

# Recombinant Activated Factor VII for Adjunctive Hemorrhage Control in Trauma

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**Background:** Recombinant activated factor VII (rFVIIa) was approved for treatment of hemorrhages in patients with hemophilia who develop inhibitors to factors VIII or IX. Conditions with increased thromboembolic risk, including trauma with or without disseminated intravascular coagulation, were considered a contraindication for the drug. The mechanism of action of rFVIIa suggests enhancement of hemostasis limited to the site of injury without systemic activation of the coagulation cascade. Therefore, use of the drug in trauma patients suffering uncontrolled hemorrhage appears to be rational.

**Methods:** Seven massively bleeding,

multitransfused (median, 40 units [range, 25–49 units] of packed cells), coagulopathic trauma patients were treated with rFVIIa (median, 120 µg/kg [range, 120–212 µg/kg]) after failure of conventional measures to achieve hemostasis.

**Results:** Administration of rFVIIa resulted in cessation of the diffuse bleed, with significant decrease of blood requirements to 2 units (range, 1–2 units) of packed cells ( $p < 0.05$ ); shortening of prothrombin time and activated partial thromboplastin time from 24 seconds (range, 20–31.8 seconds) to 10.1 seconds (range, 8–12 seconds) ( $p < 0.005$ ) and 79 seconds (range, 46–110 seconds) to 41 sec-

onds (range, 28–46 seconds) ( $p < 0.05$ ), respectively; and an increase of FVII level from 0.7 IU/mL (range, 0.7–0.92 IU/mL) to 23.7 IU/mL (range, 18–44 IU/mL) ( $p < 0.05$ ). Three of the seven patients died of reasons other than bleeding or thromboembolism.

**Conclusion:** The results of this report suggest that in trauma patients rFVIIa may play a role as an adjunctive hemostatic measure, in addition to surgical hemostatic techniques, and provides the motivation for controlled animal and clinical trials.

**Key Words:** Factor VIIa, Injury, Trauma, Hemostasis.

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Uncontrolled hemorrhage is a major cause of death in trauma victims, and is responsible for about 40% of mortality in both military and civilian trauma.<sup>1,2</sup> The distribution of mortality, however, is different: in the military, most exsanguinations occur within the first hour, before evacuation to hospital,<sup>1</sup> whereas in civilian trauma, 65% of exsanguinations occur after admission to hospital, being responsible for 40% of hospital deaths.<sup>2</sup> Introduction of an effective hemostatic agent that acts only at the site of injury, without induction of systemic activation of coagulation, may improve hemorrhage control and reduce hemorrhage-related mortality and morbidity in both military and civilian trauma victims.

Most critically ill trauma patients suffer profound coagulopathy, which directly correlates to the severity of injury.<sup>3,4</sup> Coagulopathy in trauma is multifactorial: coagulation abnor-

malities resembling disseminated intravascular coagulation (DIC), caused by systemic activation of coagulation and fibrinolysis;<sup>5</sup> excessive fibrinolysis (most probably caused by release of tissue plasminogen activator [TPA] from damaged tissues) is evident on the first day in trauma patients with extensive injury;<sup>5–7</sup> dilutional coagulopathy caused by excessive fluid treatment<sup>8</sup> of some fluids, such as hydroxyethyl starch (HES) preparations, in particular forms with a high molecular weight may directly compromise coagulation;<sup>9–11</sup> massive transfusion syndrome resulting in dilution of coagulation factors and impairment of platelet number and function;<sup>12</sup> hypothermia, mainly related to hypotension,<sup>13</sup> causing slowing of enzymatic activities of the coagulation cascade<sup>14–16</sup> and dysfunction of platelets;<sup>17</sup> and metabolic abnormalities, such as acidosis, also compromise coagulation, especially when combined with hypothermia.<sup>18</sup> Massive hemorrhage in most trauma cases presents as a combination of diffuse “coagulopathic” bleeding, and bleeding from vessels that need to be treated surgically (“surgical” bleed). Although surgical bleeding can, in most cases, be controlled by the surgeon (although the coagulopathic component may mask some bleeding vessels), control of coagulopathic bleeding is difficult, and sometimes impossible.

Recombinant activated factor VII (rFVIIa) has been successfully used to treat bleeding patients with various coagulopathies.<sup>19–24</sup> The high hemorrhage-related mortality rate in critically ill trauma patients, together with high efficacy and low risk of fatal thromboembolic complications (4 of 5,522 patients; unpublished data) with the understanding

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**Table 1** Patients

Patient	Age (y)	Sex	Trauma	PC <sup>a</sup>	FFP <sup>b</sup>	Cryo <sup>c</sup>	Plt <sup>d</sup>	Time to rFVIIa
1	19	M	Penetrating—IVC abdomen, paravertebral muscles	40	20	10	10	4 h
2	21	M	Penetrating—liver, chest	46	26	30	32	14 h
3	45	M	Penetrating—pelvis, prostate, urinary bladder, hip fracture, renal failure	70	66	139	107	30 days
4	17	M	Penetrating—pelvis, chest	27	19	28	36	9 h
5	21	F	Blunt—massive liver damage	50	10	—	10	4 h
6	75	F	Blunt—hip fracture	25	20	10	20	7 days
7	42	F	Blunt—pelvic fractures, tears in spleen, diaphragms, lungs, and intracranial hemorrhage	20	6	15	12	5 h

PRBCs, packed red blood cells; FFP, fresh frozen plasma; Cryo, cryoprecipitate; Plt, platelet units; IVC, inferior vena cava.

