Evaluation of Risk of Hemorrhagic Transformation in Local Intra-arterial Thrombolysis in Acute Ischemic Stroke by Initial SPECT

Toshihiro Ueda, MD; Takao Hatakeyama, MD, PhD; Yoshiaki Kumon, MD, PhD; Saburo Sakaki, MD, PhD; Tadao Uraoka, MD, PhD

Background and Purpose  Thrombolytic therapy was carried out on patients with acute ischemic stroke, and the risk of hemorrhagic transformation was evaluated from the residual cerebral blood flow (CBF) by pretherapeutic single-photon emission-computed tomography (SPECT).

Methods  Local intra-arterial thrombolytic therapy was carried out using urokinase or recombinant tissue plasminogen activator (rt-PA) within 6 hours from the onset in 34 patients in whom no hypodensity areas were observed on the initial computed tomography examination. In the 20 patients with carotid territory occlusion who underwent m\textsuperscript{99m}Te-labeled hexamethylpropyleneamine oxime (m\textsuperscript{99m}Te-HMPAO) SPECT, the residual CBF of the ischemic region was evaluated semiquantitatively by calculating two parameters: the ischemic regional activity to cerebellar activity ratio (R/CE ratio) and asymmetry index (AI).

Results  The occluded vessels could be recanalized in 22 (92%) of the 24 patients in the urokinase group and in all 10 of the patients in the rt-PA group. Hemorrhagic transformation appeared in 4 patients in the urokinase group and 3 patients in the rt-PA group. Among the 20 patients who underwent SPECT before the treatment, the residual CBF was lower in the 5 patients who developed hemorrhagic transformation than in the 15 who did not (P<.05). Hemorrhagic transformation occurred in all patients with R/CE ratio of less than 0.35 and AI of more than 1.5.

Conclusions  The risk of hemorrhagic transformation after recanalization of occluded vessels by local intra-arterial thrombolytic therapy was considered to be high when the pretherapeutic residual CBF was markedly reduced. (Stroke. 1994;25:298-303.)

Key Words  • cerebral ischemia • plasminogen activator, tissue-type • thrombolytic therapy • tomography, emission computed • urokinase

Thrombolytic therapy for acute cerebral infarction is designed to reestablish the blood flow by activating the fibrinolytic mechanism with thrombolytic agents. Recent advances in neuroradiographic techniques have made possible the insertion of the catheter into the main arteries of the brain and superselective infusion of a thrombolytic agent from a site close to the occluded vessel. Such local infusion therapy may supply a sufficient concentration of the thrombolytic agent to the occluded site with a lower frequency of systemic side effects of the drugs when compared with the agent given for thrombolysis through a systemic route. The development of recombinant tissue plasminogen activator (rt-PA), which has a greater affinity to fibrin than urokinase, has further increased expectations for this treatment.

For thrombolytic therapy for acute ischemic stroke to be successful, the duration of the ischemia should be shorter, and the residual cerebral blood flow (CBF) in the territory of the occluded vessel should be greater than the levels at which the viability of neuronal cells and vascular endothelial cells is preserved. Regarding the time limit of ischemic stroke, patients have been reported to have a good possibility of recovery from ischemic insults by thrombolytic therapy or embolectomy within 6 hours after the onset. However, the greatest problem has been reported to be hemorrhagic transformation, which may occur by early recanalization within a few hours after the insult in some patients and result in rapid deterioration of the patients' neurological condition. For those patients, the severity of ischemia has been considered to be one of the main factors inducing the hemorrhagic transformation associated with recanalization.

In this preliminary study, we evaluated the pretherapeutic assessment of the CBF in the territory of occluded vessels by single-photon emission-computed tomography (SPECT) in the patients who underwent superselective intra-arterial thrombolytic therapy and compared the results with the risk of hemorrhagic transformation after recanalization.

Subjects and Methods  This study was carried out on 34 patients with acute cerebral infarction admitted to our hospital between September 1989 and May 1992. The patients were 17 men and 17 women between 35 and 83 (mean±SD, 68±8) years of age. Superselective infusion thrombolytic therapy was indicated according to our three criteria: (1) no apparent hypodensity areas were observed on the computed tomographic (CT) scan on admis-
sion; (2) the patient could be treated within 6 hours, in principle, of the onset; and (3) occluded arteries suggested by symptoms were demonstrated by cerebral angiography. Three patients over 6 hours (6.5, 7, and 7.5 hours) after onset who had a good residual CBF value and were treated by thrombolysis were included in this study. Three other patients with no angiographic occlusions were excluded. No patients with symptoms mimicking acute cerebral stroke (epilepsy, hypoglycemia, etc.) were mistakenly entered in the category of therapeutic indication.

