Predictors of Clinical Improvement, Angiographic Recanalization, and Intracranial Hemorrhage After Intra-Arterial Thrombolysis for Acute Ischemic Stroke

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Background and Purpose—We sought to evaluate predictors of clinical outcome, angiographic success, and adverse effects after intra-arterial administration of urokinase for acute ischemic stroke.

Methods—We designed a Brain Attack program at University Hospitals of Cleveland for diagnosis and treatment of patients presenting within 6 hours of onset of neurological deficit. Patients with ischemia referable to the carotid circulation were treated with intra-arterial urokinase. Angiographic recanalization was assessed at the end of medication infusion. Intracerebral hemorrhage was investigated immediately after and 24 hours after treatment. Stroke severity was determined, followed by long-term outcome.

Results—Fifty-four patients were treated. There was improvement of $\geq 4$ points on the National Institutes of Health Stroke Scale from presentation to 24 hours after onset in 43% of the treated patients, and this was related to the severity of the initial deficit. Forty-eight percent of patients had a Barthel Index score of 95 to 100 at 90 days, and total mortality was 24%. Cranial CT scans revealed intracerebral hemorrhage in 17% of patients in the first 24 hours, and these patients had more severe deficits at presentation. Eighty-seven percent of patients received intravenous heparin after thrombolysis, and 9% of them developed a hemorrhage into infarction. Angiographic recanalization was the rule in complete occlusions of the horizontal portion of the middle cerebral artery, but distal carotid occlusions responded less well to thrombolysis.

Conclusions—The intra-arterial route for thrombolysis allows for greater diagnostic precision and achievement of a higher concentration of the thrombolytic agent in the vicinity of the clot. Disadvantages of this therapy lie in the cost and delay. Severity of stroke and site of angiographic occlusion may be important predictors of successful treatment. (Stroke. 1999;30:2094-2100.)

Key Words: hemorrhage ■ stroke, ischemic ■ thrombolysis

Judicious use of thrombolytic agents has greatly improved the care of patients presenting with acute ischemic stroke in the last 5 years. There are at least 2 major constraints to be considered in planning the timing and technique of thrombolytic therapy. First, it is likely that reperfusion of blocked arteries must be accomplished within 6 to 8 hours of the onset of ischemia if brain tissue is to be rescued. Second, there is a substantial risk of cerebral hemorrhage when thrombolytic agents are used in the setting of acute cerebral ischemia. If thrombolysis is to emerge as an effective clinical tool, it must be applied early in the ischemic sequence and with care to minimize the risk of hemorrhage.

Several investigations have shown that intra-arterial delivery of thrombolytic agents is effective in lysing angiographically demonstrable occlusions in the cerebral circulation. Del Zoppo and colleagues further used angiography to show that intravenous delivery of thrombolytic agents can effect lysis of vascular occlusions. Complementary clinical studies of intravenous agents in very early stages of cerebral ischemia provided evidence of clinical efficacy as well. With this information, we designed and implemented in 1993 a Brain Attack program at University Hospitals of Cleveland, using intravenous and intra-arterial delivery of thrombolytic agents in patients who presented within the first 6 hours after the onset of ischemia. We present here observations based on the treatment with intra-arterial therapy of 54 individuals with ischemia in the carotid circulation.

Subjects and Methods
This report derives from experience with 431 patients seen during the first 6 hours after onset of cerebral ischemia over a 44-month interval.
ending in August 1997. Fifty-four patients with ischemia referable to the carotid circulation were treated with intra-arterial urokinase.

**Patient Selection**

All patients were evaluated by a neurologist and/or neurorugorouge and underwent cranial CT scanning without contrast. Intra-arterial therapy was considered if it could be initiated before 6 hours had elapsed from the onset of ischemia.

Inclusion criteria included a National Institutes of Health Stroke Scale (NIHSS) of 4, age >18 and <80 years, and no clinical improvement up to the time of evaluation. Patients were excluded from consideration if there was unequivocal evidence of cerebral hemorrhage or definite mass effect on the CT scan. Low density without mass effect, loss of gray/white boundaries, or other evidence of acute ischemia did not exclude the patient. Patients were excluded if the diagnosis could be questioned (history of seizure disorder, preexisting encephalomalacia in the symptomatic arterial territory, cerebral neoplasm, dementia requiring custodial care) and if the patient was at high risk for hemorrhage (prothrombin time >15; platelets <100 000; history of gastrointestinal or genitourinary bleeding in previous 21 days; history of cardiopulmonary resuscitation, trauma, or surgery within 14 days; arterial puncture at a noncompressible site within 7 days; lumbar puncture within 7 days; pregnancy or delivery within 14 days; history of cerebral hemorrhage). No patient received intra-arterial therapy if the diastolic blood pressure was >120 mm Hg despite the use of nitroprusside as acute therapy.

