Early Computed Tomographic Findings for Thrombolytic Therapy in Patients With Acute Brain Embolism

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**Background and Purpose:** The benefits and safety of thrombolytic therapy was studied in patients with acute brain embolism.

**Methods:** We intravenously administered recombinant tissue plasminogen activator (20–30 MU for 1 hour) to 10 patients with acute (<6 hours) brain embolism and examined the neurological outcomes in relation to the findings on computed tomography and angiography.

**Results:** The symptoms ameliorated in four patients within 24 hours after onset, and reopening of the occluded arteries occurred in two of the patients immediately after recombinant tissue plasminogen activator infusion. On the initial computed tomographic scan (<3 hours), four patients had already demonstrated early indications of brain ischemia, that is, an obscure margin of the lentiform nuclei, reduced tissue attenuation, or effacement of cortical sulci. These patients failed to demonstrate reopening of the occluded arteries, and one developed a massive brain hemorrhage with clinical deterioration. Of the remaining six patients, two obtained clinical improvement with recanalization soon after the therapy and demonstrated little to slight hemorrhagic complications. The outcomes at 1 month were favorable in five patients and poor in three; death occurred in two.

**Conclusions:** Thrombolytic therapy with recombinant tissue plasminogen activator may be safe and effective when there are no early computed tomographic findings within 3 hours from the onset of embolic stroke. (Stroke 1992;23:20–23)

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ome clinical trials of thrombolytic therapy for acute brain infarction resulted in unfavorable outcomes, with conversion to hemorrhagic infarction or frank hemorrhage causing clinical worsening or death.1,2 Intra-arterial administration of streptokinase3 or urokinase4,5 has shown favorable outcomes without serious hemorrhagic complications when therapy is initiated at the earliest stage of stroke.

Recombinant tissue plasminogen activator (rt-PA) has proved effective for patients with acute myocardial infarction.6 Administration of rt-PA significantly reduced the volume of the infarcted area in experimental brain ischemia7'8 and improved neurological dysfunction in some patients.9-12 In the present study, rt-PA was administered to patients with acute brain embolism to examine the clinical indications for this treatment.

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**Subjects and Methods**

We studied 10 patients with acute brain embolism, aged 33–78 (mean 62) years, admitted to St. Mary's Hospital during the period May 1–December 31, 1989. Informed consent was obtained from the patients or their families before therapy. The inclusion criteria were 1) abrupt onset of symptoms in the territory of the internal carotid artery, 2) atrial fibrillation or other heart diseases, 3) age <80 years, 4) occlusion of the cerebral artery on angiography, and 5) rt-PA therapy initiated within 6 hours from onset of stroke.

The patients were examined by computed tomographic (CT) scan (SCT 2000, 512×512 matrix, Shimizu, Kyoto, Japan) within 3 hours (mean±SD, 103±49 minutes) from the onset of stroke and received rt-PA within 6 hours (279±42 minutes). We estimated the severity of neurological deficits by means of the Hemispheric Stroke Scale.9 The neurological state at 30 days was classified into five groups: excellent, 0–5 points; good, 6–20 points; moderate, 21–60 points; and poor, 61–100 points; and deceased.

Selective carotid angiography was performed by conventional Seldinger's method. Immediately after
the first angiography, 20–30 MU of rt-PA (SM9527; Sumitomo Pharmacy Co Ltd., Osaka, Japan) in 100 ml saline was administered intravenously for 1 hour. The doses of rt-PA for each patient were selected in accordance with age and body weight. A second carotid angiogram was performed through the same catheter soon after the rt-PA infusion. A follow-up third angiogram was conducted in five patients from 2 to 36 days after the onset of stroke. We defined the disappearance of the embolic occlusion as complete reopening and the existence of some stenotic or occlusive lesions with sufficient restoration of anterograde blood flow as partial reopening. In some patients with either mild neurological deficits or a small infarct on CT scan, anticoagulant therapy (heparin 10,000 units/day) was started at least 4 days after the onset of stroke.14,15

In addition to the initial brain CT scan, a follow-up scan was obtained at 24 hours and at 3, 7, and 30 days. Early findings in cerebral infarction were defined according to the following characteristic changes on the initial CT scan until 6 hours:16 1) an obscure margin of the lentiform nuclei, 2) a decreased tissue density, or 3) effacement of the cortical sulci in the affected area. The size of the infarcted lesion was expressed as the maximum hypodense area/ipsilateral hemisphere x 100% on day 3 and was classified as either small (<10%), medium (10–30%), or large (>30%). Hemorrhagic transformation was evaluated at 24 hours according to our classification.14

Results
The first angiogram showed the occluded lesions at the trunk of the anterior cerebral artery and the branches of the middle cerebral artery in one patient (case 1), the stem or branches of the middle cerebral artery in five patients (cases 2–6), and the top of internal carotid artery in four (cases 7–10). A reopening of the occluded arteries was revealed in two patients (cases 1 and 2) on the second angiogram (Figures 1 and 2). Four patients, including these two, showed complete recanalization on the third angiogram (cases 1, 2, 3, and 5). The remaining six patients, including all four patients with internal carotid artery top occlusion, failed to demonstrate any reopening of the occluded vessels.

