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The objective was to evaluate the efficacy and safety of recombinant activated factor VII in patients with massive bleeding. Forty-five patients with severe massive hemorrhage requiring ≥ 14 transfusion units of packed red blood cells received recombinant activated factor VII. Postdrug blood loss and transfusion requirements were assessed, and mortality was compared with predicted outcomes. Blood loss was markedly reduced in 40 of 43 (93.0%) patients, and transfusion requirements decreased after recombinant activated factor VII administration. Mortality rate in trauma patients who had massive hemorrhage was significantly reduced compared with predictions using scoring systems. This may be associated with the use of recombinant activated factor VII. This study failed to demonstrate an improvement in surgical patients. The absence of concurrent controls prevents definitive conclusions regarding actual safety or efficacy of recombinant activated factor VII.

Key words: *recombinant activated factor VII, NovoSeven, bleeding, trauma, surgery, hemostasis*

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Regardless of origin or etiology, management of massive bleeds requires immediate surgery to stop bleeding with simultaneous stabilization of hemostasis and maintenance of normovolemia. Rapid and effective minimization of blood loss reduces mortality from exsanguination and potentially avoids “the lethal triad of death”—coagulopathy, hypothermia, and acidosis [1]—as well as the longer term morbidity associated with massive transfusions [2-5].

Massive bleeds are associated with high mortality rate (40% to 60%) [6,7] and are currently managed mainly through surgical interventions, such as ligation of bleeding vessels and compression and tamponading, with simultaneous transfusion of blood and blood-derived products, such as fresh frozen plasma, platelet concentrates, and cryoprecipitates. Hemostatic agents, such as aprotinin, may also be administered but have variable efficacy [8,9]. In addition, fibrin sealants [10,11] and interventional radiology techniques [12] are sometimes used.

Beyond critical levels (prothrombin time [PT] >20 seconds; activated partial thromboplastin time [APTT] >54 seconds; fibrinogen <1.0 g/L; platelet count <80 × 10⁹), the achievement of hemostasis and reversal of coagulopathy can become more difficult. Hence, despite seemingly adequate blood component therapy, there remain situations where hemorrhage is uncontrollable by conventional methods and the resulting poor *in situ* visibility limits repair of damaged vasculature. In this setting, alternative approaches may be considered.

Recombinant activated factor VII (rFVIIa, NovoSeven; Novo Nordisk A/S, Bagsvaerd, Denmark) is a hemostatic agent that has a rapid infusion time and a short half-life (~2 hours). In the United States, it is licensed as a hemostatic agent for the treatment of bleeding episodes in congenital hemophilia patients with antibodies to factor VIII or factor IX. In Europe, rFVIIa is licensed for the treatment of spontaneous and surgical bleeding in congenital hemophilia patients with antibodies to factor VIII or factor IX and patients with acquired hemophilia. More recently, it has been licensed in Europe for treatment of bleeding episodes and for the prevention of bleeding during surgery or invasive procedures in patients with congenital FVII deficiency or patients with Glanzmann's thrombasthenia with antibodies to glycoprotein IIb/IIIa and/or human leukocyte antigen (HLA) and with past or present refractoriness to platelet transfusions. Recombinant FVIIa is thought to act by binding to tissue factor, resulting in direct amplification of conversion of factor X to Xa, thus promoting thrombin generation and fibrin clot formation. The suggestion that rFVIIa may be useful in previously noncoagulo-

pathic patients was made by Hedner and the team at Novo Nordisk [13], and this supposition has recently been supported by some study data [14] and some anecdotal reports. However, prospective randomized trials in patients undergoing partial hepatectomy [15], liver transplantation [16], major pelvic surgery [17], and trauma [18] have all failed to demonstrate substantial efficacy following treatment with rFVIIa.

This article reports data on the surrogate markers of efficacy and the safety of rFVIIa when given to trauma and surgical patients with massive uncontrollable hemorrhage after failure of conventional methods to control bleeding. Its impact on survival is assessed by comparing observed outcomes with estimated risks based on either the Physiological and Operative Severity Score for Enumeration of Mortality and morbidity (POSSUM; trauma patients and surgical patients) or the Trauma Injury Severity Score (TRISS; trauma patients).

