Combined Intravenous and Intra-Arterial Recanalization for Acute Ischemic Stroke: The Interventional Management of Stroke Study

The IMS Study Investigators

Background and Purpose—To investigate the feasibility and safety of a combined intravenous (IV) and intra-arterial (IA) approach to recanalization in patients with ischemic stroke.

Materials and Methods—Subjects ages 18 to 80 with an NIH Stroke Scale (NIHSS) ≥10 at baseline had IV recombinant tissue plasminogen activator (rt-PA) started (0.6 mg/kg, 60 mg maximum over 30 minutes) within 3 hours of onset. Additional rt-PA was then administered via microcatheter at the site of the thrombus up to a total dose of 22 mg over 2 hours of infusion or until thrombolysis. Primary comparisons were with similar subsets of placebo and rt-PA–treated subjects from the NINDS rt-PA Stroke Trial.

Results—The 80 subjects had a median baseline NIHSS score of 18. The median time to initiation of IV rt-PA was 140 minutes as compared with 108 minutes for placebo and 90 minutes for rt-PA–treated subjects in the NINDS rt-PA Stroke Trial. The 3-month mortality in Interventional Management Study (IMS) subjects (16%) was numerically lower but not statistically different than the mortality of placebo (24%) and rt-PA–treated subjects (21%) in the NINDS rt-PA Stroke Trial. The rate of symptomatic intracerebral hemorrhage (6.3%) in IMS subjects was similar to that of rt-PA–treated subjects (6.6%) but higher than the rate in placebo-treated subjects (1.0%, P=0.018) in the NINDS rt-PA Stroke Trial. IMS subjects had a significantly better outcome at 3 months than NINDS placebo-treated subjects for all outcome measures (odds ratios ≥2).

Conclusions—A randomized trial of standard IV rt-PA as compared with a combined IV and IA approach is needed.

Key Words: tissue plasminogen activator ■ thrombolytic therapy ■ controlled clinical trials

Intravenous (IV) recombinant tissue plasminogen activator (rt-PA) within 3 hours of stroke onset is the first and currently only FDA-approved therapy for acute ischemic stroke. Treatment of ischemic stroke with intravenous (IV) recombinant tissue plasminogen activator (rt-PA) may be life changing if recanalization is achieved. In angiographic controlled pilot trials of IV rt-PA, the rate of recanalization of major arterial occlusions with IV rt-PA is low, with partial or complete recanalization of only 10% of occluded internal carotid arteries and 25% of occluded proximal middle cerebral arteries.1–3 A pilot trial of IV t-PA using transcranial Doppler to monitor vascular patency has reported higher rates of early recanalization and early reoclusion in some patients. In addition, in the National Institute of Neurologic Disease and Stroke (NINDS) rt-PA Stroke Trial, only 10% of patients with a severe deficit (NIH Stroke Scale [NIHSS] >20) who received IV rt-PA had minor or no functional disability at 3 months as compared with 2% of placebo-treated patients.

Intra-arterial (IA) interventions for acute ischemic stroke have been touted as superior to IV rt-PA in their ability to recanalize major intracranial arterial occlusions.5 In the PROACT II Trial, 40% of the 121 subjects treated with IA recombinant pro-urokinase (r-proUK) and IV heparin within 6 hours of onset achieved a Rankin of 0 to 2 at 3 months as compared with 25% of the 59 subjects treated with IV heparin alone.5 Of the subjects treated with IA r-proUK, 20% had total recanalization of a middle cerebral artery occlusion, and an additional 46% had partial recanalization. However, the median time to start of IA therapy was 5.3 hours, and recanalization, when it occurred, often happened >7 hours after stroke onset.

Such a long delay to initiation of recanalization limits the effectiveness of IA therapy. Randomized trials of IV rt-PA have demonstrated that the effectiveness of rt-PA is strongly dependent on the time to start of therapy, with the greatest benefit occurring in subjects who have treatment started within 90 minutes.6 The concept of combining the advantages of IV rt-PA (speed of initiation and widespread availability)
and IA recanalization (titrated dosing, mechanical aids to recanalization, and possible superior and earlier recanalization) was first explored in a small pilot study of 35 subjects, The Emergency Management of Stroke (EMS) Study. Several subsequent case series have reported encouraging results using a combined IV and IA approach. Based on these results, the Interventional Management of Stroke (IMS) Study, funded by the NINDS, began in 2001. The goal of this study was to further investigate the feasibility and safety of a combined IV and IA approach to recanalization.

Materials and Methods
The IMS Study is a 17-center, open-labeled, single-arm pilot study. The IMS Study was designed to investigate the feasibility and safety of a combined IV and IA approach to recanalization using rt-PA in 80 subjects with ischemic stroke. Primary pre-specified comparisons of IMS subjects to historical subjects in the NINDS rt-PA Stroke Trial with similar age and baseline NIHSS scores were performed.

