Recombinant Factor VIIa as Adjunctive Therapy for Bleeding Control in Severely Injured Trauma Patients: Two Parallel Randomized, Placebo-Controlled, Double-Blind Clinical Trials

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Background: Uncontrolled bleeding is a leading cause of death in trauma. Two randomized, placebo-controlled, double-blind trials (one in blunt trauma and one in penetrating trauma) were conducted simultaneously to evaluate the efficacy and safety of recombinant factor VIIa (rFVIIa) as adjunctive therapy for control of bleeding in patients with severe blunt or penetrating trauma.

Methods: Severely bleeding trauma patients were randomized to rFVIIa (200, 100, and 100 µg/kg) or placebo in addition to standard treatment. The first dose followed transfusion of the eighth red blood cell (RBC) unit, with additional doses 1 and 3 hours later. The primary endpoint for bleeding control in patients alive at 48 hours was units of RBCs transfused within 48 hours of the first dose.

Results: Among 301 patients randomized, 143 blunt trauma patients and 134 penetrating trauma patients were eligible for analysis. In blunt trauma, RBC transfusion was significantly reduced with rFVIIa relative to placebo (estimated reduction of 2.6 RBC units, $p = 0.02$), and the need for massive transfusion (>20 units of RBCs) was reduced (14% vs. 33% of patients; $p = 0.03$). In penetrating trauma, similar analyses showed trends toward rFVIIa reducing RBC transfusion (estimated reduction of 1.0 RBC units, $p = 0.10$) and massive transfu-sion (7% vs. 19%; $p = 0.08$). Trends toward a reduction in mortality and critical compli-cations were observed. Adverse events in-cluding thromboembolic events were evenly distributed between treatment groups.

Conclusion: Recombinant FVIIa re-sulted in a significant reduction in RBC transfusion in severe blunt trauma. Simi-lar trends were observed in penetrating trauma. The safety of rFVIIa was estab-lished in these trauma populations within the investigated dose range.

Key Words: Trauma, Blunt trauma, Penetrating trauma, Recombinant factor VIIa, Hemorrhage, Coagulopathy, Blood transfusion, Massive transfusion.

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Trauma is a large burden on society, with almost 1 in 10 deaths worldwide being attributable to traumatic injury.[1] Trauma is also a disease of the young, mainly affecting people between 15 and 40 years of age. Uncontrolled bleed-ing is a leading cause of death in trauma. In civilian and in military trauma, exsanguination accounts for approximately 40% of mortality.[2,3]

Coagulopathy is a major contributing factor to bleeding-related mortality even after achieving surgical control of the hemorrhage in trauma patients, particularly when associated with metabolic acidosis and hypothermia, often referred to as the "lethal triad."[4,5] Additional factors contributing to coagu-lopathy in trauma patients are hemodilution and platelet dys-function resulting from massive blood transfusion or fluid resuscitation.[6] Standard adjunctive therapy to surgical control of bleeding has hitherto aimed at correcting the acidosis and hypothermia while transfusing blood products. Nonetheless, fresh frozen plasma, cryoprecipitate, and platelets often fail to control coagulopathy, resulting in exsanguination or massive transfusion. Treating the coagulopathy would potentially re-duce blood loss, prevent exsanguination, reduce the shock load, and thereby reduce the risk of death. Reduction of transfusion requirements might also have indirect additional benefits, because blood transfusion is associated with late complications and has been found to be an independent risk factor for development of infections[7] and multiple organ failure (MOF).[8,9]

Recombinant activated coagulation factor VII (rFVIIa, NovoSeven, Novo Nordisk A/S, Bagsvaerd, Denmark) is currently approved in North America and most other regions

of the world for the treatment of bleeding in hemophilia patients with inhibitors and in the European Union also for the treatment of patients with acquired hemophilia, FVII deficiency, and Glanzmann thrombasthenia who are refractory to platelet transfusions. Although investigational use of rFVIIa in trauma patients has shown promising results, the data supporting the use of rFVIIa within trauma have been limited to case series and anecdotal reports.[10–13] We therefore conducted two large, randomized, placebo-controlled, double-blind clinical trials to evaluate the efficacy and safety of rFVIIa as adjunctive therapy for control of bleeding in patients with severe blunt or penetrating trauma.

PATIENTS AND METHODS
Patients

Patients with severe blunt and/or penetrating trauma were enrolled at 32 hospitals throughout Australia, Canada, France, Germany, Israel, Singapore, South Africa, and the United Kingdom (see Appendix). Patients with severe trauma were eligible for inclusion. For the purpose of this trial, severely traumatized patients were defined as those suffering physical injury requiring 6 units of red blood cells (RBCs) within 4 hours of admission. Patients had to be of known age greater than or equal to 16 years (or legally of age according to local law) and younger than 65 years. Key exclusion criteria consisted of cardiac arrest prehospital or in the emergency or operating room before trial drug administration; gunshot wound to the head; Glasgow Coma Scale score < 8 unless in the presence of a normal computed tomographic scan; base deficit of > 15 mEq/L or severe acidosis with pH < 7.0; transfusion of 8 units or more of RBCs before arrival at the trauma center; and injury sustained ≥ 12 hours before randomization. The study protocol was approved by the ethics committee of each participating institution, and the trial was conducted according to Good Clinical Practice standards.[14] Informed consent was obtained from all patients or, where applicable, from a legally authorized representative. Because of the emergency conditions and the possible absence of relatives at enrollment into the trial, waived informed consent was authorized by the ethics committees. However, whenever a patient was included without written informed consent, such consent was promptly sought from a legally authorized representative and subsequently from the patient. Adequate confirmation of consent was not obtained for six patients, and their data were excluded from analysis.

