

Effect of Recombinant Activated Factor VII in Critical Bleeding: Clinical Experience of a Single Center

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Recombinant activated factor VII (rFVIIa) has been successfully used "off-label" in patients with refractory life-threatening hemorrhage. Intravenous rFVIIa was given to 31 patients unresponsive to standard therapy with blood products and surgical reexploration, who were bleeding due to trauma, surgery, organ transplantation, liver cirrhosis, ruptured uterus. We recorded their coagulation and hematologic profiles, acid-base balance, blood loss, number of red blood cells (RBC), plasma and platelet transfusions, complications, and survival. rFVIIa (mean dose $132.2 \pm 56.3 \mu\text{g/kg}$) effectively

contained the hemorrhage in 28/31 (90.3%) cases, with a mean reduction in blood loss from 12.4 ± 10.2 to 2.7 ± 2.2 L ($P < .0001$). The need for RBC, platelet, and plasma transfusion decreased significantly after rFVIIa, with a consequent significant improvement in clotting of test hematocrit, pH, and bicarbonates. Four patients had adverse events potentially related to rFVIIa. The survival rates after 1 and 30 days were 48.4% and 29.1%, respectively.

Keywords: bleeding; FVIIa; hemostasis

Introduction

Recombinant activated factor VII (rFVIIa) has been approved for the treatment of patients with acquired factor VIII and IX inhibitors, inherited factor VII deficiency, and Glanzmann's thrombasthenia.¹⁻³ Its hemostatic effect relies on its action as a bypassing factor. In the high concentrations achieved at pharmacological doses, r-FVIIa binds to tissue factor exposed by damaged tissues and may directly convert factor X into Xa on activated platelets, without needing factor VIII and IXa to do so. The subsequent generation of even small amounts of thrombin is

usually sufficient to ensure fibrin production and propagation of the clotting process.⁴

In recent years, growing interest has focused on the compassionate use of rFVIIa in patients with critical bleeding, that is, outside the above-mentioned licensed conditions. Several such experiences have been reported in various clinical settings, for example, life-threatening hemorrhage due to trauma, surgery, pregnancy, liver diseases, anticoagulant therapy, and intracerebral hemorrhage,⁵⁻¹⁰ while only a limited number of randomized clinical trials have been published to date.¹¹⁻²¹

The treatment of massive hemorrhage requires the surgical repair or embolization of damaged vessels, as well as the infusion of colloids and blood products, such as packed red blood cells (RBC), fresh frozen plasma (FFP) and platelet (PLT) concentrates to correct hypovolemia, anemia, and coagulopathy. This last condition is due mainly to the consumption of clotting factors and hemodilution, but hypothermia, acidosis, and hypocalcemia further affect hemostatic efficiency.²² Together with hypothermia and acidosis, coagulopathy is a crucial

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component of the so-called “lethal triad” in trauma, responsible for high mortality rates.²³ Massive transfusions may cause fluid overload and severe adverse reactions, including the so-called transfusion-related acute lung injury (TRALI).²⁴ Prompt coagulopathy correction is therefore a crucial clinical target, as it helps to stop the bleeding and reduces the need for transfusions. In such settings, compassionate treatment with rFVIIa seems very promising.

The off-label use of rFVIIa in patients with critical bleeding is still under evaluation, however, because the efficacy it has demonstrated in some clinical settings, for example, blunt trauma and cardiac surgery, has not been confirmed in others, such as intracerebral hemorrhage. The patient’s life expectancy (judged by the medical team), the costs of rFVIIa, and its potential adverse events, particularly thrombotic complications, should also be taken into account.²⁵ Recommendations have recently been formulated on the compassionate use of rFVIIa on the basis of published evidence.²⁶⁻²⁹

Here, we describe our single-center experience of rFVIIa treatment in 31 consecutive patients with critical bleeding refractory to conventional therapy.

Materials and Methods

The study involved 31 consecutive patients admitted to the University General Hospital in Padua between February 2005 and October 2007, comprising 21 males and 10 females with a mean age of 55.3 ± 21.2 years.

Their underlying diseases were multiple trauma (7); surgically treated cardiac diseases (3); aortic surgery (3); liver cirrhosis (2); liver, kidney and lung transplantation (3); abdominal surgery for solid neoplasms (cancer of the pancreas in 5 cases, of the ovary in 1, of the kidney in 1, of the pelvis in 1, retroperitoneal in 1, and liver metastases in 1); splenectomy for abscess (1); dorsal and lumbar arthrodesis for vertebral collapse (1); and uterus rupture (1). None of the patients were taking anticoagulant drugs.

