

Efficacy of recombinant activated Factor VII in patients with massive uncontrolled bleeding: a retrospective observational analysis

Farida F. Berkhof and Jeroen C.J. Eikenboom

BACKGROUND: Recombinant activated Factor VII (rFVIIa) is a prohemostatic agent used for treatment of hemophilia patients with inhibiting antibodies. It has also been used in the context of massive uncontrolled blood loss, but the efficacy has not been proven. The aim of this study was to evaluate the effectiveness of rFVIIa in massive uncontrolled blood loss.

STUDY DESIGN AND METHODS: In this retrospective observational analysis patients were included that had received rFVIIa between April 2004 and January 2008 in the context of bleeding that could not be controlled by conventional transfusion therapy. Data were retrieved from patient files, anesthesia reports, the electronic hospital information system, and the computer files of the hospital blood transfusion service. Baseline demographics, medication data, laboratory data, transfusion data, and surgical data were analyzed.

RESULTS: In 32 patients with massive uncontrolled blood loss, a significant reduction in transfusion requirements was observed after infusion of rFVIIa, when comparing the transfusions before and up to 48 hours after infusion of rFVIIa. Mean red blood cell (RBC) transfusions showed a reduction of 20.1 units before rFVIIa to 8.7 after rFVIIa (mean difference, 11.4 units; 95% confidence interval [CI], 6.4-16.5) and fresh-frozen plasma (FFP) transfusions showed a reduction of 19.3 units before rFVIIa to 9.3 after rFVIIa (mean difference, 9.9 units; 95% CI, 4.2-15.6). Fifty-six percent of patients receiving rFVIIa for uncontrolled life-threatening bleeding were alive at discharge from the hospital.

CONCLUSION: This study suggests that rFVIIa may play a role in patients with massive uncontrolled blood loss by reducing the amount of RBC and FFP transfusions and by improving the coagulation variables.

Coagulation Factor VII (FVII) plays an important role in coagulation. In the case of vascular injury hemostasis is initiated by the formation of a complex between FVII and tissue factor, which results in activated FVII (FVIIa). The tissue factor-FVIIa complex activates Factor X (FX). Activated FX converts prothrombin to thrombin. Thrombin eventually converts fibrinogen to fibrin, which leads to stable clot formation. Thrombin further enhances the coagulation cascade by activating platelets (PLTs), Factor V (FV), Factor VIII (FVIII), and Factor IX (F IX). Through high concentrations of exogenous FVIIa, hemostasis can be induced by enhancing the thrombin generation through direct activation of FX independent of tissue factor or the presence of FVIII or F IX.¹

Recombinant activated FVII (rFVIIa; Novoseven, NovoNordisk, Bagsvaerd, Denmark) was originally developed for the treatment of patients with hemophilia A or B with inhibitory antibodies against FVIII or F IX, respectively. rFVIIa has also been registered for the treatment of congenital FVII deficiency and Glanzmann thrombasthenia. In recent years, rFVIIa has also been used in patients without a specific (congenital) hemorrhagic disorder to improve hemostasis and to reduce blood transfusion requirements during surgery and uncontrolled

ABBREVIATIONS: AAAA = acute abdominal aortic aneurysm; APTT = activated partial thromboplastin time; FVIIa = activated Factor VII; IR = initial result; PT = prothrombin time; WR = worst result.

From the Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands.

Address reprint requests to: Dr Jeroen C.J. Eikenboom, Department of Thrombosis and Hemostasis, C2-R, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands; e-mail: h.c.j.eikenboom@lumc.nl.

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TRANSFUSION **, ** **

bleeding.¹⁻⁷ Several off-label indications for rFVIIa have been studied in clinical trials.

