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Ultrasound-aided Therapy Better Than Stroke Drug Alone, Trial Finds

Using ultrasound in combination with the drug t-PA can improve response to an ischemic stroke, according to a study involving 126 patients. This first-of-its-kind human trial compared the safety and efficacy of ultrasound and t-PA versus use of t-PA alone. The trial was funded in part by the National Institute of Neurological Disorders and Stroke (NINDS), a component of the National Institutes of Health (NIH). The finding appears in the November 18, 2004, issue of the *New England Journal of Medicine.*

Since 1996, the clot-busting drug t-PA (tissue plasminogen activator) has been the only FDA-approved therapy for acute ischemic stroke. Previous studies have shown that t-PA, when administered within 3 hours of onset of ischemic stroke, can greatly improve a patient's chance for a full recovery. t-PA cannot be used to treat the less common hemorrhagic stroke.

Researchers wanted to test the effectiveness of using transcranial Doppler ultrasound (TCD) in combination with t-PA, and to ensure that ultrasound did not cause bleeding into the brain. Utrasound is a safe, non-invasive, FDA-approved diagnostic test that uses sound waves to measure blood flow velocity in large arteries. An international team led by Andrei Alexandrov, M.D., associate professor of neurology at the University of Texas-Houston School of Medicine, examined 126 patients who suffered an ischemic stroke. All patients received intravenous t-PA within 3 hours of stroke onset. The 63 patients in the control group received t-PA alone, while the other 63 patients received t-PA in combination with continuous TCD monitoring that started shortly before the patients received the drug. A small device attached to a head frame was used to deliver the ultrasound.

Results showed that 49 percent of patients who received continuous ultrasound and t-PA showed dramatic clinical improvement and little or no

blockage within 2 hours after therapy began compared to 30 percent who received t-PA alone. Notably, 38 percent of the patients who received continuous ultrasound and t-PA showed no blockage within two hours, compared to 13 percent who received t-PA alone. In all, 73 percent of patients who received the combined therapy showed complete or partial clearance of the clot, compared to 50 percent in the control group. Bleeding into the brain was experienced by 4.8 percent of patients in both groups. This early improvement of blood flow to the brain resulted in a trend that 13.5 percent more patients who received continuous ultrasound and t-PA had recovered completely by 3 months after stroke.

The team also found that patients who experienced complete clearance of their clot within 2 hours following treatment had the greatest likelihood of regaining body strength, speech, and other functions affected by stroke. Researchers named the trial CLOTBUST (Combined Lysis Of Thrombus in Brain ischemia Using transcranial ultrasound and Systemic t-PA).

"In the past 30 years, scientists around the world have shown that ultrasound is fast, gentle, and effective in helping t-PA to break up clots. For the first time, we have demonstrated this benefit in patients. This approach enhances flow to the brain and augments clinical recovery within minutes of treatment initiation," said Dr. Alexandrov.

"Stroke can be devastating for patients and their caregivers," said Story C. Landis, Ph.D., NINDS director. "These initial findings suggest that patients who receive the combined therapy are able to leave the hospital with a greater chance for recovery following an ischemic stroke. This is an excellent example of improving on an existing therapy and providing better outcomes."

Ultrasound causes vibrations among the molecules on and within clot structures, which in turn creates more binding sites for t-PA interaction and subsequent clot breakdown. The researchers think that this "jiggle" improves drug transport to and around the clot and helps to open more blocked vessels faster than can be expected with t-PA therapy alone.

The NINDS is funding additional research to standardize the combined therapeutic delivery system and plans to study it in a larger group of patients. Other NINDS-funded research is investigating the basic biology of stroke, use of diagnostics, and treatment.

Stroke is the nation's third leading cause of death, behind heart disease and cancer. Each year about 700,000 persons in the United States have a stroke, with about 80 percent of them being ischemic strokes.

The NINDS is a component of the NIH within the Department of Health and Human Services and is the nation's primary supporter of biomedical research on the brain and nervous system.