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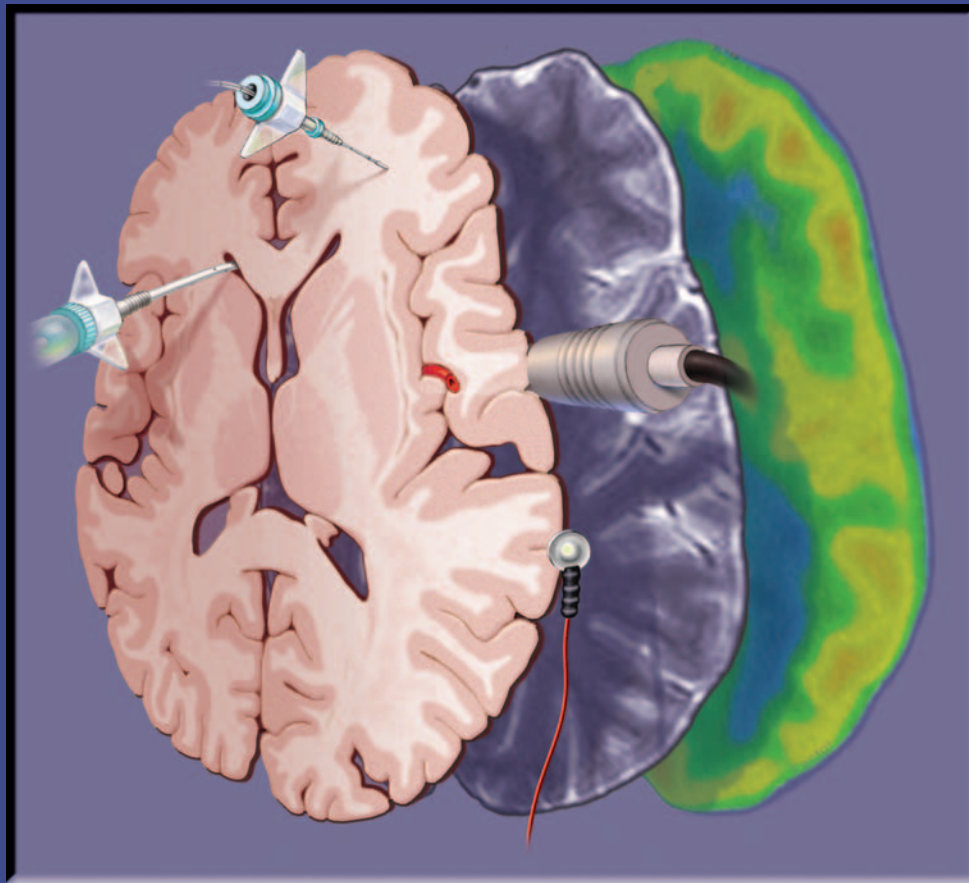
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Recombinant Activated Factor VII for Acute Intracerebral Hemorrhage

US Phase IIA Trial

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Abstract

Background and Purpose: Ultra-early hemostatic therapy may improve outcome after intracerebral hemorrhage (ICH) by preventing rebleeding and hematoma expansion. We conducted this trial to evaluate the safety of activated recombinant factor VII (rFVIIa; NovoSeven[®]) for preventing early hematoma growth in acute ICH.

Methods: In this multicenter, randomized, double-blind, placebo-controlled, dose-escalation trial, 40 patients diagnosed with ICH by computed tomography within 3 hours of onset were treated with placebo or 5, 20, 40, or 80 µg/kg of rFVIIa ($n = 8$ per group). Patients with any history of thromboembolic or vaso-occlusive disease were excluded. The primary endpoint was the frequency of adverse events (AEs).

Results: Mean age was 65 years (range 34–91) and the median admission Glasgow Coma Scale score was 14.5 (range 6 to 15). Mean ICH volume was 17 ± 19 mL; nearly three-quarters were located in the basal ganglia ($n = 29$). The mean interval from onset to treatment was 178 ± 41 minutes. Thirty-three patients experienced 186 AEs, which occurred with similar frequency in the five groups. There were 10 thromboembolic AEs, including one case of deep vein thrombosis (20 µg/kg group); one case of cerebral infarction (placebo); two cases of pulmonary embolism (20 and 40 µg/kg groups); and six instances of ischemic ECG changes or cardiac enzyme elevation (placebo [$n = 2$], 20 µg/kg [$n = 1$], 40 µg/kg [$n = 1$], and 80 µg/kg [$n = 2$] groups). No consumption coagulopathy or dose-related increase in edema-to-ICH volume ratio occurred.

Conclusions: Ultra-early rFVIIa treatment for ICH was associated with a reasonable safety profile in this preliminary study across a wide range of dosages. Further research is warranted to investigate the safety and potential efficacy of rFVIIa for minimizing ICH growth.

Key Words: Intracerebral hemorrhage; recombinant activated factor VII; coagulation; hemostasis; emergency stroke treatment.

