Progesterone for Neuroprotection in Pediatric Traumatic Brain Injury

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Abstract and Introduction

Abstract

Objective To provide an overview of the preclinical literature on progesterone for neuroprotection after traumatic brain injury and to describe unique features of developmental brain injury that should be considered when evaluating the therapeutic potential for progesterone treatment after pediatric traumatic brain injury.
Data Sources National Library of Medicine PubMed literature review.

Study Selection The mechanisms of neuroprotection by progesterone are reviewed, and the preclinical literature using progesterone treatment in adult animal models of traumatic brain injury is summarized. Unique features of the developing brain that could either enhance or limit the efficacy of neuroprotection by progesterone are discussed, and the limited preclinical literature using progesterone after acute injury to the developing brain is described. Finally, the current status of clinical trials of progesterone for adult traumatic brain injury is reviewed.

Data Extraction and Data Synthesis Progesterone is a pleiotropic agent with beneficial effects on secondary injury cascades that occur after traumatic brain injury, including cerebral edema, neuroinflammation, oxidative stress, and excitotoxicity. More than 40 studies have used progesterone for treatment after traumatic brain injury in adult animal models, with results summarized in tabular form. However, very few studies have evaluated progesterone in pediatric animal models of brain injury. To date, two human phase II trials of progesterone for adult traumatic brain injury have been published, and two multicenter phase III trials are underway.

Conclusions The unique features of the developing brain from that of a mature adult brain make it necessary to independently study progesterone in clinically relevant, immature animal models of traumatic brain injury. Additional preclinical studies could lead to the development of a novel neuroprotective therapy that could reduce the long-term disability in head-injured children and could potentially provide benefit in other forms of pediatric brain injury (global ischemia, stroke, and statue epilepticus).

Introduction

Every year in the United States alone, nearly a half million children sustain traumatic brain injury (TBI), and ~3,000 children per year die of these injuries (Centers for Disease Control and Prevention). Despite recent advances in neurointensive care and reduction in the overall mortality rate,[1] the long-term morbidity of severe TBI in childhood remains high. Survivors of pediatric TBI suffer from many long-term physical, cognitive, psychological, and emotional impairments.[2,3] After TBI, a cascade of secondary insults leads to cell death. The developing brain may be uniquely vulnerable to some of these secondary insults, due to maturational features. The steroid hormone progesterone has been studied extensively in preclinical models of adult TBI. It provides multiple mechanisms of neuroprotection that could be very important after pediatric TBI, such as reducing cerebral edema, as well as anti-inflammatory, antioxidant, antiapoptotic, and antiexcitatory properties. This review will highlight progress to date in using progesterone for neuroprotection after TBI and will discuss unique features of developmental brain injury that should be considered when evaluating the therapeutic potential for progesterone treatment after pediatric TBI.

Progesterone in Preclinical Studies of Adult TBI

Over the last 25 years, many preclinical studies have demonstrated neuroprotection by progesterone after TBI in adult animal models.[4–13]Stein[14] began investigating progesterone after observing that female rats recovered better than male rats after TBI. In initial studies, they compared three groups of adult rats (normal male rats, normally cycling female rats in proestrus, and pseudopregnant female rats with high circulating progesterone).[15] They found that normal female rats had less brain edema at 24 hours after TBI compared with male rats and that the pseudopregnant females had remarkably little brain edema compared with the other two groups. Follow-up studies showed that exogenous treatment of male rats with progesterone reduced cerebral edema, lesion volume, and neuronal loss after TBI.[15] Similarly, Bramlett and Dietrich[16] compared male rats, normal female rats, and ovariectomized female rats showing the smallest lesion volumes in normal females compared with the other two groups. Stein's group[17] also showed that the therapeutic window for progesterone could be up to 24 hours after TBI, when targeting cerebral edema, and that there is a u-shaped dose-response curve for improving cognitive outcomes, including memory acquisition in the Morris water maze.[18] In addition, they described potentially detrimental symptoms of abrupt progesterone withdrawal that may warrant tapering.[19] Other investigators have confirmed the neuroprotective properties of progesterone using a variety of TBI models in adult animals. We performed a PubMed search of all original preclinical research studies of progesterone use in adult TBI published between 1992 and 2013. The 46 identified studies (96–125) are summarized in Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/PCC/A129). In addition, a recent preclinical systematic review summarized the key aspects of progesterone treatment for neuroprotection after TBI

and cerebral ischemia in adult animals, looking at effects on lesion volume.[20] The main finding was that progesterone was neuroprotective, but limitations in the literature were identified, including insufficient examination of dose-response relationships, therapeutic windows, and evaluation in female or aged adult animals.