Patients and Methods

Patients from Austria, Canada, Czech Republic, The Netherlands, Poland, and Spain whose details were reported on the rFVIIa extended-use database—Haemostasis.com—between its launch in February 1999 and February 2004 were included in the analysis. Inclusion criteria were blood transfusion requirements of ≥14 units of packed red blood cells (PRBCs), whole blood or cell-saver blood, clinician agreement for inclusion (some clinicians, especially from Poland, Israel, and the UK, wished to report their cases independently), and no previous (or intended) publication of the case details. All eligible patients were included in the analysis. Haemostasis.com is a Web-based, anonymous repository for data on the experimental use of rFVIIa, particularly in massive hemorrhage. It is organized by Novo Nordisk A/S but administered by an independent third party under the supervision of an academic steering committee. These activities are sponsored by an unrestricted grant from Novo Nordisk A/S. At temporary closure of the database to new cases in December 2003 to facilitate review and analysis of the data (data for previously entered cases continued to be collected until February 2004), the database contained records of 1133 nonhemophilic patients who had been given rFVIIa at some stage during their stay in hospital. From this database, all patients experiencing a massive bleed (transfusion of ≥14 units of PRBCs within 4 hours) were identified for the purposes of this study, and all clinicians

responsible for these cases were contacted. Four clinicians wished to publish their own cases independently, and thus 7 cases were excluded. None of these clinicians have thus far published their data. Incomplete data were available for some patients who have been entered into our analysis, but no patients were excluded for this reason. The entry of cases into the database was voluntary and at the discretion of clinicians. Although a lack of bias on the part of case providers cannot be guaranteed, they are under no pressure or obligation to exclude cases for which outcomes are unfavorable or in which rFVIIa-related adverse events occur. However, because the registry is voluntary and does not require systematic observation or reporting of adverse events, we cannot assess the quality or completeness of the data provided. Many of the cases have been entered at the instigation of affiliates of Novo Nordisk—the manufacturer of rFVIIa. Although clinicians are encouraged to enter data onto the database, many patients may have been treated off-license with rFVIIa without their details being added to Haemostasis.com. For instance, cases from the United States and Germany were not entered into the registry because of regulatory concerns. Patients from Germany—not included in the database during the study time frame—who met the inclusion criteria were included in this analysis.

Efficacy Outcomes

Because this was a retrospective review of data after the use of rFVIIa, it was difficult to decide how to evaluate efficacy. We chose to examine a number of responses following the use of rFVIIa as surrogate markers of efficacy. The outcomes of interest were a reduction ($\geq 50\%$) in blood loss, as measured by PRBC transfusion requirements following rFVIIa administration, and improvement in expected survival scores, as measured by the TRISS and POSSUM systems [19-24]. TRISS is a widely used system that determines the probability of survival in trauma patients based on the Injury Severity Score, the Revised Trauma Score, and the patient's age. TRISS provides an estimate of the risk of hospital death for quality assurance and outcomes research purposes [19-22]. The POSSUM system uses patient physiological and operative data to predict morbidity and mortality for surgical patients and provides risk-adjusted operative mortality rates for comparative audit [23,24].

Other outcomes of interest were improved coagulation status (APTT, PT, fibrinogen, and platelet

count post-rFVIIa administration) and safety, as determined by the number of serious adverse events considered possibly or probably associated with rFVIIa use.

Statistical Analysis

The hematology data did not conform to a Gaussian distribution and were therefore described by median values and 90% ranges (calculated from the 5th and 95th percentiles of the distribution) rather than by mean values. Paired comparisons were made using the nonparametric Wilcoxon test. Standardized mortality ratios were constructed by dividing observed incidences by those predicted by the POSSUM and TRISS scores. Ninety-five percent confidence intervals were calculated for the standardized mortality ratios; if the confidence interval does not span 1, then the observed incidence is significantly different from the predicted incidence. The associations between mortality and coagulation variables, pH, and hypothermia were assessed using univariate and multivariate logistic regression analyses. A *P* value $< .05$ was considered statistically significant. All analyses were performed using Statistical Package for the Social Sciences (SPSS) software (version 11; SPSS Inc., Chicago, IL).

Results of POSSUM analyses were modified to reflect the regression model on which the equation is based.

Results

Patients

Forty-five cases (32 M) were included in the analysis—24 from Germany and 21 from 6 other countries included in the Haemostasis.com database, although not all data were available for all patients. Seven other patients entered into the database would also have met our criteria for analysis but the clinicians entering the data for these 7 patients refused permission to publish the data for their patients. Patient characteristics and the cause/location of bleeding, which were heterogeneous, are shown in Table 1. The mean patient age was 42.6 years (range 16-78 years). Thirty-six patients (80.0%; numbers 1-36) had severe hemorrhage associated with an initial traumatic cause, whereas 9 patients (20.0%; numbers 37-45) bled during or after major

surgical procedures. Of the patients for whom data were available, 17 of 42 (40.5%) had hypothermia (temperature $\leq 35^{\circ}\text{C}$) and 17 of 42 (40.5%) had low blood pressure ($\leq 80/50$ mm Hg) at admission to the hospital or operating theater (trauma patients) or just before rFVIIa use (surgery patients).