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Introduction

Intracerebral hemorrhage (ICH) is a major cause of death and disability, accounting for 15 to 30% of stroke cases worldwide (1). Between 35 and 52% of patients die within 1 month of ICH onset, and only 20% of patients regain functional independence by 6 months (2,3). Management of ICH is primarily supportive because only limited evidence from randomized trials supports specific treatments (4). In a large randomized trial, urgent surgical hematoma evacuation was not found to be effective (5), further emphasizing the need for studies investigating medical therapies for ICH.

Hemorrhage volume is a well-established determinant of survival and outcome after ICH (6). Early hematoma growth occurs in up to 38% of patients initially computed tomography (CT) scanned within 3 hours of onset, and is the principal cause of early neurological deterioration after ICH (7–11). In the only prospective study of this phenomenon, CT-documented ICH growth was detectable just one hour after the baseline scan in more than two-thirds of those who experienced substantial hemorrhage enlargement (7).

The use of hemostatic agents during the acute phase to arrest ongoing bleeding and minimize hematoma volume is a new and promising therapeutic approach to ICH (12). Recombinant factor VIIa (rFVIIa) promotes hemostasis at sites of vascular injury and is currently approved for hemophilia patients with inhibitors to factors VIII or IX (13). In Europe, rFVIIa is also licensed for use in patients with acquired hemophilia, FVII deficiency and Glanzmann's thrombasthenia. Successful use of rFVIIa for controlling hemorrhage has also been reported in coagulopathic patients undergoing neurosurgical procedures, and in patients with normal coagulation (14–16).

In a phase 2B trial of 399 patients, we recently reported beneficial effects of rFVIIa on hematoma growth, mortality, and functional outcome when given within 4 hours of ICH onset (17). However, there was a 7% frequency of serious thromboembolic adverse events with rFVIIa, compared to only 2% in placebo. This finding has raised important questions about the balance between risk and benefit with this treatment, and others have cited the need for additional safety data before the rFVIIa for ICH can be widely adopted into clinical practice. In this study, we report data from an earlier randomized, double-blind, placebo-controlled, dose-escalation study designed to evaluate the safety and feasibility of rFVIIa treatment for acute ICH.

Methods

Patients

Patients (≥ 18 years) with spontaneous ICH diagnosed by CT scan within 3 hours of symptom onset were eligible for enrolment. Exclusion criteria included: deep coma (Glasgow Coma Scale [GCS] 3–5); surgical hematoma evacuation planned or performed within 24 hours of admission; secondary ICH related to aneurysm, arteriovenous malformation (AVM), trauma, tumor, infarction, dural sinus thrombosis, or other causes; known oral anticoagulant use, coagulopathy, or thrombocytopenia; any history or acute evidence of thrombotic, hypercoagulable, or vaso-occlusive disease (i.e., stroke or coronary artery disease); acute sepsis or crush injury; pregnancy; known malignant disease or alcohol abuse; prior disability (baseline modified Rankin Scale [mRS] score > 2); known or suspected

allergy to the trial product; or participation in another trial. Medical therapy was provided according to American Heart Association guidelines (4). Informed consent was obtained from the patient or their legally authorized representative.

Trial Design

The study (protocol F7ICH-2073) was conducted at 17 US sites between November 2001 and March 2003. Forty patients were randomly assigned in four sequential dose tiers ($n = 10$ per tier) to receive placebo ($n = 2$ per tier) or 5, 20, 40, or 80 $\mu\text{g}/\text{kg}$ ($n = 8$ per tier) of rFVIIa (NovoSeven[®], Novo Nordisk A/S, Bagsvaerd, Denmark) in a dose-escalation fashion. On completion of each dose tier, a formal assessment of safety was performed by an independent Data Safety Monitoring Board (DSMB) before enrollment of patients to the next dose tier was permitted. This DSMB was also responsible for reviewing a similar phase IIA dose-escalation trial that was conducted simultaneously in Europe and Australasia (18).

Trial Intervention

The trial products, rFVIIa (NovoSeven[®], Novo Nordisk A/S, Denmark) and placebo, were supplied as sterile, freeze-dried powder in single-use vials for reconstitution with sterile water. Trial product was administered intravenously over approximately 2 minutes at a site other than a paralyzed limb within 1 hour of the baseline head CT scan and within 4 hours of symptom onset.

CT Scan Analysis

CT scans were performed at admission, 1 hour after the baseline scan, (regardless of the time of dosing), and 24 and 72 hours after dosing. ICH, intraventricular hemorrhage (IVH), and edema volumes were calculated in random order by averaging the measurements of two independent neuroradiologists using digital multi-slice planimetric techniques, as described previously (18).

Clinical Assessments

Neurological deficit was assessed using the GCS and National Institute of Health Stroke Scale (NIHSS) at admission, at 1 and 24 hours post-dose, daily to day 5, and at days 15 (or discharge if earlier) and 90. The modified Rankin Scale (mRS) and Extended Glasgow Outcome Scale (E-GOS) scores assessing global outcome and the Barthel Index (BI) assessing functional disability were conducted at day 15, or discharge if earlier, and day 90. Vital signs were assessed at all time points.

