Determinants of Intracerebral Hemorrhage Growth

An Exploratory Analysis

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Background and Purpose—We report an exploratory analysis from a randomized study of recombinant activated factor VII (rFVIIa) in patients with intracerebral hemorrhage (ICH) examining potential factors associated with hemorrhage growth.

Methods—We explored the relationship between 5 different measures of change in hemorrhage volume between baseline and 24-hour CTs (absolute and percent change in ICH volume, ICH growth—categoric [no growth if change < -33% and < 12.5 mL], absolute and percent change in ICH plus intraventricular hemorrhage [IVH] volume) and 31 demographic, clinical, imaging, historic, and baseline laboratory variables. Variables with a probability value of ≤0.10 were included in the final multivariable models.

Results—Treatment with rFVIIa and a longer time-from-onset-to-baseline CT were related to a decrease in hemorrhage growth in all 5 models. ICH volume on baseline CT was consistently associated with ICH growth in the various models. Other variables significantly related to growth of ICH or ICH+IVH in at least 1 of the 5 models include serum glucose (increased levels associated with increased growth), body mass index (heavier people have less growth), prior use of antiplatelet agent (prior use associated with increased growth), serum cholesterol (higher level associated with less hemorrhage growth), and serum creatinine (higher level associated with more hemorrhage growth).

Conclusions—Our exploratory analyses confirm that treatment with rFVIIa limits ICH growth in subjects with spontaneous ICH who met the criteria for this study. Most hematoma growth occurs early after onset of ICH. Larger hematomas on the baseline CT were associated with increased absolute ICH growth. The relationship of other factors to hemorrhage growth warrants further study. (Stroke. 2007;38:1072-1075.)

Key Words: intracerebral hemorrhage ■ intraventricular hemorrhage ■ growth ■ recombinant activated factor VII ■ volume

Little is known about the baseline factors related to intracerebral hemorrhage (ICH) growth during the first hours after ICH onset.1 Here, we report an exploratory analysis from a study of recombinant activated factor VII (rFVIIa) in ICH examining potential factors associated with hemorrhage growth.

Materials and Methods

Overall Study Design

Details of the design of this randomized, double-blind, placebo-controlled trial have been previously reported.2 In brief, 399 patients with spontaneous ICH, diagnosed by CT within 3 hours after onset, were randomized to placebo (n = 96), 40 μg/kg rFVIIa (n = 108), 80 μg/kg (n = 92), or 160 μg/kg (n = 103) within 1 hour after the baseline CT. The primary outcome measure was the percent change in ICH volume from baseline to 24-hour CT.

CT Image Analysis

Follow-up CT were performed at ~24 and 72 hours after administration of study treatment (ie, within a window of 3 hours before and after these times). When a follow-up CT was not available within the specified 24-hour period, the first follow-up scan obtained within 48 hours was analyzed, where this was available. Digital CT data were transmitted to an imaging laboratory (Bio-Imaging Technologies) and analyzed in random order with the use of Analyze software (Mayo Clinic) by 2 neuroradiologists who were blinded to treatment assignments.3 The volumes of ICH and intraventricular hemorrhage (IVH) were calculated using standard planimetric techniques.

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Multivariable Models of ICH and ICH+IVH Growth From Baseline to 24-hour CT (P values: . . . is used if variable was not significant in specific model)

<table>
<thead>
<tr>
<th>Specific Model</th>
<th>% Change in ICH</th>
<th>% Change in ICH+IVH</th>
<th>Absolute Change in ICH</th>
<th>Absolute Change in ICH+IVH</th>
<th>Categoric Change in ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment, rFVIIa vs placebo</td>
<td>0.0245</td>
<td>0.0123</td>
<td>0.0113</td>
<td>0.0184</td>
<td>0.0780</td>
</tr>
<tr>
<td>Time from onset to baseline CT, per 30 minutes</td>
<td>0.0623</td>
<td>0.0292</td>
<td>0.0252</td>
<td>0.0144</td>
<td>0.0064</td>
</tr>
<tr>
<td>ICH volume on baseline CT, per 10 mL</td>
<td>&lt;0.0001</td>
<td>0.0092</td>
<td>...</td>
<td>0.0347</td>
<td>0.0146</td>
</tr>
<tr>
<td>IVH volume on baseline CT, per 10 mL</td>
<td>...</td>
<td>0.0429</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Baseline weight, per 5 kg</td>
<td>0.0473</td>
<td>0.0462</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Glucose, per 3 mmol/L</td>
<td>...</td>
<td>0.0767</td>
<td>0.02</td>
<td>0.0306</td>
<td>...</td>
</tr>
<tr>
<td>Antiplatelet use</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Total serum cholesterol, per 1 mmol/L</td>
<td>0.0680</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Serum creatinine, per 30 μmol/L</td>
<td>...</td>
<td>0.0483</td>
<td>...</td>
<td>0.0102</td>
<td>...</td>
</tr>
</tbody>
</table>

