Intracarotid Urokinase With Thromboembolic Occlusion of the Middle Cerebral Artery

Etsuro Mori, MD, Masayasu Tabuchi, MD, Takashi Yoshida, MD, and Atsushi Yamadori, MD

Intracarotid urokinase infusion therapy was performed on 22 patients with evolving cerebral infarction due to acute thromboembolic occlusion of the middle cerebral artery. Mean time from onset of symptoms to start of infusion and mean dosage of urokinase were 4.5 hours and 927,000 units, respectively. Immediate recanalization was achieved in 10 patients (45%) after urokinase therapy. In patients with successful recanalization, rapid amelioration of symptoms followed the restoration of blood flow. Thrombolytic recanalization was associated with reduction of neurologic deficits and of computed tomography-demonstrable infarction volume. The reduction of infarction volume and functional outcome correlated highly with the degree of reflow. Hemorrhagic transformation of infarction occurred in four patients and controllable extracranial bleeding in three patients. These results support the safety and efficacy of urokinase therapy for acute thromboembolic occlusion of the middle cerebral artery. (Stroke 1988;19:802-812)

Although thrombolytic therapy with streptokinase or urokinase has been studied, previous results have suggested that these drugs are ineffective or unsafe.1-6 Fatal intracerebral hemorrhages were reported with intravenous high-dose urokinase and were stressed as an unacceptable hazard.1 In recent Japanese clinical trials, intravenous low-dose urokinase appeared to yield neither major complications nor definitive benefits for stroke.5,6 However, many criticisms have been raised concerning the designs, clinical assessments, lack of imaging techniques, and therapeutic applications of the early studies.1b With developments in clinical and radiologic assessment and understanding of the pathophysiology of brain ischemia, thrombolytic therapy again seems a feasible intervention in acute stroke.10b Recent studies suggest that an ischemic penumbra exists and that a proportion of clinical deficits is potentially reversible.12,14 In experimental animals, acute restoration of blood flow may salvage this ischemic but viable tissue.15-18 Limited clinical experiences indicate that intra-arterial infusion of streptokinase or urokinase may lead to thrombus dissolution, blood flow restoration, and clinical improvement in selected patients with acute ischemic stroke.19-24 In addition, recent favorable experiences of intracoronary thrombolysis in patients with acute myocardial infarction25-27 have prompted the use of this mode of therapy in stroke.

Since 1983, we have treated acute stroke patients with major cerebral artery occlusion by means of local intra-arterial infusion of urokinase.28 We report our initial 3-year experience with 22 patients with acute thromboembolic occlusion of the middle cerebral artery (MCA) who were treated with intracarotid urokinase infusion.

Subjects and Methods

The study group consisted of 22 patients with acute thromboembolic occlusion of the MCA or its major branches in whom intracarotid urokinase infusion was performed between July 1984 and June 1987. Criteria for thrombolysis included clinical signs of right or left MCA ischemic syndrome, an interval from onset of symptoms to infusion of usually <6 hours or <12 hours when symptoms were still evolving, age <80 years, absence of apparent computed tomographic (CT) hypodensity related to the ischemic events, and no contraindication to urokinase (such as history of gastrointestinal bleeding). During this 3-year period, urgent cerebral angiography was performed in every patient who fulfilled the above criteria. Although there were 25 patients with angiographic evidence of MCA occlusion, three were excluded from the study because of failure of selective catheterization (two patients) and failure to obtain informed consent for urokinase infusion (one patient). Clinical
characteristics of the study patients are given in Table 1. Interval from onset to presentation ranged from 5 minutes to 10 hours.

The etiology of the arterial occlusions was assumed to be embolic in 14 patients because of the abrupt onset of symptoms and the presence of cardiac diseases as a potential source of emboli. Although the cause of the embolism was not recognized as the heart, abrupt onset of symptoms suggested embolism in three other patients. In five patients, before angiography the etiology was believed to be thrombotic because of prodromal transient ischemic attacks, progression or fluctuation of symptoms, and no evidence of cardiac abnormalities as a source of emboli. The acute MCA ischemic syndromes consisted of sensorimotor deficits, neuropsychological deficits, visual field defects, and conjugate ocular deviation to the ipsilateral side. 29-30 Patients’ initial neurologic states were divided into four categories: stuporous,

