

Recombinant activated factor VII given within 4 hours of intracerebral hemorrhage reduced hematoma growth

Mayer SA, Brun NC, Begtrup K, et al. **Recombinant activated factor VII for acute intracerebral hemorrhage.** *N Engl J Med.* 2005; 352:777-85. **Clinical impact ratings:** Hospitalists ★★★★★★ Hematol/Thrombo ★★★★★★ Critical Care ★★★★★★☆ Neurology ★★★★★★

QUESTION

In patients with intracerebral hemorrhage (ICH), does recombinant activated factor VII (rFVIIa) given within 4 hours after ICH onset reduce hematoma growth?

METHODS

Design: Randomized placebo-controlled trial.

Allocation: {Concealed}†.*

Blinding: Blinded {patients, clinicians, data collectors, outcome assessors, data analysts, and data and safety monitoring committee}†.*

Follow-up period: 24 hours and 90 days.

Setting: 73 hospitals in 20 countries.

Patients: 399 patients ≥ 18 years of age (mean age 66 y, 61% men) in whom spontaneous ICH was documented by computed tomography scanning within 3 hours of symptom onset. Exclusion criteria included deep coma (score of 3 to 5 on the Glasgow Coma Scale [GCS]) and planned surgical evacuation of hematoma within 24 hours after admission.

Intervention: Intravenous (IV) rFVIIa 40 µg/kg (*n* = 108), 80 µg/kg (*n* = 92), and 160 µg/kg (*n* = 103) or placebo (*n* = 96).

Outcomes: Change in volume of ICH at 24 hours and unfavorable outcome (a score of 4 to 6 on the modified Rankin Scale = death or severe or moderate-to-severe disability, death, and thromboembolic adverse effects at 90 days).

Patient follow-up: 96% (intention-to-treat analysis).

MAIN RESULTS

63% of patients were treated within 3 hours after symptom onset. Growth in the volume of ICH was reduced more by rFVIIa (combined doses) than placebo (Table). Among specific rFVIIa dose groups, the highest dose (160 µg/kg) but not the lower doses (40 µg/kg or 80 µg/kg) reduced the volume of ICH more than placebo (Table). rFVIIa reduced death or an unfavorable outcome more than placebo (Table). rFVIIa and placebo groups did not differ for serious thromboembolic adverse events (7% vs 2%, *P* = 0.12).

CONCLUSIONS

In patients with intracerebral hemorrhage (ICH), recombinant activated factor VII (rFVIIa) given within 4 hours of ICH onset reduced hematoma growth more than placebo at 24 hours. rFVIIa also reduced death and unfavorable outcomes at 90 days.

Source of funding: Novo Nordisk.

For correspondence: Dr. S.A. Mayer, Neurological Institute, New York, NY, USA. E-mail sam14@columbia.edu. ■

*See Glossary.

†Information provided by author.

Recombinant activated factor VII at 40, 80, and 160 µg/kg vs placebo within 4 hours of intracerebral hemorrhage (ICH)†

Outcomes at 24 h	Estimated mean absolute increase from baseline				Placebo	Difference in mean increase from baseline (95% CI)	P value
	40 µg/kg	80 µg/kg	160 µg/kg	Combined doses			
Lesion volume of ICH (mL)	5.4	—	—	—	8.7	3.3 (−1.9 to 8.5)	0.13
	—	4.2	—	—	8.7	4.5 (−0.8 to 9.9)	0.04
	—	—	2.9	—	8.7	5.8 (0.6 to 11)	0.008§
	—	—	—	4.2	8.7	4.5 (0.2 to 8.8)	0.01§

Outcomes at 90 d	rFVIIa combined doses	Placebo	RRR (CI)	NNT (CI)
Death	18%	29%	37% (6 to 57)	10 (5 to 82)
Unfavorable outcome	53%	69%	23% (8 to 35)	7 (4 to 22)

†Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article. Difference in mean increase from baseline and CIs provided by author. §Significant according to the prespecified Bonferroni-corrected threshold of *P* = 0.01. ||Death or survival with severe disability (bedbound and incontinent) or moderate-to-severe disability (unable to walk without assistance); score 4 to 6 on the modified Rankin Scale.

COMMENTARY

Before the study by Mayer and colleagues, no effective interventions existed for reducing the high mortality and disability associated with primary ICH. The dose-escalation trial by Mayer and colleagues was powered to evaluate a surrogate of a good clinical outcome and reduction in hemorrhage volume at 24 hours, which is appropriate given the known relation between hematoma size and clinical outcome and the presumption that rFVIIa would limit rebleeding. Also, the change in hematoma volume should be independent of hemorrhage location, which is a key factor for predicting clinical outcome.

The relatively small number of patients in this trial (*n* = 399) may account for imbalances in baseline characteristics, which may have biased the results in favor of treatment. The placebo group had more brainstem hemorrhages, a lower range of GCS scores (as low as 3), and more men—all of which are known to predict worse outcomes. The patients who benefited most were those treated within 3 hours of symptom onset. The 115 patients treated > 3 hours after onset were probably at lower risk for rebleeding and had no reduction in hematoma volume compared with placebo.

The major concern with using rFVIIa is the occurrence of increased thrombotic events. In this study, the treatment group seemed to have

more than a 3-fold increase in myocardial and cerebral infarctions compared with the placebo group (7% vs 2%, *P* = 0.12), and 2 of the 9 cerebral infarctions were fatal. However, this difference was within the realm of chance, because the study was insufficiently powered to detect a difference of this size (if it in fact existed).

Despite these issues, the study showed that rFVIIa given within the first 4 hours of primary ICH reduced the risk for hematoma expansion and decreased mortality without an associated increase in disability. The results cannot be generalized to patients with ICH related to the use of oral anticoagulants or other secondary causes. Furthermore, patients with any history of myocardial infarction, ischemic stroke, deep venous thrombosis, or claudication would have to be excluded (which was done by the midpoint of this trial).

Although preliminary, the results of this trial are promising. We anxiously await the results of the ongoing phase III trial that will be adequately powered to address issues of clinical outcomes, safety, and treatment windows.

Vincenzo S. Basile, MD
Frank L. Silver, MD, FRCPC
University of Toronto
Toronto, Ontario, Canada