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

Hen Hallevi, MD; Nicole R. Gonzales, MD; Andrew D. Barreto, MD; Sheryl Martin-Schild, MD, PhD; Karen C. Albright, DO, MPH; Elizabeth A. Noser, MD; Kachi Illoh, MD; Aslam M. Khaja, MD; Teresa Allison, PharmD; Miguel A. Escobar, MD; Hashem M. Shaltoni, MD; James C. Grotta, MD

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 use of 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;39:473-475.)

Key Words: hematoma growth ■ intracerebral hemorrhage ■ recombinant-activated factor VII
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, Combined, n=148</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>
</tr>
<tr>
<td>NIHSS, mean (range)</td>
<td>15.9 (5–29)</td>
<td>15.6 (4–28)</td>
<td>0.08</td>
<td>15.7 (4–29)</td>
<td>13.9 (5–28)</td>
</tr>
<tr>
<td>ICH (%)</td>
<td>6 (25%)</td>
<td>8 (36%)</td>
<td>0.68</td>
<td>48 (32.4)</td>
<td></td>
</tr>
<tr>
<td>Minutes from onset to treatment, mean (range)</td>
<td>144 (70–180)</td>
<td>217 (181–300)</td>
<td>179 (70–300)</td>
<td></td>
<td>167</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.1 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%.3,7 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>Combined, 3H &amp; 4H, n=148</th>
<th>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>At baseline</td>
<td>8.9 (6–13)</td>
<td>10.1 (6.5–15.7)</td>
<td>9.4±2.6</td>
<td>18 (15.9–20.3)</td>
</tr>
<tr>
<td></td>
<td>At 24 hours</td>
<td>9.3 (6.1–13.9)</td>
<td>11.5 (7.5–17.5)</td>
<td>10.3±2.6</td>
<td>28</td>
</tr>
<tr>
<td>Absolute increase from baseline 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>
<td>4.2</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>
<td>14</td>
</tr>
</tbody>
</table>

*Hematoma volumes were calculated using the ABC³ method. Volumes were log-transformed to obtain normality. See Table 1 for abbreviations.
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, n=46</th>
<th>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>
<td>7 (2–74)</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>
<td>20 (13.5)</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>
<td>80 (54.1)</td>
</tr>
<tr>
<td>Total Thromboembolic events (% of 54 patients)</td>
<td>2 (7.4)</td>
<td>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>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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


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


Stroke. 2008;39:473-475; originally published online January 3, 2008;
doi: 10.1161/STROKEAHA.107.497651

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/39/2/473

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/