Multivariable Analysis of Predictive Factors Related to Outcome at 6 Months After Intra-Arterial Thrombolysis for Acute Ischemic Stroke

Toshihiro Ueda, MD, PhD; Saburo Sakaki, MD, PhD; Yoshiaki Kumon, MD, PhD; Shinsuke Ohta, MD, PhD

Background and Purpose—Recent reports have suggested that a rapid assessment of pretreatment residual cerebral blood flow (CBF) could be used to optimize selection criteria for thrombolysis in patients with acute ischemic stroke to improve clinical outcome. We investigated retrospectively residual CBF and other clinical factors related to outcome at 6 months after intra-arterial thrombolysis by using multivariable analysis.

Methods—Seventy-six patients received intra-arterial thrombolysis within 6 hours of symptom onset. The multiple regression method was used to analyze associations between the modified Rankin scale (MRS) at 6 months after treatment and clinical factors including age, infarction type, duration of ischemia, dose of urokinase, degree of recanalization, hemorrhage, National Institutes of Health Stroke Scale score (NIHSSS), and residual CBF evaluated by pretreatment single-photon emission-computed tomography; these values were assessed with the use of the regional-to-cerebellar activity (R/CE) ratio of ischemic region to cerebellum and asymmetry index.

Results—MRS at 6 months was good (0 to 3) in 65% and poor (4 to 6) in 35%. Factors significantly related to MRS at 6 months were R/CE ratio (P < 0.0001), NIHSSS at baseline and the following day (P < 0.0001), cardioembolic infarction (P = 0.0014), age (P = 0.0074), and recanalization grade (P = 0.007). NIHSSS of > 20, R/CE ratio of < 0.35, cardioembolic infarction, incomplete recanalization (grade < 3), and older age (> 75 years) were determined to be significant independent predictors of poor outcome.

Conclusions—The residual CBF, neurological score at baseline and the following day, age, and recanalization grade correlated significantly with long-term outcome. The NIHSSS of > 20 and R/CE ratio of < 0.35 were determined to be significant independent predictors of poor outcome by multivariable analysis. (Stroke. 1999;30:2360-2365.)

Key Words: cerebral blood flow ■ outcome ■ stroke, ischemic ■ thrombolytic therapy ■ tomography, emission computed
thrombolysis. Particularly, no analysis of the relation between pretreatment cerebral perfusion status and long-term outcome has been reported in prospective studies of either intra-arterial thrombolysis or intravenous thrombolysis. A retrospective study may still be useful to address these issues until a randomized double-blind trial of intra-arterial thrombolysis can be completed and its data made available.

The purpose of this study was to assess predictive factors, including age, infarction type, duration of ischemia, dose of an agent, degree of recanalization, hemorrhage, pretreatment and posttreatment National Institutes of Health Stroke Scale score (NIHSSS), and residual CBF evaluated by pretreatment SPECT, related to long-term outcome with the use of multivariable statistical analysis in both cardioembolic and atherosclerotic infarction patients with intra-arterial thrombolysis.

Subjects and Methods

A total of 76 consecutive patients with acute ischemic stroke treated with intra-arterial thrombolytic therapy in our institution between April 1990 and August 1996 were evaluated. There were 42 men and 34 women between 35 and 83 years of age (mean ± SD, 67 ± 12 years). Patients were classified into a cardioembolic infarction group (53 patients) and an atherosclerotic infarction group (23 patients). Cardioembolic infarction was diagnosed according to the guidelines of the Cerebral Embolism Task Force17 on the basis of onset pattern, angiographic findings, and results of cardiovascular examinations such as electrocardiography and echocardiography. The diagnosis of atherosclerotic infarction was based on clinical, computed tomography (CT), and angiographic findings. Angiographic criteria for atherosclerotic infarction were good collateral circulation with revascularization of the anterior or posterior cerebral artery and/or tapered occlusion with extensive atherosclerotic changes. Patients with stroke of unknown cause were excluded from this study.

