

EMORY*HealthNews*

Media Contact: Janet Christenbury
jmchris@emory.edu
(404) 727-8599

02 October
2006

Progesterone Shows Promise as Treatment for Traumatic Brain Injury

Emory University researchers have found that giving progesterone to trauma victims shortly following brain injury may reduce the risk of death and the degree of disability and also appears to be safe. The results of this study--the first clinical trial of its kind in the world--are available online in the October issue of the peer-reviewed journal, *Annals of Emergency Medicine*.

Researchers say the next step will be to confirm their findings in a much larger group of traumatic brain injury (TBI) patients.

"Progesterone treatment for TBI has been extensively studied in laboratory animals for more than 15 years, but this is the world's first use of progesterone to treat brain injury in humans," says Arthur Kellermann, MD, MPH, professor and chair of the Department of Emergency Medicine, Emory University School of Medicine and a co-author of the study. "Emory scientist Donald Stein was the first to discover that progesterone has neuroprotective effects, and much of the foundational work on progesterone for TBI was from his laboratory. Their results were so impressive, that we felt it was time to take this treatment to the bedside for testing in patients who had suffered a serious brain injury. We are grateful to the National Institute of Neurological Disorders and Stroke (a division of the National Institutes of Health) for their support of this work," says Kellermann.

Approximately 1.5 to 2 million people in the U.S. sustain a TBI each year, leading to 50,000 deaths and 80,000 new cases of long-term disability. It is also a major cause of death and disability among children and military personnel. Despite the enormity of the problem, scientists have failed to identify effective medications to improve outcomes following a TBI. In fact, no new medical therapies have been developed for traumatic brain injuries in over 30 years.

Emory's researchers designed a clinical trial to assess the promise of progesterone for treatment of TBI. Their three-year pilot study, called ProTECT (which stands for "Progesterone for Traumatic brain injury--Experimental Clinical Treatment"), enrolled 100 participants. Their phase II study was primarily designed to evaluate whether progesterone can be administered intravenously in a reliable way, and whether the treatment is safe to use in humans with TBI. The researchers also hoped to find preliminary evidence that

the treatment might be effective.

Although it is widely considered a "sex steroid," progesterone is also a neurosteroid that exerts protective effects on human tissue. It is naturally present in small but measurable amounts in the brains of males and females. Laboratory studies suggest that progesterone is critical for the normal development of neurons in the brain and exerts protective effects on damaged brain tissue.

Study participants were enrolled at Grady Memorial Hospital (the site of the study because it is Atlanta's only Level 1 Trauma Center). To be a candidate for the study, patients had to reach the hospital within 11 hours of injury. People enrolled in the study had a "blunt" traumatic brain injury, which typically occurs from a car accident, motorcycle crash or a fall. Enrolled patients had an initial Glasgow Coma Scale (GCS) score ranging between 4 and 12. The GCS is a widely used scale that quantifies the initial level of impairment from a TBI. A score of 4-8 signals severe TBI, usually accompanied by coma, while a score of 8-12 signals a moderate TBI.

Because study candidates were cognitively impaired, their family members or other legal representatives were asked to give proxy consent for enrollment in the study. Four out of every five patients (80 percent) enrolled received intravenous progesterone, and one of every five (20 percent) received placebo. Patients, family members, doctors nor study staff knew which participants received progesterone or placebo until the study was completed. Thirty days after injury, objective rating scales were used to assess each participant's neurological function and level of disability.

In an earlier paper, the researchers reported that progesterone can be reliably given intravenously and achieve predictable levels in the bloodstream. The new paper reports the team's findings about drug safety and effectiveness.

"We found encouraging evidence that progesterone is safe in the setting of TBI, with no evidence of side effects or serious harmful events," says David Wright, MD, assistant professor in the Department of Emergency Medicine at Emory and lead author of the study. "In addition, we found a 50 percent reduction in the rate of death in the progesterone-treated group. Furthermore, we found a significant improvement in the functional outcome and level of disability among patients who were enrolled with a moderate brain injury." The researchers evaluated disability using the Disability Rating Scale, an objective measurement tool, and assessed functional outcome using the highly validated Glasgow Outcome Scale.

The researchers found no significant differences in the rate of adverse events among patients who received progesterone compared to those who received placebo. About 30 percent of patients given placebo died within 30 days of head injury, compared to only 13 percent of those given progesterone. Most patients who died had a severe TBI. Because more severe TBI patients in the progesterone group survived, it is not surprising that they had a higher average level of disability at 30 days than survivors in the placebo group. One-year outcomes will be reported at a later date.

Progesterone is a promising treatment because it is inexpensive, widely available and has a long track record of safe use in humans to treat other diseases. The team previously reported that IV progesterone can be easily administered in an arm or hand vein rather than through a central IV line in the neck, chest or groin.

Donald Stein, PhD, Asa G. Candler Professor of Emergency Medicine and neurobiologist at Emory, discovered the neuroprotective properties of progesterone. He and members of his lab have been studying progesterone for almost 20 years.

"Our research has found that male and female rats with brain injury developed less brain swelling and recovered more completely when they are treated with progesterone shortly following the injury," Dr. Stein explains. "The hormone seems to slow or block damaging chemicals that are released after a brain injury, protecting the brain from the death of brain cells."

The research team is now planning a large, multi-center, phase III clinical trial designed to test the effectiveness of progesterone in 1000 patients with TBI and hopes to secure funding from the NIH for this project. They also hope to study the effects of progesterone treatment in animal models of blast-related brain injury, a major cause of death among combat personnel. They plan to implement a study of progesterone to treat pediatric brain injury as well, because brain injury is a leading cause of death and disability in children.

Equally exciting, animal research at Emory and elsewhere indicates that progesterone may limit damage from transient and permanent ischemic stroke. In light of these findings, Emory researchers hope to initiate a similar pilot clinical trial to study the effectiveness of progesterone or a progesterone metabolite to treat patients with acute stroke.

Emory University's Woodruff Health Sciences Center is one of the nation's pre-eminent academic health centers, devoted to Making People Healthy through research, teaching, and patient care. It includes the Emory University School of Medicine, the Rollins School of Public Health, the Nell Hodgson Woodruff School of Nursing, and the Yerkes National Primate Research Center. Its clinical arm is Emory Healthcare, Georgia's largest and most comprehensive health care system, consisting of Emory University Hospital, Emory Crawford Long Hospital, Wesley Woods Center, The Emory Clinic, the Emory Children's Center, EHCA, LLC, Emory-Adventist Hospital, and other affiliates.

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