Combined Intravenous and Intra-Arterial Recombinant Tissue Plasminogen Activator in Acute Ischemic Stroke

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Background and Purpose—A retrospective analysis was performed on 20 consecutive patients who presented with severe acute ischemic stroke and were evaluated for a combined intravenous (IV) and local intra-arterial (IA) recombinant tissue plasminogen activator (rtPA) thrombolytic approach within 3 hours of onset.

Methods—Twenty consecutive patients with carotid artery distribution strokes were evaluated and treated using a combined IV and IA rtPA approach over a 14-month period (September 1998 to October 1999). rtPA (0.6 mg/kg) was given intravenously (maximum dose 60 mg); 15% of the IV dose was given as bolus, followed by a continuous infusion over 30 minutes. A maximal IA dose, up to 0.3 mg/kg or 24 mg, whichever was less, was given over a maximum of 2 hours. IV treatment was initiated within 3 hours in 19 of 20 patients. All 20 patients underwent angiography, and 16 of 20 patients received local IA rtPA.

Results—The median baseline National Institutes of Health Stroke Scale (NIHSS) score for the 20 patients was 21 (range 11 to 31). The median time from stroke onset to IV treatment was 2 hours and 2 minutes, and median time to initiation of IA treatment was 3 hours and 30 minutes. Ten patients (50%) recovered to a modified Rankin Scale (mRS) of 0 or 1; 3 patients (15%), to an mRS of 2; and 5 patients (25%), to an mRS of 4 or 5. One patient (5%) developed a symptomatic intracerebral hemorrhage and eventually died. One other patient (5%) expired because of complications from the stroke.

Conclusions—We believe that the greater-than-expected proportion of favorable outcomes in these patients with severe ischemic stroke reflects the short time to initiation of both IV and IA thrombolysis. (Stroke. 2000;31:2552-2557.)

Key Words: fibrinolysis ■ stroke, acute ■ stroke, ischemic ■ thrombolysis ■ tissue plasminogen activator

Intravenous (IV) recombinant tissue plasminogen activator (rtPA) is the only Food and Drug Administration–approved treatment for acute ischemic stroke and is based on the findings of the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group (NINDS t-PA Stroke Trial).1 The prognosis of patients with a clinically severe ischemic stroke, however, remains relatively poor despite treatment with IV rtPA. Of treated patients with a baseline National Institutes of Health Stroke Scale (NIHSS) score of >20 in the NINDS t-PA Stroke Trial, 48% were dead at 3 months, and an additional 21% had moderately severe or severe impairment of function (modified Rankin Scale [mRS] 4 or 5).2 IV rtPA is associated with low recanalization rates for larger more proximal thromboemboli. The recanalization of proximal arterial occlusion by IV rtPA ranges from 10% for internal carotid artery (ICA) occlusion to 30% for proximal middle cerebral artery (MCA) occlusion.3 However, IV rtPA is still clinically more effective than placebo for large ischemic strokes.4 Local intra-arterial (IA) thrombolysis has the advantage of better reported recanalization rates but also has the disadvantage of a longer delay to initiation of treatment.

In the previously reported Emergency Management of Stroke (EMS) Bridging trial, we hypothesized that a combined approach that uses the speed of initiation of therapy with IV rtPA and the improved recanalization efficacy of rapidly administered local IA rtPA may improve patient outcome from major stroke. This small pilot study demonstrated that combined IV-IA rtPA was feasible with better recanalization rates but did not demonstrate improved patient outcome.5 Since the EMS Trial, we have improved the time to initiation of IV and IA rtPA treatment and report better-than-expected patient outcome in 20 patients with major hemispheric stroke.

Subjects and Methods

The clinical criteria for the present report required that patients (1) have an acute ischemic stroke in the carotid artery distribution, (2) a
Clinical exclusion criteria, based on the NINDS t-PA Stroke Trial, included the following: a history of stroke within 3 months, presentation suggestive of subarachnoid hemorrhage, prior history of intracranial hemorrhage, seizure at stroke onset, history of intracranial neoplasm, uncontrolled hypertension (systolic blood pressure >185 mm Hg, diastolic blood pressure >110 mm Hg), surgery or trauma within 30 days, head trauma within 90 days, and oral anticoagulation with an international normalized ratio >1.5. CT scan exclusion criteria were evidence of any intracranial hemorrhage, significant mass effect, intracranial neoplasm except for small meningiomas, and early clear hypodensity involving 1/3 of the MCA territory. Patients with subtle changes of parenchymal ischemia were included.