CT was performed on all patients immediately after admission. When no clear hypodensity areas were noted at the sites suggested by the clinical symptoms, SPECT using $^{99m}$Tc-labeled hexamethylpropyleneamine oxime ($^{99m}$Tc-HMPAO) was performed using a rotational gamma camera (GCA602A, Toshiba, Tokyo, Japan) with a low-energy high-resolution collimator. SPECT images were obtained at 10 minutes after intravenous injection of $^{99m}$Tc-HMPAO at 30 mCi with a sampling time of 12 seconds x 60 steps and a sampling matrix of 64 x 64. In patients with internal carotid territory occlusion, the residual CBF was evaluated. Of 12 axial slices, one slice showing the ischemic region most clearly was selected, and the regions of interest in the ischemic region in the cerebral hemisphere (a), the corresponding region on the contralateral side (b), and the whole cerebellar hemisphere on the ischemic side (c) were set and the mean count was determined in each region of interest. Linearity adjustment was made by assuming the blood flow in the normal cerebellar hemisphere to be 55 mL/100 g per minute according to the method of Lassen et al. The CBF was assessed semiquantitatively by calculating two parameters: (1) the ischmic regional activity (R) to cerebellar activity (CE) ratio (R/CE ratio = a/c) and (2) the asymmetry index (AI = $1 - |b - a|/(a + b))

Concerning cerebral angiography, digital subtraction angiography was performed by the Seldinger method using a 5F catheter by placing a 6F sheath in the right or left femoral artery. The occluded vessel was identified, and the tip of a Tracker-18 catheter (Target Therapeutics, Los Angeles, Calif) was advanced into the thrombus, or upstream or downstream from the occlusion site. Urokinase (240 000 U; Wakamoto Pharmaceutical Co, Ltd, Tokyo, Japan) or rt-PA (8 mg; Siltexplase; Dai-ichi Pharmaceutical Co, Ltd, Tokyo, Japan) was injected manually for about 10 minutes. The angiography was performed immediately after each infusion, which was repeated until recanalization of the occluded vessel was confirmed or no neurological symptoms were markedly recovered. The maximum dose of the thrombolytic agents was 1 200 000 U urokinase and 32 mg rt-PA in accordance with thrombolytic therapy for acute myocardial infarction. In 1991. Recanalization of the vessel was considered "complete" when the blood flow was clearly reestablished regardless of small residual embolus or atheromatous plaque left at the occluded site, "partial" when the embolus moved and partly occluded a distal vessel or when the vessel with multiple occlusions was partially recanalized, and "none" when no reperfusion was observed. The patients were managed by administration of 10% glycerol (200 mL) or mannitol (300 mL) before the therapy, and by intravenous injection of heparin (5000 U) and drip infusion of micromolecular dextran (500 mL) during the therapy. Ticlopidine (200 mg/d) was administered from the day after the treatment when no intracranial hemorrhage or systemic bleeding tendency was observed.

CT was performed immediately after the therapy, on the next day, and 1 week, 2 weeks, and 1 month after the therapy in all patients. Cerebral angiography was also performed on the next day. Acute ischemic stroke was classified into cardioembolic infarction (29 patients) and atherothrombotic infarction (5 patients) according to the guidelines by the Cerebral Embolism Task Force. According to the basis of the onset pattern, angiographic findings, and the results of cardiovascular examinations such as electrocardiography, echocardiography, and Holter electrocardiography.

The neurological status was evaluated on admission, immediately after treatment, and at 1 month after treatment according to the National Institutes of Health (NIH) Stroke Scale, which expresses the severity of neurological impairment numerically from 0 (normal) to 42. Comparisons were made using the NIH scores between the urokinase and rt-PA treatment groups and the hemorrhagic transformation and nonhemorrhagic group, and the improvement and outcome of the patients were evaluated. An NIH score of 42 points was applied to patients who had died within 1 month. Additionally, to determine the neurological changes obtained by the therapy, the NIH score of individual patients was evaluated immediately after the procedure on a 3-grade scale by modifying the category of Brott et al.; good (improvement of >3 points in the changes from the initial NIH score), no change (change of ±3 points), and worse (worsening of >3 points). The outcome was evaluated 1 month after onset according to the following 5-grade outcome scale: excellent (no neurological defects were observed, and the patient had returned fully to previous activities), good (mild neurological defects remained, but the patient had returned partly to previous activities), fair (rehabilitation was difficult, but no assistance was needed in activities of daily life), poor (assistance was needed in activities of daily life), and death.