Primary End Point

The primary end point was the frequency of adverse events (AEs). The local investigator was responsible for describing and classifying each AE with regard to severity, relationship to trial medication, and outcome on a standardized reporting form. AEs were assessed until day 15 or discharge if earlier, and serious adverse events (SAEs) until completion of the trial at day 90. Predefined safety end points included evidence of (1) myocardial ischemia, (2) deep vein thrombosis (DVT) or pulmonary embolism (PE), (3) cerebral artery or vein thrombosis, (4) consumption coagulopathy, and (5) excessive or

Table 1
Patient Demographics and Baseline Clinical Characteristics

	rFVIIa, $\mu\text{g}/\text{kg}$					Total (N = 40)
	5 (n = 8)	20 (n = 8)	40 (n = 8)	80 (n = 8)	Placebo (n = 8)	
Age, years	72 \pm 10	60 \pm 15	64 \pm 13	62 \pm 12	67 \pm 13	65 \pm 12
Gender	5 (63)	7 (88)	2 (25)	5 (63)	4 (50)	23 (58)
Race						
Caucasian	4 (50)	4 (50)	2 (25)	3 (38)	3 (38)	16 (40)
Asian	2 (25)	1 (13)	0 (0)	1 (13)	0 (0)	4 (10)
African	1 (13)	2 (25)	5 (63)	3 (38)	1 (13)	12 (30)
Other	1 (13)	1 (13)	1 (13)	1 (13)	4 (50)	8 (20)
Systolic BP, mmHg	182 \pm 20	205 \pm 19	201 \pm 30	211 \pm 36	178 \pm 25	195 \pm 29
Diastolic BP, mmHg	96 \pm 29	104 \pm 16	112 \pm 25	114 \pm 32	86 \pm 22	103 \pm 26
ICH volume, mL	17 \pm 9	18 \pm 11	25 \pm 44	11 \pm 14	15 \pm 17	17 \pm 19
NIHSS score	16 \pm 6	16 \pm 5	18 \pm 11	10 \pm 4	12 \pm 6	15 \pm 6
GCS score	14.5 (10–15)	15 (8–15)	10 (6–15)	15 (11–15)	15 (10–15)	14.5 (6–15)

Data are mean \pm SD, median (range), or *n* (%).

BP, blood pressure; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; NIHSS, National Institute of Health Stroke Scale; SD, standard deviation.

unusual perihematoma brain edema (edema:ICH volume ratio >2.5 at 72 hours). Planned safety assessments included (1) electrocardiography (ECG) and measurements of serum troponin I levels at baseline and 24 hours; (2) coagulation testing (d-dimer, antithrombin III activity, prothrombin time [PT], activated partial thromboplastin time [aPTT], fibrinogen, prothrombin fragment 1+2, factor VII coagulant activity [FVII:C]), at baseline, 1 and 24 hours; and (3) lower extremity Doppler ultrasonography at 72 hours.

Secondary End Points

Secondary end points included percent and absolute changes in ICH, IVH, and total hemorrhage (ICH + IVH) volume at 1 and 24 hours after baseline; the proportion of patients with substantial ICH growth ($>33\%$ or 12.5-mL increase from baseline); in-hospital neurological deterioration (decrease of ≥ 2 points in the GCS, or increase of ≥ 4 points in the NIHSS) between days 0 and 5; and the proportion of patients who were dead, alive with minimal or no disability (BI 95–100, E-GOS 8, mRS 0–1), or alive and functionally independent (BI 60–100, E-GOS 5–8, mRS 0–) at 90 days.

Statistical Analysis

Differences in ICH volume and coagulation parameters were compared between rFVIIa dose groups and placebo using analysis of covariance (ANCOVA). Covariates for the CT lesion volume analysis included baseline ICH volume, onset-to-CT time, and CT-to-needle time, and the coagulation tests were analyzed with the baseline value as a covariate. Point estimates and two-sided 95% confidence intervals for mean differences between the dose groups were calculated as appropriate. Significance was set at $p < 0.05$ for all analyses.

Results

A total of 41 patients were randomized, and 40 received trial product; 1 patient clinically deteriorated prior to dosing and underwent emergency hematoma evacuation. Mean age

was 65 years (range, 34 to 91), 58% of subjects were male, and the majority were Caucasian or African American (Table 1). Mean admission NIHSS score was 14 (range, 1 to 34), median GCS score was 15 (range, 6 to 15), and mean blood pressure was 195/103 mmHg.

The mean interval from onset to baseline CT was 131 \pm 42 minutes (range, 30 to 201 minutes), from CT-to-needle was 47 \pm 38 minutes (range, 8 to 163 minutes), and from onset-to-needle was 178 \pm 41 minutes (range, 95 to 289 minutes). Only two patients (5%) were treated beyond 4 hours after onset. Seventy-five percent were dosed on the basis of an estimated body weight that was within 5 kg of their actual body weight.