<sup>a</sup> Median, 40; 25–75 quartile range, 25–49.

<sup>b</sup> Median, 20; 25–75 quartile range, 12–24.

<sup>c</sup> Median, 15; 25–75 quartile range, 10–29.

<sup>d</sup> Median, 20; 25–75 quartile range, 10–37.

of the compartmentalized action of rFVIIa, suggests that it may be a promising adjunctive therapy for control of hemorrhage in trauma patients.

Circulating FVIIa is not active unless bound to tissue factor (TF), which is exposed at sites of vessel injury. The complex rFVIIa-TF initiates the coagulation cascade on activated platelet surfaces<sup>25–27</sup> adhering to the site of injury, resulting in the localized formation of fibrin clot at this site only.

## PATIENTS AND METHODS

After the first case of an exsanguinating Israeli soldier treated successfully with rFVIIa,<sup>28</sup> a randomized, controlled, safety and efficacy study on 10 hypothermic, coagulopathic swine with grade V liver injury (performed by us in conjunction with the Israeli and U.S. armies) supported the hypothesis of the local effect of rFVIIa.<sup>29</sup> On the basis of the above, and the recent survey of the manufacturer of rFVIIa on the low incidence of fatal thromboembolic complications (4 of 5,522 patients; unpublished data), the Ethical Committee of the Israeli Ministry of Health approved the compassionate use of rFVIIa for patients suffering massive, life-threatening bleeding as a result of trauma or surgery. Exclusion criteria included diffuse atherosclerotic disease, or a history of recent thromboembolism. Between June 1999 and January 2001, seven critically ill, coagulopathic, multitransfused trauma patients (Table 1) in whom conventional surgical and medical hemostatic treatment modalities had failed were treated with rFVIIa in six hospitals (five in Israel, one in Denmark). Patients comprised four men aged 17 to 45 years, and three women aged 21 to 75 years. Patients 1, 2, and 3 suffered penetrating trauma caused by high-velocity bullet injury. The first, previously reported by our group,<sup>28</sup> experienced penetration of the inferior vena cava with diffuse damage to paravertebral muscles, whereas in the second case the penetrating injury caused massive liver damage and lung injury. In patient 3, the bullet ripped off the prostate and urinary blad-

der, and caused hip fracture, resulting in prolonged hemorrhagic shock complicated by renal failure, and the patient continued to bleed for 30 days. Patient 4 suffered deep stabbing wounds in the pelvis and chest, and patients 5 and 6 suffered blunt trauma after a road accident with severe liver injury in one and hip fracture in the other. Patient 7, a 42-year-old female physician in our hospital, suffered severe blunt trauma with brain contusion; intracerebral bleeding in the temporofrontal region; multiple fractures including complicated pelvic fracture; and tears of the spleen, lungs, and diaphragm after falling from the fourth floor of a building. All patients suffered uncontrolled bleeding despite considerable surgical efforts and massive replacement therapy with blood products (Table 1). The patients suffered coagulopathy (Table 2) and some suffered hypothermia (body temperature, 30°–33°C) and acidosis (pH, 6.99–7.2).

Recombinant activated factor VII (Novoseven, Novo Nordisk, Bagsvaerd, Denmark) was reconstituted according to the manufacturer's instructions, and given as an intravenous bolus, the initial dose ranging from 40 to 120 µg/kg. Additional doses were allowed, as required (Table 3) To prevent rebleeding, fibrin glue (Ouxil, Omrixate, Israel) was sprayed over the wound after hemostasis was achieved.

