Combined Intravenous and Intra-Arterial r-TPA Versus Intra-Arterial Therapy of Acute Ischemic Stroke : Emergency Management of Stroke (EMS) Bridging Trial

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Combined Intravenous and Intra-Arterial r-TPA Versus Intra-Arterial Therapy of Acute Ischemic Stroke

Emergency Management of Stroke (EMS) Bridging Trial

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Background and Purpose—The purpose of this study was to test the feasibility, efficacy, and safety of combined intravenous (IV) and local intra-arterial (IA) recombinant tissue plasminogen activator (r-TPA) therapy for stroke within 3 hours of onset of symptoms.

Methods—This was a double-blind, randomized, placebo-controlled multi-center Phase I study of IV r-TPA or IV placebo followed by immediate cerebral arteriography and local IA administration of r-TPA by means of a microcatheter. Treatment activity was assessed by improvement on the National Institutes of Health Stroke Scale Score (NIHSSS) at 7 to 10 days. The Barthel Index, modified Rankin Scale, and the Glasgow Outcome Scale measured 3-month functional outcome. Arterial recanalization rates and their relation to total r-TPA dose and time to lysis were measured. Rates of life-threatening bleeding, intracerebral hemorrhage (ICH), or other bleeding complications assessed safety.

Results—Thirty-five patients were randomly assigned, 17 into the IV/IA group and 18 into the placebo/IA group. There was no difference in the 7- to 10-day or the 3-month outcomes, although there were more deaths in the IV/IA group. Clot was found in 22 of 34 patients. Recanalization was better ($P=0.03$) in the IV/IA group with TIMI 3 flow in 6 of 11 IV/IA patients versus 1 of 10 placebo/IA patients and correlated to the total dose of r-TPA ($P=0.05$). There was no difference in the median treatment intervals from time of onset to IV treatment (2.6 vs 2.7 hours), arteriography (3.3 vs 3.0 hours), or clot lysis (6.3 vs 5.7 hours) between the IV/IA and placebo/IA groups, respectively. A direct relation between NIHSSS and the likelihood of the presence of a clot was identified. Eight ICHs occurred; all were hemorrhagic infarctions. There were no parenchymal hematomas. Symptomatic ICH within 24 hours occurred in 1 placebo/IA patient only. Beyond 24 hours, symptomatic ICH occurred in 2 IV/IA patients only. Life-threatening bleeding complications occurred in 2 patients, both in the IV/IA group. Moderate to severe bleeding complications occurred in 2 IV/IA patients and 1 placebo/IA patient.

Conclusions—This pilot study demonstrates combined IV/IA treatment is feasible and provides better recanalization, although it was not associated with improved clinical outcomes. The presence of thrombus on initial arteriography was directly related to the baseline NIHSSS. This approach is technically feasible. The numbers of symptomatic ICH were similar between the 2 groups, which suggests that this approach may be safe. Further study is needed to determine the safety and effectiveness of this new method of treatment. Such studies should address not only efficacy and safety but also the cost-benefit ratio and quality of life, given the major investment in time, personnel, and equipment required by combined IV and IA techniques. **(*Stroke*. 1999;30:2598-2605.)**

Key Words: cerebral ischemia ■ cerebrovascular disorders ■ drug therapy, combination ■ stroke, acute ■ tissue plasminogen activator ■ thrombolytic therapy

Cerebral infarction, which comprises at least 80% of all strokes, is the end result of a complex series of cellular metabolic events that occur rapidly after interruption of nutrient blood flow to a region of the brain. Both duration and severity of focal cerebral ischemia are important in determining whether and how much brain infarction occurs. Acute thrombus formation or migration is the principal cause of blood flow interruption in at least 75% of cerebral infarctions.[1]

Animal and human studies have led to advances in therapy, in particular intravenous (IV) thrombolysis, which have been shown to be effective in reducing disability and possibly

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decreasing the size of the infarct.[2,3] Still, many patients are left with moderate to severe neurological deficits. Twenty-seven of 54 patients in the National Institute of Neurologic Disorders and Stroke (NINDS) pilot study[4] treated with intravenous recombinant tissue plasminogen activator (r-TPA) within 90 minutes of onset of symptoms had residual occlusion of the involved vessel by angiography despite the ultra rapid treatment.

Intra-arterial (IA) treatment is attractive because of higher rates of recanalization, lower doses of thrombolytics used compared with IV therapy, and lower rates of intracerebral hemorrhage (ICH).[5–7] The rates of recanalization are related to the size of the occluded artery and the presumed volume and composition of the clot. The neurological outcome appears to be related to the duration of ischemia before recanalization.[8,9]

Early treatment through an IV infusion of a thrombolytic agent followed by local IA therapy has not been previously tested in acute ischemic stroke patients. An IV/IA approach has the potential of combining the advantages of IV TPA (fast and easy to use) with the advantages of IA treatment (higher ratio of reported recanalization) so as to maximize the speed and frequency of recanalization. The purpose of this trial was to test the feasibility and provide preliminary data on the relative benefits and risks of a combined IV and local IA r-TPA therapy as compared with IV placebo and local IA r-TPA therapy in patients with ischemic stroke treated within 3 hours of onset of symptoms. This trial was carried out before Food and Drug Administration approval of r-TPA for acute ischemic strokes within 3 hours of onset.