Inclusion and exclusion criteria are listed in Table I (available online at http://stroke.ahajournals.org). To maximize early treatment of subjects, each treatment center was mandated to begin IV rt-PA within 2 hours of onset in at least 2 subjects of each 7-patient block (rule of two). The protocol was approved by the Institutional Review Board at each participating center.

Study Protocol
After all inclusion and exclusion criteria had been met and informed consent was obtained, subjects received IV rt-PA (Activase 0.6 mg/kg, 60 mg maximum, 15% of the dose as a bolus over 1 minute with the remainder administered over 30 minutes) followed by immediate cerebral angiography (Figure 1). The IV dose and protocol were the same as that used for the earlier EMS study except for the bolus dose, which was increased from 10% to 15%. The reason for slightly increasing the percentage administered as a bolus in the IMS Study was to make the bolus equivalent to the total IV bolus of rt-PA used for the NINDS rt-PA Stroke Trial.

If a thrombus was identified in an appropriate intracranial artery such as the middle cerebral artery, anterior cerebral, posterior cerebral artery, or basilar artery, then no further injections were administered and IA thrombolytic therapy was initiated immediately, as per the following protocol. If the patient did not have an occlusion in the vascular territory appropriate for the patient’s symptoms, then no IA rt-PA was administered and the angiographic procedure was terminated. See online journal article for complete angiographic protocol.

After initiation of IV rt-PA therapy, the subject was transported immediately to the neuro-angiography suite. The femoral artery was
punctured using a Seldinger single wall and/or micropuncture technique by an experienced interventionist. An appropriate size sheath (5 French to 7 French) was placed into the accessed femoral artery, and the sheath side arm was connected to a continuous heparinized saline flush (1000 U/1000 mL 0.9% normal saline) at 30 mL/h. The sheath was sutured in place to prevent inadvertent dislodgement.

A diagnostic 4-French to 7-French catheter was then placed through the sheath and advanced under fluoroscopic guidance into the symptomatic artery. If the suspected distribution of ischemia was in the carotid artery, then injection into the common carotid artery was performed to examine the carotid bifurcation. If it was technically difficult to gain safe access of the high cervical internal carotid artery, then the catheter could be left in the common carotid artery. If a carotid occlusion was identified, with failure to opacify the carotid terminus, then the opposite carotid artery and/or vertebral artery was injected to identify collateral flow. If the suspected arterial distribution was the vertebral basilar system, then selective injection of one or both vertebral arteries was performed.

A 2000-unit bolus of IV heparin was administered once the thrombus was identified and the decision was made to administer IA rt-PA. A heparin infusion was maintained at 450 U per hour during the IA study drug infusion and was discontinued at the end of the procedure. A heparin flush solution (approximately 40 U of heparin per hour) was administered via access sheath and the guide catheter was retracted into the thrombus, and 2 mg of rt-PA was injected over 2 minutes directly into the thrombus. Infusion of rt-PA was then started at the rate of 9 mg/h for up to 2 hours of infusion time using an infusion pump. Two centers used a pulse-spray technique approximating the rate of 9 mg/h for up to 2 hours of infusion time using an infusion pump. Two centers used a pulse-spray technique approximating the rate of 9 mg/h for up to 2 hours of infusion time using an infusion pump. Two centers used a pulse-spray technique approximating the rate of 9 mg/h for up to 2 hours of infusion time using an infusion pump. Two centers used a pulse-spray technique approximating the rate of 9 mg/h for up to 2 hours of infusion time using an infusion pump.

Figure 2. IMS patient flow.

A 2.3-French tapered, variable stiffness, end-hold rapid transit or proximal microcatheter was then passed over the micro-guidewire to the level of occlusion. IA rt-PA had to begin within 5 hours of symptom onset. Two mg of rt-PA was injected through the catheter over 2 minutes beyond the thrombus. The catheter was then retracted into the thrombus, and 2 mg of rt-PA was injected over 2 minutes directly into the thrombus. Infusion of rt-PA was then started at the rate of 9 mg/h for up to 2 hours of infusion time using an infusion pump. Two centers used a pulse-spray technique approximating the infusion rate. Repeat arteriogram was performed every 15 minutes after the start of infusion, using isomolar contrast. If at the time of the repeat arteriogram the vessel was not patent or had recanalized partly, then the catheter could be introduced further into the vessel for additional thrombus access. The guidewire and microcatheter could also be passed through the thrombus every 15 minutes. The infusion was continued for a maximum of 2 hours or until thrombolysis was achieved. The patient’s neurologic function was evaluated every 15 minutes during the intra-arterial (IA) procedure. If the arterial catheter could not be maneuvered to the site of the thrombus, then rt-PA at the same dose was selectively infused into the artery proximal to the site of the thrombus (regional infusion). The total maximum dose of rt-PA (both IV and IA) in the study was 82 mg as compared with a maximum dose of 90 mg in the NINDS rt-PA Stroke Trial.