Mean ICH volume at baseline was 17 \pm 19 mL. Hemorrhages were located in the thalamus ($n = 16$), putamen ($n = 13$), lobar regions ($n = 5$), cerebellum ($n = 1$), pons ($n = 1$), or other ($n = 4$). Although there was substantial variability in baseline ICH volume between the dose groups, these differences were not significant.

Thirty-three patients experienced 186 AEs (Table 2). No noticeable differences in the type, frequency, or severity of AEs were observed between dose groups. The most common AEs were urinary tract infection ($n = 11$), fever ($n = 10$), constipation ($n = 11$), and somnolence ($n = 5$). There were 12 AEs that were deemed to be possibly or probably treatment-related by the investigator (Table 3). Among the pre-specified safety end-points, there was one case of DVT detected at 72 hours in the 20 $\mu\text{g}/\text{kg}$ group, two cases of PE in the 20 and 40 $\mu\text{g}/\text{kg}$ groups; one case of cerebral infarction in the placebo group; and six patients with ischemic ECG changes, minor cardiac enzyme elevation, or both in the placebo ($n = 2$), 20 $\mu\text{g}/\text{kg}$ ($n = 1$), 40 $\mu\text{g}/\text{kg}$ ($n = 1$), and 80 $\mu\text{g}/\text{kg}$ ($n = 2$) groups (Table 3). Of these six cardiac events, only one occurred within 72 hours of dosing, and this was in a placebo patient. Eight patients had an edema/ICH volume ratio exceeding 2.5 at 72 hours; they were evenly distributed across the groups (Table 2), and there were no cases of clinical deterioration attributed to excessive brain edema. There was no evidence of a dose-related increase in the ratio of edema-to-ICH volume at 72 hours (Figure 1).

Table 2
Overview of Adverse Events

	<i>rFVIIa</i> , µg/kg				<i>Placebo</i> (<i>n</i> = 8)	<i>Total</i> (<i>N</i> = 40)
	5 (<i>n</i> = 8)	20 (<i>n</i> = 8)	40 (<i>n</i> = 8)	80 (<i>n</i> = 8)		
No. of patients experiencing AEs	5	8	6	6	8	33
No. of AEs	44	40	26	38	38	186
Mild	26	17	13	21	21	98
Moderate	12	17	5	14	12	60
Severe	6	6	8	3	5	28
No. of SAEs	5	7	6	6	3	27
AEs possibly or probably related to treatment						
No. of AEs	0	2	2	0	5	9
No. of SAEs	0	1	0	1	1	3
Deep vein thrombosis at 72 hours*	0	1	0	0	0	1
Ischemic electrocardiogram changes at 72 hours*	0	0	0	0	1	1
Excessive edema (edema/ICH ratio >2.5) at 72 hours*	2	0	2	2	2	8
No. of Deaths	2	2	3	0	1	8

AE, adverse event; SAE, serious adverse event.

*All subjects were screened with CT, ECG, and Doppler ultrasonography at 72 hours.

Table 3
Thromboembolic or Possibly Treatment-Related Adverse Events

<i>Dose group</i>	<i>Patient number</i>	<i>Age</i>	<i>Complication</i>	<i>Serious</i>	<i>Relationship to study drug</i>
20 µg/kg	6402	64	Hyperbilirubinemia	Yes	Probable
	6705	82	Nonspecific ECG changes for several days after dosing	No	Possible
	7201	65	Hypotension	No	Possible
	7301	62	Deep vein thrombosis 3 days after dosing	No	Unlikely
	6102	45	Pulmonary embolism 36 days after dosing	Yes	Unlikely
40 µg/kg	5501	56	Bradycardia	No	Possible
			Anterolateral and inferior T-wave abnormalities 24 hours after dosing, no cTI elevation	Yes	Unlikely
	6501	54	Hyperbilirubinemia	No	Possible
	6103	73	Pulmonary embolism 13 days after dosing	Yes	Unlikely
80 µg/kg	6901	51	Inferior T-wave inversions and cTI elevation (1.4 ng/mL) 24 hours after dosing	Yes	Possible
	7203	65	cTI elevation (0.3 ng/mL), ischemic ECG changes and new RBBB in the setting of GI bleed and hypotension 15 days after dosing	Yes	Unlikely
Placebo	5301	75	Minor cTI elevation	No	Possible
			Infusion site erythema	No	Possible
			Conjunctivitis	No	Possible
			Urinary retention	No	Possible
	6701	91	Non-specific ST-T wave changes 24 hours after dosing, no cardiac enzyme elevation	No	Unlikely
	5303	59	Injection site swelling	No	Possible
	6706	69	Right temporal-parietal cerebral infarction 8 days after dosing (presumed cardioembolic)	Yes	Possible

Designations regarding the seriousness of AEs, and their possible relationship to treatment, were made by the local investigator. cTI, cardiac troponin I; ECG, electrocardiogram; RBBB, right bundle branch block.