A randomized double-blind controlled trial concerning retropubic prostatectomy demonstrated a reduction in blood loss and transfusion requirements.⁵ In patients with an acute intracerebral hemorrhage, a dose finding study suggested a reduction of growth of the hematoma and improved survival and functional outcome; however, this was recently not confirmed in a large Phase III trial.⁸ Several double-blind placebo-controlled randomized trials in the context of liver transplant surgery, cardiopulmonary bypass surgery, and bleeding esophagus varices showed no convincing reduction in need of blood transfusion products.⁹⁻¹⁴ In these studies rFVIIa was given perioperatively as prophylactic use and not in a situation of already existing massive uncontrolled blood loss. A double-blind randomized controlled trial in blunt and penetrating trauma surgery patients showed a possible benefit of infusion of rFVIIa with a reduction in number of patients requiring transfusion, but with no reduction of mortality. However, this effect was only seen when analysis was restricted to patients with a blunt trauma still alive after 48 hours; overall there was no benefit.¹⁵ In general, the beneficial effect of early or prophylactic use of rFVIIa to reduce transfusion requirements in these randomized trials is disappointing.¹⁶

At present, there are no randomized controlled trials on the use of rFVIIa in the setting of massive uncontrolled bleeding. There are multiple case reports on the administration of rFVIIa when conventional therapy failed to stop blood loss. Case series on intraabdominal hemorrhage, massive obstetric hemorrhage, bleeding in pancreatitis, massive bleeding after lung resection, and hemorrhage after massive trauma indicate less bleeding after infusion of rFVIIa, improvement of coagulation variables, and reduction of transfusion requirements.^{2,17-20} Since 2004 we have used rFVIIa to control massive bleeding when conventional therapy failed. Because randomized controlled trials for this indication of rFVIIa are still missing, we have retrospectively evaluated the effectiveness of rFVIIa in our series of patients.

MATERIALS AND METHODS

Patients

Patients from the Leiden University Medical Center with massive blood loss that could not be controlled by conventional transfusion therapy and who were treated with rFVIIa were registered from April 2004 to January 2008. Patients included in the study were adults (age >18 years) who met the criteria of massive blood loss: more than 10 units of red blood cell (RBC) transfusions transfused in 24 hours, loss of 100 percent of circulating volume in 24 hours, loss of 50 percent of circulating volume in 3 hours, or blood loss of 150 mL per minute.

For analysis, patients were categorized in two groups: 1) primary bleeding with secondary surgery, for example, when a patient was initially bleeding because of an acute abdominal aortic aneurysm (AAAA) and therefore undergoes secondary surgery (referred to as "primary bleeding" group), and 2) primary surgery with secondary bleeding, for instance, a patient undergoing transplant surgery and during or after surgery suffers from secondary bleeding (referred to as "primary surgery" group).

Data collection

Data were retrieved from paper and electronic patient files, anesthesia reports, the electronic hospital information system, and the computer files of the hospital blood transfusion service. Data were recorded concerning baseline demographics (sex, age, weight, length, days of hospitalization), cause of bleeding, cause of death, dose of rFVIIa, medication (use of PLT aggregation inhibitors or anticoagulant therapy before operation), laboratory data (blood count and coagulation profile), transfusion data (number of units of RBCs, fresh-frozen plasma [FFP] and PLTs before and up to 48 hr after the infusion of rFVIIa), and surgical data (type and indication of operation, type and indication of reoperation, duration of operation).

The blood count and coagulation profile is based on measurements of hemoglobin (Hb), PLTs, activated partial thromboplastin time (APTT), prothrombin time (PT), and fibrinogen. Because this is a retrospective study, blood was not drawn at predetermined time points and intervals. Nevertheless to compare the blood counts and coagulation profiles from each patient we used, when available, measurements at the following time points: initial result (IR) before surgery or bleeding; worst result (WR) during surgery or bleeding; result immediately before infusion of rFVIIa; result immediately after infusion of rFVIIa; and results closest to 12, 24, and 48 hours after infusion of rFVIIa. The IR is the most recent measurement up to 1 month before surgery or the start of bleeding, and the WR is the most abnormal measurement between the start of bleeding and the infusion of rFVIIa.

