Hemorrhage in the Interventional Management of Stroke Study

The IMS Study Investigators

Background and Purpose—The incidence of hemorrhage after combined intravenous (IV) and intra-arterial (IA) recombinant tissue plasminogen activator (rt-PA) was examined in patients entered into the Interventional Management of Stroke (IMS) trial. We also analyzed factors predicting symptomatic and asymptomatic intracerebral hemorrhage (ICH).

Methods—The IMS study treated patients within 3 hours of stroke onset with 0.6 mg/kg IV rt-PA followed by up to 22 mg IA rt-PA. Any hemorrhage within 36 hours associated with clinical deterioration was considered symptomatic. Logistic regression analysis was applied to possibly relevant variables selected from the baseline data to test for associations between these factors and symptomatic hemorrhage, asymptomatic hemorrhage, and all hemorrhage.

Results—Symptomatic hemorrhage occurred in 6% and asymptomatic hemorrhage in 43% of patients. The rate of symptomatic hemorrhage was similar to the National Institute of Neurological Disorders and Stroke (NINDS) trial with IV rt-PA alone. Asymptomatic hemorrhage was more frequent but consistent with the rate observed in more recent IV and IA thrombolytic trials. The small number of symptomatic hemorrhages precluded meaningful analysis of risk factors. Significant factors associated with ICH in univariate analysis were baseline National Institutes of Health Stroke Scale score (asymptomatic and all ICH), edema or mass effect on initial computed tomography (asymptomatic ICH), atrial fibrillation (all ICH), and location of arterial occlusion (internal carotid artery [ICA] compared with middle cerebral artery [MCA]; asymptomatic and all ICH). In multivariate analysis, ICA versus MCA occlusion remained an independent factor associated with asymptomatic and all hemorrhage, and atrial fibrillation was significantly associated with all hemorrhage.

Conclusions—Symptomatic and asymptomatic hemorrhage with combined IV and IA rt-PA occurred at rates similar to previous thrombolytic trials. Site of vascular occlusion and atrial fibrillation may be risk factors for hemorrhagic transformation. (Stroke. 2006;37:847-851.)

Key Words: hemorrhage ■ thrombolysis ■ thrombolytic therapy

Intravenous (IV) recombinant tissue plasminogen activator (rt-PA) improves outcomes when given within 3 hours of stroke onset,1 and a recent combined analysis of several trials suggests there may be benefit up to 4.5 hours.2 The major complication of thrombolytic therapy is intracerebral hemorrhage (ICH). Symptomatic ICH is often associated with significant residual disability or death. Asymptomatic ICH occurs more frequently after thrombolysis but may not alter outcome.

Considerable variability in the rates of symptomatic and asymptomatic ICH has been reported in previous studies of intravenous (IV)1,3–6 and intra-arterial (IA) thrombolysis.7,8 The combination of IV and IA therapy combines immediate administration of an IV thrombolytic agent with the more directed and potentially more effective clot dissolution of IA infusion and may be advantageous in improving arterial recanalization in patients with large artery occlusions. The present report examines factors that might predict symptomatic or asymptomatic ICH among subjects enrolled in the Interventional Management of Stroke (IMS) trial.

Methods

The IMS study included 80 patients in a pilot trial of combined IV and IA thrombolysis. A complete description of the protocol and overall results were published previously.9 Briefly, IV rt-PA was given within 3 hours of stroke onset at a dose of 0.6 mg/kg (60 mg maximum), with a 15% bolus and the remainder infused over 30 minutes. Angiography was then performed, and if thrombus was identified, rt-PA was infused intra-arterially up to a total dose of 22 mg. The mean total dose of t-PA administered was 59 mg (range 3.4 to 82 mg) and was similar to the total dose that would have been administered based on the standard 0.9 mg/kg IV dose. The mean time delay from the end of the IV infusion to the start of IA treatment was 50 minutes (range 17 to 141 minutes). A 2000-unit bolus of IV heparin was administered once the thrombus was identified and the decision was made to administer IA rt-PA. A heparin flush solution (≈40 U of heparin per hour) was administered via access sheath and the guide catheter and continued until the catheter was removed.