## Statistical Analysis

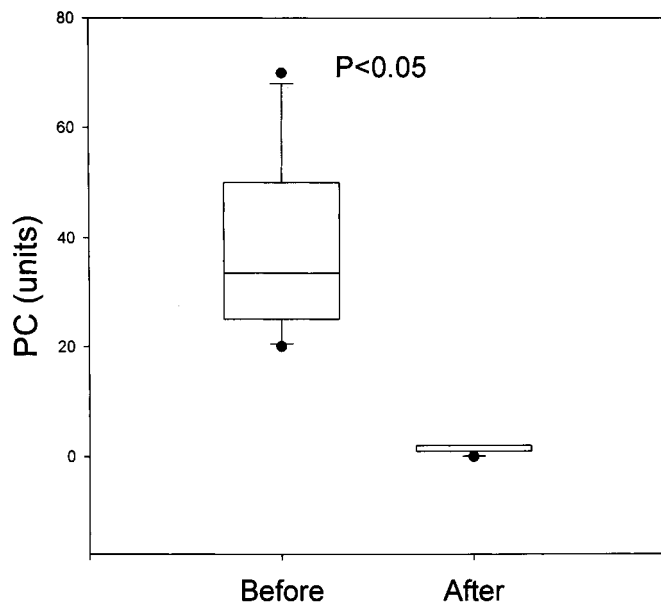
Groups were compared by paired *t* test or the equivalent nonparametric test using SPSS (version 9.0) for Windows

**Table 2** Coagulation Profile before rFVIIa

Test	Normal Range	Median (25–75 Quartile Range)
PT (sec)	10.7–13	24 (20–31.8)
PTT (sec)	18–30	79 (46–110)
Fibrinogen (mg/dL)	200–400	150 (110–194)
Platelets	130–440 × 10 <sup>3</sup>	98 (62–126)
D-dimers (µg/mL)	<0.5	1–4

**Table 3** Doses of rFVIIa

	Doses ( $\mu\text{g}/\text{kg}$ )
1	60, 60
2	120
3	120, 60, 60
4	120
5	40
6	70, 60
7	120, 80, 80

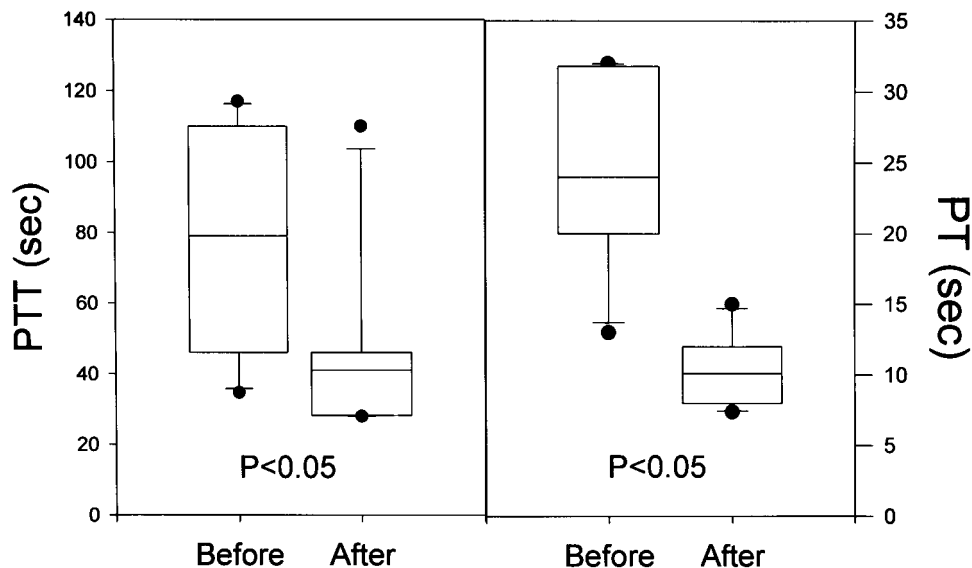


**Fig. 1.** Blood requirements before and after administration of rFVIIa.

(SPSS, Inc., Chicago, IL). Values are displayed as medians with 25 to 75 interquartile range. A  $p$  value  $< 0.05$  was considered significant.

**RESULTS**

In all patients, the diffuse bleeding “dried out” within 5 to 15 minutes after administration of one to three doses of rFVIIa (Table 3), exposing a few vessels that required surgical hemostasis. Blood requirements decreased significantly after rFVIIa (Fig. 1), from 36.5 packed cell units (range, 25–50) to 2 (range, 1–2) packed cell units ( $p < 0.05$ ) (data of patient 2, who died at completion of surgery, are excluded). The prothrombin time and activated partial thromboplastin time shortened significantly after administration of rFVIIa (Fig. 2), from 24 seconds (range, 20–31.8 seconds) to 10.1 seconds (range, 8–12 seconds) ( $p < 0.05$ ), and 79 seconds (range, 46–110 seconds) to 41 seconds (range, 28–46 seconds) ( $p < 0.05$ ), respectively. A median of 2 doses (range, 1–2.75 doses) of rFVIIa with a total dose of 120  $\mu\text{g}/\text{kg}$  (range, 120–212  $\mu\text{g}/\text{kg}$ ) were required to achieve hemostasis. The factor VII level increased markedly after administration of rFVIIa, from 0.7 IU/mL (range, 0.7–0.92 IU/mL) to 23.7 IU/mL (range, 18–44 IU/mL) ( $p < 0.05$ ) (or from 70% to 2,370%). Three of seven patients died—patient 2 suffered profound shock, hypothermia, and acidosis for 14 hours before administration of rFVIIa and died toward the end of surgery, and patients 5 and 6 died 4 weeks after the trauma (from sepsis and liver failure related to the extensive liver hypoxia, respectively). No clinical evidence of venous, arterial, or central nervous system thromboembolic complications were observed. No autopsies were performed in the three fatal cases.



