Baseline Blood Pressure but Not Early Computed Tomography Changes Predicts Major Hemorrhage After Streptokinase in Acute Ischemic Stroke

A.K. Gilligan, MBBS, FRACP; R. Markus, MBChB, FRACP; S. Read, MBBS, PhD, FRACP; V. Srikanth, MBChB, FRACP; T. Hirano, MD; G. Fitt, MBBS, FRCR; M. Arends, MBBS; B.R. Chambers, MD; S.M. Davis, MD; G.A. Donnan, MD; for the Australian Streptokinase Trial Investigators

Background and Purpose—Intracerebral hemorrhage is the most serious complication of thrombolytic therapy for stroke. We explored factors associated with this complication in the Australian Streptokinase Trial.

Methods—The initial CT scans (≤4 hours after stroke) of 270 patients were reviewed retrospectively by an expert panel for early signs of ischemia and classified into the following 3 categories: no signs or ≤1/3 or >1/3 of the vascular territory. Hemorrhage on late CT scans was categorized as major or minor on the basis of location and mass effect. Stepwise, backward elimination, multivariate logistic regression analysis was used to identify risk factors for each hemorrhage category.

Results—Major hemorrhage occurred in 21% of streptokinase (SK) and 4% of placebo patients. Predictors of major hemorrhage were SK treatment (odds ratio [OR], 6.40; 95% CI, 2.50 to 16.36) and elevated systolic blood pressure before therapy (OR, 1.03; 95% CI, 1.01 to 1.05). Baseline systolic blood pressure >165 mm Hg in SK-treated patients resulted in a >25% risk of major secondary hemorrhage. Early ischemic CT changes, either ≤1/3 or >1/3, were not associated with major hemorrhage (OR, 1.58; 95% CI, 0.65 to 3.83; and OR, 1.11; 95% CI, 0.45 to 2.76, respectively). Minor hemorrhage occurred in 30% of the SK and 26% of the placebo group. Predictors of minor hemorrhage were male sex, severe stroke, early CT changes, and SK treatment. Ninety-one percent of patients with major hemorrhage deteriorated clinically compared with 23% with minor hemorrhage.

Conclusions—SK increased the risk of both minor and major hemorrhage. Major hemorrhage was also more likely in patients with elevated baseline systolic blood pressure. However, early CT changes did not predict major hemorrhage. Results from this study highlight the importance of baseline systolic blood pressure as a potential cause of hemorrhage in patients undergoing thrombolysis. (Stroke. 2002;33:2236-2242.)

Key Words: blood pressure ■ computed tomography ■ intracerebral hemorrhage ■ stroke, ischemic ■ thrombolysis

Recent trials of thrombolytic agents in acute ischemic stroke1–10 and subsequent clinical use of tissue plasminogen activator (TPA) have stimulated interest in interpretation of CT of the brain in the acute setting. Particularly important are signs of cerebral ischemia on early CT and hemorrhagic transformation on late CT. The sensitivity, specificity, pathophysiology, and prognostic value of these signs continue to be debated.11–26

Early CT changes in cerebral ischemia occur within hours of ischemic stroke onset and can be assessed before thrombolytic therapy.11 Specific criteria are used to estimate the percentage of the middle cerebral artery territory affected: none, ≤33% (small), or >33% (extensive).17,18 In treatment guidelines, these criteria are now used to exclude patients with extensive changes from TPA therapy because of a perceived high risk-to-benefit ratio.22 In particular, investigators from phase 4 studies of TPA and retrospective studies of the European Australasian Cooperative Acute Stroke Study Group (ECASS) and National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group have raised concerns that any early changes in CT increase the risk of hemorrhagic transformation.28–31

Hemorrhagic transformation occurs spontaneously at a rate between 10% and 43% in CT studies of acute stroke.13,15,32–36 Thrombolytic drugs such as streptokinase (SK) or TPA increase the risk of hemorrhagic transformation by ~2- to 3-fold.28–31,36–41 Combined with aspirin, these rates are even higher.29,31,37 Hemorrhagic transformation ranges from pete-
chial or punctate bleeding (hemorrhagic infarction) to confluent, dense, space-occupying bleeds [called hematoma or parenchymal hemorrhage (PH)]. Intracerebral hemorrhage, fatal hemorrhage, and asymptomatic and symptomatic hemorrhagic transformation are also terms that have been used.