Trial Design and Procedures

Two parallel randomized, placebo-controlled, double-blind trials (one in blunt trauma and one in penetrating trauma) were conducted simultaneously. Patients were evaluated for inclusion into the trials at admission to the trauma center, and eligible patients were assigned to either the blunt or penetrating trauma trial (patients who had incurred both blunt and penetrating trauma were considered as blunt trauma patients). On receiving 6 units of RBCs within a 4-hour period, eligible patients within each trauma population were equally randomized to receive either three intravenous injections of rFVIIa (200, 100, and 100 μg/kg) or three placebo injections. The first dose of trial product was to be administered immediately after transfusion of the eighth unit of RBCs, given that the patient—in the opinion of the managing physician—would require additional transfusions. The second and third doses followed 1 and 3 hours after the first dose, respectively. Trial product was administered in addition to standard treatment for injuries and bleeding at the participating hospitals, and no restrictions were imposed on procedures deemed necessary by the attending physician, including surgical interventions and resuscitation strategies. However, before patient enrolment, each participating trauma center had or developed transfusion guidelines that were generally in line with the transfusion guidelines provided in the study protocol.

Patients were monitored closely during the 48-hour period after the first dose of trial product. This included recording transfusion and infusion requirements, adverse events, and surgical procedures. Blood was drawn at frequent intervals (0, 1, 4, 8, 12, 24, 36, and 48 hours after the first dose of trial product) to evaluate changes in coagulation and blood biochemistry parameters. Local diagnostic procedures were followed in case of clinical symptoms of thromboembolic events. Mortality, time on the ventilator, time in the intensive care unit (ICU), and serious adverse events including predefined critical complications (MOF and acute respiratory distress syndrome [ARDS]) as reported by the trial sites were recorded until day 30. As guidance for the reporting of ARDS and MOF, ARDS was defined according to the criteria proposed by the American-European Consensus Conference on ARDS[15] and the following definitions on cut-off values of organ dysfunction based on the Denver MOF scale[16] were provided: respiratory, ARDS score > 5; renal, creatinine > 1.8 mg/dL; hepatic, bilirubin > 2.0 mg/dL; and cardiac, minimal inotropes. An independent data safety monitoring board was established to perform ongoing safety evaluation.

Endpoints

To assess the hemostatic effect of rFVIIa, the primary endpoint was the number of RBC units (autologous RBCs, allogeneic RBCs, and whole blood) transfused during the 48-hour period after the first dose of trial product. Outcome of therapy was further assessed through requirement for other transfusion products, mortality, days on the ventilator, and days in the ICU. Safety outcomes comprised frequency and timing of adverse events, and changes in coagulation-related laboratory variables (activated partial thromboplastin time, platelets, fibrinogen, D-dimer, antithrombin III, prothrombin fragments 1 and 2, and thrombin-antithrombin complex). Because of the bimodal distribution of survival in a trauma population, mortality as an endpoint presents analytic challenges. Therefore, in addition, we studied a composite endpoint of death and critical complications (MOF and ARDS)

as previously suggested.[17] Safety reporting on MOF and ARDS was based on prespecified definitions provided in the study protocol.

Statistical Analysis

We calculated sample size according to the transfusion data of a retrospective study in a severe blunt trauma patient population.[17] Severely traumatized patients with a Glasgow Coma Scale score $\geq$ 8, similar to the patients intended for this trial, received 12.4 units of RBCs in the first 48 hours after trauma (i.e., 4.4 units above the threshold of 8 units established for infusing rFVIIa or placebo in this trial). We proposed that a 60% reduction in the postdose 48-hour RBC requirement from 4.4 units to 1.8 units would be clinically significant, and we calculated that 140 patients would be required in each trauma trial (blunt and penetrating trauma) to detect this difference with 80% power and 5% type I error. The two trauma trials were analyzed separately. Results pertain to all consented and randomized patients who received the trial drug. All analyses were defined a priori, unless otherwise stated.

The total number of RBC units transfused within 48 hours from the start of trial product treatment (the primary endpoint) was compared between treatment groups by use of one-sided Wilcoxon-Mann-Whitney rank test. A one-sided test was selected, as it was not expected that administration of rFVIIa would increase transfusion requirements. Separate analyses on the primary endpoint were performed where patients who died within 48 hours were either excluded or assigned to the worst outcome. Priority was given to the analysis where patients who died within 48 hours were excluded because (1) 48-hour transfusion requirements could not be objectively assessed for patients who were alive for only a few hours and (2) in a large proportion of these patients the severe clinical condition of the patient precluded drug intervention from changing the outcome. The Hodges-Lehmann estimate[18] was used to estimate the difference in RBC transfusions. Total RBC units were calculated as the sum of autologous RBCs, allogeneic RBCs, and whole blood, with each component normalized to standard units of RBCs (equal to a volume of 295 mL with a hematocrit of 63%, as this was the average across all sites).

The Fisher's exact test was used to compare the number of patients requiring massive transfusion (defined post hoc as > 20 units of RBC inclusive of the 8 predose units) and the number of patients experiencing either MOF, ARDS, or death within 30 days. The relative risk reduction of massive transfusion and the number of patients needed to treat (NNT) to avoid one massively transfused patient were calculated with corresponding 95% confidence intervals (CIs). Effects on 48-hour mortality were analyzed using χ^2 testing. Ventilator-free and ICU-free days within 30 days of trial product treatment were analyzed post hoc using the Wilcoxon-Mann-Whitney rank test.

