Large Ischemic Lesions on Diffusion-Weighted Imaging Done Before Intravenous Tissue Plasminogen Activator Thrombolysis Predicts a Poor Outcome in Patients With Acute Stroke

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Background and Purpose—MRI is useful for detecting early ischemic lesions before administration of tissue plasminogen activator in patients with hyperacute ischemic stroke. However, it is unclear whether early ischemic change seen on diffusion-weighted imaging (DWI) can be used to predict patient outcomes.

Methods—Consecutive patients with anterior circulation ischemic stroke treated with tissue plasminogen activator within 3 hours of stroke onset were prospectively studied. The National Institutes of Health Stroke Scale score was obtained before and 7 days after tissue plasminogen activator administration. MRI, including DWI, was done before tissue plasminogen activator thrombolysis. The relationship between the DWI Alberta Stroke Programme Early CT Score (ASPECTS) and patients’ outcomes was assessed.

Results—The subjects consisted of 49 consecutive patients with stroke (27 males; mean age, 72.9±10.3 years). The median (range) of the baseline DWI ASPECTS value was 9 (3–10). Dramatic improvement was seen in one of 8 patients with an ASPECTS ≤5 compared with 21 of 41 patients with a DWI ASPECTS >5 (P=0.0592). On the other hand, worsening was noted more frequently in patients with a DWI ASPECTS ≤5 (3 of 8 patients) than in patients with an ASPECTS >5 (4 of 41 patients; P=0.0753). Bad outcome was seen more frequently in patients with a DWI ASPECTS ≤5 (6 of 8 patients) than in patients with a DWI ASPECTS >5 (2 of 41 patients; P<0.0001). Multivariate logistic regression analysis demonstrated that a DWI ASPECTS ≤5 was the only independent predictor of a bad outcome (OR, 33.4; 95% CI, 2.7 to 410.8; P=0.0062).

Conclusion—DWI ASPECTS appears to be a reliable tool for predicting bad outcome. Patients with a DWI ASPECTS >5 should be considered eligible for tissue plasminogen activator therapy. (Stroke. 2008;39:2388-2391.)

Key Words: outcome ■ tissue plasminogen activator ■ MRI ■ DWI ■ acute stroke
Three measures of clinical recovery based on modified methods used in previous studies were used.8 “Dramatic improvement” was defined as a /H11350/10-point reduction in the total NIHSS score or a total NIHSS score of 0 or 1. “Good improvement” was defined as a /H11350/4-point reduction in the total NIHSS score. “Worsening” was defined as a /H11350/4-point increase in the total NIHSS score. Symptomatic cerebral hemorrhage was defined as a /H11350/4-point increase in the total NIHSS score. A bad outcome was defined as an NIHSS score /H11350/20 at 7 days after tPA infusion.

Before tPA infusion, MRI studies, including DWI, MR angiography, and T2*, were done to identify occluded arteries. Subsequently, follow-up T2* was performed 5 and 7 days after tPA administration to determine the presence or absence of intracerebral hemorrhage. The MRI was performed using a commercially available echoplanar instrument operating on a 1.5-T unit (Signa EXCITE XL version 11.0; GE Healthcare, Milwaukee, Wis). DWI ASPECTS was used to evaluate the affected middle cerebral artery territory. The presence of large artery occlusion was assessed using MR angiography. Occluded arteries on initial MR angiography were identified as follows: M1 occlusion, M2 occlusion, and internal cerebral artery occlusion.

Kappa statistics were used to assess the researchers’ agreement (KK, YI) on the DWI ASPECTS. Statistical analysis was performed using StatView version 5 statistical software. Spearman’s rank correlation coefficients were used to test the association between the baseline DWI ASPECTS value and the baseline NIHSS score and between the NIHSS score 7 days after tPA infusion and the /Δ/NIHSS score. The significance of intergroup differences was assessed using Fisher exact test for categorical variables and the Mann–Whitney U test and the Kruskal-Wallis U test for continuous variables. Multivariate logistic regression analysis was performed to determine factors that could be considered to be independent predictors of worsening and bad outcome after tPA thrombolysis. Variables showing a value of /P/ < 0.1 on univariate analysis were included in the multivariate model. Values of /P/ < 0.05 were considered statistically significant.