If the patient had a significant stenosis or occlusion of the internal carotid, vertebral, or basilar arteries proximal to occlusive thrombus, then the stenosis/occlusion could be traversed with the microcatheter to approach a distal occlusive thrombus.

Termination of the IA treatment procedure occurred if there was: (1) arteriographic mass effect that could not be explained by early edema; (2) suspicion of extravasation of contrast suggesting vessel rupture; (3) CT demonstration of hemorrhage (ie, for a patient whose condition deteriorates and the procedure is interrupted for a CT, the procedure could be re-started if the CT shows no hemorrhage); (4) worsening of clinical deficit that was not explained by arteriographic findings; (5) seizure; (6) achievement of thrombolysis in myocardial infarction (TIMI) 3; or (7) 120 minutes of IA infusion of rt-PA that had occurred. IA infusion of rt-PA was to be discontinued beyond 7 hours from symptom onset. No angioplasty or stenting procedure was allowed as part of the protocol. In addition to these criteria for stopping IA rt-PA, investigators were also allowed to apply clinical judgment in determining when to stop IA therapy based on the perceived risks and benefits.

Medical Management and Evaluation (See Online Journal Version)

Medical management of subjects enrolled into the study followed the National Institute of Neurologic Disease and Stroke (NINDS) rt-PA Stroke Trial protocol.11 An NIH Stroke Scale (NIHSS)12 to 14 was performed in every patient at baseline, immediately before initiation of IV rt-PA, after completion of IA rt-PA therapy, at 24 ± 6 hours, at 5 days, or at discharge from hospital, and 90 ± 7 days after the stroke. In addition, a modified Rankin scale (MRS)15 to 17 to indicate the patient’s functional status before the qualifying stroke (pre-event) was obtained at baseline. Functional outcome at 3 months was assessed by the Barthel index,11 the MRS,15 and the Glasgow Outcome Scale.16
Primary Measures of Safety and Outcome
The primary safety measure of the study was life-threatening bleeding complications during the first 36 hours after completion of rt-PA infusion, as it was for the NINDS rt-PA Stroke Trial.11,17 A significant life-threatening bleeding complication was defined as: (1) development of intracerebral hematoma or hemorrhagic infarction with clinical deterioration likely to result in permanent disability or death; or (2) other severe systemic bleeding complications such as groin hematoma, retroperitoneal hematoma, or gastrointestinal bleeding requiring transfusion of ≥3 units of blood replacement or major surgical intervention. Intracerebral hematomas were classified radiographically according to the method used by Von Kummer et al in the ECASS Trials: parenchymal hematoma (PH)-1, PH-2, hemorrhagic infarction (HI)-1, and HI-2 (see Table 3 for definitions).18

The primary measure of outcome for this pilot study was a modified Rankin scale (MRS) of 0 or 1 at 3 months. Secondary efficacy endpoints included: (1) patient outcome as measured by the MRS (with favorable outcome defined as 0 to 2 at 3 months); (2) NIHSS (with favorable outcome defined as NIHSS score ≤2) at 24 hours; (3) the rate of recanalization (thrombolysis in myocardial infarction [TIMI] grades 2 or 3) at completion of angiography; (4) other favorable patient outcomes as measured by Barthel index score of 95 to 100, Glasgow Outcome Scale score of 0 to 1, and NIHSS score of 0 or 1; (5) quality of life at 3 months as defined by the EuroQol scale;19 and (6) global outcome endpoint that included the MRS, NIHSS, Barthel index, and Glasgow Outcome Scale at 3 months. The NINDS Data Safety Monitoring Committee reviewed all safety and outcome results of the IMS Study.

Statistical Methodology
The purpose of this pilot study was to assess the safety and outcome of combined IV and IA therapy to determine if it is futile to proceed to a larger randomized trial. For our sample size estimation, we used the proportions of successful outcomes obtained from subsets of placebo and rt-PA–treated subjects from parts I and II of the NINDS rt-PA Stroke Trial whose ages were 18 to 80 with a baseline NIHSS score ≤23. These included the NIHSS score, time to treatment, and age. We also performed a secondary logistic regression analysis that included other variables that were significantly different between IMS subjects and the comparison groups from the NINDS rt-PA Stroke Trial.

A global test24 (using the 4 primary outcome measures in the NINDS rt-PA Stroke Trial) was also performed, again adjusting for baseline co-variates.

With the exception of the primary analysis of the proportion of successful outcome (MRS=0 or 1), interpretation of P values should be made with caution because multiple analyses, considered exploratory, were performed.