Our Brain Attack program was approved by the Institutional Review Board of the University Hospitals of Cleveland. All patients signed informed written consent before cerebral angiography and intra-arterial urokinase were given.

**Technique of Therapy**

Cerebral angiography was performed via a femoral artery approach. Intra-arterial therapy was provided only in the instance of unequivocal vascular occlusion in intracranial vessels (top of the carotid, M1 to M3 branches, A1 or A2 branches); we did not attempt to treat carotid occlusion below the siphon. We used rapid-transit Prowler-14 catheters (Cordis) and Mach 16 select and Fast Dasher 14 wires (Target Therapeutics). The initial dose of urokinase was 250 000 U diluted in 20 mL of a saline solution and infused over 20 minutes. The initial dose of urokinase was 250 000 U diluted in 20 mL of a saline solution and infused over 20 minutes proximal to the clot. A second dose of 250 000 U diluted in 3 mL of a saline solution was administered over 5 minutes in close proximity to the clot. Repeated doses were given as needed to achieve recanalization. The total dose of urokinase was to be limited to 1.4 million U (3 patients actually received between 1.4 and 1.7 million U). In all instances, mechanical disruption of clot remnants was attempted after urokinase was infused.

**Interpretation of Images**

Vascular occlusions visualized during angiography were categorized as partial or complete. Partial occlusion was defined by passage of contrast material past the area of obstruction but with a slowed rate of filling of distal vessels and of clearance of contrast from the distal bed. Complete restoration of flow was defined as passage of contrast past the previous area of obstruction, with filling and clearance rates comparable to those of patent vessels. Partial restoration of flow was defined as passage of contrast beyond the original area of obstruction but with a rate of clearance perceptibly slower than that of comparable normal arteries.

CT scans were categorized as without diagnostic abnormality (no changes in the arterial territories considered on clinical grounds to be ischemic), early signs of infarction, hemorrhagic infarction, or hemorrhage into infarction. Early signs of infarction included low density and loss of gray-white junctions, without mass effect (mass effect excluded the patient from thrombolytic therapy). In CT scans obtained promptly after intra-arterial thrombolysis, increased density could reflect contrast enhancement, hemorrhage, or both. We described areas of increased density in such scans as hemorrhagic infarction if we could not recognize the presence of a blood clot. In scans obtained 24 hours after thrombolysis, hemorrhagic infarction was defined as the presence of increased density, without apparent clot. Symptomatic intracranial hemorrhage was defined as neurological worsening of ≥4 points on the NIHSS attributable to the presence of the clot.

**Anticoagulation**

In the treatment protocol designed for this cohort, all patients were subsequently anticoagulated with an infusion of heparin unless CT scanning after thrombolysis revealed hemorrhage into infarction. In several patients, evidence of clot growth or reformation during thrombolysis led to the institution of heparin infusion during thrombolysis, before the CT scanning performed at the end of the procedure. Heparin was infused at a rate of 1000 U/h without prior bolus administration. Coagulation tests were obtained every 4 hours after initiation of anticoagulation to ensure levels 1.5 to 1.7 times baseline values.

**Outcome Measures**

The NIHSS was determined within 30 minutes of arrival, 24 hours after arrival, and 5 days after arrival. Definite neurological improvement was defined as a 4-point improvement on the NIHSS in the initial 24 hours after onset of symptoms. We performed angiography in 62 patients ending in August 1997. Fifty-four patients with ischemia referable to the carotid circulation were treated with intra-arterial urokinase. We used rapid-transit Prowler-14 catheters (Cordis) and Mach 16 select and Fast Dasher 14 wires (Target Therapeutics). The initial dose of urokinase was 250 000 U diluted in 20 mL of a saline solution and infused over 20 minutes. The initial dose of urokinase was 250 000 U diluted in 20 mL of a saline solution and infused over 20 minutes proximal to the clot. A second dose of 250 000 U diluted in 3 mL of a saline solution was administered over 5 minutes in close proximity to the clot. Repeated doses were given as needed to achieve recanalization. The total dose of urokinase was to be limited to 1.4 million U (3 patients actually received between 1.4 and 1.7 million U). In all instances, mechanical disruption of clot remnants was attempted after urokinase was infused.