**Fig. 2.** The shortening effect of rFVIIa on prothrombin time and partial thromboplastin time.

## DISCUSSION

Hemorrhage is a major problem in trauma patients: death in military trauma occurs in 18% of injured soldiers, approximately 94% of whom die within the first hour (immediate death), 2% within 1 to 4 hours (early death), and 4% later (hours to weeks). About 40% of immediate deaths and 86% of early deaths are caused by hemorrhage, accounting for 40% of the total mortality, according to experience gained from the 1982 war in Lebanon.<sup>1</sup>

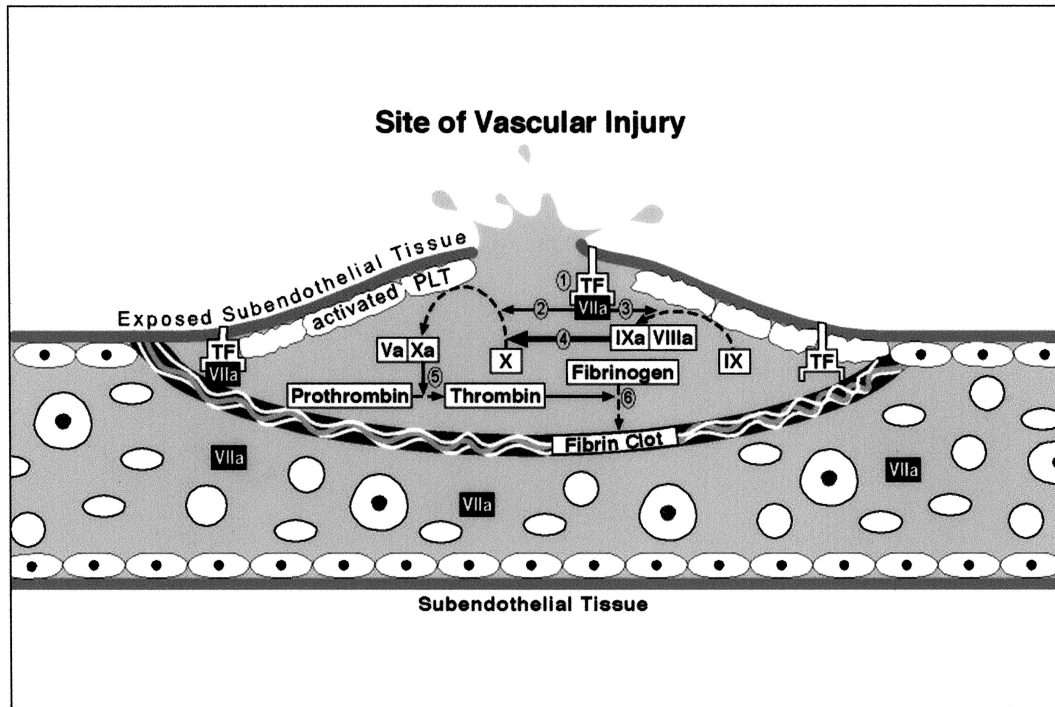
In civilian trauma, hemorrhages are responsible for about 40% of the deaths, but here 65% of the hemorrhagic mortality occurs after admission to hospital.<sup>2</sup> The proportion of hemorrhage-related deaths is in fact higher if mortality caused by organ failure is added (60% of late mortality or 10–20% of all deaths).<sup>2</sup>

Most trauma patients who develop massive, life-threatening bleeds have a combination of coagulopathic diffuse bleed, together with bleeding from larger vessels (surgical bleed). Although hemostasis of the surgical bleed can be performed by the surgeon (except for bleeding of some vessels that may be masked by the diffuse bleed), ability to control the diffuse bleed is limited, and in many cases not feasible. Introduction of drugs that could control this component of the bleed may reduce mortality and morbidity. Coagulopathy is common in trauma, and its degree correlates with the severity of injury.<sup>3,4</sup> The causes for coagulopathy are as follows:

1. Consumption coagulopathy: exposure of subendothelial TF at the site of injury initiates the coagulation cascade at this site, which in turn activates the fibrinolytic system that degrades fibrin clots, but also breaks down fibrinogen and other hemostatic factors, such as factor VIII and von Willebrand factor. In the case of extensive injury, these processes cause a DIC-like picture,<sup>5,30</sup> with decrease of coagulation factors and platelets, and increase in activation markers of coagulation and fibrinolysis (such as thrombin-antithrombin complexes, D-dimers, fibrin split products, fibrinopeptide A and B, and prothrombin fragment 1+2<sup>5,30</sup>). It is important to emphasize that these changes do not represent a true DIC, since there is no diffuse intravascular coagulation or formation of microthrombi, but rather consumption coagulopathy causing hemorrhagic diathesis.
2. Excessive fibrinolysis: contradicting data exist concerning response of the fibrinolytic system to trauma: some claim increased fibrinolysis,<sup>7</sup> whereas others claim decreased fibrinolysis.<sup>31</sup> Extensive tissue damage increases both TPA and plasminogen activator inhibitor type 1,<sup>32</sup> and the overall response of fibrinolytic activity is not clear. However, in severe trauma, the increase of TPA is far higher than plasminogen activator inhibitor type 1 in the initial hours;<sup>32</sup> thus, some patients may suffer hyperfibrinolysis, causing further degradation of coagulation factors.

3. Dilutional coagulopathy: massive hemodilution caused by infusion of large volumes of crystalloids and colloids is not a rare event in wounded soldiers, especially if evacuation is delayed. This further decreases the level of coagulation factors and platelets.<sup>29</sup> Some resuscitation fluids, such as HES preparations, further compromise coagulation,<sup>9</sup> potato-origin HES being worse than corn-origin HES.<sup>10</sup> High-molecular-weight HES formulation ( $M_r > 400,000$ ) may markedly decrease FVIII von Willebrand level far below the dilution level, causing an acquired von Willebrand syndrome.<sup>11</sup>
4. Hypothermia is frequently observed in trauma victims, causing slowing of enzymatic processes of the coagulation cascade and impaired platelet function.<sup>14–17,33</sup> In most centers, coagulation tests are performed at 37°C and the coagulopathic effect of hypothermia is underestimated.
5. Multitransfusion syndrome: administration of large volumes of stored blood, depleted of clotting factors and viable platelets, causes marked coagulopathy. Transfusion of fresh frozen plasma and cryoprecipitate in sufficient quantities may restore the level of coagulation factors, but platelet function is restored to a lesser extent by administration of platelet concentrates. The reason for this is that during preparation of platelet concentrates, the largest and most active platelets are sedimented together with the red blood cell fraction, leaving the smaller and less active platelets in the transfusion bag.<sup>34</sup> Hence, the correction of platelet function after cardiac surgery by 1 unit of fresh blood is equal to 20 units of platelet concentrates.<sup>35</sup> The bleeding in cardiac surgery patients treated with fresh packed cells after removal of platelet units was significantly less than in those who received the platelet fraction of the same blood units.<sup>34</sup> Therefore, platelet counts in the multitransfused patient do not reflect their real hemostatic function, and the patient may bleed even with a normal platelet count.
6. Metabolic changes, such as acidosis and a high load of blood component citrate, also compromise the coagulation system, especially in the presence of hypothermia.<sup>4,18</sup>

The mechanism of rFVIIa (Fig. 3) suggests its enhancement of hemostasis at the site of injury without inducing a systemic, hypercoagulable state. Naturally occurring FVIIa circulating in small quantities is not biologically active unless bound to TF that is exposed at the site of injury (Fig. 3, step 1). The complex TF-VIIa initiates the coagulation cascade by activating factors X and IX (steps 2 and 3). Activated factor IX forms a complex with its cofactor FVIIIa on the phospholipid membrane of activated platelets adhering to the site of injury, and activates factor X 50-fold faster than the TF-VIIa complex (step 4) (in turn, factor Xa further activates factor VII to VIIa). Factor Xa forms a complex with its cofactor, factor V (also on the phospholipid membrane of activated



**Fig. 3.** The mechanism of action of rFVIIa.

platelets), which activates prothrombin to produce a small amount of thrombin (step 5). At this stage, this small amount is insufficient to convert fibrinogen to a fibrin clot, but further accelerates the coagulation cascade by activating factors V and VIII and additional platelets. After this acceleration, a large amount of thrombin is formed that subsequently changes soluble fibrinogen to insoluble fibrin clots (step 6). Administration of a high dose of rFVIIa results in a huge increase of factor VIIa level, compared with the physiologic state, leading to faster and higher thrombin generation.<sup>27</sup> 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 (“superclot”) compared with normal clots.<sup>36–38</sup> One of the mechanisms for this resistance to fibrinolysis is via activation of thrombin-activatable fibrinolysis inhibitor, which only occurs in the presence of high thrombin concentration.<sup>39</sup>

In vitro experiments, together with animal and clinical studies, support the compartmentalized effect of rFVIIa at the site of injury without systemic activation of coagulation. Supplementation of plasma with rFVIIa to final concentration of 150 IU/mL (which is 50% higher than the level after bolus injection of 120  $\mu\text{g}/\text{kg}$ ), did not cause an increase in free thrombin and factor Xa.<sup>40</sup> Administration of a high dose of rFVIIa caused no significant changes in activation markers of coagulation, either in hemophilia patients<sup>41</sup> or in the swine model of grade V liver damage,<sup>29</sup> and an animal study in a rabbit stasis model of thrombosis reached similar results.<sup>42</sup> Extensive histologic examination of lungs, kidneys, and small

intestine performed in the swine with grade V liver injury treated with 180  $\mu\text{g}/\text{kg}$  of rFVIIa revealed no signs of microthrombi.<sup>29</sup> The typical prothrombin time shortening (to shorter than normal values) after administration of the drug is caused by the presence of TF and phospholipid in the test system, and therefore does not reflect a hypercoagulable state, but rather simulates the process at the site of injury.