Mean TRISS scores and mortality predicted by POSSUM calculations are compared with observed mortality in Table 2. The mean TRISS score for the trauma patients ($n = 35$) was 58.4% (median 62.4%; 90% range 10.1% to 99.1%). POSSUM analysis gave a predicted mortality of 26 deaths (59.1%) for all patients scored ($n = 44$). POSSUM scores predicted 22 deaths (62.9%) in the trauma population ($n = 35$) and 4 deaths (44.4%) for surgery patients ($n = 9$).

rFVIIa Dose

The median dose of rFVIIa administered was 90 $\mu\text{g}/\text{kg}$ (range 34.0-120.1 $\mu\text{g}/\text{kg}$), and the majority of patients (28 of 44, 63.6%) received doses of 80-120 $\mu\text{g}/\text{kg}$. The number of doses administered ranged from 1 to 9 (median = 1): the majority of patients (28 of 45, 62.2%) received 1 dose, 15 patients (33.3%) received 2 doses, 1 (2.2%) received 3 doses, and 1 (2.2%) received 9 doses. Apart from 1 surgery patient who received 9 doses (number 42, Spain), there was no difference in the number of doses administered to patients with traumatic bleeds versus those with major surgical bleeds. The main reasons for administering rFVIIa were uncontrollable intraoperative blood loss ($n = 14$, 31.1%) and postoperative bleeding with cardiac instability ($n = 7$, 15.6%). Other reasons included massive postoperative bleeding from vessels with no possibility of reoperation owing to high surgical risk ($n = 3$, 6.7%), failure of other treatments ($n = 3$, 6.7%), uncontrollable blood loss ($n = 3$, 6.7%), uncontrollable preoperative blood loss ($n = 2$, 4.4%), massive bleeding or oozing despite efforts to optimize coagulation in soft tissue defects or facial fractures ($n = 2$, 4.4%), and massive bleeding ($n = 2$, 4.4%).

Efficacy

Recombinant activated FVII was effective in stopping or markedly reducing blood loss in 40 of 43 patients (93.0%); blood loss stopped or was markedly reduced following treatment with rFVIIa although a cause and effect relationship cannot be

established. Three patients (7.0%)—all of whom were trauma patients—did not respond to treatment. Two of these latter patients died from exsanguination (number 3, Canada, and number 20, Germany). In the majority of patients who responded (26 of 40, 65.0%), bleeding was stopped within 30 minutes of administration. Median time for cessation of bleeding after first dose was approximately 15 minutes (90% range: 5-360 minutes). The median number of units of PRBC used was 20 (90% range: 14.0-45.5; $n = 44$) before and 2 (90% range: 0-22.8; $n = 43$) after the administration of rFVIIa ($P < .001$). The median rate of blood loss (L/h) was 3 (90% range: 0.08-9.6; $n = 27$) before and 0.15 (0-3.9; $n = 33$) after the administration of rFVIIa ($P < .001$).

Observed mortality rate for all patients was 14 of 44 (31.8%). For trauma patients the observed mortality was 11 of 35 (31.4%), including the 2 patients who died from exsanguination, and for surgery patients it was 3 of 9 (33.3%). Compared with the values predicted from the POSSUM and TRISS scores, rFVIIa administration was associated with a significantly reduced incidence of mortality ($P < .05$) for trauma patients but was not associated with a significant reduction in mortality for surgical patients (Table 2).

Coagulation parameters pre- and post-rFVIIa are shown in Figure 1. APTT was prolonged (>37 seconds) in 30 of 38 patients (78.9%) before administration of rFVIIa and in 23 of 38 patients (60.5%) after rFVIIa therapy. The majority of coagulation markers showed statistically significant changes after administration of rFVIIa compared with baseline: median (90% range) APTT decreased from 59.0 seconds (28.4-152.5 seconds, $n = 38$) to 39.0 seconds (28.8-66.0 seconds, $n = 38$, $P < .001$); PT (%) increased from 40.0% (6% to 99.8%, $n = 26$) to 89.5% (22.7% to 132.6%, $n = 26$, $P < .001$). PT (seconds) decreased from 20.0 seconds (10-36.5 seconds, $n = 7$) to 10.5 seconds (9.6-12.1 seconds, $n = 6$, $P = .028$); fibrinogen increased from 180.0 mg/dL (63.1-872.8 mg/dL, $n = 26$) to 210 mg/dL (103.4-753.8 mg/dL, $n = 25$, $P = .031$), and the median (90% range) platelet count was $83 \times 10^3/\mu\text{L}$ (13.4-329.2 $\times 10^3/\mu\text{L}$, $n = 35$) before administration of rFVIIa and $83.5 \times 10^3/\mu\text{L}$ (34.3-293.3 $\times 10^3/\mu\text{L}$, $n = 30$) after rFVIIa therapy ($P = .191$).

