

Successful Reversal of Deleterious Coagulopathy by Recombinant Factor VIIa

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Effective treatment of severe or uncontrolled bleeding is a challenge for physicians in the operating room and intensive care unit. However, even aggressive conventional therapy may ultimately fail in some patients. Administration of recombinant activated factor VII (rFVIIa) may be the only remaining therapeutic option to stop life-threatening coagulopathic bleeding. We here describe the clinical course of 5 patients exhibiting severe continuous bleeding that could not be stopped by surgical intervention and appropriate hemostatic management but resolved after a mean dose

of 90 $\mu\text{g}/\text{kg}$ of rFVIIa (range, 90–120 $\mu\text{g}/\text{kg}$). Four of the five patients recovered completely, and one patient died after developing sepsis in multiorgan failure. In all patients, bleeding from wound surfaces stopped within minutes of the administration of rFVIIa. Coagulation measurements improved, and transfusion requirements declined considerably. No adverse effects associated with rFVIIa were observed.

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Recombinant activated factor VII (rFVIIa) (Novoseven[®], Novo Nordisk, Bagsvaerd, Denmark) has been approved for treatment of patients with congenital hemophilia and inhibitors of factor VIII or IX, as well as for patients with acquired hemophilia. However, rFVIIa is also likely to provide hemostasis in other situations of profuse bleeding and impaired thrombin generation. rFVIIa enhances thrombin generation at sites of vascular injury by forming tissue factor VIIa complex and thereby activating factor X to Xa, as well as by providing Xa on the surface of already activated platelets (1,2).

We describe five patients who were successfully treated with rFVIIa at our university hospital. All patients exhibited persistent severe bleeding that was unresponsive to surgical treatment, traditional transfusion therapy, or administration of coagulation factors.

Case Reports

Case 1

A 68-yr-old man suffering from severe aortic stenosis and regurgitation developed cardiogenic shock and was transferred to our hospital for immediate aortic valve replacement surgery. Intraoperative and postoperative bleeding

from the surgical site was massive and persistent. Therefore, the operation site was packed and the chest left open. Despite transfusion of 92 U of red blood cell concentrates (RBCs), 177 U of fresh frozen plasma (FFP), 17 U of platelets, substitution of coagulation factor concentrates (Table 1), including factor VIII/vWF concentrate, and 3 unsuccessful surgical attempts to stop mediastinal bleeding, blood loss continued over several days. Interestingly, coagulation variables revealed a prothrombin time (PT) of 62% (normal range, 70%–120%) and an activated partial thrombin time (aPTT) of 39 s (normal range, 26–40 s). After injection of a single dose of 90 $\mu\text{g}/\text{kg}$ of rFVIIa, bleeding decreased markedly within 15 min. Coagulation testing demonstrated a PT of 75% and an aPTT of 40 s (Table 2). The chest was closed 2 days later. Despite initial stabilization the patient developed candida sepsis and died 2 wk later. Necropsy showed postmortem changes consistent with septic shock and multiorgan failure but no sign of thrombosis.

Case 2

A 31-yr-old woman was admitted to our emergency department showing acute abdominal pain and abdominal distension with concomitant livid discoloration of the left leg. Soon after admission, she developed hypovolemic shock and pulseless electrical activity. Cardiopulmonary resuscitation was successful, and emergency laparotomy showed severe bleeding from a ruptured venous malformation of the left iliac vein and retroperitoneal hematoma. Although surgical control of the bleeding source was immediately performed, the patient remained hemodynamically unstable and showed severe diffuse microvascular bleeding. After return of spontaneous circulation the first thrombelastogram (modified thrombelastometry-ROTEM[®]) showed hyperfibrinolysis, and therefore, aprotinin was administered. Furthermore,

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Table 1. Transfusion Requirements Before and After rFVIIa Therapy

Patient	RBC		FFP		Plt		Fib		PPSB		AT III	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1	92	3	177	8	17	1	5	0	3500	1000	5000	1000
2	33	2	27	20	5	0	6	0	2000	1000	2000	0
3	28	2	5	8	3	1	17	0	6000	0	3000	0
4	28	4	57	9	5	2	7	0	5000	1000	2500	1000
5	29	5	37	5	3	1	2	0	1000	0	1000	0

rFVIIa = recombinant activated factor VII; RBC = units of red blood cell concentrate; FFP = units of fresh frozen plasma; Plt = units of platelets (apheresis only); Fib = fibrinogen concentrate [g]; PPSB = prothrombin complex concentrate [IU]; and AT III = antithrombin III concentrate [IU].