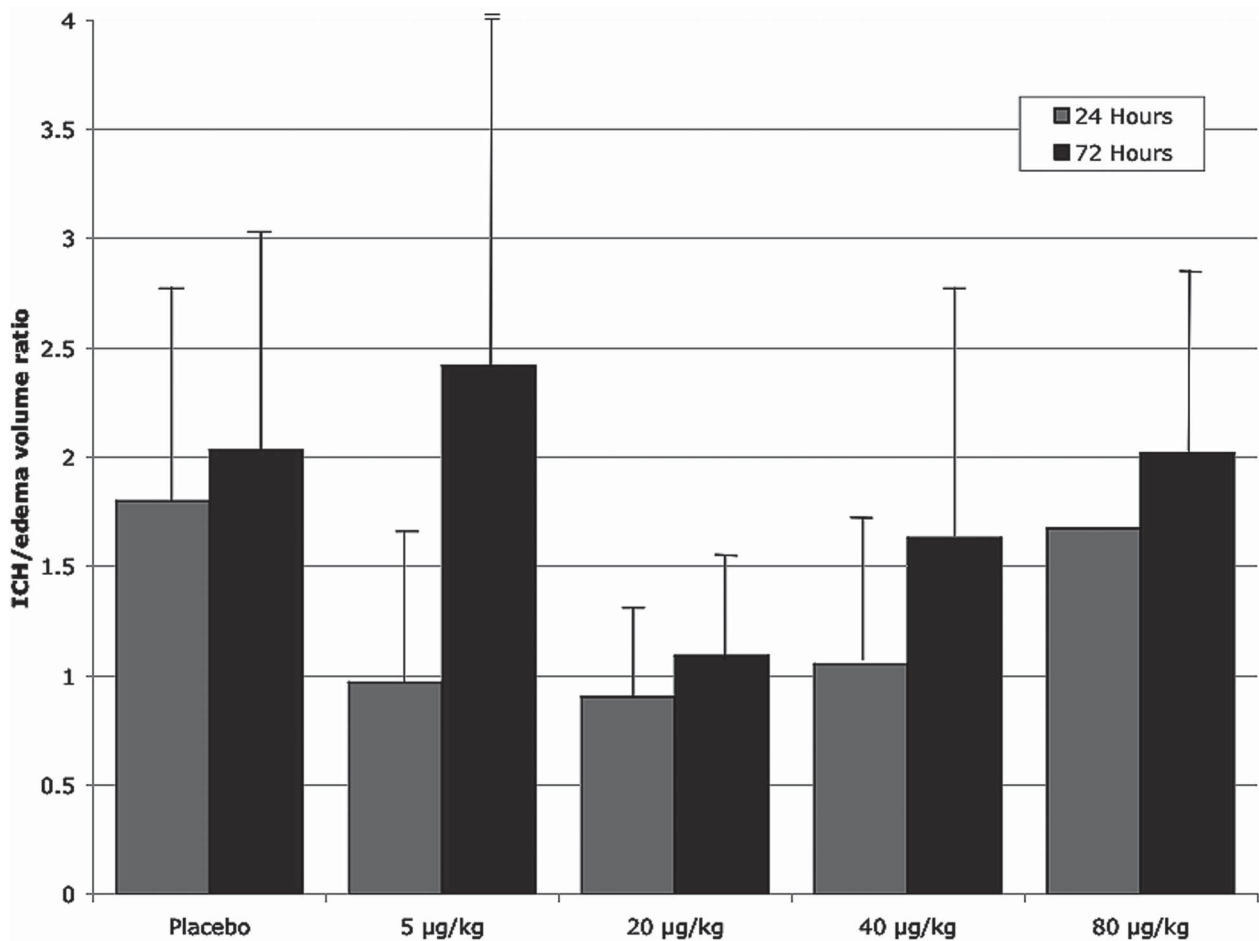


Fig. 1. Edema-to-ICH volume ratios, by treatment group. No dose–response relationship is evident. The bars represent standard deviation.

Seventeen patients experienced 27 SAEs, including ICH-related neurological deterioration ($n = 10$), respiratory failure or cardiac arrest ($n = 5$), myocardial ischemia or infarction ($n = 3$), pulmonary embolism ($n = 2$), and cerebral infarction, abdominal pain, urinary tract infection, atelectasis, hyperbilirubinemia, renal failure, and seizures (each $n = 1$). The number of SAEs was approximately twice as high in the rFVIIa-treated patients than in the placebo group (Table 2), but this difference was not statistically significant. One of the eight placebo-treated patients (13%) and 7 of 32 rFVIIa-treated patients (22%) died during the 90-day trial period. All deaths occurred within 32 days of admission; in each case ICH was identified as the primary cause of death.

