

## IN FOCUS

# Guidelines for the use of recombinant activated factor VII (rFVIIa) in uncontrolled bleeding: a report by the Israeli Multidisciplinary rFVIIa Task Force

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**Summary.** *Background:* Recombinant activated factor VII (rFVIIa) has been approved by the U.S. Food and Drug Administration (FDA) for almost a decade for hemophilic patients with inhibitors. Its off-label use as a hemostatic agent in massive bleeding caused by a wide array of clinical scenarios is rapidly expanding. While evidence-based guidelines exist for rFVIIa treatment in hemophilia, none are available for its off-label use. *Objectives:* The aim of this study is to develop expert recommendations for the use of rFVIIa in patients suffering from uncontrolled bleeding (with special emphasis on trauma) until randomized, controlled trials allow for the introduction of more established evidence-based guidelines. *Methods:* A multidisciplinary task force comprising representatives of the relevant National Medical Associations, experts from the Medical Corps of the Army, Ministry of Health and the Israel National Trauma Advisory Board was established in Israel. Recommendations were construed based on the analysis of the first 36 multi-trauma patients accumulated in the prospective national registry of the use of rFVIIa in trauma, and an extensive literature search consisting of published and pre-published controlled animal trials, case reports and series. The final consensus guidelines, together with the data of the first 36 trauma patients treated in Israel, are presented in this article. *Results:* Results of the first 36 trauma patients: The prolonged clotting assays [prothrombin time (PT) and partial thromboplastin time (PTT)] shortened significantly within

minutes following administration of rFVIIa. Cessation of bleeding was achieved in 26 of 36 (72%) patients. Acidosis diminished the hemostatic effect of the drug, while hypothermia did not affect it. The survival rate of 61% (22/36) seems to be favorable compared with published series of similar, or less severe, trauma patients (range 30%–57%). *Conclusions:* As a result of the lack of controlled trials, our guidelines should be considered as suggestive rather than conclusive. However, they provide a valuable tool for physicians using rFVIIa for the expanding off-label clinical uses.

**Keywords:** bleeding, guidelines, hemorrhage, rFVIIa, recombinant activated FVII, trauma.

## Introduction

Uncontrolled massive bleeding is the leading cause of early in-hospital mortality (within 48 h of admission) and the second leading cause of prehospital death in victims of both military and civilian trauma, accounting for 40%–45% of the total fatalities [1,2].

Massive hemorrhage after traumatic injury, or complicated surgical procedures, is frequently a combination of surgical and coagulopathic bleeding [3]. Surgical bleeds originate from a recognizable source at the site of surgery, or trauma, and are typically corrected using surgical measures, such as packing, or tamponading the bleeding area, ligating the damaged vessels, or inducing localized thrombosis via invasive radiology [4].

Coagulopathic bleeding results from impaired thrombin generation. Coagulopathy develops early after injury and is present in 25%–36% of trauma victims upon admission to the emergency department [5,6]. Coagulopathy correlates to the severity of trauma and is associated with an increased risk of mortality beyond that expected from the severity of the injury [6].

As only limited coagulation tests are readily performed [such as prothrombin time (PT), partial thromboplastin time (PTT),

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platelet count and fibrinogen levels] the actual extent of injury-related coagulopathy may be underestimated. The mechanism of coagulopathy in trauma is complex and multifactorial:

- 1 Dilutional coagulopathy results from the dilution of coagulation factors and platelets caused by the infusion of large volumes of crystalloids, colloids, or blood products, which are administered to improve oxygen delivery. The severity of dilutional coagulopathy is determined by both the volume and type of fluids infused. Whereas permissive hypotension and reduced fluid volume in the prehospital setting and early in-hospital treatment may decrease the extent of such coagulopathy, newly developed types of fluids, such as hypertonic saline (with or without dextran), new colloids, and artificial oxygen carriers, may exacerbate it [7–10].
- 2 Hypothermia is a common complication of both civilian and combat injuries, leading to severe coagulation impairment. This is due to the decline in both platelet and coagulation enzyme activities [11–13]. These effects are often underestimated as most laboratories re-warm blood samples to 37°C before testing for clotting assays, i.e. PT, PTT. Even if these plasma-clotting assays were performed at the patient's body temperature, they would still underestimate the magnitude of the coagulopathy, as these assays do not reflect the *in vivo* coagulation process occurring on cell membranes, such as tissue factor (TF)-bearing cells and activated platelets [14]. Furthermore, platelet functions, which are significantly impaired by hypothermia [15], are not monitored routinely, contributing to the underestimation of the hemostatic defect.
- 3 Acidosis resulting from decreased perfusion and production of anaerobic metabolism leading to the accumulation of lactic acid is common among trauma victims. Even a slight decrease in pH compromises the function of both coagulation enzymes and platelets, particularly in the presence of hypothermia [11]. A decrease in pH from 7.4 to 7 reduces prothrombin (FII) activation by the prothrombinase complex (FXa/FVa) by 70% [15].
- 4 Hyperfibrinolysis may be more common in trauma patients than was previously realized. The failure to detect this condition stems from the lack of routine laboratory tests for fibrinolysis. A recent study using rotational thromboelastography (roTEG) has shown that approximately 20% of multi-trauma patients suffering from massive bleeding have marked hyperfibrinolysis (M. Vorweg and M. Doehn, Personal Communication). The reproduction of these findings in larger patient series would support the theory that early administration of antifibrinolytic agents may be beneficial for hemorrhage control in trauma. Treatment with recombinant activated factor VII (rFVIIa), which reduces clot susceptibility to fibrinolysis partly by the induction of thrombin-activated fibrinolytic inhibitor (TAFI), may also be of value in hyperfibrinolysis [16].
- 5 Anemia-induced coagulopathy: In addition to their role in oxygen delivery, red blood cells (RBC) provide important mechanical and biochemical functions in the coagulation process. Therefore, anemia causes prolongation of the bleeding time, which can be corrected with a RBC transfusion

[17–19]. Furthermore, reduction of the hematocrit (Hct) inhibits platelet adhesion and aggregation, e.g. Hct of 20% restricts aggregation to a degree similar to that observed with 20 000 platelets mL<sup>-1</sup> [20].

- 6 Consumption coagulopathy is induced by exposure of TF at the site of injury, leading to activation of the coagulation cascade at this site. Massive injury may cause extensive consumption with depletion of platelets and coagulation factors. This process results in laboratory findings resembling disseminated intravascular coagulation (DIC), such as prolonged PT and aPTT, low levels of platelets and fibrinogen, and high levels of D-dimers and other markers of coagulation and fibrinolysis activation. However, in most cases, these findings do not reflect DIC, as there is no evidence of microthrombi formation and, thus, no intravascular clotting [21].

### Treatment of coagulopathic bleeding

The conventional treatment of coagulopathic bleeding involves administration of blood products, such as RBC, fresh frozen plasma (FFP), cryoprecipitate, and platelets to replace the blood components lost in the process of diffuse hemorrhage. However, such replacement therapy is associated with increased risks of mortality and morbidity [22]. These include complications such as ABO incompatibility, transfusion-related acute lung injury (TRALI), multi-organ dysfunction syndrome (MODS), and transmission of infectious agents (e.g. viruses, bacteria, prions) [23].

Moreover, blood products are becoming scarce because of a rising demand of complex surgery in the growing geriatric population; safety concerns also diminish supply. The possibility of reducing blood storage time because of the accumulating (yet weak) evidence of its negative effect on prognosis may reduce the supply even further [24,25].

Perhaps the most compelling limitation of replacement therapy in patients with massive bleeding is the occasional failure to arrest coagulopathic bleeding. For instance, refractory coagulopathic bleeding was found to be responsible for approximately half the mortality rate among trauma patients in the operating room [26]. In another series of patients, 52% of mortality caused by trauma resulted from exsanguination despite massive replacement therapy [27]. The frequently encountered limitations of replacement therapy emphasize the need for additional pro-hemostatic agents.

Antifibrinolytic agents, such as aprotinin, tranexamic acid and ε-aminocaproic acid, have been shown to reduce blood requirements in various types of surgery (e.g. cardiac, hepatic, orthopedic). 1-Deamino-8-D-arginine vasopressin (DDAVP) has been shown to have some hemostatic efficacy in patients with uremia, hepatic failure and some platelet dysfunction. However, none of these agents have been beneficial in stopping massive coagulopathic bleeding [28]. Fibrin glues are also ineffective in most cases of massive bleeding. The use of these products requires direct application at the site of bleeding. Even when the site is accessible, the fibrin clot may be washed away

by the blood flow. Therefore, these products are most appropriate for the prevention of re-bleed rather than the arrest of massive bleeding [29].

#### *Recombinant activated factor VII as a hemostatic agent in uncontrolled bleeding*

Undoubtedly, there is a clinical need for one or more new hemostatic agents to supplement a limited armamentarium of therapeutic options for bleeding that cannot be controlled by surgical intervention, local hemostatic agents, and transfusion of blood products [30].