All the patients had developed critical bleeding refractory both to RBC, FFP, and PLT concentrate transfusions and to resurgery or other invasive procedures. Critical bleeding was defined as the loss of the whole blood volume in 24 hours or loss of more than 50% of the blood volume in 3 hours.

Recombinant activated factor VII (NovoSeven, Novo Nordisk, Denmark) was given as an intravenous

bolus at a dosage between 90 and 120 ug/kg body weight (bw) in all except 3 patients with trauma, who received higher doses (180-200 ug/kg bw); in nonresponders, second and possibly third boluses were given after a 2- to 3-hour interval. The decision to attempt compassionate rFVIIa administration was always discussed and approved by a multidisciplinary medical team, including an anesthesiologist, a surgeon, and a hematologist. Patients considered unsalvageable at the time were excluded.

In each patient, blood samples were drawn before and 3 ± 1 hours after rFVIIa infusion to assay the following parameters: prothrombin time (PT), activated partial thromboplastin time (aPTT), antithrombin, fibrinogen, hemochrome, and arterial gas analysis. Whole blood was anticoagulated with Na citrate 0.13 mol/L for coagulation tests, with EDTA for hemochrome and with heparin for arterial gas analysis. Prothrombin time was tested using the chromogenic method with human recombinant thromboplastin (Dade Innovin; Dade Behring, Marburg, Germany). Activated partial thromboplastin time was assayed using the same method, with soy phosphatides and ellegic acid as reagents (Dade Actin FS Activated PTT Reagent; Dade Behring). Antithrombin activity was measured using the chromogenic substrate method (Berichrom Antithrombin III; Dade Behring). Fibrinogen was assayed with a photometric coagulation analyzer using human recombinant thromboplastin (Dade Innovin; Dade Behring). Hemochrome and arterial gas analysis were conducted using standard procedures.

Blood loss and the number of RBC, FFP, and PLT units transfused before and after administering rFVIIa were recorded to assess the hemostatic effect of rFVIIa treatment.

The mortality rates within 24 hours and 30 days of rFVIIa administration were evaluated, as were any complications potentially related to rFVIIa use. Given the short half-life of rFVIIa (2-3 hours), complications were arbitrarily considered as early or late if they occurred within or after 4 hours of rFVIIa infusion, respectively.

Statistical Analysis

The results were calculated as mean \pm standard deviation (SD), median, and range. The Wilcoxon test for paired data was used to compare continuous variables. Univariate logistic regression was used to detect significant associations between the

parameters analyzed. The univariate Kaplan-Meier method was used for survival analysis. A “*P*” value <.05 was considered statistically significant.

Results

The mean dose of rFVIIa given to our patients was 10.05 ± 4.68 mg (median 8.2 mg, range 1.2-15.6), corresponding to 132.25 ± 56.48 $\mu\text{g}/\text{kg}$ bw (median 110 $\mu\text{g}/\text{kg}$, range 40-285 $\mu\text{g}/\text{kg}$). Of the 31 patients (90.3%), 28 achieved a complete or partial hemostatic response after rFVIIa administration, that is, bleeding stopped completely in 5 cases and was significantly reduced in 23. Among the 28 responders, treatment with rFVIIa was effective immediately after a single bolus in 18 cases (64.2%), after 2 in 9 (32.1%), and after 3 in 1 (3.5%). Three patients, aged 61 ± 21.3 years, failed to respond to the treatment and died of the consequences of hemorrhagic shock (2 after a first rFVIIa bolus and 1 after 2 boluses).

All 31 patients with critical bleeding had been transfused with RBC, FFP, and/or PLT before rFVIIa was administered. Twenty patients had undergone major surgery, with procedures lasting an average 7.94 ± 4.23 hours. Nineteen patients underwent resurgery, for massive bleeding in 6 cases and for other reasons in 13.

The 28 responders required significantly lower amounts of blood products after rFVIIa administration, as shown in Figure 1. In particular, the mean RBC units given before rFVIIa amounted to 24.0 ± 11.4 and dropped to 5.5 ± 4.0 U after rFVIIa infusion ($P < .0001$). A similarly significant reduction was observed for both FFP ($P < .0004$) and PLT units ($P < .0001$). In patients undergoing surgery, the blood loss significantly decreased from 12.2 ± 9.4 to 2.9 ± 2.2 L after rFVIIa infusion ($P < .0001$; Figure 1).

