Clinical and MRI Predictors of No Early Recanalization Within 1 Hour After Tissue-Type Plasminogen Activator Administration

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**Background and Purpose**—The aim of the present study was to investigate independent clinical and MRI factors associated with no early recanalization within 1 hour after tissue-type plasminogen activator (tPA) administration.

**Methods**—Patients with acute stroke within 3 hours of onset who were treated with tPA were studied prospectively. Patients with internal carotid artery, M1, and M2 occlusion were enrolled, and independent clinical and MRI factors associated with no early recanalization within 1 hour after tPA administration were examined using multivariate logistic regression analysis.

**Results**—One hundred thirty-two patients (63 men; mean age, 76.4±10.2 years; internal carotid artery occlusion in 37 patients, M1 occlusion in 58, and M2 occlusion in 37) were enrolled. Follow-up MR angiography within 60 minutes after tPA infusion revealed early recanalization in 49 (37.1%) patients (complete in 16 patients, partial in 33) and no recanalization in 83 (62.9%). Using 8 variables (atrial fibrillation, time from stroke onset to treatment ≥140 minutes, use of warfarin, glucose ≥135 mg/dL, large artery diseases, internal carotid artery occlusion, M1 occlusion, and M1 susceptibility vessel sign on T2*) identified on univariate analysis at \( P < 0.2 \), multivariate logistic regression analysis revealed that M1 susceptibility vessel sign was the only independent factor associated with no early recanalization (OR, 7.157; 95% CI, 1.756 to 29.172; \( P = 0.006 \)). The sensitivity, specificity, positive predictive value, and negative predictive value of M1 susceptibility vessel sign for predicting no early recanalization were 31.3%, 93.9%, 89.7%, and 44.7%, respectively.

**Conclusions**—Of clinical and MRI factors before tPA infusion, M1 susceptibility vessel sign on T* is the only independent factor associated with no early recanalization within 1 hour after tPA administration. (Stroke. 2011;42:00-00.)

**Key Words:** MRA, T2* - recanalization - susceptibility vessel sign - tissue-type plasminogen activator

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**Intravenous administration of tissue-type plasminogen activator (tPA) can improve clinical outcomes in patients with acute ischemic stroke.** Early arterial recanalization has been recognized as a marker of good outcome after tPA infusion. Alexandrov et al reported that, during tPA infusion, recanalization was complete in 30% and partial in 40% of patients on transcranial Doppler. Thus, approximately one third of patients with acute stroke treated with tPA do not undergo early recanalization. Therefore, intravenous tPA therapy has some limitation.

Lewandowski et al reported that combined intravenous and local intra-arterial tPA therapy in patients with stroke within 3 hours of onset was feasible and provides better recanalization. Recently, the Mechanical Embolus Removal in Cerebral Ischemia (MERCi) trial reported the efficacy of the Merci Retriever for opening intracranial vessels in patients ineligible for tPA. Furthermore, Multi MERCi investigators reported that mechanical thrombectomy is efficacious in opening intracranial vessels in patients with acute ischemic stroke who have failed intravenous tPA. Failed tPA patients may benefit from thrombectomy within 6 hours of stroke onset. Therefore, to add endovascular therapy to intravenous tPA in failed tPA patients, predicting no early recanalization before tPA infusion would be important.

Diabetes, delayed time from onset to treatment, noncardioembolic stroke, and atrial fibrillation have been reported to be associated with no early recanalization after tPA therapy. MRI but not CT can accurately assess the ischemic infarct volume on diffusion-weighted imaging, the occluded artery on MR angiography (MRA), and the susceptibility vessel sign (SVS) on T2* in the superacute phase of stroke. Internal carotid artery (ICA) occlusion and M1 SVS on T2* were also reported to be associated with failed tPA. Therefore, we added MRI findings to clinical factors and investigated independent clinical and MRI factors associated with no early recanalization within 1 hour after tPA administration using multivariate logistic regression analysis.
Occluded arteries on initial MRA were identified as follows: M1 occlusion in 37 patients, M2 occlusion in 37 patients, and no occlusion in 28 patients. Thus, 132 patients (63 men, 69 women; mean age, 76.4 years) were enrolled in the present study.