Mechanism of Neuroprotection by Progesterone

Progesterone is a pleiotropic agent with beneficial effects on various secondary injury cascades that are set into motion after TBI (Fig. 1).[21,22] The main therapeutic effect of progesterone and its metabolites is thought to be via decreasing cerebral edema.[10,23–25] By modulating p-glycoprotein and aquaporin 4 (AQP4) levels, it helps maintain blood-brain barrier (BBB) integrity.[25] Progesterone up-regulates p-glycoprotein levels leading to increases in efflux pump in BBB and decreases in cerebral edema.[25,26]AQP4 is from a family of water-selective membrane channels, which is mainly expressed in perivascular astrocytic endfeet.[27] Guo et al[25] showed that bilateral contusion injuries of the medial frontal cortex resulted in increased water content in the pericontusional area accompanied by increased expression of AQP4 in the pericontusional area and lateral ventricles. In contrast, there was a significant decrease in AQP4 expression in the tissue surrounding the third ventricle. Progesterone treatment decreased brain water content and AQP4 expression in the pericontusional areas and in the tissue surrounding the lateral ventricles, while increasing AQP4 expression in the tissue adjacent to the third ventricle. The authors speculated that by increasing AQP4 expression in the osmosensory areas in the hypothalamus surrounding the third ventricle, progesterone might have contributed to enhanced water drainage leading to preservation of osmotic equilibrium in the brain. Corroborating the importance of AQP4 as a therapeutic target for pediatric TBI, a recent study showed decreased edema formation, decreased BBB disruption, and improved motor and long-term cognitive function with inhibition of AQP4 expression by injection of small-interfering RNA targeting AQP4 after controlled cortical impact injury in the developing brain.[28]

(Enlarge Image)

Figure 1.

The putative neuroprotective mechanisms of the pleiotropic agent progesterone are detailed in the figure. These mechanisms all play a role in secondary injury following traumatic brain injury. BBB = bloodbrain barrier, GABA = γ-aminobutyric acid Progesterone has been shown to have anti-inflammatory effects by suppressing generation of proinflammatory cytokines and reducing microglial activation.[4,23,24,29,30] These anti-inflammatory effects could be especially important after TBI, where marked neuroinflammation contributes to many aspects of secondary brain

injury, such as vascular endothelial injury and disruption of the BBB.[31] Progesterone administration after TBI in animal models decreased production of tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, toll-like receptor (TLR)-2, TLR-4, and nuclear factor-κB-binding activity.[4,23,24] In addition, primary microglia cultures which were exposed to lipopolysaccharide or proinflammatory cytokines (interferon-γ and TNF-α) showed an increase in nitric oxide (NO) levels and administration of progesterone decreased levels of NO by inhibiting the production of inducible nitric oxide synthase which catalyzes the synthesis of NO.[29,30]Likely related to its anti-inflammatory effects, progesterone has been shown to reduce lipid peroxidation.[9] By up-regulating expression of superoxide dismutase, progesterone might also have a direct effect in the control of excess superoxide generation after TBI.[9,32]

A direct antiapoptotic effect of progesterone has been postulated based on the work showing that progesterone increases antiapoptotic Bcl-2 protein levels, decreases proapoptotic Bax and Bad protein levels, and inhibits TBI-induced release of mitochondrial proapoptotic factor cytochrome c and activation of caspase 3, resulting in improved functional outcome.[13,33]