<table>
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<tr>
<th>Case/age/sex</th>
<th>Onset</th>
<th>Cause</th>
<th>Initial neurologic state</th>
<th>Occlusion</th>
<th>Interval (min)</th>
<th>Dose (x10^4 units)</th>
<th>Recanalization</th>
<th>Outcome</th>
<th>Treatment after urokinase</th>
<th>Infarction (ml)</th>
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<td>1/40M</td>
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<td>280</td>
<td>36</td>
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<td>Good</td>
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<td>120</td>
<td>Stenotic</td>
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<td>Good</td>
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<td>Fair</td>
<td>G, As</td>
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<td>Puncture site hemorrhage</td>
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<td>LM2S</td>
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<td>AF</td>
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<td>RM1P</td>
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<tr>
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<td>90</td>
<td>No</td>
<td>Good</td>
<td>D, H</td>
<td>32</td>
<td>None</td>
</tr>
</tbody>
</table>

M, male; F, female; VSD, ventricular septal defect; ICA, internal carotid artery; MCA, middle cerebral artery; AF, atrial fibrillation; L, left; R, right; M1P, proximal M1; MID, distal M1; M2I, inferior division of M2; M2S, superior division of M2; A, anterior cerebral artery; P, posterior cerebral artery; G, intravenous glycerol; H, heparin; D, hypervolemic or isovolemic hemodilution; As, aspirin. Interval from onset to start of urokinase infusion. Volume of infarction estimated by computed tomography 3 days after onset.
obtundation associated with hemiplegia, conjugate ocular deviation, and ipsilateral instinctive grasp reaction; severe, severe sensorimotor and neuropsychological deficits (global aphasia and severe right hemisphere syndrome including anosognosia and ipsilateral instinctive grasp reaction); moderate, moderate sensorimotor and/or neuropsychologic deficits (e.g., hemiparesis with strength of 2-3/5, Broca’s or Wernicke’s aphasia, unilateral neglect syndrome not associated with anosognosia, acute confusional state, and agitated delirium); and mild, moderate neuropsychologic deficits (e.g., Broca’s or Wernicke’s aphasia, unilateral neglect syndrome) with minimal limb weakness and sensory impairments, or moderate hemiparesis with minimal neuropsychological syndrome (e.g., mild word-finding difficulty, mild dyscalculia, mild dysgraphia, constructional disability, and extinction phenomena). The pretreatment evaluation classified 5 patients as stuporous, 6 as severe, 6 as moderate, and 6 as mild.

The outcome at the end of the third month after onset was divided into five categories: excellent, no neurologic deficit, normal life possible; good, slight neurologic deficit remained but social life possible; fair, social life impossible but domestic life could be conducted without assistance; poor, assistance required for domestic life; and dead.

After obtaining a brief medical history, physical, neurologic, and neuropsychological examinations, blood for routine laboratory work, CT of the brain, and informed consent for the procedure from the patient or an accompanying relative, patients underwent emergency cerebral angiography. Before transfer to the angiography laboratory, all patients received 250-500 ml of 10% low-molecular-weight dextran in an attempt to increase residual cerebral perfusion. The right or left femoral artery was entered with a 7-French side-arm valved sheath. A 7-French catheter was used for selective carotid angiography. Intra-arterial thrombus was identified by an abrupt cutoff in the main stem or main branches of the ischemia-related MCA. If either the ipsilateral anterior cerebral artery (ACA) or ipsilateral posterior cerebral artery (PCA) could not be identified, the contralateral carotid artery and/or the vertebral artery were then studied to examine the status of collateral blood flow.

After advancing the catheter to just below the cavernous portion of the internal carotid artery (ICA), 180,000-1,320,000 units urokinase in 50 ml was continuously infused into the artery at a rate of 6,000-48,000 units/min (150-600 units/kg/min). Urokinase infusion was initiated a mean of 4.5 (range 0.83-12) hours after onset. Carotid angiography was repeated every 10-15 minutes in some cases, only after 30 minutes in others, to watch for dissolution of thrombus. Once reperfusion was established, the infusion was discontinued. If reperfusion was not established by 30 minutes, urokinase infusion was stopped. Duration of infusion ranged from 10 to 30 minutes, with mean urokinase dosage of 927,000 (range 180,000-1,320,000) units. After completion of the infusion, the sheath in the femoral artery was sutured in place. Delaying removal of the sheath until the following day decreased the incidence of bleeding at the site of arterial entry.

