A review of the use of rFVIIa to reverse anticoagulant therapy was recently published [29]; however, data on the timing of treatment and standardized dosing are lacking.

There have also been reports of patients receiving rFVIIa for treatment of traumatic brain injury without prehospital use of warfarin. Again, a clinical improvement in hemorrhage was seen by Dutton and colleagues [18] in all 20 patients, but there was a 75% mortality in this group, most likely attributable to their brain injury. Similarly, another case series of nine patients undergoing neurosurgical intervention, two with coagulopathy and traumatic brain injury, three on warfarin for atrial fibrillation and four with end-stage liver disease, was reported in 2003 [30]. That study demonstrated a clinical improvement in coagulation parameters with early rFVIIa use before neurosurgical intervention [30]. There were no procedural or operative complications, and no post-operative hemorrhagic complications were reported.

Therapy with rFVIIa has also been used for septic coagulopathy associated with MOF [18]. All patients clinically stopped bleeding; however, the average prothrombin time was only 14 s before treatment with rFVIIa. Three out of the four patients survived. Similar findings were reported by Holcomb and coworkers [31] in a case report of a patient with septicemia.

Dose

Because of the off-label use of rFVIIa in trauma, the appropriate dosing and repeat dosing is currently unknown. The dosage of rFVIIa in the trauma literature varies from 40 to 212 μg/kg (Table 1) [12-14,17-22,32]. The double-blind study in patients with blunt and penetrating trauma used an initial dose of 200 μg/kg, followed by an additional 100 μg/kg if bleeding persisted and a further 100 μg/kg if required, but there is currently no label for rFVIIa in trauma [23,25]. The recommended dose in hemophilia is 90 μg/kg. When it is administered to a trauma patient, nonsurgical bleeding treated with rFVIIa appears to be controlled relatively quickly (within 10–15 min) or stops at once, but if bleeding is noted to resume then additional doses have been given. The serum half-life of rFVIIa is 2.7 hours. The more common dosing for acute traumatic hemorrhage is 50–100 μg/kg. More recently doses as low as 10 μg/kg have been described [28]. Most of the lower doses have been used for reversal of anti-coagulation and intracranial bleeds [28,33].

Currently, there are too few data to speculate on a minimum effective dose in trauma, particularly given all the potential variables and confounders in this mixed patient group. Perhaps the greatest reported drawback of treatment with rFVIIa is the cost. An average dose of 4.8 mg (50 μg/kg in a 70 kg adult) costs US$3000–4000. Most agree that there is a financial burden of cost for rFVIIa in a trauma population, which is difficult to quantify secondary to its immeasurable benefit in terms of patient survival.

Laboratory monitoring

Coagulation parameters have not been well studied with use of rFVIIa. At the University of Maryland, the typical prothrombin time decreased from 17.5 to 9.3 s and the INR dropped from 2.2 to 0.58 [18]. Thromboelastogram recordings before and after rFVIIa use have been utilized to determine the quality of the clot formed. Thromboelastogram demonstrated an improvement in the time to onset of clotting, the rate of clot formation, the maximum amplitude, the time to reach stable clot, and the rate of subsequent clot lysis [18]. There are no conclusive studies recommending the best therapeutic monitoring modality for rFVIIa, so should the need for repeated dosing be based on clinical response? Platelets are required for the formation of a stable clot and appear to be a necessary component of rFVIIa-induced coagulation. Dutton and coworkers observed several patients with platelet counts below 50,000 cells/l who did not clinically form clot after rFVIIa administration until they received a platelet transfusion. The authors recommended that the platelet count at the time of FVIIa administration be verified, and that platelets be given concurrently if the count is under 50,000 cell/l [18].

In their case series Martinowitz and coworkers [12] reported that the median fibrinogen level in patients before rFVIIa administration was 150 mg/dl (25–75 quartile range: 110–195 mg/dl), whereas the normal range is 200–400 mg/dl. Despite the lowered fibrinogen levels, adequate hemostasis was achieved in these patients.