Results
The IMS Study began enrollment at the first IMS center on January 31, 2001. The last of the 17 centers became eligible for enrollment on May 7, 2001; 1477 subjects were screened to enroll the pre-specified 80 subjects. Study recruitment was completed on October 23, 2001, approximately 14 months earlier than expected. Seventy-nine of the subjects continued participation as planned. One patient was lost to follow-up after the 7-day follow-up had been completed.

Of the 80 subjects (40 men), there were 64 whites, 7 blacks, 4 Hispanics, 4 Asians, and 1 Middle Easterner. Flow of subjects in the study is presented in Figure 2.

Twenty-nine of the 80 subjects had IV rt-PA started within 2 hours of stroke symptom onset, and the median time to initiation of IV rt-PA was 140 minutes, as shown in Table 1. Of the 80 patients, 13 had IV t-PA started at a community hospital and were then transferred to the tertiary center. The mean time to start of IV t-PA in these 13 patients was 134 minutes (SD=26 minutes) and the mean time to start of IA t-PA was 231 minutes (SD=30). Twelve of the 80 patients were evaluated at a community hospital and then transferred to the referral hospital for start of IV t-PA therapy. The mean time to start of t-PA was in these patients was 169 minutes (SD=14), with a mean delay of 35 minutes compared with those in whom IV t-PA was started before transfer. Fifty-five patients presented to the tertiary hospital. The mean time to treatment with IV t-PA was 130 minutes (SD=30). Table 1 also summarizes the time to angiography, and time to initiation of IA rt-PA. The mean total dose of rt-PA for IMS subjects (59 mg; SD=14.4) was significantly less than the dose of IV rt-PA in subjects treated as part of the NINDS rt-PA Stroke Trial (69 mg; SD=13.5; P<0.0001).

### Table 1. Time to Treatment in the IMS Study

<table>
<thead>
<tr>
<th>Time Point</th>
<th>No. of Subjects</th>
<th>Time (min) (mean±SD)</th>
<th>Time (min) (median±intermedian quartiles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom onset to IV rt-PA</td>
<td>80</td>
<td>136±30.2</td>
<td>140 (110, 158)</td>
</tr>
<tr>
<td>Symptom onset to angiogram</td>
<td>77</td>
<td>183±45.4</td>
<td>180 (150, 209)</td>
</tr>
<tr>
<td>Symptom onset to IA rt-PA</td>
<td>62</td>
<td>217±46.7</td>
<td>212 (180, 250)</td>
</tr>
</tbody>
</table>

### Table 2. Safety Results: IMS and NINDS rt-PA Trial Cohorts (Ages 18-80 and Baseline NIHSS≥10)

<table>
<thead>
<tr>
<th></th>
<th>IMS Study (n=80)</th>
<th>NINDS Placebo (n=211)</th>
<th>P Value*</th>
<th>NINDS rt-PA (n=182)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality at 3 mo</td>
<td>13/80 (16%)</td>
<td>50/211 (24%)</td>
<td>0.17</td>
<td>39/182 (21%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Symptomatic ICH ≤36 h</td>
<td>5/80 (6.3%)</td>
<td>2/211 (1.0%)</td>
<td>0.018</td>
<td>12/182 (6.6%)</td>
<td>0.91</td>
</tr>
<tr>
<td>PH2 ICH ≤36 h</td>
<td>6/80 (7.5%)</td>
<td>1/211 (0.5%)</td>
<td>0.002</td>
<td>6/182 (3.4%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Asymptomatic ICH ≤36 h</td>
<td>34/80 (43%)</td>
<td>12/211 (5.7%)</td>
<td>&lt;0.0001</td>
<td>11/182 (6.0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serious systemic bleeding events ≤36 h</td>
<td>3%</td>
<td>0.5%</td>
<td>0.18</td>
<td>1%</td>
<td>0.58</td>
</tr>
</tbody>
</table>

*P value from χ² test comparing IMS to NINDS–placebo. †P value from χ² test comparing IMS to NINDS–IPA. ‡Includes subjects categorized as hyperdense infarcts in the NINDS rt-PA Stroke Trial that are categorized as HI in IMS Study.
Table II (available online at http://stroke.ahajournals.org) compares the baseline characteristics of the IMS subjects and the placebo and rt-PA-treated cohorts from the NINDS rt-PA Stroke Trial. IMS subjects were more likely to have early CT changes on the baseline CT, atrial fibrillation, a higher baseline systolic blood pressure, and lower baseline serum glucose; they were less likely to be black and to have a previous myocardial infarction. IMS subjects had IV rt-PA begun significantly later (median 140 minutes) as compared with placebo (108 minutes) and rt-PA–treated subjects (90 minutes) in the NINDS rt-PA Stroke Trial.