On exploratory logistic regression analysis, a prolonged APTT (odds ratio [OR] = 1.152, $P = .028$) and a low increase in PT (OR = 0.959, $P = .028$) after administration of rFVIIa were significantly associated with increased mortality rate. No vari-

(text continues on p. 35)

Table 1. Patient Characteristics and Cause of Bleed

Patient No.	Country	Age (years)	Sex	Cause of Bleed	Site of Bleed
Trauma patients					
1	Canada	76	F	Multiple stab wounds to abdomen and thorax	Emergency general surgery; lung resection; surgical control of liver bleed; splenectomy
2	Canada	27	M	GSW to chest	Repair portal vein and liver pack
3	Canada	34	M	GSW to abdomen	Thoracotomy; X-clamp; laparotomy
4	Germany	24	M	Polytrauma: left pneumothorax, bilateral femoral fracture, fracture of left humerus, ankle fracture	Facial skull fracture
5	Germany	56	F	Polytrauma: blunt abdominal trauma, bilateral hemothorax, bilateral fracture of pelvic ring, fracture of right femur, bilateral tibial fracture	Bilateral lower leg bleed (large soft tissue defect)
6	Germany	60	M	Fall	Abdominal plastic aortic graft
7	Germany	23	M	Three GSWs to abdomen	Vessel repair: renal artery and vein, subclavian artery and vein, internal jugular vein
8	Germany	45	F	Fall causing multiple fractures	Fractures of femur, tibia, and humerus
9	Germany	33	M	Multiple fractures after car crash	External fixator, pelvic fracture, and intramedullary femoral nail
10	Germany	28	F	RTA polytrauma; multiple fractures	External fixator, pelvic fracture and intramedullary femoral nail
11	Germany	55	M	Fall: multiple fractures; rupture of femoral vein	Ligature of femoral vein, femoral nail
12	Germany	39	M	Multiple fractures of left hip and femur	Hip replacement; femoral nail
13	The Netherlands	16	M	RTA polytrauma; right renal artery rupture, right lung contusion, liver rupture	Abdominal and thoracic bleeds during laparotomy and surgery
14	Germany	40	M	Polytrauma: blunt abdominal trauma (liver rupture), rib fractures, fracture of tibia	Abdominal bleed from ruptured liver
15	Germany	31	F	Liver rupture plus polytrauma, multiple pelvic fractures, fractures of femur, tibia and fibula	Abdominal bleeding from liver
16	Germany	59	M	Polytrauma: traumatic subarachnoid hemorrhage; bilateral serial rib fractures, blunt abdominal trauma, rupture of mesentery, open-book fracture of pelvis, bilateral femoral fracture, fracture of tibia	Intraoperative abdominal bleed from liver and mesentery

(continued)

Table 1. (continued)

Patient No.	Country	Age (years)	Sex	Cause of Bleed	Site of Bleed
17	Germany	58	F	Polytrauma: serial rib fractures on left side, bilateral hemothorax, bleeding from the left mammary artery, blunt abdominal trauma, rupture of spleen, rupture of right ventricle	Bleeding from chest drainage after repair of ruptured right ventricle and ligation of torn mammary artery
18	Germany	57	M	RTA polytrauma: multiple fractures, ruptured spleen, bilateral hemothorax	External fixators of femur and humerus, laparotomy, splenectomy, suture of diaphragm, bilateral pelvic fracture, bilateral drainage of thorax
19	Germany	21	M	RTA polytrauma: open-book fracture of pelvis, multiple fractures, amputation of left leg	Pelvic fracture, external fixator of left arm, amputation of left leg
20	Germany	22	M	Polytrauma: open-book fracture of pelvis, injury of right internal iliac artery, fracture of femur, left hemothorax	External fixator of pelvis and femur, embolization of internal iliac artery
21	Germany	23	M	RTA polytrauma: unstable pelvic fracture, multiple fractures of upper and lower extremities (bilateral), ruptured spleen	External fixator of pelvis, bilateral upper and lower leg fractures, laparotomy
22	Germany	74	M	RTA polytrauma: bilateral pelvic fracture, rupture of liver and spleen, left hemothorax	Pelvic fracture, mesenteric tear at laparotomy, coagulation of liver and spleen, thoracoscopy
23	Germany	52	M	RTA polytrauma: amputation of lower leg, fracture of femur, rupture of rectum	Amputation of left leg, external fixator of right femur, laparotomy and resection of rectum
24	Germany	57	F	Polytrauma (blunt): pelvic and sacral fractures, injury of internal iliac and gluteal arteries and bilateral hemothorax	Embolization of branch of right internal iliac and gluteal arteries, external fixator of pelvis, bilateral drainage of thorax
25	Austria	41	F	Fall: polytrauma (blunt), subdural and subarachnoid hematomas, laceration of the external iliac artery and pudendal artery, multiple left rib fractures with hemothorax, multiple fractures of limbs and pelvis	Arterial injuries in abdomen and head/neck, multiple fracture sites
26	Canada	21	F	RTA trauma: ruptured spleen, lacerations of liver, pelvic fracture	Retroperitoneal hemorrhage, severed left internal iliac artery
27	Czech Republic	26	M	Polytrauma: hemorrhagic shock, unilateral lung lacerations, bilateral lung contusions, unilateral kidney contusion, laceration of liver, multiple pelvic fractures	Retroperitoneal hematoma, injury to arteries in abdomen and thorax, pelvic fractures

