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# Safety and Efficacy of Delayed Intraarterial Urokinase Therapy with Mechanical Clot Disruption for Thromboembolic Stroke

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**PURPOSE:** To evaluate safety and efficacy of delayed intraarterial urokinase therapy with mechanical disruption of clot to treat thromboembolic stroke. **METHODS:** Thirteen patients with cerebral thrombotic disease (10 carotid territory, 3 basilar territory) were treated with catheter-directed intraarterial urokinase therapy with mechanical disruption of the clots. All patients were excluded from a 6-hour multicenter thrombolytic trial by either time, recent surgery, age, seizure, or myocardial infarction. Time elapsed before treatment ranged from 3.5 to 48 hours ( $12 \pm 13$  hours), with 200 000 to 900 000 U of urokinase used. **RESULTS:** Ten patients had successful vessel recanalization, confirmed by repeat angiography. Cases with distal branch vessel occlusions were less likely to recanalize. Asymptomatic hemorrhagic conversion occurred in 2 patients on repeat scans. Both acute neurologic and functional outcomes were assessed with significant improvement occurring in 9 (69%) of 13 patients at 48 hours (greater than four-point change on the National Institutes of Health scale) and in 100% of 3-month survivors. All patients who improved had normal initial CT scans. **CONCLUSIONS:** Intraarterial cerebral thrombolysis with mechanical disruption of clot seems to be a useful therapy in selected stroke cases even after 6 hours.

**Index terms:** Thrombolysis; Thrombosis, cerebral; Drugs, intraarterial injection; Brain, infarction; Interventional neuroradiology

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Thromboembolic occlusion remains the most common cause of ischemic stroke (1). Recent favorable experiences with thrombolytic agents have suggested that they may play a role in acute stroke treatment (2, 3). These studies, consisting of small series or preliminary controlled safety studies, have shown variable degrees of thrombolytic efficacy (4). Based on these encouraging results, various multicenter randomized trials using intravenous tissue plasminogen activator (a relatively fibrin-specific

agent) are in progress (5). Because of concerns regarding the risk of cerebral and systemic hemorrhage, all current intravenous studies limit patient enrollment to no more than 6 hours after the onset of the stroke (6).

Recent advances in techniques of intracranial vascular catheterization have made it possible to deliver thrombolytic agents intraarterially directly into the thrombus. Experimental studies have demonstrated that intraarterial administration produces more rapid thrombolysis at a lower dose than intravenous administration (7). Clinical cardiac thrombolysis studies suggest that intraarterial delivery may have less risk of systemic hemorrhagic complications (8). This study was undertaken to evaluate whether intraarterial urokinase could successfully treat selected patients who were excluded from systemic thrombolysis treatment protocols.

## Patients and Methods

Between July 1991 and May 1993, 13 consecutive patients with acute ischemic stroke were treated with intraarterial urokinase. All patients or their relatives gave

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written informed consent to participate, with treatment being offered on a compassionate-use basis. Selection criteria for treatment included: (a) a neurologic deficit on clinical exam with signs suggesting "large vessel" occlusion; (b) an essentially normal initial head computed tomographic (CT) scan without evidence of hemorrhage (cases with very early subtle sulci effacement were allowed); and (c) evidence of vessel occlusion on initial angiogram consistent with the patient's symptoms. All patients were excluded from a 6-hour-window systemic recombinant tissue plasminogen activation study by either time (8 patients), recent surgery (2 patients), age (1 patient), seizure (1 patient), or myocardial infarction (1 patient).

Each patient had a complete neurologic exam, routine lab tests, and head CT scan before angiogram. The patient's initial neurologic exam was rated using the 42-point National Institute of Neurologic Disorders and Stroke Scale (9). This scale has been previously validated in acute stroke assessment. It is in widespread use in ongoing stroke treatment trials with a 4-point improvement in this scale defined as a major neurologic improvement (10).