Recombinant activated factor VII (NovoSeven®; Novo Nordisk A/S, Bagsvaerd, Denmark) has been approved by the U.S. Food and Drug Administration (FDA) for nearly a decade for the prevention and treatment of bleeding episodes in hemophilic patients with inhibitors to coagulation factor VIII or factor IX. Despite its beneficial effect in hemophilia and a variety of congenital and acquired coagulation and platelet defects [31,32], its use in trauma was avoided until recently because of the theoretical increased risk of thromboembolic complications.

Since the first report in 1999 of the use of rFVIIa in an exsanguinating trauma patient [33], an increasing number of case series and reports have described its efficacy in controlling massive hemorrhage [3,4,34–39]. These reports discussed a wide array of bleeding situations in patients without prior coagulopathy, such as trauma, postpartum hemorrhage, general surgery in adult and pediatric patients, cardiac surgery, and prostatectomy among others.

#### *Mode of action of rFVIIa*

The recently developed cell base model of coagulation [14] suggests rFVIIa enhances hemostasis at the site of injury without a systemic, hypercoagulable effect. Naturally occurring FVIIa circulates in small quantities and has a very weak enzymatic activity until it binds to TF that normally is not exposed to the circulating blood. When TF is exposed at the site of injury, the complex TF–VIIa initiates the coagulation cascade by activating FX and FIX. Activated FIX (IXa) forms a complex with its cofactor FVIIIa on the phospholipid membrane of activated platelets (adhered to the site of injury) and activates FX 50-fold faster than the TF–VIIa complex. FXa forms a complex with its cofactor FV (also on the phospholipid membrane of activated platelets), which activates prothrombin to produce a small amount of thrombin. At this stage, the small concentration of thrombin is insufficient to convert fibrinogen to a fibrin clot, but further accelerates the coagulation cascade by activating FV, VIII, FXI, and additional platelets. Following this acceleration, a large amount of thrombin is formed that subsequently changes soluble fibrinogen to insoluble fibrin clots. Administration of a high dose of rFVIIa results in a huge increase of VIIa level, compared with the physiological state, causing faster and higher thrombin generation. In addition, pharmacological

concentrations of rFVIIa initiate the activation of a platelet-dependent TF-independent mechanism that augments the coagulation process [14].

*In vitro* analysis of the fibrin clots formed in the presence of a high thrombin concentration has shown that such clots have a different type of architecture that is stronger and far more resistant to degradation by fibrinolytic enzymes compared with normal clots. This is partially explained by the TAFI, which is activated by the high thrombin burst [40,41].

An animal model of uncontrolled arterial hemorrhage demonstrated that resuscitation induced rebleeding occurred at a significantly higher mean arterial pressure in the rFVIIa-treated group than in the placebo group [42]. This provides *in vivo* evidence for the stronger architecture and adherence force of the clot to the site of injury.

#### *Safety*

The localized activation of coagulation only at the site of injury probably explains the excellent safety profile of rFVIIa. Less than 0.05% of serious thromboembolic events occurred in over 400 000 doses administered to patients with hemophilia [43,44].

Accumulated data from over 1000 patients without hemophilia participating in various studies demonstrated no statistically significant difference in thromboembolic events between the study and placebo groups. A recent multicenter, randomized trauma trial revealed no more adverse events, including thromboembolic complications, MODS and ARDS in the rFVIIa-treated patients compared with the control group (unpublished data, information received from the manufacturer).

#### *Compassionate use of rFVIIa for patients with massive bleeding*

The compassionate use of rFVIIa for uncontrolled bleeding was approved by the Ethical Committee of the Israeli Ministry of Health in late 1999. Since then, more than 200 trauma, surgical and medical patients have been treated with rFVIIa in Israel.

The data of the first consecutive 57 trauma cases treated with rFVIIa in Israel was collected. Non-salvageable patients (dead on arrival;  $n = 8$ ) and patients with isolated traumatic brain injury (TBI) ( $n = 13$ ) were excluded from the analysis as isolated TBI is a different clinical entity from that of multi-trauma. Cases of TBI as part of multi-trauma were included ( $n = 10$ ), and 36 cases were analyzed. Sixteen of these cases (Table 1, no. 1–16) have previously been published [3,33,34].

