Critical Review Form

Therapy

Recombinant Activated Factor VII for Acute Intracerebral Hemorrhage, *NEJM* 2005; 352: 777-85

Objective: In patients with intracerebral hemorrhage, hematoma growth has been shown to occur within the first three hours. This study was designed to determine if recombinant Factor VIIa (NovoSeven) can reduce hematoma growth after intracerebral hemorrhage and improve outcomes.

Methods: Double-blind, placebo controlled trial from August 2002 through March 2004 of 399 patients at 73 hospitals in 20 countries. Although sponsored by Novo Nordisk, the manufacturer of NovoSeven, "the authors had full access to the data, directed the data analysis and were responsible for decisions regarding publication." Exclusion criteria included GCS ≤ 5, planned surgical evacuation of hematoma within 24 hours after admission, aneurysm or trauma related ICH, known use of anticoagulants, thrombocytopenia, sepsis, DIC, pregnancy, or pre-existing disability. Midway through the trial, the authors added any history of thrombotic or vaso-occlusive disease to the exclusion criteria (p. 778).

Randomization was performed in blocks of 4 patients to IV doses of 40 µg, 80 µg, 160 µg, or placebo based upon ideal body weight administered no later than one hour after the CT and four hours after symptom onset. Follow-up CT occurred at 24- and 72-hours with independent readings by two blinded neuro-radiologists (p. 778-779). Clinical follow-up occurred at 24-hours and 90-days after treatment and included the following measurements: GCS, NIHSS, modified Rankin Scale, Extended Glasgow Outcome Scale, and Barthel Index. All analyses were performed on an intention-to-treat basis. When contacted later to identify who is blinded the authors listed the following: patients, clinicians, data collectors, outcome assessors, data analysts, and data/safety monitoring committee (ACP Journal Club 2005; 143: 34).

The primary endpoint was the change in volume of ICH. The authors used a conservative approach in utilizing Bonferroni's correction ($\alpha = 0.0167$) and assigning the worst scores for neurological outcome in patients who died before 90-days. They utilized a cumulative logit model to adjust for age, baseline ICH volume, ICH location, and baseline functional status on 90-day outcomes. The main adverse event was the frequency of thromboembolic episodes at 90 days.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	Yes. See below.
1.	Were patients randomized?	Yes. Patients were randomized to either placebo (standard care) or one of three treatment arms with escalating doses of Factor VII. Randomization was performed in blocks of four patients at multiple sites.

2.	Was randomization concealed (blinded)?	Yes. Patients were all given either a placebo or Factor VII, both of which were delivered as a powder that was re-constituted before administration. See discussion above from ACP Journal Club about who exactly was blinded.

3.	Were patients analyzed in the groups to which they were randomized?	Yes—Intention to treat analysis (p. 779).
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Table 1 demonstrates the baseline patient characteristics at the time of treatment. Gender, race, location of hemorrhage, GCS score, NIHSS, systolic BP, and time from onset of bleed to treatment, all of which were similar. Of note, only 12% of patients presented to study sites that collected "complete screening data." Therefore, the majority of study sites failed to record all of the screening data requested.
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	No—thus minimizing recall bias
2.	Were clinicians aware of group allocation?	No--- thus minimizing measurement and selection bias.
3.	Were outcome assessors aware of group allocation?	No—physicians reading CT scans and performing clinical evaluations were blinded to patient assignment to Factor VII or placebo, thus minimizing ascertainment bias.
4.	Was follow-up complete?	Nearly. 400 patients enrolled in the study and were randomized, 1 later withdrew consent, leaving 399. 396 baseline CT scans and 384 24-hour scans were available for analysis (96 percent of study patients). Patients who died before day 90 were given worst possible scores for neuro impairment and functional outcome. Twenty patients (5%) were alive but lacked complete functional outcome data at 90 days, so scores from day 15 were carried forward. Unfortunately, the authors do not provide a CONSORT diagram to permit readers to identify what happened to each member of the study cohort.
II.	**What are the results (answer the questions posed below)?**	