Table 2. Laboratory Measurements Before and 1 h After rFVIIa Administration

Patient	PT (%)		aPTT (s)		Pit (g/L)		Fib (mg/dL)	
	Before rFVIIa	After rFVIIa	Before rFVIIa	After rFVIIa	Before rFVIIa	After rFVIIa	Before rFVIIa	After rFVIIa
1	62	75	39	40	96	79	382	413
2	33	70	115	57	21	122	116	122
3	68	130	200	40	78	40	228	241
4	51	109	103	52	29	50	102	194
5	10	84	200	72	76	157	50	216

Normal value ranges for these coagulations are the following: PT = prothrombin time (70%–120%); aPTT = activated partial thrombin time (26–40 s); Plt = platelet count (150–440 g/L); Fib = plasma fibrinogen concentration (160–400 mg/dL).
rFVIIa = recombinant activated factor VII.

she received 23 U of RBCs, 27 U of FFP, 5 U of platelets, fibrinogen concentrate, and prothrombin complex concentrate. However, profuse bleeding from wound sites continued, spontaneous oral mucosal bleeding developed, and hemorrhagic infarction of the gut was assumed from a colonoscopy performed because bleeding from the gut was suspected. During continuing transfusion supply, the coagulation values were as follows: PT 33% and aPTT 116 s. After transfusion of 2 more units of platelets and administration of a single dose of 120 µg/kg of rFVIIa, bleeding for the first time slowed and coagulation tests improved (PT 70% and aPTT 57 s). The subsequently required colectomy and the patient's postoperative course were complicated by sepsis and renal failure. However, 31 days after admission, the patient was transferred from the intensive care unit (ICU) to an acute care unit and subsequently enjoyed complete recovery.

Case 3

A 53-yr-old patient was admitted to the ICU with continuous uncontrolled diffuse bleeding in the right abdominal wall after elective laparoscopic cholecystectomy. However, the suspected injury of a vessel was not localized by angiography. Despite massive transfusion (Table 3), bleeding continued. Under these conditions, coagulation studies demonstrated a PT of 68% and an aPTT of 200 s. After administration of 80 µg/kg of rFVIIa, the bleeding stopped immediately and PT improved to 130% and aPTT to 40 s. The patient was discharged from the ICU 13 days later and recovered completely.

Case 4

A 44-yr-old patient was admitted to the hospital suffering from an acute type A aortic dissection caused by Marfan

Table 3. Patients Treated with rFVIIa

Patient	Age (yr)	Sex	Trauma	Dose of rFVIIa [µg/kg]
1	68	M	Cardiogenic shock	90
2	31	F	Ruptured venous vessel	120
3	53	F	Bleeding abdominal wall	80
4	44	M	Cardiac surgery	90 + 120
5	41	F	Multiple trauma	90

rFVIIa = recombinant activated factor VII.

syndrome. A Bentall operation was performed. After discontinuation of cardiopulmonary bypass, the patient exhibited massive microvascular bleeding without an identifiable surgical source. A coagulation test performed before rFVIIa administration revealed a PT of 51% and an aPTT of 103 s. A single dose of 90 µg/kg of rFVIIa was given without a significant decrease in bleeding. Therefore, the operation site was packed and the patient transferred to the ICU. Despite further aggressive treatment with RBCs, FFPs, platelets, prothrombin complex concentrate, fibrinogen concentrate, and factor VIII/vWF and factor XIII concentrates (Table 1), severe bleeding continued over the next 10 h. A second dose of 120 µg/kg of rFVIIa was consequently administered; it successfully stopped profuse bleeding, and coagulation variables improved markedly (PT 109% and aPTT 52 s). Twenty-four hours later, the packing was uneventfully removed without rebleeding. The patient was discharged from the ICU on Day 30 and recovered completely.

Case 5

A 41-yr-old woman was presented in the emergency department with multiple trauma after jumping off a roof in a

suicide attempt. Clinical examination and computer tomography scans revealed a subdural and subarachnoidal hematoma, laceration of the right external iliac artery and the right internal pudendal artery, multiple rib fractures with hemopneumothorax, hip fracture, and femur and open tibial fracture. After drainage of the hemothorax and surgical stabilization of the fractured limbs, the patient was admitted to the ICU. She had persistent, severe diffuse bleeding that was unresponsive to massive transfusion (Table 3). Coagulation testing revealed a PT of 10% and an aPTT of 200 s. A single dose of 90 $\mu\text{g}/\text{kg}$ of rFVIIa was administered, which was followed by a marked decrease in bleeding and improved coagulation values (PT 84% and aPTT 72 s). The patient was transferred to the ward after five weeks and recovered completely.

