Big disappointment: Citicoline does not improve functional, cognitive status in patients with traumatic brain injury

November 20 2012

Although approved for use for treating traumatic brain injury (TBI) in nearly 60 countries, use of citicoline in a randomized trial that included more than 1,200 participants with TBI did not result in improvement in functional and cognitive status, according to a study appearing in the November 21 issue of *JAMA*.

"Despite considerable advances in emergency and critical care management of TBI as well as decades of research on potential agents for neuroprotection or enhanced recovery, no effective pharmacotherapy has yet been identified," according to background information in the article. Citicoline, an endogenous (produced within the body) compound, offers potential neuroprotective properties as well as neurorepair post injury. Citicoline is widely available in the United States as a nutraceutical (product that reportedly provides health and medical benefits) and is used by patients with a range of neurologic disorders, yet it has not been evaluated in a large randomized clinical trial for TBI.

Ross D. Zafonte, D.O., of Harvard Medical School, Spaulding Rehabilitation and Massachusetts General Hospital, Boston, and colleagues conducted a study to evaluate the efficacy of citicoline for improving cognitive and functional status among patients with TBI. The Citicoline Brain Injury Treatment Trial (COBRIT), a phase 3, randomized clinical trial, was conducted between July 2007 and February 2011. The study, which included 1,213 patients at 8 U.S. level

1 trauma centers, examined the effects of 90 days of enteral or oral citicoline (2,000 mg) vs. placebo initiated within 24 hours of injury in patients with complicated mild, moderate, and severe TBI.

The researchers found that the citicoline and placebo groups did not differ significantly at the 90-day evaluation on measures of cognitive and functional status. "Rates of favorable improvement for the Glasgow Outcome Scale-Extended were 35.4 percent in the citicoline group and 35.6 percent in the placebo group. For all other scales the rate of improvement ranged from 37.3 percent to 86.5 percent in the citicoline group and from 42.7 percent to 84.0 percent in the placebo group."

There was no significant treatment effect in the two severity subgroups (moderate/severe and complicated mild TBI). In patients with moderate/severe TBI, no statistically significant difference was observed between treatment groups at the 180-day evaluation.

The overall proportion of patients reporting serious adverse events was similar between the placebo and citicoline groups.

"The COBRIT study indicates that citicoline was not superior to placebo as an acute and postacute therapy among participants with a broad range of severity of TBI. The worldwide use of citicoline for TBI should now be questioned."

In an accompanying editorial, Robert L. Ruff, M.D., Ph.D., and Ronald G. Riechers II, M.D., of the Cleveland VA Medical Center, and Case Western Reserve University (Dr. Ruff), write that the primary importance reported by this trial "is that it conclusively demonstrated the lack of efficacy of citicoline monotherapy for TBI."

"It is unlikely that this finding can be accounted for by limitations in the study design or conduct. The broader implication of the COBRIT study

may be that no single therapeutic agent is likely to be sufficient to improve functional outcomes for patients with TBI. The diverse and complex nature of the pathological mechanisms activated by TBI suggests that multimodal treatment interventions may be needed to improve recovery. Future studies of TBI treatment should be designed to incorporate multiple treatment interventions and comprehensive TBI rehabilitation strategies, either as components of the intervention or standardized across study treatment groups."

More information: *JAMA*. 2012;308(19):1993-2000
JAMA. 2012;308(19):2032-2033