Our inclusion criteria for intra-arterial thrombolytic therapy were as follows: (1) no apparent hypodensity areas were observed on the admission CT scan, (2) the patient could be treated within 6 hours, in principle, of symptom onset, and (3) occluded arteries suggested by symptoms were demonstrated by cerebral angiography. Six patients who were treated 6 to 7.5 hours after symptom onset were included in this study because they had a good CBF value by pretreatment SPECT. Informed consent was obtained from all patients or their relatives. The exclusion criteria were (1) recent hemorrhagic stroke, (2) critical systemic condition, (3) serious diabetic retinopathy, (4) classic contraindications to thrombolytic therapy (recent surgical operation, known bleeding tendency, etc.). This study was approved by the institutional ethics committee.

The patient’s neurological status was evaluated on admission, the following day, and 1 week and 1 month after treatment according to NIHSSS, which expresses the severity of neurological status numerically from 0 (normal) to 42. Clinical outcome at 6 months after treatment was assessed according to the modified Rankin scale (MRS)16: grades 0 to 5 and 6 (death). Factors related to clinical outcome were investigated in all patients, cardioembolic infarction group, and atherosclerotic infarction group. Patients were classified by the MRS into 2 groups: good outcome (MRS 0 to 3) and poor outcome (MRS 4 to 6). First, the multivariable analysis performed with the multiple regression method investigated the association between the MRS at 6 months and clinical factors including age, infarction type, duration of ischemia, dose of urokinase, degree of recanalization, hemorrhage, pretreatment and posttreatment (the following day) NIHSSS, and residual CBF evaluated by SPECT in all patients and cardioembolic infarction group. The MRS at 6 months was analyzed as the dependent variable, whereas the other clinical factors were analyzed as independent variables. There was no analysis of the atherosclerotic infarction group because there were not enough patients for multivariable assessment. Second, significant predictive values of variables of the poor outcome group compared with those of the good outcome group were identified.

CT was performed on all patients immediately after admission. When no clear hypodensity area was noted at the sites suggested by the clinical symptoms, SPECT was performed with the use of Tc-HMPAO and a 4-head gamma camera (SPECT 2000H-40, Hitachi) with a low-energy, high-resolution collimator. Details of our method of analyzing SPECT data were described in previous reports.8,9 In short, of 16 axial sections, the section most clearly showing the ischemic region was selected, and regions of interest (ROIs) were set within the ischemic region (a), the corresponding region on the contralateral side (b), and the entire cerebellar hemisphere on the ischemic side (c), and the mean count was determined in each region. Linear adjustment19 was made by assuming the blood flow in the normal cerebellar hemisphere to be 55 mL/100 g per minute.20 The CBF was assessed semiquantitatively by calculating 2 parameters: (1) the ischemic regional-to-cerebellar activity (R/CE) ratio (R/CE = a/c) and (2) the asymmetry index (AI = 1+[(b−a)/(a+b)]). The ROIs were hand-drawn in apparent whole ischemic areas based on qualitative inspection of the CBF maps. The contralateral, mirror-image ROI was drawn automatically.

Digital subtraction angiography was performed with the use of a 5F catheter through a femoral artery. Patients were given an intravenous injection of heparin (5000 U) before angiography. The tip of a FastTracker-18 (Target Therapeutics) was advanced into the thrombus or upstream from the occlusion site up to a 0.014-inch Taper Dasher guide wire (Target Therapeutics). Urokinase (240 000 U) was dissolved in 20 mL of physiological saline and injected manually for ∼10 minutes. The maximum dose of urokinase was 960 000 U. Comparing the preinfusion and postinfusion angiograms, restoration of arterial patency was classified into 5 categories by use of the method described by Mori et al:21 grade 0, unchanged; grade 1, movement of thrombus not associated with any improvement in perfusion; grade 2, partial recanalization with reperfusion in <50% of the ischemia-related area; grade 3, partial recanalization with reperfusion in >50% of the ischemia-related area; and grade 4, complete or near-complete recanalization with full return of perfusion. CT was also obtained immediately, the next day, 1 or 2 weeks, and 1 month after treatment.

For statistical analysis, the values were expressed as mean ± SD, and differences among 2 or more groups were examined by ANOVA. Multiple regression analyses with and without backward stepwise method were performed to assess the correlation of MRS (dependent variable) with other clinical factors (independent variables). Logic regression analysis was applied to identify the significant predictive values of variables of the poor outcome group compared with the good outcome group. GB-STAT software (Dynamic Microsystems Inc) was used for computerized statistical analyses.