Statistical analyses

For patient demographics and baseline characteristics, the descriptive statistics, mean and standard deviation (SD), or median and range values are reported. To evaluate the differences in blood count, coagulation profile, and transfusion requirement between the primary bleeding and primary surgery groups the independent samples t test was used. The 95 percent confidence intervals (CI) were estimated for differences. The paired-samples t test was used to compare transfusion data before and after administration of rFVIIa. One-way analysis of variance was used to compare the different groups of preoperative

anticoagulant medication. Significance was assumed at a p value of less than 0.05. Statistical analyses were performed with statistical software (Statistical Package for the Social Sciences, SPSS 14.0 for Windows, SPSS, Inc., Chicago, IL) and graphs were prepared with graph-generating software (Graph-Pad Prism Version 4.02, for Windows, GraphPad Software, San Diego, CA).

RESULTS

Patient demographic and baseline characteristics

From April 2004 to January 2008, 38 patients were identified with life-threatening bleeding who were treated with rFVIIa. Six patients were excluded: the paper patient files of 2 patients were lost, 4 patients were children, who therefore did not meet the inclusion criterion of more than 18 years of age. In total 32 patients were included in the analysis, 15 males and 17 females. None of these patients had any of the registered indications for use of rFVIIa (hemophilia A or B with inhibiting antibodies, FVII deficiency, and Glanzmann thrombasthenia). All included patients met the criteria of massive blood loss. Patients were hospitalized for a median time of 12.5 days. All 32 patients received a first dose of rFVIIa because of massive uncontrolled bleeding; however, dosage data could be retrieved from the patient files for 22 patients only (median dose, 90 µg/kg). Only 8 patients received a second dose, with a median of 88 µg per kg rFVIIa. The patient demographics and baseline characteristics are summarized in Table 1.

The primary bleeding group shows as most important causes of bleeding AAAA, trauma, and liver hemorrhage in hemolysis elevated liver enzymes low PLTs (HELLP) syndrome. Eleven patients fall into this group. The other group, primary surgery, displays as main causes of bleeding transplant surgery, cardiac surgery, and tumor resection. Twenty-one patients were included in this group (Table 2). Of the 32 patients, 19 had a laparotomy, 11 a thoracotomy, 1 a craniotomy, and 1 a therapeutic endoscopy.

Effect of rFVIIa on coagulation variables and blood counts

The course of the coagulation variables and blood counts are illustrated in Fig. 1. Measurements were not available for each time point in all included 32 patients. The number of patients per measurement is indicated in Fig. 1.

TABLE 1. Patient demographics and baseline characteristics

Number of patients	32
Age (years), median (range)	54 (19-82)
Sex, n (%)	
Male	15 (46.9)
Female	17 (53.1)
Preoperative anticoagulant medication, n (%)	
PLT inhibitors	3 (9.4)
Vitamin K antagonists	9 (28.1)
PLT inhibitors plus vitamin K antagonists	2 (6.3)
No anticoagulant medication	18 (56.3)
First dose of rFVIIa (µg/kg), n	22*
Median (range)	90 (69-189)
Second dose of rFVIIa (µg/kg), n	8
Median (range)	88 (57-98)
Days of hospitalization, median (range)	12.5 (2-120)
Criteria of massive blood loss, n (%)†	
1. >10 RBC units in 24 hr	23 (71.9)
2. Loss of total circulating blood volume in 24 hours	4 (12.5)
3. Loss of 50% of total circulating blood volume in 3 hr	5 (15.6)
4. Blood loss of >150 mL/min	0 (0)

* All 32 patients received first dose, but data of dosage are missing for 10 patients.

† Fulfillment of the criteria of blood loss was assessed hierarchically in the order of Item 1 to Item 4.

TABLE 2. Indications of rFVIIa

Indications	n (%)
Primary bleeding, secondary surgery	11
Trauma	2 (18.2)
AAAA	3 (27.3)
Liver hemorrhage in HELLP syndrome	2 (18.2)
Other*	4 (36.4)
Primary surgery, secondary bleeding	21
Transplantation†	3 (14.3)
Tumor resection‡	4 (19)
Cardiac surgery§	8 (38.1)
Other	6 (28.6)

* One patient with bleeding because of heparin, one patient with cardiac tamponade due to ventricular rupture, and two spontaneous bleedings of unknown cause.

† Liver, kidney, and pancreas transplantation.

‡ Two patients with resection of gastrointestinal stromal tumor, one chondrosarcoma, and one cerebral metastasis of Grawitz tumor.