Informed consent was obtained from family members for lower-dose IV treatment, angiography, and local IA treatment. The total (IV and IA) dose of rtPA was based on the standard IV dose of 0.9 mg/kg. An IV dose of 0.6 mg/kg was given, with 15% given as an initial bolus and the remainder given as a constant infusion over 30 minutes. Up to 0.3 mg/kg or 24 mg, whichever was less, was then available for IA administration.

Angiography was performed as quickly as possible in all patients, and could begin before completion of IV rtPA infusion. By use of a single-wall approach for arterial puncture, a 6F arterial sheath was placed. A 6F guide catheter (Cordis Envoy, Cordis Endovascular Systems) was used in most cases. In cases of ICA occlusion, the microcatheter and microguide-wire were used to gently probe the occluded artery. For patients with proximal and distal ICA occlusion, the initial goal was to open the carotid terminus region to allow for potential collateral flow from either the anterior or posterior communicating arteries.

Before IA rtPA infusion, the microcatheter system was advanced well into the clot. The microguidewire was used to traverse the occluded segments several times in an attempt to disrupt the clot. With the microcatheter embedded within the clot, an initial bolus of rtPA ranging from 2 to 5 mg was administered, followed by a constant infusion of rtPA at 10 mg/h at a concentration of 1 mg/mL. The microcatheter was initially positioned in the proximal clot and advanced distally during the procedure. Diagnostic angiography (typically through the guide catheter) was performed at 15- to 20-minute intervals.

CT scans performed 24 hours after rtPA were evaluated for the presence of intracranial hemorrhage and parenchymal contrast staining. NIHSS score evaluations were performed by physicians 24 hours after treatment and at discharge. After 2 months, a research study nurse assessed long-term patient outcomes over the telephone. Patient recovery was assessed by use of mRS.

### Results

Between September 1998 and October 1999, a total of 20 patients were treated with a combined IV and local IA rtPA approach (Table 1). This group consisted of 9 men and 11 women aged 36 to 89 (median 69) years. The initial NIHSS score ranged from 11 to 31 (median 21).

Fifteen patients (75%) presented to community hospitals and were evaluated at the community hospitals by physicians.
of the Greater Cincinnati/Northern Kentucky Stroke Team. After inclusion and exclusion criteria were met, IV rtPA was initiated, and then patients were transferred by either helicopter or ambulance to our institution for local IA rtPA. Five patients (25%) presented directly to 1 of our 2 facilities capable of immediate angiography and local IA treatment. IV rtPA was initiated at a median of 2 hours and 2 minutes (range 1 hour and 12 minutes to 4 hours and 10 minutes) from stroke onset. Local IA rtPA was initiated at a median of 3 hours and 30 minutes (range 2 hours and 35 minutes to 4 hours and 52 minutes) from stroke onset. Based on weight and a total IV dose of 0.6 mg/kg rtPA, the mean IV dose of rtPA was 45 mg. In the 16 patients receiving local IA rtPA, the mean dose of rtPA was 20 mg.

Diagnostic angiography after IV rtPA demonstrated the following: 6 cervical ICA occlusions, 4 carotid terminus occlusions, 8 proximal M1 segment occlusions, 1 M2 segment occlusion, and 1 severe carotid origin stenosis. Three of the 6 cases of ICA occlusion were suspected to be secondary to carotid dissection (Figure 1). There were no angiographically related complications, aside from mild groin hematomas, none of which required surgery or transfusion.

Recanalization was assessed by use of the Thrombolysis in Myocardial Infarction (TIMI) classification after completion of IA thrombolysis (maximum time was 2 hours from the start of IA treatment) in 16 patients. Three (19%) of 16 cases were classified as TIMI 3, 8 (50%) of 16 cases were TIMI 2, and 5 (31%) of 16 were TIMI 0 or 1.