Results

Patient Characteristics and Treatment Results

The baseline characteristics and treatment results are shown in Table 1. The interval from symptom onset to recanalization of the occluded vessel was between 1 and 7.5 hours (4.9 ± 1.6 hours), which included 1 to 3 hours (8 patients, 11%), 3 to 6 hours (62 patients, 82%), and 6 to 7.5 hours (6 patients, 7%). Occluded vessels were the internal carotid artery (7 patients in the cardioembolic infarction group and 5 patients in the atherosclerotic infarction group), the middle cerebral artery (39 and 15 patients), the anterior cerebral artery (2 and 0 patients), and the basilar artery (5 and 3 patients). Complete (grade 4) and partial (grades 3 and 2) recanalization of the occluded vessel was observed in 43% and 40%, respectively. The NIHSSS on the following day, at 1 month, and 6 months was reduced significantly from the baseline NIHSSS in both
cardioembolic infarction and overall patient groups ($P<0.01$). The NIHSSS at 1 month and 6 months was also reduced significantly from that on the following day in all 3 groups ($P<0.01$). The MRS at 6 months was good (scores of 0 to 3) in 65% and poor (scores of 4 to 6) in 35%.

Symptomatic and asymptomatic hemorrhagic transformation occurred in 9 cases (12%) and 4 cases (5.3%), respectively. A total of 15 patients died after treatment. The causes of death were primary cerebral infarction in 6 patients, hemorrhagic transformation in 6 patients, acute myocardial infarction in 2 patients, and pneumonia in 1 patient.

**Multivariable Outcome Studies**

Factors significantly related to the MRS at 6 months were as follows: R/CE ratio ($P=0.0001$), NIHSSS at baseline ($P<0.0001$), NIHSSS on the following day ($P<0.0001$), cardioembolic infarction ($P=0.0014$), age ($P=0.0074$), and recanalization grade ($P=0.007$) in the overall patient group (Table 2). Duration of ischemia ($P=0.616$), dose of urokinase ($P=0.688$), hemorrhage ($P=0.369$), and asymmetry index ($P=0.957$) were not significantly related to the MRS at 6 months.

In the cardioembolic infarction group, R/CE ratio ($P=0.0001$), NIHSSS at baseline ($P<0.0001$), NIHSSS on the following day ($P<0.0001$), asymmetry index ($P=0.002$), age ($P=0.0074$), and recanalization grade ($P=0.0426$) were significantly correlated to the MRS at 6 months (Table 3).

There were several significant differences between the good outcome group and the poor outcome group (Table 4): (1) younger age ($P=0.0007$); (2) different distribution of stroke territories (overall analysis, $P=0.006$), with a higher proportion of patients with middle cerebral artery occlusion and lower proportion of patients with internal carotid artery or basilar artery occlusion; (3) higher amount of SPECT
values including both R/CE ratio and AI (P<0.0001); (4) lower NIHSSS at baseline, the following day, and 1 month after treatment; and (5) lower incidence of hemorrhage (P=0.0004).

A model of baseline variables exhibiting significant predictive values of poor outcome compared with good outcome was proposed. When logic regression was applied to this model, it selected 6 significant variables (Table 5): (1) NIHSSS >20 (odds ratio (OR)=6.17, confidence interval (CI)=2.57 to 14.8, P<0.0001); (2) cardioembolic infarction (OR=3.6, CI=1.31 to 9.86, P=0.0113); (3) R/CE ratio <0.35 (OR=3.0, CI=1.23 to 7.16, P=0.0118); (4) hemorrhage (OR=2.88, CI=1.61 to 5.13, P=0.0003); (5) recanalization grade <3 (OR=2.87, CI=1.58 to 5.21, P=0.0004); and (6) age >75 years (OR=2.81, CI=1.57 to 5.02, P=0.0004). There were 32 (42%) patients with an NIHSSS of >20; of 21 poor outcome patients, 13 died. There were 12 (29%) patients with an R/CE ratio of <0.35; of 10 poor outcome patients, 7 died.

**Discussion**

Because the underlying cause of acute ischemic stroke is multifactorial and a number of factors may influence clinical outcome, there is a great need for more information about factors related to clinical outcome. Although this study was not designed to investigate the efficacy of intra-arterial urokinase infusion for improvement of clinical outcome, we attempted to assess retrospectively predictive variables related to long-term outcome in patients with acute stroke who were treated with intra-arterial thrombolysis with the use of multivariable analysis.