There were no clinically significant changes in coagulation-related parameters indicating a systemic activation of the coagulation cascade in the rFVIIa treated patients. One hour after dosing, both PT and fibrinogen were significantly reduced in the rFVIIa-treated patients compared to placebo (Table 4). However, mean values for each group remained within the normal range, and these differences had normalized by 24 hours. Apart from a small number of outlier values, rFVIIa had no effect on platelet, d-dimer, antithrombin-III, or prothrombin fragment 1+2 levels. Factor FVII:C activity was significantly increased at one hour in a dose-dependent

fashion, and returned to essentially undetectable levels at 24 hours (Figure 2).

The overall frequency of ICH growth (>33% or 12.5-mL increase from baseline) was 25% (10 of 40) at both 1 and 24 hours (Table 5). There were no significant differences in percent or absolute change in ICH volume between any of the dose groups and placebo at 1, 24, or 72 hours. However, the numbers evaluated were too small to allow meaningful comparisons.

Between baseline and day 5, 12 patients (26%) experienced neurological deterioration according to the GCS (≥ 2 point fall) and 9 (14%) according to the NIHSS (≥ 4 point increase). There were no significant differences in the proportion of patients classified as dead or severely disabled at 90 days between the treatment groups (Table 6). The Barthel index and NIHSS indicated a mild-to-moderate degree of residual neurological deficit and disability on average among those who survived to 90 days, with no significant differences between the groups.

Discussion

The use of hemostatic agents as treatment for acute ICH is a novel therapeutic approach with the potential to improve outcome and reduce mortality. In this dose-escalation safety and feasibility trial, doses of 5 to 80 µg/kg rFVIIa were

Table 4
Coagulation Testing

	Time after dosing, hours	rFVIIa, µg/kg				Placebo
		5	20	40	80	
PT, seconds	0	11.5 ± 1.0	12.1 ± 1.0	11.7 ± 0.6	12.3 ± 0.9	11.9 ± 1.2
	1	9.3 ± 0.2 ^a	9.4 ± 0.4 ^a	9.2 ± 0.2 ^a	9.1 ± 0.0 ^a	11.7 ± 0.5
	24	11.8 ± 1.0	12.8 ± 1.8	11.5 ± 1.2	12.5 ± 2.3	13.5 ± 2.2
PTT, seconds	0	30 ± 4	31 ± 7	29 ± 6	33 ± 8	32 ± 3
	1	27 ± 3	30 ± 9	29 ± 8	26 ± 5 ^a	31 ± 4
	24	31 ± 4	31 ± 7	27 ± 4	29 ± 4	37 ± 13
Fibrinogen, mg/dL	0	422 ± 148	323 ± 127	422 ± 163	489 ± 109	455 ± 116
	1	342 ± 142	305 ± 231 ^a	304 ± 144 ^a	251 ± 95 ^a	466 ± 130
	24	516 ± 100	479 ± 138	456 ± 152	490 ± 145	500 ± 169

ANCOVA showed significant between-group differences at 1 hour for PT ($p < 0.0001$) and fibrinogen ($p = 0.02$).

^aSignificantly different from placebo at 1 hour ($p < 0.05$).

PT, prothrombin time; PTT, partial thromboplastin time.