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**Statistical Analysis**

The Kolmogorov-Smirnov test for normality and the equal variance test were performed before any statistical procedure was used. A Wilcoxon signed rank test was used to analyze the NIHSS. The unpaired t test or the Mann-Whitney rank sum test was used to evaluate differences between patients with and without intracerebral hemorrhage. Differences in angiographic recanalization were measured on a nominal scale with the Fisher exact test. Simple linear regression models were calculated to evaluate the associations between NIHSS on admission, NIHSS at 24 hours, and time to therapy. A value of $P<0.05$ was considered significant. All values are expressed as mean±SD or median.

**Results**

There were 431 patients evaluated in the first 6 hours after onset of ischemia. We performed angiography in 62 patients with the intention of providing intra-arterial thrombolysis, but only 54 received thrombolytic agent; of the remaining 8, 4 had complete internal carotid artery occlusions, 1 had a calcified vascular occlusion of uncertain nature, 1 had several occlusions in very small arterial branches, and 2 had no demonstrable arterial occlusion.

**Time of Therapy**

It had been our intention to initiate angiography only when we thought that intra-arterial therapy could be started before 6 hours had elapsed since the onset of symptoms. However, 10 patients (19%) received therapy after 6 hours had passed. In 7 instances, this reflected technical difficulties during the procedure. Two other patients were younger than 30 years and aphasic; the protocol violation was predicated on the hope that younger age would support a favorable outcome despite the delay in therapy. In the final patient, angiography and therapy were delayed because the patient appeared to be improving during the initial evaluation and abruptly worsened thereafter.
Initial Outcome
Measures of initial response to therapy are summarized in Table 1. A histogram of the change in the NIHSS from presentation to 24 hours after onset (Figure 1) shows that 43% of patients improved by ≥4 points. This improvement was statistically significant and was maintained 5 days after treatment. The likelihood of early improvement was probably related to the severity of the initial deficit (Figure 2; correlation coefficient, 0.785 at 95% CI). However, there was not a simple relationship between initial outcome and the time until the initial delivery of urokinase (Figure 3). Eight patients received urokinase before 3 hours elapsed, and only 1 worsened in the first 24 hours (this patient died with an intracerebral hemorrhage). Ten patients received therapy between 3 and 4 hours after the onset, and only 1 worsened slightly. Of the 36 patients treated after 4 hours, 9 worsened in the first 24 hours (25%). Interestingly, 10 patients received therapy after 6 hours, and only 1 worsened; in this cohort, there was no obvious time after which benefit was not obtained.

Twenty-three patients were discharged to home, and an additional 23 patients were transferred for rehabilitation. Eight patients died during the acute hospitalization, and only 1 of these deaths was not related to the initial stroke or the complications of therapy. An additional 5 patients died within 90 days of the onset of symptoms, for a total mortality of 24% at 90 days. Of patients surviving at 90 days, 26 patients had a Barthel score of 95 to 100 (48%), 13 had Barthel score of 55 to 90 (24%), and 8 had a score of 0 to 50 (15%). Twenty-five patients (48%) had a modified Rankin scale score of ≤1.

Cerebral Hemorrhage
Cranial CT scans were obtained within 1 hour of the completion of intra-arterial thrombolysis (Table 2). These are “contrast-enhanced” scans, and increased density on such scans might reflect hemorrhage, contrast, or both. Immediately after angiography and intra-arterial thrombolysis, 3 scans showed evidence of hemorrhage into the infarction, and 23 scans were interpreted as hemorrhagic infarction (increased density but no clot). Of these 23 patients, 5 developed hemorrhage into infarction in the next 24 hours. The outcome of the 8 patients with hemorrhage into infarction in the first 24 hours was poor: 5 died during the initial hospitalization (63%).

The average time between onset and initial therapy in patients who developed a hemorrhage in the first 24 hours was 4 hours and 53 minutes (for the entire 54-patient cohort, the average time was 4 hours and 45 minutes), and the median NIHSS score at admission was 20. The latter was signifi-
cantly different from that of the population that did not experience intracerebral hemorrhage ($P<0.001$). The other factor associated with hemorrhage was higher serum glucose (166±8 compared with 126±6 mg/dL in patients without hemorrhage; $P=0.007$). There were no statistical associations with serum fibrinogen concentration, recanalization rate, and blood pressure measurements.