Although NIHSSS has been reported to be an important prognostic indicator in patients with acute ischemic stroke,22-24 few reports have analyzed predictive factors related to outcome in patients with intravenous and particularly intra-arterial thrombolysis.14,25,26 The NINDS trial suggested that outcome at 3 months after intravenous r-TPA was related to older age with higher baseline NIHSSS, older age with higher administration mean arterial pressure, and early CT finding.25 Trouillas et al26 reported that significant predictors of poor outcome at 1 year after treatment in 100 patients with intravenous r-TPA were low baseline neurological score, early CT finding, and proximal internal carotid thrombosis. In addition, Gönner et al14 indicated that good outcome at 3 months after treatment in 45 patients with intra-arterial thrombolysis was associated with a baseline NIHSSS of <20, improvement by [me]4 points on NIHSSS within 24 hours, and vessel recanalization.

Our data show that the MRS at 6 months after intra-arterial thrombolysis was significantly related to R/CE ratio, NIHSSS at baseline, NIHSSS on the following day, cardioembolic infarction, age, and recanalization grade in the overall patient group and R/CE ratio, NIHSSS at baseline, NIHSSS on the following day, asymmetry index, age, and recanalization grade in the cardioembolic infarction group. Although only 11% of patients were treated within 3 hours from symptom onset and most patients (82%) were treated between 3 and 6 hours, the interval from symptom onset to treatment does not appear to have a direct effect on clinical outcome at 6 months.

The incidence of hemorrhage was 17% (13 patients), and 30% (4 patients) of hemorrhage was asymptomatic. Therefore hemorrhage may not be a significant predictive factor in the overall patient group; however, it had a significant predictive value of poor outcome compared with good outcome.

Severe neurological condition (NIHSSS >20) (OR=6.17, CI=2.57 to 14.8) is likely to be a significant independent predictor of poor outcome. In some recent trials, patients who had severe neurological deficits were excluded.15,27 In our study, there were 32 (42%) patients with a baseline NIHSSS of >20; however, 11 (34%) of these patients had a good outcome. Therefore severe neurological deficits (NIHSSS >20) may not be appropriate as a single exclusion criterion. It may be necessary for optimized patient selection to combine neurological deficits with other predictive variables. In addition, cardioembolic infarction (OR=3.6, CI=1.31 to 9.86), incomplete recanalization (recanalization grade <3) (OR=2.87, CI=1.58 to 5.21), and older age (>75 years) (OR=2.81, CI=1.57 to 5.02) were also significant independent predictors of poor outcome.

A number of natural history studies in the acute stroke setting have reported the relation between SPECT findings and outcome,28-31 whereas no reports have assessed the predictive value of pretreatment SPECT for long-term outcome in patients with acute stroke who had undergone intra-arterial thrombolysis. Grotta and Alexandrov22 reported that SPECT measurement of cerebral perfusion before and after intravenous r-TPA infusion correlated with outcome and response to therapy. Our data indicate that the residual CBF evaluated by pretreatment SPECT significantly correlated with long-term outcome and was also a key independent predictor of poor outcome (OR=3.0, CI=1.23 to 7.16).
Unfortunately, the value of rapid assessment of tissue reversibility before treatment has not been addressed in recent clinical trials of thrombolytic therapy for acute ischemic stroke. Recently, however, Ueda et al\(^9\) reported that the residual CBF assessed by pretreatment SPECT in patients with acute ischemic stroke with intra-arterial thrombolysis provided important information for determining whether thrombolysis was useful in predicting ischemic outcome, including associated hemorrhagic risk and neurological outcome at any given time. The present study also supports the usefulness of pretreatment SPECT for predicting clinical outcome at 6 months after treatment.