Subjects and Methods

The Emergency Management of Stroke (EMS) Bridging Trial is a pilot, double-blind, randomized, placebo-controlled multi-center Phase I study comparing the safety and feasibility of 2 treatment strategies administered to patients with acute focal brain ischemia within 3 hours of symptom onset. The study was undertaken from February 1995 through March 1996 (including a 90-day follow-up period), before the publication of the NINDS r-TPA Stroke Study.[3] Informed consent was obtained from each patient, their legal guardian, or their next of kin. The respective institutional review board approved the protocol at each institution. Each patient received a noncontrast pretreatment diagnostic cerebral CT scan to rule out a hemorrhagic lesion. Patients meeting study entry criteria and completing informed consent requirements were randomly assigned to 1 of 2 treatment arms. The inclusion and exclusion criteria were based on those used in the NINDS r-TPA Stroke Study[3] but differed in the following ways: the upper age limit was 84 years, an NIH Stroke Scale Score (NIHSSS) of >5 was required, patients with previous strokes within 6 weeks were excluded as were those with surgery, biopsy, or hemorrhage within the 30 days before randomization. In the first treatment arm, patients received IV r-TPA (0.6 mg/kg, 60 mg maximum, 10% of the dose as a bolus over 1 minute and the remainder over 30 minutes) followed by immediate cerebral arteriography and local IA administration of r-TPA through the catheter if a clot in the appropriate arterial distribution was identified. In the second treatment arm, patients received intravenous placebo in an identical manner to the latter group followed by immediate cerebral arteriography and local IA administration of r-TPA through the catheter. Arterial patency was measured by arteriography at the end of the IA therapy.

Hypotheses

The primary hypotheses were designed to test clinical activity and safety of these treatment strategies. Clinical activity was assessed by comparing the proportion of patients in each treatment arm who had either a 7-point or more improvement on the NIHSSS between baseline and 7 to 10 days or a NIHSSS of 0 to 1 at 7 to 10 days.[10]

The proportion of patients in each treatment arm with life-threatening bleeding complications was compared to assess the safety and the relative risks of these strategies. A significant life-threatening bleeding complication was defined as the development of an ICH, either parenchymal hematoma (PH) or hemorrhagic infarction (HI), within 24 hours of randomization that was clinically associated with deterioration likely to result in permanent disability or death. It was anticipated that there would be a concomitant deterioration in the NIHSSS of 4 points or more and that ICH would be associated with a confluent, hyperdense appearance with significant mass effect on the CT scan. Any PH or HI requiring surgical evacuation within 24 hours was designated as life threatening. A PH was defined as CT findings of a typical homogenous, hyperdense lesion with a sharp border with or without edema or mass effect within the brain. This hyperdense lesion could arise within or outside of the vascular territory of the presenting ischemic stroke. Hemorrhage with an intraventricular extension was considered an intracerebral hematoma. A HI was defined as CT findings of acute infarction with punctate or variable hypodensity/hyperdensity with an indistinct border within the vascular territory suggested by the signs and symptoms.

Other complications such as groin hematoma, retroperitoneal hematoma, or gastrointestinal bleeding were operationally defined as significant life-threatening bleeding complications if they required transfusion of 3 or more units of blood replacement within 24 hours or major surgical intervention. A groin hematoma requiring only local vascular repair and not transfusion did not qualify as a significant life-threatening bleed.

Safety was also evaluated by noncontrast CT at 72 ± 6 hours for evidence of asymptomatic or symptomatic PH or HI. Symptomatic ICH was defined as a CT-documented hemorrhage that was temporally related to deterioration in the patient's clinical condition as judged by the clinical investigator. The 72-hour period was chosen to minimize the potential of residual angiographic contrast that could show up as a hyperdensity on CT scan. Termination of the study was considered for any evidence of a predefined excess of patients with clinical neurological deterioration associated with any form of intracranial hemorrhage. The External Data and Safety Monitoring Committee received clinical data on a continuous basis, including all safety data, and received a detailed report from the coordinating investigator after the treatment of every 10 patients.

The secondary hypotheses were (1) The functional outcome of the combined treatment group would be significantly better at 3 months, when the functional outcome was measured by comparison of the medians of the Barthel Index, the modified Rankin Scale, and the Glasgow Outcome Scale. (2) The rate of peri-access hematoma and of blood transfusion would be significantly higher in the combined treatment group than in the group treated with IV placebo and IA r-TPA. Bleeding events were classified as mild if bleeding was greater than normally observed but <250 mL, moderate if the estimated blood loss was 250 to 500 mL (possibly with blood replacement), and severe if the estimated blood loss was >500 mL, requiring blood replacement. (3) The rate of partial or total arterial patency as measured by arteriography at a maximum of 2 hours after the start of IA therapy would be greater in the combined treatment group. Arterial patency was rated by the Thrombolysis In Myocardial Infarction (TIMI) classification,[11] in which 0 indicates no perfusion, 1 indicates penetration beyond obstruction but no perfusion of distal beds, 2 indicates incomplete recanalization with slower distal perfusion, and 3 indicates full perfusion. (4) The frequency of recanalization defined by central interpretation (by T.A.T.) of TIMI 2 or 3 flow and the time to recanalization would vary directly with the total dose of r-TPA administered.