Assessments
Measurement data from ICH and IVH volumes enabled 5 different dependent variables (4 continuous and 1 categoric) to be assessed, to measure and evaluate changes in hemorrhage volume between baseline and 24-hour CT: absolute and percent change in ICH volume, ICH growth—categoric (no growth if change <33% and <12.5 mL), and absolute and percent change in ICH+IVH volume.

Statistical Analyses
Data were available for 31 different covariates: demographic variables, baseline systolic and mean blood pressures, hemorrhage characteristics (such as volume and location), concomitant illnesses, use of antiplatelet drugs, and baseline laboratory data such as platelet count. Missing values of laboratory data were replaced by the median for that covariate to limit bias in the multivariable analysis. For each of the 4 continuous end points, a mixed model with reader and subject as random effects, and treatment with rFVIIa as fixed effects, was used as the basic model. Both the percent change in ICH and ICH+IVH volumes were log-transformed (log [variable + 100]) to fulfill the normality assumption. For the categoric end point, a logistic model with treatment as covariate was used as the basic model. Treatment was evaluated as placebo versus rFVIIa in all cases.

Each covariate was analyzed individually (univariate analysis) to find possible significant predictors for the outcome under evaluation (F test used for all variables); the covariates found to be significant at the P=0.25 level were then included in a multivariable model, which was reduced by successively removing the least significant covariate from the model. All covariates with P<0.10 were kept in the final model.

Results
Univariate Analyses
Three hundred and eighty-two people had CT scans at the 2 timepoints defined in the Materials and Methods section that were available for analysis. The supplemental Table I (available online at http://stroke.ahajournals.org) presents the univariate analyses for the 5 measures of hemorrhage growth. Factors associated with P=0.25 and included in the multivariable modeling are highlighted in bold. Variables that did not reach the probability value cut-off (P=0.10) in any of the 5 measures of ICH growth included sex, race, presence of IVH on baseline CT, location of ICH, activated partial thromboplastin time, history of hypertension, t-dimers, international normalized ratio, and serum fibrinogen.

Multivariable Analyses
The Table presents the results of the 5 multivariable models of hemorrhage growth. Twenty-nine patients had missing serum creatinine, glucose or cholesterol (27 overlapping for the 3 values), and 38 had missing prothrombin times, international normalized ratios and fibrinogens (all 38 overlapping).

Treatment with rFVIIa was related to a decrease in hemorrhage growth in all models. Dose of rFVIIa as a continuous variable (eg, 0, 40, 80 or 160 μg/kg) was tested in the univariate analysis and found to be a statistically significant predictor for absolute change in ICH and ICH+IVH volumes. However, the dose-response relationship was nonlinear. To improve statistical power, all dose levels were pooled for comparison with placebo in the final multivariable models.

Increased delays from symptom onset to CT resulted in smaller growth of ICH and ICH+IVH being observed from baseline to 24-hour CT. Further analysis on the interaction between treatment group (ie, rFVIIa versus placebo) and time from onset to baseline CT showed that delays from onset to baseline CT were associated with a smaller volume expansion being detected. This effect was more noticeable for patients treated with rFVIIa than placebo (P<0.05 for absolute ICH change, P<0.10 for absolute and percent ICH+IVH change).

ICH volume on baseline CT was associated with ICH growth. In the models of absolute change in ICH+IVH volume and categoric measure of ICH growth, larger ICH volume on baseline CT was associated with hemorrhage growth. However, when analyzing percent change in ICH and ICH+IVH volume, smaller ICH volume on baseline was associated with higher percent changes. This relates in part to issues of measuring relative versus absolute change. For a given volume of hemorrhage growth, a 1 mL increase in ICH volume translates to a much higher percentage growth in small hematomas compared with larger ones. Similarly, a small percent change of additional bleeding into a large hematoma as a few more millimeters can translate to a relatively large absolute change in volume. No significant interaction between treatment and baseline ICH hemorrhage volume was demonstrated (P>0.12 in all instances).