After the urokinase infusion was completed, the patients were transported to the neurological intensive care unit. They were treated with either hypervolemic or isovolemic hemodilution or with 10% intravenous glycerol according to their hemodynamic state and their state of brain swelling. To prevent recurrence of occlusion, selected patients also received some combination of aspirin and heparin. The physician in charge chose the treatment after urokinase infusion. Clotting factors were determined. Follow-up CTs were obtained 24 hours, 3 days, 1 week, 2 weeks, and 3 weeks after onset. Total volume of the hypodense lesions or, when the lesions contained hemorrhages, total volume of both the hypodense and hyperdense lesions was measured on CTs obtained 3 days after onset using a personal computer and a graphics tablet.

Results

Occlusion was identified at both the proximal side of the main stem of the MCA and at the main branch of the ipsilateral ACA and/or PCA in four patients (ACA and PCA in three, ACA in one), at the proximal side of the trunk of the MCA proximal to the lenticulostriate branching in eight patients, at the distal end of the trunk of the MCA distal to the lenticulostriate branching in three patients, and at the proximal end of the superior or inferior division of the MCA in seven patients (superior in four, inferior in three). Collateral blood flow through leptomeningeal anastomoses with the ACA and/or PCA were visualized in the late phase in all but the three patients in whom the ACA and PCA were concomitantly occluded. In addition, atherosclerotic plaque with ulceration was found in six patients (Table 1).

The acute results (recanalization) of intracarotid urokinase infusion in the 22 patients are also shown in Table 1. Treatment recanalized the occluded MCA in 10 patients (recanalization group); in four patients, recanalization and restoration of blood flow appeared complete (Figures 1 and 2); in four patients, although residual mild stenosis or partial occlusion was seen in the branches, blood flow appeared effectively restored (Figure 3); and in two patients, because of severe residual stenosis in the originally occluded site after recanalization, restoration of blood flow was restricted (Figure 4). Opening of the occluded vessel in two patients (Cases 7 and 8) whose MCA occlusion was initially believed to be thrombotic in etiology was so complete that the diagnosis should be corrected to artery-to-artery embolism from the ICA ulcerated plaque despite the nonsudden onset of symptoms. Recanalization was not achieved in the MCA of 12 patients (no-recanalization group).
**FIGURE 1.** Serial angiography of Case 1. A: Before intracarotid urokinase infusion. Left middle cerebral artery (MCA) is occluded by thrombus at origin. B: After 360,000 units of urokinase. Thrombus has moved distally in main stem of MCA. C: After 720,000 units of urokinase. Branches of MCA are partially recanalized; however, fragments of thrombus are still visible in main stem and peripheral branches (arrows). D: After 1,080,000 units of urokinase. MCA is completely recanalized.
FIGURE 2. Angiography of Case 5. A: Before intracarotid urokinase infusion. Left middle cerebral artery (MCA) is occluded in proximal portion. Note ulcerated atherosclerotic plaque in carotid bifurcation (arrow). B: After completion of urokinase therapy. MCA is completely recanalized.

FIGURE 3. Angiography of Case 6. A: Before intracarotid urokinase infusion. Left middle cerebral artery (MCA) main stem is occluded in origin. B: After completion of urokinase therapy. Superior division of MCA was recanalized; however, fragments of clot are left in MCA trunk (arrow), and inferior division remains occluded at stem (arrowhead). Good collateral blood flow through leptomeningeal arteries from reopened superior division was seen at venous phase.
Characteristics of the two groups are summarized in Table 2. Clinical characteristics at entry (such as age, sex, affected side, initial neurologic state, site of arterial occlusion, and interval from onset to start of urokinase therapy) did not differ significantly between groups. The no-recanalization group included mostly patients with embolism of cardiac origin, but the recanalization group included more patients with embolism of noncardiac than cardiac origin; the difference was significant. Although the four patients with Ml + ACA and/or PCA occlusion were all in the no-recanalization group, this difference in distribution was not significant (p = 0.068, Fisher’s exact probability test). Total dose of urokinase ranged from 360,000 to 1,320,000 (mean ± SD 894,000 ± 324,000) units in the recanalization group and from 180,000 to 1,200,000 (mean ± SD 955,000 ± 280,000) units in the no-recanalization group; the difference was nonsignificant. There was no significant difference in the treatments after urokinase infusion between the two groups.