To date, there are no reports in which thrombolytic therapy was investigated on the basis of the cause of the stroke, including cardioembolic and atherosclerotic infarction. Although it is difficult to distinguish between cardioembolic and atherosclerotic infarction in some patients, it may be important to plan treatment strategy considering the cause of acute ischemic stroke. Intra-arterial thrombolysis for cardioembolic infarction was characterized by severe neurological deficits (19.7 of a mean baseline NIHSSS), a high recanalization rate (83% of grade 3 to 4), and a symptomatic hemorrhagic rate (17%). On the other hand, intra-arterial thrombolysis for atherosclerotic infarction showed a high nonrecanalization rate (30%) and no symptomatic hemorrhage. These differences may be due to residual CBF in the ischemic lesion and atherosclerotic changes in the vessel. The mean R/CE ratio and mean asymmetry index assessed by pretreatment SPECT were 0.38 and 0.15, respectively, in patients with cardioembolic infarction and 0.60 and 0.11, respectively, in those with atherosclerotic infarction. In addition, it can be difficult to recanalize completely an occluded vessel with atherosclerotic changes in patients with atherosclerotic infarction.

In conclusion, the residual CBF evaluated by pretreatment SPECT, the NIHSSS at baseline and the following day, age, and recanalization grade correlated significantly with the MRS at 6 months after intra-arterial thrombolysis for acute ischemic stroke. The NIHSSS of \(\geq 20\), R/CE ratio of \(<0.35\), cardioembolic infarction, incomplete recanalization (recanalization grade \(<3\)), and older age (\(>75\) years) were determined to be significant independent predictors of poor outcome by multivariable analysis.

### TABLE 4. Comparison of Clinical, Therapeutic, and Pathogenetic Characteristics Between the Good and Poor Outcome Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Good</th>
<th>Poor</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>49</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>(63 \pm 12)</td>
<td>(72 \pm 8.7)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Interval, h</td>
<td>(4.8 \pm 1.5)</td>
<td>(4.9 \pm 1.2)</td>
<td>0.6969</td>
</tr>
<tr>
<td>Dose of urokinase, (\times 10^3) U</td>
<td>(621 \pm 242)</td>
<td>(698 \pm 208)</td>
<td>0.1684</td>
</tr>
<tr>
<td>Infarction type</td>
<td>Cardioembolic/atherosclerotic</td>
<td>32/17</td>
<td>21/6</td>
</tr>
<tr>
<td>Site of occlusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td>1 (2%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>BA</td>
<td>3 (6%)</td>
<td>5 (18%)</td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>4 (8%)</td>
<td>8 (30%)</td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>41 (84%)</td>
<td>13 (48%)</td>
<td></td>
</tr>
<tr>
<td>Recanalization grade</td>
<td>3.27±1.27</td>
<td>2.74±1.26</td>
<td>0.882</td>
</tr>
<tr>
<td>SPECT values ((n=41))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R/CE ratio</td>
<td>0.53±0.15 ((n=24))</td>
<td>0.29±0.11 ((n=17))</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asymmetry index</td>
<td>1.26±0.11 ((n=24))</td>
<td>1.50±0.17 ((n=17))</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NIHSSS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>16.1±5.9</td>
<td>23.6±4.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Following day</td>
<td>9.4±5.7</td>
<td>21.4±4.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1 mo</td>
<td>3.7±3.8</td>
<td>15.4±6.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hemorrhagic transformation</td>
<td>3 (6.1%)M</td>
<td>10 (37%)</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

ACA indicates anterior cerebral artery; BA, basilar artery; ICA, internal carotid artery; MCA, middle cerebral artery; R/CE ratio, regional-to-cerebellar activity ratio; and NIHSSS, National Institutes of Health Stroke Scale score.

### TABLE 5. Multivariable Odds Ratios and 95% Confidence Intervals for Predictive Factors of Poor Outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSSS&gt;20</td>
<td>6.17</td>
<td>2.57, 14.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardioembolic infarction</td>
<td>3.6</td>
<td>1.31, 9.86</td>
<td>0.0113</td>
</tr>
<tr>
<td>R/CE ratio&lt;0.35</td>
<td>3.0</td>
<td>1.23, 7.16</td>
<td>0.0118</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>2.88</td>
<td>1.61, 5.13</td>
<td>0.0003</td>
</tr>
<tr>
<td>Recanalization grade&lt;3</td>
<td>2.87</td>
<td>1.58, 5.21</td>
<td>0.0004</td>
</tr>
<tr>
<td>Age&gt;75 y</td>
<td>2.81</td>
<td>1.57, 5.02</td>
<td>0.0004</td>
</tr>
</tbody>
</table>
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References
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