As shown in Table 1, treatment with rFVIIa induced a significant improvement in clotting parameters, that is, normalized PT values ($P < .0001$) and a shorter aPTT ($P < .0001$). As for the hemochromocytometric parameters, the mean hemoglobin (Hb) values increased significantly after rFVIIa ($P < .0001$), and so did the hematocrit levels ($P < .0001$). In contrast, antithrombin levels and platelet counts were only minimally modified by rFVIIa administration ($P = .012$, and $P = .048$, respectively), and fibrinogen levels did not change.

The combined effect of transfusions and rFVIIa was analyzed. Hb levels significantly increased after RBC transfusions and an additional improvement

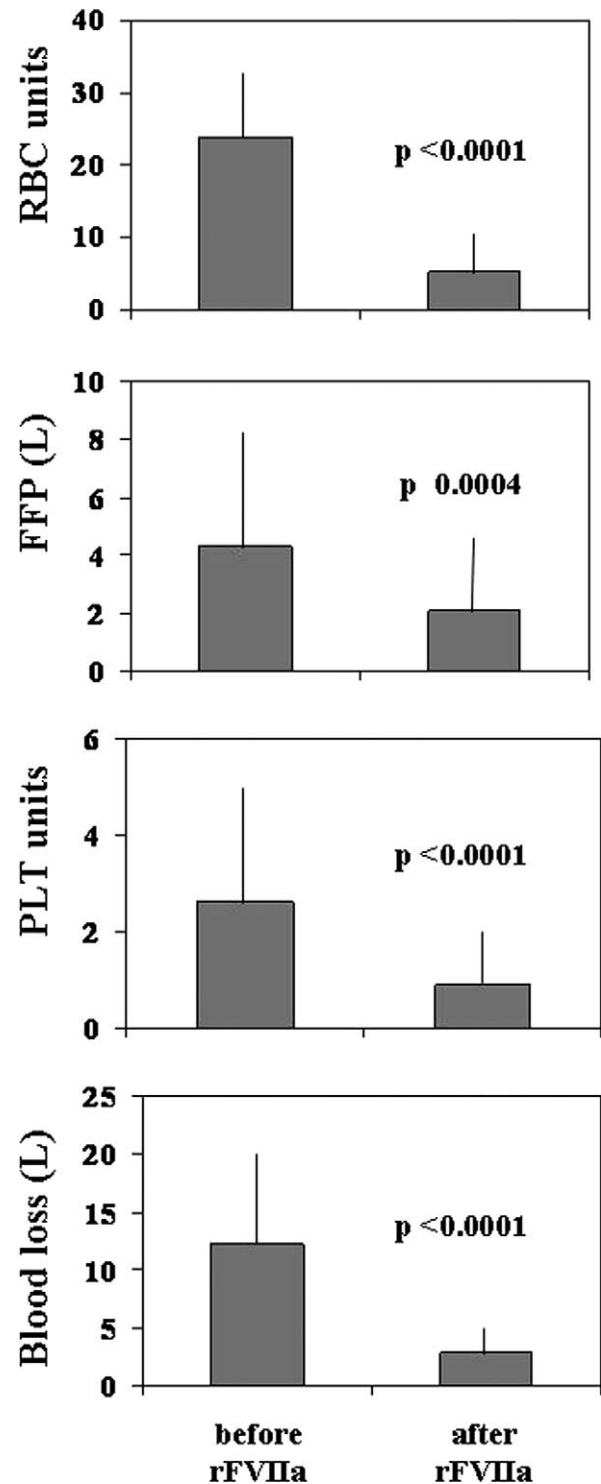


Figure 1. Mean (\pm SD) transfusion of red blood cells (RBC), fresh frozen plasma (FFP), and platelets (PLT) units, and mean (\pm SD) blood loss in 28 responders before and after treatment with recombinant activated factor VII (rFVIIa).

was seen after rFVIIa; likewise, both PT and aPTT values were partially corrected by FFP transfusions

Table 1. Mean (\pm SD) Clotting, Hemochromocytometric, and Acid-Base Parameters Before and After rFVIIa Infusion for Critical Bleeding in 28 Responders