28	Czech Republic	20	M	RTA trauma: injury to the common iliac vein and internal iliac artery, ruptured spleen, pelvic fractures	Injury to arteries in abdomen and head/neck, pelvic fractures
29	Czech Republic	27	M	GSW to chest	Arterial injury to thorax
30	Czech Republic	62	M	RTA polytrauma: cranial injury with subarachnoid bleeding, subdural hematoma, swelling of brain, chest fractures, right pneumothorax	Hemothorax
31	Czech Republic	38	M	RTA trauma: multiple rib fractures, fractured sternum, contusion of the mediastinum, lung contusion, hemothorax, lacerations of the pericardium, cardiac contusion	Thoracic bleeding
32	Poland	47	M	Traumatic rupture of left S-shaped sinus and left epidural hematoma	Emergency left craniectomy, Tamponade of lacerated superior wall of S-shaped sinus with use of temporal muscle
33	Poland	19	F	RTA; polytrauma; open-book pelvic fracture; blunt abdominal trauma (right renal rupture); facial skull fracture Le Fort II	Retroperitoneal space
34	Poland	21	M	RTA; polytrauma; blunt abdominal trauma (spleen–hilar vascular injury and rupture of pancreas tail); blunt neck trauma (multiple fractures of laryngeal cartilages); serial rib fracture on left side; femoral fracture	Surface bleeding in all operation sites
35	Poland	24	M	RTA; polytrauma; multiple open pelvic fractures; retroperitoneal rupture of bladder, urethra and rectum; femoral fracture	Retroperitoneal space
36	Poland	47	M	RTA; polytrauma; blunt abdominal trauma (liver rupture); multiple pelvic fracture; femoral fracture	Abdominal bleeding from ruptured liver
Surgery patients					
37	Germany	64	M	Colon carcinoma; resection of sigma	Surgical: massive arterial bleed; sudden hypovolemic shock
38	Germany	57	M	Acute MI; rTPA-lysis therapy; bleeding from liver hemangioma	Repair of bleeding liver hemangioma

(continued)

Table 1. (continued)

Patient No.	Country	Age (years)	Sex	Cause of Bleed	Site of Bleed
39	Germany	53	M	Acute MI; secondary reanimation for 30 min; rTPA-lysis; liver rupture	Stitching and tamponading of the liver
40	Germany	53	M	Re-op after perineal prostatectomy: anamnestic; polio during childhood	Local bleeding after surgery
41	Poland	55	F	Kidney transplantation and implantation of external iliac artery and reimplantation of renal artery because of dissection	Intraoperative hemorrhagic; evac hematoma; surgical revision for arterial bleed
42	Spain	70	M	Ileocolic bypass and abscess drainage: rectal bleeding 3 days after laparotomy and ileocolic anastomosis	Surgical; rectal bleeding
43	Spain	78	F	ERCP to enlarge previous papillotomy	Pancreato-duodenal bleed
44	Spain	25	F	Morbid obesity	Retroperitoneal hematoma postsurgery
45	Czech Republic	61	M	Elective abdominal; duodenopancreatectomy	Abdominal

ERCP – endoscopic retrograde cholangiopancreatography; GSW – gunshot wound; MI – myocardial infarction; RTA – road traffic accident; rTPA – recombinant tissue plasminogen activator.