Nine of the 10 patients had a score of >60 points on the Hemispheric Stroke Scale on admission (range 47–93, mean 71 points). Four patients (cases 1, 2, 3, and 5), including the two patients with immediate recanalization, were remarkably improved, and their initial Hemispheric Stroke Scale scores were reduced by ≥30 points at 24 hours after thrombolytic therapy. Five patients (cases 1–5) achieved either an excellent or good outcome 1 month after stroke onset. Two patients (cases 8 and 10) died within 8 days, probably due to cerebral herniation. The other three patients had a poor outcome. The size of the infarcted lesion on day 3 was well correlated with the outcome of the patient: small in cases 1–4, medium in case 5, and large in cases 6–10.

Soon after rt-PA infusion, three patients showed negligible gingival bleeding or hematuria. Hemorrhagic transformation was seen in five of the 10 cases. Four patients (cases 2, 3, 4, and 8) showed only petechial hemorrhage or small hematoma,
Figure 2. Serial computed tomographic (CT) scans of case 2. Left: Before thrombolytic therapy, no abnormal findings of cerebral ischemia were illustrated. Right: Localized small, low-density area was observed in left insular cortex on follow-up CT scan on day 1.

whereas one (case 6) demonstrated massive parenchymal hemorrhage with clinical deterioration.

Four patients (cases 5, 6, 9, and 10) who had early CT findings (Figure 3, top) showed failed arterial recanalization on the second angiogram. The area of early CT findings changed into an apparent infarcted lesion on a later scan (Figure 3, bottom), but one patient (case 5) who had MCA branch occlusion had a

Figure 3. Initial (top) and follow-up computed tomographic (CT) scan on day 1 or 3 (bottom) of four cases (cases 5, 6, 9, and 10) showing early findings of cerebral infarction. Areas with early ischemic abnormalities developed apparent infarcts, with massive brain hemorrhage in one patient (case 6).
good outcome. Among the other six patients without early CT findings, two had reopening just after the thrombolytic therapy, and four patients showed either excellent or good outcomes at 1 month. Hemorrhagic transformation was not significant.

Discussion

Thrombolytic therapy at an early stage of ischemic stroke could result in either a clinical improvement with a reopening of the occluded arteries or a deterioration from hemorrhagic complications. The most important factor is probably the time interval from the onset of stroke until the therapy. Sufficient collateral blood flow may also be necessary for rt-PA to reach the thrombus. In the present study, all four patients with internal carotid artery top occlusion failed to demonstrate reopening and had poor outcome. An angiographic study at a very early stage may provide reliable information for thrombolytic therapy as well as a reasonable prediction of prognosis. However, it is impossible to perform angiography for all acute stroke patients, and we assume that severity of the initial neurological deficits and CT findings provide sufficient information for the presence of large arterial occlusion and the indication for rt-PA therapy. We propose, therefore, that intravenous rt-PA therapy should be started as soon as possible, even without angiographic assessment, in the future.

Four of 10 thromboembolic patients in the present study developed early CT findings within 3 hours. Morphological changes indicative of ischemia in nerve cells were observed 2 hours after embolic microinfarction or within 2 hours of ischemia by reduced cerebral blood flow <10 ml/100 g/min. Thus, early CT findings of <3 hours found in our study seem to represent the severity of the thromboembolism, that is, the irreversibility of ischemic damages. We believe that the initial CT images are important in deciding the potential risk versus benefit of rt-PA therapy.

None of our patients without early CT findings developed later "brain hemorrhage." Hemorrhagic transformation was more closely correlated with the severity of the neurological deficits and was independent on rt-PA treatment when it was given within 90 minutes or 3 hours from the onset of brain ischemia. Thus, thrombolysis with rt-PA may rarely cause severe hemorrhagic complications when rt-PA is given very early after the onset of stroke.

The number of patients in our study was too small to draw conclusions concerning the usefulness of intravenous rt-PA therapy, and further hemodynamic as well as follow-up studies are required. We believe that the significance of early (within 3 hours) CT findings should be evaluated in future large controlled trials of rt-PA therapy.

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References


Key Words • embolism • plasminogen activator, tissue-type • tomography, x-ray computed • thrombolytic therapy
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