Test	Before rFVIIa, Mean \pm SD	After rFVIIa, Mean \pm SD	P
PT (%)	29.3 \pm 22.1	73.4 \pm 33.3	<.0001
aPTT (seconds)	106.0 \pm 81.5	56.8 \pm 44.1	<.0001
Antithrombin (%)	32.1 \pm 17.8	41.1 \pm 15.0	.012
Fibrinogen (g/L)	1.7 \pm 1.6	1.6 \pm 0.8	NS
Platelet count ($\times 10^9/L$)	56.2 \pm 61.3	62.0 \pm 31.3	.048
Hemoglobin (g/L)	80.7 \pm 17.0	106.2 \pm 20.1	<.0001
Hematocrit (%)	23.3 \pm 4.6	30.0 \pm 5.6	<.0001
pH	7.20 \pm 0.18	7.28 \pm 0.19	<.0001
HCO ₃ (mEq/L)	20.1 \pm 5.0	22.1 \pm 4.4	<.0001

NOTES: aPTT = activated partial thromboplastin time; PT = prothrombin time; rFVII = recombinant activated factor VII.

and further improved after rFVIIa administration (Figure 2).

Recombinant activated factor VII treatment induced a reduction in acidosis, as demonstrated by the increase in mean pH ($P < .0001$) and bicarbonate values ($P < .0001$; Table 1). The relationship between acid-base balance and coagulopathy was assessed by logistic regression analysis: an inverse correlation between pH and aPTT ($\beta = -.60$, $P = .003$) and a direct correlation between pH and PT ($\beta = .66$, $P = .001$) was seen after treatment with rFVIIa.

Similar results emerged on analyzing all 31 patients' transfused blood products, blood loss, and laboratory findings before and after rFVIIa infusion, as shown in Table 2.

Autopsy in the 3 nonresponders revealed previously unidentified sources of major bleeding, namely an ulcerative hemorrhagic infiltration of the duodenum from a pancreatic cancer already treated with arterial embolization, a splenic rupture after surgical correction of an abdominal aortic aneurysm, and a 3-cm laceration of the left uterine artery in woman in her 32nd week of gestation, who underwent hysteroadnexectomy for a ruptured uterus with massive hemoperitoneum. The 3 nonresponders had received a mean dose of 9.86 ± 4.61 mg (120 ± 51.4 μ g/kg bw) of rFVIIa. Blood tests were severely altered at baseline (PT $25.3 \pm 17.6\%$, aPTT 159.6 ± 104.5 seconds, fibrinogen 1.0 ± 0.2 g/L, PLT $27.7 \pm 28.5 \times 10^9/L$, pH 7.1 ± 0.2) and changed only minimally after rFVIIa. These 3 patients died after 2, 11, and 72 hours, respectively.

Any adverse events potentially linked to rFVIIa administration were considered in all 31 patients treated. As shown in Table 3, 4 patients (12.8%) had adverse events, which were early in 2 cases (1 ischemic stroke associated with intestinal infarction and 1