RESULTS

During the period from March 2002 to September 2003, 158 and 143 patients were randomized into the blunt and penetrating trauma trials, respectively. In the blunt trauma trial, 10 patients were withdrawn before receiving trial drug, and waived informed consent was not subsequently confirmed for 5 of the remaining 148 patients who received trial drug, leaving 143 patients eligible for analysis. In the penetrating trauma trial, 8 patients were withdrawn before receiving trial drug, and waived informed consent was not subsequently confirmed for 1 patient, leaving 134 patients eligible for analysis (Fig. 1). Treatment groups were well matched in terms of baseline characteristics within each of the trauma populations (Table 1). Patients were predominantly young male patients and were characterized by being coagulopathic, acidotic, and hypothermic. Causes of penetrating trauma were primarily gunshots (68%) and stab wounds (30%), whereas 77% of blunt trauma was attributable to traffic-related injury. One patient had both blunt and penetrating trauma and was included in the blunt trauma trial.

Transfusion Requirements

The primary endpoint, RBC requirements during the 48-hour observation period after the initial dose of trial product, is shown for patients alive at 48 hours in Figure 2. In patients with blunt trauma, rFVIIa significantly reduced 48-hour RBC requirements by 2.6 units (Hodges-Lehmann estimate) compared with placebo ($p = 0.02$). The need for massive transfusion was reduced from 20 of 61 (33%) patients in the placebo group to 8 of 56 (14%) in the rFVIIa group. This represents a relative risk reduction of 56% (95% CI, 9–79%; $p = 0.03$) (Fig. 3), which translates to an NNT of 5.4 (95% CI, 3–33). In patients with penetrating trauma, no significant effect of rFVIIa was observed with respect to 48-hour RBC requirements with an RBC reduction of 1.0 unit ($p = 0.10$). The need for massive transfusion in penetrating trauma was reduced from 10 of 54 (19%) patients in the placebo group to 4 of 58 (7%) in the rFVIIa group. This represents a relative risk reduction of 63% (95% CI, −12–+88%; $p = 0.08$) (Fig. 3), which translates to an NNT of 8.6. When assigning patients who died to the worst outcome (i.e., highest rank in the nonparametric Wilcoxon-Mann-Whitney rank test), statistical significance was not reached in either trauma population (Table 2). No significant differences between treatment groups were observed in either trauma population with respect to administration of fresh frozen plasma, platelets, or cryoprecipitate (data not shown).

Clinical Outcome and Safety

Results for adverse events, mortality, ventilator-free days, and ICU-free days are summarized in Table 3. Positive trends in favor of rFVIIa were observed for these endpoints, especially those concerning death and critical complications (ARDS and MOF). Survival curves are depicted in Figure 4.

Adverse events occurred at similar frequency and severity between treatment groups. Overall, the adverse event profile was similar between rFVIIa-treated and placebo-treated patients in both trials, and there were no apparent treatment-dependent patterns in the types of adverse events reported. As can be expected in these severely injured patient populations, the three most frequently reported serious adverse events were ARDS, MOF, and sepsis.

A total of 12 thromboembolic adverse events were reported by the investigators during the two trials: 6 in rFVIIa-treated patients and 6 in placebo-treated patients. In patients with blunt trauma, two cases of pulmonary embolism and one subclavian vein thrombosis (after central line placement) were recorded in the placebo group, whereas one jugular vein thrombosis (after central line placement) and one arterial limb thrombosis were recorded in rFVIIa-treated patients. In patients with penetrating trauma, one cerebral infarction and one deep vein thrombosis was noted in each treatment group. In addition, a mesenteric vein thrombosis was recorded in the placebo group and an intestinal infarction (at the site of operation) and an event of phlebothrombosis were noted in the rFVIIa group.

DISCUSSION

In these two trials in severely traumatized patients, we found evidence of the efficacy of rFVIIa as an adjuvant therapy in the management of hemorrhage caused by trauma. Among blunt trauma patients, rFVIIa significantly reduced the need for RBC transfusion and massive blood transfusions. We found similar trends in penetrating trauma patients, without reaching statistical significance. These trials demonstrate that rFVIIa is safe in trauma patients because it not only did not increase the incidence of adverse events, including thromboembolism and systemic coagulation, but was also associated with a trend toward fewer critical complications such as MOF and ARDS.