Previous clinical experience with rFVIIa supports the hemostatic efficacy and high safety of the drug in patients with hemophilia and other congenital and acquired coagulopathies.<sup>19–24</sup> Serious adverse events occurred in < 1%, with only 0.2% possibly related to thrombotic complications in patients who had other reasons for these complications.<sup>43</sup> A recent survey revealed a low incidence of fatal thromboembolic complications in 4 of 5,522 patients treated with rFVIIa between 1996 and 2000 (unpublished data). Immediate hemostasis was achieved by rFVIIa in patients without preexisting coagulation abnormalities suffering intractable bleeds, as in cardiac<sup>44</sup> and abdominal surgery,<sup>45,46</sup> as well as a significant decrease in bleeding in cases where the drug was given prophylactically before prostatectomy<sup>47</sup> and liver transplantation (unpublished data). No increased thromboembolic complications were observed in these patients (a total of 30), which further supports the high benefit/risk ratio of the drug. In a group of 10 patients treated for subarachnoid hemorrhage, one developed brain infarction,<sup>48</sup> a well-recognized complication that is probably caused by vasospasm. This raises the possibility that subarachnoid hemorrhage may not be an appropriate indication, although wider experience is required. Recombinant factor VIIa could potentially induce thrombotic complications in situations where

large amounts of TF are exposed to flowing blood, such as in gram-negative sepsis, in which endotoxin (lipopolysaccharide) activates circulating monocytes to express TF on the cell membrane.<sup>49</sup> Tissue factor is also present at high levels in all cellular elements and extracellular lipid core of atherosclerotic plaques.<sup>50,51</sup> Thus, TF may come into contact with circulating blood when the plaque ruptures which, most probably, is the mechanism for acute myocardial infarctions observed in rare cases after administration of rFVIIa.<sup>52</sup> Since the mean age of civilian trauma victims is about 36 years,<sup>2</sup> and in military trauma the victims are even much younger, this risk seems to be negligible. However, the use of the drug in elderly patients with predisposing cardiovascular disease should be limited to desperate cases.

Until recently, conditions with activation of coagulation were considered as contraindicated for rFVIIa (summary of manufacturer's product characteristics) and, because trauma with or without DIC fits this criterion, the use of the drug was avoided in such patients. As previously elucidated, coagulation abnormalities resembling DIC in trauma patients reflect consumption coagulopathy—activation and consumption of platelets and coagulation factors at the site of tissue damage, without the diffuse intravascular microthrombi component seen in true DIC. In fact, most patients with severe trauma suffer at the early stage from hemorrhagic diathesis rather than hypercoagulation; therefore, the contraindication mentioned is not applicable to these patients. The absence of clinical evidence of thromboembolic complications in our patients, who had coagulation abnormalities “resembling DIC,” as well as the absence of microthrombi in the aforementioned swine with grade V liver injury who had a similar coagulopathy,<sup>29</sup> supports this assumption.

The dose of rFVIIa in trauma needs further evaluation in larger studies. A median of 2 doses (range, 1–2.75 doses) with a total of 120  $\mu\text{g}/\text{kg}$  (range, 120–212  $\mu\text{g}/\text{kg}$ ) was required to achieve hemostasis in our seven cases. As low as a single dose of 40  $\mu\text{g}/\text{kg}$  was sufficient to control the bleeding in patient 5, but 120  $\mu\text{g}/\text{kg}$  had no effect in two (patients 3 and 7), who required two additional doses (Table 3) before hemostasis was reached (the effect was determined by observation in the operating room). The variations probably stem from the different state of the coagulation system: *in vitro* experiments have shown that a higher concentration of rFVIIa is required to induce thrombin burst in the presence of severe quantitative or qualitative coagulation factors and platelet defects.<sup>27</sup> Such patients may require higher doses of rFVIIa or coagulation factors and platelet supplementation. Patient 7 had markedly compromised hemostasis with a platelet count of 30,000; therefore, the first dose had no effect. The second dose, given after administration of additional blood components with platelet counts of 128,000, shortened prothrombin time to below normal values, and partially corrected activated partial thromboplastin time, but had not