A computed tomography (CT) scan was repeated at 24 to 36 hours and for evaluation of any clinical deterioration. The primary safety

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end points were death by 90 days and life-threatening bleeding within the first 36 hours after rt-PA treatment. Life-threatening bleeding included ICH or hemorrhagic infarction associated with clinical deterioration and systemic hemorrhage requiring infusion of $\geq 3$ U of blood or surgical intervention. ICHs were classified according to the European Cooperative Acute Stroke Study (ECASS) criteria as PH1, PH2, HI1, or HI2. Hemorrhage was considered symptomatic if clinical deterioration occurred at the time of hemorrhage. All hemorrhages were reviewed and adjudicated by an independent physician study monitor.

Baseline variables with a possible relationship to ICH were selected from the IMS database (Table 1). To analyze variables potentially associated with the small number of symptomatic hemorrhage, Fisher exact test was used for dichotomized variables, and Wilcoxon rank sum test was used for continuous variables. Univariate logistic regression analysis was used for variables associated with asymptomatic and all intracranial hemorrhage. Multivariate analysis using a multiple logistic regression model included variables found to be significant on univariate analysis to determine whether any of these variables were independently associated with ICH.

### Results

CT evaluation within 36 hours was obtained in all 80 patients enrolled in the IMS trial. Symptomatic ICH occurred in 5 (6%) subjects and asymptomatic hemorrhage occurred in 34 (43%). HI1 occurred in 10 subjects (all asymptomatic), HI2 in 10 (all asymptomatic), PH1 in 13 (1 symptomatic, 12 asymptomatic), and PH2 in 6 (4 symptomatic, 2 asymptomatic). All hemorrhages were in the area of ischemic injury.

The greatest differences observed between the 5 patients with symptomatic ICH and 41 patients with no hemorrhage were a history of atrial fibrillation (80% versus 12%), age (74 versus 62), and baseline National Institutes of Health Stroke Scale (NIHSS) score (21 versus 17; supplemental Table I, available online at http://stroke.ahajournals.org). Statistical confidence with such a small number of end points is quite limited, although these variables were significant based on the applied tests.

### Table 1. ORs of ICH by Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Asymptomatic Hemorrhage (n=34)</th>
<th>OR (95% CI)</th>
<th>All Hemorrhage (n=39)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline NIHSS (per unit)</td>
<td>1.119 (1.003–1.248)</td>
<td></td>
<td>1.14 (1.024–1.269)</td>
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<tr>
<td>Age</td>
<td>1.024 (0.987–1.062)</td>
<td>1.032 (0.995–1.07)</td>
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<tr>
<td>Female sex</td>
<td>1.654 (0.660–4.144)</td>
<td>1.351 (0.561–3.254)</td>
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<tr>
<td>Baseline systolic blood pressure</td>
<td>0.992 (0.977–1.008)</td>
<td>0.992 (0.977–1.007)</td>
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<tr>
<td>Baseline glucose</td>
<td>1.009 (0.998–1.012)</td>
<td>1.006 (0.996–1.017)</td>
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<tr>
<td>Baseline platelet count</td>
<td>0.995 (0.988–1.001)</td>
<td>0.994 (0.998–1.000)</td>
<td></td>
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<tr>
<td>Black vs other race</td>
<td>3.36 (0.609–18.553)</td>
<td>2.862 (0.522–15.746)</td>
<td></td>
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<tr>
<td>ICA vs MCA</td>
<td>3.115 (1.04–9.325)</td>
<td>3.00 (1.031–8.733)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema or mass effect on initial CT</td>
<td>2.671 (1.036–6.886)</td>
<td>2.282 (0.928–5.607)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous aspirin-use</td>
<td>0.569 (0.227–1.428)</td>
<td>0.674 (0.277–1.637)</td>
<td></td>
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</tr>
<tr>
<td>History of myocardial infarction</td>
<td>1.689 (0.351–8.131)</td>
<td>1.919 (0.426–8.648)</td>
<td></td>
<td></td>
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<tr>
<td>History of atrial fibrillation</td>
<td>3.048 (0.921–10.059)</td>
<td>4.083 (1.299–12.840)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of diabetes</td>
<td>1.571 (0.472–5.228)</td>
<td>1.556 (0.485–4.989)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recanalization: TIMI 0-1 vs TIMI 2-3</td>
<td>0.706 (0.252–1.975)</td>
<td>0.794 (0.292–2.158)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to IV rt-PA (per min)</td>
<td>1.003 (0.988–1.018)</td>
<td>1.001 (0.986–1.016)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIME to IA rt-PA (per min)</td>
<td>1.003 (0.992–1.014)</td>
<td>1.002 (0.992–1.013)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to TIMI 2-3 reperfusion (per min)</td>
<td>0.998 (0.987–1.000)</td>
<td>0.997 (0.986–1.007)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total IA rt-PA dose</td>
<td>1.049 (0.994–1.107)</td>
<td>1.049 (0.996–1.104)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total IV+/IA rt-PA dose</td>
<td>1.026 (0.992–1.062)</td>
<td>1.029 (0.996–1.064)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bold indicates significant variables.

