

Progesterone offers no significant benefit in traumatic brain injury clinical trial

December 10 2014

Treatment of acute traumatic brain injury with the hormone progesterone provides no significant benefit to patients when compared with placebo, a NIH-funded phase III clinical trial has concluded.

The results are scheduled for publication Dec. 10 in the *New England Journal of Medicine*.

The study, named ProTECT III, involved 49 trauma centers across the United States between July 2009 and November 2013. The study was originally planned to include 1,140 patients, but was stopped after 882 patients because safety monitors determined that additional enrollment would be futile.

Survival and favorable outcomes, measured by improvements in patients' Glasgow Coma Scores, were not significantly different in the progesterone-treated group than in the placebo-treated group. Favorable outcomes occurred in 51 percent of those who received progesterone and 56 percent of those who received placebo. Mortality after six months was 18.8 percent for progesterone and 15.7 percent for placebo.

"These results are plainly disappointing," says David Wright, MD, associate professor and vice chair for research in emergency medicine at Emory University School of Medicine, who served as lead investigator for the national study. "The preclinical data on progesterone's neuroprotective effects are compelling, but we were not able to translate them to a multi-center clinical trial with human traumatic brain injury."

The study was funded by the National Institute of Neurological Disorders and Stroke and organized as part of the NETT (Neurological Emergencies Treatment Trials) network, with the University of Michigan providing oversight and coordination and the Medical University of South Carolina providing data analysis. Michael Frankel, MD, professor of neurology at Emory, was site principal investigator at Grady Memorial Hospital.

Similar results from a separate industry-funded clinical trial of progesterone in traumatic brain injury are scheduled for publication in the same issue of NEJM.

Participating patients were 74 percent male, and the average age was 35. The results were not significantly different in men versus women, or in Caucasians, African Americans or Latinos. The most common mechanism of injury was motor vehicle accident.

Progesterone, administered by infusion for four days, was generally well tolerated, with similar rates of adverse events in both progesterone- and placebo-treated groups. Phlebitis (inflammation of a vein) was more common in the progesterone group.

The rationale for testing progesterone grew out of the observation that women tend to respond to treatment and recover better than men after traumatic brain injury. Both men and women naturally produce progesterone, a steroid hormone important for brain development as well as reproductive functions.

Many research teams, including those at Emory led by Don Stein, PhD, have found in animal experiments that progesterone can protect brain cells from the toxic environment that emerges after traumatic injury. Two smaller clinical trials of progesterone in traumatic brain injury also gave encouraging results.

"The trial results were not what we had hoped. Scientists must now redouble their efforts to develop treatments that protect the brain and enhance its natural recovery mechanisms," says Walter Koroshetz, MD, acting director of the National Institute of Neurological Disorders and Stroke. "Most importantly we need to aggressively pursue whether or not the drugs showing promise in animal studies indeed achieve the desired biologic effect in people before moving to late stage trials. Without such indicators we never learn whether we chose the right dose, duration or even the right drug."

Part of the difficulty in translating drugs with solid preclinical efficacy to the clinic may come from the variability in injury from any given traumatic event, Wright says. The location and extent of injuries to the brain, time elapsed before reaching the hospital, doctors' management and the patient's underlying health and resilience may all affect outcomes and obscure the effects of a proposed neuroprotective agent.

"There are several other examples of drugs that show large disparities between preclinical data and clinical efficacy in both stroke and brain injury, and together these results may push investigators in this field to re-examine how experimental therapies are evaluated," he says.

Wright is part of a UCSF-led project supported by the Department of Defense, called the TBI Endpoints Development Award, which is working to develop better methods for selecting patients for clinical trials and measuring patient outcomes.

In the ProTECT III study, patients' functional recovery was measured by looking for improvements in their Glasgow Coma Scores, an assessment of the severity of brain injury ranging from 3 (deep unconsciousness) to 15 (awake and alert). It includes three components: patients' eyes, their ability to speak and their motor responses. Those with less severe initial injuries needed to have a better recovery than those with more severe

injuries to achieve a favorable outcome.

Because of a limited time frame (within four hours) for administering progesterone after brain injury, this study was conducted under exception from informed consent (EFIC), following Food and Drug Administration regulations. EFIC is allowed only when testing treatments for life-threatening conditions and when consent from the patient is not possible and treatment efficacy is thought to depend on being administered quickly.

When legally authorized representatives were available, written informed consent was obtained prior to enrollment. For patients enrolled under EFIC, they or their representatives were notified of enrollment as soon as possible and asked for written consent to continue in the study.

Provided by Emory University

Citation: Progesterone offers no significant benefit in traumatic brain injury clinical trial (2014, December 10) retrieved 14 July 2023 from

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