#### **Patients and methods**

The median age of the 36 patients was 19.5 years (range, 14–65 years). Types of injury were as follows: penetrating (44%), blunt (42%), blast (14%). Ten (28%) had concomitant TBI. All 36 patients were critically ill, with an Injury Severity Score (ISS) of 25–75 in 25 of 29 (86%) in whom ISS was

**Table 1** Patients' data

Pt. No.	Age (years)	Sex	Details of trauma	ISS	Response	Outcome Reference
1	19	M	P-GSW: tears in IVC, massive paravertebral muscle damage	25	Yes	Recovered <sup>*†‡</sup>
2	42	F	BL-MVA: multiple fractures (including pelvis), TBI bleed	66	Yes	Recovered <sup>†‡</sup>
3	17	M	P-stabbing: face, pelvis + chest, scrotum femoral artery (stabbing)	34	Yes	Recovered <sup>†‡</sup>
4	40	M	P-GSW pelvis-prostate	25	Yes	Recovered <sup>†‡</sup>
5	18	F	BL-MVA (terror): fracture pelvic + vascular, TBI	50	Yes	Recovered <sup>‡</sup>
6	18	F	BL-MVA (terror): pelvic fracture, TBI	43	Yes	Recovered <sup>‡</sup>
7	15	F	Blast + P-tears vena cava, multiple fractures (+L3) vascular (explosion and shrapnel)	43	Yes	Recovered <sup>‡</sup>
8	19	M	BL-MVA: fracture L4, retroperitoneal bleed	32	Yes	Recovered <sup>‡</sup>
9	29	M	P-GSW: pelvic fracture, tears of colon, bladder, massive psoas damage	41	Yes	Recovered <sup>‡</sup>
10	18	M	BL-MVA: tears spleen, diaphragm, liver lacerations, bilateral pneumohemothorax, pelvic fracture, TBI (intraventricular hemorrhage)	36	Yes	Recovered <sup>‡</sup>
11	15	M	P-stabbing: chest, vascular (subclavian vein), lung	16	Yes	Recovered <sup>‡</sup>
12	14	F	BL-MVA: multiple fractures (ribs, pubis, radius, ulna) rupture spleen, pneumohemodiastinum, liver laceration, TBI (frontal contusion)	57	Yes	Recovered <sup>‡</sup>
13	18	M	BL-MVA, vascular (multiple – veins + arteries) hemopneumothorax-massive, cardiac tamponade, grade V liver lacerations, TBI (thalamus and intraventricular hemorrhage)	36	Yes	Died (6 days) sepsis <sup>‡</sup>
14	19	M	P-GSW: liver injury grade V + chest	50	No	Died (4 h) exsanguination <sup>†‡</sup>
15	19	M	BL-MVA tears aorta, spleen, pancreas diaphragm, multiple fractures	34	No	Died (4 h) exsanguination <sup>‡</sup>
16	17	M	P-GSW: multiple tears in GIT, bladder, iliac artery, retroperitoneal bleeding	25	No	Died (4 h) exsanguination <sup>‡</sup>
17	60	M	BL-fall, open book fracture pelvis, tears – bladder and urethra, hemoperitoneum, retroperitoneal hematoma (failure of embolization bilateral lung contusion, TBI-subarachnoid hemorrhage)	NA	Yes	Died (1 week) sepsis
18	14	F	Blast + BL + P: fracture lower limbs (femur + tibia), multiple shrapnel, vascular	34	Yes	Recovered
19	20	M	BL-MVA: retroperitoneal (adrenal) fracture vertebra, pneumohemothorax, TBI (subarachnoid bleeding)	27	Yes	Recovered
20	41	M	BL-fall: open pelvic fracture, retroperitoneal hematoma, L1–L2 fracture bilateral ankle, fracture diffuse axonal injury	25	Yes	Recovered
21	28	F	BL-MVA: (pregnancy 26 weeks) multiple fractures (femur, tibia, ankles, T1, liver laceration, mesenteric laceration)	38	Yes	Recovered
22	28	F	BL-MVA: multiple fractures: pelvis (comminuted), limbs; liver laceration	34	Yes	Recovered
23	20	F	BL-MVA: grade V liver damage, fracture limbs	NA	Yes	Recovered
24	22	M	P-GSW: left femur, right humerus comminuted fracture	16	Yes	Died (1 week) MODS
25	17	M	Blast + P + BL: severe multi-trauma: lacerations – large and small bowel, pelvic and ileal open fracture, arm amputation, extensive soft tissue injury, TBI	NA	Yes	Died (3.5 months) sepsis
26	28	M	BL-MVA: multiple fractures legs – bilateral amputation, pelvic fracture, rupture of urethra, colon, pelvic hematoma	NA	No	Died (8 days) sepsis
27	17	M	P-GSW: pelvis + abdomen-bladder, ileum, calf	16	Yes	Recovered
28	51	M	P-GSW: sacral and femur fracture	NA	Yes	Recovered
29	15	M	P-stab wound of abdomen, liver grade V, laceration of right portal vein, right hepatic artery, right hepatic duct, severe hemorrhagic shock, hemopneumothorax	NA	Yes	Recovered
30	72	M	BL-MVA: intraventricular bleeding, brain contusion, multiple fractures (ribs, zigoma, humerus, sacrum, ileum, pubis, fibula, transverse process L4–5) contusion of lung, hemopneumothorax TBI-contusion + intraventricular hemorrhage	NA	Yes	Recovered
31	31	M	BL-MVA: multi-trauma – pelvic fracture multivascular	41	No	Died (15 h) exsanguination
32	34	M	P-stabbing: vascular + liver	25	No	Died (8.25 h) exsanguination
33	56	F	P-GSW: grade V liver injury, left kidney, knee	29	No	Died (9.5 h) respiratory insuff
34	65	M	P-GSW: tears – splenic large and small bowel, femur fracture	25	No	Died (3.25 h) exsanguination
35	35	M	P-multiple (25) stabbing (cardiac, vertebral and temporal arteries)	18	No	Died (6 h) exsanguination
36	26	F	P + BL: multiple stabbing and fall: tears-liver (severe), lung diaphragm, pelvis (massive retroperitoneal hematoma), lumbar arteries	32	No	Died (4 h) exsanguination