Twelve patients received heparin during and after thrombolysis; 11 of these had hemorrhagic infarction on cranial CT scans immediately after the procedure, and 1 developed hemorrhage into infarction while on heparin; thus, 8.3% of these patients treated with heparin during and after thrombolysis despite hemorrhagic infarction developed further hemorrhage. An additional 34 patients received heparin after thrombolysis; 11 had hemorrhagic infarctions evident immediately after thrombolysis, and 2 of these developed hemorrhage into infarction (18%). One patient received heparin only during the intra-arterial infusion of urokinase; the CT scan after thrombolysis revealed hemorrhage into infarction, and the heparin was discontinued. Finally, 1 patient received heparin after thrombolysis despite equivocal evidence of hemorrhage into infarction; this patient’s hemorrhage enlarged and eventually contributed to death. In summary, 48 of the 54 patients received heparin after thrombolysis; 5 of the 48 developed a hemorrhage into infarction (10%) (Table 2).

### Angiographic Changes During Thrombolysis

The efficacy of thrombolysis, as judged by dissolution of angiographically demonstrable occlusions, varied with the location of the occlusion (Table 3). Distal carotid occlusion responded least well angiographically, despite the relative accessibility of the clot to mechanical effects of the selective catheters; in 5 cases, 3 failed to open and 1 opened only the anterior cerebral artery. There was a 40% mortality, all in patients in whom recanalization had failed. By contrast, recanalization was the rule in complete occlusions of the horizontal portion of the middle cerebral artery. However, there was a 33% incidence of hemorrhage into infarction in patients whose complete M1 occlusions had been entirely opened by thrombolysis. In this cohort, distal (M3) occlusions were relatively resistant to thrombolysis but also were not associated with subsequent hemorrhage into infarction.

### Discussion

We have used intra-arterial delivery of urokinase to effect thrombolysis of vascular occlusions in the carotid circulation through 8 hours after the onset of symptoms. The angiographic improvement was often accompanied by substantial clinical improvement, even in patients treated from 5 to 8 hours after onset, but there was also a high risk of intracerebral hemorrhage.

Thrombolysis is least dangerous when it can be performed as early in the disease process as possible. If patients can be given intravenous tissue plasminogen activator (tPA) within 3 hours of the onset of symptoms, approximately 47% have a clinical improvement of $\geq 4$ points in the NIHSS in the initial 24 hours, with a risk of symptomatic intracerebral hemorrhage of approximately 6.4% and a mortality of approximately 13% in the first month. In the 54 patients described here, 43% improved by $\geq 4$ points in the first 24 hours, but the risk of intracerebral hemorrhage was 17% in the first 24 hours, and the mortality during the initial hospitalization was 15%. By comparison, the risk of cerebral hemorrhage reported by the European Cooperative Acute Stroke Study (ECASS) for patients treated with intravenous tPA in the initial 6 hours after onset is approximately 19.4%. If the patients in the 3 groups were entirely comparable, it would seem that thrombolysis performed between 6 and 7 hours after the onset of clinical symptoms carries with it a risk of cerebral hemorrhage 2- or 3-fold greater than that of intravenous therapy delivered in the first 3 hours. This was
also confirmed by a recent trial reporting on the use of intra-arterial prourokinase in acute middle cerebral artery stroke.23 The authors found a 15.4% incidence of symptomatic intracerebral hemorrhage and 42.3% incidence of hemorrhagic transformation within 24 hours of treatment. However, if patients with signs of major infarction by head CT scanning are excluded, the administration of intravenous recombinant tPA within 6 hours of symptom onset may be associated with an 8.8% incidence of symptomatic hemorrhages.24 This is less than that in the cohort reported in the present study but more than that in the National Institute of Neurological Disorders and Stroke (NINDS) trial.

There are some important differences between the prospective uncontrolled cohort reported here and the populations described in the 3 trials of intravenous tPA. First, we, similar to the prourokinase study, treated only patients with vascular occlusions visible on angiography; therefore, none of the patients reported here had ischemia referable to intrinsic disease of small penetrating vessels. We suspect that the volume of ischemic brain was, on the average, greater in the group described here. The NIHSS score was not very different in the 3 groups. However, we believe that disease in penetrating vessels can cause a deficit with a large NIHSS score because of ischemia in a relatively small volume of myelinated axons, while the volume of cortex that would have to be rendered ischemic to generate a similar score is substantially greater. If the risk of cerebral hemorrhage is proportional to the volume of ischemic tissue and the severity of the ischemia,13 then larger volumes carry a greater risk of hemorrhage.

Mortality after intravenous administration of tPA was lower than in the placebo group (17%) at 3 months in the NINDS study,1 whereas in the ECASS trial it was higher (19.4%) in the treated population.2 These mortality rates are smaller than ours (24%). However, the 90-day mortality in the prourokinase trial was slightly higher (26.9%) in the treated population.23 Our cohort may have included sicker patients, as noted by high serum glucose concentrations, which have been associated with greater mortality and poorer survival in patients with intracranial disease.25

The management of arterial hypertension also varied in our group. We used intravenous nitroprusside to control hypertension, and it was not necessary to withhold thrombolytic therapy in any instance because of refractory hypertension. The NINDS study excluded patients refractory to labetalol therapy.1 It is possible, therefore, that our group included a larger proportion of patients with severe hypertension than the NINDS population.

