Asymptomatic Hemorrhage After Thrombolysis May Not Be Benign

Prognosis by Hemorrhage Type in the Canadian Alteplase for Stroke Effectiveness Study Registry

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Background and Purpose—There is ongoing controversy about the impact of hemorrhagic transformation after thrombolysis on long-term functional outcome. We sought to study the relation between the type of hemorrhagic transformation on CT scans and functional outcome.

Methods—Data were obtained from the Canadian Alteplase for Stroke Effectiveness Study. This study was established as a registry to prospectively collect data for acute stroke patients receiving intravenous alteplase within 3 hours from stroke onset between February 1999 and June 2001. Follow-up was completed at 90 days, and good functional outcome was defined as a modified Rankin Scale score of 0 or 1. Copies of head CT scans obtained at 24 to 48 hours after starting treatment were read in consensus by a central reading panel consisting of 1 neuroradiologist and 1 stroke neurologist. According to European Cooperative Acute Stroke Study criteria, hemorrhagic transformation was classified as none, hemorrhagic infarction (HI-1 and HI-2), or parenchymal hematoma (PH-1 and PH-2). We compared outcome across groups and performed a multivariable analysis including previously determined important predictors of good outcome in acute ischemic stroke.

Results—From 1135 patients enrolled at 60 centers across Canada, 954 follow-up CT scans were assessable. We observed some hemorrhagic transformation in 259 of 954 (27.1%) patients (110 HI-1, 57 HI-2, 48 PH-1, and 44 PH-2). Proportions of patients with good outcome were 41% with no hemorrhagic transformation, 30% with HI-1, 17% with HI-2, 15% with PH-1, and 7% with PH-2 (P<0.001, χ² test). After adjustment for age, baseline serum glucose, baseline Alberta Stroke Program Early CT score, and baseline National Institutes of Health Stroke Scale score, HI-1 was not a predictor of outcome. However, HI-2 (odds ratio=0.38, 95% CI=0.17 to 0.83), PH-1 (odds ratio=0.32, 95% CI=0.12 to 0.80), and PH-2 (odds ratio=0.14, 95% CI=0.04 to 0.48) were all negative predictors of outcome.

Conclusions—The likelihood of a poor outcome after thrombolysis was proportional to the extent of hemorrhage on CT scans. HI grades of hemorrhagic transformation may not be benign. (Stroke. 2007;38:75-79.)

Key Words: acute stroke ▪ intracranial hemorrhage ▪ thrombolysis ▪ thrombolytic treatment

The fear of thrombolysis-related hemorrhagic transformation of ischemic brain tissue after stroke thrombolysis is a major obstacle toward the goal of extending this treatment modality to a higher proportion of patients with acute ischemic stroke. There is concern that severe thrombolysis-related hemorrhagic transformation might dramatically worsen an individual patient’s prognosis. However, it is still a matter of debate how the extent of hemorrhagic transformation influences each patients’ short- and long-term functional outcomes.1–3 The radiological finding of hemorrhagic transformation of infarcted brain tissue on follow-up imaging is not always responsible for the clinical deterioration observed within the first hours and days after thrombolysis, and thus, the definition of “thrombolysis-related symptomatic intracerebral hemorrhage” (ICH) can be problematic.2 Hacke et al4,5 and Pessin et al6 proposed grading hemorrhagic transformation according to radiological criteria; these were used as safety end points for thrombolysis-related hemorrhagic transformation in the European Cooperative Acute Stroke Studies (ECASS). Secondary analyses of the ECASS data suggested that large parenchymal hematomas (PHs) but not hemorrhagic infarction (HI) predicted a poor outcome at 3 months.7,8 In patients

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with middle cerebral artery occlusions who have received intravenous tissue plasminogen activator, HI was a marker of early reperfusion and improved short- and long-term clinical outcomes compared with both the absence of any hemorrhagic transformation and the presence of PH. These data suggest that the extent of hemorrhagic transformation might not be linearly related to patient outcome.

