


ICH Pathophysiology: Key Concepts for the Emergency Physician



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ICH Hemorrhage Volume

- Old concept- Hemorrhage is static process; bleeding complete in a minutes
- New concept- Hemorrhage is dynamic; process continues for several hours



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ARTICLES

Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality

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BACKGROUND AND PURPOSE: The aim of this study was to determine the 30-day mortality and morbidity of intracerebral hemorrhage in a large metropolitan population and to determine the most important predictors of 30-day outcome. **METHODS:** We reviewed the medical records and computed tomographic films for all cases of spontaneous intracerebral hemorrhage in Greater Cincinnati during 1988. Independent predictors of 30-day mortality were determined using univariate and multivariate statistical analyses. **RESULTS:** The 30-day mortality for the 188 cases of intracerebral hemorrhage was 44%, with half of deaths occurring within the first 2 days of onset. Volume of intracerebral hemorrhage was the strongest predictor of 30-day mortality for all locations of intracerebral hemorrhage. Using three categories of parenchymal hemorrhage volume (0 to 29 cm³, 30 to 60 cm³, and 61 cm³ or more), calculated by a quick and easy-to-use clipped method, and two categories of the Glasgow Coma Scale (9 or more and 8 or less), 30-day mortality was predicted correctly with a sensitivity of 90% and a specificity of 90%. Patients with a parenchymal hemorrhage volume of 60 cm³ or more or those with a Glasgow Coma Scale score of 8 or less had a predicted 30-day mortality of 91%. Patients with a volume of less than 30 cm³ and a Glasgow Coma Scale score of 9 or more had a predicted 30-day mortality of 19%. Only one of the 71 patients with a volume of parenchymal hemorrhage of 30 cm³ or more could function independently at 30 days. **CONCLUSIONS:** Volume of intracerebral hemorrhage, in combination with the initial Glasgow Coma Scale score, is a powerful and easy-to-use predictor of 30-day mortality and morbidity in patients with spontaneous intracerebral hemorrhage.



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ICH Volume and Outcome


- Broderick: 1993 Stroke
- Goals: "to determine the most important predictors of morbidity and mortality...in the treatment of intracerebral hemorrhage."
- Methods: 188 cases, retrospective review
- "We report a study of the natural history of intracerebral hemorrhage in the 1.26 million metropolitan population of Greater Cincinnati"
- Study funded by the American Heart Association



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ICH Volume and Outcome

- Results:
 - 162 cases (26 excluded-lost CT, autopsy, IVH alone)
 - Mortality 44% with half in first 2 days
- Key Concept:
 - Volume of parenchyma hemorrhage was the most important predictor of 30-day survival for all ages and locations of hemorrhages
 - Initial Glasgow Coma Scale was also significant predictor of 30 day mortality



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Prognosis

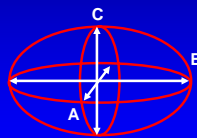
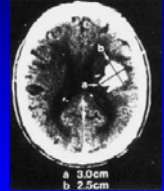


- **Worse**
 - Volume > 60 cm³ and GCS < 9
 - 91% dead at 30 days
 - Patients with > 30 cm³
 - Only 1/71 independent at 30 days
 - Other: age, seizures, intraventricular extension
- **Better**
 - Volume < 30 cm³ and GCS 9 or higher
 - 19% dead at 30 days

Broderick, Stroke 1993;24:987- 93) FERNE/EMRA

Hematoma Volume

- Formula for volume of an ellipsoid
 - $4/3\pi (A/2)(B/2)(C/2)$
 - Simplified $A*B*C / 2$

A-greatest hemorrhage diameter
 B-diameter 90 degrees to A
 C-approximate number of CT slices with hemorrhage multiplied by slice thickness in cm

a 3.0cm
b 2.5cm

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TABLE 3. Model of 30-Day Mortality Using Volume of Parenchymal Hemorrhage and Glasgow Coma Scale

Glasgow Coma Scale score	ICH volume (cm ³)	No. in risk group	Dead	Expected dead	Probability of death by 30 days
≥9	<30	77	13	15	0.19
≥9	30-60	19	11	9	0.46
≥9	>60	17	12	13	0.75
≤8	<30	15	7	7	0.44
≤8	30-60	15	11	11	0.74
≤8	>60	19	17	17	0.91

ICH, intracerebral hemorrhage.

Broderick, Stroke 1993;24:987- 93) FERNE/EMRA

ICH Volume Growth

Early Hemorrhage Growth in Patients With Intracerebral Hemorrhage

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Background and Purpose The goal of the present study was to prospectively determine how frequently early growth of intracerebral hemorrhage occurs and whether this early growth is related to early neurological deterioration.