@file:///Users/aaron/Downloads/local%20intra-arterial%20thrombolysis%20localizacion%20%20envasado%20en%20la%20angiografa%20ForMember%20and%20Partners%20only%20.pdf

Blood coagulation and fibrinolytic components were measured in arterial blood through a short 6F sheath placed in the right or left femoral artery before the thrombolytic therapy, just after each injection of fibrinolytic agent, and 24 and 48 hours after the therapy. Fibrinogen-fibrin degradation product (FDP), fibrinogen, and a 2-plasmin inhibitor were assayed by latex agglutination, a sodium sulfite precipitation, and the chromogenic substrate S-2251 (Kabi Diagnostica, Stockholm, Sweden), respectively. D-Dimer, plasmin-a 2-plasmin inhibitor complex, and thrombin-antithrombin III complex were examined by an enzyme-linked immunosorbent assay.

For statistical analysis, the values were expressed as the mean±SD, and differences between the two groups were examined by Student's t test, the Mann-Whitney U test, or Scheffe's F test. This study was performed with the approval of the ethical committee at Kita-Ishikai Hospital.

Results

Urokinase was administered in 24 patients (urokinase group) and rt-PA in 10 (rt-PA group). No significant difference was observed in the age, sex ratio, disease type, or the interval from the onset to the treatment. Complete or partial recanalization was observed in 92% of the patients in the urokinase group and 100% of those in the rt-PA group. The vessel was reoccluded after complete recanalization in 2 patients. In 1 patient, cardioembolic right middle cerebral artery (M1) occlusion had once recanalized with residual embolic material when 32 mg rt-PA infusion, but it reoccluded on the day after the treatment. In the other patient, atherothrombotic left middle cerebral artery (M1) occlusion had reoccluded with residual embolic material after 32 mg rt-PA infusion, but it reoccluded on the day after the treatment. The NIH score immediately after the treatment was not reduced significantly from the mean baseline score for all the patients, but 22 of the 34 patients (65%) showed apparent improvement according to the 3-grade scale. At 1 month after the treatment, the NIH score did not show any significant reduction, but 17 patients (50%) had an excellent or good outcome classified by the 5-grade outcome scale. Death was observed in a total of 7 patients; 3 suffered brain death caused by
hemorrhagic transformation, 1 suffered brain swelling without hemorrhagic transformation, 1 suffered brain death caused by reocclusion, 1 died of pneumonitis, and 1 died of multiple organ failure.

Hemorrhagic transformation occurred in a total of 7 patients (21%): 4 in the urokinase group and 3 in the rt-PA group. Of these patients, neurological symptoms were exacerbated in the following 4 patients. Massive parenchymal hematoma was observed in 1 urokinase-group patient, and localized hematoma was observed in the territory of the lenticulostriate arteries in 1 urokinase-group patient (Fig 1). In 1 patient each in both groups, symptoms had been relieved with complete recanalization and only mild brain edema had been observed by CT immediately after the end of the treatment, but hemorrhage with extensive brain edema occurred with a sudden increase in the blood pressure 6 to 7 hours after the treatment (Fig 2). None of the patients showed a systemic bleeding tendency.

$^{99m}$Tc-HMPAO SPECT was carried out in 23 patients before the treatment, and complete recanalization was observed in 20. Hemorrhagic transformation occurred in 5 of these 20 patients (Table). No significant difference was observed in the age, interval from onset, baseline score, dose of the thrombolytic agent, or the occlusion site between the two groups. However, the NIH score and the outcome at 1 month were signifi-
Comparison of Hemorrhagic Transformation and Nonhemorrhagic Groups With Complete Recanalization of Carotid Territory Occlusions