### Table 2. Relationship of Site of Occlusion and ICH

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Symptomatic Hemorrhage</th>
<th>Asymptomatic Hemorrhage</th>
<th>No Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA occlusion</td>
<td>28</td>
<td>2 (7%)</td>
<td>18 (64%)</td>
<td>6 (29%)</td>
</tr>
<tr>
<td>MCA occlusion</td>
<td>33</td>
<td>2 (6%)</td>
<td>13 (39%)</td>
<td>18 (55%)</td>
</tr>
<tr>
<td>V-B occlusion</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3 (100%)</td>
</tr>
<tr>
<td>Stenosis/distal occlusion – no treatment</td>
<td>10</td>
<td>0</td>
<td>2 (20%)</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>No AOL</td>
<td>3</td>
<td>0</td>
<td>1 (33%)</td>
<td>2 (67%)</td>
</tr>
<tr>
<td>No angiogram</td>
<td>3</td>
<td>1 (33%)</td>
<td>0 (0%)</td>
<td>2 (66%)</td>
</tr>
<tr>
<td>Total</td>
<td>80</td>
<td>5 (6%)</td>
<td>34 (43%)</td>
<td>41 (51%)</td>
</tr>
</tbody>
</table>

V-B indicates vertebral or basilar; AOL, arterial occlusive lesion.
TABLE 3. Relationship of Time to Treatment, Time to TIMI 2-3 Reperfusion, and ICH

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic Hemorrhage</th>
<th>Asymptomatic Hemorrhage</th>
<th>No Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom onset to IV rt-PA (min)</td>
<td>124±26 (n=5)</td>
<td>139±29 (n=34)</td>
<td>136±32 (n=41)</td>
</tr>
<tr>
<td>Symptom onset to IA rt-PA (min)</td>
<td>209±53 (n=4)</td>
<td>220±43 (n=29)</td>
<td>214±51 (n=29)</td>
</tr>
<tr>
<td>Symptom onset to reperfusion (min)</td>
<td>304±16 (n=3)</td>
<td>321±41 (n=15)</td>
<td>332±86 (n=17)</td>
</tr>
</tbody>
</table>

univariate analysis were baseline NIHSS score, edema or mass effect on initial CT, and location of arterial occlusion (Table 1). In the multivariate analysis, ICA versus middle cerebral artery (MCA) occlusion remained a significant independent factor (odds ratio [OR], 3.303; 95% CI, 1.056 to 10.325). When asymptomatic and symptomatic ICH were combined, baseline NIHSS score, ICA versus MCA occlusion, and a history of atrial fibrillation were significant variables in the univariate analysis. Both ICA versus MCA occlusion (OR, 4.196; 95% CI, 1.229 to 14.325) and history of atrial fibrillation (OR, 7.294; 95% CI, 1.567 to 33.956) remained significant in the multivariate analysis. The relationship between ICH and location of arterial occlusion is detailed in Table 2.