Progesterone also has effects on γ-aminobutyric acid (GABA) and *N*-methyl D-aspartate (NMDA) receptors. One of the key mechanisms of secondary injury after TBI is excitotoxicity, which is mediated by the release of excitatory neurotransmitter glutamate into the extracellular space leading to the activation of both ionotropic receptors, labeled according to specific agonists (NMDA, kainate, and [α]-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA]) and receptors linked to second messenger systems, called metabotropic receptors. Activation of these receptors leads to calcium influx through receptor-gated or voltage-gated channels or through the release of intracellular calcium stores. Increased intracellular calcium concentration is the trigger for a number of processes that can lead to neuronal death (reviewed in[21]). Thus, inhibitors of receptor-gated or voltage-gated rise in intracellular calcium after injury are expected to result in prevention of neuronal death. Progesterone has been shown to attenuate the rise in intracellular calcium by its effects on both the receptor-gated and the voltage-gated channels after focal cerebral ischemia in vivo or prolonged depolarization of striatal neurons in vitro.[34,35] Progesterone also has effects on the receptors that respond to GABA, the chief inhibitory neurotransmitter in the CNS. Studies in oxygen-glucose deprivation model of neuronal ischemia show that progesterone increases GABAergic activity, resulting in decreased neuronal excitability and consequent protection from excitotoxicity.[36] It is likely that progesterone increases GABAergic activity indirectly, through metabolites that potentiate $GABA_A$ receptors, thus prolonging miniature inhibitory postsynaptic current (chloride), and hyperpolarizing postsynaptic neurons that inhibit further excitation receptor activity.[36–38] The studies in ischemia and epilepsy models support a role for progesterone against excitotoxicity after TBI. Direct investigation of the effects of progesterone on GABA and NMDA receptors after TBI is more limited. Studies using the medial frontal cortex injury showed no effect of progesterone on $GABA_A$ receptor expression in the medial dorsal thalamic nucleus, an area with significant cell loss in this model.[18] The authors suggested that evaluation of specific subunits of the $GABA_A$ receptor may correlate better with functional outcome.

Additional studies by this group showed that abrupt progesterone withdrawal, as prompted by intermittent injections, could lead to abrupt decreases in $GABA_A$ activity and a more excitotoxic environment.[39] Therefore, the approach to progesterone dosing is important when considering NMDA/GABA receptor effects.
A final important aspect of progesterone neuroprotection is through effects on remyelination. The process of remyelination is an important part of long-term recovery following TBI. During remyelination after injury, expression of messenger RNA for cytochrome P450scc (converts cholesterol to pregnenolone), 3β-hydroxysteroid dehydrogenase (converts pregnenolone to progesterone), and progesterone receptors are increased.[40] Supporting a positive effect of progesterone on remyelination, it has been shown that progesterone treatment increases the number of mature oligodendrocytes and the rate of myelin formation in Schwann cells,[41–45] while blocking progesterone biosynthesis results in demyelination.[41]

Progesterone Metabolism and Progesterone Receptors in the Developing Brain

A complete discussion of neurosteroid production, metabolism, and receptor action is out of the scope of this review. The reader is referred to several key reviews in the field.[46–50] Briefly, progesterone is synthesized from pregnenolone by 3β-hydroxysteroid dehydrogenase, an enzyme that has been shown to be present in both neurons and glia in rat brains.[50–53]Baulieu et al[54] showed that progesterone is a true neurosteroid, by documenting the synthesis of progesterone in the brain. Progesterone is metabolized by the enzyme 5α-reductase to 5α-dihydroprogesterone and then to the neurosteroid allopregnanolone by the reversible enzyme 3α-hydroxysteroid dehydrogenase.[55] Allopregnanolone is felt to be one of the key metabolites responsible for neuroprotection after brain injury. The synthesis, concentration of, and metabolism of progesterone and allopregnanolone change throughout development and vary by brain region studied. A recent review summarizes these development- and region-specific changes in neurosteroids.[50]

In addition to developmental changes in progesterone brain concentration, there are developmental changes in progesterone receptor expression. The laboratory group of Wagner et al[49,56])had produced a large body of work evaluating the role of progesterone and progesterone receptors during normal brain development. They suggest that the influence of progesterone on the perinatal brain has been overlooked and that progesterone may play a role in the development of brain and behavior. Furthermore, the progesterone receptor is expressed throughout the forebrain during critical stages of brain maturation in the rodent and may influence neuronal migration, synaptogenesis, and cell death.[57,58] Importantly, Wagner et al[49]suggest that this could be true in human brain development, as children of women who were treated with progesterone during pregnancy for prevention of miscarriage had improved intellectual and behavioral performance in childhood.[59,60]

In summary, the endogenous brain levels of progesterone, as well as regional brain expression of progesterone receptors, are influenced throughout development by species studied, other brain hormones, and specific developmental timepoint being

studied. These complex interactions need to be understood and taken into consideration when planning to use progesterone for neuroprotective therapy after pediatric TBI.