Assessment of the effect of any hemostatic drug in the setting of major hemorrhage poses significant difficulties in study design. The primary aim of this study was to assess the
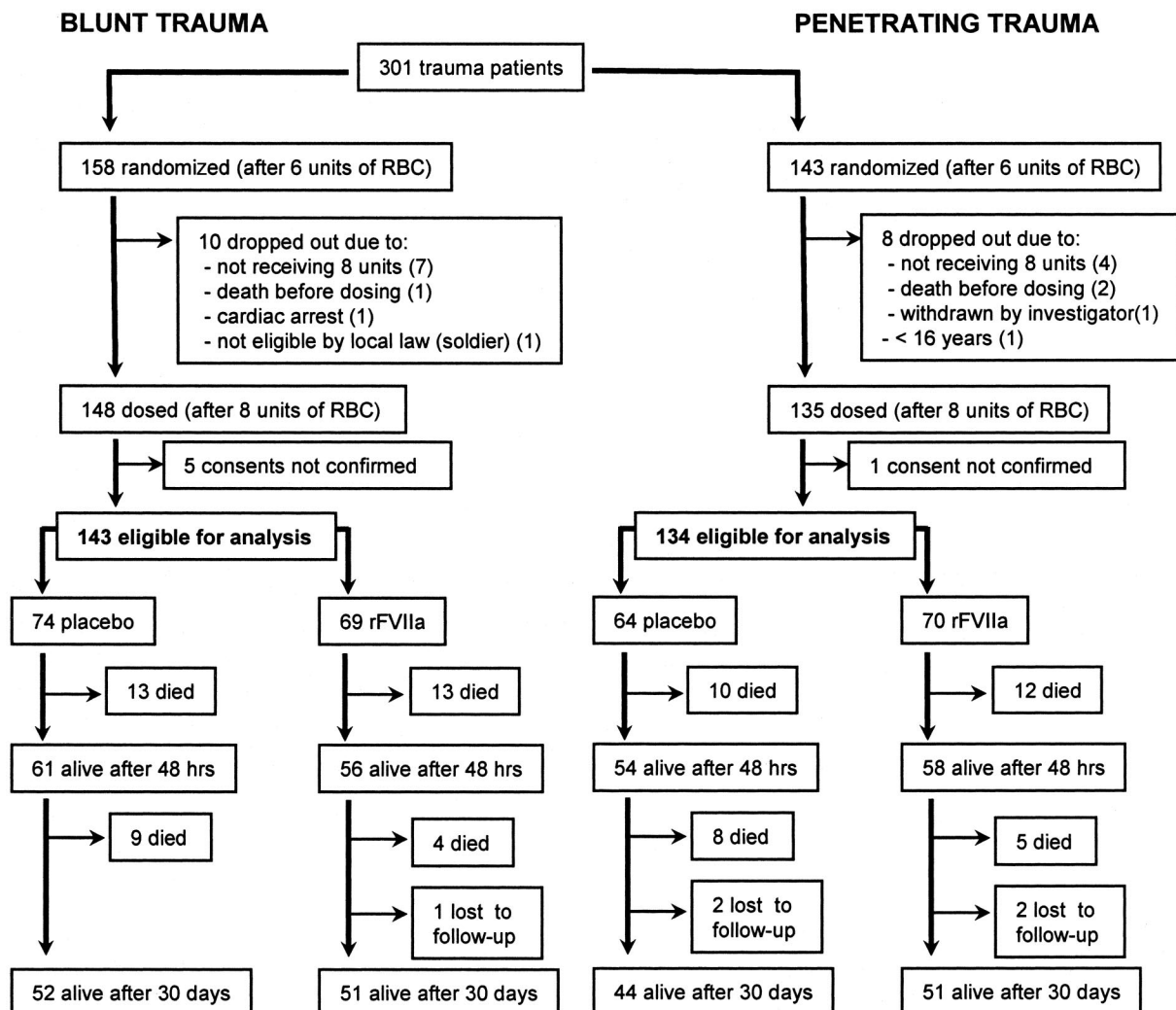

Fig. 1. *Trial profiles.*

Table 1 Baseline Characteristics

Variable	Blunt trauma		Penetrating trauma	
	Placebo (N = 74)	rFVIIa (N = 69)	Placebo (N = 64)	rFVIIa (N = 70)
Male sex	52 (70%)	48 (70%)	60 (94%)	66 (94%)
Age (years)	35 ± 13	33 ± 13	32 ± 10	29 ± 10
ISS	32 ± 12	33 ± 13	26 ± 11	26 ± 15
Number of ISS body regions injured*				
1	4 (5%)	6 (9%)	25 (39%)	21 (30%)
2–3	36 (49%)	29 (42%)	36 (56%)	43 (61%)
>3	32 (43%)	33 (48%)	3 (5%)	6 (9%)
Glasgow Coma Scale[†]				
≤8	8 (11%)	11 (16%)	5 (8%)	4 (6%)
9–12	18 (24%)	11 (16%)	8 (13%)	6 (9%)
13–15	48 (65%)	47 (68%)	51 (80%)	60 (86%)
Time from injury to hospitalization				
0–1 hours	23 (31%)	20 (29%)	33 (52%)	34 (49%)
1–2 hours	26 (35%)	23 (33%)	17 (27%)	15 (21%)
2–4 hours	10 (14%)	12 (17%)	3 (5%)	3 (4%)
>4 hours	6 (8%)	3 (4%)	1 (2%)	3 (4%)
Unknown	9 (12%)	11 (16%)	10 (16%)	15 (21%)
Time from hospitalization to trial product dosing				
0–2 hours	14 (19%)	16 (23%)	8 (13%)	9 (13%)
2–4 hours	23 (31%)	19 (28%)	22 (34%)	25 (36%)
4–6 hours	17 (23%)	13 (19%)	16 (25%)	15 (21%)
>6 hours	16 (22%)	19 (28%)	16 (25%)	19 (27%)
Unknown	4 (5%)	2 (3%)	2 (3%)	2 (3%)
Vital signs[◊]				
Systolic arterial blood pressure (mmHg)	111 ± 27	102 ± 24	114 ± 25	111 ± 24
Body temperature (°C)	35.3 ± 1.6	35.2 ± 1.6	35.2 ± 1.2	35.3 ± 1.3
Biological variables[◊]				
Hemoglobin (g/dL)	9.1 ± 2.8	9.3 ± 2.5	8.8 ± 3.0	8.5 ± 2.8
pH	7.26 ± 0.11	7.24 ± 0.13	7.28 ± 0.11	7.27 ± 0.09
aPTT (seconds)	51 ± 28	49 ± 24	54 ± 26	49 ± 27
PT (seconds)	19 ± 5	20 ± 8	22 ± 6	18 ± 5

Data intervals refer to means ± SD. Other data refer to number (and percentage) of patients.
* Body regions as defined for the Injury Severity Score.
[†] Prehospital assessment if available; otherwise screening assessment.
[◊] Measurements obtained at screening.
aPTT, activated partial thromboplastin time; PT, prothrombin time.

impact of rFVIIa on bleeding, but because it is difficult to measure the volume of blood loss accurately in trauma patients, we chose to assess the number of RBC units transfused as a surrogate marker of the magnitude of the bleeding and the response to the intervention. In the analysis of the primary endpoint, all RBC components were normalized to standard units of RBCs to account for possible differences between sites. The estimated reduction of 2.6 RBC units per patient seen in the blunt population is encouraging. However, the distribution of RBC requirements was skewed, and this estimated reduction does not fully reflect the 56% reduction in the number of blunt trauma patients receiving massive transfusion (receipt of >20 units of RBCs). A recent retrospective study in approximately 5,000 trauma patients found mortality to be significantly correlated with the amount of RBCs transfused.[19] In that study, mortality was increased from 30% to more than 50% in patients receiving more than 20 units of

RBCs relative to patients receiving 11 to 20 units, independent of the severity of injury. This highlights the importance of the observed reduction in massive transfusion in the present study. It is furthermore noteworthy that the hemostatic effect of rFVIIa was achieved in trauma patients who were characterized by being hypothermic, which invariably complicates severe hemorrhage.[20,21]

Statistical significance was not reached on the RBC transfusion endpoints in the penetrating trauma population. This is likely explained by the higher proportion of surgically treatable bleeding in penetrating trauma. Furthermore, blunt trauma patients required nearly twice as many RBC units than penetrating trauma patients, and the power to detect a reduction in RBC requirement was consequently lower for the penetrating trauma population.