Table 2. Observed Mortality and Mortality Predicted by TRISS and POSSUM Scores

	Surgery	Trauma	Combined
No. patients scored	9	35 ^a	44
Observed mortality rate (%)	33.3	31.4	31.8
Predicted mortality, POSSUM (%)	44.4	62.9	59.1
(Range)	(42.8–46.0)	(61.5–64.7)	(57.7–62.0)
Mean TRISS score (%)	NA	58.4	NA
(Range)		6–99.6	
Standardized mortality ratio, POSSUM	0.75	0.50	0.54
(95% CI)	(0.16–2.19)	(0.25–0.90)	(0.29–0.90)
Standardized mortality ratio, TRISS	NA	0.55	NA
(95% CI)		(0.28–0.98)	

TRISS – Trauma Injury Severity Score; POSSUM – Physiological and Operative Severity Score for Enumeration of Mortality and Morbidity; CI – confidence interval.

a. TRISS and POSSUM scores are not available for patient 29.

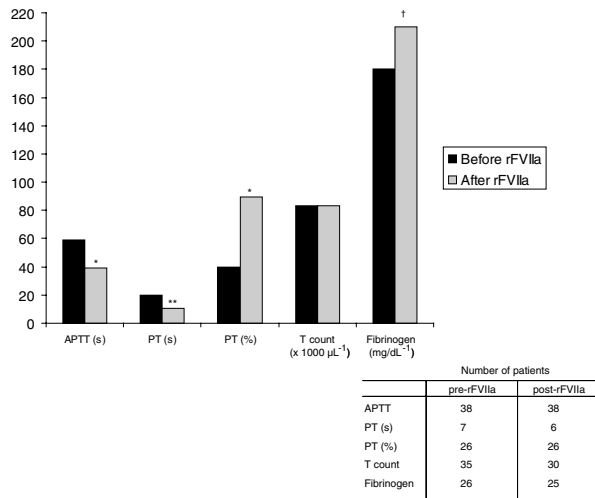


Fig 1. Coagulation status before and within 30 minutes of recombinant activated factor VII (rFVIIa) administration (median values). APTT = activated partial thromboplastin time; PT = prothrombin time; T count = platelet count.

* $P < .001$; ** $P = .028$; † $P = 0.031$.

ables achieved statistical significance on multivariate analysis, although a low increase in PT showed the strongest association with mortality ($P = .052$).

Concurrent Use of Other Medications

Aprotinin was administered to 1 surgical patient and to no trauma patients, whereas tranexamic acid was administered to 1 trauma patient and to no surgical patients.

Safety

Ten patients (22.2%), 8 of whom were trauma patients and 2 of whom were surgery patients,

experienced adverse events (Table 3). Of these patients, 7 trauma patients experienced immediate adverse events, 1 trauma patient experienced delayed adverse events, and 1 trauma patient experienced both. Two surgery patients experienced delayed adverse events. Two adverse events—1 delayed event in a trauma patient (gangrene of the colon) and 1 delayed event in a surgery patient (necrotizing colitis)—were considered possibly related to rFVIIa administration. The trauma patient had received a single rFVIIa dose of 80 $\mu\text{g}/\text{kg}$ intraoperatively for an abdominal bleed and responded rapidly. This patient developed septic shock with acute renal and liver failure early after the operation during which tearing of the mesentery was found; for safety reasons, the abdomen was tamponaded rather than relying on cessation of bleeding. Gangrene of the colon was detected on the fourth day after the initial trauma when the tamponade was removed. At day 42, the patient suffered deep vein thrombosis but survived. The surgery patient received a single rFVIIa dose of 66 $\mu\text{g}/\text{kg}$ intraoperatively for bleeding related to stitching and tamponading of the liver and responded within 20 minutes. Necrotizing colitis developed on the fourth day following surgery and the patient died of intracerebral hemorrhage on the eleventh postoperative day. A total of 14 patients (31.1%) died after trauma ($n = 11$) or surgery ($n = 3$, Table 3). None of the deaths were considered, by their attending clinicians, to be directly related to rFVIIa.

