Commentary

Progesterone in traumatic brain injury: time to move on to phase III trials

Marianne Vandromme, Sherry M Melton and Jeffrey D Kerby

Section of Trauma, Burns, and Surgical Critical Care, Department of Surgery, University of Alabama at Birmingham, 19th Street South, Birmingham, Alabama 35294, USA

Corresponding author: Jeffrey D Kerby, jkerby@uab.edu

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See related research by Xiao *et al*., http://ccforum.com/content/12/3/R61

Abstract

There are several candidate neuroprotective agents that have been shown in preclinical testing to improve outcomes following traumatic brain injury (TBI). Xiao and colleagues have performed an in hospital, double blind, randomized, controlled clinical trial utilizing progesterone in the treatment of patients sustaining TBI evaluating safety and long term clinical outcomes. These data, combined with the results of the previously published ProTECT trial, show progesterone to be safe and potentially efficacious in the treatment of TBI. Larger phase III trials will be necessary to verify results prior to clinical implementation. Clinical trials networks devoted to the study of TBI are vital to the timely clinical testing of these candidate agents and need to be supported.

Traumatic brain injury is a serious public health problem causing disability and significant health care expenditures for those affected. While the clinical management of traumatic brain injury has greatly improved with the development of standardized approaches to care, there are currently no medical treatment adjuncts that have been shown effective in improving mortality or limiting disability following injury. The current study by Xiao and colleagues [1] is the second published clinical study evaluating progesterone in the treatment of traumatic brain injury. While there were distinct differences noted between this study and the initial Progesterone for Traumatic Brain Injury: Experimental Clinical Treatment (ProTECT) study by Wright and colleagues [2] (for example, inclusion criteria, dosage of progesterone, administration route, and length of follow up), they each have shown decreases in mortality in those given progesterone, with the current study also showing improvements in functional outcome for those with severe injury. Both studies also confirmed the drug to be safe and well tolerated in head injured patients.

The ProTECT study found improved dichotomized Glasgow Outcome Score-Extended (GOS-E) with progesterone only in the patients with an initial Glaasgow Coma Scale (GCS) 9-12 [2]. The current study found improved GOS-E with treatment in patients with severe traumatic brain injury (GCS ≤ 8) at both three and six months following injury. It should be noted that in the ProTECT study there was a high rate of poor neurological outcome at 30 days, with nearly 79% of the patients in the treatment group either dead, with vegetative survival, or with severe disability. In the current study, the rate of poor neurological outcome in the treatment group was 52% at 3 months and 40% at 6 months following injury. Whether the rates of poor neurological outcome in the initial study would have improved over time cannot be assessed. This, along with differences in study design, makes it difficult to make comparisons between the two studies with regard to neurological outcomes.

It is presumed that progesterone provides a neuroprotective effect by decreasing overall cerebral edema, protecting and rebuilding the blood-brain barrier, down-regulating the inflammatory cascade, and limiting cellular necrosis and apoptosis [3,4]. With edema being the simplest clinically measurable potential neuroprotective aspect of progesterone, a decrease in cerebral edema ideally would correlate to decreased intracranial pressure and, thus, prevention of secondary neuronal injury. Intracranial pressures were continuously monitored in nearly 50% of the study patients for the first 7 days post-injury; it is interesting that although there was a small reduction of pressures in the progesterone group, the reduction was not significant. Similar intracranial pressure readings were found in the previous clinical trial during the initial days of treatment, but again did not meet significance [2]. This

GCS = Glasgow Coma Scale; GOS-E = Glasgow Outcome Score-Extended; ProTECT = Progesterone for Traumatic Brain Injury: Experimental Clinical Treatment.

suggests that mechanisms other than prevention of cerebral edema had more of an effect on improving the clinical outcomes seen in these studies.

Regardless of mechanism, the results of this clinical trial are promising and provide compelling evidence to support the use of progesterone in head injured patients. While this trial provides further safety data and longer term clinical outcomes to support efficacy, in the final analysis it does not add much to what the ProTECT trial has already shown us; that progesterone is safe in patients with head injury, may be efficacious, and that expanded multicenter trials are necessary. The challenge moving forward will be the design of an appropriate multicenter phase III trial with several questions remaining to be resolved. For example, what is the most appropriate therapeutic window for progesterone to provide maximal benefit? In the previous studies, patients were enrolled up to 11 hours following their injury. Would earlier enrollment and administration of the drug improve efficacy? Would enrollment of patients and administration of drug in the pre-hospital setting further improve the potential benefits of the drug? These issues have to be weighed against the ethical and regulatory concerns of research in the emergency setting. Narrowing the therapeutic window will most likely require performance of these trials under exception from informed consent. While this would increase the regulatory burden on the trial, the safety data available for this drug will certainly help to justify this approach.

We anxiously await the results of phase III trials with progesterone in traumatic brain injury. In the meantime, the scientific community needs to continue to pursue similar, early phase trials with other candidate neuroprotective agents that have shown benefit in preclinical models [5]. Established and appropriately funded clinical networks of investigators working in unison to bring these agents through the various stages necessary from preclinical promise to clinical reality are vital to those of us seeking to expand our armamentarium of therapeutic options in the treatment of these injuries [6-8].

Competing interests

SMM is an investigator in the Traumatic Brain Injury Clinical Trials Network. JDK is a Principal Investigator in the Resuscitation Outcomes Consortium.

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