Unique Features of the Developing Brain

Many of the pathologic cascades that are activated following TBI are developmentally regulated. Some developmental features could confer improved benefits compared to the adult brain, while other developmental features could limit progesterone's effectiveness after pediatric TBI. For example, progesterone influences neurotransmission by inhibiting NMDA receptors and potentiating $GABA_A$ receptors. The balance of excitatory and inhibitory neurotransmission is different in the young brain. There is a heightened sensitivity of the very young brain to excitotoxicity after hypoxic-ischemic injury,[61,62] and regional expression of glutamate receptors (NMDA, AMPA, and kainate) changes throughout brain development.[63,64]Furthermore, the $GABA_A$ receptor, which is responsible for inhibitory neurotransmission in the adult brain, can be excitatory in early development.[65,66] Taken together, these developmental differences in glutamate receptors could results in increased sensitivity of the young brain to excitotoxicity after injury, making progesterone treatment even more effective than in the adult brain. However, in the very young brain, the excitatory nature of the $GABA_A$ receptor could make progesterone treatment result in neurotoxicity.

A second important consideration is that the baseline and postinjury antioxidant capacity of the immature brain is significantly reduced compared with a mature brain (reviewed in[67,68]). For example, the activity of key antioxidant enzymes, such as Cu, Zn superoxide dismutase, manganese superoxide dismutase, and glutathione peroxidase, is 20–40% lower in the young brain compared with the adult brain.[68] An in-depth discussion of these developmental vulnerabilities and their influence after TBI in the immature brain is found in a review by Bayir et al.[68] Overall, this would suggest that the antioxidant capacity of progesterone would be especially beneficial in pediatric TBI. Posttraumatic inflammation is a significant contributor to neuropathology after TBI. Progesterone has anti-inflammatory effects by suppressing microglial activation and generation of proinflammatory cytokines. In early development, microglia are predominantly present in the white-matter tracts and play a crucial role in remodeling and restructuring,[69] moving to the cortex by about 2 years of age in humans.[70] Microglial activation after brain injury could damage surrounding oligodendrocytes, worsening the normal myelination process occurring during brain development.[71,72]Progesterone's ability to limit inflammation could therefore have age- and brain region-specific neuroprotection.

A fourth key aspect of the immature brain is the dominant role that apoptotic cell death cascades play after injury. With normal programmed cell death that occurs in the postnatal period, proapoptotic proteins are expressed at higher levels in the immature brain. This could increase vulnerability to molecular cell death cascades after developmental brain injury.[73]Accordingly, progesterone's ability to increase

antiapoptotic Bcl-2 protein levels while decreasing proapoptotic protein levels could be beneficial. There are many other aspects of developmental neurobiology that could influence efficacy of progesterone in the young brain, such as protection against mitochondrial dysfunction and improvement in neurogenesis. In summary, studies evaluating the neuroprotective features of progesterone must take into account the age-specific mechanisms of secondary injury and recovery after pediatric TBI.

Overview of Studies Utilizing Progesterone in the Developing Brain

There are few studies which evaluated the effects of progesterone in the developing brain. One of the important questions regarding progesterone treatment is whether TBI leads to alterations in the levels of progesterone or its receptor. Although this has not been examined after pediatric TBI, experimental studies in immature seizure and ischemia models report changes in progesterone and its receptor levels early after injury depending on the insult and time after injury. For example, when postnatal day 7 (P7) old female rats were exposed to hypoxia only (6.5% oxygen for 50 min) or hypoxia plus ischemia (HI, ligature of the right carotid artery), progesterone receptor levels decreased at 48 hours after hypoxia and markedly increased at 7 days after hypoxia and HI versus control.[74] Progesterone and estradiol secretion at 3 and 8 months were unaffected by HI, but levels were not evaluated at earlier times. González-Ramírez et al[75] showed that serum progesterone levels increase 5- to 6-fold at 30 minutes and 24 hours after pentylenetetrazol-induced seizures in P10 male and female rats. These limited studies of progesterone and progesterone receptor levels after brain injury would suggest that the mechanism of injury and timing after injury are important considerations when evaluating progesterone for treatment.