All study protocols followed the principles outlined in the Declaration of Helsinki, and written informed consent was obtained from all patients.

Results

Sixty consecutive patients with stroke received tPA treatment. One patient was excluded because he had a pacemaker. Ten patients had a posterior circulation stroke. As a result, 49 patients (27 males, 22 females; mean age, 72.9 ± 10.3 years) were enrolled in the present study. The times from symptom onset to the initial MRI study and tPA bolus were 94.3 ± 30.3 minutes and 141.6 ± 27.1 minutes, respectively.

The median (range) of baseline NIHSS score was 14 (1–25). The median (range) of the baseline DWI ASPECTS value was 9 (3–10). The baseline DWI ASPECTS was correlated with the baseline NIHSS score (/r/ = −0.575, /P/ < 0.0001; Figure A) and the 7-day NIHSS score (/r/ = −0.489, /P/ = 0.0004; Figure B). Figure C shows the baseline DWI ASPECTS value and /Δ/NIHSS. The correlation

Figure. A, Baseline DWI ASPECTS value and NIHSS score before tPA administration. Baseline DWI ASPECTS was correlated with the baseline NIHSS score (/r/ = −4.41, /P/ < 0.0001). B, Baseline DWI ASPECTS value and the NIHSS score 7 days after tPA thrombolysis. Baseline DWI ASPECTS was correlated with the NIHSS score 7 days after tPA (/r/ = −0.48; /P/ = 0.0021). C, Baseline DWI ASPECTS value and /Δ/NIHSS, defined as the NIHSS score 7 days after tPA thrombolysis minus the baseline NIHSS score. The correlation was not significant (/P/ = 0.9781).
Age, years 75.8 ± 8.2
Female 5 (62.5%) 17 (41.5%) 0.4397
Time from symptom onset to treatment, minutes 145.0 ± 27.9 141.0 ± 27.2 0.6456
Hypertension 2 (25.0%) 25 (61.0%) 0.1172
Diabetes mellitus 1 (12.5%) 5 (12.2%) 0.9999
Hyperlipidemia 1 (12.5%) 7 (17.1%) 0.9999
Right to left shunt 2 (25.0%) 15 (36.6%) 0.6964
Previous myocardial infarction 0 4 (9.8%) 0.9999
Arterial stenotic diseases 1 (12.5%) 2 (4.9%) 0.4214
Atrial fibrillation 5 (62.5%) 19 (45.3%) 0.4635
Stroke type
Cardioembolic stroke 6 (75.0%) 22 (78.6%) 0.1337
Large artery diseases 1 (12.5%) 2 (4.9%) 0.4214
Undetermined stroke 1 (12.5%) 14 (34.1%) 0.4061
Occluded artery
Internal carotid artery 6 7 0.0025
M1 2 17 0.4583
M2 0 6 0.5413
Use of antiplatelet therapy
Warfarin 0 (0%) 2 (4.9%) 0.9999
Aspirin 1 (12.5%) 12 (29.3%) 0.6631
NIHSS score 20.5 ± 4.0 12.1 ± 6.1 0.0011
Systolic blood pressure, mm Hg 164.8 ± 20.6 162.9 ± 23.6 0.6359
Diastolic blood pressure, mm Hg 96 ± 17.7 90.5 ± 16.0 0.3862
Glucose, mg/dL 135.6 ± 24.9 138.0 ± 45.9 0.5979

was not significant (P=0.3148). When patients were divided into 2 groups using the DWI ASPECTS value (≤5 versus >5), the NIHSS score at 7 days was higher in the 8 patients with a DWI ASPECTS ≤5 than in the 41 patients with a DWI ASPECTS >5 (22.9 ± 11.0 versus 7.0 ± 8.2, P=0.0001). Table 1 shows the clinical background characteristics of patients with DWI ASPECTS values ≤5 and those with values >5. Kappa statistics of agreements with DWI ASPECTS between 2 investigators was 0.803.