Methods We performed a prospective observational study of patients with intracerebral hemorrhage within 3 hours of onset. Patients had a neurological evaluation and CT scan performed at baseline, 1 hour after baseline, and 20 hours after baseline.

Results Substantial growth in the volume of parenchymal hemorrhage occurred in 26% of the 103 study patients between the baseline and 1-hour CT scans. An additional 12% of patients had substantial growth between the 1- and 20-hour CT scans. Hemorrhage growth between the baseline and 1-hour CT scans was significantly associated with clinical deterioration, as measured by the change between the baseline and 1-hour Glasgow Coma Scale and National Institutes of Health Stroke Scale scores. No baseline clinical or CT prediction of hemorrhage growth was identified.

Conclusions Substantial early hemorrhage growth in patients with intracerebral hemorrhage is common and is associated with neurological deterioration. Randomized treatment trials are needed to determine whether this early natural history of ongoing bleeding and frequent neurological deterioration can be improved. (Stroke. 1997;28:1-5)

Key Words • computed tomography • intracerebral hemorrhage • prognosis

Subjects and Methods

Study Objectives The primary objective of this prospective observational study

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Early Hemorrhage Growth

- Stroke, 1997
- Goals: To prospectively determine how frequently early growth in intracerebral hemorrhage occurs and whether this early growth is related to neurological deterioration

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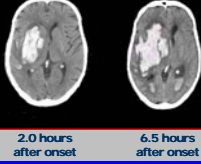
ICH Growth Study Design

- 103 patients (39 patients excluded-incomplete CT, Anticoag, vascular abnorm)
- CT scan baseline 1 and 20 hours
- Positive-increase hemorrhage 33%
- 38% patients with > 33% growth in volume of parenchyma hemorrhage


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ICH Progression

- Symptoms often progress, associated with ICH growth
 - 2/3 with progression of symptoms
 - 1/3 maximal at onset
- Within hours from onset:
 - 26% with >33% growth in next 1^o
 - 12% with >33% growth 1-20^o



(Brott, Stroke 1997;28:1-5)





Safety and Feasibility of Recombinant Factor VIIa for Acute Intracerebral Hemorrhage

Stephan A. Mayer, MD, Nikolai C. Brun, MD, PhD, Joseph Broderick, MD, Stephen Davis, MD, Michael N. Diringer, MD, Brent E. Skolnick, PhD, Thorsten Steiner, MD, for the Europe/Asia/Australia/Novoseven ICH Trial Investigators

Background and Purpose—Hematoma growth occurs in 38% of intracerebral hemorrhage (ICH) patients scanned by computed tomography (CT) within 3 hours of onset. Activated recombinant factor VII (rFVIIa) promotes hemostasis at sites of vascular injury and may minimize hematoma growth after ICH.

Methods—In this randomized, double-blind, placebo-controlled, dose-escalation trial, 48 subjects with ICH diagnosed within 3 hours of onset were treated with placebo (n=12) or rFVIIa (10, 20, 40, 80, 120, or 160 µg/kg, n=6 per group). The primary endpoint was the frequency of adverse events (AEs). Safety assessments included serial electrocardiography (ECG), troponin I and creatinine testing, lower extremity Doppler ultrasonography, and calculation of volume-ICH volume ratios.

Results—Mean age was 61 years (range, 30 to 93) and 57% were male. At admission, mean National Institutes of Health Stroke Scale (NIHSS) score was 14 (range, 1 to 25), median Glasgow Coma Scale score was 14 (range, 6 to 15), and mean ICH volume was 21 mL (range, 1 to 113). Mean time from onset to treatment was 181 minutes (range, 120 to 265). Twelve serious AEs occurred, including 5 deaths (mortality 13%). Six AEs were considered possibly treatment-related, including rash, vomiting, fever, ECG T-wave inversion, and 2 cases of deep vein thrombosis (placebo and 20 µg/kg groups). No myocardial ischemia, consumption coagulopathy, or dose-related increase in volume-ICH volume occurred.


Conclusion—This small phase II trial evaluated a wide range of rFVIIa doses in acute ICH and raised no major safety concerns. Larger studies are justified to determine whether rFVIIa can safely and effectively limit ICH growth. (Stroke. 2006;36:74-79)

Key Words: cerebral hemorrhage ■ coagulation ■ emergency medical services ■ fibrinolysis ■ stroke



Safety Factor FVIIa in ICH

- Mayer: 2005 Stroke Phase II trial
- Goals: Hematoma growth occurs in 38% of ICH
- Key Concept: FVIIa is safe when given within 3 hours of presentation
- Data: 48 patients, 6 doses tested
- Data: No safety issues preclude phase III
- Implications: Larger study is justified, given data on hemorrhage volume growth and outcome



completely resolved by 24 hours, consistent with the 2.6-hour half-life of rFVIIa.¹⁶ The magnitude of these observations were equivalent to those observed in patients with hemophilia¹⁷ and anticipated normal subjects given similar doses.