ISS, injury severity score; IVC, inferior vena cava; P, penetrating; BL, blunt; TBI, traumatic brain injury; MVA, motor vehicle accident; GSW, gun shot wound; MODS, multi-organ dysfunction syndrome; GIT, gastrointestinal tract; NA, not available.

Cases previously published: \*Ref [33], †Ref. [3], ‡Ref. [34].

available (Table 1). All suffered massive, life-threatening bleeds; the median blood requirement was 21 units of packed RBC [interquartile range (iqr) 15–38 U; range 5–105 U] transfused over a mean of  $5.2 \pm 4$  h from injury (excluding three patients treated  $\geq 1$  week after injury).

Furthermore, all patients were hypothermic (mean temperature:  $34.1 \pm 2.5^\circ\text{C}$ ), acidotic (mean pH:  $7.2 \pm 0.15$ ), and coagulopathic (median platelet number  $89.5 \times 10^9 \text{ L}^{-1}$ ; iqr 59.5–121.5; range 30–235); median fibrinogen levels:  $149 \text{ mg dL}^{-1}$  (iqr 112–258; range 23–634); mean PT and aPTT:  $20.6 \pm 8.3$  s and  $75.0 \pm 41.0$  s, respectively.

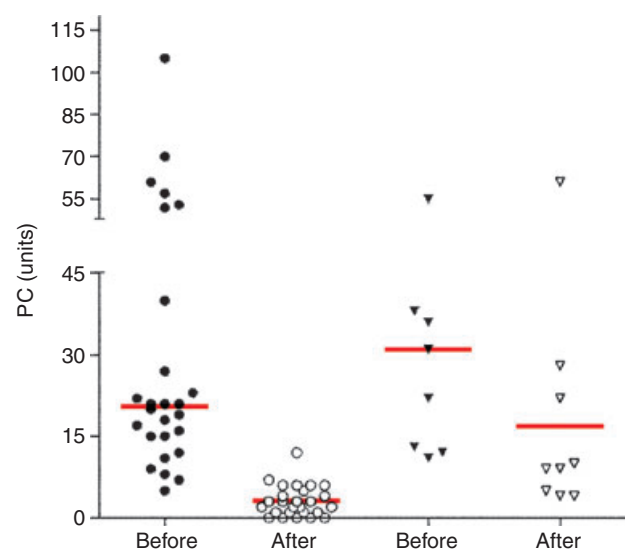
Replacement therapy included FFP (median 15 U; iqr 6–24; range 1–76 U), cryoprecipitate (median 17.5 U; iqr 10–30; range 0–139), and platelets (median 20 U; iqr 10–36; range 0–107). When these measures failed to arrest bleeding and exsanguination seemed inevitable, rFVIIa was administered as an intravenous bolus in a titratable manner. The initial dose was based on the recommended hemophilia dose of  $90 \mu\text{g kg}^{-1}$ , but because of the more complex and severe coagulopathy in our trauma patients compared with hemophilic patients, the dose was increased by about 30%. If clinically necessary, additional doses were administered within a short interval (approximately 15–30 min).