Thrombolysis in myocardial ischemia (TIMI) 2 or 3 (partial or complete) reperfuptions assessed at the completion of the IA infusion for asymptomatic and symptomatic hemorrhage subjects were 15 of 30 (50%) and 3 of 4 (75%), respectively. Among those with no hemorrhage, 17 of 29 (59%) had TIMI 2 or 3 reperfusion. TIMI 3 (complete) reperfusion occurred in 7% (2 of 30) of patients with asymptomatic ICH, 25% (1 of 4) with symptomatic ICH, and 14% (2 of 30) of those without ICH. A trend toward earlier reperfusion was observed in patients with ICH (Table 3).

Results of activated clotting time (ACT) or activated partial thromboplastin time (PTT) during interventional treatment were available in a limited number of patients. ACT values >200 seconds occurred in 6 of 37 patients for whom this information was recorded (5 asymptomatic ICH and 1 without ICH). The highest recorded ACT was 289 seconds. In 2 patients with symptomatic hemorrhage, ACT was 151 and 184 seconds during the procedure. In another patient with symptomatic ICH, PTT was 125 seconds at 1 hour of intra-arterial therapy and 49 seconds at 2 hours.

**Discussion**

The IMS trial is the largest prospectively studied group of patients treated with combined IV and IA thrombolysis. Despite a greater stroke severity, the rate of symptomatic hemorrhage in the IMS study was similar to the NINDS rt-PA trial and lower than several other IV or IA thrombolysis trials with longer time windows8,11,12 (Tables 4 and 5). The symptomatic hemorrhage rate was also comparable to the frequency observed in previous series of patients treated with combined IV and IA thrombolysis.13–17 These results indicate that combining IV and IA thrombolysis does not increase the risk of symptomatic intracranial hemorrhage when initiated within 3 hours of stroke onset.

Asymptomatic hemorrhage occurred in 43% of IMS subjects, a frequency higher than observed in previous IV thrombolytic trials but similar to more recent reports of IV thrombolysis12 and IA thrombolysis alone.8,11,18,19 The increased rate of asymptomatic ICH in the IMS as compared with the NINDS rt-PA Stroke Trial may be related to several factors, including higher resolution CT technology, residual angiographic contrast in the infarcted bed with IA therapy that may be difficult to differentiate from blood, concomitant use of heparin during IA therapy (forbidden in the NINDS rt-PA Stroke Trial), and more frequent early reperfusion with combined therapy.

Whether symptomatic and asymptomatic ICHs represent a spectrum of severity with the same pathophysiology or are attributable to different mechanisms remains controversial. Most symptomatic hemorrhages are associated with PH2, a hematoma occupying ≥30% of the infarct area.10 Asymptomatic hemorrhages more often appear on CT as hemorrhagic infarction (HI1 or HI2) and frequently occur in the setting of clinical improvement.10,12 Thus, the clinical consequences of symptomatic and asymptomatic ICH are quite different, and a greater rate of asymptomatic hemorrhage does not necessarily indicate a safety concern.

Previous thrombolytic studies reported risk factors for hemorrhage similar to those found in this study. Baseline NIHSS score was significantly associated with symptomatic hemorrhage rate in target population; †all hemorrhage; 0, any clinical worsening considered related to hemorrhage by treating physician. PI indicates primary investigator.
or hemorrhage in the NINDS study\textsuperscript{20} and with all hemorrhagic infarction in ECASS I.\textsuperscript{21} Baseline CT abnormalities predicted symptomatic hemorrhage in NINDS\textsuperscript{20} and ECASS II.\textsuperscript{22} In ECASS I\textsuperscript{21} and Multicenter Acute Stroke Trial-Europe,\textsuperscript{23} CT changes were associated with all hemorrhagic complications. In patients treated with IA thrombolysis, Kidwell et al\textsuperscript{18} found initial NIHSS score to predict hemorrhagic conversion. NIHSS score was also an independent risk factor for hemorrhage in several series of patients treated with IV rt-PA alone.\textsuperscript{24–26} Age has been a strong predictor of ICH in previous thrombolytic studies including increased rates of PH2 hemorrhage.\textsuperscript{21,22,24–26} A higher rate of symptomatic ICH occurred in patients \(\geq 80\) years of age.\textsuperscript{15,27} Because of these reports, patients \(>80\) years of age were excluded from the IMS study, and this exclusion possibly accounts for the lack of relationship between age and hemorrhage in the IMS trial. Baseline serum glucose was associated with symptomatic hemorrhage in PROACT II\textsuperscript{8} and with all hemorrhage in several other reports of patients treated with thrombolytic therapy.\textsuperscript{11,18,24–26} In our patients, neither glucose nor a history of diabetes was found to be a risk factor for hemorrhage. Time to treatment was also not significantly associated with hemorrhage in the IMS study, similar to other reports of patients treated with IV rt-PA within 3 hours of stroke onset\textsuperscript{2,28} and IV or IA thrombolysis beyond 3 hours.\textsuperscript{2,29}