Randomization and Treatment

Patients were assigned to 1 of the 2 arms by use of a stratified, blocked-randomization scheme, by clinical center. The investigator and/or neurologist, neuroradiologist, and the patient were blinded to

TABLE 1. Baseline Characteristics

	IV/IA (n=17)	Placebo/IA (n=18)	P
Age, y	65.6±11.2	67.3±12.3	0.68
Sex, male	9 (53%)	10 (56%)	0.88
Race, white	7 (41%)	10 (56%)	0.40
Hypertension	9 (53%)	8 (47%)	0.73
Diabetes	3 (18%)	2 (11%)	0.58
Prior stroke	3 (18%)	2 (11%)	0.58
Baseline NIHSSS*	16 (9, 21)	11 (9, 16)	0.13

Data expressed as n (%) or mean±SD.
*Baseline NIHSSS reported as median with 25th and 75th percentiles.

the actual contents of the IV medication (r-TPA or placebo). However, all local IA treatments were with open-label r-TPA. Patients received placebo or r-TPA (Activase alteplase, Genentech, South San Francisco) in a dose of 0.6 mg/kg of estimated body weight (maximum 60 mg.); 10% was given as an IV bolus over 1 minute followed by a controlled 30-minute infusion of the remaining dose. The placebo was packaged and labeled identically to alteplase and consisted of a lyophilized product as a white powder. It contained 0.2 mol/L arginine phosphate <0.01% polysorbate 80, pH 7.4 after reconstitution. The protocol required that no anticoagulants or antiplatelet agents be given during the first 24 hours and that blood pressure be maintained <180/105 according to the American Heart Association Guidelines.[12] If heparin was clinically indicated after 24 hours, a cerebral CT scan was obtained to exclude ICH. The investigator performing the 7- to 10-day NIHSSS was blinded to the contents of the IV medication.

Cerebral CT Scans

Third- and fourth-generation CT scanners had to be available 24 hours a day. CT standards were established before the start of the trial. A noncontrast cerebral CT scan was performed at baseline, 72±6 hours, and 7 days ±24 hours after study drug infusion for assessment of intracranial hemorrhage and infarct size. An emergency head CT was performed for any signs of acute neurological deterioration. The clinical centers sent CT scan films to the coordinating center for analysis. The coordinating center neuroradiologist (T.A.T.) was responsible for the central interpretation. A detailed analysis of the CT findings will be the subject of a subsequent report.

Catheterization and IA Protocol

An introducing sheath was placed in the femoral artery by use of a 1-wall puncture, and arteriography was performed in the standard fashion. If the suspected distribution of ischemia was the carotid artery, injection into the common carotid artery for examination of the carotid bifurcation as well as for intracranial examination was performed. If the suspected arterial distribution was the vertebral or basilar artery, selective injection of both vertebral arteries was performed. Four thousand units of heparin was administered intravenously as a bolus at the beginning of the procedure. No post-bolus IV heparin infusion was administered. Per standard neurointerventional procedure, a heparin flush solution (eg, 1000 U in 500 mL normal saline at ≈10 gtt/min, ≈2 U of heparin/min) was used through the access sheath and was continued until the sheath was removed.

After the diagnostic cerebral arteriogram (distal subtraction arteriography or cut-film arteriography) was performed, a 3F, tapered, variable-stiffness, end-hole Tracker microcatheter was passed over a micro–guide wire to the level of occlusion. One milligram of r-TPA was injected beyond the thrombus. The catheter was retracted into the proximal thrombus, and 1 mg of r-TPA was injected directly into the thrombus followed by infusion at the rate of 10 mg/h (10 mg/25 mL normal saline) with the use of an infusion pump. Repeat arteriography was performed every 15 minutes after the start of infusion with isosmolar contrast. If at the time of the repeat arteriogram the vessel was not patent, the infusion was continued. If the vessel had partially recanalized, the infusion catheter was introduced further into the vessel for thrombus access. The infusion was continued for a maximum of 2 hours. The infusion was not terminated in stable patients before 2 hours unless complete lysis had been accomplished (arteriographic outcome of TIMI 3 flow). A maximum local IA dose of 20 mg was given including the 2 injections of 1 mg each. The patient's neurological function was evaluated every 15 minutes during the IA procedure, including assessment of level of consciousness and upper extremity motor function (items la, lb, 5 from the NIHSSS).[10] If the arterial catheter could not be introduced to the site of the thrombus, r-TPA at the same dose was selectively infused into the artery proximal to the site of the thrombus.

If the patient did not have an occlusion on the initial arteriogram in the vascular territory appropriate for the patient's symptoms, no r-TPA was given, and the procedure was terminated (these patients were included in the overall analysis).

