The Effect of Activated Factor VII for Intracerebral Hemorrhage Beyond 3 Hours Versus Within 3 Hours

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Background and Purpose—Recombinant-activated factor VII (rFVIIa) is an investigational treatment for intracerebral hemorrhage (ICH). We have evaluated the drug’s treatment effect based on time to treatment.

Methods—ICH patients treated up to 4 hours from symptom onset were divided based on time to treatment: ≤3 hours (3H) and 3 to 4 hours (4H). Head CT was done at baseline and 24 hours. Outcome measures included: ICH growth at 24 hours, mortality, favorable outcome and discharge disposition. A cohort of nontreated matched ICH patients was used to assess the clinical efficacy.

Results—Forty-six patients were treated with rFVIIa: 24 in the 3H group (range 70 to 180 minutes), 22 in the 4H group (range 181 to 300). One hundred and forty-eight patients formed the control group. Mean baseline ICH volume was 8.8 mL for 3H and 10.1 mL for 4H. Mean 24-hour volume was 9.3 mL for 3H (absolute increase 1.05 mL, relative increase 11.9%) and 11.5 mL for 4H (absolute increase 1.1 mL, relative increase 10.9%); P=0.47 is for the difference in relative increase. Mortality was 12.5% for 3H group, 13.6% for 4H, and 13.1% for the control. In the 3H group, 58.3% were discharged with a poor outcome, compared with 54.5% in 4H and 54.1% in the control. Thrombotic adverse events occurred in 11.1% of patients treated with rFVIIa.

Conclusions—In our off-label with rFVIIa, we did not find evidence of a treatment effect based on time to treatment. Other criteria should be sought to identify patients who might benefit clinically from rFVIIa. (Stroke. 2008;39:000-000.)

Key Words: hematoma growth ■ intracerebral hemorrhage ■ recombinant-activated factor VII

Spontaneous intracerebral hemorrhage (ICH) comprises 20% of all strokes. Early hematoma expansion occurs in one-third of patients. Recombinant-activated factor VII (rFVIIa) is a direct hemostatic agent being studied for ICH treatment. Current data suggest a reduction in hematoma growth but no overall benefit. A subgroup analysis of the phase II trial suggested no benefit in patients treated beyond 3 hours from onset. The purpose of this study was to compare ICH patients receiving rFVIIa beyond 3 to 4 hours from symptom onset with those treated 0 to 3 hours and control patients receiving standard treatment.

Methods

The study was approved by the Institutional Review Board. Informed consent was obtained in all treated patients. Our off-label protocol allowed treatment of ICH patients with rFVIIa 80 μg/kg within 1 hour of the initial CT, no more than 4 hours from symptom onset. Exclusion criteria included: Glasgow Coma Score <5, secondary ICH and recent thrombotic events. Patients with warfarin-related ICH received a lower dose of 40 μg/kg. Head CT was repeated at 24 hours for all treated patients.

ICH volume was calculated using the ABC2 method by 2 authors (H.H. and N.R.G.), who were blinded to clinical outcome. We did not calculate edema volume or intraventricular hemorrhage volume. Patients were allocated into 2 treatment groups: 0 to 3 hours (3H group) and 3 to 4 hours from symptom onset (4H group). Study end points were hematoma growth at 24 hours, in-hospital mortality, and modified Rankin Scale (mRS) on discharge. Poor outcome was defined as mRS 4 to 6. The safety analysis included all the major thrombotic events during hospital stay.

To further assess the clinical efficacy of rFVIIa treatment we used a cohort of ICH patients not treated with rFVIIa either because they presented later than 4 hours from onset or before the rFVIIa protocol was implemented. They were matched to the rFVIIa group by age and baseline National Institutes of Health Stroke Scale range, ICH volume range and proportion of intraventricular hemorrhage. Both treatment and control groups received routine ICH care in the intensive care unit or stroke unit by the same stroke team.

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Table 1. Baseline Characteristics and Timing of Treatment

<table>
<thead>
<tr>
<th></th>
<th>TTT 0–3H, n=24</th>
<th>TTT 3–4H, n=22</th>
<th>P Value, 3H vs 4H</th>
<th>Combined, 3H &amp; 4H</th>
<th>Controls, n=148</th>
<th>rFVIIa Phase II, 80 µg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range)</td>
<td>61.6 (40–87)</td>
<td>58.2 (38–82)</td>
<td>0.66</td>
<td>59.6 (38–87)</td>
<td>57.8 (40–80)</td>
<td>65</td>
</tr>
<tr>
<td>NIHSS, mean (range)</td>
<td>15.9 (5–29)</td>
<td>15.6 (4–28)</td>
<td>0.98</td>
<td>15.7 (4–29)</td>
<td>13.9 (5–28)</td>
<td>12</td>
</tr>
<tr>
<td>ICH (%)</td>
<td>6 (25)</td>
<td>8 (36)</td>
<td>0.68</td>
<td>8.6 (35)</td>
<td>48 (32.4)</td>
<td>167</td>
</tr>
<tr>
<td>Minutes from onset to treatment, mean (range)</td>
<td>144 (70–180)</td>
<td>217 (181–300)</td>
<td>0.45</td>
<td>179 (70–300)</td>
<td>167</td>
<td></td>
</tr>
</tbody>
</table>

TTT indicates time to treatment, rFVIIa Phase II, −80 µg/kg treatment arm of the phase II rFVIIa trial; ICH, intraventricular hemorrhage; NIHSS, National Institutes of Health Stroke Scale.

Statistical Analysis
The analysis was carried out using SPSS for Windows v. 11.5. All volumes were log transformed to obtain normality. P<0.05 was considered significant.