The present trials demonstrated a good safety profile of rFVIIa in a high-risk trauma population, because no increased

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BLUNT TRAUMA PENETRATING TRAUMA
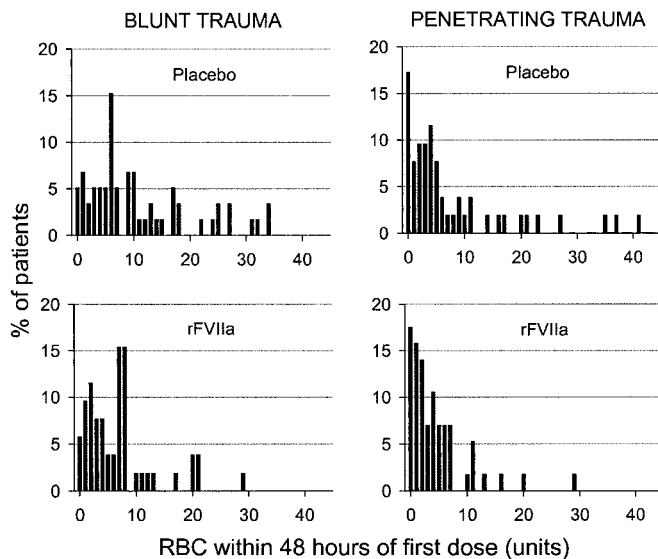
Fig. 2. *Distribution of RBC requirements within the 48-hour observation period after the first dose of trial product. Data for patients who died within 48 hours are excluded.*

risk of adverse events including thromboembolic adverse events and no indication of induction of systemic coagulation was observed. This result is highly relevant from a clinical perspective because trauma patients are known to be at high risk of thromboembolic events.[22] Moreover, microthrombi-generated ARDS and MOF was previously a potential issue when dosing rFVIIa because of the concern for extensive and systemic activation of the tissue factor-dependent coagulation pathway in plasma.[23–26] Our results clearly do not give cause for such a concern. On the contrary, complications theoretically associated with microthrombus generation such as MOF and ARDS tended to be less frequent in rFVIIa-treated patients. The absence of rFVIIa-induced systemic activation of

Fig. 3. *Massive transfusion. Percentage of patients alive at 48 hours receiving more than 12 units of RBCs within 48 hours of the first dose, which equals greater than 20 units of RBCs inclusive of the 8 predose units.*

the coagulation system may be explained by the mode of action of rFVIIa, confining propagation of coagulation to the site of blood vessel damage.[27,28] Given this hypothesized localized effect of rFVIIa, an increased incidence of thromboembolic complications or intravascular coagulation after dosing with rFVIIa would not be expected.[29,30]

The trends toward improved clinical outcome (as reflected by the incidence of critical complications, ventilator requirement, and days in ICU) are encouraging and collectively point toward a possible benefit of rFVIIa. It should be emphasized that the studies were not powered for these endpoints. Two mechanisms may account for the trends toward improved clinical outcome with rFVIIa. First, and as a direct effect of rFVIIa, reduced severity of hypovolemic shock and hypoperfusion could be an explanation for the reduction in the incidence of organ failure.[31,32] Second, and mediated indirectly through the reduction in RBC transfusion, rFVIIa may contribute to a reduction in the late complications, as blood transfusion previously has been identified as a consistent risk factor for postinjury MOF and ARDS,[8,9] and a clear dose-dependent correlation between RBC transfusion and postinjury infection has been observed in a prospective study in approximately 1,500 trauma patients.[7]

Some limitations of the study should be noted. First, as the majority of blunt trauma patients were still in the hospital at the end of the 30-day follow-up period, the effect of treatment on days in ventilator dependency and hospitalization requirement could have been more optimally assessed if the observation period had been extended beyond 30 days. Second, data on thromboembolic complications were collected through adverse event reporting only, and Doppler examination was not systematically performed across trial sites. Underreporting of asymptomatic thromboembolic events is likely to explain the apparent low overall incidence of thromboembolic complications in this patient population, where thromboembolic adverse events were recorded for 4% of all patients. Third, the selection criteria were specifically targeted at severely bleeding trauma patients who had already been given 6 units of RBCs within a 4-hour period at the time of randomization. Although a selected trauma population, we believe that this constitutes the subgroup of trauma patients most likely to benefit from rFVIIa treatment. Including patients too early in the course of treatment might have resulted in too many patients with no therapeutic need for a hemostatic agent (i.e., patients in whom surgical hemostasis would be obtained satisfactorily with conventional treatment). In contrast, including patients too late would include too many patients in whom treatment would be futile because of surgically uncontrollable bleeding and irreversible hemorrhagic shock. Fourth, bias in investigator assessments might have been introduced in cases where routine monitoring of prothrombin time could have potentially revealed whether a patient received rFVIIa or placebo. Because of the emergency medical nature of the trial population and the requirement of adherence to protocol-defined transfusion guidelines, we
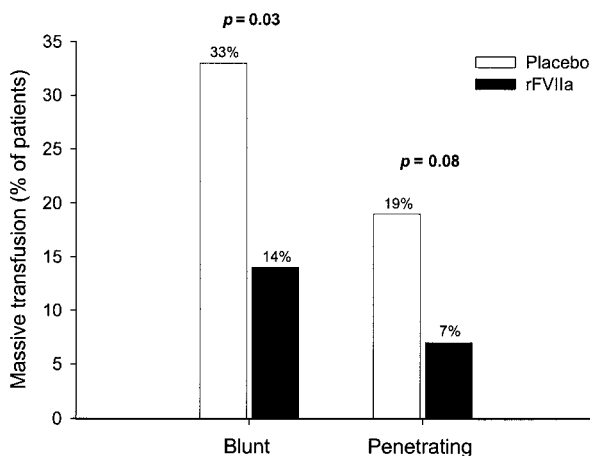
Table 2 Total RBC Transfusions (Units) During 48 Hours After First Dose of Trial Drug