#### Statistical analysis

Data were recorded and analyzed using SAS statistical software (SAS, Cary, NC, USA). Various parameters were compared between survivors and non-survivors and also between responders (bleeding ceased) and non-responders. Mean and standard deviation values are reported for continuous data with normal distribution. Statistical tests included Pearson's chi-square for categorical data, *t*-tests for continuous variables, and Wilcoxon non-parametric tests where variables were abnormally distributed. A value of  $P < 0.05$  was considered to be statistically significant.

#### Results

Cessation of bleeding as determined by observation and hemodynamic stabilization was achieved in 26 of 36 (72%) patients after administration of rFVIIa (responders). Nine of the 10 patients in whom the bleeding did not respond to rFVIIa (non-responders) exsanguinated within  $< 24$  h. Blood requirements decreased dramatically in the responders from a median of 20.5 U (iqr 13.5–46; range 5–105) given within a mean of  $5.2 \pm 4$  h to a median of 2.5 U (iqr 1–5.5; range 0–12) of packed RBC administered during the 24 h following rFVIIa administration ( $P = 0.0001$ ). There was also a decrease in transfusion requirements in the non-responders from 31 U (iqr 12.5–42; range 11–55) before rFVIIa to 9 U (iqr 4.5–25; range 4–61), over the 24-h period following rFVIIa administration (Fig. 1). However, this comparison is both statistically and clinically insignificant as most of the non-responders (9/10) died within  $< 24$  h of rFVIIa administration while actively bleeding (Table 1). If these patients would have survived  $> 24$  h while

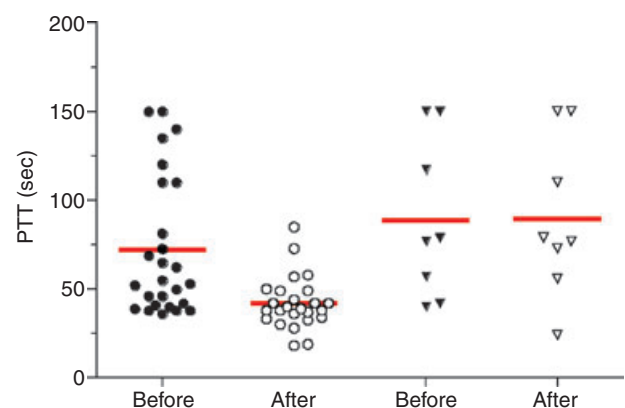


**Fig. 1.** Decline of packed red blood cell consumption (PC) before and after rFVIIa administration. A significant ( $P < 0.0001$ ) decline was observed only in the 'responders' (circles) but not in 'non-responders' (triangles).

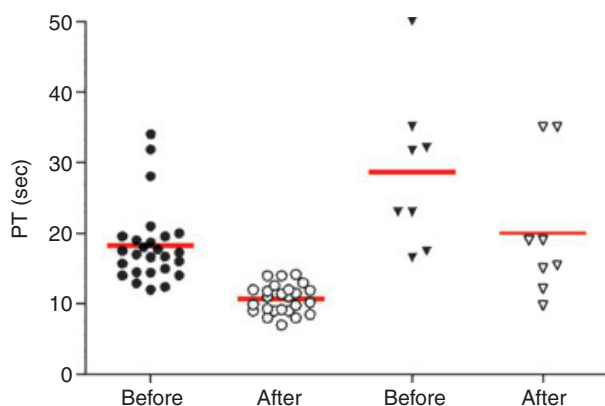
continuing to bleed, they would have required many more blood units.

Within 15–20 min of rFVIIa administration, the mean PT and aPTT shortened significantly in the responders from  $18.2 \pm 5.4$  s and  $72.0 \pm 38$  s to  $10.7 \pm 2$  s and  $42 \pm 14$  s, respectively ( $P = 0.0001$ ). Significant shortening of PT also was observed in the non-responders from  $28.5 \pm 11$  s to  $20 \pm 9.7$  ( $P = 0.016$ ), but aPTT did not shorten (Figs 2 and 3). The median total dose of rFVIIa administered was  $140 \mu\text{g kg}^{-1}$  ( $70$ – $540 \mu\text{g kg}^{-1}$ ) injected over a mean of  $1.6 \pm 0.7$  doses.

A trend towards improved survival was observed in patients who received a higher initial dose (median  $120 \mu\text{g kg}^{-1}$ ; iqr 98–138; range, 60–320  $\mu\text{g kg}^{-1}$ ) compared with those who received a lower first dose (median  $98 \mu\text{g kg}^{-1}$ ; iqr 50–120;



**Fig. 2.** Shortening of PTT values before and after administration of rFVIIa was significant ( $P = 0.0001$ ) in the 'responders' (circles) but not in 'non-responders' (triangles).