Three patients in the no-recanalization group who had proximal Ml + ACA and/or PCA occlusion and little collateral circulation died of brain herniation resulting from massive hemispheric infarction with edema. In eight of the 10 patients in the recanalization group, symptoms ameliorated quickly after restoration of blood flow and steadily improved for several days thereafter. By contrast, no patient in the no-recanalization group showed such a dramatic improvement after urokinase infusion; only two patients showed a considerable recovery during the first 24 hours. The overall outcomes for the 22 patients are reported in Table 1 and for the two groups in Table 2 and Figure 9. Although the initial neurologic state in the recanalization group was not significantly different from that in the no-recanalization group, the prognosis was better in the former than in the latter (Table 2). Prognosis was correlated with restoration of blood flow ($r_s = 0.603$, p = 0.003, Spearman’s rank correlation test) and initial neurologic state ($r_s = 0.803$, p < 0.001; Figure 5). There was no correlation between initial neurologic state and recanalization. Neither interval from onset to infusion nor dose of urokinase correlated with prognosis.

CTs obtained 24 hours after onset demonstrated some evidence of infarction in seven of 10 patients in the recanalization group and in all 12 patients in the no-recanalization group. Infarctions were apt to affect the basal ganglia (Figure 6). The mean infarction volume demonstrated in CTs obtained 3 days after onset was 35.5 ± 55.4 ml in the recanalization group and 172.8 ± 122.6 ml in the no-recanalization group; the difference was significant (Table 2). The volume of hypodensity was reduced in proportion to the degree of recanalization ($r_s = 0.812$, p < 0.001; Figure 7) and was correlated with initial neurologic state ($r_s = 0.758$, p < 0.001) and outcome ($r_s = 0.946$, p < 0.001).

Hemorrhagic transformation occurred within the first 24 hours in four patients (Table 1), one in the recanalization group and three in the no-recanalization group (Figure 8). It was uncertain whether the three cases of hemorrhagic transformation in the no-recanalization group had delayed recanalization after angiography. Follow-up CTs after the first 24 hours...
TABLE 2. Comparison of Recanalization and No-recanalization Groups

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<th>Recanalization</th>
<th>No recanalization</th>
<th>Difference</th>
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</thead>
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<td>62.6±10.5</td>
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<td>Sex ratio</td>
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<td>Volume of infarction (ml)</td>
<td>35.5±55.4</td>
<td>172.8±122.6</td>
<td>p&lt;0.01t</td>
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ACA, anterior cerebral artery; PCA, posterior cerebral artery.
* Student's t test (two-tailed), t Fisher's exact probability test.
\( t \) Mann-Whitney U test (two-tailed).

FIGURE 5. Relation between initial neurologic state and outcome, i, complete recanalization; O, partial but effective recanalization; A, recanalization with severe stenosis; *, no recanalization.


did not demonstrate hemorrhagic infarction in any other patients. In the one patient in the recanalization group, petechial hemorrhage was restricted to the basal ganglia, and the patient's symptomatic recovery was uninterrupted. One patient of the no-recanalization group had a multiple-artery occlusion, massive infarction in the whole territory of the MCA and PCA, and aggravated hematoma with considerable mass effects in the basal ganglia and temporal lobe. The patient died 3 days after onset and urokinase therapy. In the remaining two patients of the no-recanalization group the hemorrhages occurred in the basal ganglia, perforating into the ventricles in one patient and extending into the subcortical white matter in the other, and appeared to have substantial mass effects as demonstrated by CT. In the latter two patients, no apparent further deterioration occurred except for some clouding of consciousness. Fibrinogen was markedly decreased in two, and prothrombin time (PT) was prolonged in three of the four patients with hemorr-
In our series of 22 patients, early and quick recanalization was demonstrated in 10 patients (45%) with angiographic examinations at short intervals. The process of recanalization, that is, movement, fragmentation, and lysis of clot, demonstrated in our study is probably similar to that of spontaneous recanalization and represents an important model of the disappearance of an occlusive process, something that has rarely been demonstrated. The recanalization in our study is considered to be mostly urokinase-induced and, although our rate approximates that of spontaneous recanalization in the literature (40–59%),27,37 the recanalization in our study seemed to occur much earlier. In the Harvard Stroke Registry, within 2 days after onset, not more than 14 of 52 patients (27%) with embolic strokes had recanalization.39 Moreover, recanalizations completed within a short period (<1 hour), like those in our study, seem to be rare in the natural course of cerebrovascular occlusion. Dalal et al35 and Liebeskind et al described only a few patients in whom the movement or disappearance of clots was demonstrated in angiographic studies at short intervals. Thus, fibrinolytic therapy appears to increase the chance of immediate recanalization although it is not yet certain what proportion of that immediate recanalization occurs in the natural course.