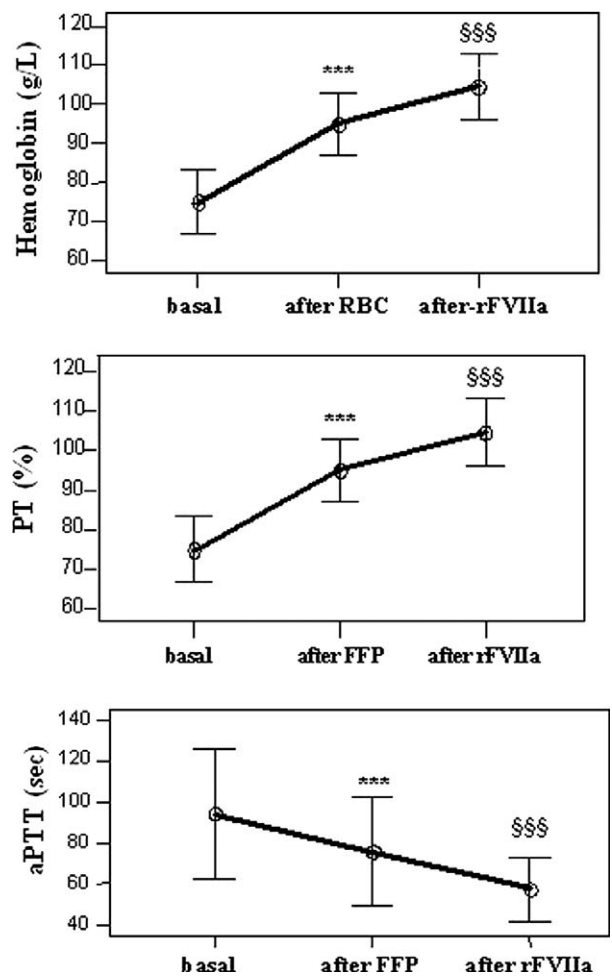


Figure 2. Variation in hemoglobin levels after red blood cells (RBC) transfusion and recombinant activated factor VII (rFVIIa) infusion, and variation in prothrombin time (PT) and activated partial thromboplastin time (aPTT) values after fresh frozen plasma (FFP) transfusion and rFVIIa infusion. *** $P < .001$ versus basal; §§§ $P < .001$ versus values after blood product transfusion.

Table 2. Transfused Blood Products, Blood Loss and Clotting, Hemochromocytometric, and Acid-Base Parameters Before and After rFVIIa Infusion in all 31 Patients With Critical Bleeding Included in the Study

	Before rFVIIa, Mean \pm SD	After rFVIIa, Mean \pm SD	P
Transfusions			
RBC (U)	23.6 \pm 11.0	5.7 \pm 4.1	<.0001
FFP (L)	4.21 \pm 4.79	2.11 \pm 2.63	.004
PLTs (U)	2.9 \pm 4.2	0.9 \pm 1.7	<.0001
Blood loss (L)	12.4 \pm 10.2	2.6 \pm 2.1	<.0001
PT (%)	28.9 \pm 21.5	71.1 \pm 35.2	<.0001
aPTT (seconds)	111.6 \pm 83.6	61.1 \pm 46.5	<.0001
Antithrombin (%)	31.1 \pm 17.5	39.5 \pm 16.2	<.02
Fibrinogen (g/L)	1.6 \pm 1.5	1.5 \pm 0.7	NS
Platelet count ($\times 10^9$ /L)	53.3 \pm 59.1	61.6 \pm 29.8	.038
Hemoglobin (g/L)	82.4 \pm 17.5	104.5 \pm 23.1	<.0001
Hematocrit (%)	23.7 \pm 4.6	29.5 \pm 6.4	<.0001
pH	7.1 \pm 0.1	7.2 \pm 0.1	<.0001
HCO ₃ (mEq/L)	19.9 \pm 4.7	21.8 \pm 4.3	<.0001

NOTES: aPTT = activated partial thromboplastin time; FFP = fresh frozen plasma; PT = prothrombin time; RBC = red blood cells; rFVII = recombinant activated factor VII.

Table 3. Adverse Events Potentially Linked to rFVIIa in 31 Patients With Critical Bleeding

Patients, Sex—Age (years)	Adverse Events	Timing of Onset (Hours)	No of Cases	Prevalence (%)
M ^a —47	Cerebral stroke plus intestinal infarction	4	1	3.2
M—72	DIC ^b	3	1	3.2
F ^c —76	DIC	12	1	3.2
F—52	Myocardial infarction	14	1	3.2
Total			4	12.8

^a Male.

^b Disseminated intravascular coagulation.

^c Female.

disseminated intravascular coagulation), and late in 2 (1 myocardial infarction and 1 disseminated intravascular coagulation). Disseminated intravascular coagulation was diagnosed on the basis of clinical and laboratory evidence of multiple organ failure, prolonged PT and aPTT, declining fibrinogen, antithrombin, and platelet counts, and rising D-dimer levels.

Other complications recorded were due mainly to ischemic-reperfusion processes and massive transfusion. In particular, they included: septic shock (2), hypovolemic shock (9), multiple organ failure (4), ventricular fibrillation (1), subarachnoid hemorrhage (1), and pericardial effusion (1).

Finally, we assessed the outcome at 24 hours and 30 days in all 31 patients included in the study. After 24 hours of administering rFVIIa, 15 of 31 patients (48.4%) were still alive; in the other 16, death occurred a mean 17.2 ± 1.5 hours (95% confidence interval [CI], 14.3-20.2 hours) after the rFVIIa treatment, and in 8 cases it was due to hypovolemic shock. In all, 9 of the 31 (29.1%) patients were alive after

30 days; the mean survival after the rFVIIa treatment of the 22 patients who died was 255.7 ± 56.9 hours (95% CI, 144.0-367.4 hours) or 9.4 ± 2.4 days (95% CI, 6.0-15.3 days). The cumulative survival at 24 hours and 30 days is detailed in Figure 3.