The 3-month mortality in IMS subjects was numerically lower but not statistically different than the mortality of placebo and rt-PA–treated subjects in the NINDS rt-PA Stroke Trial (Table 2). Seven of the 13 deaths in IMS subjects occurred within 7 days. One was judged to be definitely related (1) and one remotely related to study drug or procedure. Both were subjects with symptomatic intracerebral hemorrhage (ICH). Five deaths were related to the severity of the initial stroke.

Four deaths occurred between 7 and 30 days. Of these, one was judged as probably related and another possibly related to the study drug or procedure. Both were subjects with symptomatic ICH. The third death was related to a new ischemic stroke that occurred 9 days after therapy, and the fourth patient’s death occurred at 19 days and was related to the severity of the initial stroke. The 2 deaths between 30 and 90 days were related to cardiac causes (severe aortic stenosis).

The rates of symptomatic intracerebral hemorrhage, PH2 intracerebral hemorrhages, and severe systemic hemorrhage in IMS subjects were similar to those of rt-PA–treated subjects in the NINDS rt-PA Stroke Trial (Tables 2 and 3, Figure 3). The rate of symptomatic intracerebral hemorrhage was higher than the rate in placebo-treated subjects in the NINDS rt-PA Stroke Trial. The rate of asymptomatic intracerebral hemorrhage in IMS subjects was higher than the rate of asymptomatic intracerebral hemorrhage in the rt-PA–treated subjects in the NINDS rt-PA Stroke Trial.

Procedure-related complications included 2 pseudoaneurysms at the puncture site. One of these events was considered severe because it resulted in a retroperitoneal hematoma that required transfusion of 3 units of packed red cells. Three other complications at the groin site included “severe” oozing or hematomas. One patient had a retroperitoneal hematoma that required transfusion of 3 units of packed red cells; the second patient had a groin hematoma and other sites of oozing that required 2 units of packed red cells; and the third patient had severe oozing at the groin site that did not require transfusion.

### TABLE 3. Categorization of Intracerebral Hemorrhages IMS Study by ECASS Criteria

<table>
<thead>
<tr>
<th>CT Scan Hemorrhage Score Within 36 Hours — IMS Study</th>
<th>CT Images</th>
<th>Symptomatic</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>HI type 1 Small petechiae along margin of the infarct</td>
<td>10</td>
<td>—</td>
<td>10</td>
</tr>
<tr>
<td>HI type 2 More confluent petechiae within the infarcted area but without space-occupying effect</td>
<td>10</td>
<td>—</td>
<td>10</td>
</tr>
<tr>
<td>PH type 1 Hematoma in &lt;30% of the infarcted area with some slight space-occupying effect</td>
<td>13</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>PH type 2 Dense hematoma &gt;30% total of the infarcted area with substantial space-occupying effect or as any hemorrhagic area outside the infarcted area</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>5</td>
<td>34</td>
</tr>
</tbody>
</table>

Figure 3. Five subjects with symptomatic ICH in the IMS Study.
Two additional severe bleeding events required transfusion. One occurred in a patient with a gastrointestinal hemorrhage of an undetermined source that resulted in transfusion 21 days after rt-PA administration. Another similar event, anemia of undetermined origin, also required transfusion of 3 units of packed red cells. This patient experienced a severe transfusion reaction.

Three suspected vessel perforations of occluded middle cerebral arteries occurred during the angiographic procedure (contrast extravasation) without subsequent documentation of intracranial bleeding. Two perforations occurred in the M1 segment of the middle cerebral artery and were thought to be related to blind navigation secondary to the pathologic thrombus. No IA rt-PA was administered in these 2 subjects. A third perforation involved the posterior division of the middle cerebral artery and was related to patient movement. This patient had received 8.5 mg of rt-PA intra-arterially before ending the procedure after extravasation of contrast was noted. All 3 cases are reported as asymptomatic ICHs.

There were 4 recurrent strokes (see online article for details). Two of these recurrent strokes were intracerebral hemorrhages. The first occurred on day 20 after carotid endarterectomy for severe carotid stenosis in the distribution of the original stroke. The second intracerebral hemorrhage occurred on day 64 when the patient had an international normalized ratio (INR) of 6 while administered Coumadin. The 2 new ischemic strokes occurred on day 1 and day 8. Four subjects underwent hemicraniektomy because of severe brain edema and mass effect. Mild angioedema occurred in 1 patient.

During the first 24 hours after enrollment, muscle relaxants were administered to 16 (20%) of the 80 subjects, and 57 (71%) received sedative medications. Study investigators at the 24-hour NIHSS assessment, a secondary efficacy endpoint, noted that 7 (9%) of the subjects in the population had an assessment that was affected by sedation and/or muscle relaxant medications.