Follow-up MRA within 60 minutes after tPA infusion revealed recanalization in 49 (37.1%) patients (complete in 16 patients, partial in 33) and no recanalization in 83 (62.9%). There were no differences in clinical characteristics between patients with complete recanalization and partial recanalization (Table 1). Then, we divided patients into 2 groups: early recanalization group (n=49) and no early recanalization group (n=83). Table 2 shows the 2 groups’ clinical characteristics. The glucose level was higher in the no early recanalization group than in the early recanalization group (158.6 ± 63.0 mg/dL versus 137.1 ± 34.2 mg/dL, P=0.0400). ICA occlusion was more frequently observed in the no early recanalization group than in the early recanalization group (34.9% versus 16.3%, P=0.0214). M1 SVS was observed in 29 patients (22.0%, ICA 19.0%) versus 13.7% in the early recanalization group. Of the 132 patients, 106 (80.7%) underwent transcatheter recanalization (with guidewires and stents in 61 patients). Median recanalization rate was 60 minutes after tPA infusion (IQR, 50-120 minutes).

Receiver operator characteristic analysis using variables with P<0.2 on univariate analysis, which were considered to be potential factors associated with no early recanalization. Cutoff values for continuous variables were determined using the areas under receiver operating characteristic curves. Values of P<0.05 were considered significant. All study protocols were approved by the ethics committee of Kawasaki Medical School.

Results
A total of 193 consecutive patients with stroke was treated with tPA. Four patients were excluded because they had a pacemaker, and 29 patients had vertebral–basilar stroke. Of the remaining 160 patients, initial MRA demonstrated ICA occlusion in 37 patients, M1 occlusion in 58 patients, M2 occlusion in 37 patients, and no occlusion in 28 patients. Thus, 132 patients (63 men, 69 women; mean age, 76.4±10.2 years) were enrolled in the present study.

Follow-up MRA within 60 minutes after tPA infusion revealed recanalization in 49 (37.1%) patients (complete in 16 patients, partial in 33) and no recanalization in 83 (62.9%). There were no differences in clinical characteristics between patients with complete recanalization and partial recanalization (Table 1). Then, we divided patients into 2 groups: early recanalization group (n=49) and no early recanalization group (n=83). Table 2 shows the 2 groups’ clinical characteristics. The glucose level was higher in the no early recanalization group than in the early recanalization group (158.6±63.0 mg/dL versus 137.1±34.2 mg/dL, P=0.0400). ICA occlusion was more frequently observed in the no early recanalization group than in the early recanalization group (34.9% versus 16.3%, P=0.0214). M1 SVS was observed in 29 patients (22.0%, ICA occlusion in 19 and M1 occlusion in 10). Regarding site of occlusion, 19 (51.4%) of 37 patients with ICA occlusion had M1 SVS, and 10 (17.2%) of 58 patients with M1 occlusion had 1.

Subjects and Methods
Consecutive patients with acute anterior circulation ischemic stroke treated with tPA within 3 hours of stroke onset between October 2006 and March 2011 were prospectively studied. Patients with heart valve replacements, pacemakers, or clipping of cranial arteries were excluded due to contraindications for MRI. Patients with M1, M2, and ICA occlusion on MRA before tPA infusion were studied. The following clinical data were collected from all patients: (1) patient age and sex; (2) arterial blood pressure before tPA infusion; (3) National Institutes of Health Stroke Scale score before tPA infusion; (4) presence of arterial occlusion on MRA before tPA infusion; (5) presence or absence of early recanalization of occluded arteries within 60 minutes after tPA administration; (6) M1 SVS on T2* before tPA infusion; (7) ischemic volume on diffusion-weighted imaging before tPA infusion; (8) vascular risk factors including hypertension, diabetes mellitus, and hyperlipidemia; (9) presence of potential cardiac sources of emboli; (10) stroke subtype; (11) laboratory parameters before tPA infusion; and (12) administration of antithrombotic agents such as antiplatelet agents and warfarin. Inclusion and exclusion criteria for intravenous tPA were in accordance with the Japan Alteplase Clinical Trial.20

Before tPA infusion, MRI studies including diffusion-weighted imaging, MRA, and T2* were performed to measure ischemic volume using National Institutes of Health Image software and to identify and assess the occluded arteries and M1 SVS. Follow-up MRA within 60 minutes after tPA infusion re-

Statistical analysis was performed using StatView Version 5 statistical software to establish associations between no early recanalization and clinical factors. 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 independently associated with no early recanalization using variables with P<0.2 on univariate analysis, which were considered to be potential factors associated with no early recanalization. Cutoff values for continuous variables were determined using the areas under receiver operating characteristic curves. Values of P<0.05 were considered significant. All study protocols were approved by the ethics committee of Kawasaki Medical School.
M1 SVS was more frequent in the no early recanalization group (31.3% versus 6.1%, \(P=0.0007\)). Although 89.7% of patients with M1 SVS had no early recanalization, 55.3% of patients without the M1 SVS sign had no early recanalization (\(P=0.0007\); Figure 2). There were no significant differences in the other clinical characteristics between the 2 groups.