Discussion

Recombinant FVIIa is believed to exert its hemostatic effects at pharmacological doses by increasing the rate of thrombin generation on activated platelets that accumulate at the site of blood vessel

Table 3. Adverse Events Observed After Administration of Recombinant Activated Factor VII (rFVIIa)

Patient No.	Adverse Event	Delayed Adverse Events	Death
Trauma patients			
1	–	–	Yes
3	–	–	Exsanguination
7	–	–	2.5 hours after gunshot
14	–	–	7.5 hours after accident
16	Septic shock; acute renal and liver failure	Gangrene of colon on day 4 (possible relation to rFVIIa); DVT on day 42	–
18	Necrosis and further bleed; patient tetraplegic	–	–
20	Further bleed, DIC, hemorrhagic shock	–	Exsanguination (after 1 day in ICU)
22	Septic shock; acute renal and liver failure	–	After 31 days in ICU
23	Septic shock	–	After 29 days in ICU
24	Wound infection; fulminant septic shock with hypotension, tachycardia and dyspnea	–	After 18 days in ICU
26	–	–	Yes
27	Multiple organ failure	–	–
28	–	–	After 3 days in ICU
29	–	Multiple organ failure, septic shock	After 14 days in ICU
Surgery patients			
37	–	Prolonged ARDS (18 days), MRSA infection	–
39	–	Necrotizing colitis 4 days after rFVIIa (possible relation to rFVIIa)	Massive ICH 11 days after MI and accident
41	–	–	Retroperitoneal abscess 2 months after admission
42	–	–	After discharge to another hospital

DVT – deep vein thrombosis; DIC – disseminated intravascular coagulation; ICU – intensive care unit; ARDS – acute respiratory distress syndrome; MRSA – methicillin-resistant *Staphylococcus aureus*; ICH – intracerebral hemorrhage; MI – myocardial infarction.

damage. This helps to ensure a tight fibrin clot that is resistant to premature lysis [25,26]. Although several case reports [27-29] suggest that rFVIIa may help to control bleeding in a variety of clinical settings, all prospective randomized trials in nonhemophiliac patients except 2 [14,31] have thus far failed to show substantial efficacy of rFVIIa for treatment of bleeding.

Some studies in patients without hemophilia in whom rFVIIa was administered prophylactically have failed to show any beneficial effect of rFVIIa on bleeding or mortality [15-18, 30]; other prospec-

tive, randomized studies, in which rFVIIa was administered to patients without hemophilia in response to an urgent need, have shown some benefits [18]. For example, in a randomized double-blind study of the use of rFVIIa in semielective pelvic acetabular fracture reconstruction following trauma, there was no reduction in perioperative blood loss [17], and in hepatic resection surgery, prophylactic use of rFVIIa resulted in no reduction in the number of patients transfused or in the volume of blood products administered [15]. In a study comparing the outcome of patients requiring more

than 10 units blood transfusion against patients who required more than 10 units transfusion but also received rFVIIa, there was no significant difference in outcome [30]. However, in a more recent study in severely bleeding trauma patients or patients with penetrating injuries who received extremely large doses of rFVIIa (200, 100 and 100 µg/kg) in addition to standard treatment [18], there were some improvements in the groups treated with rFVIIa. The primary study end point was number of red cell units needed within the first 48 hours. Overall, no reduction in red blood cell (RBC) use was observed in the patients given rFVIIa compared with placebo; 21% of patients died within 48 hours. In a second analysis, the authors excluded the patients with penetrating trauma and further excluded those blunt trauma patients who died; the authors then reported that among surviving blunt trauma patients, the total RBC use was significantly lower in patients given rFVIIa by an estimated 2.6 units. Although there was a trend toward reduction in RBC use in the penetrating trauma group, this did not reach significance.

Interestingly, there are some differences between the cases reported in this article and the results from the international multiple-center study of the use of rFVIIa in trauma [18]. In that study 14% of the blunt trauma patients required more than 12 units of PRBCs after administration of the first dose of rFVIIa, whereas in the cases reported here most of the patients apparently stopped bleeding or at least had a marked decrease in the rate of blood loss. It is possible that these are 2 slightly different groups of patients. In the study by Boffard and colleagues [18], rFVIIa was given to a patient when the patient had been transfused 8 units of PRBCs, regardless of whether major surgical hemostatic control had been achieved, whereas the patients reported in this study were not given rFVIIa until after at least 14 units of PRBC transfusion and after major surgical hemostatic control had been achieved. Thus, in all our cases surgical control had been achieved, and oozing and bleeding were consequences of generalized coagulation dysfunction associated with dilution of coagulation factors, disseminated intravascular coagulation, acidosis, and hypothermia, not continued major hemorrhage.

Recombinant FVIIa has also been used in other bleeding situations in patients without hemophilia, namely upper gastrointestinal bleeding (UGIB) [31] and intracranial hemorrhage [32]. Initial studies suggested that rFVIIa may be of value in patients with cirrhosis and esophageal bleeding because of the ability of rFVIIa to normalize prothrombin time

[33,34]. The results from these 2 initial studies [33,34] were encouraging, suggesting the rFVIIa may be a useful adjunct to therapy to UGIB in patients with cirrhosis. However, in a placebo-controlled trial, cirrhotic patients with UGIB received 8 doses of rFVIIa (100 µg/kg) in addition to standard pharmacological and endoscopic therapy [31], and no overall improvement in outcome was observed in those patients receiving rFVIIa. In another placebo-controlled trial, a single dose of rFVIIa (40, 80, or 160 µg/kg) within 4 hours of the onset of intracranial hemorrhage limited the growth of the hematoma, reduced mortality rate, and improved functional outcomes at 90 days [32].