IMS subjects had a better outcome than NINDS placebo-treated subjects for the primary outcome measure (MRS of 0 or 1 at 3 months, Table 4). IMS subjects also had a better outcome by all secondary measures after adjustment for baseline NIHSS, age, and time to treatment (Table 4). IMS subjects had a similar 3-month outcome as compared with subjects treated with rt-PA in the NINDS rt-PA Stroke Trial, although odds ratio trended in favor of IMS subjects (Table 4). There was no statistically significant difference in any outcome measure for those patients treated at the top 3 enrolling sites versus all other sites.

Of the 77 subjects who underwent an angiographic procedure, 28 had major occlusions or high-grade stenoses of the internal carotid artery in addition to distal disease in the middle cerebral artery and its branches. For the 62 subjects who received IA rt-PA in addition to IV t-PA, the rate of complete recanalization (TIMI 3 flow) was 11% (7/62) and the rate of partial or complete recanalization (TIMI 2 or 3 flow) was 56% (35/62) after a maximum of 2 hours of infusion (see Table III for data concerning sites of occlusion and recanalization; available online at http://stroke.ahajournals.org). Of the 35 patients who achieved TIMI 2 or 3 flow, 34% had a favorable outcome (MRS of 0 to 1 at 3 months) as compared with 12% of those patients who achieved only TIMI 0 or 1 flow (P = 0.013). Of those subjects who received IA rt-PA within 3 hours of onset, 43% (7/16) had MRS of 0 to 1 at 3 months as compared with 13% (3/24) of subjects who received IA rt-PA within 3 to 4 hours and 27% (6/22) of those who received IA rt-PA after 4 hours (IA ≤3 hours versus IA >3 hours; 0.095 by Fisher exact test).

Protocol violations included no angiogram in 1 patient (magnetic resonance angiography showed no occlusion in this patient who had returned to near normal). IV heparin use after the angiographic procedure but before the 24-hour CT occurred in 3 subjects. One patient had IV rt-PA started at 3 hours and 1 minute. Another patient had IA rt-PA started after 5 hours from onset and received IA infusion of rt-PA beyond 7 hours. One patient had placement of a carotid stent outside of the protocol. Finally, no administration of IA rt-PA was administered in 1 patient who had a 99% stenosis of the intima carotid artery with thrombus plus emboli in the fourth divisions of the middle cerebral artery. Medication errors occurred in 4 subjects who had the proper dose of commercially available rt-PA delivered intravenously, rather than study drug, after informed consent had been obtained.

### TABLE 4. Three-Month Outcome: IMS and NINDS rt-PA Trial Cohorts (Ages 18–80 and Baseline NIHSS ≥10)

<table>
<thead>
<tr>
<th>Measure</th>
<th>IMS Study</th>
<th>NINDS Placebo</th>
<th>Odds Ratio* (95% CL)</th>
<th>NINDS rt-PA</th>
<th>Odds Ratio† (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS (0–1) at 90 days</td>
<td>24/80 (30%)</td>
<td>38/211 (18%)</td>
<td>2.26 (1.15, 4.47)</td>
<td>59/182 (32%)</td>
<td>1.00 (0.51–1.96)</td>
</tr>
<tr>
<td>NIHSS ≥1 at 90 days</td>
<td>22/80 (28%)</td>
<td>31/211 (15%)</td>
<td>2.51 (1.21, 5.18)</td>
<td>45/182 (25%)</td>
<td>1.45 (0.73, 2.90)</td>
</tr>
<tr>
<td>Barthel (95–100) at 90 days</td>
<td>37/80 (46%)</td>
<td>63/211 (30%)</td>
<td>2.17 (1.20, 3.91)</td>
<td>76/182 (42%)</td>
<td>1.39 (0.76, 2.54)</td>
</tr>
<tr>
<td>Glasgow 91 at 27 days</td>
<td>28/80 (35%)</td>
<td>47/211 (22%)</td>
<td>1.91 (1.01, 3.60)</td>
<td>63/182 (35%)</td>
<td>1.12 (0.59, 2.14)</td>
</tr>
<tr>
<td>Global test</td>
<td>—</td>
<td>—</td>
<td>2.36 (1.35, 4.14)</td>
<td>—</td>
<td>1.35 (0.78, 2.37)</td>
</tr>
<tr>
<td>mRS (0–2) at 90 days</td>
<td>34/80 (43%)</td>
<td>59/211 (28%)</td>
<td>2.18 (1.20, 3.99)</td>
<td>71/182 (39%)</td>
<td>1.28 (0.70, 2.33)</td>
</tr>
<tr>
<td>NIHSS ≥2 at 90 days</td>
<td>25/80 (31%)</td>
<td>42/211 (20%)</td>
<td>2.11 (1.08, 4.13)</td>
<td>60/182 (33%)</td>
<td>1.08 (0.57, 2.06)</td>
</tr>
<tr>
<td>NIHSS ≥2 at 24 hours</td>
<td>11/80 (14%)</td>
<td>7/211 (3%)</td>
<td>5.39 (1.80, 16.19)</td>
<td>26/182 (14%)</td>
<td>1.77 (0.71, 4.39)</td>
</tr>
</tbody>
</table>