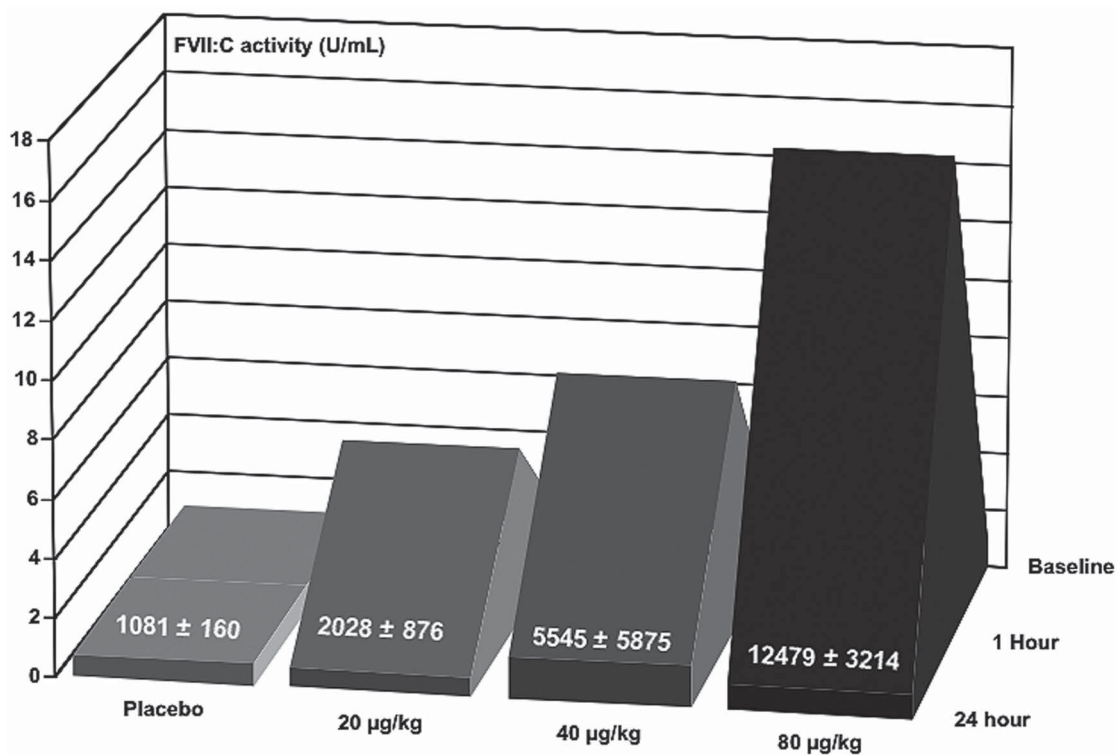


Fig. 2. Mean factor VII:C activity at baseline, 1 and 24 hours after dosing, by treatment group. Numbers represent the mean ± SD area under the curve in U•seconds/mL. A dose-response relationship is evident ($p < 0.001$ at 1 hour compared to placebo, ANCOVA).

administered to acute ICH patients without a high frequency of thromboembolic AEs compared to placebo. In the 32 patients who received active treatment, the most concerning events were two cases of PE and one case of documented DVT. A parallel phase IIA study of 47 spontaneous ICH patients that evaluated doses as high as 160 µg/kg has demonstrated similar encouraging results (18).

Overall, the frequency of thromboembolic AEs was 30% in the placebo group (3 events in 10 patients) versus 23% (7 events

in 30 patients) in the rFVIIa-treated patients (Table 3). Of these 10 events, 6 were classified as serious, and only 2 of these were judged by the local investigator to be possibly related to treatment: a case of cerebral infarction (presumably cardioembolic) that occurred 8 days after dosing in a patient given placebo, and a case of mild cardiac troponin I elevation with ECG changes that developed 24 hours after dosing in the 80 µg/kg group.

Prospective screening with lower extremity Doppler ultrasonography for DVT at 72 hours detected only one case in the

Table 5
Changes in ICH Volume From Baseline

Dose ($\mu\text{g}/\text{kg}$)	1 hour			24 hours		
	Substantial growth	Absolute change, mL	Percent Change	Substantial growth	Absolute change, mL	Percent Change
5	5 (63)	7 \pm 7	40 \pm 45	3 (38)	13 \pm 19	64 \pm 106
20	3 (38)	10 \pm 21	81 \pm 172	2 (25)	10 \pm 21	79 \pm 172
40	1 (13)	0 \pm 1	10 \pm 19	4 (50)	1 \pm 2	37 \pm 51
80	0 (0)	0 \pm 1	2 \pm 10	0 (0)	1 \pm 2	4 \pm 9
Placebo	1 (13)	0 \pm 1	6 \pm 20	1 (13)	2 \pm 4	11 \pm 18

Values are n (%), or mean \pm SD. Each dose group had 8 patients. The value for the 1 hour scan was carried forward to 24 hours for one patient each in the 20 and 40 $\mu\text{g}/\text{kg}$ groups. Substantial hematoma growth is defined as a $>33\%$ or 12.5-mL increase from baseline.

Table 6
Neurological Deterioration and 3-Month Outcome

Dose ($\mu\text{g}/\text{kg}$)	n	Day 15		Day 90			
		GCS worsening ^a	NIHSS worsening ^b	mRS 4–6 ^c	E-GOS 1–4 ^d	Barthel Index ^e	NIHSS ^f
Placebo	8 [7]	4 (50)	3 (38)	4 (50)	6 (75)	80 (0–100)	7 \pm 9
5	8 [6]	5 (63)	4 (50)	5 (63)	5 (63)	65 (0–95)	9 \pm 6
20	8 [4]	4 (50)	3 (38)	3 (38)	4 (50)	80 (50–95)	4 \pm 3
40	8 [5]	4 (50)	2 (25)	5 (63)	7 (88)	90 (0–100)	6 \pm 7
80	8 [7]	4 (50)	3 (38)	2 (25)	4 (50)	75 (0–100)	5 \pm 5

Data are mean \pm SD, median (range), or N (%). The number of patients in brackets refers to the number evaluated with the Barthel Index and NIHSS at day 90. E-GOS, Extended Glasgow Outcome Scale. GCS, Glasgow Coma Scale; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

^aWorsening defined as a ≥ 2 point drop in GCS score between baseline to day 15.

^bWorsening defined as a ≥ 4 point increase in NIHSS score between baseline to day 15.

^cmRS is scaled 0 = no symptoms or disability to 6 = death. Scores of 4–6 indicate outcomes of moderate-severe disability (unable to walk or tend to bodily needs without assistance) to death.

^dE-GOS is scaled 8 = upper good recovery to 1 = dead. Scores of 1–4 indicate outcomes of death to dependent with severe disability.