Other variables associated with growth in at least 1 of the multivariable models included baseline glucose (a higher baseline level of glucose is associated with an increased
hemorrhage growth), baseline weight/body mass index (heavier people have a significantly smaller percent change in hemorrhage growth than those of normal weight), use of antiplatelet agents before study (more likely to have ICH growth), serum cholesterol (higher baseline level associated with hemorrhage growth), and creatinine (higher baseline level of serum creatinine associated with an increased hemorrhage growth).

Discussion

Our exploratory analyses demonstrate that the use of rFVIIa limits growth of ICH in subjects with spontaneous ICH who met the criteria for this study. In addition, early timing of the baseline CT and an increasing ICH volume on baseline CT are associated with increased absolute ICH growth on the subsequent CT. Other potential factors related to ICH growth included body weight or body mass index, prior antiplatelet use, elevated glucose, serum cholesterol, and serum creatinine. Of note, hemorrhage growth was not related to baseline blood pressure. Our study cannot address factors related to growth in other populations of patients with ICH that were excluded from the present trial, such as those on anticoagulants or ICH attributable to head trauma.

There are limited prospective data concerning factors related to early ICH growth. In one prospective cohort study (n = 103) no factors significantly related to ICH growth were found, although an association between a delay from symptom onset to baseline CT and decreased likelihood of growth approached statistical significance (P = 0.08). In another prospective study, patients with early hemorrhage growth were enrolled slightly earlier (5.7 hours) than those without early hemorrhage growth (5.9 hours), but this difference was not significant. Our current study had significantly more power to evaluate this relationship because of its 4-fold greater sample size. One can infer from these findings that the more quickly an active hemostatic agent is administered, the more likely is the impact on ICH growth and clinical sequelae.

We found that larger baseline ICH volumes are associated with a greater likelihood of absolute ICH growth. This observation supports the findings of the above prospective study in which early ICH growth occurred in 15 (22.3%) of 67 patients with baseline ICH < 20 mL, and in 39 (33.6%) of 116 patients with baseline ICH ≥ 20 mL.4,5 One possible explanation of the association between heavier weight and decreased likelihood of growth may be a volume-based dose relationship of rFVIIa, which was administered based on estimated body weight. However, blood volume is not linearly related to weight, and percent change in blood volume is less than percent change in body weight. This could result in a relatively higher rFVIIa plasma concentration in heavier-weight patients. Given the dose-response relationships seen in the primary outcome measure of this study, it is possible that weight-based effects merely mirror differences in plasma concentrations. Such a relationship between weight and the effectiveness of lytic drugs has been seen in randomized trials of acute myocardial infarction.6

Elevated serum glucose and a history of diabetes have been associated with a greater risk of ICH in patients treated with lytic agents.7,8 To our knowledge, the present trial is the first to suggest a relationship between elevated glucose and increased risk of hemorrhage growth in spontaneous ICH and requires confirmation in other larger trials of ICH. Certainly, serum glucose becomes elevated in response to increased stroke severity and may be a marker for larger ICH and patient stress rather than a contributing cause of hemorrhage growth. Whether there is a causal relationship between elevated blood glucose and hemorrhage size remains uncertain.

In one of our models, prior antiplatelet use was linked to growth of spontaneous ICH. Neither of the previous prospective studies reported such a relationship.9,5 A retrospective study reported a relationship between prior antiplatelet use and hemorrhage growth as measured by follow-up CT on the second hospital day.9 In addition, a retrospective chart review demonstrated a relationship of prior aspirin use with mortality and ICH expansion.10 Although the relationship between prior antiplatelet agent use and increased hemorrhage growth is biologically quite plausible, this observation needs to be confirmed in subsequent trials.

In our analyses, higher serum creatinine levels were linked with increased hemorrhage growth whereas higher serum cholesterol was associated with decreased hemorrhage growth. A biological explanation for the first relationship could be that creatinine is a recognized marker of longstanding hypertension with accumulated vascular injury and increased fragility of small vessels. However, history of hypertension was not found to be a significant factor in our analyses. Similarly, elevated creatinine levels may reflect severe renal dysfunction, which is associated with impaired platelet function.11 Baseline creatinine values of 0.4 to 8.14 mg/dL indicated that there were some (n = 25) patients with significant renal dysfunction in our study population. Elevated cholesterol has been associated with a decreased risk of ICH occurrence but has not been previously linked to ICH growth.12 These observations should be explored in future studies.

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References


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