A fourth major difference is the use of heparin anticoagulation after intra-arterial thrombolysis. Both the NINDS and

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ICA indicates internal carotid artery. This table describes only the most proximal occlusion and its response. In many instances, dissolution of a proximal clot was followed by appearance of distal occlusions. Anterior cerebral artery occlusions were not excluded from this analysis, but in this cohort, there was invariably a more proximal clot in another vessel.
ECASS studies excluded the use of intravenous heparin in the first 24 hours. The design of our protocol was influenced by published experience with thrombolysis for peripheral vascular disease, which pointed out that heparin together with the thrombolytic agent might decrease the risk of clot reformation.26 Forty-four of the 54 patients reported here received intravenous heparin. Of the 8 patients who developed hemorrhage into infarction in the first 24 hours, 2 were receiving heparin after thrombolysis and 1 received heparin during and after thrombolysis. We used heparin during thrombolysis when it appeared that thrombi were enlarging and when extracranial stenosis appeared to limit flow (for example, severe internal carotid stenosis at the bifurcation that was exacerbated by the presence of catheter). At least 2 of the patients reported here developed reocclusion after thrombolysis (1 despite heparin), and a third occlusion in the M1 segment clearly enlarged during thrombolysis without heparin (this enlargement was recognized at the completion of the procedure). At present, there is insufficient information to determine whether the risk of reocclusion justifies the additional risk of cerebral hemorrhage. However, the prourokinase study results suggest that recanalization is enhanced by the addition of heparin, with a higher frequency of intracranial hemorrhages.23

The value of the intra-arterial route for thrombolysis includes the greater precision of diagnosis and the opportunity of using the smallest effective dose of thrombolytic agent. Since we relied on angiographic detection of persisting intravascular occlusion, we did not run the risk of treating individuals in whom spontaneous clot lysis had already occurred. In the group reported here, we performed angiography in 62 patients but found clot in only 54; 8 (13%) were thus spared the risks associated with thrombolysis. Del Zoppo and colleagues7 also failed to detect intravascular clots in 19% of the angiograms they performed to monitor thrombolysis. The frequency of absent occlusions in the carotid territory in the prourokinase study was 23%.23 Because we could image the dissolution of clots, we were able to limit therapy to less than the maximum in 48 patients (89%). It is clear that higher doses of intravenous tPA are associated with increased risk of hemorrhage into clinically normal brain,9 and we infer that smaller doses of intra-arterial urokinase are also likely to decrease the risk of hemorrhage in ischemic brain.

Intra-arterial therapy probably achieves a higher concentration of the thrombolytic agent in the clot, and there may be additional advantages of mechanical disruption of the clot by the catheter.16-18 The latter may explain the lower recanalization rate after intra-arterial prourokinase administration (57.7%)23 compared with our cohort in the same vascular territory (100%). We frequently observed that blood in lumen of the middle cerebral arterial proximal to an occlusion in the M1 segment was relatively static; the entry of fresh arterial blood into the portion of vessel adjacent to the clot was limited by the rate of runoff in the small penetrating vessels. If thrombolysis depended on diffusion of the thrombolytic agent from arterial blood adjacent to the clot, the availability of the agent to the clot would be limited by the concentration of agent in arterial blood and the turnover of arterial blood adjacent to the clot. Intravenous administration of thrombolytic agent attains a much lower concentration in the arterial blood adjacent to the clot than is accomplished by injection at that site through a catheter. Moreover, injection by catheter into the clot circumvents the limitations of arterial flow proximal to the clot.

The disadvantages of intra-arterial therapy lie in the cost and delay. For intra-arterial therapy to be available for emergency care of ischemic stroke, personnel and equipment must be in constant readiness. Despite our best efforts, the median time from arrival in the emergency department to delivery of urokinase was 130 minutes; the minimal time was 45 minutes, but the median was strongly influenced by several complex procedures. A recent symposium strongly argued for delivery of intravenous agent within 1 hour of presentation27; by that standard, intra-arterial therapy in our hands necessitates a median of 70 minutes of undesirable delay.

Our experience with this uncontrolled population thus far indicates that the administration of intra-arterial urokinase may improve outcome in patients with acute ischemic stroke. Severity of stroke, not timing, as well as site of angiographic occlusion may be important predictors of successful treatment.

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References


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