*From logistic regression model for favorable outcome adjusted by baseline NIHSS, age, and time to treatment (continuous) comparing IMS to NINDS Placebo. †From logistic regression model for favorable outcome adjusted by baseline NIHSS, age, and time to treatment (continuous) comparing IMS to NINDS t-PA cohort. §From global test adjusted for baseline NIHSS, age, gender, and time to treatment (continuous) comparing IMS to NINDS Placebo. ¶From global test adjusted for baseline NIHSS, age, gender, and time to treatment (continuous) comparing IMS to NINDS t-PA cohort.
Sixteen subjects received <18 mg of IA rt-PA via infusion for reasons other than the defined protocol criteria. In 10 subjects, the treating investigator indicated achievement of maximum lysis that was determined to be <TIMI 3 flow on subsequent review by the central angiographic reader. In 6 instances, the treating investigator indicated major clinical improvement as the reason for stopping IA T-PA despite incomplete recanalization. Of these 6 subjects, 5 did not achieve a TIMI 3 flow but averaged an NIHSS improvement of 7.6, as measured by the immediate pre-IA and post-IA NIHSS. One subject showed no documented change on NIHSS on the post-IA NIHSS but was heavily sedated. This patient improved by 4 points on the NIHSS at 24 hours.

Discussion

The IMS Study demonstrates that a combined IV and IA approach to recanalization, using rt-PA begun within 3 hours of onset, is feasible and may have comparable safety to full-dose IV rt-PA as administered during the NINDS rt-PA Stroke Trial. In addition, as compared with placebo subjects of similar baseline severity and age in the NINDS rt-PA Stroke Trial, IMS subjects were significantly more likely to have an excellent outcome at 3 months, both before and after adjustment for baseline NIHSS, age, and time to treatment (odds ratio of ≥2). Based on these pre-specified comparisons with historical controls from the NINDS rt-PA Stroke Trial, a randomized concurrently controlled trial of standard IV rt-PA as compared with a combined IV and IA approach started within 3 hours of stroke onset is warranted.

The IMS subjects represent the most severely affected group of subjects treated as part of a controlled trial of recanalization therapy. To our knowledge, a median baseline NIHSS score of 18 is the highest of any controlled trial of recanalization published to date. In addition, the amount of vascular disease and burden of thrombus exceeds that in any other previous recanalization trial. Of the 80 IMS subjects, 28 (35%) had major occlusions of the carotid artery, usually in addition to distal occlusions in the middle cerebral artery. By comparison, the PROACT II Study included only those subjects with an M1 or M2 occlusion. Such severely affected subjects with a large thrombus burden are most appropriate for a combined IV/IA approach. IV rt-PA alone results in partial or total recanalization in 10% of subjects with an internal carotid artery occlusion, and only in one third of subjects with occlusions of the middle cerebral artery.1–3

The mortality rate and rate of symptomatic intracerebral hemorrhage in the IMS Study are similar to those in other reported series of combined IV/IA rt-PA.4–7 In addition, the proportion of favorable outcome at 3 months in the IMS Study is similar to what has been reported in these case series of combined IV/IA rt-PA. The great advantage of the combined approach, as compared with IA therapy alone, is that effective treatment can begin much more quickly before referral to the comprehensive stroke center. In addition, it is likely that some of the IMS subjects who had no visible thrombus or with distal occlusions on the first baseline angiographic images may have had larger proximal occlusions before initiation of IV rt-PA.

Although the mortality rate and rate of symptomatic intracerebral hemorrhage was similar between IMS subjects and rt-PA–treated subjects in the NINDS rt-PA Stroke Trial, the rate of asymptomatic intracerebral hemorrhage during the first 36 hours was higher in the IMS Study. However, only 6 (7.5%) subjects had PH2-type hematomas that have been associated with neurologic deterioration and poor outcome.8

In addition, the total overall rate of intracerebral hemorrhage in the IMS Study is similar to the overall rate of intracerebral hemorrhage in the PROACT II Study of 54%.5 IMS subjects with occlusions of the internal carotid artery, with or without distal occlusions, were particularly likely to have hemorrhagic change (20 of 28 [71%]). By comparison, only 15 of the 36 (42%) subjects with occlusions in the middle cerebral artery or vertebral artery system had any hemorrhagic change. We have subsequently begun an IMS II pilot study in a predetermined sample of 72 subjects. This study is identical to IMS I, except that the catheter infusing the rt-PA into the thrombus also delivers low-intensity ultrasound within the thrombus to accelerate thrombolysis (EKOS MicroLysUS System). After completion of the IMS II study, we plan to proceed to a randomized trial of combined IV/IA recanalization as compared with standard IV rt-PA, each begun within 3 hours of onset. Improved methods of recanalization and better outcome in patients with acute ischemic stroke are clearly needed.