If the patient had a significant stenosis or occlusion of the internal carotid, vertebral, or basilar arteries, the stenosis was traversed with the microcatheter to approach a distal occlusive thrombus.[13] Angioplasty was not a part of this protocol. After arteriography, an arterial sheath was left in place for 24 hours and was removed after laboratory demonstration of normal fibrinogen and clotting studies.

Arteriograms were analyzed and the site of occlusion was documented. Posttreatment arteriography included ipsilateral AP and lateral carotid injections (2 frames/second) or vertebral-basilar system in AP and lateral projections if this was the involved arterial system (with digital subtraction arteriography or cut-film arteriography). In patients with a carotid distribution thrombus, a contralateral carotid and a vertebral injection were not required. In patients with a vertebrobasilar distribution thrombus, carotid injections were not

TABLE 2. Clinical Outcome

	IV/IA (n=17)	Placebo/IA (n=18)	P
Change in NIHSSS (baseline to 7 d)	4 (24%)	4 (24%)	1.00
Barthel (median score), 90 d	90 (0, 100)	95 (60, 100)	0.26
Rankin (median score), 90 d	3 (1, 5)	1.5 (1, 3)	0.20
Glasgow (median score), 90 d	2 (1, 5)	1 (1, 2)	0.10
NIHSSS			
72 h	11 (5, 28)	6 (3, 13)	0.20
7 d	7 (3, 15)	4 (3, 12)	0.29
3 mo	5.5 (2, 35)	1 (0, 13)	0.04
Mortality rate	5 (29%)	1 (5.5%)	0.06

Data expressed as n (%) or median (25th percentile, 75th percentiles).

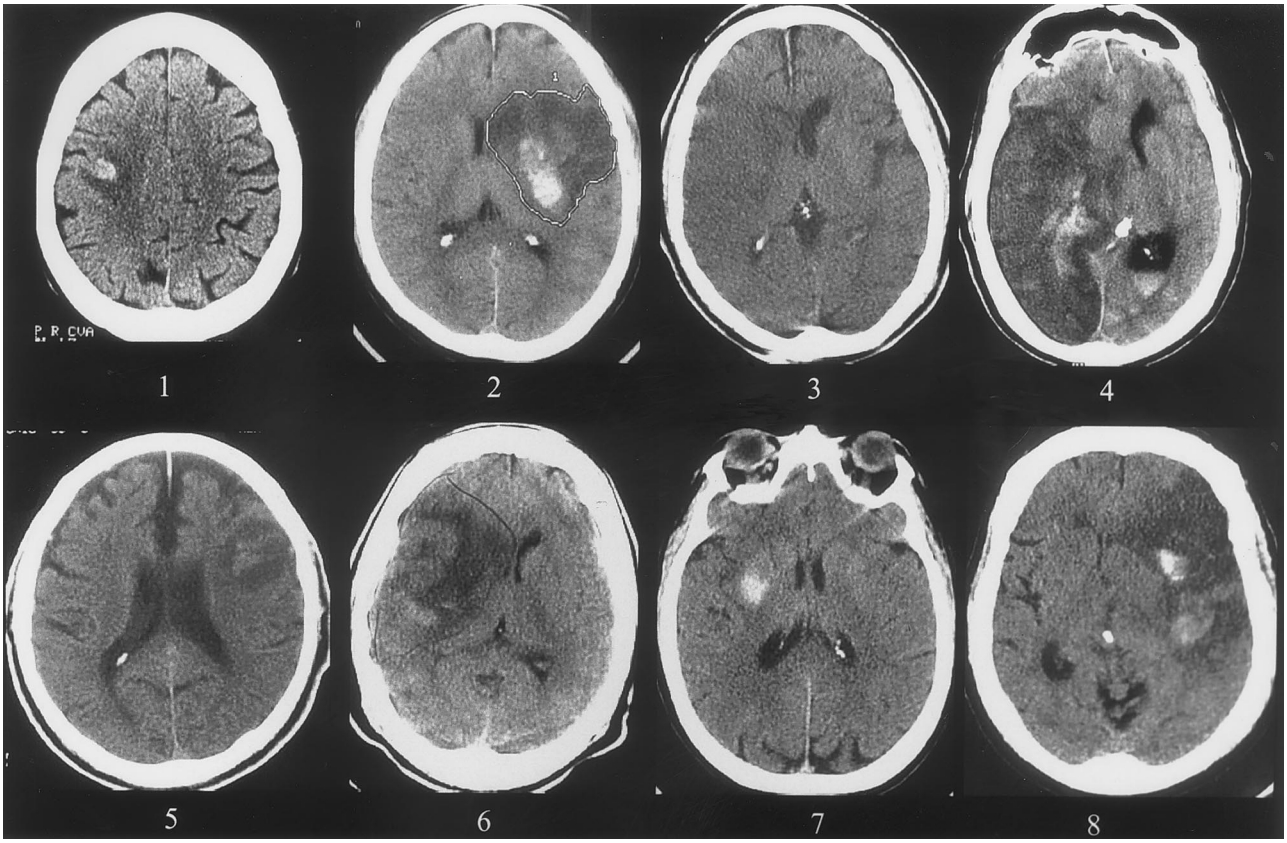

Figure 1. Representative sections of CT scans from all ICH.

required. All arteriograms were read centrally by an investigator blinded to the treatment group (T.A.T.).