The rate of recanalization after local fibrinolytic therapy in our study was similar to that of MCA recanalization reported by Zeumer (2 of 4) but relatively lower than the rate of recanalization of the vertebrobasilar system (100%), the carotid siphon (4 of 4), and the coronary artery (approximately 75%).25-27 In our series, recanalization was more common with presumed intra-arterial emboli than with emboli of cardiac origin. The volume of the thrombus seems to explain the difference. It is likely that thrombus originating in the heart is larger than that originating in a carotid plaque, for the former is often wide enough to plug the common carotid artery or proximal ICA; by contrast, the width of emboli of arterial origin never exceeds the carotid lumen size. The thrombus, altering in length and width at different points of the artery and moving distally, may lodge in the MCA. Thus, thrombus of cardiac
Prognosis of middle cerebral artery occlusion: Comparison of thrombolytic, conventional, and surgical therapy.

The outcome for patients in the recanalization group was significantly better than that for patients in the no-recanalization group and was considerably better than that of patients with MCA occlusion treated with conventional therapy or acute embolectomy (Figure 9). The outcomes for the no-recanalization group were approximately the same as those in the literature. Furthermore, the volume of CT-demonstrable infarctions in the recanalization group was smaller than that of infarctions in the no-recanalization group. Therefore, it may be hypothesized that restoration of blood flow following intracarotid urokinase infusion minimizes the neurologic deficits and volume of infarction.

Critical factors determining the efficacy of restoring blood flow must include the duration and degree of ischemia. Animal models of experimental occlusion of the MCA have suggested that brain tissue is viable and that neurologic deficits can be reversible after 2-6 hours of ischemia. Clinically, the time elapsed between the onset of symptoms and the completion of a surgical MCA embolectomy with a favorable outcome has been as long as 18 hours. Zeumer has estimated that thrombolytic therapy for occlusion of the ICA or MCA should start not more than 5 hours after the onset of stroke. However, both our results and those of the study of embolectomy suggest that the time elapsed before restoration of blood flow does not necessarily predict outcome reliably. Since the lenticulostriate arteries have little collateralization, occlusion at their origin produces complete ischemia that may damage the total supply area, including the vessel wall, very early. Even if recanalization could be achieved immediately, the basal ganglia would probably not escape ischemic insult due to early infarction from a lack of marginal collateral flow or hemorrhage resulting from ischemic damage to the vessel wall. The vulnerability of the basal ganglia and the lenticulostriate arteries to ischemia has been repeatedly suggested by the experience of patients with ICA or MCA occlusion whether they received thrombolytic therapy or not.

Because of the unfavorable effects of the fibrinolytic agent per se (systemic lytic state) and of reperfusion, use of thrombolytic therapy in stroke has generally been considered to be contraindicated. Recanalization with restoration of blood flow may cause intracerebral hemorrhage when ischemia has already damaged vessels and may enhance edema formation in the ischemic area due to reperfusion injury and an increase in blood flow. Our results indicate that brain hemorrhage occurs primarily in those patients without early recanalization, in contrast to the conventional wisdom that reperfusion is important in hemorrhagic transformation. The rates of hemorrhagic transformation of the overall series (18%) and the no-recanalization group (25%) was similar to that of the natural course. In the recanalization group, hemorrhagic transformation occurred in only one patient (10%). Early urokinase-induced reperfusion can salvage the vessels and prevent extravasation if the vessels remain alive for a period after neural function has been observed as a sign of transient ischemic attack in the ICA territory. Although extracranial bleeding had been controllable, anti-
coagulation after urokinase therapy might be hazardous and thus should be avoided. Results of a clotting factor study suggest that > 1,080,000 units of urokinase (20,000 units/kg) might increase risk of hemorrhagic complications.

Intracarotid urokinase infusion appears to increase the chance of recanalization occurring quickly enough to reduce the volume of infarction and the neurologic deficit after acute MCA occlusion in selected patients. Hemorrhagic transformation seems to occur more often when the MCA is not recanalized. Whereas controlled trials are required to verify these assumptions, the development of fibrin-specific thrombolytic agents that do not cause a systemic lytic state (e.g., tissue plasminogen activator\(^49\) and prourokinase\(^50\)), as well as careful patient selection after angiographic diagnosis of appropriate lesions, might make fibrinolytic therapy safe and effective in the treatment of acute ischemic stroke.

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