Results

A median single dose of 120 (range, 80–120) $\mu\text{g}/\text{kg}$ of rFVIIa was administered IV to stop bleeding (Table 3). In all patients, bleeding stopped or markedly decreased immediately after administration of rFVIIa. In only one case was a second dose of rFVIIa required to reverse coagulopathy.

Table 2 shows the laboratory measurements before and 1 h after rFVIIa administration. PT increased after administration of rFVIIa from 45.5% (27.2%–63.5%) to 83% (73.2%–114.2%). Similarly, measurements of aPTT decreased from 119 s (187.7 s–50.2 s) to 49.5 s (63.2 s–35.9 s) after rFVIIa therapy.

Transfusion requirements (Table 1), including coagulation factor concentrates, decreased remarkably after rFVIIa administration.

One patient (Case 1) died 2 wk after the administration of rFVIIa because of septic shock with multiorgan failure. Necropsy showed no sign of thromboembolism; the surviving patients also showed no thromboembolic complications from rFVIIa administration.

Information on actual costs of rFVIIa therapy and average costs associated with routine management of bleeding patients were obtained from our internal cost allocation. These data are summarized in Table 4. The listed costs for the operating room (OR) and angiographic intervention include personnel resources, infrastructure, and consumable supplies calculated for a treatment interval of 100 min.

Discussion

rFVIIa was developed, and is now licensed in many countries, for treatment of patients with hemophilia and inhibitors. However, data from animal studies (3,4), and several case reports summarized elsewhere (1), suggest that rFVIIa is a valuable general hemostatic drug for various bleeding episodes other than those for which it is currently approved. Beside the fact that general recommendations cannot be drawn

Table 4. Average Costs for Surgical or Radiologic Intervention and Costs for Blood Components (Innsbruck Medical University, 2004)

Intervention/therapy	Costs (€)
100 min/cardiac OR	4274 (\$5,207)
100 min/angiography	3780 (\$4,605)
Leukocyte-filtered RBC (unit)	110 (\$134)
Fresh frozen plasma (unit)	69 (\$84)
Platelet concentrate (unit)	577 (\$703)
rFVIIa 90 $\mu\text{g}/\text{kg}$ (70 kg)	3760 (\$4,580)

OR = operating room; RBC = red blood cells.

from anecdotal reports, one of the major concerns of these case studies is that many of these patients suffered mainly from inadequate diagnosis and treatment of coagulopathy (5,6). We report our experience using rFVIIa in patients exhibiting coagulopathy unresponsive to appropriate conventional therapy. Our patients were closely monitored with serial global coagulation tests and blood cell count. Global coagulation tests show low sensitivity, specificity, and accuracy in predicting the cause of perioperative bleeding, and the results are available only after an unacceptable delay. However, these tests are usually cited in review articles and guidelines for treatment of massive blood loss (7–10). Derived from *in vitro* dilution of normal plasma, it is assumed that critical levels of coagulation factors are reached when PT and aPTT values are more than 1.5 the normal value (11). The recommended doses of FFP for treating such conditions are approximately 10 mL/kg to correct coagulopathy, whereas platelets are recommended at 50 g/L (10). However, these recommendations are mainly based on studies conducted in the area of whole blood transfusion and thus are of little actual help. A recent study in ICU patients clearly shows that global coagulation tests are of limited value in diagnosing coagulation-factor deficiency and that the usual dose of FFP is not able to correct existing deficits (12).

At our institution, we additionally use ROTEM[®] monitoring for diagnosis and treatment of coagulopathy, which has been shown to be accurate in predicting bleeding tendency (13,14). We administer approximately 30 mL/kg of FFP, additional fibrinogen concentrate and prothrombin complex, and anti-thrombin III concentrate or platelets (apheresis only) according to detected deficits. This method also enabled us to verify and consequently correct hyperfibrinolysis in one patient described here (Case 2). However, diffuse microvascular bleeding continued in this patient, probably because of consumptive coagulopathy. Because the continuous blood loss and consequent hemodynamic instability requiring massive catecholamine support was of primary concern in this patient, rFVIIa was administered to stop this vicious circle.