Safety

Because of a current lack of level I evidence, potential risks, benefits, and costs should be considered before rFVIIa is used. During the period 1996–2000 more than 140,000 doses of rFVIIa were administered for hemophilia, with a complication rate of less than 0.02% [34]. An adverse effect is the potential for thromboembolism, which has been associated with advanced atherosclerotic disease, septicemia, crush injury, and disseminated intravascular coagulation. The two main safety concerns specifically in trauma patients are an increased risk for deep vein thrombosis and pulmonary embolism, and increased microvascular coagulation and subsequent acute lung injury and MOF.

A recent study conducted by Roberts and coworkers [34] suggested that inappropriate thrombosis occurring after rFVIIa administration is unlikely to be due to the need for

exposed tissue factor at the site of vascular injury as well as activated platelets. Despite theoretic concerns, no increased incidence of prothrombotic complications has been reported [35]. In a recently published, matched, case–control investigation into the use of rFVIIa to manage intractable blood loss after cardiac surgery [36], 51 treated patients had undergone a variety of procedures, including – either singly or in combination – coronary artery bypass grafting (CABG) surgery ($n = 21$), valve replacement and/or repair ($n = 28$), ascending aorta or aortic arch replacement and/or repair ($n = 15$), complex congenital abnormality repair ($n = 8$), heart transplantation ($n = 4$), or insertion of a left ventricular assist device ($n = 1$). In this series, the rFVIIa dosing was 4.8 mg (approximately 70 μg/kg) intravenous bolus for patients with severe, uncontrolled blood loss and 2.4 mg (approximately 35 μg/kg) intravenous bolus for patients with less severe, controlled blood loss. In the 21 patients who underwent CABG surgery, rFVIIa therapy was not associated with an increased risk for myocardial infarction, end-organ failure, or death, but it was associated with some measures of morbidity (renal dysfunction and length of ICU and hospital stay). This increased morbidity in patients undergoing CABG may be due to the effects of rFVIIa therapy, the greater blood loss in the rFVIIa-treated patients, or a combination of the two factors.

The safety profile reported by Roberts and coworkers [34] has not validated a substantial risk for diffuse thrombosis. In the series reported by Martinez and coworkers [21] there was one deep vein thrombosis. No thrombotic events were reported by Eikelboom and coworkers [19]. One iliac artery thrombosis in patients with aortoiliac disease was reported by Sifri and coworkers [22]. In studies utilizing rFVIIa for a variety of indications, the incidence of thrombotic complications is slightly higher than when trauma patients are studied alone, suggesting that despite the slightly higher risk for a hypercoaguable state in trauma patients an increased rate of thrombotic complications has not been observed.

Conclusion

There remain numerous open questions about the use of rFVIIa in the setting of trauma. What is the best timing for administration? How many units of blood and/or blood products should be transfused? What is the proper dose? How many doses should be used? What are the indications and contraindications of rFVIIa use? When is the use of rFVIIa futile? Although rFVIIa has been shown to be a valuable tool in the armamentarium of trauma resuscitation with rescue from coagulopathic bleeding, reduction in intracranial hemorrhage, and reversal of anticoagulants, more prospective studies are needed to confirm that rFVIIa use is safe. There is no doubt that a large prospective, placebo-controlled trial will answer some as yet unanswered questions in trauma patients as well as delineate the drug's anticipated efficacy.

Competing interests

RPD has received speaking and consulting fees from Novo Nordisk and is a member of their steering committee for trauma trials. JD works as a clinical investigator for Novo Nordisk.