The difficulty is how to identify clinically significant cerebral hemorrhage. Hemorrhagic infarction may often be asymptomatic and appears to have less impact on long-term outcome. PH is less common than hemorrhagic infarction but has a worse prognosis. Fiorelli et al reviewed data from ECASS I, reclassified hemorrhagic transformation into 5 categories, and concluded that PH type 2 (PH2; >30% of the infarcted area affected by hemorrhage with mass effect and/or extension outside the infarct) was the only one to be associated with neurological deterioration and poor outcome. Investigators from other studies found that only large parenchymal or extraparenchymal hemorrhage is associated with poorer prognosis. Because of the complexity and variation in definitions of hemorrhagic transformation between studies, we propose a simple classification of major cerebral hemorrhage (equivalent to large PH or PH2, poor outcome) and minor cerebral hemorrhage (all remaining hemorrhagic transformation, better outcome). This terminology will be used for the remainder of the article.

Do patients with extensive early CT changes have an increased risk of major hemorrhage beyond the inherent risk in ischemic stroke? In ECASS I, only 52 patients had extensive early CT changes. Von Kummer et al stated that a relationship “could not be proved because of the small number of patients.” The available data from ECASS II included only 36 patients with extensive early CT changes, all protocol violations, of whom 3 had PH2. In the study by Barber et al, 65 patients (41%) had extensive CT changes, 9 of whom had symptomatic hemorrhages. Again, these were protocol violations. Furthermore, in postmarketing studies of TPA, higher rates of symptomatic hemorrhages have been found to be associated with protocol violations. Patients with extensive early CT changes in the NINDS rt-PA Stroke Study were at higher risk of symptomatic intracerebral hemorrhage (all remaining hemorrhagic transformation, better outcome). This terminology will be used for the remainder of the article.

In previous studies, investigators have identified other factors associated with hemorrhagic transformation, including increased age, hyperglycemia, diabetes, congestive heart failure, and time to treatment. Elevated baseline diastolic blood pressure (DBP) was identified as a risk factor for secondary hemorrhage in the pilot phase of the NINDS rt-PA Stroke Study. and subsequently, all trials excluded patients with blood pressures above a certain threshold. The Australian Streptokinase (ASK) Trial inclusion criteria allowed a systolic blood pressure (SBP) up to 200 mm Hg and DBP to 120 mm Hg on enrollment, which are higher than other studies.

In light of these considerations and the similar rate of hemorrhagic complications for most thrombolytic agents, we undertook a review of CT scans from the ASK trial, focusing on predictors of hemorrhage and specifically early CT changes.

Methods

Study Design

A retrospective analysis of CT scans from ASK was undertaken. Details of the ASK trial have been published previously. Briefly, it was a multicenter, randomized, placebo-controlled trial of intravenous SK (1.5 million U) given within 4 hours of onset of acute ischemic stroke. All patients received aspirin (100 mg) orally or via nasogastric tube if unable to swallow. The use of heparin or warfarin was prohibited within 48 hours of administration of trial medication. Patients were recruited between June 1992 and December 1994. Initial CT scans were undertaken before therapy, and follow-up scans were performed at days 7 to 10 or earlier if clinically indicated. CT scans were performed on second- and third-generation scanners, and CT slice thickness varied between 5 and 10 mm. For this analysis, patients with clinically defined hemisphere or lacunar syndromes were included, whereas those with brainstem syndromes were excluded.

CT Image Interpretation:

Reinterpretation of the original early and late CT scans (days 7 to 10) was undertaken by consensus among a panel of neuroradiologists and neuroradiologists trained in ECASS criteria. The panel was informed of the side of clinical deficit but was blinded to other clinical information, prior CT readings, and subsequent outcomes.

