Ultrasound Plus Clot Buster Better for Acute Stroke

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Patients suffering from acute ischemic stroke are significantly more likely to achieve recanalization and/or early or dramatic clinical recovery if thrombolytic therapy is combined with continuous transcranial Doppler sonography, according to a study by Andrei V. Alexandrov, M.D., of the University of Texas, Houston, and colleagues.

Of 63 patients receiving ultrasound combined with tissue plasminogen activator (t-PA), 31 (49%) achieved recanalization and/or clinical recovery within 2 hours, compared with 19 of 63 patients (30%) who received t-PA combined with sham sonography. Within 2 hours, 16 (25%) of the patients in the treatment group experienced both recanalization and clinical recovery, compared with 5 (8%) of the control group. Both differences were statistically significant (N. Engl. J. Med. 2004;351:2170-8).

All patients had occlusions of the middle cerebral artery, and all were treated within 3 hours of the onset of symptoms. The patients were randomly assigned to the treatment or the control group.

Known as the Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic t-PA (CLOTBUST) trial, the study was funded in part by the National Institute of Neurological Disorders and Stroke, a unit of the National Institutes of Health.

This phase II study, although not designed to look at clinical outcomes 3 months after treatment, showed that of the 53 patients eligible for follow-up, 22 (42%) had achieved a modified Rankin score of 0 or 1, compared with 4 of the 15 eligible patients (27%) in the control group. Investigators calculated that a phase III study would need just 274 patients in each group to replicate the results with statistical significance.

"At our center, it's the standard of care right now," he said. "Both [t-PA and transcranial Doppler sonography] are FDA-approved technologies, and the trial was exempt from investigational new drug status by FDA because these results would not change the labels. Right now in our institution, when we give systemic t-PA within 3 hours [after a stroke], we always put a transcranial Doppler probe on the scalp to help the patient pass the clot faster."

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Nevertheless, "I will not stand here and recommend that everybody else should do the same," Dr. Alexandrov said. "The reason is that to do it right, you have to pass through a very lengthy and labor-intensive training that is not a routine part of any neurology residency. To do the protocol, you need 1-6 months of daily practicing of this technique under supervision, and that's something that very few programs can do in the United States."

Dr. Alexandrov is involved in an effort to design an operator-independent device that would obviate the need for an experienced operator. With such a device, "an emergency department physician could do it, a neurologist could do it, and a nurse could mount the ultrasound machine on the head," he said.

The mechanism by which transcranial Doppler sonography improves thrombolysis is still unclear. In a commentary accompanying Dr. Alexandrov's paper, Joseph F. Polak, M.D., of Tufts University, Boston, weighs a number of the possibilities (N. Engl. J. Med. 2004;351:2154-5).

It's clear that the mechanism does not involve cavitation, which ultrasound at high energies can cause. It's also unlikely that the relatively low energies used in transcranial Doppler ultrasound could accelerate thrombolysis by producing heat.

Dr. Alexandrov believes that the combined treatment works because ultrasound is causing a gentle mechanical pressure wave, which delivers more t-PA molecules to and through the clot.

The study was sparked by a observation, Dr. Alexandrov said. "Patients who were wearing these transducers for diagnostic purposes started to move their paralyzed arms and legs and to talk to us much faster than we ever expected otherwise." ■

References: 1. Sandrini G, Färkkilä M, Burgess G, Forster E, Haughie S, for the Eletriptan Steering Committee, Eletriptan vs sumatriptan: a double-blind, placebo-controlled, multiple migraine attack study. *Neurology.* 2002;59:1210-1217. **2.** Mathew NT, Schoenen J, Winner P, Muirhead N, Sikes CR. Comparative efficacy of eletriptan 40 mg versus sumatriptan 100 mg. *Headache.* 2003;43:214-222.