reached a sufficient clinical effect, which suggests that the number of viable platelets was still low. Therefore, the third dose was postponed until the patient received 2 units of “fresh” blood (unrefrigerated, but virally tested and irradiated) that contained viable and active platelets. “Fresh,” unrefrigerated blood alone can reduce bleeding in multitransfused trauma patients,<sup>53</sup> but in this patient its administration had no effect on hemostasis until administration of the third dose. No firm recommendation can be made with regard to dosage, and our current protocol is derived from the standard dose in hemophilia (around 90  $\mu\text{g}/\text{kg}$ ), which we think should be increased in such desperate cases to an initial dose of about 120  $\mu\text{g}/\text{kg}$ . This is followed by a second dose of 60 to 90  $\mu\text{g}/\text{kg}$ , if hemostasis is not achieved within 20 minutes. Should the second dose not be effective, supplementation with viable platelets (from plateletpheresis or unrefrigerated, virally tested blood units) is given before the third dose, regardless of the platelet counts. Higher initial doses may overcome coagulation abnormalities and reduce the need for additional doses or blood components, but further studies are required to evaluate the safety and efficacy of higher doses. Concomitant use of fibrinolytic inhibitors is avoided unless there is marked fibrinolysis and no response to rFVIIa.

All patients received FVIIa after transfusion of numerous packed cells and other blood components, when all conventional treatment modalities failed and fatal outcome seemed inevitable. Surgical hemostatic measures such as cauterization, ligation, packing, and even argon beam (patient 3) were used concomitantly with rFVIIa. However, these measures were ineffective before, but achieved hemostasis only after administration of rFVIIa, which suggests a role for rFVIIa in the hemostatic process. Fibrin glue was only used after hemostasis was achieved. Fibrin glue is ineffective during massive bleeds, since it is washed away by the flowing blood and its role in such cases is to prevent bleeding recurrence. The rationale for addition of fibrin glue to rFVIIa is the short half-life of the latter (about 2 hours), which may expose the patient to the risk of rebleeding when the effect is over. This theoretical risk may not be real, since the formation of a strong and resistant clot (“superclot”) by rFVIIa may prevent rebleeding, but more experience is required to evaluate this assumption. Earlier treatment with rFVIIa may prevent deterioration of the patient's condition and reduce bleeding-related mortality and morbidity, as well as complications related to massive transfusions, but this remains to be proven in larger studies. The present report of a small number of anecdotal cases is by no means conclusive, but raises the possibility that rFVIIa may play a beneficial role as an adjunctive, hemostatic measure in addition to the conventional surgical hemostatic techniques in hemorrhage control in trauma patients, and deserves further controlled animal and clinical studies.

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## DISCUSSION

**Dr. John Holcomb** (Houston, Texas): Dr. Martinowitz and colleagues have presented the first series of five cases documenting the use of factor VIIa in nonhemophilic trauma patients with significant acquired coagulation disorders. This report complements their activities in nontrauma patients with or without hemophilia. Furthermore, Dr. Martinowitz and I recently collaborated on an animal study evaluating the effectiveness of the drug.

Recombinant factor VIIa is a Food and Drug Administration–approved drug for use in hemophiliacs and has been safely used since described by Dr. Hedner in 1988. Although unfamiliar to most surgeons, in hemophilic patients it is considered standard care and safe enough even for home use, as Dr. Martinowitz has said. What is new is that in this series the drug was used as an adjunct to control the bleeding in a group of trauma patients with an acquired coagulopathy that have a very high mortality.

Intravenous forms of hemorrhage control in trauma patients have either been ignored or significantly underused. In conjunction with good surgical technique, damage control

maneuvers, and the other hemostatic drugs and devices that are being developed, I think that this site-specific intravascular approach to hemostasis is right on target.

These results are exciting in their promise; however, I am not sure that this study really delivers more than just a hint of what may come later. I have several comments followed by several more questions.

The comments are that this was a short series of case reports and, therefore, there was no control group, and thus we really don't know if the patients would have survived with or without drug treatment. There is no clear uniform indication for treatment and there was a highly variable drug regimen used. There is no clear indication that there was or was not an increased incidence of diffuse intravascular clotting, deep venous thrombosis, pulmonary embolism, myocardial infarction, or stroke.

Now, the questions. Dr. Martinowitz, how do you monitor this drug in this clinical use, and is there a laboratory value that correlates with clinical efficacy? In the two patients that lived, were their complications related to drug use?

Third, what exactly were these patients bleeding from; large main vessels, small vessels, or microvascular bleeding secondary to the coagulopathy? Fourth, in your clinical experience, how fast do you see a clinical effect after injection of the drug?

Significant blunt tissue or brain injury may release tissue factor into the bloodstream. If the drug is used in this type of patient, will intravascular clotting result?

Does the normalization of prothrombin time despite the hypothermia equate to clinical effectiveness? You alluded to this in your discussion, but can you elaborate on how you are currently using the drug in Israel?