The overall frequency of ICH growth in our study, defined as a 33% or 12.5-mL increase from baseline, was 38% at 24 hours, which is lower than the 38% frequency found in Brott's prospective study. Two retrospective studies of ICH patients scanned within 3 hours of onset reported frequencies of ICH growth of 18% and 36%.^{18,19} The comparatively low rate of ICH growth observed in our study might be related to random sample variation, as suggested by the fact that ICH growth occurred in only 1 of 11 placebo-treated patients. There were no significant differences in percent change in ICH volume between placebo and the dose groups tested, but the number of patients in each group was too small to allow meaningful comparisons.

In summary, acute treatment of ICH patients with rFVIIa is feasible and in this small phase II study was safe across a wide range of doses. A large (n=500) multicenter trial of similar design comparing 40, 80, and 160 µg/kg rFVIIa with placebo is currently underway to determine whether this treatment can effectively limit ICH growth. Given the current lack of effective medical and surgical therapies for ICH, our findings indicate that larger studies investigating the potential efficacy of rFVIIa for limiting early expansion are justified.

Appendix: Trial Personnel

Steering Committee
 Stephan A. Mayer, MD, New York, NY (Chairman); Joseph Broderick, MD, Cincinnati, OH; Nikoleta C. Brun, MD, PhD, Bingham, Denmark (co-chair); Brent Davis, MD, Milwaukee, Wisconsin; Michael N. Diringer, MD, Los Angeles, CA; Brent E. Skolnick, PhD, Bingham, NY; Thorsten Steiner, MD, Bielefeld, Germany.

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 Novartis Institute for Biomedical Research, Basel, Switzerland

Statistical

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Recombinant Activated Factor VII for Acute Intracerebral Hemorrhage

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ABSTRACT

BACKGROUND
 Intracerebral hemorrhage is the least treatable form of stroke and is associated with high mortality. Among patients who undergo computed tomography (CT) within three hours after the onset of intracerebral hemorrhage, one third have an increase in the volume of the hematoma related to subsequent bleeding. We sought to determine whether recombinant activated factor VII (rFVIIa) can reduce hematoma growth after intracerebral hemorrhage.

DESIGN
 We randomly assigned 399 patients with intracerebral hemorrhage diagnosed by CT within three hours after onset to receive placebo (96 patients) or 40 µg of rFVIIa per kilogram of body weight (108 patients), 80 µg per kilogram (92 patients), or 160 µg per kilogram (103 patients) within one hour after the baseline scan. The primary outcome measure was the percent change in the volume of the intracerebral hemorrhage at 24 hours. Clinical outcomes were assessed at 90 days.

RESULTS
 Hematoma volume increased more in the placebo group than in the rFVIIa groups. The mean increase was 29 percent in the placebo group, as compared with 14 percent, 14 percent, and 13 percent in the groups given 40 µg, 80 µg, and 160 µg of rFVIIa per kilogram, respectively (P<0.01 for the comparison of the three rFVIIa groups with the placebo group). Growth in the volume of intracerebral hemorrhage was reduced by 3, 5 mL, 4.5 mL, and 3.8 mL in the three treatment groups, as compared with that in the

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FVIIa Safety, Efficacy in ICH

- Mayer: 2005 NEJM
- Key Concept: FVIIa is safe when given within 3 hours of presentation
- Data: 399 pts, 3 doses, ICH growth, 90-day
- Data: Less ICH growth, improved outcome
- Data: Thromboembolic events noted
- Implications: Larger study is critical in order to establish clear benefit, safety

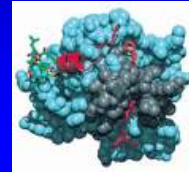
Study supported by
 Novo Nordisk



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Factor VIIa

- Placebo, 40, 80, 160 mcg/kg F-VIIa
- 38% relative reduction in mortality
- 11% absolute mortality reduction
- Double the odds of improvement by one level on the modified Rankin scale at 90 days



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Exclusion Criteria

- GCS 3-5
- Planned surgical evacuation
- Aneurysm, AV malformation, trauma or other cause
- Oral anticoagulants
- Acute sepsis
- Crush injury
- DIC
- Pregnancy
- Pre-existing disability
- Symptomatic vaso-occlusive disease (angina, claudication, DVT, CVA, MI) within 30 days before the ICH