All patients were initially treated with hypervolemic therapy, usually with 500 mL of a colloid solution, and heparin (5000-U bolus, then 1000 U/h). If a common carotid angiogram showed occlusion of the internal carotid artery, the catheter was navigated into the internal carotid artery for a more selective angiogram. Thrombus located within the supraclinoid internal carotid artery often gave the angiographic appearance of a cervical internal carotid artery occlusion on the common carotid artery angiogram. A 7-F sheath was placed in the femoral artery for access. Angiography was performed to evaluate the site of occlusion and condition of vessels proximal to the occlusion. A Tracker-18 Unibody catheter (Target Therapeutics, Fremont, Calif) was navigated over a 0.014-inch Taper Select or Dasher guide wire through the guiding catheter into the occluded vessel. The tip of the Tracker catheter was navigated over the guide wire into the occluded segment of the vessel and beyond into the patent distal portion. Urokinase (Abbokinase, Abbott Laboratories, Chicago, Ill) was then infused in 1-mL volumes (50 000 U/mL) as a bolus into the distal portion of the vessel, directly into the occluded segment of the vessel, and proximal to the occlusion. The urokinase was typically delivered with a gentle pulse spray of 0.10 mL, delivering 1 mL over 5 to 10 minutes. The catheter was moved frequently through the occluded segment to provide some degree of mechanical disruption. If the emboli were in a distal middle cerebral artery branch (cases 7, 8, and 9), the catheter was placed as close to the occlusion as possible. Middle cerebral artery occlusion in association with internal carotid artery occlusion was documented by either vertebral or contralateral carotid artery injections to show flow through the communicating arteries or by passing the Tracker catheter through the occluded portion of the internal carotid artery and performing selective supraclinoid internal carotid artery or middle cerebral artery angiography. The course of the thrombolysis was followed by injection of

contrast material through the Tracker catheter. When antegrade flow of a contrast through the occluded segment was clearly established, the thrombolytic therapy was stopped. A CT scan was obtained immediately after the thrombolytic therapy. Heparin was continued to maintain the partial thromboplastin time at 45 to 65 seconds. Hypervolemic therapy was continued. The 7-F sheath was left in place, and a follow-up angiogram was performed the next day. If there was any thrombus within the vessel, the anticoagulation was continued and the sheath removed. If there was no thrombus in the vessel and no source for embolus identified, the heparin was stopped. Hemostasis at the femoral artery puncture site was always obtained within 30 minutes.

Reperfusion was reassessed by a repeat angiogram 12 to 24 hours after treatment. Reperfusion was graded as: 0, no reperfusion; 1, partial reperfusion; or 2, complete reperfusion. Repeat CT was performed approximately 24 hours after treatment to evaluate infarct size and determine whether hemorrhage was present. Intracerebral bleeding was classified as symptomatic or asymptomatic and defined as hemorrhagic infarction or hematoma based on published criteria (11).

All patients were monitored in the Neurologic Critical Care Unit for at least 24 hours. Repeat National Institute of Neurologic Disorders and Stroke Scale assessments were done at 48 hours and at a 3-month follow-up. A major neurologic improvement was defined as a greater than four-point improvement in the scale. All patients were treated with warfarin sodium (Coumadin) for at least 3 months.

## Results

The clinical, initial CT, and angiographic features of all patients entered in this study are given in the Table. There were six female and seven male patients 12 to 81 years of age. All patients had major neurologic symptoms before treatment. The initial head CT was negative for acute ischemic changes in all cases except one. On initial angiographic studies, there were two cases of basilar occlusion, one posterior cerebral artery occlusion, seven cases of isolated middle cerebral artery or combined internal carotid and middle cerebral artery occlusion, and three distal branch middle cerebral artery occlusions. The interval from the onset of symptoms to the start of intraarterial urokinase was  $12 \pm 13$  hours (mean  $\pm$  SD; range, 3.5 to 48.0 hours).