Definitions

Early CT changes in cerebral ischemia were defined as parenchymal hypodensity and/or loss of gray-white differentiation, including loss of insular ribbon and/or obscuration of lentiform nucleus and/or effacement of sulci. These were then subdivided into small changes (≤33% of the vascular territory) or extensive changes (>33% of the vascular territory, in most cases the middle cerebral artery territory). Any early CT change included both ≤33% and >33% categories. Minor hemorrhage was defined as petechial, patchy, or confluent hemorrhage contained within the infarct without independent mass effect. This would correlate with hemorrhagic infarction type 1 and 2 and PH type 1 (PH1) as defined by the ECASS group (see Figure 1 for example). Major hemorrhage was defined as confluent dense blood exerting independent mass effect and/or extending outside the borders of the infarct. All patients with intraventricular blood or bleeding remote from the infarct were included in this category, (see Figure 2 for example). Clinical deterioration was defined as a significant change in conscious state or motor function or new neurological signs before day 7 as judged by the treating physician.

Statistical Analysis

The main basis for the data analysis was binomial logistic regression, with the presence or absence of cerebral hemorrhage as the dependent variable. Major hemorrhage, minor hemorrhage, and any cerebral hemorrhage were analyzed separately by the same technique. The analyses were done by stepwise backward elimination with P>0.05 as the criterion for elimination. All the independent (predictive), pretreatment variables listed in Tables 1 and 2 were initially entered into the model. The reference level for categorical variables was always absence or, in the case of sex, female sex. When the main effects had been established, the interaction(s) between SK therapy and each of the other main effects were added to the model in turn to arrive at the best final model. Factors that remained significant at P<0.05 were included. Interactions were accepted only if corresponding individual effects achieved P<0.05 in the final model. The effects of the independent posttreatment variables heparin and warfarin were analyzed by separate univariate logistic regressions. Analyses were done with SYSTAT version 9 (SPSS Inc). The outcomes of the analyses are presented as odds ratios (ORs), 95% CIs for the ORs, and probability values. P=0.05 was regarded as statistically significant. The final logistic regression model was used to calculate the risk of major cerebral hemorrhage for each level of SBP over the observed range of 100 to 210 mm Hg.
according to whether SK therapy was given. Univariate analysis was undertaken separately for time to CT and appearance of early CT changes and association with major hemorrhage.

Results
A total of 340 patients were randomized into the ASK trial. After exclusion of 20 patients with brainstem events, 15 patients who died before the second CT, and 35 patients whose CT scans were lost or of poor quality, 270 patients were available for analysis. No major hemorrhages were reported among the 35 patients whose scans were lost or were not interpretable.

Mean age was 69 years (range, 27 to 85 years). Clinical deficit was severe (Canadian Neurological Score < 4) at onset in 93 patients (34%). One hundred thirty-four patients (50%) were given SK therapy. There was no statistical difference between the placebo- and SK-treated groups in vascular risk factors, pretreatment clinical factors, or subsequent therapies (Table 1). Any changes in early CT were seen in 176 patients (65%) overall; small changes were seen in 82 (30%); and extensive changes were present in 94 (35%). These groups were evenly distributed within each category of early CT changes in both treatment arms (Table 2). Patients in whom early CT changes were isolated to the anterior cerebral or posterior cerebral territories alone were not identified in this study. Any early CT changes were no more common in the group scanned < 3 hours (120 of 186) compared with those scanned 3 to 4 hours from stroke onset (56 of 84) (OR, 1.10; 95% CI, 0.62 to 1.98).