§ Prosthetic heart valve replacement, mitral and aorta valve replacement because of endocarditis, reconstruction aortic aneurysm (Crawford procedure).

|| Hemicolectomy, bronchial stent placement, relocation of intrathoracic herniation of stomach and intestine, pancreatico-tomy because of necrosis, cesarean section, and endoscopic dilatation of stenosis of proximal jejunum.

HELLP = hemolysis elevated liver enzymes low PLTs.

Typically for rFVIIa is the shortening of the PT immediately after infusion of rFVIIa, from a median of 16 seconds before infusion of rFVIIa to 10 seconds immediately after infusion of rFVIIa. After this extreme, instantaneous correction of the PT, the PT gradually increases again to a normal value of 14 seconds after 48 hours. After infusion of rFVIIa, the PT can be so short that the clot will not be detected by the automated coagulation analyzer. In that case the PT result will be "no clot detectable." Because this is an artifact, those

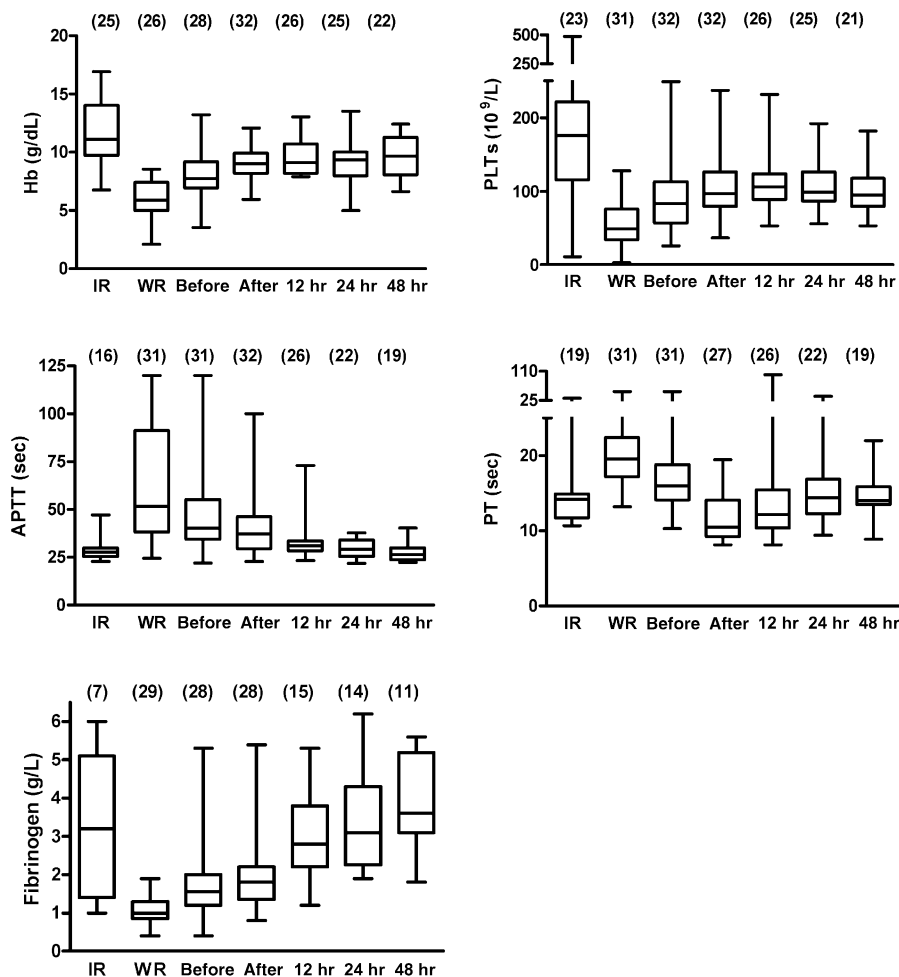


Fig. 1. Blood count and coagulation profile before and after administration of rFVIIa. IR = initial result before surgery or bleeding; WR = worst result during surgery or bleeding; before = result immediately before infusion of rFVIIa; after = result immediately after infusion of rFVIIa; 12 hr, 24 hr, and 48 hr = results closest to 12, 24, and 48 hours after infusion of rFVIIa (see Materials and Methods). Box plots indicate interquartile range, the median, and the extreme values. The number of patients with available results for the corresponding measurement is indicated in parentheses above each box.

