Recombinant Activated Factor VII for Acute Intracerebral Hemorrhage

Stephan A. Mayer, MD, FCCM

Abstract—Intracerebral hemorrhage is the least treatable form of stroke and is associated with 30% to 50% mortality rate. Early hematoma growth occurs in 18% to 38% of patients scanned within 3 hours of intracerebral hemorrhage onset, and hematoma volume is an important predictor of poor outcome. Recombinant activated factor VII, a potent initiator of hemostasis, is currently approved for the treatment of bleeding in hemophilia patients with inhibitors and has also been shown to promote hemostasis in patients with normal coagulation. A recent phase IIB randomized, double-blind, placebo-controlled, dose-ranging “proof-of-concept” trial enrolled 399 intracerebral hemorrhage patients to determine whether recombinant activated factor VII can limit ongoing bleeding and improve outcome. An approximate 50% relative reduction in hematoma growth was evident with all 3 doses that were tested (40, 80, and 160 μg/kg), which translated into an average reduction in absolute intracerebral hemorrhage volume growth of 5 milliliters. More importantly, recombinant activated factor VII was associated with a 38% relative reduction in mortality and significantly improved functional outcome among survivors, despite a 5% frequency of arterial thromboembolic events (primarily ischemic stroke and myocardial infarction). A large phase III trial (the FAST trial [Factor Seven for Acute Hemorrhagic Stroke Treatment]) is now in progress to confirm these findings. (Stroke. 2007;38[part 2]:763-767.)

Key Words: intracerebral hemorrhage ■ recombinant activated factor VII

Intracerebral hemorrhage (ICH) is widely regarded as the deadliest and least treatable form of stroke. ICH causes ≈10% of stroke cases in the US and Europe and 20% to 30% in Asian populations. Data for the US in 1997 indicated that of an estimated 37,000 patients presenting with ICH, 35% to 52% had died within 1 month, 10% were living independently after 1 month, and only 20% were independent at 6 months.

In contrast to the many therapeutic advances that have been developed for ischemic stroke and subarachnoid hemorrhage in recent years, there remains a lack of effective treatment for ICH. Existing therapy is primarily supportive in nature, focusing on control on ventilatory support, blood pressure reduction, intracranial pressure monitoring, osmotherapy, fever control, seizure prophylaxis, and nutritional supplementation. Although ICH has long been considered a neurosurgical disease, the recently published International Surgical Trial in Intracerebral Hemorrhage (STICH) showed no effect on functional outcome or mortality with a policy of early surgery within 72 hours of onset compared with best medical management. The current situation regarding therapy for ICH was summarized in a recent scientific statement from the American Heart Association: “Well-designed and well-executed treatment studies of ICH are urgently needed. We hypothesize that ultra-early treatment will be critical for patients with ICH.”

Early Hematoma Growth after ICH

Historically it was thought that the bleeding associated with ICH was completed within minutes of event onset and that the neurological deterioration observed during the first day after the bleed was attributed to cerebral edema and mass effect around the hemorrhage. In the early 1990s, it was recognized that substantial enlargement of hematoma volume can occur in the earliest hours after ICH, even in the absence of coagulopathy (Figure 1). Data from pathological studies, CT analysis, and clinical observations suggest that during the first several hours after onset a form of “ultra-early rebleeding” into congested and damaged tissue around the hematoma can occur. In the only prospective study of this phenomenon, substantial hemorrhage enlargement occurred in 38% of 103 patients initially CT scanned within 3 hours of symptom onset, and in two-thirds of these cases, the increase in hematoma size was already evident 1 hour after the baseline scan. This phenomenon has been corroborated in many large retrospective studies as well (Table).

The time window during which early ICH growth occurs is primarily limited to the first few hours after onset. The only
consistently identified predictor of early hematoma growth is the interval from the onset of symptoms to CT: the earlier the first scan is obtained, the more likely subsequent bleeding will be detected on a follow-up scan. Accordingly, hematoma growth occurs in only 5% of patients who are initially scanned beyond 6 hours of symptom onset.

Ultra-Early Hemostatic Therapy: A New Therapeutic Paradigm

The high frequency of early hematoma growth that occurs when ICH patients are rapidly diagnosed, combined with the well-established relationship between hemorrhage volume and outcome, represents a promising target for therapeutic intervention. Conceptually, ultra-early hemostatic therapy can be viewed as the emergency department counterpart to tissue plasminogen activator for acute ischemic stroke: an urgent intervention that stops ongoing bleeding, reduces tissue injury, and improves functional outcome. The ideal hemostatic agent for use in ICH patients would be one that inhibits fibrinolysis and activates coagulation locally, allowing fast and effective hemostasis without causing systemic thromboembolic adverse events. Although antifibrinolytic agents such as 6-aminocaproic acid and tranexamic acid have been tested in pilot studies to see whether they can prevent ultra-early rebleeding after ICH, the initial experience was not encouraging, which may reflect the fact that these agents can prevent dissolution of existing clot, but do not promote or accelerate the formation of new clot. Aprotinin, an inhibitor of serine proteases such as trypsin, chymotrypsin, plasmin, and kallikrein, interferes with both fibrinolysis and coagulation when blood comes into contact with foreign surfaces, and has been demonstrated to reduce blood loss during cardiac surgical procedures involving cardiopulmonary bypass. However, its potential role in the treatment of ICH is unknown.