<table>
<thead>
<tr>
<th>Group</th>
<th>Hemorrhagic Transformation</th>
<th>Nonhemorrhagic</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>5</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>73±10</td>
<td>68±7.1</td>
<td>NS‡</td>
</tr>
<tr>
<td>Interval, hr</td>
<td>5.4±0.6</td>
<td>5.2±0.9</td>
<td>NS‡</td>
</tr>
<tr>
<td>rt-PA dose, mg</td>
<td>18±1.5 (3)</td>
<td>24 (3)</td>
<td>NS‡</td>
</tr>
<tr>
<td>UK dose, ×10⁶ U</td>
<td>84±36 (2)</td>
<td>88±25 (12)</td>
<td>NS‡</td>
</tr>
<tr>
<td>Site of occlusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>MCA (M1)</td>
<td>1</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>(M2)</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td>0</td>
<td>1</td>
<td>NS§</td>
</tr>
<tr>
<td><strong>Tc-HMPAO SPECT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R/CE ratio</td>
<td>0.22±0.08</td>
<td>0.52±0.16</td>
<td>P&lt;.05‡</td>
</tr>
<tr>
<td>Al</td>
<td>1.63±0.10</td>
<td>1.26±0.13</td>
<td>P&lt;.05‡</td>
</tr>
<tr>
<td>NIH scores*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline score</td>
<td>24±3.3</td>
<td>19±5.7</td>
<td>NS‡</td>
</tr>
<tr>
<td>Immediately after treatment</td>
<td>19±6.2†</td>
<td>12±6.9†</td>
<td>NS‡</td>
</tr>
<tr>
<td>1 Month after treatment</td>
<td>31±13†</td>
<td>11±13†</td>
<td>P&lt;.05‡</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>0</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>3</td>
<td>2</td>
<td>P&lt;.05§</td>
</tr>
</tbody>
</table>

rt-PA indicates recombinant tissue plasminogen activator; UK, urokinase; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior carotid artery; **Tc-HMPAO SPECT, **Tc-labeled hexamethylpropyleneamine oxime single-photon emission-computed tomography; R, ischemic regional activity; CE, cerebellar activity; and Al, asymmetry index.

*National Institutes of Health Stroke Scale score.
†No significant difference from baseline score (Scheffé’s F test).
‡Student’s t test.
§Mann-Whitney U test.

significantly better in the nonhemorrhagic group. Furthermore, semiquantitative assessment of the CBF by SPECT revealed significant differences in both the R/CE ratio and Al between the hemorrhagic transformation group and the nonhemorrhagic group (P<.05). In all 5 patients with hemorrhagic transformation, the R/CE ratio and Al were less than 0.35 and more than 1.5, respectively (Fig 3).

There was no significant difference in the FDP level between the urokinase and rt-PA groups in the nonhemorrhagic group. The FDP level in 3 patients showing hemorrhagic transformation treated with 960 000 and 1 200 000 U urokinase and 32 mg rt-PA was markedly higher than that in those in the nonhemorrhagic group. The fibrinogen level slightly decreased in the urokinase group during and after the thrombolytic therapy, but showed almost no change throughout the study in the rt-PA group. There were no marked distinctions in other coagulation or fibrinolytic activation markers between the two groups.

Discussion

Critical problems still remain unsolved regarding the thrombolytic therapy for acute ischemic stroke including its indication, the route and dose of thrombolytic agents, and the risk of therapy. To avoid the risk of fatal or severe complications following recanalization in thrombolytic therapy, the indication must be strictly determined based on the duration and severity of ischemia. In the past, the duration of occlusion was regarded mainly as an important prognostic factor in hemorrhagic transformation associated with recanalization, and occluded vessels were reopened safely if the duration of occlusion was within 4 to 6 hours.17,18 However, hemorrhagic transformation was reported to have occurred even after an occlusion time of only 2 hours, and the residual CBF21 was emphasized as another important factor. Seki et al.21 reported that a reduction of the CBF to less than about 50% is critical for developing hemorrhagic infarction in dogs when the occluded vessel was recanalized after 6 hours of isch-
The thrombolytic agent can be administered either intravenously or intra-arterially, and intra-arterial administration can be made selectively using a microcatheter. According to recent reports, the recanalization rate (partial and/or complete) was 34% to 53%\(^{24-30}\) by intravenous infusion, 36% to 56%\(^{24,31,32}\) by selective infusion, and 44% to 100%\(^{1,4,33}\) by superselective infusion. The outcome of the therapy was satisfactory in 15% to 50%\(^{24-30}\) of the patients by intravenous infusion, 56% to 68%\(^{24,31,32}\) by selective infusion, and 50% to 75%\(^{1,4,33}\) by superselective infusion. In this study, the rate of complete recanalization was 59% in the urokinase group and rt-PA group combined, the recanalization rate including partial recanalization was 94%, improvement immediately after treatment was seen in 65%, and the 1-month outcome was satisfactory in 68%, which was similar to the recent other reports.