Eight variables identified on univariate analysis at \(P<0.2\) were selected. The area under receiver operating characteristic curves analysis yielded cutoff levels predicting no early recanalization with high sensitivity and high specificity as follows: time to stroke onset to treatment \(\geq 140\) minutes (sensitivity of 59.0% and specificity of 55.1%) and glucose \(\geq 135\) mg/dL (54.2% and 51.0%). Multivariate logistic regression analysis revealed that M1 SVS was the only independent factor associated with no early recanalization (OR, 7.157; 95% CI, 1.756 to 29.172; \(P=0.0060\); Table 3). Sensitivity, specificity, positive predictive value, and negative predictive value of M1 SVS for predicting no early recanalization were 31.3%, 93.9%, 89.7%, and 44.7%, respectively.

**Discussion**

M1 SVS was the only independent factor associated with no recanalization after tPA administration. The positive predic-
The magnetic susceptibility effect of deoxygenated hemoglobin in red thrombi may result in hypointense signals on T2*-weighted gradient echo imaging (GRE). Cho et al\(^1\) reported that red thrombi in occluded vessels were visualized as hypointense signals within vascular cisterns on T2*. They called such radiological findings the “GRE susceptibility vessel sign (GRE SVS).” The GRE SVS may reflect thrombus composition. Hemoglobin desaturation from oxyhemoglobin to deoxyhemoglobin occurs within a few hours. Thus, in hyperacute clot cases, the main component may still be oxyhemoglobin, and such emboli would not be identified as GRE SVS on T2*. In other words, the GRE SVS is present in older thrombi, which may be resistant to tPA therapy.

Zangerle et al\(^7\) reported that recanalization was infrequent in patients with diabetes. The present finding showed that the glucose level before tPA infusion but not HbA1c was higher in the no early recanalization group than in the early recanalization group. Therefore, the blood glucose level, rather than the presence or absence of diabetes, is closely associated with no early recanalization. These results were compatible with the results of previous studies. The glucose level before tPA infusion was higher in the group with no early recanalization than in the group with early recanalization. These findings suggest that the glucose level before tPA infusion may be a useful indicator for predicting no early recanalization.

Table 2. Clinical Characteristics and MRI Findings Before Tissue-Type Plasminogen Activator Infusion Between Patients With Early Recanalization and Nonearly Recanalization

<table>
<thead>
<tr>
<th>Clinical Symptoms, %</th>
<th>All Patients (N=132)</th>
<th>Early Recanalization (N=49)</th>
<th>No Early Recanalization (N=83)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female</strong></td>
<td>69 (52.3%)</td>
<td>24 (49.0%)</td>
<td>45 (54.2%)</td>
<td>0.5606</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td>76.4±10.2</td>
<td>76.3±10.4</td>
<td>76.5±10.2</td>
<td>0.9737</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>84 (63.6%)</td>
<td>31 (63.3%)</td>
<td>53 (63.9%)</td>
<td>0.9457</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>28 (21.2%)</td>
<td>8 (16.3%)</td>
<td>20 (24.1%)</td>
<td>0.2914</td>
</tr>
<tr>
<td><strong>Hyperlipidemia</strong></td>
<td>24 (18.2%)</td>
<td>7 (14.3%)</td>
<td>17 (20.5%)</td>
<td>0.3725</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>36 (27.1%)</td>
<td>15 (30.6%)</td>
<td>21 (25.0%)</td>
<td>0.4822</td>
</tr>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td>85 (64.4%)</td>
<td>28 (57.1%)</td>
<td>57 (68.7%)</td>
<td>0.1813</td>
</tr>
</tbody>
</table>

**Stroke type**

- Cardioembolic stroke: 87 (65.9%) vs. 29 (59.2%) vs. 58 (70.0%) (P=0.2104)
- Large artery disease: 9 (6.8%) vs. 1 (2.0%) vs. 8 (10.0%) (P=0.1529)

**Use of antiplatelet therapy**

- Warfarin: 15 (11.4%) vs. 3 (6.1%) vs. 12 (14.5%) (P=0.1449)
- Aspirin: 33 (25.0%) vs. 13 (26.5%) vs. 20 (24.1%) (P=0.7550)