Little information is available regarding the association between location of arterial occlusion and hemorrhagic complications after thrombolysis. We found that ICH after combined IV/IA thrombolysis was more likely to occur with ICA occlusions compared with MCA disease. In most previous IV thrombolytic studies, no vascular imaging was performed, and the location of arterial occlusion was unknown. The largest randomized interventional thrombolytic trial with angiography, the PROACT II trial, enrolled only patients with MCA occlusions.\textsuperscript{8} In a series of 54 patients treated with IA urokinase, hemorrhagic infarction occurred in 19 of 46 patients with MCA occlusive disease and 3 of 5 with ICA occlusion.\textsuperscript{11} The reason for a greater likelihood for hemorrhage with ICA occlusion is uncertain and warrants further investigation.

Atrial fibrillation was also a significant risk factor for asymptomatic and all hemorrhage and remained a significant independent risk factor for all hemorrhage in the multivariate analysis. Previous thrombolytic trials found an association between atrial fibrillation and parenchymal hemorrhage\textsuperscript{21} or symptomatic hemorrhage,\textsuperscript{20} but this factor did not remain significant in multivariate analysis. Further investigation of the association between atrial fibrillation and hemorrhage risk is warranted.

In the IMS study, reperfusion did not occur significantly more frequently in patients with symptomatic and asymptomatic hemorrhage, although the small number of patients in each group may have obscured a minor difference. Previous studies of IA\textsuperscript{18} and IV therapy\textsuperscript{30} suggested that hemorrhage occurred more frequently after arterial recanalization, and the association between recanalization and hemorrhage was stronger with later recanalization.\textsuperscript{18,30} Reperfusion of ischemic brain leads to leakage of blood in areas of vascular injury.\textsuperscript{31} Presumably, the longer interval to reperfusion allows a greater amount of brain to undergo irreversible ischemia and vascular injury, increasing the likelihood of hemorrhage. This hypothesis is supported by the higher hemorrhage rates after IV rt-PA in patients with early changes on initial CT\textsuperscript{2,23,25} and in patients with MRI\textsuperscript{24,33} or Xenon CT\textsuperscript{34} correlates of severe ischemia. In the IMS Study, ICH was not associated with longer time interval to reperfusion. In fact, there was a trend toward earlier reperfusion with hemorrhage; however, the differences between groups were small and limited by the small sample size and preponderance of patients with reperfusion later in the time window. Reperfusion was only assessed at 2 hours after initiation of IA therapy, and it is possible that in some cases, reperfusion or reocclusion occurred after completion of the angiogram.

This analysis is limited by the number of patients in this pilot trial. The small number of symptomatic hemorrhages limits any conclusions regarding associations and precludes meaningful multivariate analysis for independent risk factors. Patients \(>80\) years of age were excluded from the IMS study, possibly obscuring the relationship between hemorrhage and age. The age limit may also have reduced the incidence of hemorrhage. Subgroups resulted in even smaller numbers of patients, producing large CIs. Associations with hemorrhage may not have been detected because of this limitation.

**Acknowledgments**

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References


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