Predictors of Major Hemorrhage
Thirty-four patients developed major hemorrhage, and 31 (91%) deteriorated clinically. Major hemorrhage occurred in 28 (21%) of the SK-treated group compared with 6 (4%) in placebo group (Table 2). The rates of major hemorrhage in each category of early CT changes varied from 11% to 16%. On univariate analysis, extensive early CT changes or any early CT changes were not associated with major hemorrhage (OR, 1.11; 95% CI, 0.45 to 2.76; and OR, 1.35; 95% CI, 0.58 to 3.19; P > 0.5). Major hemorrhage was higher in the SK group but was no more likely in the extensive group, but the CIs are wide and overlap (Table 2). Thirty-three of the 34 patients (97%) fulfilled the criteria for PH2. In 1 patient, the hematoma was affecting slightly less than the anterior third of a large middle cerebral artery infarct, but because there was halolike perihematoma edema, it was classified as a major hemorrhage.

On multivariate analysis, only SK therapy and elevated SBP before treatment were statistically significant predictors of major hemorrhage (Table 3). On multivariate analysis including the SK-treated group alone, baseline SBP was the only significant factor (OR, 1.03; 95% CI, 1.01 to 1.05). There was a notable increase in risk of major hemorrhage with increasing SBP for both SK- and placebo-treated patients (Figure 3), but there was no significant interaction between SK and SBP in the multivariate model. Baseline SBP > 165 mm Hg in SK-treated patients resulted in a > 25% risk of major secondary hemorrhage. In the SK group alone, early CT changes, either extensive or small, were not significant in
Predictors of Minor Hemorrhage

Seventy-five patients had minor hemorrhage, of whom only 17 (23%) deteriorated clinically. Minor hemorrhage occurred in 40 (30%) of the SK group and 35 (26%) of the placebo group. Two hundred thirty-six patients, excluding the 34 with major hemorrhage, were included in multivariate analysis for predictors of minor hemorrhage (Table 4). SK (OR, 1.84; 95% CI, 1.02 to 3.31), male sex (OR, 2.48; 95% CI, 1.32 to 4.63), stroke severity (OR, 2.24; 95% CI, 1.22 to 4.12), and small (OR, 2.23; 95% CI, 1.02 to 4.86) or extensive (OR, 3.05; 95% CI, 1.47 to 6.33) early CT changes were predictive of minor hemorrhage. Neither heparin nor warfarin use was associated with minor hemorrhage (P ≥ 0.1). An analysis including all 270 patients was undertaken for any secondary cerebral hemorrhage with similar predictors as for minor hemorrhage, with the only addition being SBP (OR, 1.01; 95% CI, 1.01 to 1.03; P = 0.026).

Of the 15 patients who died before the second CT, 9 received SK and 6 received placebo. Extensive early CT changes were present in 8 patients (5 placebo, 3 SK). Of the 15 patients, 9 died as a direct consequence of stroke (4 placebo and 5 SK). It seems unlikely that there was an overrepresentation of deaths in patients with early extensive CT changes who were given SK.

Discussion

The results from this study highlight the importance of baseline SBP as a potential cause of intracerebral hemorrhage in patients receiving thrombolytic therapy. Baseline SBP > 165 mm Hg in SK-treated patients resulted in a >25% risk of major secondary hemorrhage. In contrast, extensive early CT changes in ischemia appeared to have no effect on the risk of major hemorrhage.

Predictors of major hemorrhage were SK therapy and elevated baseline SBP. It is of interest that baseline SBP was also identified as a risk for PH in ECASS II. Furthermore, DBP before therapy was associated with increased risk of hematoma in the pilot phase of the NINDS rt-PA Stroke Study. The NINDS rt-PA Stroke Study Investigators subsequently excluded patients with baseline SBP > 185 mm Hg or DBP > 110 mm Hg. BP exclusion criteria in ASK were less stringent (SBP > 200 and DBP > 120 at randomization), which may account for the increased rate of major hemorrhage in this study.