Statistical Methods and Data Management

Data management and analysis were performed with the use of SAS (SAS Institute Inc). Baseline characteristics were tabulated and differences between the treatment groups were examined. The efficacy of r-TPA in the treatment of thromboembolic stroke was evaluated by comparing treatment groups and adjusting for baseline differences as necessary. Finally, an evaluation of the safety variables and adverse events was made.

Baseline characteristics were compared between treatment arms by use of the *t* test or Wilcoxon rank sum test for continuous variables, depending on the distribution of the variable, and χ^2 test was used to compare the treatment arms for the categorical variables.

The primary efficacy end point for r-TPA in this study, clinical improvement defined as a decrease of 7 or more points on the NIHSSS from baseline to 7 days (±24 hours) or a score of 0 to 1 at 7 days (±24 hours), was analyzed by use of the χ^2 test. Logistic regression was used to compare treatment arms after adjusting for baseline NIHSSS. Secondary end points are described above: (1) functional outcome was compared by use of the Wilcoxon rank sum test, (2) the rates of adverse events were compared by use of Fisher's exact test, and (3) the association of degrees of patency was examined by use of the χ^2 test for regression.

Laboratory values were tabulated, and values falling outside normal ranges were identified and verified. Descriptive summary statistics were computed and presented. Changes in key hematologic and coagulation determinations were computed and tested for differences from baseline values by ANOVA techniques. Differences between treatment groups were similarly examined.

The relation between the NIHSSS and the presence of clot by arteriography was studied with the use of logistic regression with receiver operator curve analysis and the Mantel-Haenszel χ^2 test.

Adverse events were listed by treatment group and by type of event. Incidences of key adverse events, including infarct hemorrhagic transformation and parenchymal hematoma, were identified and differences between treatment groups were tested as stated above.

Safety standards were established for significant bleeding. If the lower boundary of the 95% confidence interval of the significant bleed rate became ≥20% at any time during the study, the External Data and Safety Committee was to be convened to determine whether the study should continue.

A sample size of ≈30 patients was chosen. If an α level of 0.05 is assumed and 15 patients were in each arm, the power to detect a significant difference in efficacy between the 2 groups was low unless the expected difference was quite large. A study power of 80% would require a 30% response rate in the IV placebo and local IA r-TPA group and an 80% response rate in the combined IV and local IA r-TPA group. The power to detect a significant difference between the 2 groups in life-threatening bleeding complications was also low unless the expected difference was quite large. Thus the primary purpose of this study was to obtain experience and initial data for use in planning a much larger randomized study.

Results

Thirty-five patients were entered into the trial: 17 were randomly assigned to the combined therapy group (IV/IA) and 18 to the IV placebo and local IA group (placebo/IA). Median (25th, 75th percentiles) time from onset of symptoms to IV therapy was 2.6 (2.3, 2.8) hours in the combined treatment group and 2.7 (1.9, 2.9) hours in the placebo/IA groups. One patient did not undergo arteriography because of femoral artery access problems. None of the patients had the IA introducer sheath placed before completion of the 30-

TABLE 3. Arterial Patency in Those With Clot and Completed Angiogram

TIMI score	IV/IA* n=11	Artery	TPA dose, mg	Placebo/IA n=10	Artery	TPA dose, mg
0	0 (0%)			2 (20%)	M2, M1	20.0
1	2 (18%)	2-ICA	59±0.85	3 (30%)	M1, ICA, M1+ICA	20.0
2	3 (27%)	2-M1, M2	63.4±11.7	4 (40%)	2-M2, M1/2, BA	20.0
3	6 (54%)	3-M1, M1-d 2-M2	62.8±10.9	1 (10%)	ICA	20.0

ICA indicates internal carotid artery; M1, middle cerebral artery stem; M2, middle cerebral artery division; d, distal; BA, basilar artery.

*IV/IA group has better arterial patency by χ^2 for regression (P=0.03) with a central interpretation of the angiograms. One patient was not included because of an incomplete angiogram caused by an aortic dissection with the origin of the common carotid occluded.

minute IV infusion of r-TPA or placebo, although 1 patient had a femoral puncture during IV infusion and 1 patient had a femoral sheath in place from a cardiac catheterization. The arterial catheter could not be introduced into the site of the thrombus in 1 patient; therefore r-TPA was infused into the proximal artery as per protocol. The arterial catheter was pushed through more proximal stenosis to reveal more distal occlusions in 3 patients. The patients in the IV/IA group had a median time (25th, 75th percentile) of 3.3 (3.0, 3.8) hours from symptom onset to arteriography, and the patients in the placebo/IA group had a median time of 3.0 (2.4, 3.5) hours from symptom onset to arteriography (P=0.12). No patients were lost to follow-up.