Our observational study suggests that there may be benefit in using rFVIIa in cases of massive hemorrhage that are uncontrollable by conventional methods. We included both trauma and surgery patients in this study, with mortality benefits observed in the trauma group. There were insufficient numbers of surgical patients to make any reliable comments about the efficacy or safety of the use of rFVIIa in the surgical group. The majority of patients only required a single dose of rFVIIa, and most patients appeared to respond to therapy within 30 minutes of administration. The majority of patients received doses of 80-120 µg/kg.

Perhaps controversially, we suggest that the use of rFVIIa may be associated with significantly reduced mortality rate in trauma patients. Our suggestion is based on the prediction of mortality and morbidity according to both the TRISS and the POSSUM databases. The TRISS score suggests that trauma patients would be expected to have a mortality rate of 58.4%, whereas the observed mortality rate was 31.4%—a statistically significant difference ($P < .05$). The majority of POSSUM scores (27 of 35) in trauma patients was calculated preresuscitation, and therefore great caution must be taken when interpreting the data because POSSUM scores may overestimate mortality in this population. McIlroy et al [35] showed an ~30% improvement in survival following preoperative resuscitation in surgical patients; in trauma patients, impressive improvements in the physiological variable following appropriate resuscitation are also likely.

Because this was an observational study of reports of the use of rFVIIa to an international registry, it was difficult to ensure that data were collected at all time points in a similar fashion at all centers. We therefore attempted to use the difference in blood loss, before and after the use of rFVIIa, as a surrogate marker for the efficacy of the agent. We appreciate that this is not an end point that might be considered “firm evidence” of efficacy

in the context of a prospective, randomized, placebo-controlled study, but in the context of the available information, it gives an indication of the potential results that may accrue from appropriate use of the drug. Blood loss was markedly reduced after treatment with rFVIIa, as were blood transfusion requirements. These observations were accompanied by statistically significant improvements in coagulation status; after treatment with rFVIIa, APTT and PT (seconds) decreased and PT (%) and fibrinogen levels increased (Figure 1). Further studies are warranted to examine these outcomes in greater detail.

Logistic regression analyses were performed to determine if any associations existed between mortality and pH, hypothermia, platelet count, fibrinogen levels, APTT, and PT. Some statistically significant associations between coagulation factors and mortality were identified. There was insufficient statistical power for an extensive multivariate analysis.

None of the 14 deaths occurring in this study were considered by the attending clinicians to be related to rFVIIa. However, we have no information on whether autopsies were performed on any of the patients or whether autopsies included examination for microvascular occlusions or subclinical infarcts. These types of investigations should be the subject of further study. No cases of stroke or myocardial infarction were reported. Two delayed adverse events (gangrene of the colon and necrotizing colitis) were considered by the attending clinicians to be possibly related to treatment with rFVIIa, and this definitely warrants further study. However, these patients had also had massive bleeds and had received high doses of catecholamines, which may have led to these complications.

This form of drug efficacy and safety analysis has several obvious weaknesses that are inherent in the use of global registries as a mechanism of data collection. These include incomplete and subjective (observational) data, heterogeneous patient types and treatment practices, inherent difficulties in defining blood loss before and after the use of rFVIIa, and logistic difficulties in data collection. In addition, patient data available for analysis were limited by the treating physicians' wish to publish data independently and our avoidance of dual publication of cases. We are only reporting 45 cases from an international registry of 1133 cases, but it should be remembered that not all treated patients were reported to the registry and not all patients in the registry were available for our analysis; this report may suffer from a bias of selection that would mean that the results are not generalizable. In addition, we compared observed mortality rates

to a predicted model and not an observed control group. As a consequence, it is difficult to draw any definite and meaningful conclusions regarding the safety of rFVIIa from the data. We recommend that future studies be designed to avoid these sorts of limitations.

In conclusion, our analysis of a selected subgroup of patients reported to a company-sponsored registry suggests that the use of rFVIIa reduced mortality rate among trauma patients compared with that predicted from the POSSUM and TRISS scoring systems. Our database included only a very small number of surgical patients, and a significant reduction in mortality was not noted in this group. Our findings need to be confirmed by prospective, randomized, placebo-controlled trials.

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