A recent study in adult TBI show that compared with controls, cerebrospinal fluid (CSF) progesterone levels were significantly and persistently elevated during the first 2 days after TBI, and high CSF progesterone levels were associated with worse Glasgow Outcome Scale (GOS) at 6 months in bivariate analysis.[76] In multivariate analysis, high CSF progesterone was indirectly associated with worse outcome through its interactions with cortisol as progesterone is a precursor to cortisol. Thus, it is possible that brain interstitial and CSF levels of progesterone and its physiologically active metabolites (such as allopregnanolone) may be an important determinant of recovery in the injured brain. Progesterone and its metabolites have been associated with anticonvulsant effects,[77,78] most likely by acting as powerful positive modulators of $GABA_A$ receptors in the brain.[79,80]Corroborating this finding, Holmes and Weber[81] demonstrated that while progesterone does not have effect on kindling in the adult animal, it markedly inhibits kindling in immature animals and prevents generalization of seizures.

As discussed in the previous section, GABA is excitatory for immature neurons, whereas it is inhibitory for mature neurons. Consistent with this, a recent study reported that exogenous administration of progesterone and allopregnanolone exacerbated brain injury in an age-dependent manner.[82]Progesterone (10 mg/kg), allopregnanolone (10 mg/kg), or vehicle was intraperitoneally administered immediately before and then subcutaneously at 6 and 24 hours after hypoxia-ischemia, using the Rice-Vannucci

model,[83]to P7, P14, and P21 male and female rats. Both progesterone and allopregnanolone exacerbated hemispheric volume loss and histopathological injury score in P7 and P14 rats but not in P21 rats. Coadministration of the $GABA_A$ receptor antagonist, bicuculline, partially mitigated the exacerbating effect of allopregnanolone. The authors concluded that the detrimental effects of progesterone were most likely due to GABAergic neuroexcitatory activity of allopregnanolone. Although the authors identified a potential mechanism for the detrimental effects of progesterone and allopregnanolone in their model, levels of progesterone, allopregnanolone in serum and brain, and their corresponding receptors in the brain were not analyzed. It is possible that if the levels of progesterone receptor are decreased after injury as shown previously,[74] one might observe off-target effects of the drug more often. Nevertheless, this study suggests that caution is required when considering progesterone and its metabolites for neuroprotection in the immature brain.

Two recent studies evaluated the neuroprotective effect of progesterone alone or in combination with magnesium after TBI in the developing brain.[84,85] Mixed gender 7-day-old Wistar rats were exposed to weight drop injury, and progesterone or magnesium sulfate was administered intraperitoneally immediately after TBI. Combination therapy was found to be superior to progesterone alone for improving long-term (3 wk) neuronal survival in the dentate gyrus, while treatment with progesterone alone, magnesium alone, or the two in combination reduced the extent of apoptotic cell death profiles. Furthermore, spatial learning and memory retention at 3 weeks after injury were improved by treatment with progesterone alone, magnesium alone, or the two in combination.[84] In a separate study, the authors reported that progesterone decreased TBI-induced anxiety in the immature rat,[85] thought to be related to attenuation of TBI-induced changes in circulating corticosterone and insulin-like growth factor levels by progesterone. Further studies in different models of TBI in the immature brain are needed to determine whether progesterone is beneficial in contusional head injury.

Interestingly, studies performed in a single center in extremely preterm infants report improved neurodevelopmental outcome with exogenous combined estrogen and progesterone administration.[86,87] The initial aim of these studies was to evaluate the impact of estradiol and progesterone replacement on postnatal bone mineral accretion.[86,88] Male and female infants less than 1,000 g were randomized to receive either estradiol and progesterone emulsion or placebo containing same amount of lipids for 4 weeks after birth. The authors followed circulating estrogen and progesterone levels in the patients and aimed to maintain plasma levels equaling intrauterine levels. At the follow-up examination at 5-year corrected age,[87] a significant time-response relationship was found: every day of treatment with estrogen and progesterone was associated with a reduced risk for cerebral palsy, spasticity, and ametropia. Although these results are promising, multicenter trials are necessary to test beneficial effects of estrogen and progesterone on neurodevelopmental outcome in extremely preterm infants.