Baseline Characteristics

Baseline characteristics were not different between the 2 groups for age, sex, race, incidence of hypertension, prior stroke, or incidence of diabetes. The IV/IA group had a higher median NIHSSS at baseline (NIHSS=16) than the placebo/IA group (NIHSS=11) (P=0.13; Table 1).

Outcome

There was no difference in the treatment groups in the primary clinical outcome as measured by the proportion of patients with a 7-point or greater improvement in the NIHSSS or a score of 0 or 1 at 7 days (24% for both groups). Further, there was no difference in the 90-day outcomes as measured by the median Barthel Index, Modified Rankin Score, or Glasgow Outcome Score (Table 2). Of the 21 patients completing IA therapy (irrespective of IV treatment), 33% had an NIHSSS of 0 to 1, 33% had a Rankin score of 0 to 1, and 38% had a Barthel Index of 95 to 100. Mortality was greater in the IV/IA group, with 5 deaths within 90 days compared with 1 death in the placebo/IA group (P=0.06). In the IV/IA group, 1 death was from an acute aortic dissection that presented as a stroke, 1 was from a patient with breast cancer who died 87 days after treatment, 1 was from a fatal myocardial infarction after a hemorrhage because the patient had pulled out the femoral sheath, 1 was from cerebral edema on day 2, and 1 was from an acute myocardial infarction on day 39; the death in the placebo group was related to acute renal failure 38 days after randomization.

Safety

Life-threatening and ultimately fatal bleeding complications occurred in 2 patients, both in the combined treatment arm: As referred to above, 1 patient had an aortic dissection that presented as a stroke and later hemopericardium, and 1 patient had an acute myocardial infarction after bleeding from pulling out the femoral sheath.

All ICH (n=8) that occurred were HI; no PH occurred in this study (Figure 1). Symptomatic ICH within 24 hours occurred in 1 patient from the placebo/IA treatment arm but none in the IV/IA arm. Symptomatic ICH, beyond the initial 24 hours, occurred as a hemorrhagic infarction in 2 patients in the combined treatment arm. There was no difference between the groups in the rate of symptomatic ICH at the predefined end point of 24 hours (0% IV/IA vs 5.5% placebo/IA, P=0.32) or at 72 hours (11.8% IV/IA vs 5.5% placebo/IA, P=0.51). Asymptomatic ICH occurred in 4 patients in the IV/IA group and 1 patient in the placebo/IA group.

Other moderate to severe bleeding complications occurred at similar rates (P=0.26) involving 2 IV/IA patients, both with groin oozing, and 1 placebo/IA patient with hematuria. Fifteen other mild bleeding events occurred in 7 patients, all in the combined treatment arm. These included 6 episodes of groin hematoma or oozing in 5 patients, 3 episodes of IV site oozing or hematoma in 2 patients, hematuria in 3 patients, gingival oozing in 2 patients, and a mild gastrointestinal bleed in 1 patient. Overall, other bleeding events were more frequent in the IV/IA group (P=0.02).

Arterial Recanalization, r-TPA Dose, and Time to Lysis

Clot was found in 22 of 34 patients who underwent arteriography and was in the appropriate distribution of the clinical stroke in all. Arterial recanalization was better in the IV/IA group compared with the placebo/IA group, as measured by TIMI 3 flow at 2 hours (6 of 11 or 54% vs 1 of 10 or 10%, P=0.03). Nine of 14 patients with TIMI 2 or 3 flow were in the combined treatment arm (Table 3).

The average IV dose of r-TPA given to the 17 patients in the IV/IA group was 45.6 mg, and the IV/IA group also received a mean dose of 11.0 mg of r-TPA IA. The placebo/IA group

TABLE 4. Patient Summary

Patient No.	Clot Location	TIMI Flow	NIHSSS Baseline	NIHSSS 7–10 d	Rankin 90 d	ICH sx/asx, time	Death by 90 d
Placebo/IA Group							
1	M2	2	9	3	2		No
2	None		9	1	1		No
3	M1/M2	2	7	16	2		No
4	None		8	7	1		No
5	ICA/M1	1	13	12	5	asx HI, 34 h	No
6	None		13	4	3		No
7	No angio		9	4	1		No
8	ICA	3	23	14			Yes (38 d)
9	None		11	1	1		No
10	Basilar	2	20	4	1		No
11	None		7	5	2		No
12	ICA/M1	1	19	21	3		No
13	M2	2	11	3	1		No
14	None		11	10	3		No
15	M1	1	16	13	5	sx HI, 5 h	No
16	M2	0	17	NA	0		No
17	None		7	3	0		No
18	M1	0	10	1	1		No
Combined IV/IA Group							
19	M2	3	7	1	0		No
20	None		9	2	NA	asx HI, 10 d	Yes (87 d)
21	M1	3	23	15	2	sx HI, 34 h	No
22	None*		8	6	1		No
23	None*		6	5	1		No
24	CCA	0	31	35*	NA		Yes (0 d)
25	None		14	8	4		No
26	ICA/M1	1	19	35*	NA	sx H1, 31 h	Yes (2 d)
27	M2	3	11	3	1	asx HI, 80 h	No
28	M1	3	20	7	NA		Yes (39 d)
29	M1	3	20	7	3	asx HI, 61 h	No
30	M2	2	9	0	1		No
31	None		12	2	1		No
32	M1	3	22	15	3		No
33	ICA/P1	1	21	35*	NA		Yes (1 d)
34	M1	2	27	28	5	asx HI, 64 h	No
35	M1	2	16	15	2		No