values were not included in the analyses. The APTT follows the same course as the PT except for the extreme correction immediately after rFVIIa infusion. The value immediately before rFVIIa is prolonged, with a median of 40.2 seconds. After 48 hours the APTT normalizes to a median of 26.3 seconds. Fibrinogen has a median of 1.5 g per L immediately before rFVIIa. After infusion of rFVIIa the concentration of fibrinogen gradually increases, with a median of 3.6 g per L after 48 hours. Hb (Fig. 1) shows a median of 7.7 g per dL immediately before infusion of rFVIIa. Forty-eight hours after infusion of rFVIIa, Hb stabilizes at 9.7 g per dL. The PLT count has a median of 83.5×10^9 per L immediately before infusion of rFVIIa. The value increases 48 hours after infusion of rFVIIa to a median of 95×10^9 per L. Therefore, a clear direct effect of rFVIIa administration was seen for PT only. The gradual correction of the other variables over time also reflects the consequences of sub-

sequent transfusion of blood products and the natural recovery of the patients.

Comparing the primary bleeding group with the primary surgery group, blood counts and coagulation variables mainly follow a similar course, with a few exceptions. The primary bleeding group has a significantly shorter mean PT immediately after rFVIIa of 9.9 seconds in contrast to a mean of 12.5 seconds of the primary surgery group ($p = 0.028$). The WR of fibrinogen is somewhat lower in the primary bleeding group, 0.92 g per L versus 1.2 g per L ($p = 0.029$). The mean IR of PLTs is significantly higher in the primary bleeding group, 297×10^9 per L versus 176.9×10^9 per L in the primary surgery group ($p = 0.040$). Twenty-four hours after infusion of rFVIIa, a significantly higher amount of PLTs of the primary surgery group can be measured of 119.3×10^9 per L compared to 85.3×10^9 per L in the primary bleeding group ($p = 0.024$).

Effect of rFVIIa on transfusion requirements

Transfusion requirements before and in the first 48 hours after administration of rFVIIa are shown in Fig. 2. A marked and significant reduction in transfusion requirements for RBCs, from a mean of 20.1 units before rFVIIa to a mean of 8.7 units after rFVIIa ($p < 0.001$), and FFP, from a mean of 19.3 units before rFVIIa to a mean of 9.3 units after rFVIIa ($p = 0.001$), can be observed in the first 48 hours after administration of rFVIIa (Fig. 2 and Table 3).

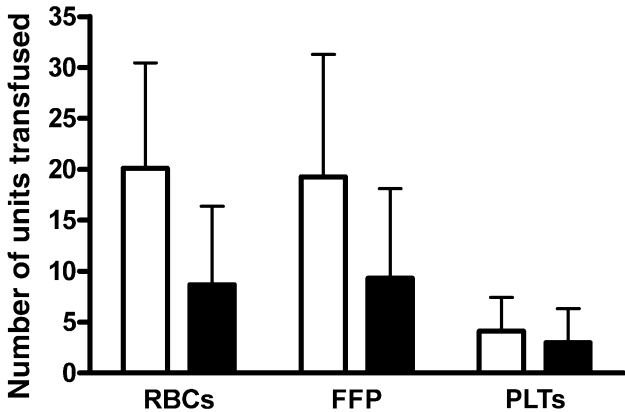


Fig. 2. Transfusion requirements before and after infusion of rFVIIa. Indicated are the mean numbers of units RBCs, FFP, and PLTs. The error bars indicate 1 SD. Twenty-eight patients instead of 32 patients are included because for 4 patients it was not possible to assign transfusions to before or after rFVIIa infusion. (□) Number of transfusions before infusion of rFVIIa; (■) number of transfusions from rFVIIa infusion up to 48 hours.

The primary bleeding group received significantly more RBCs (26.4 units) before the infusion of rFVIIa than the primary surgery group (16.6 units) ($p = 0.014$). Apart from this difference, the overall transfusion requirements were the same for the groups of primary bleeding and primary surgery. There were no differences in transfusion requirements between users and nonusers of anticoagulant medications (PLT inhibitors or vitamin K antagonists) before bleeding or operation.