Repeat angiography performed between 12 and 24 hours after treatment revealed complete recanalization of the symptomatic vessels in seven patients, partial opening of the middle cerebral arteries or their branches in three cases, and no openings in three cases (77% at



## Results of intraarterial treatment of ischemic stroke

Case/Sex/ Age, y	Cause	CT	Site	Time Lapse to Treatment, h	Recanal- ization Grade	Dose of Urokinase, IU	Period of Urokinase Infusion, h	Compli- cations	NIHSS at Baseline	NIHSS at 48 h	NIHSS at 3 mo
1/M/58	Carotid atheroma	-	R ICA/MCA	04.0	2*	900 000	4.00	None	16	12	6
2/F/31	Carotid dissection	-	R ICA/MCA	06.5	2†	250 000	3.00	None	22	10	4
3/F/16	Emboli	-	Basilar	48.0	2	300 000	4.00	None	29	10	2
4/F/12	Atrial myxoma	-	L MCA	07.0	0	800 000	2.50	None	24	14	9
5/M/76	Atheroma	-	Basilar	36.0	2	400 000	1.00	Asymptomatic hemorrhage conversion	25	18	10
6/M/57	Carotid atheroma	-	L MCA	10.0	2	280 000	2.00	None	27	13	6
7/M/48	Hypercoagulable state	+	L MCA branch	10.0	1	150 000	1.00	Asymptomatic hemorrhage conversion	22	20	E
8/M/32	Emboli	-	L MCA branch	04.5	0	550 000	1.50	None	11	11	5
9/F/81	Emboli	-	L MCA branch	05.0	0	350 000	1.00	Asymptomatic hemorrhage conversion	28	E	E
10/M/56	Emboli	-	L PCA	03.5	2	200 000	1.00	None	14	4	2
11/F/63	Emboli after coronary angiogram	-	L MCA	05.5	1	700 000	0.75	Cardiac rupture	24	E	E
12/F/64	Cardiac emboli	-	L MCA	09.0	2	800 000	2.50	None	21	14	10
13/M/49	Cardiac emboli	-	L MCA	07.0	1	750 000	1.00	None	22	9	NA

Note.—Causes are atherosclerosis, dissection, vasculitis, myxoma emboli, unknown thrombosis, and cardiac emboli. - indicates no sign of acute stroke; +, sulcal effacement present; ICA, internal carotid artery; MCA, middle cerebral artery; and PCA, posterior cerebral artery. Recanalization: 0 indicates none; 1, partintra-arterial; 2, completion of symptomatic vessel. NIHSS indicates National Institute of Health Stroke Scale.

\*ICA and MCA.

†MCA only (ICA purposefully occluded with platinum coils).

least partial opening). These three cases included one case secondary to atrial myxoma emboli and two cases with distal branch emboli. Examples of angiographic and CT outcomes are shown in Figures 1, 2, and 3.

Hemorrhagic infarction producing no new neurologic deficits was seen in three patients (23%) on repeat head CT scans between 12 and 24 hours after treatment. There were no cerebral hematomas. There was one case of fatal cardiac rupture. In this patient (case 11 in the Table) an anterior myocardial infarction developed during a cardiac catheterization. Thirty minutes later she had an embolic left middle cerebral artery stroke. She was treated with urokinase at 5.5 hours after her stroke. She showed no change in her neurologic exam until 3 hours after thrombolysis, when she had a cardiac arrest. Autopsy confirmed an anterior wall cardiac rupture. There were two additional

deaths: one patient (case 7) had a pulmonary embolus 1 week after treatment, and one patient (case 9) died of cerebral edema 36 hours after treatment.

The degree of neurologic recovery as measured by the National Institute of Neurologic Disorders and Stroke Scale is shown in the Table. The average baseline score was  $22 \pm 5$  (mean  $\pm$  SD) with 9 of 13 patients showing major neurologic improvement at 48 hours (National Institute of Neurologic Disorders and Stroke Scale,  $12 \pm 5$ ). These patients continued to improve with an average 3-month scale value of  $5 \pm 3$ .

## Discussion

In this study, we found that intraarterial urokinase given by selective catheterization during an acute stroke produced a high rate of cerebral