*Patients who died before the 7- to 10-day NIHSSS were the highest, worst-possible score of 35.

received a mean IA dose of 11.1 mg. Patients without a clot at angiography received no IA TPA. The total r-TPA dose was significantly greater in the IV/IA group (mean dose of 56.6 mg for the IV/IA group and 11.1 mg for the placebo/IA group, $P=0.001$). The recanalization as measured by TIMI score correlated to the total dose of r-TPA given (correlation coefficient 0.36, $P=0.05$) (Table 3). The mean r-TPA dose given to patients with clot on initial arteriography and final flow of TIMI 0 was 20 mg but was 35.6±21.4 mg for those with TIMI 1 flow, 38.6±24.2 mg for those with TIMI 2 flow, and 56.7±19.0 mg for those with TIMI 3 flow.

There were no significant differences in the time intervals from symptom onset to clot lysis between the groups. For those patients with clot at arteriography, the mean time from symptom onset to clot lysis was 6.3±1.0 hours for the IV/IA group and 5.6±1.0 hours for the placebo/IA group ($P=0.22$). The mean time from the start of the IV infusion to clot lysis was 3.1±0.6 hours for the placebo/IA group and 3.7±1.0

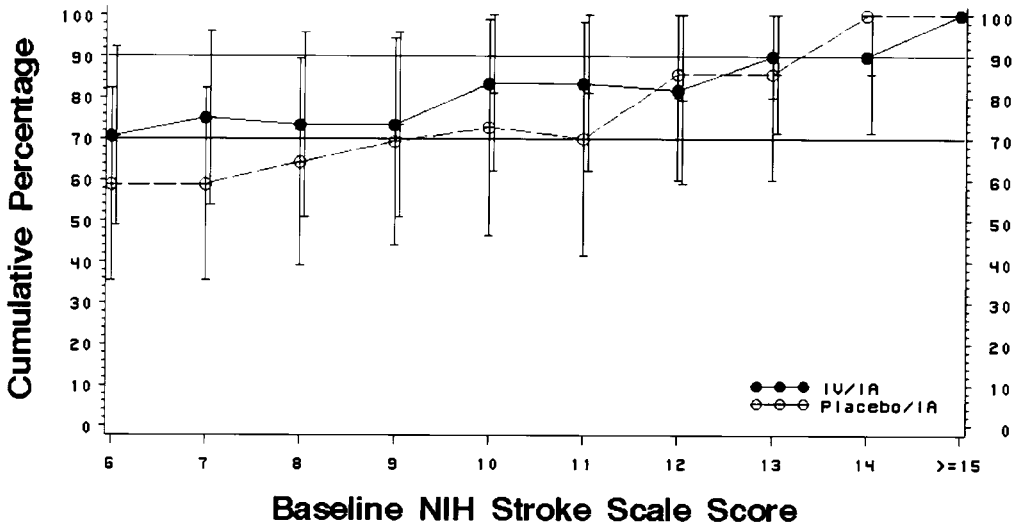

Figure 2. Reading left to right, cumulative percentage refers to the percentage of patients for a given NIHSSS or higher with a clot identified that was consistent with the presenting symptoms. For example, 70% of the IV placebo-IA TPA patients with an NIHSSS of 9 or higher had such a clot.

hours for the IV/IA group ($P=0.14$). The mean time from the start of IA treatment to clot lysis was 1.8±0.9 hours for the placebo/IA group and 1.7±0.9 hours for the IV/IA group ($P=0.84$).

NIHSSS and Frequency of Clot

There was a direct relation between the baseline NIHSSS and the likelihood of presence of clot ($P=0.007$) on initial arteriography (Table 4). For an increase by 1 point in the NIHSSS, the odds ratio for presence of clot was 1.37 (95% CI 1.09, 1.73) (Figure 2). This relation also was present with the use of specific cutpoints ($P=0.001$). All patients with a baseline NIHSSS ≥15 were found to have appropriate clots; 4 (44%) of 9 patients with NIHSSS of 10 to 14 had clots, and 4 (36%) of 11 patients with NIHSSS 5 to 9 had clots.

Discussion

This pilot study demonstrates the feasibility of treatment of patients within 3 hours of onset of acute ischemic stroke symptoms with a combined regimen of IV followed by local IA r-TPA. Despite this success, neurological outcome was not improved compared with IA treatment alone, but inference is limited because of a small numbers of patients, an excess of adverse events unrelated to treatment assignment in the combined treatment arm, and an imbalance of randomization such that patients with larger neurological deficits at baseline were more prevalent in the combined treatment arm.