^eScaled 0 = complete dependence, 100 = fully independent in activities of daily living.

^fScaled 0 = no neurological deficit, 51 = comatose and quadriplegic.

20 $\mu\text{g}/\text{kg}$ group. Two cases of PE also occurred in the 20 and 40 $\mu\text{g}/\text{kg}$ groups, but these events occurred approximately 2 weeks after dosing, and were rated as unlikely to be related to study drug by the investigator. The 7% frequency of PE in the rFVIIa-treated patients is comparable to the 5% frequency that has been previously reported in ICH patients treated with low dose subcutaneous heparin (19).

Thrombin has been hypothesized to be a major cause of perihematomal inflammation and edema after ICH (20,21). To evaluate whether rFVIIa can exacerbate perihematomal edema, edema-to-ICH volume ratios were compared between dose groups. There was no evidence of an increased edema-to-ICH volume ratio between the rFVIIa-treated patients and placebo at 72 hours (Figure 1).

D-dimer and prothrombin fragment 1+2 levels were not significantly increased with rFVIIa in this trial, indicating that there was no subclinical activation of systemic coagulation, which is consistent with findings in patients with hemophilia (22,23) and in warfarin-treated normal volunteers (24). As expected, rFVIIa treatment did result in a dose-dependent increase in FVII:C activity at 1 hour, as well as reductions in the PT and fibrinogen. All of these findings had fully normal-

ized by 24 hours, which is consistent with the 2.6-hour half-life of rFVIIa (13). In a similar parallel phase IIA trial we found similar results across a wider range of doses (18). The mode of action of rFVIIa may explain the lack of effect on systemic clotting (25). It acts at the site of vascular injury where tissue factor is expressed and activated platelets are found, to promote localized thrombin generation and fibrin clot formation (13,25).

For ultra-early hemostatic therapy to work, early treatment is critical (6). Dosing within 4 hours of ICH onset was achieved for 95% of patients, with a mean time from onset of symptoms to administration of 178 minutes, indicating that it is feasible to treat ICH patients within an early time window.

Our results confirm the finding by Brott and colleagues that hematoma expansion is detectable within 1 hour in the majority of patients who experience ICH growth (7). The overall frequency of substantial ICH growth (a greater than $>33\%$ or 12.5-mL increase from baseline) was 25% at both 1 and 24 hours, which is somewhat smaller than has been previously reported, including the 38% frequency reported by Brott (7–11). However, the median time from onset to CT scanning in the present pilot study of rFVIIa was 131 minutes, compared to 89 minutes in Brott's prospective observational study.

The main weakness of this pilot feasibility and safety trial is its small size. There were substantial discrepancies in baseline disease severity; for instance, mean baseline ICH volume in the 80 µg/kg group was twice that of the 40 µg/kg group (Table 1). This limits our ability to make any conclusions regarding the relative safety or efficacy of one dose compared to another.

No conclusions about the efficacy of rFVIIa for preventing hematoma growth in ICH can be made based on our data because the number of treated patients was small. Similarly, our numbers were too small to meaningfully evaluate the effect of rFVIIa treatment on mortality or functional outcome. Overall mortality was 20%, which is lower than typically occurs after ICH, and is likely the result of selection bias towards smaller hemorrhages in this trial.

In summary, this preliminary dose-escalation safety trial and a similar trial conducted in Europe and Australasia (18) have not shown an unexpectedly high frequency of thromboembolic AEs when rFVIIa is given in doses ranging from 5 to 160 µg/kg during the acute phase of ICH. Although the overall frequency of SAEs was approximately twice that in the rFVIIa-treated patients compared to placebo in the present study, there was no increase in SAEs deemed possibly- or probably related to treatment (Table 2). A large, multicenter, randomized, placebo-controlled trial of 400 patients to evaluate the efficacy and safety of rFVIIa at doses of 40, 80, and 160 mg/kg for limiting hematoma growth in acute ICH has recently been completed (17), with promising results, and additional studies are in progress.

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Disclosures

S.A.M. developed the original concept for the trial and wrote the trial protocol, with input from the authors, who comprise the trial steering committee (J.B., S.D., M.N.D., T.S.) and two non-voting employees of the sponsor (N.C.B. and B.E.S.). The steering committee was responsible for the scientific oversight of the trial, had full access to the data, and takes responsibility for the integrity of the data and the data analysis. The sponsor and trial contract research organization (CRO, Quintiles Transnational Corp.) shared responsibility for selecting trial sites, with input from the steering committee. The CRO was responsible for data collection, and performed the statistical analysis according to a plan developed by the steering committee. The steering committee was responsible for the data analysis and interpretation, and for drafting the manuscript. The sponsor agreed prior to initiating the trial to present and publish the results regardless of outcome. Members of the steering committee received consulting fees as compensation for time devoted to the project. S.M.D., M.N.D., S.A.M. and T.S. have received speaking honoraria from

Novo Nordisk. The authors have no other potential conflicts of interest to disclose.

Appendix

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