Dramatic improvement, good improvement, and worsening 7 days after tPA infusion were observed in 22, 8, and 7 patients, respectively. Dramatic improvement was less common in patients with a DWI ASPECTS ≤5 (one of 8 patients) than in patients with an DWI ASPECTS >5 (21 of 41; P=0.0592; Table 1). On the other hand, worsening was more common in patients with a DWI ASPECTS ≤5 (3 of 8 patients) than in patients with a DWI ASPECTS >5 (4 of 41; P=0.0753; Table 2). Bad outcome was more common in patients with an ASPECTS ≤5 (6 of 8 patients) than in patients with a DWI ASPECTS >5 (2 of 41 patients; P<0.0001; Table 2). Symptomatic cerebral hemorrhage within 7 days after tPA infusion was observed in one patient with a baseline NIHSS score of 7 and a DWI ASPECT value of 11. T2* imaging showed an asymptomatic cerebral hemorrhage in 20 patients.

On multivariate logistic regression analysis using presence or absence of internal cerebral artery occlusion, baseline NIHSS score (≤15 versus >15), and DWI ASPECTS (≤5 versus >5) as variables showing P<0.1 on univariate analysis, DWI ASPECTS ≤5 was not an independent factor associated with worsening (OR, 7.5; 95% CI, 0.6 to 97.2; P=0.1212), but was independently associated with bad outcome (OR, 33.4; 95% CI, 2.7 to 410.8; P=0.0062).

Table 2. Clinical Recovery, NIHSS Score, and Cerebral Hemorrhage on T2* 7 Days After tPA Treatment and Baseline DWI ASPECTS (≤5 versus >5) and NIHSS Score (≤15 Versus >15)

<table>
<thead>
<tr>
<th>DWI ASPECTS</th>
<th>Dramatic</th>
<th>Good</th>
<th>Worsening</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5 (n=8)</td>
<td>1 (12.5%)</td>
<td>1 (12.5%)</td>
<td>3 (37.5%)</td>
</tr>
<tr>
<td>&gt;5 (n=41)</td>
<td>21 (51.2%)</td>
<td>7 (17.0%)</td>
<td>4 (9.8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NIHSS score</th>
<th>≤15 (n=28)</th>
<th>&gt;15 (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤15 (n=28)</td>
<td>14 (50.0%)</td>
<td>8 (38.1%)</td>
</tr>
<tr>
<td>&gt;15 (n=21)</td>
<td>10 (47.6%)</td>
<td>13 (61.9%)</td>
</tr>
</tbody>
</table>

*Symptomatic (n=1) and asymptomatic (n=20) DWI ASPECTS: P=0.086 in the clinical recovery; P=0.0001 in the NIHSS score at 7 days; P=0.0263 in the cerebral hemorrhage. NIHSS score: P=0.086 in the clinical recovery; P=0.015 in the NIHSS score at 7 days; P=0.040 in the cerebral hemorrhage.
early recanalization after tPA infusion occurred in such patients, the ischemic damage was so severe that clinical recovery was not likely. Therefore, patients with a DWI ASPECTS > 5 should be considered eligible for tPA therapy.

Barber et al reported that ASPECTS values of 7 or less of CT findings could predict poor functional outcome. Our results also show that a DWI ASPECTS ≤ 5 was independently associated with bad outcome after tPA thrombolysis. Our cutoff DWI ASPECTS value of 5 was lower than the value of 7 used by Barber et al, because DWI may be more sensitive than CT for detecting early ischemic changes.

The present study had several limitations. Perfusion-weighted MRI can detect hypoperfused tissue, and the combination of DWI and perfusion-weighted MRI may identify a penumbra area with normal DWI but with perfusion-weighted MRI showing hypoperfused tissue. However, to not delay the start of tPA treatment, we did not include perfusion-weighted MRI examinations in the present study. Second, it is more likely that there is a linear relationship between the amount of early ischemic changes and the functional outcome. We would need more patients to elucidate the issue.

In conclusion, the present study demonstrated that DWI ASPECTS was reliable and could predict a poor outcome. Poorer response to intravenous tPA therapy should be expected in patients with baseline DWI ASPECTS ≤ 5 and these patients should also be excluded from studies of thrombolysis beyond the 3-hour time window.

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Disclosures
None.

References
7. Yamaguchi T, Mori E, Minematsu K, Nakagawa J, Hashi K, Saito I, Shizoharu Y. Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan Alteplase Clinical Trial (J-ACT). Stroke. 2006;37:1810–1815.
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