The safety of a combined approach was acceptable in this small pilot study. The rate of symptomatic ICH was 6%, which is similar to the rate of the NINDS study.[3] There was no difference in the rate of symptomatic ICH between the 2 treatment groups despite a higher mortality rate in the combined treatment arm. There were several serious adverse events in the combined treatment group that were not judged to be directly related to the combined approach but contributed to the increase in mortality rate and reduced likelihood of recovery. These events included patients with the following problems: a patient with an acute aortic dissection presenting as an ischemic stroke and development of a fatal hemopericardium after IV r-TPA, a patient who removed her femoral sheath, which caused enough blood loss to precipitate myocardial infarction and arrest, and a patient who died of breast cancer late in the follow-up period. Because of these complexities, and because of the small sample size and insufficient power with regard to our safety end points, we can make no firm conclusions with regard to safety.

No difference was found between the 2 groups in the frequency of IA thrombus at the time of initial arteriography. The higher NIHSSS in the combined group probably indicated a greater clot burden, reducing the likelihood of a normal arteriogram after IV r-TPA. Likewise, there was no difference in patency after IV treatment between the 2 treatment groups as manifested by frequency of normal initial arteriograms. Despite this, the frequency of reperfusion was better for the patients in the combined arm who were found to have clot compared with patients who were not pretreated with IV r-TPA and subsequently received IA r-TPA. This suggests that a combined approach might be particularly applicable for patients with persistent thrombus after IV r-TPA.

Prolyse in acute cerebral thromboembolism trial (PROACT-1),[13] the largest randomized study that has been published on intra-arterial thrombolysis for patients with acute ischemic stroke randomly assigned with a M1 or M2 thrombus, showed that the rate of recanalization was higher for patients treated with direct infusion of pro-urokinase than in the control patients. Applying the PROACT criteria to the present study yields 9 patients in the combined arm and 6 in the control group who would have met the criteria for treatment. Partial or complete reperfusion was obtained for all 9 patients in the combined arm and only 3 of the patients in the control group in our study. Thus it appeared that this combined IV/IA approach might be useful for patients with these neurovascular findings.

This is the first study to show that the presence of thrombus in a major cerebral artery is directly related to the NIHSSS in

patients with acute ischemic stroke symptoms. A previous pilot study suggested this might be the case on the basis of observations of posttreatment arteriography.[15] Recent studies with cerebral arteriography in the first few hours after ischemic stroke have found occlusion in 76% to 81% of the patients.[13,14] In the EMS Bridging Trial, all patients with a score >15 had an occluding thrombus found at the time of arteriography. Thus it appears that the NIHSSS is a useful tool for predicting the likelihood of an occluded artery in this setting.

The EMS Bridging Trial was a pilot study that showed that patients treated with combined IV and IA r-TPA were more likely to have partial or complete reperfusion of an occluded intracerebral artery, although this was not associated with an improved clinical outcome by prespecified measures. Furthermore, the numbers of symptomatic ICH were similar between the 2 groups, which suggests that this approach is technically feasible and may be safe. Additional study is needed to determine the safety and effectiveness of this new method of treatment for acute ischemic stroke. Such studies should address not only efficacy and safety but also the cost-benefit ratio and quality of life, given the major investment in time, personnel, and equipment required by combined IV and IA techniques.

Appendix

EMS Clinical Sites and the EMS Bridging Trial Investigators (in order of recruitment): *Henry Ford Hospital (10):* C. Lewandowski, S. Levine, G. Tokarski, W. Sanders, B. Mehta, P. Mitsias, M. Gorman, C. Gymnopoulos, L. D'Olhaberriague, R. Dafer, G. Tietjen, D. Morris, S. Grover, S. Daley, P. Booker. *Emory University (7):* M. Frankel, R. Dawson, S. Sailor, J. Braimah. *University of Cincinnati (7):* T. Brott, J. Broderick, T. Tomsick, J. German, R. Kothari, R. Gregg, J. Braunlin, J. Spilker, R. Cornelius, R. Ernst, M. Gaskill-Shipley. *Barrow Neurological Institute (4):* J. Frey, B. Dean, N. Borden, J. Zabramski, J. Hodak, R. Flom, C. Black, D. Coffman, D. Dungan, S. Rand, P. Ricci, J. Minor. *Oregon Health Sciences University (3):* W. Clark, S. Barnwell, B. Coull, M. Wynn, J. Quinn, K. Kearns. *University of California at Los Angeles (2):* S. Starkmann, J. Saver, F. Vinuela, G. Duckwiler, G. Schubert, Y.P. Gobin. *University of Texas–Houston (2):* J. Grotta, L. Morgenstern, D. Chiu, R. Rizzo, M. Young.

Concept Consultants: Robert Ferguson, Andrew Ku, Richard Latchaw, Patrick Lyden, Dennis Landis, and Robert Tarr.

External Data and Safety Monitoring Committee: E. Clark Haley, University of Virginia; Jacques Dion, University of Virginia; and Harold P. Adams, University of Iowa.

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