Three patients significantly improved during the diagnostic angiogram after receiving IV rtPA and before receiving IA rtPA. One patient had a proximal ICA occlusion with a recanalized M1 occlusion and distal M3-4 emboli (Figure 1). The patient improved markedly on the angiographic table, and 0.3 mg/kg IV rtPA was further administered because the patient was still within 3 hours of symptom onset. Diffusion-weighted imaging at 8 hours shows no lenticulotemporal diffusion abnormality (bottom right) but a small cortical diffusion abnormality in the posterior frontal convexity (bottom center). Spin-echo (repetition time 3000 ms, echo time 120 ms) 2 days later (bottom right) confirmed ischemic edema in the lenticular nucleus, as was expected from the initial CT. NIHSS score at discharge was 0.

In 11 of 16 patients who received local IA rtPA, a heparin bolus ranging from 2000 to 4000 U was administered. Seven patients were started on a heparin infusion after the procedure to preserve vessel patency. Three patients improved with IV rtPA alone and were begun on a heparin infusion ranging between 800 and 1400 U/h.

CT scans performed 24 hours after rtPA were reviewed and demonstrated 1 large parenchymal hematoma, 3 hemorrhagic infarcts, 1 contrast staining of the basal ganglia, and 1 contrast extravasation. The large parenchymal hematoma was the only symptomatic hemorrhage, and that patient expired.
The median baseline NIHSS score was 21 (range 11 to 31). The 24-hour median NIHSS score was 9 (range 2 to 42). The median NIHSS score on discharge was 3, with a range of 0 to 26 (available in 15 of 18 patients and not including the 2 patients who died). Long-term patient outcomes were assessed by mRS. Patient follow-up consisted of phone interviews by our nurse clinician. Follow-up intervals ranged from 2 to 11 months. Overall, 10 (50%) of 20 patients recovered to an mRS of 0 or 1. Three (15%) patients recovered to an mRS of 2. Five (25%) patients had an mRS of 4 or 5, and 2 (10%) patients expired.

Four patients who received only IV rtPA had a median baseline NIHSS score of 17 (range 11 to 31), and 3 (75%) patients improved dramatically on the angiographic table and achieved an mRS of 0 to 1 at 90 days. The fourth patient had a near total ICA occlusion with 2 cm of thrombus in the carotid bulb and proximal ICA above the stenosis, with M3-4 emboli distally, and was not treated with IA rtPA.

Of 16 patients receiving both IV and IA therapy, the median baseline NIHSS score was 21 (range 14 to 28). Seven (43.8%) of 16 patients achieved an mRS of 0 to 1, 3 (18.8%) of 16 achieved an mRS of 2, 4 (25%) of 16 achieved an mRS 4 to 5, and 2 (12.5%) expired, with 1 death (6.2%) due to posttreatment hemorrhage related to therapy.

Discussion
The NINDS rt-PA Stroke Study Group documented improved clinical outcomes at 3 months in patients treated with IV rtPA within 3 hours of the onset of ischemic stroke. The NINDS study showed that treatment within 0 to 90 minutes is more likely to lead to a favorable outcome than treatment within 91 to 180 minutes, despite the fact that patients presenting in the earlier time window had a greater mean neurological deficit by NIHSS score. IV rtPA was of benefit for all stroke patients, including those patients with a baseline NIHSS score >20. Although these patients with high stroke scale scores did better with IV rtPA, their overall prognosis was still poor. Earlier treatment was associated with better outcome in the trial; the odds ratio for favorable outcome was 2.11 in the 0- to 90-minute stratum and 1.69 in the 90- to 180-minute stratum. A review of post-NINDS patients treated in the Greater Cincinnati/Northern Kentucky region with IV tPA also demonstrated that time to treatment was an important factor, suggesting that a delay of 20 to 30 minutes in treatment may decrease the probability of clinical improvement by ≈10%.8

