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TRAUMATIC BRAIN INJURY

No benefit of progesterone therapy in patients with TBI

Two recently completed randomized phase III clinical trials have demonstrated that progesterone provides no benefit to patients recovering from severe traumatic brain injury (TBI). The results, published in the *New England Journal of Medicine*, raise serious questions about how best to conduct future studies of treatments for TBI.

"A substantial body of experimental animal work exists documenting a role of progesterone as a neuroprotective agent," explains Brett Skolnick, lead author of the SYNAPSE trial report. "In these experiments, progesterone has been shown to reduce cerebral oedema, thus limiting or preventing intracranial pressure increases that can lead to secondary injury." According to Skolnick, progesterone has also shown anti-inflammatory and antiapoptotic effects.

A substantial portion of the damage caused by TBI arises from the physical and biochemical processes that occur hours to days after the injury event. Thus, the rationale behind both of the trials was that early adminstration of progesterone might prevent or attenuate secondary damage, thereby improving recovery.

Skolnick and colleagues enrolled 1,195 patients who had been admitted to trauma centres across 21 countries after severe TBI. Patients were randomly assigned to receive intravenous progesterone or placebo, and treatment started within 8 h of injury and was delivered continuously for 120 h in total.

The investigators followed up the patients for 6 months after injury, and assessed their recovery using the standard and extended versions of the Glasgow Outcome Scale. "The unique aspect of the trial methodology was to use baseline prognostic variables to classify patients into three groups—with the worst, intermediate or best expected outcomes—and then to perform an analysis termed the sliding dichotomy to evaluate relevant improvements," says Skolnick.

Outcomes were assessed for 1,179 patients who received the study drug, using a modified intention-to-treat analysis. The proportion of patients with outcomes that were generally favourable did not differ between the progesterone and placebo groups, at 50.4% and 50.5%, respectively. This lack of difference also held for the sliding dichotomy, a secondary analysis. Skolnick notes that the percentages of patients who died or were in persistant vegetative state were essentially identical—22.2% after progesterone treatment versus 22.3% after placebo.

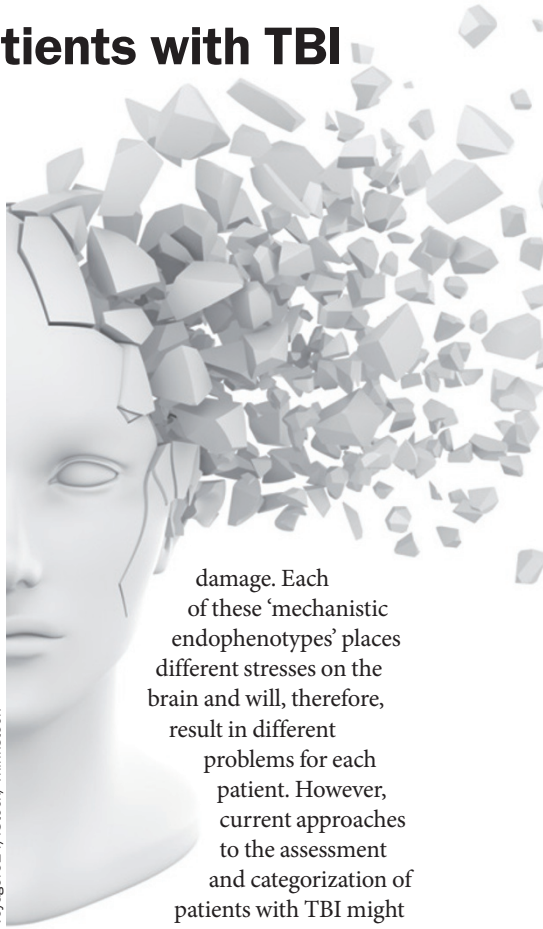
In the PROTECT III trial, which was conducted in parallel to SYNAPSE, David Wright and colleagues enrolled patients from 22 centres in the USA. These investigators were granted an exemption from the requirement to obtain informed consent prior to treatment, which enabled them to administer progesterone or placebo to patients within just 4 h of injury. Treatment was continuous for 96 h, involving a high 'loading' dose followed by maintenance and taper phases.

The PROTECT III investigators intended to enroll 1,140 patients, but the trial was abandoned for futility after 882 people had been assessed. Favourable outcomes were observed in 51% of patients who received progesterone after TBI, compared with 55.5% of controls. Stratification of the patients on the basis of injury severity did not reveal any effect of progesterone on recovery.

No serious adverse events were seen in either the SYNAPSE or PROTECT III trials, although a significant increase in minor phlebitis or thrombophlebitis after progesterone was observed in the latter trial.

In light of these new results, it is clear that progesterone does not represent a viable treament option for patients with severe TBI. What remains unclear is whether additional criteria need to be met before entering phase III, possibly entailing more-rigorous experimental modelling, or larger, more-definitive early-phase trials.

TBI encompasses a broad range of neurological insults, including contusions, diffuse axonal injury and compression damage. Each of these 'mechanistic endophenotypes' places different stresses on the brain and will, therefore, result in different problems for each patient. However, current approaches to the assessment and categorization of patients with TBI might not be sensitive enough to reflect individual variation.



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"My personal recommendations are that we should focus attention on determining if there are meaningful ways to further differentiate TBI into more granular characteristics that could complement the traditional measures," says Skolnick. "We can try to focus in on the individual components of injury, and then ultimately develop a multitherapeutic approach for a tailored treatment of the person with TBI."

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Original articles Skolnick, B. E. *et al.* A clinical trial of progesterone for severe traumatic brain injury. *N. Engl. Clin. Med.* doi:10.1056/NEJMoa1411090 | Wright, D. W. *et al.* Very early administration of progesterone for acute traumatic brain injury. *N. Engl. Clin. Med.* doi:10.1056/NEJMoa1404304

Further reading Menon, D. K. & Maas, A. I. Progress, failures and new approaches for TBI research. *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2014.261