

Progesterone for Traumatic Brain Injury

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The National Institutes of Health recently announced an important phase III study of the beneficial effects of progesterone on Traumatic Brain Injury (TBI). Seventeen medical centers in fifteen states will enroll over eleven hundred patients for this important study. These include Emory University, Henry Ford Hospital, The Medical Colleges of Virginia and Wisconsin, New York Presbyterian Hospital, Oregon Health and Science University, Stanford and Temple University and the Universities of Arizona, California, Cincinnati, Kentucky, Maryland, Minnesota, Pennsylvania and Texas, and Wayne State University.

The goal of the study is to determine whether intravenous progesterone started within four hours of a moderate to severe TBI, given over a total of ninety-six hours is more effective than placebo in treating victims. This will be a randomized, double blind placebo controlled study. Outcomes will be determined through the Glasgow Outcome Scale-Extended (GOSE) score at six months post injury. Secondary outcome measures include mortality, cognitive, neurological, and functional outcomes. The study is scheduled to begin in March 2010 and last up to five years.

An initial loading dose of 0.714 mg/kg will be given followed by a continuous infusion of 0.5mg/kg over a seventy-two hour period, and tapered over an additional twenty-four hours. Those eligible for the study will be men and women eighteen years of age and older. Inclusion criteria are moderate to severe TBI (Glasgow Coma Scale 4-12), from blunt closed head injury. Arrival to the hospital must be less than four hours after injury. Exclusion criteria include persons who do not speak English or Spanish, other non-survivable injury, bilateral dilated unresponsive pupils, severe intoxication (ETOH > 2.50 mg.%), spinal cord injury with neurological deficits, cardiopulmonary arrest, status epilepticus on arrival, systolic blood pressure < 90 on arrival or for at least five minutes prior to enrollment, O₂ saturation < 90 on arrival or for at least five minutes prior to enrollment, prisoner or ward of the state, pregnant female, active breast or reproductive organ cancers, known allergy to progesterone or egg yolk, and known history of thromboembolic events. Dr. David W. Wright of Emory University is the lead investigator.

In approving the design for the phase III study, NIH reviewed a number of prior animal and human studies. A great deal of credit goes to Donald G. Stein, Ph.D., who observed some years ago that female rats given experimental TBI seemed to recover better than male rats. Animal studies suggest that progesterone exerts a significant neuroprotective effect upon the central nervous system through protecting or rebuilding the blood-brain barrier, decreasing the cerebral edema, down-regulating the inflammatory cascade of excitatory neurotoxic events and limiting cellular necrosis and apoptosis through axonal remyelination and enhancing synaptogenesis and dendritic arborization. The mechanism of action in humans remains unclear, but it likely involves more than one neuroprotective mechanism.

An earlier Emory University study looked at 100 adult trauma patients who had arrived within eleven hours after injury with post resuscitation GCS scores ranging from 4-12 (Ann. Emerg. Med. 2007 April; 49 (4): 391-402). The use of progesterone demonstrated an improvement in outcome using the GOSE and disability rating scale scores with no ill effects. Those with a moderate TBI who received progesterone had better outcome scores than those who received placebo. The lead author was Dr. David W. Wright.

Dr. G. Xiao, et al., published an article titled, "Improved Outcomes From the Administration of Progesterone for Patients with Acute Severe Traumatic Brain Injury, A Randomized Controlled Study," in Critical Care 2008, 12: 2. The study, conducted in Hangzhou China, randomized 159 patients in the neurotrauma center of the teaching hospital who had a GCS of 8 or less, into a randomized, placebo-controlled trial of progesterone. It also used the GOSE three months and six months after injury with the Modified Functional Independence Measure (MFIM). Those who had received progesterone exhibited more favorable outcomes than patients who did not. The mortality rate of the progesterone group was significantly lower at six-month follow-up. Intracranial pressure values at seventy-two hours and seven days after injury were lower in the progesterone group, but statistical significance was not found. Next of kin consent was not required if the Institutional Review Board approved a subject's inclusion.

Newsworthy Event

Based upon earlier studies with promising results, a fifteen state, multi-center NIH sponsored study of progesterone in moderate and severe TBI will begin soon.

Relevance to Forensic Psychiatrists

Many forensic psychiatrists conduct brain injury evaluations in medicolegal settings. If the NIH study finds in a large-scale model, what earlier studies found, it is likely that more individuals with severe TBI will be surviving, and those with both severe and moderate TBI may, with progesterone, have better outcome scores. When hours matter and patients are incompetent to give informed consent, informed consent issues will be relevant.

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