Midway through the trial, symptomatic vaso-occlusive disease was amended to exclude patients with any history of thrombotic or vaso-occlusive disease



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Factor VII

- Serious thromboembolic adverse events, mainly myocardial infarction or cerebral infarction occurred in 7 percent of the F-VIIa treated patients, as compared with 2 percent of those given placebo
- Number needed to benefit is 9
- Number needed to harm is 20



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Functional Outcome Scales

- Modified Rankin scale (mRS)
- Barthel Index (BI)
- Glasgow Outcome Scale (GOS)
- Utilize scored assessments of patient's functional status
- Can be used to gauge:
 - pre-morbid baseline
 - outcome



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Modified Rankin Scale

Score	Description
6	Dead
5	Severe disability: bedridden, incontinent, and requiring constant nursing care and attention
4	Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance
3	Moderate disability: requiring some help, but able to walk without assistance
2	Slight disability: unable to carry out all previous activities, but able to look after own affairs without assistance
1	No significant disability: despite symptoms, able to carry out all usual duties and activities
0	No symptoms at all

Good outcome = score of 0 - 1


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Factor VII

- The FDA will not approve label indication for F-VIIa for acute ICH until safety and potential dose-response issues are clarified
- Pending completion of the ongoing phase III trial, we do not recommend use of Factor VIIa outside of a clinical trial protocol
- Cost is \$1020-\$1369 per 1.2 mg vial

Modern Treatment Options for Intracerebral Hemorrhage; Freeman, Brotti, Critical Care Neurology; 2006 8:145-151 FERNE/EMRA



Thromboembolic Adverse Events After Use of Recombinant Human Coagulation Factor VIIa

Abstract The US Food and Drug Administration (FDA) issued a warning to patients who have been receiving Factor VIIa (FVIIa) for the treatment of acute intracerebral hemorrhage (ICH) on March 20, 2006. The warning states that FVIIa may increase the risk of thromboembolic adverse events (AEs) in patients who have been receiving FVIIa for the treatment of acute ICH.

Background The US Food and Drug Administration (FDA) issued a warning to patients who have been receiving Factor VIIa (FVIIa) for the treatment of acute intracerebral hemorrhage (ICH) on March 20, 2006. The warning states that FVIIa may increase the risk of thromboembolic adverse events (AEs) in patients who have been receiving FVIIa for the treatment of acute ICH.

Objective To review current thromboembolic adverse events (AEs) reported to the FDA in patients receiving FVIIa for the treatment of acute ICH.

Methods A total of 41 AEs were reported to the FDA in patients receiving FVIIa for the treatment of acute ICH between January 1, 2000, and February 28, 2006. The AEs were categorized by type of event and by patient characteristics.

Results A total of 41 AEs were reported to the FDA in patients receiving FVIIa for the treatment of acute ICH between January 1, 2000, and February 28, 2006. The AEs were categorized by type of event and by patient characteristics.

Conclusions Most reported thromboembolic AEs followed the use of FVIIa for the treatment of acute ICH. The AEs were categorized by type of event and by patient characteristics.

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FVIIa Adverse Events

- O'Connell JAMA 2006; 295:293-298
- Adverse events reported to the FDA
- 1999-2004
- 431 reported, 185 thrombo-embolic
- 39 CVA, 34 MI, 32 PE, 26 Art. Thrombus
- 52% occur in the first 24 hours
- Thromboembolic AE's follow off label use

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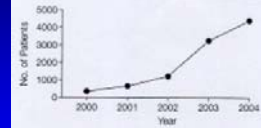


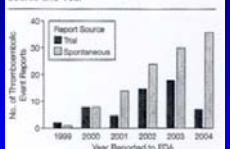
Figure 1. Estimated Number of Patients Treated With Recombinant Human Coagulation Factor VIIa by Year



Year	Estimated Number of Patients
2000	~1,000
2001	~1,500
2002	~2,500
2003	~3,500
2004	~4,500

Estimations were based on Premier RxMarket Advisor (Premier Healthcare Informatics, Premier Inc, Charlotte, NC).


Figure 2. Number of Thromboembolic Event Reports With Recombinant Human Coagulation Factor VIIa Reported to FDA by Source and Year



Year	Retail Source	Hospital
1999	~5	~5
2000	~10	~10
2001	~15	~15
2002	~20	~20
2003	~25	~25
2004	~30	~35

FDA indicates US Food and Drug Administration. Some reports had more than 1 thromboembolic event.

Regions Hospital Alumni Day



TPA vs. Factor VIIa

- TPA-risk is bleeding
- Factor VIIa-risk is clotting in at risk vascular beds (Cardiac, Cerebral, DVT, etc)

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