Appendix

Please see online appendix for complete list of participating hospitals, centers, and investigators (available online at http://www.ahajournals.org).

Acknowledgments

This study was funded by the National Institute of Neurological Diseases and Stroke (NINDS #NS39160). rt-PA was supplied by Genentech, Inc. and the microcatheters were supplied by Cordis Neurovascular, Inc.

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Editorial Comment

More Than One Way to Lyse a Clot

Intravenous tissue plasminogen activator (IV tPA) is generally effective in a wide range of patients with acute stroke, and can be administered in nearly any acute care hospital, at least theoretically, because no advanced resources are necessary. IV tPA is therefore the best option for most patients.

However, one of the major lessons learned from the pivotal NINDS trial establishing the efficacy of IV tPA for acute stroke was that, despite aggressive therapy, the majority of patients were still left disabled or dead. New strategies are desperately needed to improve outcome. IV tPA is essentially one-size-fits-all treatment, based only on clinical presentation and CT of the brain, not visualization of the target thrombus. Recanalization rates of major occlusions may be much longer to initiate than IV thrombolysis, particularly in the absence of procedural success. Unfortunately, IA thrombolysis takes much longer to initiate than IV thrombolysis, particularly during off hours, and is only available in a relatively small number of specialized centers. Clinicians who use IA therapy have to deal with the question, “How can we get patients to tertiary centers and start treatment sooner?”

The Interventional Management of Stroke (IMS) Study sought to combine the advantages of these two methods, improving time to initiation of treatment with IV tPA, then bridging to more directed treatment and possibly more complete recanalization with IA thrombolysis. After initial treatment with low dose (0.6 mg/kg) IV tPA alone, only ~5% of patients appeared to have partially or completely recanalized. Of 62 patients subsequently given IA tPA for major arterial occlusions, recanalization (TIMI 2 or 3 flow) was achieved in 56% of patients. There was no placebo arm in the IMS study, so comparisons were made to patients in the NINDS t-PA trial. The safety profile of the combined approach was comparable to that of standard dose IV tPA. The efficacy results may at first seem unimpressive despite the high rate of recanalization; outcome with combined IV/IA therapy was clearly better than with placebo, but only equivalent to or perhaps modestly better than IV tPA alone. Is this aggressive and resource-intensive intervention necessary if the results are similar to IV tPA by itself? The limitations
of the historical cohort used for this comparison must be considered in answering this question. Patients in the IMS study had persistent major vascular occlusions despite early IV tPA treatment and probably greater clot burden than those treated in the NINDS trial, had more atrial fibrillation (possibly contributing to larger embolic occlusions), and were treated later, but still tended to have better outcomes. Thus, the IMS results are promising, and suggest the possibility of greater efficacy over IV tPA alone.

If ultimately proven effective, combining IV/IA thrombolysis in practice will be logistically challenging. To traverse existing technology and resource gaps, IV treatment may start at community hospitals, followed by transfer to comprehensive stroke centers for IA lysis. However, there are too few interventional neuroradiologists to provide this treatment everywhere, and neurologists, cardiologists, and surgeons may be called on to be trained in this technique.

One great achievement of the IMS trial was its completion in record time, about three times faster than expected. This amazing pace, particularly at the top enrolling centers, attests to the benefits of regionally organized stroke care in improving access to acute therapy. However, it may have been relatively easy to obtain informed consent for participation in this study since there was neither a placebo arm nor randomization. Subsequent trials will likely require randomization to compare therapeutic strategies, and obtaining consent will likely become more difficult. The Prolyse in Acute Cerebral Thromboembolism (PROACT-II) trial took over 2 and a half years to enroll 180 patients, and a comparison of IV/IA versus IV thrombolysis alone would probably need about 400 patients in each arm to demonstrate superiority of the combined approach.

The NINDS tPA trial revolutionized acute stroke therapy, but it is clear that IV tPA alone is not enough. The IMS study has now set the standard for testing other interventions that might augment the efficacy of tPA, such as combinations of thrombolysis with glycoprotein IIb/IIIa antagonists, direct thrombin inhibitors, external or local ultrasound, mechanical clot retrieval or maceration, neuroprotective strategies, and others. We can probably improve on a good thing, and there is more than one way to lyse a clot.

Scott E. Kasner, MD

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Combined Intravenous and Intra-Arterial Recanalization for Acute Ischemic Stroke: The Interventional Management of Stroke Study
The IMS Study Investigators

Stroke. 2004;35:904-911; originally published online March 11, 2004;
doi: 10.1161/01.STR.0000121641.77121.98

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