Coagulation factor VII is a naturally occurring initiator of hemostasis; normally, only 1% of factor VII circulates in its active form. Recombinant activated factor VII (rFVIIa; NovoSeven; Novo Nordisk; Bagsvaerd, Denmark) was developed for the treatment of spontaneous and surgical bleeding in patients with hemophilia A or B and inhibitors to factors VIII or IX, respectively. rFVIIa binds to the surface of activated platelets where it generates activated factor X allowing partial restoration of platelet surface thrombin generation. Through its action of enhancing local hemostasis after binding to exposed tissue factors, rFVIIa has been shown recently to be an effective initiator of hemostasis in patients with normal coagulation systems. Moreover, its efficacy has been reported in promoting hemostasis in central nervous system bleeding in patients with hemophilia. The relatively low frequency of systemic activation of coagulation associated with rFVIIa use, together with its rapid action at the site of bleeding and short half-life of 2.5 hours, suggest

<table>
<thead>
<tr>
<th>Interval From ICH Onset to CT, h</th>
<th>Prospective</th>
<th>Retrospective</th>
</tr>
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<tbody>
<tr>
<td>0–3</td>
<td>38</td>
<td>NA</td>
</tr>
<tr>
<td>3.1–6.0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>0–6</td>
<td>NA</td>
<td>21</td>
</tr>
<tr>
<td>6.1–24.0</td>
<td>NA</td>
<td>NA</td>
</tr>
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</table>

NA indicates not available.

that rFVIIa may be an ideal agent for use during the earliest stages of ICH.²²

The Phase 2B rFVIIa ICH Trial
In February of 2005, a randomized, placebo-controlled, dose-ranging study testing rFVIIa in noncoagulopathic spontaneous ICH patients was published.²³ The main objective of the study was to determine whether rFVIIa could limit ongoing bleeding and effectively reduce hematoma growth in acute ICH, and thereby improve outcome. The study compared the efficacy of 3 different doses of rFVIIa (40, 80 and 160 µg/kg) to placebo, administered intravenously over 1 to 2 minutes. Patients with ICH diagnosed by CT scan within 3 hours of symptom onset were enrolled, and according to the study protocol treatment was administered within 1 hour of the baseline CT scan. The primary outcome measure was the mean percentage change in ICH volume between baseline and 24 hours as determined by CT scan. In addition, clinical outcomes at 3 months were determined using the following assessment instruments: the modified Rankin Scale (mRS), the Barthel Index, the Extended Glasgow Outcome Scale, and the National Institutes of Health Stroke Scale (NIHSS). The main safety outcome measure was the frequency of thromboembolic serious adverse events at day 90.

In total, 399 patients (61% male, mean age 66 years and predominantly white) were randomized to treatment: placebo (n=96) or 40 µg/kg (n=108), 80 µg/kg (n=92), or 160 µg/kg (n=103) of rFVIIa. Mean ICH volume at baseline was 24 mL, mean interval from symptom onset to baseline CT scan was 114±35 minutes, and mean onset-to-needle time was 167±32 minutes. Approximately 12% of all ICH patients treated at the study centers during the trial period were enrolled and randomized.

The mean percentage increase in ICH volume was 29% after placebo treatment, compared with 16%, 14% and 11% in the rFVIIa 40, 80 and 160 µg/kg groups, respectively (P=0.01 for the comparison of the 3 rFVIIa groups with the placebo group; Figure 2). Mean absolute growth in ICH volume was reduced by 3.3, 4.5 and 5.8 mL with the 40, 80, and 160 µg/kg doses of rFVIIa, respectively (P=0.01, rFVIIa combined versus placebo). Thus, rFVIIa treatment resulted in the prevention slightly <1 teaspoon of additional bleeding into the brain.

Notably, the hemostatic effect of rFVIIa treatment was most pronounced when administered within 3 hours of symptom onset. In the subset of patients where this criterion was met (n=269), the mean percentage increase in ICH volume was 34% in the placebo group compared with 13% for rFVIIa-treated patients (P=0.004). The absolute increase in ICH volume in this subset was 10.7 mL and 4.4 mL for placebo- and rFVIIa-treated patients, respectively (P=0.009). By contrast, there was essentially no difference in mean percent ICH growth between rFVIIa and placebo among patients treated after 3 hours of onset.