1.	How large was the treatment effect?	1.) **Hematoma Growth—**Table 2 shows that at 24 hours, intracranial hematoma volume increased 29% from baseline, as compared to (doses of Factor VII) 16% for 40mcg/kg, 14% for 80mcg/kg, and 11% for 160 mcg/kg. This translated into a reduction in volume growth for ICH of about 5ml for the combined treatment group over placebo. Findings for net increase in "Volume of ICH plus IVH plus edema" at 72h showed a reduction of 11ml for the combined Factor VII groups over placebo. 2.) **Clinical Outcome: Death/Disability—**Percentage of patients who were dead or severely disabled at 90 days was 69% for placebo group and 53% for the combined treatment group. This is a RRR of 24%, and an ARR of 16%, for a **NNT of just over 7 patients to prevent one from death or severe disability** (Table 3, p. 783). 3.) **Clinical Outcome: Mortality**—(the ultimate clinical outcome) Placebo group had a 29% mortality at 3 months, vs. 18% in the combined treatment groups, for a RRR of 38%, and ARR of 11%, **NNT to save 1 life=10 patients** (not bad at all). 4) **NNH = 21** (adverse event rate 6.9% versus 2.1% in placebo arm). Although fatal or disabling thromboembolic events that were possibly or probably related to treatment occurred in 2% of both the placebo and treatment arms.
2.	How precise was the estimate of the treatment effect?	Although insufficient data was provided in the paper to calculate Confidence Intervals, the authors did provide the information for the ACP Journal Club review referenced earlier: **Mortality 10 (5-82)** **Unfavorable outcome 7 (4 to 22)** To assess precision as a clinician, ask yourself if either extreme would alter your therapeutic recommendation to the patient.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	

1.	Were the study patients similar to my patient?	The study patients are not like the patient in the vignette, because patients on warfarin were excluded from this study. Of note, there were multiple other exclusion criteria in this study, which decreases the applicability of its findings to patients with: poor GCS scores, planned surgical evacuation of hematoma, bleeding caused by anything other than HTN, thrombocytopenia, sepsis, crush injury, DIC, pregnancy, or history of DVT, CVA or MI. This would exclude a large proportion of patients we see in the ED.
2.	Were all clinically important outcomes considered?	Clinically important outcomes were well evaluated in this study, including death, neurologic disability and functional outcomes as measured by the extended Glasgow Coma Scale, the Barthel Index, the modified Rankin scale, and the NIHSS.
3.	Are the likely treatment benefits worth the potential harm and costs?	Table 3 shows adverse thrombotic events occurred in 2% of the placebo group, and 7% of the Factor VII group. These consisted of both arterial and venous thromboses. Arterial thromboses occurred in 5% of Factor VII patients, including 7 MI's, 9 cerebral infarctions (two of which were fatal). With the exception of one anterior STEMI, all of the MI's were NSTEMI's, with "small troponin elevations" (not specified), and good recoveries. However, given that these patients were all included in the outcomes analysis of death and severe disability, the benefit of using this medication seems to outweigh the potential complications. The price of NovoSeven is another matter (~$8000 per patient).

Limitations

1) **Multiple exclusion criteria were used in this study, including significant co-morbid conditions that patients with ICH we see will have (CAD, hx of CVA). This does limit the generalizability (external validity) of these findings somewhat. However, there is still a large population of ICH patients whose only significant prior history is HTN.**
2) **Initial screening data were complete for only 12% of patients. However, for these patients the baseline characteristics were similar for treatment and control groups.**
3) **Unequal allocation of important risk factors (brainstem hemorrhage, initial GCS) may have favored the treatment arm. Also, the authors provided no information about blood pressure control in the hours following the hemorrhagic stroke, although in a later Letter to the Editor (NEJM 352: 2133-2134) they note no difference in BP control between treatment arms.**

4) **Lack of adjustment for the withdrawal of care may have biased the results in either direction (over-estimating or under-estimating treatment efficacy).**
5) **Industry sponsored trial with obvious competing interest, although the authors seem to have controlled the dissemination of findings.**

Bottom Line

For patients with acute intracerebral hemorrhage less than 3 hours from onset of symptoms, Factor VII limits hematoma growth, reduces mortality (NNT = 9), and improves functional outcomes (NNT = 6). We can say nothing about its benefits for patients who would not have met the exclusion criteria for this study, including those on warfarin. There is a significantly increased risk of arterial and venous thrombotic complications in those who receive this medication. Therefore, until additional safety and efficacy data (Phase III trials) are available, caution should be exercised in giving Factor VII to those patients who are felt to be at high risk for those complications.