References

1. Como JJ, Dutton RP, Scalea TM, Edelman BB, Hess JR: **Blood transfusion rates in the care of acute trauma.** *Transfusion* 2004, **44:**809-813.
2. Riou B, Landais P, Vivien B, Stell P, Labbene I, Carli P: **Distribution of the probability of survival is a strategic issue for randomized trials in critically ill patients.** *Anesthesiology* 2001, **95:** 56-63.
3. Sauaia A, Moore FA, Moore EE, Moser KS, Brennan R, Read RA, Pons PT: **Epidemiology of trauma deaths: a reassessment.** *J Trauma* 1995, **38:**185-193.
4. Shackford SR, Mackersie RC, Holbrook TL, Davis JW, Hollingsworth-Fridlund P, Hoyt DB, Wolf PL: **The epidemiology of traumatic death. A population-based analysis.** *Arch Surg* 1993, **128:**571-575.
5. Kushimoto S, Arai M, Aiboshi J, Harada N, Tosaka N, Koido Y, Yoshida R, Yamamoto Y, Kumazaki T: **The role of interventional radiology in patients requiring damage control laparotomy.** *J Trauma* 2003, **54:**171-176.
6. Velmahos GC, Chahwan S, Falabella A, Hanks SE, Demetriades D: **Angiographic embolization for intraperitoneal and retroperitoneal injuries.** *World J Surg* 2000, **24:**539-545.
7. Lawson JH, Murphy MP: **Challenges for providing effective hemostasis in surgery and trauma.** *Semin Hematol* 2004, **41:** 55-64.
8. Martinowitz U, Michaelson M: **Guidelines for the use of recombinant activated factor VII (rFVIIa) in uncontrolled bleeding: a report by the Israeli Multidisciplinary rFVIIa Task Force.** *J Thromb Haemost* 2005, **3:**640-648.
9. Ferrara A, MacArthur JD, Wright HK, Modlin IM, McMillen MA: **Hypothermia and acidosis worsen coagulopathy in the patient requiring massive transfusion.** *Am J Surg* 1990, **160:**515-518.
10. Malone DL, Dunne J, Tracy JK, Putnam AT, Scalea TM, Napolitano LM: **Blood transfusion, independent of shock severity, is associated with worse outcome in trauma.** *J Trauma* 2003, **54:**898-905.
11. Levy JH: **Novel pharmacologic approaches to reduce bleeding.** *Can J Anaesth* 2003, **50:**S26-S30.
12. Martinowitz U, Kenet G, Segal E, Luboshitz J, Lubetsky A, Ingerslev J, Lynn M: **Recombinant activated factor VII for adjunctive hemorrhage control in trauma.** *J Trauma* 2001, **51:**431-438.
13. Kenet G, Walden R, Eldad A, Martinowitz U: **Treatment of traumatic bleeding with recombinant factor VIIa.** *Lancet* 1999, **354:**1879.
14. O'Neill PA, Bluth M, Gloster ES, Wali D, Priovolos S, DiMaio TM, Essex DW, Catanese CA, Strauss RA: **Successful use of recombinant activated factor VII for trauma-associated hemorrhage in a patient without preexisting coagulopathy.** *J Trauma* 2002, **52:**400-405.
15. Martinowitz U, Holcomb JB, Pusateri AE, Stein M, Onaca N, Freidman M, Macaitis JM, Castel D, Hedner U, Hess JR: **Intravenous rFVIIa administered for hemorrhage control in hypothermic coagulopathic swine with grade V liver injuries.** *J Trauma* 2001, **50:**721-729.
16. Schreiber MA, Holcomb JB, Hedner U, Brundage SI, Macaitis JM, Aoki N, Meng ZH, Tweardy DJ, Hoots K: **The effect of recombinant factor VIIa on noncoagulopathic pigs with grade V liver injuries.** *J Am Coll Surg* 2003, **196:**691-697.
17. Dutton RP, Hess JR, Scalea TM: **Recombinant factor VIIa for control of hemorrhage: early experience in critically ill trauma patients.** *J Clin Anesth* 2003, **15:**184-188.
18. Dutton RP, McCunn M, Hyder M, D'Angelo M, O'Connor J, Hess JR, Scalea TM: **Factor VIIa for correction of traumatic coagulopathy.** *J Trauma* 2004, **57:**709-718.
19. Eikelboom JW, Bird R, Blythe D, Coyle L, Gan E, Harvey M, Isbister J, Leahy M, McIlroy D, Rahimpanah F, *et al.*: **Recombinant activated factor VII for the treatment of life-threatening haemorrhage.** *Blood Coagul Fibrinolysis* 2003, **14:**713-717.
20. Harrison TD, Laskosky J, Jazaeri O: **'Low dose' Recombinant activated factor VII (rFVIIa) results in less packed red blood (pRBC) use in traumatic hemorrhage.** *J Trauma* 2004, **57:**1383.