Comparing the survival curves of the series as a whole versus responders at 24 hours and 30 days revealed no significant differences (log-rank test: $P = .84$ and $P = .75$, respectively).

Discussion

Recombinant activated factor VII is used for licensed indications at our center, but in 2005, based on reports in the literature, we extended its indications to the compassionate treatment of selected patients with uncontrollable hemorrhage refractory to transfusions and invasive procedures (including surgical revision), based on an internal protocol shared with surgeons and anesthesiologists. Because the

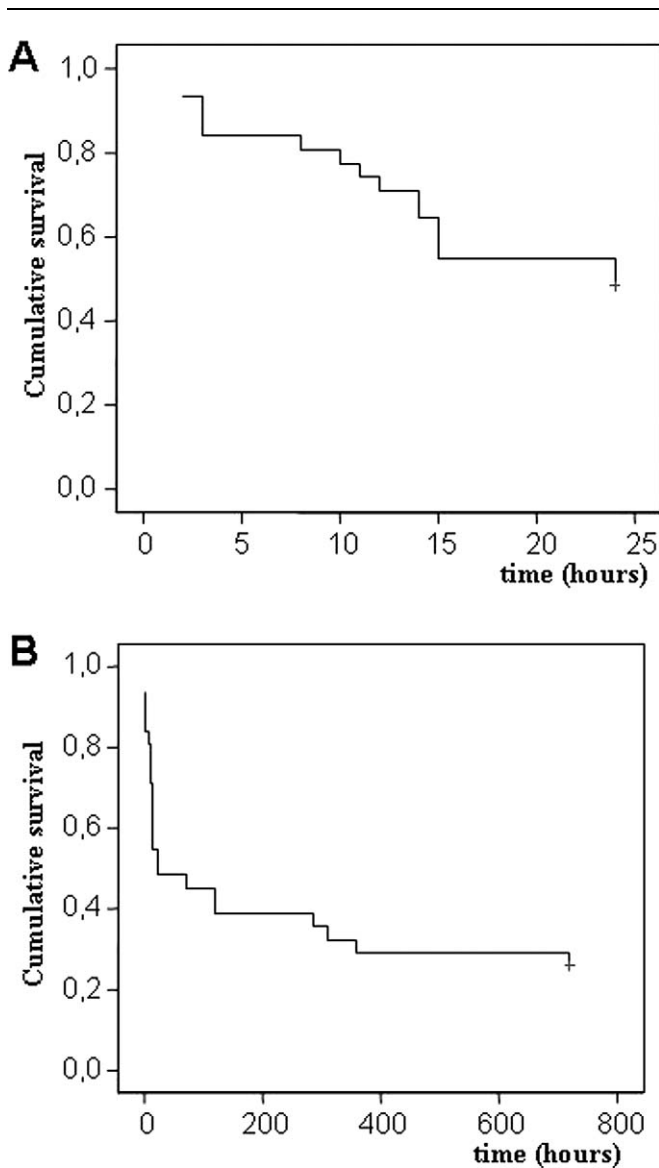


Figure 3. Cumulative survival at 24 hours (panel A) and at 30 days (panel B) in 31 critically bleeding patients treated with recombinant activated factor VII (rFVIIa).

hemostatic efficacy of rFVIIa demands adequate levels of fibrinogen (≥ 1.0 g/L), platelets ($\geq 50 \times 10^9$ /L), and pH (≥ 7.2),²⁶ every effort was made to correct these parameters before administering rFVIIa. Our aim in this study was to ascertain the effectiveness of rFVIIa treatment in stopping or containing bleeding, judging from subsequent transfusion needs, blood loss, and anemia. Recombinant activated factor VII was effective in 90.3% of our cases at conventional dosages (median 110 μ g/kg), which led to a drastic reduction in transfusions and blood loss, with a consequent rise in hemoglobin levels and their stabilization. Higher doses were used in 3 of 7 trauma

patients, based on the recommendations of recent trials.^{11,12} The beneficial effect became evident soon after a single bolus in most patients, and only 1 patient needed 3 doses to control bleeding. Our data are consistent with other reports on patients with trauma or undergoing cardiac, general, and gynecological surgery,^{6,8-11,30} and they further support the conviction that rFVIIa can contribute substantially to the conventional treatment of critical hemorrhage.

