Intraarterial TPA Can Break Up Resistant Clots in Severe Stroke

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

KISSIMMEE, FLA. — A combination of intravenous and intraarterial thrombolysis significantly improved outcomes in stroke patients whose clots did not clear with initial thrombolytic therapy, Dr. Joseph Broderick reported at the 31st International Stroke Conference.

"We already know that tissue plasminogen activator (TPA) is an effective drug, but it doesn't open the artery in every patient," Dr. Broderick, chairman of the neurology department at the University of Cincinnati, said in an interview. "We need another way to help these people."

The Interventional Management of Stroke Study-II (IMS-II) included 73 patients with severe stroke (median National Institutes of Health Stroke Scale score of 19). All received an initial course of low-dose intravenous TPA within the first 3 hours of stroke onset (median time 41 minutes).

The initial thrombolysis cleared the clot in 22 patients, none of whom received further therapy. The remaining 51 patients, however, still had a clot blocking an artery in either the neck or the head.

Those patients were treated with an additional dose of TPA (maximum 22 mg). In 33 patients, the drug was delivered directly to the clot by an infusion catheter equipped with a low-dose ultrasound transducer at the distal tip. The ultrasound energy creates microfractures in the clot, which enables the better delivery of the thrombolytic agent.

The remaining 18 patients received the additional therapy with a standard catheter.

Dr. Broderick compared outcomes in the 51 patients who received the intraarterial therapy with those of patients matched for age and stroke severity who received intravenous recombinant TPA in a 1995 study called the National Institute of Neurological Disorders and Stroke (NINDS) rtPA [recombinant tissue-type plasminogen activator] Stroke Study Group (N. Engl. J. Med. 1995;333:1581-8).

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DR. BRODERICK

The patients in the IMS-II study had significantly lower mortality at 3 months (16% vs. 21%), and more of them had a Rankin score of 0-2 at 3 months (45% vs. 39%; odds ratio 1.65), compared with the NINDS study patients.

Symptomatic intracranial bleeds occurred more frequently in the IMS-II group than in the NINDS group (11% vs. 6.6%), as did asymptomatic bleeds (29% vs. 6%). This is not surprising, given that the invasive nature of the second course of TPA, Dr. Broderick said at the conference, which was sponsored by the American Stroke Association.

The increased risk of bleeding indicates that intraarterial therapy should be reserved for those patients with severe stroke. Older patients should be carefully evaluated before receiving the treatment, he warned.

The IMS-II trial didn't distinguish the effect of the interventional device versus the thrombolytic drug, Dr. Broderick noted. "We weren't testing an individual device; we were testing a therapeutic approach."

A third IMS trial, sponsored by NINDS, is designed to evaluate the combined thrombolytic approach using a number of different devices. Physicians will be allowed to use any FDA-approved clot removal device; if additional devices are approved during the course of the trial, they will be allowed.

The treatment advantage of this trial design is clear, Dr. Broderick noted.

"There's no one choice that is good for all clots. Physicians will get to choose the right tool for the job. The important thing is to maximize the quickest possible opening of the blocked artery," he said.

He hopes to include 50 centers and 900 patients in the new trial. ■

Mild Stroke Outcomes Improved With TPA

BY SHARON WORCESTER
Southeast Bureau

KISSIMMEE, FLA. — Mild stroke symptoms should not preclude thrombolytic therapy in eligible patients, Dr. Nicole R. Gonzales said at the 31st International Stroke Conference.

Patients with mild acute ischemic stroke are often excluded from thrombolytic therapy despite presenting within the 3-hour window for recombinant tissue plasminogen activator (r-TPA) treatment, because it is assumed they will do well without the therapy.

However, in a large prospective study, administration of r-TPA to patients with mild stroke improved their chances of an excellent outcome and appeared to reduce the risk of death, said Dr. Gonzales of the University of Texas, Houston.

Of 885 patients presenting with acute ischemic stroke over a 14-month period, 238 had a National Institutes of Health Stroke Scale (NIHSS) score of between 1 and 7, indicating minimal symptoms (103 patients) or mild symptoms (135 patients).

Overall, 41 patients were treated with r-TPA. Of 46 who arrived within the 3-hour treatment window, 72% were excluded due to mild symptoms.