rt-PA is a potent fibrinolytic agent for recanalization of coronary artery occlusion in acute myocardial infarction compared with urokinase. In the present study, the recanalization rate (complete and partial) in the rt-PA group tended to be higher than that in the urokinase group, but the incidence of hemorrhagic transformation was higher in the rt-PA group (30%) than in the urokinase group (17%). The higher incidence of hemorrhagic transformation in the rt-PA group is considered to be attributable to a higher frequency of proximal arterial occlusion (60%) such as internal carotid artery occlusion or M1-portion occlusion of the middle cerebral artery than in the urokinase group (46%).

The greatest problem in thrombolytic therapy is a promoting risk factor for transforming the ischemic lesion to hemorrhagic transformation, although hemorrhagic infarction may also occur spontaneously in cerebral embolism (7.5% to 43%). Hemorrhagic transformation can be classified as the hemorrhagic lesion with or without extensive brain edema. The former often exacerbates the neurological symptoms and the latter infrequently aggravates the neurological symptoms. The incidence of hemorrhagic transformation with and without neurological exacerbation after intravenous infusion is reported to be 4%\(^{16}\) in patients who received the treatment within 90 minutes from onset, but to be 21% to 52%\(^{22,27,29-30}\) in those treated within 8 hours of onset. Hemorrhagic transformation with neurological exacerbation was observed in 9.6% to 11%\(^{24,30}\) of the patients who received intravenous infusion and 0% to 17%\(^{1,4,24,31,32}\) of those who received intra-arterial infusion. In this study, hemorrhagic transformation occurred within 48 hours after onset in 7 patients (21%), and aggravation of neurological symptoms was observed in 4 of them (12%). The occurrence of hemorrhagic transformation irrespective of symptomatic aggravation is a deviation from the objective of the treatment, and the therapy is not considered to have been successful in these patients. In the present study, it was clearly demonstrated that, apart from the duration of ischemia, the occurrence of hemorrhagic transformation was closely related to the residual CBF in the ischemic area. The residual CBF value less than 0.35 of the R/CE ratio and more than 1.5 of AI was shown in the patients with hemorrhagic transformation, indicating that the residual CBF in the ischemic region was significantly lower in the hemorrhagic transformation group than in the nonhemorrhagic group.

As for coagulation and fibrinolytic activation in thrombolytic therapy, the FDP level was markedly high in some patients of the hemorrhagic transformation group compared with the nonhemorrhagic group. The increase in the FDP level may indicate fibrinolytic
activation and bleeding tendency and may promote hemorrhagic transformation in the hemorrhagic group. Although a close relation was not observed between the dose of the thrombolytic agents and the increase of FDP in the present series of patients, a higher concentration of the drug should be given close to the occluded site with a lower total drug dose to reduce systemic side effects on the coagulation and fibrinolytic system.

In conclusion, pretherapeutic CBF by SPECT in the ischemic area was found to be significantly lower in the patients suffering hemorrhagic transformation than in the patients without hemorrhage. The risk of hemorrhagic transformation is considered to be reduced by determining the indication for the thrombolytic therapy on the basis of the residual CBF. Although this study is preliminary and the effectiveness of the procedure should be evaluated by well-designed randomized clinical trials in a large number of patients, the present results should encourage future trials in acute ischemic stroke.

Acknowledgments
The author is deeply grateful to Dr. Yoshifumi Sugawara, Dr. Yasuyoshi Nishiyama, and all the staff members of the Division of Radiology, Kita-Ishikai Hospital, who cooperated in this study, which required a 24-hour system to perform this therapy in patients with acute ischemic stroke.

References
Evaluation of risk of hemorrhagic transformation in local intra-arterial thrombolysis in acute ischemic stroke by initial SPECT.
T Ueda, T Hatakeyama, Y Kumon, S Sakaki and T Uraoka

Stroke. 1994;25:298-303
doi: 10.1161/01.STR.25.2.298

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/25/2/298