	Placebo		rFVIIa		Estimated RBC reduction with 90% CI*	$p^†$
	N	Median (range)	N	Median (range)		
Blunt		N = 74		N = 69		
Alive at 48 h	59	7.5 (0–35)	52	7.0 (0–29)	2.6 [0.7;4.6]	0.02
All patients	72	7.2 (0–35)	64	7.8 (0–48)	2.0◊ [0.0;4.6]	0.07◊
Penetrating		N = 64		N = 70		
Alive at 48 h	52	4.2 (0–41)	57	3.9 (0–30)	1.0 [0.0;2.6]	0.10
All patients	61	4.8 (0–41)	69	4.0 (0–37)	0.2◊ [−0.9;2.4]	0.24◊

* Hodges-Lehmann point estimate of the shift in transfusion amount from placebo to active group, including 90% confidence interval (CI).
† *p*-value for the one-sided Wilcoxon-Mann-Whitney rank test.
◊ Patients who died within 48 hours were assigned the highest rank.

judge the effect of such bias on trial results to be small if not negligible. Finally, because of the complexity of the study population and the diversity of choices faced by trauma teams in the management of these patients, differences in patient management across regions and trial centers were anticipated despite adherence to the trial protocol. Although there may have been minor differences in local transfusion guidelines between the participating centers, each center essentially acted as its own control inasmuch as patients were equally randomized to rFVIIa and placebo within each center. The potential influence of site-specific effects on the statistically significant RBC reduction was assessed by a parametric analysis of the ranks including a site effect and a site-treatment interaction. The effect of treatment was independent of site (*p* = 0.24 for the site-vs.-treatment interaction). We also examined the effect on outcomes of removing the patients from each of the three largest sites and found no change in the results.

In conclusion, rFVIIa significantly improved bleeding control—as reflected by the decrease in RBC transfusion requirements and the number of patients requiring massive transfusion—in a population of blunt trauma patients with severe bleeding and coagulopathy secondary to the traumatic injury. Similar trends were observed in a population of patients with penetrating trauma. The safety of rFVIIa was established in these two trauma populations for the investigated dose. The incidence of adverse events including thromboembolic events was not increased by rFVIIa dosing in either trial, and no indications of induction of systemic coagulation were observed. Trends toward improved clinical outcome were observed in both trials. Administration of rFVIIa appears to be a promising adjunct to existing therapy within trauma, as it directly targets the coagulopathy, thereby helping to break the vicious cycle of coagulopathy, acidosis, and hypothermia.

ACKNOWLEDGMENTS

Table 3 Adverse Events and Clinical Outcomes

	Blunt trauma			Penetrating trauma		
	Placebo (N = 74)	rFVIIa (N = 69)		Placebo (N = 64)	rFVIIa (N = 70)	
Serious adverse events						
Patients with events	49 (66%)	44 (64%)		36 (56%)	36 (51%)	
Number of events	109	91		76	57	
Thromboembolic adverse events						
Patients with events	3 (4%)	2 (3%)		3 (5%)	4 (6%)	
Number of events	3	2		3	4	
48-hour mortality	13 (18%)	13 (19%)	p = 1.00	10 (16%)	12 (17%)	p = 1.00
30-day mortality	22 (30%)	17 (25%)	p = 0.58	18 (28%)	17 (24%)	p = 0.69
Patients with critical complications within 30 days						
ARDS	12 (16%)	3 (4%)	p = 0.03	5 (8%)	4 (6%)	p = 0.74
MOF	9 (12%)	5 (7%)	p = 0.41	7 (11%)	2 (3%)	p = 0.09
Patients with ARDS, MOF or death	31 (42%)	20 (29%)	p = 0.16	22 (34%)	20 (29%)	p = 0.57
Ventilator-free days* (median and range)	13 (0–29)	17 (0–29)	p = 0.43	20 (0–29)	25 (0–29)	p = 0.21
ICU-free days* (median and range)	8 (0–29)	12 (0–29)	p = 0.31	18 (0–29)	23 (0–29)	p = 0.34

MOF, Multiple organ failure; ARDS, Acute respiratory distress syndrome; ICU, Intensive care unit.
* Within 30 days of trial product treatment.
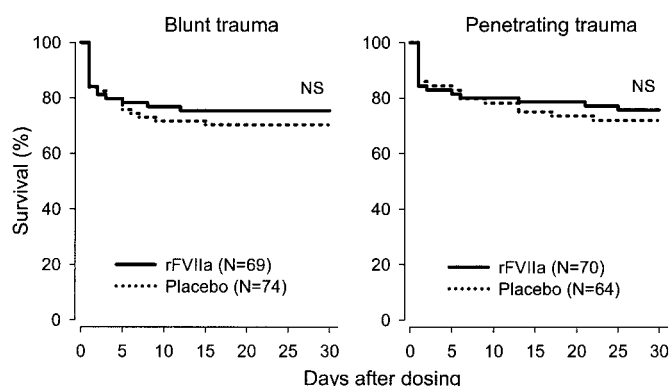
Fig. 4. *Survival curves for blunt and penetrating trauma populations. The difference between treatment groups was not significant (log-rank test, not significant).*