Only 30% to 40% of major occluded arteries partially or completely recanalize with IV rtPA, as determined by cerebral angiography, creating some enthusiasm for achieving better recanalization with local IA therapy. The first large controlled trial of IA thrombolytic therapy for acute stroke was recently published. Recombinant Prourokinase in Acute Cerebral Thromboembolism II (PROACT II) was a multicenter, randomized, controlled trial designed to assess clinical outcome in 180 patients with MCA stroke after treatment with IA recombinant prourokinase (r-ProUK) within 6 hours of symptom onset. Patients with angiographically proven MCA occlusions were randomized 2:1 to either a 120-minute IA infusion of 9 mg r-ProUK directly into the clot plus low-dose IV heparin or IV heparin alone. All patients underwent repeat angiography to assess recanalization. The patients in this trial had a median NIHSS score of 17. Of note, the median time to initiation of r-ProUK was 5.3 hours.

The results of this trial demonstrated that 40% of r-ProUK patients and 25% of controls were rated as independent, with mild or no disability (mRS ≤2) 90 days after therapy (P=0.043). Recanalization was significantly better in the r-ProUK patients than in the control patients (66% versus 18% had TIMI grade 2 or 3 at 2 hours). Although there was an increase in symptomatic intracranial hemorrhage within 36 hours with r-ProUK treatment (10.2% versus 1.8%, P=0.06), there was no difference in 90-day mortality between the groups (25% for r-ProUK patients and 27% for controls).9,10

Other recently published uncontrolled case series also focus attention on time to treatment as an important factor in good outcomes. Suarez et al described a series of 54 patients with a variety of arterial occlusive lesions, primarily M1 and M2 occlusions, who underwent cerebral angiography and were treated with IA urokinase. Patient inclusion was similar to the NINDS criteria, with time from onset to treatment up to 6 hours. The patients selected had a mean age of 65±15 years (67±10 years for NINDS tPA patients) and a median NIHSS of 12 (14 for NINDS tPA patients). The median time from emergency department arrival to initiation of therapy was 130 minutes. The average time from symptom onset to initial therapy was 4 hours and 45 minutes. MRS scores of 0 to 2 were achieved in 54% of patients.

Bendszus et al recently reported 12 patients with MCA occlusion with treatment begun within 4 hours of onset. Although the neurological scores at baseline were not documented, mRS scores of 0 to 2 were achieved in 66% of the patients.

Although the results from Suarez et al, Bendszus et al, and the PROACT II study are encouraging regarding IA thrombolysis, the time required for IA therapy may be considerable. In the study by Suarez et al, the median time from emergency department arrival to initiation of therapy was 2 hours and 10 minutes, and the average time from symptom onset to initial therapy was 4 hours and 45 minutes. In the PROACT II study, the median time from symptom onset to initiation of thrombolysis was 5.3 hours. Successful clot lysis usually does not occur for an additional 1 to 2 hours.

One study of combined IV and IA thrombolytic therapy has been completed. The EMS Bridging Trial was a multicenter pilot trial designed to evaluate safety and potential efficacy for patients with acute ischemic stroke who can be treated within 3 hours with combined therapy. Thirty-five patients were randomized to receive IV rtPA (0.6 mg/kg) or placebo over 30 minutes. Cerebral angiography was then carried out on all patients. If the cerebral angiogram localized an occlusion appropriate to the patient’s symptoms, the patient received IA tPA at 10 mg/h for up to 2 hours after a bolus injection of 2 mg into the clot. The mean time of stroke onset to IV treatment was 2 hours and 30 minutes (±32 minutes); the time of stroke onset to IA treatment was 4 hours and 10 minutes. The pilot study demonstrated improved recanalization rates in the combined IV-IA group and the feasibility of combined IV and IA therapy initiated within 3
hours of symptom onset. Whereas safety was acceptable, the small sample size limited insight into potential efficacy. However, there were 15 patients with M1 or M2 occlusions in the study. Of 9 in the combined IV-IA group with a mean baseline NIHSS score of 17.2, 6 (66%) achieved an mRS of 0 to 2 at 3 months. Of 6 patients treated with only IA tPA (mean NIHSS score 11.6), 5 (83%) achieved an mRS of 0 to 2 at 3 months. These results were superior to the expected outcome (25% with mRS 0 to 2) in control patients from the PROACT II study and superior to the outcome (40% with mRS 0 to 2) in patients treated with prourokinase. Again, better outcomes need not be so much a result of the drug itself nor the combination of IV and IA therapy only but may relate to more rapid time to treatment (Table 2).