Outcome at discharge was excellent in 59% of all stroke patients who were treated, regardless of the severity of the stroke, compared with 44% of those not treated.

Of those with minimal stroke symptoms according to the NIHSS score, 90% of those treated had an excellent outcome. The differences were statistically significant, compared with only 58% of those not treated.

Nearly 50% of those with mild symptoms according to the NIHSS score who were treated, compared with 32% who were not treated, also had an excellent outcome, however the numbers in this group were too small to show statistical significance.

None of the treated patients with minor or mild symptoms died, while two in the untreated group died, although these numbers were also too small to show statistical significance.

"The findings argue strongly against exclusion of patients from thrombolytic therapy based on minimal or mild symptoms," Dr. Gonzales said.

The conference was sponsored by the American Stroke Association. ■

Microbubbles Plus Ultrasound Strengthen Thrombolysis

BY SHARON WORCESTER
Southeast Bureau

KISSIMMEE, FLA. — The administration of microbubbles bolsters the combined thrombolytic effects of ultrasound-enhanced systemic thrombolysis and tissue plasminogen activator and improves outcomes in patients with atherothrombotic stroke, Dr. Marta Rubiera reported at the 31st International Stroke Conference.

In a study of 155 consecutive patients with stroke attributable to middle cerebral artery (MCA) occlusion, patients were allocated to one of three groups. One group received intravenous tissue plasminogen activator (TPA) treatment plus continuous 2-hour, 2-MHz–pulsed-wave transcranial Doppler ultrasound and three intravenous doses of galactose-based microbubbles given at 2, 20, and 40 minutes after TPA bolus. The remaining patients received TPA and ultrasound without microbubble administration or TPA with placebo monitoring.

The 2-hour complete recanalization rate was significantly higher in the microbubble group, compared with the ultrasound and control groups (42% vs. 40% and 24%, respectively), said Dr. Rubiera of the Hospital Vall d'Hebron, Barcelona.

The differences were significant only for those with atherothrombotic stroke, compared with cardioembolic and "undetermined" or "other" types of strokes (which comprised 24%, 49%, 23%, and 4% of stroke types in the study, respectively). In the 37 patients with atherothrombotic stroke, microbubbles increased the success rate of 2-hour recanalization 1.5-fold over TPA plus ultrasound (39% vs. 26%), and nearly twofold over TPA alone (39% vs. 21%).

Ultrasound has been shown to improve thrombolysis by accelerating TPA penetration into clots. Microbubbles appear to disrupt clots via cavitation.

Furthermore, at 3-month follow-up atherothrombotic stroke was significantly associated with a poor outcome in the ultrasound and control groups, but not in the microbubble group, as determined by modified Rankin Scale score, Dr. Rubiera noted.

Patients in the study had a median National Institutes of Health Stroke Scale (NIHSS) score of 16. On transcranial Doppler ultrasound, 76% of the 155 patients had occlusion of the proximal MCA, and 24% had occlusion of the distal MCA. Of those 37 patients with atherothrombotic stroke, 96% had occlusion of both the MCA and internal carotid artery (ICA) occlusion. Patients in all stroke subtype categories were similar with regard to baseline NIHSS, clot locations, and time to treatment.

Ultrasound used for monitoring has been shown to safely enhance thrombolysis by accelerating the transport and penetration of TPA into the clot, according to Dr. Rubiera and her associates.

Microbubbles, small air- or gas-filled microspheres approved for use in Europe and Japan as a contrast agent for ultrasound, appear to disrupt blood clots via cavitation. In a recently published article on the effects of microbubbles on clot lysis during ultrasound monitoring, Dr. Rubiera and her colleagues explained that by acting as cavitation nuclei, microbubbles lower the amount of energy needed for cavitation, and that high–acoustic-pressure ultrasound induces nonlinear oscillations of microbubbles. This process leads to continuous absorption of energy, which eventually causes the bubbles to explode, releasing the absorbed energy, they noted.

"Thus ultrasound-mediated microbubble destruction may further accelerate the clot-dissolving effect of ultrasound," they wrote (Stroke 2006;37:425-9).

The expanded data presented at the conference, which was sponsored by the American Stroke Association, provide further evidence that microbubble administration during continuous ultrasound monitoring and systemic thrombolysis improves recanalization and outcomes in patients with tandem ICA and MCA occlusion, Dr. Rubiera concluded. ■