**Fig. 3.** Shortening of PT values before and after administration of rFVIIa was significant in both 'responders' (circles;  $P = 0.0001$ ) and 'non-responders' (triangles;  $P = 0.016$ ). However, in the latter group, mean PT values before and after treatment were significantly higher.

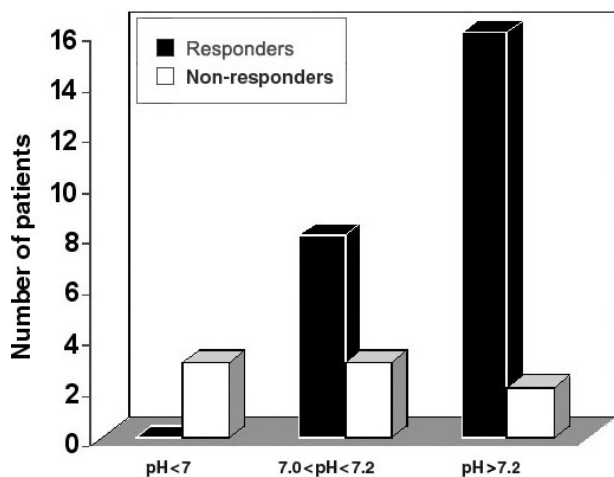
range 23–245), but studies with larger patient populations are required to significantly support this finding.

Acidosis was associated with a statistically significant reduced response to rFVIIa (Fig. 4), which is consistent with a recent *in vitro* study demonstrating marked decrease of thrombin generation in response to rFVIIa with lower pH levels [15]. In contrast, hypothermia did not affect the efficacy of rFVIIa, a finding that concurs with our previous animal trial [21] and recent *in vitro* study [15].

While there was a trend ( $P = 0.06$ ) for higher mortality in patients with acidosis, this difference did not reach statistical significance, probably because of the small number of patients.

A total of 22 of 36 patients (61%) survived at 90 days and one patient died after 4 months. Causes of death were exsanguination [8/14 (57%)], sepsis [4/14 (28.5%)], and MODS [2/14 (14%)].

The survival rate of our registry seems encouraging compared with the reported survival of 30%–57% for



**Fig. 4.** Acidosis and hemostatic response to rFVIIa: \* $P = 0.01$  for pH < 7 vs. pH  $\geq$  7 (Fisher's exact test); chi-square test for pH levels in patients who responded to rFVIIa vs. those who did not respond,  $P = 0.004$ .

massively bleeding trauma patients treated only with blood products [27,45–48]. These data further support the notion that rFVIIa is a promising hemostatic treatment alternative for control of trauma-associated hemorrhage.

### Recommendations for the use of rFVIIa in uncontrolled hemorrhage

The lack of controlled trials on the use of rFVIIa in trauma patients, the limited data on patient-selection dosages, and the timing of administration and monitoring that will not be provided even by the recently completed multicenter randomized trauma trial prompted us to establish a Multidisciplinary Task Force to develop preliminary guidelines for the use of rFVIIa in cases of uncontrolled bleeding. These guidelines are based on the analysis of our cases and an extensive literature search consisting of published and prepublished controlled animal trials, case reports and series relating to the complex nature of coagulopathy and the use of rFVIIa.

#### Indication

Any salvageable patient suffering from massive, uncontrolled hemorrhage that fails to respond to appropriate surgical measures and blood component therapy.

#### Definitions

Massive bleeding is defined as one of the following [49,50]:

- 1 Loss of entire blood volume within 24 h (10 U of packed RBC in a patient weighing 70 kg).
- 2 Loss of 50% of blood volume within 3 h.
- 3 Blood loss at a rate of 150 mL min<sup>-1</sup>.
- 4 Blood loss at a rate of 1.5 mL kg<sup>-1</sup> min<sup>-1</sup> for  $\geq$ 20 min.

Failure to arrest the hemorrhage despite:

- 1 Application of all accepted and available surgical measures (e.g. ligation of damaged vessels, tamponading, or packing of the bleeding site, and induction of localized thrombosis).

Appropriate replacement therapy: [50–52]

- 1 FFP: 10–15 mL kg<sup>-1</sup> (4–6 U for a patient weighing 70 kg).
- 2 Cryoprecipitate: 1–2 U 10 kg<sup>-1</sup> (10–15 U for a patient weighing 70 kg).
- 3 Platelets: 1–2 U 10 kg<sup>-1</sup> (10–15 U for a patient weighing 70 kg).
- 4 Correction of acidosis (defined as pH  $\geq$  7.2).
- 5 Warming of hypothermic patients (recommended, but not mandatory for administration of rFVIIa).

