



Evidence-Based Medicine Journal Club

EBM Journal Club Section Editor: Eric B. Milbrandt, MD, MPH

Journal club critique

Early recombinant activated factor VII for intracerebral hemorrhage reduced hematoma growth and mortality, while improving functional outcomes

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Published online: 6 January 2006

This article is online at <http://ccforum/content/10/1/304>

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Critical Care 2006, 10: 304 (DOI 10.1186/cc3978)

Expanded Abstract

Citation

Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T: Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2005, 352:777-785 [1].

Hypothesis

Recombinant activated factor VIIa (rFVIIa) can effectively reduce hematoma growth and improve outcomes when given within 4 hours of symptom onset in patients with acute intracerebral hemorrhage.

Methods

Design: International multi-center randomized placebo-controlled trial.

Setting: Emergency departments and intensive care units in 73 hospitals in 20 countries.

Subjects: 399 adults age 18 years or older with spontaneous intracerebral hemorrhage documented by CT scanning within 3 hours of onset of symptoms. Exclusion criteria included a score of 3 to 5 on the Glasgow Coma Scale (indicating deep coma); planned surgical evacuation of hematoma within 24 hours after admission; secondary intracerebral hemorrhage related to aneurysm, arteriovenous malformation, trauma, or other causes; known use of oral anticoagulant agents; known thrombocytopenia; history of coagulopathy, acute sepsis, crush injury, or disseminated intravascular coagulation; pregnancy;

preexisting disability; and symptomatic thrombotic or vaso-occlusive disease within 30 days before the onset of symptoms of intracerebral hemorrhage. Midway through the trial, the last criterion was amended to exclude patients with any history of thrombotic or vaso-occlusive disease.

Intervention: Patients were randomly assigned to receive a single intravenous dose of 40 µg, 80 µg, or 160 µg per kilogram of rFVIIa (NovoSeven, Novo Nordisk) or placebo. Treatment was given within one hour after the baseline CT and no later than four hours the symptom onset.

Outcomes: The primary outcome was percent change in volume of intracerebral hemorrhage at 24 hours. Secondary outcomes included 90-day mortality and functional status.

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 16 percent, 14 percent, and 11 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 3.3 ml, 4.5 ml, and 5.8 ml in the three treatment groups, as compared with that in the placebo group ($P=0.01$). At 90 days, 69% percent of placebo-treated patients died or were severely disabled (as defined by a modified Rankin Scale score of 4 to 6), as compared with 55 percent, 49 percent, and 54 percent of the patients who were given 40, 80, and 160 µg of rFVIIa,

respectively ($P=0.004$ for the comparison of the three rFVIIa groups with the placebo group). Mortality at 90 days was 29 percent for patients who received placebo, as compared with 18 percent in the three rFVIIa groups combined ($P=0.02$). Serious thromboembolic adverse events, mainly myocardial or cerebral infarction, occurred in 7 percent of rFVIIa-treated patients, as compared with 2 percent of those given placebo ($P=0.12$).

Conclusion

Treatment with rFVIIa within four hours after the onset of intracerebral hemorrhage limits the growth of the hematoma, reduces mortality, and improves functional outcomes at 90 days, despite a small increase in the frequency of thromboembolic adverse events.

Commentary

Intracerebral hemorrhage (ICH) is a devastating form of acute stroke; only 38% of affected patients surviving the first year [2]. Those that do survive are likely to be functionally impaired. The size of the hematoma is directly related to outcome [3] and measures that have the potential to reduce hematoma growth, typically due to early rebleeding, may reduce morbidity and mortality. rFVIIa is approved for the treatment of bleeding in patients with hemophilia and it has been reported to reduce perioperative blood loss after major surgery in subjects without coagulopathy [4]. The current study by Mayer et al. [1] represents the first evidence that rFVIIa may also be helpful for patients with ICH.

This was a well-designed, phase IIb, international, multi-center, randomized placebo-controlled trial that evaluated escalating doses of rFVIIa given within four hours of primary intracranial hemorrhage. Not only was early hematoma growth reduced in the group treated with rFVIIa, but long-term (90-day) clinical outcomes, including mortality and functional status, were also significantly improved.

The potential implications of this study for patients with ICH are enormous, yet a few limitations deserve consideration. The trial was relatively small ($n=399$). Though patients were randomly allocated to the two treatment groups, there were some baseline differences between the arms of the trial, such as more brainstem hemorrhages in the placebo group, which could have biased the results in favor of rFVIIa. While not significantly different, there were greater numbers of thrombotic events (7% vs. 2%, $P=0.12$) in those randomized to rFVIIa, a finding that is not surprising considering the drug's mechanism of action. In fact, exclusion criteria were amended midway through the trial to exclude subjects with any history, as opposed to a history within the prior 30 days, of thrombotic or vaso-occlusive disease. The results of this study only apply to the treatment of *primary* ICH, which is

due to spontaneous rupture of small vessels in the setting of chronic hypertension or amyloid angiopathy [2]. Whether the benefits extend to patients with *secondary* ICH, typically due to anticoagulation, vascular abnormalities, trauma, or tumors, remains to be seen.

A phase III trial of rFVIIa designed to address many of these issues is currently underway [5]. This study will enroll 675 patients with primary ICH within 3 hours of symptom onset, with the primary goal of reducing disability and improving clinical outcome after 3 months. The neurological critical care community will anxiously await the results of the trial. Until then, clinicians and pharmacy and therapeutics committees will struggle to balance the potential benefits, harm, and expense of this drug.

Recommendation

Until the results of the phase III trial are available, we cannot recommend widespread use of rFVIIa for the treatment of primary ICH. Should individual clinicians choose rFVIIa in this setting, its use should be restricted to those patients meeting entry criteria, including timeframe, of the Mayer et al. study [1].

Competing interests

The authors declare that they have no competing interests.

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