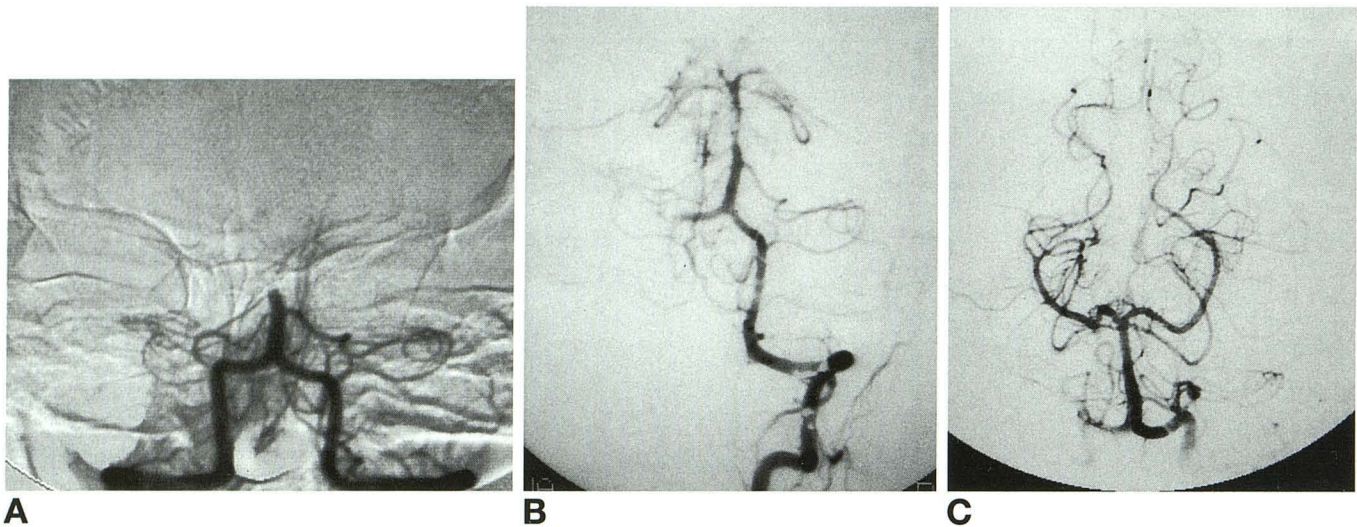


Fig 1. Case 3. Sixteen-year-old girl with 48-hour history of progressive brain stem dysfunction.

A, Anteroposterior view of a left vertebral artery angiogram demonstrates occlusion of basilar artery above the anterior inferior cerebellar arteries.

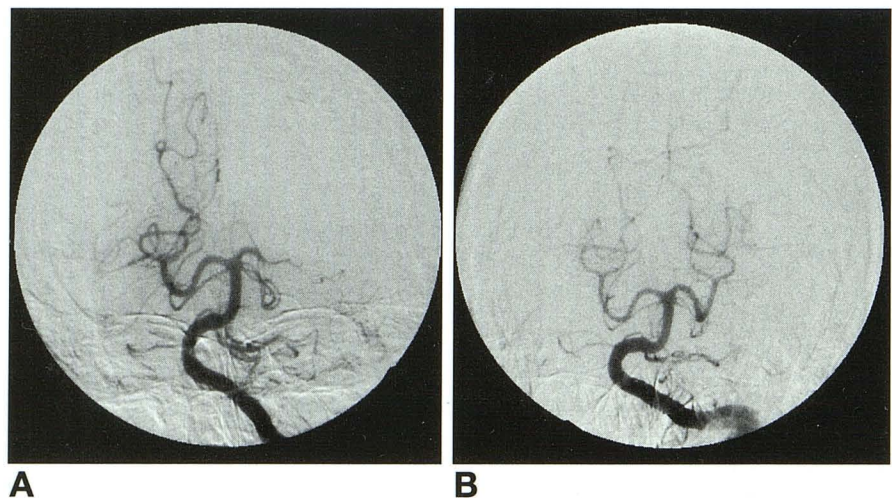
B, Anteroposterior view of a left vertebral artery angiogram after 200 000 IU of urokinase infused into the occluded segment. There is still some residual clot in the distal basilar artery.

C, Anteroposterior view of a left vertebral artery angiogram 24 hours after thrombolytic therapy. There has been further clearing of clot.

Fig 2. Case 10. Fifty-six-year-old man in whom anomia, lethargy, hemiparesis, and a homonymous hemianopsia developed 3.5 hours before thrombolysis.

A, Towne's view of a left vertebral artery angiogram demonstrates occlusion of the P2 segment of the left posterior cerebral artery.