APPENDIX

Data and safety monitoring board: Howard Champion, MD, Annapolis, Maryland (Chairman); Abe Fingerhut, MD, Paris, France; Richard Weiskopf, MD, San Francisco, California; and Miguel A. Escobar, MD, Houston, Texas. Ad hoc member: Torben Soerensen, MSc (statistician), StatCon Aps, Alleroed, Denmark. Sponsor: Novo Nordisk A/S, Bagsvaerd, Denmark. Statistician: Tine Soerensen, MSc, Novo Nordisk, Bagsvaerd, Denmark.

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DISCUSSION

Dr. Howard R. Champion (Annapolis, Maryland): Dr. Mizobata, Peitzman, Croce: I'd like to thank both organizations for the opportunity to discuss this important study on this important drug, which is being used widely in the United States off label as an adjuvant for hemorrhage control in both trauma and transplant surgery.

The authors reported two parallel studies, blunt and penetrating injury, conducted in 32 hospitals in eight countries powered to a specific endpoint which was transfusion reduction.

They concluded that rfVIIa assisted in the control of bleeding and resulted in significant reduction in red blood cell use in blunt trauma. They also allayed the fears of many that microvascular thrombi in non-injured areas of the body could increase the incidences of organ failure in this patient population.

No one should underestimate the difficulty of acute resuscitation research in this high-risk nocturnal population. This study was a formidable and ground-breaking undertaking.

As chair of the Independent Data Safety Management Board, I observed up close and can testify to the steep learning curve engaged in by the researchers, the company sponsor and the contact research organizations. I must congratulate all of those concerned for writing and responding to the many challenges involved in standing up this project. All of us will benefit from absorbing lessons learned in this study.

I have a number of general questions, and I would be remiss if I didn't solicit further comment on the following topics. Uniformity of care is a big issue in research.

In the European Union, multi-institutional trial cancer researchers regard the surgeon as a confounding variable in outcomes research and insist on proctored detailed standardization of the operative surgery. What steps were taken to standardize care? In particular, please comment on transfusion therapy. This could be regarded by many as a confounding variable in this study, and yet, it is used as the primary dependent variable. Is there some comment you'd like to offer of the use of a confounding variable, potentially serious confounding variable as a primary dependent variable?

Can you comment on the indications for this drug, its cost benefit, and whether the dose could be reduced? Could you elucidate as to why the success was seen in the blunt group as opposed to the penetrating group? You made one comment with respect to that, but there are others that you probably would like to make.

Your data supports the conclusion regarding reduction in red cell use. You also conclude that you reduced hemorrhage. Is this a warranted or unwarranted extrapolation or a type 3 error in your conclusions?

Plans are underway to stand up a U.S. study that will convince the FDA to label this drug for use in trauma. How have you advised your U.S. colleagues towards achieving that goal?

This drug is changing our practice. Its value needs to be documented. This study represents an important and critical step in that process. Thank you.

Dr. Charles Lucas (Detroit, Michigan): That was a nice study, Dr. Boffard, but I do have some questions on the physiology of coagulation. We all know that factor VII has the lowest molecular weight, the shortest half-life, and that about 55% of it is present in the interstitial fluid space.

We also know that the influence or the efficacy that factor VII would have on the factor VIII, factor IX complex in the intrinsic pathway or the thrombin in the common pathway is comparable to the influence that a forceful fart by Dr. Erwin Thal would have in a wind storm. (Laughter)

We also know that if you have a heparinized patient where you have blocked both the intrinsic pathway and the common pathway, that you could give the whole wind storm full of factor VII, and you'd never get a clot.

So my first question is: Is this a selective decrease in factor VII which, of course, converts to VIIA intravascularly that you're describing in this patient? If it is a selective decrease, why aren't the patients clotting through the intrinsic and the common pathways? We're getting back to the first year of medical school.

Now, one of the commonly used protocols in patients with multiple transfusions is to initiate fresh frozen plasma and to give two units of fresh frozen plasma for every five transfusions. It's very efficacious. If anyone in this room doesn't use it, I'll tell you over chardonnay tonight why you ought to use it.

Now, in your two groups of patients you should have had about an average of three units of fresh frozen plasma in your two groups of patients who received about 7.5 transfusions of red blood cells.

In your patients who received 20 units of red blood cells, whom are the current patients you're really concerned about, you should have given about eight units of fresh frozen plasma.

So what I want to know is in your dose, which is 600 pg of activated rfVIIa per person, how does that compare to three units of the rfVIIa, which is present in all of us in patients who got 7.5 transfusions and how many micrograms – in other words, how many micrograms of factor VII is present in a unit of plasma? I enjoyed your presentation.

Dr. Errington Thompson (Tyler, Texas): Errington Thompson from Tyler, Texas. I really enjoyed your discussion. It seems that in East Texas, we have a large elderly population that comes to retire there, and for some reason, they all get put on one of the three deadly drugs or one combination of all the three deadly drugs which would include: Plavix, Coumadin and aspirin.

My question to you is in these head injury patients that we see, these elderly patients that fall, what role do you think factor VII would have in these elderly patients? Thank you.

Dr. Steve Ross (Camden, New Jersey): Ross from Camden, New Jersey. As a procoagulant, knowing whether or not we've got increased use of red cells is important, but further, is the impact on the use of other transfusions. Is there data regarding the use of differential use of FFP in these populations or coagulopathy?

Dr. Gregory J. Jurkovich (Seattle, Washington): Jurkovich, Seattle. Ken, just two questions, and they both relate to the matching of the two populations, the placebo and the activated VIIa.