As a matter of course, hypothermia and acidosis, which themselves contribute to the development of coagulopathy, were treated immediately in all patients using convective warming devices, warmed fluids, and sodium bicarbonate according to our clinical routine. All patients were aggressively treated but showed severe abnormal global coagulation tests (except Case 1) and continuing transfusion demand. In addition, in all cases, surgical attempts to stop bleeding failed. Therefore, rFVIIa was the last available therapeutic option, and this treatment was successful in all cases. We administered a median dose of 120 $\mu\text{g}/\text{kg}$ of rFVIIa based on the experience reported by Martinowitz et al. (15). The fact that rFVIIa therapy first failed to restore hemostasis in Case 4 is most likely due to the very low platelet count and fibrinogen concentrations at first administration. Because rFVIIa/TF complex activate factor X on activated platelets, thereby bypassing FVIII and FIX, and fibrinogen is the required substrate on which the delivered thrombin burst can form a stable clot, effectiveness of rFVIIa correlates with fibrinogen concentrations and platelet counts at the time of administration. Generally, platelets of approximately 30 g/L and fibrinogen of approximately 100 mg/dL increase the efficacy of treatment, although spontaneous bleeding was effectively stopped in a patient with smoldering leukemia and platelet counts as low as 5 g/L (16).

Meanwhile, at our institution, 14 patients received rFVIIa as the last option to stop continuous blood loss. Of the 14 patients, 12 ultimately survived: one patient died from sepsis (Case 1), and one patient with severe polytrauma (not described here) developed cardiac arrest. As mentioned by others (17), we assume that these patients who unfortunately died would have had a better chance to survive if therapy with rFVIIa had been commenced earlier. Despite the off-label use of rFVIIa described here, cost is the reason why rFVIIa is used as the very last therapeutic option. It was not our intention to investigate the cost effectiveness of VIIa, and we therefore did no detailed cost-effectiveness analysis. However, we obtained information on actual costs of rFVIIa as well as on costs associated with routine management of bleeding patients from our internal cost allocation. These data are summarized in Table 4. Assuming that during revision for bleeding in the OR or during angiographic intervention a patient additionally requires transfusion of 5 U of RBCs, 5 U of FFP, and one platelet concentrate, this would increase OR costs to a total of 5,746 euros (\sim \$ 7,000) and 5,139 euros (\sim \$6,260), respectively. In contrast, giving the patient (70 kg) 90 $\mu\text{g}/\text{kg}$ of rFVIIa would cost of 3,780 euros (\sim \$4,605). Intrinsically, costs arising as the consequence of prolonged hemodynamic instability, huge transfusion volumes required, and their likely adverse effect on

microcirculation, susceptibility to infection, and consequent multiorgan failure should also be considered in further studies investigating the cost effectiveness of rFVIIa. It is anticipated that the results of recently completed randomized controlled studies in polytraumatized patients and patients with intracerebral hematomas will not only confirm the efficacy and safety but also the cost effectiveness of rFVIIa. Regarding efficacy, the data of a randomized study in patients undergoing retropubic prostatectomy (18) were recently published. In these patients, administration of rFVIIa significantly reduced blood loss and transfusion requirement as compared with placebo. Although, in our opinion, the insignificant blood loss usually associated with prostatic surgery does not justify using rFVIIa, that study shows that rFVIIa is able to enhance even normal coagulation, and thereby reduce blood loss. This fact was also observed in an *in vitro* study using ROTEM[®] to investigate the coagulation mechanism of rFVIIa (19). More than 170,000 standard doses of rFVIIa have been administered, predominately to hemophilic and some nonhemophilic patients, and only few thromboembolic complications have been reported (1). In most of these patients exhibiting venous thrombosis, myocardial infarction, or ischemic stroke, predisposing factors were present. Thus, the etiological role of rFVIIa in thromboembolism in these patients remains uncertain.

Our results confirm and supplement the existing and growing excellent experience with rFVIIa administration in unresponsive severe bleeding initiated by various conditions. General recommendations, of course, require results from larger controlled trials. However, in our patients, rFVIIa proved to be a powerful therapeutic option for management of life-threatening bleeding. A rough estimate of costs arising from rFVIIa and from accepted conventional therapy shows that rFVIIa is cost-effective and might even be cost saving. To increase the rate of success, every attempt should be made to temporarily achieve fibrinogen concentrations of 100 mg/dL and platelet counts of 30 g/L, because these are pivotal in the coagulation-promoting action of rFVIIa (19).

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