B, Towne's view of a left vertebral artery angiogram after thrombolysis with 200 000 IU of urokinase over 30 minutes demonstrates recanalization of the vessel. The patient improved during the procedure.



vessel recanalization with a relatively low rate of adverse side effects. Prior studies have shown both angiographic and clinical efficacy of local intraarterial infusion of urokinase into either the carotid or vertebral artery (12-14; Mori E, Tabuchi Y, Oshumi Y, et al, "Intraarterial Urokinase Therapy in Acute Thromboembolic Stroke" [abstract], *Stroke* 1990;23 [suppl 1]:1-74). In these studies urokinase was infused via catheters into the proximal carotid or vertebral artery with regional blood flow delivering the drug to the thrombus. Our study used a Tracker catheter to deliver the drug directly into the

thrombi. The potential advantages of this microcatheter technique include reliable delivery of a highly concentrated drug and actual mechanical disruption of the thrombi by the catheter. This disruption may increase the surface fibrin that is accessible to urokinase. These potential advantages may allow larger clots to be dissolved than would systemic administration. Even if a large internal carotid artery clot is not dissolved, the microcatheter can pass through the clot to access and lyse the symptomatic middle cerebral artery and allow flow through the circle of Willis. In the three cases (cases 7, 8,



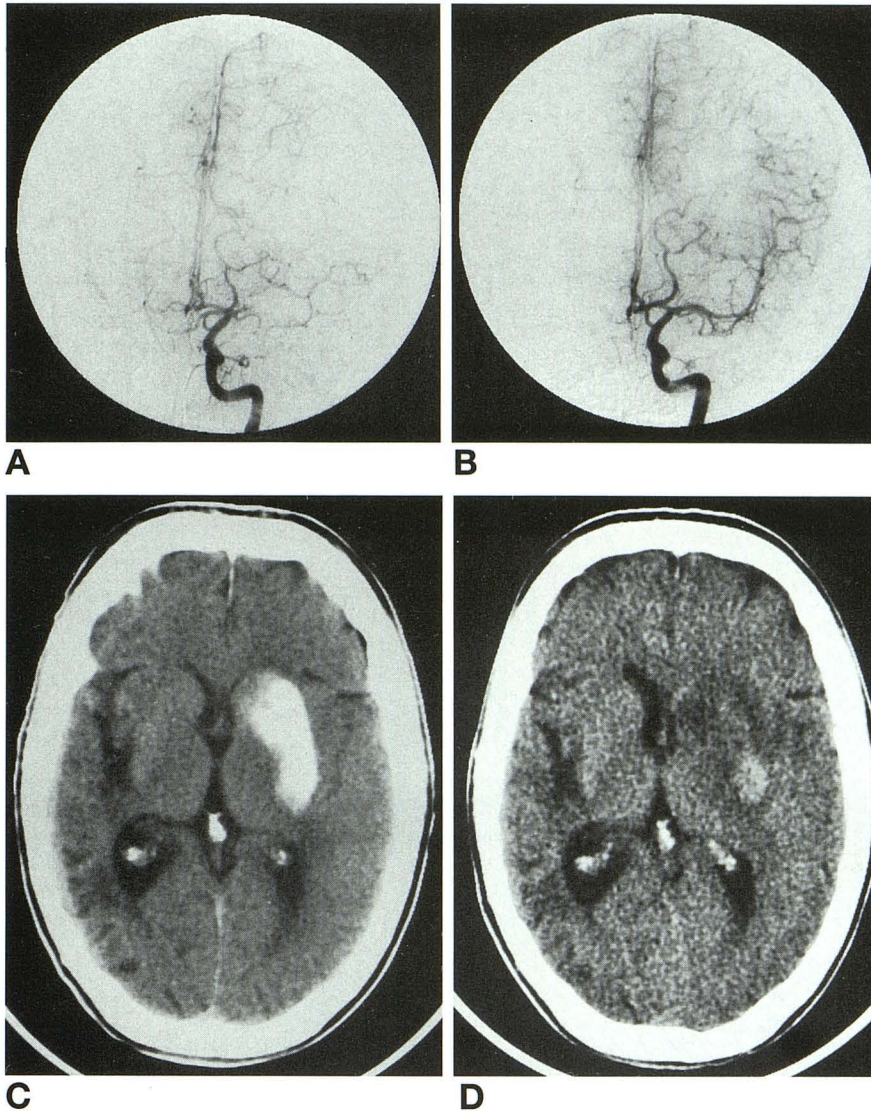


Fig 3. Case 12. Sixty-four-year-old woman with onset of aphasia and a right hemiplegia 9 hours before thrombolysis.