We sought to determine the relation between the extent of hemorrhagic transformation on posttreatment CT scans and long-term functional outcome in the Canadian Alteplase for Stroke Effectiveness Study. We hypothesized that HI would be a better predictor of excellent functional outcome at 3 months than the absence of any hemorrhagic transformation or the presence of PH.

**Patients and Methods**

The Canadian Alteplase for Stroke Effectiveness Study was a prospective, observational, cohort study established as a Canadian registry to collect data from acute ischemic stroke patients receiving intravenous alteplase within 3 hours from stroke onset between February 1999 and June 2001, as previously described in detail.10

A cranial CT scan was mandatory at baseline and at 24 to 48 hours. Each center was asked to submit all CT scans for prospective assessment by a central reading panel consisting of stroke neurologists (M.H., P.B., A.D.) and a neuroradiologist (J.P.). The scoring of hemorrhage type was determined by consensus. The readers independently applied the Alberta Stroke Program Early CT Score (ASPECTS) to all available baseline CT scans. The median was used as a consensus score. In addition, the panel rated all follow-up CT scans for signs of hemorrhagic transformation according to the ECASS classification: HI-1 (small petechiae); HI-2 (confluent petechiae); PH-1 (hematoma in <30% of the infarcted area, with a mild space-occupying effect); and PH-2 (hematoma in >30% of the infarcted area, with a significant space-occupying effect). Subarachnoid or intraventricular hemorrhage was not specifically scored. One patient who died from a large, isolated, intraventricular hemorrhage was graded as PH-2. Symptomatic ICH was defined by the investigators as any decline in neurological status in the first 24 hours after thrombolysis consistent with the presence of hemorrhagic transformation on the follow-up CT scan when the hemorrhage was the main cause of neurological deterioration.

Baseline variables, including National Institutes of Health Stroke Scale (NIHSS) score, were obtained, and the modified Rankin Scale (mRS) score was assessed at 90 days. Protocol violations were primarily time violations (>3-hour onset-to-treatment time).

**Statistical Analysis**

Our primary outcome measure was excellent functional outcome at 3 months, defined as an mRS score of 0 or 1. This outcome was adjusted for baseline (prestroke) mRS score as described previously.10 Secondary outcome measures were mortality and poor outcome (mRS score of 5 or 6) at 3 months. The incidence of each hemorrhagic transformation subtype and functional outcome across hemorrhagic transformation groups were compared by a χ² test. We considered the degree of hemorrhagic transformation (none through PH-2) as an ordered categorical variable. We used dummy variables to represent each category within a multivariable logistic-regression analysis, with “no hemorrhagic transformation” as the reference. We included known predictors of outcome at baseline, such as age, onset-to-treatment-time, baseline glucose, ASPECTS value, NIHSS score, systolic blood pressure, mean arterial pressure, history of congestive heart failure, diabetes, hypertension, smoking, coronary artery disease, valvular heart disease, dementia, atrial fibrillation, antiplatelet therapy, and protocol violation and computed odds ratios (ORs) for both excellent and poor functional outcomes.

**Results**

From 1135 patients enrolled at 60 centers across Canada, 954 follow-up CT-scans were available for assessment. The rate of symptomatic ICH among patients without assessable follow-up CT scans was 5.5% compared with 4.4% among scans available to the reading panel (P=0.559, Fisher exact test). Our final cohort had a median age of 73.5 years (range, 20 to 97 years), a median onset-to-treatment-time of 153 minutes (interquartile range, 126 to 175 minutes), and a median NIHSS score of 14 (interquartile range, 9 to 19). Baseline characteristics across hemorrhagic transformation groups are described in Table 1. Patients who experienced PH were more likely to have a history of diabetes mellitus, higher blood glucose level, and higher systolic blood pressure at baseline. We observed hemorrhagic transformation in 259 of 954 patients (27.1%). HI-1 was more frequent than HI-2, PH-1, and PH-2 (Table 1). In 42 of 954 patients (4.4%), hemorrhagic transformation was judged to be symptomatic.