#### Contraindications

**Absolute** Unsalvageable patients, as identified according to the clinical evaluation of the treating medical team.

**Relative** History of thromboembolic events (e.g. pulmonary emboli, myocardial infarction, cerebrovascular accident, deep vein thrombosis) within the previous 6 months.

### Administration guidelines for rFVIIa

- 1 The blood bank should be immediately alerted to incidents of massive bleeding to facilitate timely preparation of the various blood components required [50].
- 2 rFVIIa should be administered as early as possible (after conventional treatments have failed to arrest bleeding), and should be given in conjunction with transfusion of 8–10 U of packed RBC in order to avoid further loss of clotting factors, exacerbation of acidosis, and further lowering of body temperature (all of which adversely affect the prognosis).

### Preconditions for rFVIIa administration

**Hematological parameters** As rFVIIa acts on the patient's own clotting mechanism, its administration should be considered after blood component therapy has achieved the following:

- 1 Fibrinogen levels of  $\geq 50$  mg dL<sup>-1</sup> (preferably 100 mg dL<sup>-1</sup>).
- 2 Platelet levels of  $\geq 50\,000 \times 10^9$  L<sup>-1</sup> (preferably  $100\,000 \times 10^9$  L<sup>-1</sup>).

If these parameters cannot be monitored on an immediate basis (i.e., in 'real time' by point of care testing), as is usually the case, the patient should receive appropriate empirical replacement therapy (as previously defined).

**pH** Clinical and laboratory evidence suggests that the efficacy of rFVIIa decreases at a pH of  $\leq 7.1$  [15]. Hence, correction of the pH to  $\geq 7.2$  is recommended prior to its administration.

**Body temperature** rFVIIa retains its activity in the presence of hypothermia, hence, the latter does not limit its use. Nonetheless, body temperature should be restored to physiological values as much as possible.

*Note:* As laboratory tests are conducted at 37°C, they may not demonstrate the true measure of coagulopathy in a hypothermic patient.

### rFVIIa and surgical hemostasis

- 1 It is recommended that rFVIIa be administered as an adjunctive therapy to concomitant surgical measures, as the agent arrests coagulopathic, rather than surgical, bleeding.
- 2 If packing was performed, unpacking should be considered before administration of rFVIIa. This is recommended because the cessation of diffuse coagulopathic bleeding induced by rFVIIa and the hemodynamic improvement that follows may serve to expose surgical bleeding sites that could not be previously identified.
- 3 For the same reason, if hemorrhage is encountered outside the operating room, angiography or a 'second look' should be considered (depending on the clinical circumstances) to rule out surgical bleeding.

It is important to mention that there are cases where administration of rFVIIa alone, prior to, or even without

surgical intervention, led to cessation or marked slow-down of the bleeding.

### Dosage

The recommended initial dose of rFVIIa for treatment of massive bleeding is  $\cong 120$  (100–140)  $\mu\text{g kg}^{-1}$  administered intravenously over 2–5 min. This is based on the experience in hemophilia patients and analysis of data of our trauma patients.

### Repeat dosage

If hemorrhage persists beyond 15–20 min, following the first administration of rFVIIa, an additional dose of  $\cong 100$   $\mu\text{g kg}^{-1}$  should be considered.

If the response remains inadequate following a total dose of  $> 200$   $\mu\text{g kg}^{-1}$ , the preconditions for rFVIIa administration should be re-checked, if possible, and corrected as necessary before a third dose is considered. If this is not feasible, the empirical administration of FFP (10–15 mL kg<sup>-1</sup> or 4–6 U for 70 kg), cryoprecipitate (1–2 U 10 kg<sup>-1</sup> or 10–15 U for 70 kg), and platelets (1–2 U 10 kg<sup>-1</sup> or 10–15 U for 70 kg) should be considered, and the pH and calcium should be checked and corrected. Only after these measures have been applied should a third dose of rFVIIa  $\cong 100$   $\mu\text{g kg}^{-1}$  be administered.

### Monitoring

Currently, there is no laboratory method for monitoring the effect of rFVIIa. The best available indicator of rFVIIa efficacy is the arrest of hemorrhage judged by visual evidence, hemodynamic stabilization and a reduced demand for blood components. The PT is expected to shorten, frequently below the normal expected range (as there is TF in the test tube), but this does not reflect efficacy. Rotation thromboelastography and thrombin generation are tests that need evaluation of efficacy.

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