Table 2. Relationship Between Early CT Changes in Cerebral Ischemia and Secondary Major Hemorrhage According to Administration of SK or Placebo

<table>
<thead>
<tr>
<th>Early CT Changes</th>
<th>Placebo</th>
<th>SK</th>
<th>Total Major Hemorrhage Rates per ECTC Category, n/total (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No changes</td>
<td>1/46</td>
<td>9/48</td>
<td>10/94 (11)</td>
<td>1.0</td>
</tr>
<tr>
<td>Small (&gt;33%)†</td>
<td>3/45</td>
<td>10/37</td>
<td>13/82 (16)</td>
<td>1.58 (0.65–3.83)</td>
</tr>
<tr>
<td>Extensive (&gt;33%)†</td>
<td>2/45</td>
<td>9/49</td>
<td>11/94 (12)</td>
<td>1.11 (0.45–2.76)</td>
</tr>
<tr>
<td>Total</td>
<td>6/136</td>
<td>28/134</td>
<td>34/270 (13)</td>
<td>10.4 (1.3–85.7)</td>
</tr>
</tbody>
</table>

ECTC indicates early CT changes.

n = 270.

*OR was calculated relative to absence of early CT changes on univariate analysis.
†Of the middle cerebral artery territory.
Early CT changes in cerebral ischemia did not predict major hemorrhage in ASK. In contrast, early CT changes in cerebral ischemia were predictive of minor hemorrhage. Other predictors of minor hemorrhage were male sex, SK, and stroke severity.

Early CT changes are more common in severe strokes and predict poor outcome. In ECASS I, in the group of patients with extensive early CT changes, there was an overall trend for worse outcome. Pooled data from the 4 large SK trials did not reveal any effect of SK on the rate of death and disability at 3 months in patients who had early CT changes. In the NINDS rt-PA Stroke Study, no statistical interaction between early CT findings and TPA therapy was found, and although early CT changes alone still predicted worse outcome, the TPA-treated group had better outcome than the placebo group. Although natural history and postmarketing TPA studies confirm that early CT changes predict poor outcome, there has been some uncertainty as to whether this is influenced by thrombolysis. Interestingly, Patel et al from the NINDS rt-PA Stroke Study Group have shown that this group can potentially benefit from thrombolysis. Further studies to assess risks or benefits of thrombolysis in patients with extensive early CT changes are needed.

ASK had the largest number of patients (94, 35%) with extensive early CT changes of all the thrombolytic trials. Extensive early CT changes were present in 52 (9%) in ECASS I, 36 (5%) in ECASS II, and 84 (14%) in the NINDS rt-PA Stroke Study. There were 105 (63%) in MAST-E and 85 (14%) in MAST-I with any early CT changes, but these were not subdivided. The differences between trials are explained by differences in stroke severity, exclusion criteria, and time windows. In all of these studies, the number of patients with early CT changes of ischemia was still small.

On the basis of information available from the trials of thrombolysis conducted so far, the link between major hemorrhage and extensive early CT changes is uncertain. MAST-E investigators found an association between hemispheric sulcal attenuation and symptomatic hemorrhages after SK treatment. In ECASS I, although there was an association between early CT changes and hemorrhagic infarction (minor hemorrhage), there was no association with PH (including PH1 and PH2). In ECASS II, Larrue et al found an association between any early CT changes and PH. Although the authors’ interpretation of ECASS II data suggested a straightforward relationship between the extent of early CT changes and PH, there were only 3 patients with PH2 among the 36 patients with extensive early CT changes compared with 33 with PH2 in total. These were protocol violations because the appearance of extensive early CT changes was an exclusion criterion for the study. Investigators who have conducted postmarketing studies of TPA have identified a higher rate of symptomatic hemorrhages in association with protocol violations. Hence, the findings may not be generalizable to most patients with extensive early CT changes. Berger et al also examined ECASS II data and reported no association between small early CT changes and PH2 but an association between extensive early CT changes and PH2 with an OR of 4.4 (95% CI, 1.1 to 16.8). Our calculations on the same data showed no significant association (OR, 2.20; 95% CI, 0.41 to 7.66). The NINDS rt-PA Stroke Study found an association between small and extensive early CT changes and symptomatic intracerebral hemorrhage within 36 hours of TPA therapy, but once corrected for stroke severity, these associations were no longer significant. In their study, 20% of hemorrhages in the TPA-treated group occurred in areas remote from the area of infarct, and in ECASS I, 35% of PH in the treated group was remote, raising the possibility of alternative mechanisms.