We found a negative graded relation between the proportion of patients with excellent functional outcome and the extent of hemorrhagic transformation. Mortality and poor outcome were more prevalent in the PH hemorrhage types (Table 1 and the Figure). Compared with no hemorrhagic transformation, HI-1 was not a predictor of outcome. However, HI-2, PH-1, and PH-2 were all negative predictors of excellent outcome (Table 2). Other negative predictors of excellent outcome were advanced age, high baseline serum glucose, low baseline ASPECTS score, and high baseline NIHSS score.

**Discussion**

Among Canadian patients with acute ischemic stroke who were treated open-label with intravenous tissue plasminogen activator according to current clinical guidelines, the extent of hemorrhagic transformation on follow-up CT scans determined patient outcome at 3 months after stroke: the larger the extent of hemorrhagic transformation, the lower the likelihood for a favorable clinical course.

Hemorrhage into an infarction bed is a common occurrence in ischemic stroke. Autopsy series show petechial hemorrhage into infarcted brains in 50% to 70% of patients with embolic stroke.11,12 Magnetic resonance imaging with echoplanar imaging–gradient-recalled echo sequences seems to have higher diagnostic accuracy (incidence, 48%) in detecting poststroke hemorrhagic transformation than does CT (incidence, 6% to 43%),13 implying the possibility of misclassified hemorrhagic transformation in some patients by CT. Possible misclassifications, however, are likely to be HI-1, which did not influence outcome in our study.

A clear relation between the extent of hemorrhagic transformation after acute ischemic stroke and functional outcome has not been previously established. Varying definitions of hemorrhagic transformation and varying intervals between thrombolysis and follow-up imaging have complicated comparison among studies.1 For our study, we applied widely accepted radiographic criteria introduced by Pessin et al10 and later used in the ECASS trials.4,5 The incidence of hemorrhagic transformation after intravenous thrombolysis in the ECASS I and II trials was 30% and 29.5%, respectively,
compared with 27.1% in our analysis. We speculate that this lower rate among our patients may be associated with earlier initiation of thrombolysis (2.3 hours versus 6 hours in the ECASS studies).

One explanation for our findings may be that patients without evidence of hemorrhagic transformation tended to have slightly lower baseline NIHSS and higher ASPECTS scores. The higher ASPECTS value implies a lower likeli-
hood of intracranial occlusion and reduced risk of hemorrhagic transformation.\textsuperscript{14,15} However, even after accounting for these small differences, the effect of hemorrhage was robust in predicting poorer outcome.

It is well established that the finding of a space-occupying, thrombolysis-related PH is associated with a high likelihood of poor long-term functional outcome. We used the same definition of PH-2 as in the combined analysis of the ATLANTIS, ECASS, and NINDS trials.\textsuperscript{16} We found a similar incidence and associated PH-2 as in the combined analysis of the ATLANTIS, ECASS, thrombolysis-related PH is associated with a high likelihood of robust in predicting poorer outcome.

The clinical significance of small amounts of blood within infarcted brain tissue (as in HI-1, HI-2, and PH-1) after thrombolysis, however, seems to be less straightforward. Our results suggest that, in routine clinical practice, both HI-2 (OR = 0.38) and PH-1 (OR = 0.32) have a negative impact on patient outcome when compared with patients without intraparenchymal blood on follow-up CT. Our data differ from a pooled analysis of 1197 patients with ischemic stroke randomized to intravenous recombinant tissue plasminogen activator within 6 hours of onset.\textsuperscript{1} That study did not find a statistically significant effect of asymptomatic hemorrhage on functional outcome at 3 months (relative risk = 0.69, 95% CI = 0.4 to 1.1) but concluded that the study was underpowered in this regard. We also note that that study compared randomized patients, whereas ours compared treated patients only. What this study demonstrates is that hemorrhage among thrombolysed stroke patients is associated with a poorer outcome.