A word of caution: this drug may become very useful in patients who undergo massive transfusions; however, the potential risk of diffuse intravascular coagulation should not be ignored and deserves further study.

Saying that, I firmly believe that prospective controlled trials are required to delineate the true risk/benefit ratio of this drug. From these studies, I think we will answer many of the previously asked questions.

In closing, this drug holds great promise. The intravascular approach with site-specific drugs for hemorrhage control complements the methods that our group and others have been studying over the last several years.

One can envision that at some time in the future a combination of these advanced hemorrhage control techniques will be routinely used by surgeons and prehospital personnel. I would like to thank the Association for the privilege of new membership and the opportunity to discuss this interesting and very worthwhile study.

**Dr. Kenneth L. Mattox** (Houston, Texas): Six surgeons died here in San Antonio 150 years ago at the massacre at the Alamo. Unknown to most people in this audience, there was one survivor. There were several survivors, but one of the survivors of the Alamo was a surgeon by the name of Dr.

Sullivan. Had I been Dr. Sullivan and you had a supply of rFVIIa and we were in the United States without a phase I or II study and you could have given me, Dr. Sullivan, all of the rFVIIa I wished, would you have given it to me to save more people at the Alamo with the knowledge base that you have?

**Dr. Martin A. Schreiber** (Houston, Texas): Dr. Martinowitz, Dr. Holcomb raised concerns about patients with soft tissue injuries and brain injuries where a large amount of tissue factor may be exposed. What about patients with long bone fractures and the potential for fat embolism syndrome where these patients have diffuse thrombosis as well?

**Dr. Uri Martinowitz** (closing): Thank you, Dr. Holcomb. Yes, I agree that it is not a controlled trial and has a limited validity. However, I believe that we can learn a valuable lesson from these cases: until our first trauma case, nobody was even daring to think to use rFVIIa outside of hemophilia; but the first case that was reported in newspapers around the world, quoted in *Lancet News* and published as a fast track publication in the *Lancet*, raised an immediate interest.

Shortly thereafter, the surgeon general sent me to San Antonio to start animal studies on the efficacy and safety of the drug on a swine trauma model. Two weeks later, John Holcomb and his team came to my institution to continue the study (results reported in the meeting by John Holcomb).

The animal study together with the present cases support the compartmentalized action of rFVIIa at the site of injury rather than systemic activation of the coagulation cascade. It raises the possibility that the drug may have a beneficial role in hemorrhage control in trauma and that the subject deserves further controlled animal and clinical trials.

Now, how do we monitor? The best monitoring is to look at the patient and see if the bleeding ceased. Presently, there is no laboratory test that correlates directly to clinical response. We usually measure prothrombin time, and typically it is shortened to below the normal range (to 7–9 seconds). However, this is a laboratory effect that only shows that the patient has received rFVIIa, but does not predict or prove a clinical effect.

Dr. Mattox, the answer is not easy; this is a complicated ethical problem. Our first soldier was very close to exsanguination, but my young on-call physician, who was present in the operating room and who was convinced that this was the

patient's only chance to survive (at that stage, the surgeons had left the operating room to tell the parents that the patient was dead!) refused to inject the drug.

This is not an off-label use but a treatment against a written contraindication, where the patient's chance to survive seems to be close to zero, and it may be inconvenient if the patient dies immediately after the injection and the autopsy will show diffuse thrombosis—you may be sued and even lose your license. However, can you leave a young soldier to die when you are convinced—from a deep knowledge of the literature and the mechanism of action—that you have something that may save his life? Can you live with the idea that a young man died because you are coward?

In any case, I had to rush to the operating room and inject the drug myself. The anesthesiologist wrote in the chart: “Dr. Martinowitz himself is injecting rFVIIa on his own responsibility.” I had a few moments of cold sweat. The next morning, in the hematology round, all 22 of our hematologists admitted that they would be afraid. But surgeons have more guts, and I am sure many would do the same.

Dr. Schreiber, I don't know the answer. Theoretically, in all these cases, when you have a release of tissue factor, you have at the same time a release of the tissue factor pathway inhibitor that may inhibit it, but it has to be investigated. At least one of our patients (our doctor that fell from a building) had multiple fractures and multiple organ damage with brain contusion and hemorrhage, and there were no thrombotic complications.

In Thailand, they gave it to three patients with Dengue fever with stormy DIC where tissue factor is known to be expressed on the surface of monocytes, and they saved the life of the patients without evidence of thrombotic complication. We gave it to two patients with gram-negative sepsis with DIC (where tissue factor is known to be present on monocytes) and nothing happened. We didn't see thromboembolic complications. However, we may see more thrombotic side effects with wider use of the drug. According to a recent survey of the company, among about 5,500 patients (mostly hemophiliacs and a few dozen nonhemophiliacs), the incidence of fatal thromboembolic complications was less than 1%. So if you have a case that is exsanguinating in your hands, the risk seems negligible.