Would you give us insight into the number of operations or the type of operations that were performed within that first window of time between the two groups? Were those different?

Similarly, could you give us some insight into the type of injuries that occurred such as AIS scores or specific organ injury body cavities between the two groups? Was there any difference in that part of their population, and which parts of the body were injured? Thank you.

Dr. Mauricio Lynn (Miami, Florida): Mauricio Lynn from Miami. First of all, I wanted to congratulate you, Ken, for this great presentation and this great study.

I only have one question. Since you presented that only 2% of the patients get 20 units of blood or more, then therefore, 98% got less than 20 units –- correct?

Those were the numbers; therefore, if you randomize them, or you include in the study of eight units, and the majority would get somewhere around 10 to 12 units, would it be reasonable to randomize them early on when you have the first clinical signs of bleeding? Maybe when they get the first or second unit of blood, but they are true indicators that they are bleeding; therefore, at the end of the road, you can actually show a larger decrease in blood transfusion. Thank you.

Dr. Lawrence Pitts (San Francisco, California): Pitts, San Francisco. I know that you excluded coma scores of less than eight from your study, but did you have enough patients in the moderate head injury category with intracranial hemorrhage to have any feeling about effect of the activated factor VII on delayed traumatic cranial hemorrhage?

Dr. Martin A. Croce (Memphis, Tennessee): I'll take the privilege of the podium and ask the final question. Ken, you did a great job of presenting. To be fair, I was wondering if you would comment on the control for transfusions for this particular study, since transfusions was one of the outcomes in addition to ventilator weaning, since ventilator-free days was also one of the outcomes.

Dr. Kenneth D. Boffard (closing): I'd like to thank all of the discussants for their comments, and Dr. Champion, both for running a very careful data set monitoring board and also his insightful comments on some of the complexities that we faced.

With regard to the specific questions, in terms of the uniformity of care, the trouble with trauma patients is that the confounding variable is the patient rather than the surgeons, as some would have us believe.

What we relied upon was that the patients who entered the trial as placebo versus those who entered the trial as rfVIIa, acted to some extent as their own control across the census.

The uniformity of care has been analyzed in terms of overall outcomes and would appear to have been similar across the census. We did not attempt to dictate to individual centers, "thou shalt do this or the other," in the hope that, the standard of practice for most of the centers that were selected was compatible both with each other, and with what we would regard as the upper level of standard of care.

The indications are there. The question is where is the cost benefit? There is no doubt that the substance at the moment is extremely expensive. But I think we're only a little way down that line.

I think that the first statement is this stuff is safe. I'll come back to it in traumatic brain injuries. If it's safe, in which case, what dose is the most optimum dose? The dose that was chosen was at the upper limit of normal, because this was intended as a safety trial as much as anything else. So the reduction in dose– if it works, and we feel it does– and the increased production is going to make a big difference to the cost of the drug itself. If you add into that, the number of ICU days and ventilator days it may be possible to save, then becomes a cost-effective drug. But I think the greater research is still required for that.

The question was raised of *why* our increased successes in blunt injury? I think, as all of us are surgeons know there are three sorts of bleeding. There is the bleeding that you can see that you can press on. There is the bleeding that you can hear. In other words, a bleeding you can feel rather which is you can put your finger on. Then there is that audible bleeding, which no amount of drug is ever going to stop. Audible bleeding is going to continue to need a surgeon in an operating room.

But I think with blunt injury, there is a significant amount of smaller vessel bleeding, which is too small to embolize, too small to surgically stop, but it's asking to be stopped in a pharmacological fashion, and I think that's where the strength of this study is.

In terms of the question of how to advise our U.S. colleagues and the FDA on a future trial in America: fortunately, American surgery, although there is variation because it is within one country, tends to be a little bit more controllable, I think that particularly, with the penetrating injury the standard of care can be controlled.

I would exclude extremity injury for obvious reasons. I think laying down closer transfusion requirements and that moves me a little bit onto Dr. Lucas' question.

No two centers quite define massive transfusion with the same numbers. No two centers apply quite the same amount of cryoprecipitation, fresh frozen plasma is the next one.

I think that that has to be standardized. I think the second thing that does have to be standardized is the way patients are removed from a ventilator or removed from an intensive care unit. For example, if you have a patient who has major surgery who would come off a ventilator, but the orthopedist is going to do some big operation tomorrow, will you keep them on the ventilator over night or take them off?

The drug provides a much higher level in the plasma than cryo or any of the fresh frozen plasmas. The total dose given was 400 pg/kg, and that was targeted to achieve a dose in the plasma of roughly 40 ng/L.

Fresh frozen plasma and cryo only approaches about a third of that, bearing in mind also that you have a dilutional aspect as you tend to transfuse these patients with lactated Ringer's or anything else.

Dr. Thompson, the head injury patients are the source of a separate research project, which will be presented at a later stage, but at this stage we do not see any dangers in those particular patients.

Dr. Ross, we don't have data on the use of FFP for the reasons I have given. Dr. Jurkovich, to answer your question, the AIS scores on one, two, and three bodily systems were identical between the various groups.

We do not have specific data on which operations were performed, other than to say that most surgery took place within the first 24 hours, and the surgery was similar between the two groups.

To answer Dr. Mauricio's question, remember that these patients received eight units of blood. In principle, nobody is going to transfuse blood until you've lost blood. Very few people are going to transfuse until they've lost maybe four or five units already; their hemoglobin is down to somewhere around 10. So these patients had received eight units and probably lost 12 before they were entered.

I think that they should be randomized earlier, and this is the subject of discussion for a future trial with the FDA. Dr. Croce, would you care to repeat your question? I'd like to thank, again, both organizations and a number of airlines for the privilege of being here. (Laughter)