A, Anteroposterior view of a left internal carotid artery angiogram shows occlusion of the M1 segment of the middle cerebral artery.

B, Anteroposterior view of a left internal carotid artery angiogram 16 hours after thrombolytic therapy shows resolution of clot in the middle cerebral artery.

C, CT scan immediately after thrombolysis shows dense contrast stain within the basal ganglia.

D, CT scan 16 hours later shows resolution of contrast from the basal ganglia.

and 9) of distal branch occlusion in which mechanical disruption could not be performed, the degree of recanalization was not complete.

The 77% rate of symptomatic vessel recanalization (complete or partial) in this study is higher than that reported with systemic recombinant tissue plasminogen activator (average, 54% [4]). Previous studies using more proximal intraarterial urokinase infusion have produced variable results. Mori et al found a 45% recanalization rate in 22 middle cerebral artery cases, 12% in internal carotid artery cases, and 25% in basilar cases (Mori et al, "Intraarterial Urokinase Therapy"). Hacke et al reported a 44% recanalization rate in vertebrobasilar thrombosis using local urokinase (12). Two of our cases without vessel recanalization had occlusions in distal branch arteries. Because we were unable to in-

ject urokinase directly into the clot in these cases, drug delivery may have been reduced in these small end arteries. To limit the amount of urokinase given and possibly reduce hemorrhagic complications, the drug was stopped when anterograde perfusion was restored. There was often a major angiographic improvement noted 12 to 24 hours after the thrombolytic therapy. Once anterograde flow is established, the combination of heparin and the body's own thrombolytic mechanism may have cleared the residual thrombus.

The incidence of hemorrhagic infarction in our study (23%) is similar to that reported with local intraarterial infusion (25%) (15) or systemic recombinant tissue plasminogen activator (average of 18 studies, 17%) (4). All cerebral hemorrhage events seemed to be hemor-



rhagic transformations of the infarcted territory without clinical deterioration. We did not observe any cases of intracerebral hematoma formation with clinical deterioration. There were two cases of contrast staining of areas that went on to infarction (Fig 3). This early contrast enhancement probably results from ischemic disruption of the blood-brain barrier (16). This staining may be reduced by using a lower concentration and amount of contrast while evaluating the course of the thrombolysis.

Although cardiac rupture can occur spontaneously after a myocardial infarction, it is possible that our case (case 11) was related to thrombolytic treatment. A recent review indicates that the risk of cardiac rupture increases when thrombolysis is used after 7 hours (17). Our patient was treated approximately 6 hours after myocardial infarction.

We used the absence of a defined infarct on initial CT as a guide to patient selection in this study. This guideline was based on the theory that a well-defined lesion on CT may correlate with irreversible brain injury. Although magnetic resonance scans are more sensitive than CT to early changes (18), we thought that these early magnetic resonance changes could represent areas with reversible injury. The one patient (case 7) who had edema and significant sulcal effacement on the initial CT showed minimal response to recanalization.

Ideally, a stroke treatment would be administered immediately after the diagnosis is made. However, all thrombolytic agents have a requisite delay related to obtaining an initial CT to exclude hemorrhage. Compared with systemic thrombolysis, intraarterial administration has an additional delay related to angiography and selective catheterization. In our study, this additional delay ranged from 45 to 180 minutes per case. Collateral circulation may delay the time before irreversible ischemic damage occurs. Comparative controlled trials are needed to determine whether the potential benefits of intraarterial administration outweigh this treatment delay. An alternative approach is to start systemic thrombolysis and proceed to intraarterial treatment in patients who do not immediately respond.

Selective intraarterial thrombolysis seems to be a safe and efficacious method of restoring blood flow during stroke. Clinically beneficial

results may be possible even after the standard 6-hour time window for thrombolytic treatment, especially in cases with basilar thrombosis. Further studies comparing various thrombolytic agents or combined intraarterial and systemic administrations are needed.

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