Survival

All 32 patients received rFVIIa as salvage therapy because of fear of exsanguination when blood loss could not be controlled. In the first 12 hours after infusion of rFVIIa, 6 patients died. In three cases, rFVIIa failed to stabilize massive uncontrolled bleeding and these patients died because of hypovolemic shock. In the next 24 hours, another patient died because of hypovolemic shock. Forty-eight hours after infusion of rFVIIa, 2 more patients had died. In the days beyond 48 hours after rFVIIa infusion, 5 more patients died. Eventually, 56 percent of the patients survived the massive uncontrolled bleeding and were alive at discharge from the hospital (46% of the patients of the primary bleeding group and 62% of the patients of the primary surgery group). Survival and causes of death are summarized in Table 4.

DISCUSSION

The effect of rFVIIa on transfusion requirements, course of coagulation variables, and mortality in massive uncon-

TABLE 3. Difference in transfusion requirements before and after infusion of rFVIIa

Transfusions*	Mean before rFVIIa	Mean after rFVIIa	Mean difference (SD)	95% CI†	p Value
Number of units of RBCs	20.1	8.7	11.4 (13.1)	6.4-16.5	<0.001
Number of units of FFP	19.3	9.3	9.9 (14.8)	4.2-15.6	0.001
Number of units of PLTs	4.1	3	1.1 (4.6)	-0.64-2.9	0.2
Number of units for total transfusion	43.5	21.4	22.1 (30.0)	10.5-33.8	0.001

* n = 28 patients; for 4 patients it was not possible to assign transfusions to before or after rFVIIa infusion.
 † 95 percent CI of the difference.

TABLE 4. Survival of patients after receiving rFVIIa

Clinical outcome	After rFVIIa	After 12 hr	After 24 hr	After 48 hr	Alive at discharge
Survival, n (%)	32	26 (81.3)	25 (78.1)	23 (71.9)	18 (56.3)
All	32	26 (81.3)	25 (78.1)	23 (71.9)	18 (56.3)
Primary bleeding	11	8 (72.7)	7 (63.6)	7 (63.6)	5 (45.5)
Primary surgery	21	18 (85.7)	18 (85.7)	16 (76.2)	13 (61.9)
Cause of death*					
Hypovolemic shock		3	1		1
Cardiac failure		1			1
Multiple organ failure		1			1
Other†		1		2	2

* The values in each column refer to the causes of death in the observation period preceding the time point indicated in the heading.
 † Two patients died of cerebral anoxia, one of diffuse intravascular coagulation, one of septic shock, and one of unknown cause.

trolled blood loss was analyzed in a retrospective observational analysis. The main result of this study suggests that infusion of rFVIIa in patients with massive uncontrolled blood loss, despite optimal conventional treatment, may be of benefit. Coagulation variables, especially PT, improved after rFVIIa administration. The transfusion requirements of RBCs and FFP were significantly reduced in the observation period after rFVIIa administration compared to before rFVIIa. The overall survival in the study was 56 percent.

Recent studies of off-label use of rFVIIa show varying degrees of success. A recent Cochrane review of all randomized controlled trials comparing rFVIIa with placebo for the prevention or treatment of bleeding in patients without hemophilia (off-label indications) concluded that the effectiveness of rFVIIa as a general prohemostatic agent remains uncertain.¹⁶ In those randomized trials rFVIIa was used either prophylactically to prevent bleeding or therapeutically to control bleeding. However, in the therapeutic trials the rFVIIa was given early in the course of bleeding.