Despite having a higher baseline NIHSS score than in the NINDS and PROACT II studies, our group of patients had a more favorable outcome with a lower mortality rate compared with patients in those studies. The rate of symptomatic hemorrhage (5%) in our group of patients was similar to the overall hemorrhagic rate reported in the NINDS and PRO- ACT II studies (Table 2) but better than the 17% hemorrhagic rate in patients with NIHSS >20 reported in NINDS. The patient in our series with a fatal symptomatic hemorrhage had excellent recanalization after thrombolysis. However, this patient had labile blood pressure after the procedure.

We attribute this better-than-expected patient outcome in our present series to the very early initiation of treatment of both IV and IA rtPA as well as the improved efficacy of a combined approach of IV and IA thrombolysis for larger more proximal vessel occlusions. The advantages of giving IV rtPA include a shorter time to initiate therapy, and IV rtPA alone will be sufficient in a minority of cases. In the present analysis, 3 (15%) of 20 patients showed significant clinical improvement during angiography, with evidence of partial recanalization; therefore, IA rtPA was not administered. In addition, IV rtPA may potentiate the efficacy of IA thrombolysis. Twelve (75%) of 16 patients demonstrated good recanalization (TIMI grade 2 or 3) compared with a 30% to 40% recanalization rate with IV rtPA alone and a 66% recanalization rate as noted in the PROACT II study.3,9,13,14

The impact of rapid treatment, with improved recanalization with IA therapy, is emphasized in Figure 3, which graphically depicts that better outcomes are obtained in these recently reported studies with early treatment. In fact, delays of 30 minutes in IA therapy may translate into ≈10% less likelihood of favorable outcome. The time chart also suggests that good outcomes may not be possible with current thrombolytic methods in ≈30% of rapidly treated patients. Other treatment adjuncts, such as neuroprotective agent administration or more rapid clot removal, may be required to further improve outcomes.

This combined IV-IA approach appeared to improve expected patient outcomes in this group of 20 patients with high stroke scale scores (median 21 NIHSS score) compared with outcomes reported in prior published IV or IA thrombolytic studies. A subgroup of patients with carotid terminus occlusions did surprisingly well. In our series, 5 (25%) of 20 patients presented with carotid terminus occlusions, including 2 patients with cervical ICA occlusions. Four of 5 patients recovered to an mRS of 0, and the other patient recovered to an mRS of 2. The mean NIHSS score on discharge of the subgroup was 3.2.

This analysis is primarily limited by the nonblinded retrospective collection of data and the small number of patients. Yet these data support the preliminary insights gained in the EMS study that a combined IV-IA rtPA treatment approach initiated within 3 hours in patients with large ischemic strokes may improve patient outcomes and reduce mortality rates, with a relatively low incidence of symptomatic hemorrhage. We feel that this is primarily due to rapid treatment and higher recanalization rates. A prospective study with a larger number of patients will be required to confirm our observations. A study comparing IV tPA with combined IV-IA therapy within 3 hours will ultimately be required to determine the optimal therapy for patients with major ischemic strokes.

### Table 2. Comparison Studies

<table>
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<th>Study</th>
<th>Median Time to Treatment, h:min</th>
<th>Treatment</th>
<th>Median Baseline NIHSS</th>
<th>Symptomatic Hemorrhage, %</th>
<th>Mortality rate at 90 d, %</th>
<th>Outcome of 0–2 mRS, %</th>
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<td>IV+IA</td>
<td>21</td>
<td>5</td>
<td>10</td>
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**Figure 3.** Graph demonstrating percentage of patients recovering to mRS of 0 to 2 with respect to time to initiation of IA therapy. The group of patients from the EMS study were only those with M1 or M2 occlusions. Control group is the group of patients in PROACT II, treated only with IV heparin.
References
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