Although SK and TPA differ in half-life and process of thrombolysis, the mechanism of secondary hemorrhage is probably similar. Hence, the higher rate of hemorrhagic complications in SK trials may relate to higher baseline SBP, excessive doses of SK, and/or concurrent use of aspirin.

### TABLE 3. Multivariate Predictors of Major Hemorrhage Retained in Model After Stepwise Logistic Regression

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Major Hemorrhage (n=34), n</th>
<th>No Major Hemorrhage (n=236), n</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SK</td>
<td>28</td>
<td>106</td>
<td>6.40</td>
<td>2.50–16.36</td>
<td>0.0001</td>
</tr>
<tr>
<td>SBP before therapy*</td>
<td>1.03</td>
<td>1.01–1.05</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n=270.

*Continuous variable.

The formula for % risk was 100(1-Odds/1+Odds) as calculated from the multivariate logistic regression model.

The range of SBP observed was 100–200 mm Hg in the placebo group and 105–210 mm Hg in the SK group.

**Figure 3.** Risk of major hemorrhage and baseline SBP before therapy in patients receiving SK and placebo. The formula for percent risk was 100(1−Odds/Odds) as calculated from the multivariate logistic regression model. Range of SBP observed was 100 to 200 mm Hg in the placebo group and 105 to 210 mm Hg in the SK group.
CT interpretation of ischemic changes in acute stroke can be difficult even for those with specific training.17–19,21–25 Our review of CT scans from ASK, performed after training in the ECASS criteria for early CT changes, identified an additional 10% of cases that had not been diagnosed initially. Similarly, the NINDS rt-PA Stroke Study Group’s CT review identified a further 8% with extensive early CT changes.26 The reliability of the criteria in a wider setting remains uncertain.20,22,25 In a recent study, there was agreement on extensive early CT changes in only 77% of cases (κ=0.39), suggesting only moderate agreement beyond chance.25 Interpretation of early CT changes in ischemia requires expertise that may not be available after hours in many centers, reducing the number of patients potentially eligible for thrombolysis. Other methods of quantifying acute CT changes, such as that used by Barber et al.,24 the Alberta Stroke Program Early CT Score, may have better interobserver reliability and prognostic value. Currently, despite shortcomings, the ECASS criteria are the most widely used.27,30

This retrospective study has highlighted 3 important issues concerning thrombolysis in acute stroke. First, classification of secondary hemorrhage needs to be standardized to allow direct comparisons. Second, elevated SBP at baseline is an important contributor to the risk of major hemorrhage, with higher risk with SK therapy at SBP levels >165 mm Hg. Third, the findings from this study in which SK was used do not support the view that extensive early CT changes increase the risk of major hemorrhage. Further studies of thrombolysis in acute stroke patients are required to improve our understanding of the factors influencing the appearance of major hemorrhage.

Acknowledgments

The ASK trial was funded by the National Health and Medical Research Council of Australia, Brain Foundation, National Stroke Foundation, and Austin Hospital Research Foundation. SK and placebo were supplied by Hoechst (Melbourne, Australia, and Marburg, Germany). We would like to thank the ASK Trial Investigators for their contributions to this work and Lichun Quang for her assistance with data management and analysis. Our appreciation goes to Dr John Ludbrook, MD, DSc, ChM, FRCS, FRACS, Astat (director, Biomedical Statistical Consulting Service) for his assistance and advice.

References


Baseline Blood Pressure but Not Early Computed Tomography Changes Predicts Major Hemorrhage After Streptokinase in Acute Ischemic Stroke

for the Australian Streptokinase Trial Investigators

Stroke. 2002;33:2236-2242
doi: 10.1161/01.STR.0000027859.59415.66

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 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/33/9/2236