21. Martinowitz U, Kenet G, Lubetski A, Luboshitz J, Segal E: **Possible role of recombinant activated factor VII (rFVIIa) in the control of hemorrhage associated with massive trauma.** *Can J Anaesth* 2002, **49:**S15-S20.
22. Sifri Z, Hauser CJ, Lavery R: **Use of recombinant factor VIIa in exsanguinating, coagulopathic trauma patients.** *J Trauma* 2002, **53:**1212.
23. Riou B, Boffard K, Warren B: **Recombinant Factor VIIa (NovoSeven) as adjunctive therapy for bleeding control in trauma – a randomized, placebo-controlled trial.** *Shock* 2004, **21:**76.
24. Rossaint R, Boffard KD, Warren BL: **Decreased transfusion utilization using recombinant Factor VIIa as an adjunct in trauma.** *Intensive Care Med* 2004, **30:**S199.
25. Rossaint R, Riou B, Boffard K, Kluger Y, Warren B, Iau P, and the NovoSeven Trauma Study Group: **A randomised, placebo-controlled, double-blind study to investigate the efficacy and safety of recombinant activated factor VII as adjunctive therapy for control of bleeding in patients with severe blunt trama - a reanalysis following the exclusion of early (<48 hours) deaths [abstract].** *Crit Care* 2005, **9:**S142.
26. Meng ZH, Wolberg AS, Monroe DM, III, Hoffman M: **The effect of temperature and pH on the activity of factor VIIa: implications for the efficacy of high-dose factor VIIa in hypothermic and acidotic patients.** *J Trauma* 2003, **55:**886-891.
27. Stein DM, Dutton RP: **Uses of recombinant factor VIIa in trauma.** *Curr Opin Crit Care* 2004, **10:**520-528.
28. Deveras RA, Kessler CM: **Reversal of warfarin-induced excessive anticoagulation with recombinant human factor VIIa concentrate.** *Ann Intern Med* 2002, **137:**884-888.
29. Levi M: **Recombinant factor VIIa: a general hemostatic agent? Not yet.** *J Thromb Haemost* 2004, **2:**1695-1697.
30. Park P, Fewel ME, Garton HJ, Thompson BG, Hoff JT: **Recombinant activated factor VII for the rapid correction of coagulopathy in nonhemophilic neurosurgical patients.** *Neurosurgery* 2003, **53:**34-38.
31. Holcomb JB, Neville HL, Fischer CF, Hoots K: **Use of recombinant FVIIa for intraperitoneal coagulopathic bleeding in a septic patient.** *Curr Surg* 2003, **60:**423-427.
32. Gunst M, Pickard B, White C: **Recombinant activated factor VII: an adjunct to damage control in the coagulopathic trauma patient.** *J Trauma* 2004, **58:**217.
33. Mayer SA, Brun NC, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T: **Safety and feasibility of recombinant factor VIIa for acute intracerebral hemorrhage.** *Stroke* 2005, **36:**74-79.
34. Roberts HR, Monroe DM, III, Hoffman M: **Safety profile of recombinant factor VIIa.** *Semin Hematol* 2004, **41:**101-108.
35. Porte RJ, Leebeek FW: **Pharmacological strategies to decrease transfusion requirements in patients undergoing surgery.** *Drugs* 2002, **62:**2193-2211.
36. Karkouti K, Beattie WS, Wijeysundera DN, Yau TM, McCluskey SA, Ghannam M, Sutton D, van Rensburg A, Karski J: **Recombinant factor VIIa for intractable blood loss after cardiac surgery: a propensity score-matched case-control analysis.** *Transfusion* 2005, **45:**26-34.