Results
We treated 54 patients with rFVIIa. Three patients had a coagulopathy and 5 underwent hematoma evacuation and were excluded from the efficacy analysis. There were 24 patients in the 3H group (range 70 to 180 minutes) and 22 in the 4H group (range 181 to 300). Two patients in the 4H group were treated 264 and 300 minutes from symptom onset (Table 1). Inter-rater agreement for hematoma volume calculations was excellent (r=0.9).

Hematoma Expansion
Mean baseline ICH volume was 8.8 mL for 3H and 10.1 mL for 4H (t test P=0.63). The control group had a significantly higher baseline volume (18.9 mL; t test P=0.01). At 24 hours mean volume increased to 10.1 mL for 3H and 11.5 mL for 4H (11.9% and 10.9% relative increase for 3H and 4H, respectively; t test P=0.47; Table 2).

Clinical Outcome
Mortality was 12.5% (3/24) in 3H and 13.6% (3/22) in 4H (χ² P=0.9). In 3H 58.3% (14/24) had a poor outcome versus 54.5% in 4H (12/22) (χ² P=0.96). In the control group, mortality was 13.5% (20/148), and 54.1% (80/148) had a poor outcome. This rate was not different from the treatment group (χ² P=0.8) (Table 3).

Safety
A total of 7 (12.9%) thrombotic events occurred in 6 patients in the treatment group: 2 in 3H group and 5 in 4H group (Fisher exact test P=0.54). There were 4 myocardial infarctions (occurring within 24 hours of treatment), 2 deep vein thrombosis (76 to 96 hours) and 1 pulmonary embolus (120 hours; Table 3).

Discussion
We did not detect a significant difference in the magnitude of ICH growth between groups based on time to treatment, and the clinical outcome was comparable. The smaller increase in ICH volume in the 4H group could be explained by reduced rate of continued bleeding beyond 2 to 3 hours from symptom onset.1 Also, there was no difference in clinical outcome compared with the control group. This replicates the preliminary results from the phase III trial.2 One explanation for the lack of clinical benefit is that rFVIIa treatment is only beneficial in a more selected patient population, ie, those most likely to experience hematoma enlargement. The time window for rFVIIa treatment is probably important given the dynamic nature of ICH in the first few hours.3 Our data suggest that this window can be extended up to 4 hours.

This study is limited by its small sample size. This may not enable detection of minor differences between the 2 treatment groups. It is further limited by its retrospective nature. ICH volumes in our treatment group were lower than the control. A selection bias cannot be excluded; however, this is less likely because the inclusion and exclusion criteria were largely clinical and the majority of control patients were not eligible for treatment because of their late arrival to the hospital.

The safety of rFVIIa is an ongoing issue.6 Previous trials with rFVIIa found adverse events in the range of 4% to 14%.7 Our results of 12.9% are similar.

In summary, our data indicate that patients treated with 80 µg/kg of rFVIIa 3 to 4 hours from symptom onset produces similar hemostatic effect and clinical outcome compared with patients treated within 3 hours.

Table 2. Hematoma Volumes*

<table>
<thead>
<tr>
<th></th>
<th>TTT 0H–3H, n=24</th>
<th>TTT 3H–4H, n=22</th>
<th>P Value, Combined, Controls, n=148</th>
<th>rFVIIa Phase II, 80 µg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH volume in mL, mean (95% CI for the mean)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>8.9 (6–13)</td>
<td>10.1 (6.5–15.7)</td>
<td>0.63</td>
<td>18 (15.9–20.3)</td>
</tr>
<tr>
<td>At 24 hours</td>
<td>9.3 (6.1–13.9)</td>
<td>11.5 (7.5–17.5)</td>
<td>0.45</td>
<td>10.3±2.6</td>
</tr>
<tr>
<td>Absolute increase in mL, mean±SD</td>
<td>1.05±1.4</td>
<td>1.1±1.3</td>
<td>0.49</td>
<td>1.09±1.37</td>
</tr>
<tr>
<td>Percent increase from baseline, mean±SD</td>
<td>11.9±15.9</td>
<td>10.9±12.9</td>
<td>0.47</td>
<td>11.6±14.6</td>
</tr>
</tbody>
</table>

*Hematoma volumes were calculated using the ABC2 method. Volumes were log-transformed to obtain normality. See Table 1 for abbreviations.
Sources of Funding
James Grotta reports having received research grant support from Novo Nordisk.

Disclosures
Nicole Gonzales reports receiving a one-time consulting fee from Novo Nordisk; Miguel Escobar served as a consultant for Novo Nordisk and has served on the DSMB for Novo Nordisk clinical trials.

References

Table 3. Outcome and Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>TTT 0H–3H, n=24</th>
<th>TTT 3H–4H, n=22</th>
<th>P Value, Combined, Controls, n=148</th>
<th>rFVIIa Phase II, 80 µg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay in days, median (range)</td>
<td>9 (2–29)</td>
<td>9.5 (3–72)</td>
<td>0.37</td>
<td>9 (2.72)</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>3 (12.5)</td>
<td>3 (13.6)</td>
<td>0.9</td>
<td>6 (13.0)</td>
</tr>
<tr>
<td>Poor outcome (%)</td>
<td>14 (58.3)</td>
<td>12 (54.5)</td>
<td>0.96</td>
<td>26 (56.5)</td>
</tr>
<tr>
<td>Thromboembolic events (% of 54 patients)</td>
<td>Total 2 (7.4) 5 (18)</td>
<td>0.54</td>
<td>7 (12.9)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>MI</td>
<td>1</td>
<td>3</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>DVT</td>
<td>1</td>
<td>1</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>PE</td>
<td>0</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; PE, pulmonary embolus; DVT, deep vein thrombosis. See Table 1 for other abbreviations.
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