**Laboratory data**

- HbA1C, %: 5.7±1.0 vs. 5.6±0.5 vs. 5.8±1.2 (P=0.7392)
- Glucose, mg/dL: 150.6±54.9 vs. 137.1±34.2 vs. 158.6±63.0 (P=0.0400)
- C-reactive protein, mg/dL: 0.6±1.3 vs. 0.7±1.4 vs. 0.6±1.3 (P=0.9268)
- Leucocytes, ×10 000/μL: 6980.0±2596.7 vs. 7248.8±3076.7 vs. 6821.4±2272.0 (P=0.7829)
- Erythrocytes, ×10 000/μL: 417.3±65.0 vs. 415.2±58.9 vs. 418.5±68.6 (P=0.6993)
- Platelets, ×10 000/μL: 19.6±5.2 vs. 19.8±5.6 vs. 19.6±5.0 (P=0.8672)
- Creatinine, mg/dL: 0.9±0.7 vs. 0.9±0.8 vs. 0.9±0.6 (P=0.8524)
- PT-INR: 1.1±0.2 vs. 1.1±0.2 vs. 1.1±0.2 (P=0.4887)
- D-dimer, μg/mL: 3.1±6.1 vs. 2.2±2.0 vs. 3.7±7.5 (P=0.6599)
- M1 SVS: 29 (22.0%) vs. 3 (6.1%) vs. 26 (31.3%) (P=0.0077)

**Site of occlusion**

- ICA: 37 (28.0%) vs. 8 (16.3%) vs. 29 (34.9%) (P=0.0214)
- M1: 58 (43.9%) vs. 26 (53.1%) vs. 32 (38.6%) (P=0.1047)
- M2: 37 (28.0%) vs. 15 (30.6%) vs. 22 (26.5%) (P=0.6118)

**Ischemic volume, mL**

- 30.1±58.9 vs. 23.2±28.5 vs. 34.4±71.7 (P=0.8454)

PT-INR indicates prothrombin time international normalized ratio; SVS, susceptibility vessel sign; ICA, internal carotid artery.
with those of a previous report. However, the multivariate regression model did not reveal that blood glucose level was an independent factor associated with no early recanalization. Molina et al reported that early recanalization was more frequent in patients with cardioembolic stroke compared with other stroke types. In fact, patients with cardioembolic stroke more frequently had early recanalization than those with large artery diseases, but the difference was not significant (33.3% versus 11.1%, \( P = 0.2653 \)). Using our univariate analysis, ICA occlusion was more frequent in the no early recanalization group than in the early recanalization group. Several investigators reported that tPA was not effective in patients with ICA occlusion. The reason for this was that the embolus responsible for ICA occlusion was larger than that responsible for other arterial occlusions, and such an embolus was likely to be resistant to tPA. However, the multivariate regression model did not identify ICA occlusion as an independent factor associated with no early recanalization.

Recently, the REcanalisation using Combined intravenous Alteplase and Neurointerventional ALgorithm for acute Ischemic Stroke (RECANALISE) study demonstrated that the combined intravenous tPA and endovascular approach group had higher recanalization than the only intravenous tPA therapy group in patients with stroke within 3 hours of onset. However, early neurological improvement and favorable outcome were not different between the 2 groups. A better clinical outcome was associated with recanalization in the 2 groups and time to recanalization in the combined intravenous tPA and endovascular approach group. Therefore, time to recanalization appears to be most important for patient outcome. If we can identify patients who will fail tPA before tPA infusion, it may be better to start with endovascular therapy in such patients to achieve earlier recanalization of the occluded artery. Therefore, in patients with acute stroke within 3 hours of onset, M1 SVS may be a sign for endovascular therapy instead of intravenous tPA as first-line therapy.

The present study had several limitations. First, MRA is somewhat inaccurate for detection of vessel occlusion or stenosis. Second, MRI cannot be performed in patients with implanted metallic materials such as pacemakers and metal clips; 4 patients were excluded from our study. Third, there are potential pitfalls of the use of SVS on T2*. Blood clots of acute, subacute, and chronic stage can appear as signal loss on T2* because any paramagnetic substance including deoxyhemoglobin, intra- and extracellular methemoglobin, and hemosiderin can appear hypointense on T2*. Therefore, fresh clots seem to be indistinguishable from flowing blood. Thus, when the presence of M1 SVS is identified, ICA or M1 occlusion must be confirmed by MRA to distinguish fresh clots from blood flow. In the present study, to exclude those potential pitfalls, we always used MRA to confirm the occluded artery. Finally, the sample size was small. A larger sample size is needed to confirm these results.

In conclusion, of clinical and MRI factors before tPA infusion, M1 SVS on T2* is the only independent factor associated with no early recanalization within 1 hour after tPA administration. In patients with M1 SVS who are unlikely to respond to tPA therapy, we may consider therapeutic strategies such as combined intravenous tPA and endovascular therapy or endovascular therapy alone instead of intravenous tPA as first-line therapy.

Disclosures

None.

References


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