At 3 months 29% of the placebo-treated patients were dead compared with 18% of the rFVIIa-treated patients, consistent with a relative mortality reduction of 38% (P=0.02). Furthermore, all 4 global outcome scale assessments at 3 months showed more favorable outcomes with rFVIIa compared with placebo, and these results reached statistical significance for the mRS, Barthel Index, and NIHSS (Figure 3). These results indicated that rFVIIa more than doubled the odds of improving by 1 level on the mRS, and decreased the proportion of patients who died or became disabled from 69% in the placebo group to 53% with rFVIIa treatment (P=0.004). The number-needed-to-treat to prevent 1 additional outcome of dead or severe disability (mRS score of 4 to 6) was slightly >6.

Of course, most medications have side effects, and in this trial rFVIIa was no exception. Thromboembolic serious adverse events occurred in 2% of patients receiving placebo compared with 7% overall for those receiving rFVIIa, and the frequency or arterial thromboembolic adverse events was 0% in placebo compared with 5% with rFVIIa (P=0.01). These serious adverse events included 7 myocardial ischemic events and 9 cases of cerebral infarction that occurred within 4 days of dosing. However, fatal or disabling thromboembolic serious adverse events that were considered possibly or probably related to treatment occurred in 2% of patients receiving placebo and in 2% of rFVIIa-treated patients. A recent analysis of US Food and Drug Administration data found that

Figure 2. Estimated mean ICH volume at baseline, 24, and 72 hours according to treatment group in the Phase 2B Recombinant Activated Factor VII ICH trial.
venous thrombosis (23%) was the most common thromboembolic adverse event reported after rFVIIa administration, followed by ischemic stroke (21%), myocardial infarction (18%), and pulmonary embolism (17%).

The results obtained with rFVIIa treatment in this study are encouraging and offer new hope for ICH patients, for whom there is a tremendous unmet need for effective acute intervention. Perhaps the most surprising finding of this trial was the enormous effect on clinical outcome that resulted from the prevention of a few additional milliliters of bleeding into the brain. Although very promising, however, further research is needed to confirm these results and to determine whether a lower dose might be both safer and just as effective as the 3 doses tested in the phase 2B trial. A large phase III trial (Factor Seven for Acute Hemorrhagic Stroke Treatment, the FAST trial) is now underway. This trial will randomize a total of 816 patients to placebo, 20, and 80 μg/kg of rFVIIa (n=272 per group). The main outcome measure of this trial is a comparison of the proportion of patients who are dead or severely disabled at day 90 according to the mRS. Enrollment was completed in November 2006.

The Potential Role of rFVIIa for Coagulopathic ICH

Warfarin use increases the risk of ICH 5- to 10-fold, and ICH in the setting of anticoagulation carries a particularly grave prognosis, with twice the mortality rate of noncoagulopathic ICH (52% versus 26%). Patients on oral warfarin who present with acute ICH are typically reversed with fresh frozen plasma (15 to 30 mL/kg) or prothrombin complex concentrate (15 to 30 U/kg) and vitamin K (10 mg IV daily for 3 days) immediately in an attempt to avoid progressive bleeding, which occurs more often and over a much longer period of time than in noncoagulopathic ICH. Unfortunately, the effectiveness of this approach is often hampered by the large volumes administered and the long period of time needed to normalize the international normalized ratio (INR), which can take as long as 24 hours.

An attractive alternative to conventional factor replacement for reversing warfarin anticoagulation is rFVIIa administration. Almost any intravenous dose of rFVIIa can normalize the INR in an anticoagulated patient within minutes, but the duration of this effect is short-lived and the duration of INR normalization depends on the amount given: doses of 5 to 20 μg/kg normalize the INR (<1.5) for 6 to 9 hours, doses of 40 to 80 normalize the INR from 9 to 12 hours, and doses ≥120 μg/kg normalize the INR from 12 to 24 hours. Published series indicate that a wide range of rFVIIa doses can rapidly normalize elevated INR values in patients with oral anticoagulant-related ICH (Figure 4). In the majority of patients rFVIIa was given in addition to conventional therapy with fresh frozen plasma and vitamin K, and the dose of rFVIIa in these reports generally ranged from 60 to 90 μg/kg. No thrombotic complications occurred. Although the
use of rFVIIa for anticoagulant-associated ICH is promising, we know far too little at this point about how it should be dosed, and whether this treatment approach is truly safe in a patient population that is at high risk for thromboembolic complications. There is an urgent need for dose-ranging studies to determine whether rFVIIa can safely attenuate ongoing bleeding in oral anticoagulant-related ICH.

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References

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