It remains relevant that hemorrhage on the CT scan after stroke thrombolysis may simply be a marker for other poor prognostic factors; in other words, it could be an epiphenomenon. For example, hemorrhage could be associated with persistent occlusion, late reperfusion, severe infarction, or longer duration of ischemia. Hemorrhage is known to be associated with hyperglycemia,\textsuperscript{17} which itself is associated with poor outcome. Other undetermined factors could precede hemorrhage in the causal chain leading to poor outcome.

Kent et al\textsuperscript{3} reviewed 9 previous studies that compared outcomes in patients with acute ischemic stroke with and without hemorrhagic transformation. Seven of those studies did not show a statistically significant effect of hemorrhagic transformation on outcome but seemed to be underpowered. One study found that HI was associated with a less favorable outcome.\textsuperscript{18} Another study demonstrated that HI was associated with better functional outcomes.\textsuperscript{9} Molina et al\textsuperscript{9} monitored arterial status in a highly selective cohort of patients with middle cerebral artery occlusion treated with recombinant tissue plasminogen activator within 3 hours of onset. In their study, HI was a marker of early (<6 hours) reperfusion, reduced infarct size, and hence, improved functional outcome, whereas PH was a marker of delayed (>6 hours) reperfusion and poor outcome. Patients with HI were more likely to be functionally independent at 3 months than patients without any hemorrhagic transformation on follow-up CT. These data suggest that the presence and time point of arterial reperfusion might be a significant confounding factor in determining outcome after thrombolysis-related hemorrhagic transformation. Our study is limited by the fact that we did not determine the presence of intracranial occlusion and reperfusion.

Our hypothesis that HI was a predictor of better outcome (based on data from Molina et al\textsuperscript{9}) than no hemorrhage was not confirmed. The combination of these and prior data suggest that no hemorrhage is likely to be associated with the best outcome. The bulk of evidence suggests that thrombolysis-related hemorrhage is clinically significant only if a PH is present. It is intriguing that the recent SAINT trial\textsuperscript{19} showed a relative risk of symptomatic ICH with Nxy-059 treatment of 0.39 (0.15 to 0.98), suggesting that the risk of hemorrhage after thrombolysis has the potential to be modified by pharmacological treatment. Our study raises questions about the significance of hemorrhagic transformation. Further study of hemorrhage and its reduction after ischemic stroke thrombolysis is warranted.

Disclosures

None.

References


TABLE 2. Adjusted ORs for Excellent Outcome (mRS 0–1) at 3 Months After Thrombolysis-Related Hemorrhagic Transformation

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No HT</td>
<td>1*</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>HI-1</td>
<td>0.77</td>
<td>0.46–1.28</td>
<td>0.31</td>
</tr>
<tr>
<td>HI-2</td>
<td>0.38</td>
<td>0.17–0.83</td>
<td>0.02</td>
</tr>
<tr>
<td>PH-1</td>
<td>0.32</td>
<td>0.13–0.78</td>
<td>0.02</td>
</tr>
<tr>
<td>PH-2</td>
<td>0.14</td>
<td>0.04–0.48</td>
<td>0.002</td>
</tr>
<tr>
<td>Age, per year older</td>
<td>0.98</td>
<td>0.97–0.99</td>
<td>0.001</td>
</tr>
<tr>
<td>Baseline NIHSS score, per unit increase</td>
<td>0.91</td>
<td>0.88–0.93</td>
<td>0.000</td>
</tr>
<tr>
<td>Baseline glucose, per mmol/L increase</td>
<td>0.88</td>
<td>0.83–0.94</td>
<td>0.000</td>
</tr>
<tr>
<td>Baseline ASPECTS score, per unit increase</td>
<td>1.14</td>
<td>1.05–1.25</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Abbreviations are as defined in text.

*Reference variable.


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