In our patients, rFVIIa infusion induced a rapid improvement in the hemostatic profile, with shorter PT and aPTT, and stabilized fibrinogen levels and platelet counts; the amount of FFP and PLT units transfused also dropped significantly after administering rFVIIa. It is crucial to stop the bleeding to correct the associated coagulopathy, which is due to several factors such as hemostatic component consumption, hemodilution, acidosis, and secondary fibrinolysis.³¹ Our patients' antithrombin levels were very low, thus suggesting a dilutional coagulopathy not corrected with FFP or other therapeutic measures.

The clinical effect of rFVIIa was associated with an improvement in coagulation parameters, suggesting that these variables may reflect the therapeutic effectiveness of rFVIIa and may be useful for monitoring purposes. We also recorded a slight improvement in the clotting parameters of patients failing to respond to rFVIIa treatment, however. As in other studies, the parameter that best correlated with the treatment's effectiveness in our experience was the clinical response, that is, the control of hemorrhage. In fact, shorter clotting times are known to reflect the enzymatic activity of rFVIIa *in vitro* but may not correspond to the therapeutic effect of rFVIIa *in vivo*.³²

Acidosis is of the utmost relevance in critical patients, because its severity correlates with the death risk.³³ It can affect the hemostatic process by reducing the protease activity of clotting factors. It has also been shown that rFVIIa may prove ineffective if acidosis is not corrected.^{26,34} We found a correlation between improvements in clotting parameters (PT and aPTT) and in pH values after rFVIIa treatment.

In our 3 nonresponder patients, the reason why rFVIIa failed to take effect was only subsequently found to lie in unrecognized hemorrhagic lesions of medium- to large-sized vessels or richly vascularized organs. Because surgical hemostasis was inadequate, it was impossible for rFVIIa alone to control such bleeding. Although it is of paramount importance to ascertain the source of critical bleeding before

considering rFVIIa, we all know that this is easier said than done in emergency situations.

All our patients were critically ill and about half of them died within 24 hours as a result of their hemorrhage, even if rFVIIa succeeded in stopping the bleeding. Because no control group was considered, we cannot say to what degree rFVIIa influenced survival. We can only surmise that the mortality rate would probably have been even higher if the hemorrhage had not been brought under control. In our clinical experience, in fact, the estimated mortality for critical bleeding may reach as high as approximately 95% of cases within hours. The use of rFVIIa should be discussed and its dosage tailored to each patient, paying special attention to underlying diseases and life expectancy. All our patients with solid neoplasms were judged eligible for surgery because their clinical conditions and life expectancy were adequate. Given its demonstrated hemostatic effect in some clinical settings, rFVIIa infusion should probably be considered before the catastrophic consequences of critical bleeding can develop, with a view to gaining a survival advantage and balancing its costs and effects.

Adverse events that might have been triggered by a procoagulant state after rFVIIa treatment were observed in about 13% of our patients. The risk of thrombotic complications has been highlighted in some studies, with a prevalence ranging between 9% and 25%,^{7,11,35,36} while other reports found the frequency of adverse events associated with rFVIIa similar to the situation in placebo-treated patients.^{10,20,37} The half-life of rFVIIa is 2 to 3 hours and early complications (within 4 hours of rFVIIa infusion) only occurred in 2 of our patients. Moreover, the hemorrhage itself may have had a causal role in the onset of the complications observed, leading to tissue hypoperfusion and coagulopathy. Either way, we agree with the recommendation that rFVIIa should be used with caution in patients with known atherosclerotic lesions. As for any other potential adverse events, we observed no allergic reactions to the drug.

We acknowledge that a major drawback of the current study is the lack of a control group not treated with rFVIIa. However, the clinical characteristics and underlying diseases of our patients were so heterogeneous that it would have been hard to identify a comparable historical population.

In conclusion, our study demonstrates that the compassionate use of rFVIIa in critical bleeding, in addition to conventional treatment, may be hemostatically effective, drastically reducing blood losses and

transfusion needs, and improving coagulopathy. The patient's life expectancy and any comorbidities carrying a risk of adverse events should be carefully considered before such treatment, however. Further studies are needed to establish the right clinical setting and the best timing for rFVIIa treatment to achieve the maximum advantage in terms of cost-effectiveness and survival.

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