No randomized controlled trials have been performed for the setting of massive uncontrolled blood loss when rFVIIa is administered as a last resort. It will be very difficult to conduct a randomized controlled study in that setting and it may not even be feasible. For this indication we have to rely on descriptive studies. Some case reports of rFVIIa in massive uncontrolled blood loss show improvement of coagulation variables and a reduction in transfusion requirements.^{2,17-20} Case series of infusion of rFVIIa in subdural or intracerebral bleeding showed conflicting results.^{21,22} Another observational study of patients with massive tissue trauma and uncontrolled blood loss showed a significant reduction of transfusion requirement.²³ In that small study 13 nonhemophilia patients with uncontrolled bleeding received rFVIIa as salvage treatment and transfusion requirements were registered during 24 hours before and after rFVIIa administration. They observed a reduction of mean number of units of RBCs infused before rFVIIa of 28.1 to 9.9 after rFVIIa. For FFP the reduction was from 17 units before rFVIIa to 14 units after rFVIIa and for PLTs 3.2 units before rFVIIa to 2.2 after rFVIIa. Although the observation period is different from our study, those data are roughly comparable to our study (Table 3).

In our study we observed an improvement of all coagulation variables. Because all patients received multiple transfusions before rFVIIa was administered, most coagulation variables were already partly corrected compared to the worst measurements. After rFVIIa the coagulation variables and blood counts further normalized. This could be the result of rFVIIa, but the degree of influence of the massive transfusions on the improvement of the variables cannot be determined. A significant shortening was observed for the PT immediately after infusion of rFVIIa, indicating a direct improvement of coagulation by rFVIIa.

Another striking observation is the significant reduction in transfused units of RBCs and FFP after administration of rFVIIa. At the time that rFVIIa was infused, the blood loss in the patients was still uncontrolled, but the transfusion requirements up to 48 hours after rFVIIa were significantly lower than in the much shorter period during bleeding and operation before rFVIIa. However, because this is not a controlled trial we cannot be certain that the reduction in transfusion requirements can be attributed to rFVIIa. Therefore the results need to be interpreted with caution.

Of all included patients 56 percent were alive at discharge from the hospital. All patients experienced massive bleeding and despite conventional therapy bleeding could not be controlled. We do not have a suitable control group for comparison; however, survival after uncontrolled bleeding in surgical and trauma patients not receiving rFVIIa has been reported to vary between 40 and 60 percent.²⁴⁻²⁶ Other observational studies on the effect of rFVIIa in the setting of uncontrolled bleeding report survival rates of 47 to 76 percent.^{3,4,6,7} We have observed a survival comparable to these literature data; however, there seem to be no obvious differences in survival with and without rFVIIa administration. After infusion of rFVIIa the uncontrolled bleeding stabilized in most of our patients and in 4 patients there was immediate stoppage of bleeding upon rFVIIa administration with no further requirement of RBC transfusion. Nevertheless for 3 patients rFVIIa failed to stabilize the bleeding. These patients died of hypovolemic shock. Twenty-four hours after infusion of rFVIIa 1 more patient had died of hypovolemic shock. Some patients who survived the imminent exsanguination eventually died of other complications. In total 14 of 32 patients died, but without stabilizing the bleeding none of the patients might have survived. Whether this effect is to be attributed to rFVIIa can only be answered by future randomized controlled trials. Whether those trials will ever be performed in this extreme setting of impending exsanguination is doubtful.

The administration of rFVIIa could potentially lead to thromboembolic adverse events. We observed two cases of death related to cerebral anoxia (Table 4), but in both cases this was clearly caused by existing comorbidity. One other patient died of diffuse intravascular coagulation. This patient had severe mitral valve insufficiency due to endocarditis and was operated for mitral valve replacement. In addition, for circulatory assistance a biventricular cardiac assist device was introduced. The patient developed sepsis and cardiac failure and died. Autopsy revealed diffuse intravascular thrombotic occlusions. This diffuse intravascular coagulation may have been triggered by rFVIIa, but could very well be due to the ventricular cardiac assist device. To conclude, we did not observe evident thromboembolic adverse events. However, the

limited literature on randomized trials that have been performed for off-label indications of rFVIIa show a trend toward increase of thromboembolic events in the rFVIIa-treated groups (relative risk, 1.28; 95% CI, 0.84-1.95).¹⁶

In conclusion, rFVIIa may be of benefit to patients with massive uncontrolled bleeding, by improving coagulation variables, stabilizing the bleeding, and reducing the transfusion requirements. Considering the lack of controlled trials in this setting and the high costs of rFVIIa, it should be used with great reserve for off-label indications.

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