Clinical Trials of Progesterone for Adult TBI

To date, two human trials of progesterone for TBI in adults have been published.[89,90] A phase II trial was conducted by Wright et al[89] in 2007 to gather data on drug safety and to determine the pharmacokinetics of IV progesterone in moderate-to-severely injured adult patients (age > 17 yr; Glasgow Coma Scale [GCS] scores, 4–12). One hundred patients were randomly assigned to receive either a 72-hour IV infusion of progesterone (0.71 mg/kg over 1 hr and then 0.5 mg/kg/hr given by infusion for 12 hr/d for 3 d, with a 2-day taper) or an equal volume of placebo. No serious adverse events were attributed to the study drug. Patients treated with progesterone had mortality rates less than one half of controls and had nearly identical rates of adverse events compared with controls. Moderately brain-injured patients treated with progesterone were less disabled 30 days after injury than similarly injured patients treated with placebo ($p = 0.02$). These findings suggested that IV progesterone is safe at the dose selected.

Another recent phase II trial demonstrated the potential of progesterone to treat brain-injured adults. This was a single-site, prospective, randomized, placebo-controlled trial of progesterone conducted in Hangzhou, China, by Xiao et al.[90] The primary purpose of this trial was to assess the long-term efficacy of progesterone on neurologic outcome of patients with severe TBI (GCS ≤ 8). A total of 159 patients were enrolled and randomized to receive either intramuscular progesterone (1 mg/kg intramuscular Q12 for 5 d) or placebo. The primary endpoint was the GOS score 3 months after brain injury. Secondary efficacy endpoints included the modified Functional Independence Measure (FIM) score and mortality. Three months after treatment, the dichotomized GOS showed a favorable outcome for 47% of the patients given progesterone and 31% in the placebo group ($p = 0.034$) and an unfavorable outcome for 53% of the patients given progesterone and 70% in the placebo group ($p = 0.022$), with similar outcomes at 6 months. The 6-month-modified FIM scores suggested good functional outcome in the patients treated with progesterone. There were no adverse events associated with progesterone.

The Neurologic Emergencies Treatment Trials Network has commenced a large, multicenter National Institutes of Health (NIH)-funded phase III trial of progesterone for adults with moderate-to-severe TBI (Progesterone for Traumatic Brain Injury: Experimental Clinical Treatment: Phase III Clinical Trial III).[91,92] The purpose of this trial is to determine the efficacy of administering IV progesterone (initiated within 4 hr of injury, administered for 72 hr, with an additional 24-hr taper) versus placebo for treating adult victims of moderate-to-severe acute TBI (GCS score, 4–12), using the same dosing as previously discussed in the study by Wright et al.[89] The main outcome measure is the GOS-Extended score at 6 months post injury. The total sample size was planned for 1,140 subjects. The NIH announced in January 2014 that enrollment in the trial had been stopped by the independent Data Safety Monitoring Board, when interim review indicated that it was very unlikely that progesterone would demonstrate better outcomes compared with placebo in this trial.

In addition, BHR Pharma LLC is conducting SyNAPSe (Study of the Neuroprotective Activity of Progesterone in Severe Traumatic Brain Injuries), a global, phase 3, multicenter trial in severe TBI.[93] This study evaluates the effectiveness of its proprietary BHR-100 progesterone product as a neuroprotective agent for treating patients with severe TBI. Approximately 1,200 patients who are 16–65 years old with severe (GCS scores, 3–8), closed-head TBI are being enrolled in the study at ~150 centers worldwide. Patients are randomized in a one-to-one allocation to receive progesterone or placebo. The treatment is administered as a 5-day/120-hour, continuous IV infusion starting within 8 hours after injury. The primary study endpoint is the GOS at 6 months. This study completed enrollment, and we await the final results regarding outcome. The stopping of the ProTECT III trial certainly has implications for the future study of progesterone treatment for pediatric TBI. It is likely that investigators will need to evaluate the results of the completed SyNAPSe study, as well as the interim results of the ProTECT III study, before moving forward to clinical trials in pediatric TBI.

Future Studies and Conclusions

Traumatic brain injuries differ between children and adults. Although it is believed that the immature brain recovers more fully from TBI, studies indicate that cerebral edema after TBI is three times more likely to occur in children than in adults. This suggests that a novel therapy such as progesterone, which decreases cerebral edema, may have a greater effect on children than adults. Although neurocognitive outcomes are better for children than for adults after TBI in general, neurocognitive recovery and its measurement after TBI are dependent on age and developmental level.[94,95] Because of the differences between children and adults, and the lack of effective treatment for TBI, there is a need to complete the preclinical studies necessary to prepare for a potential pediatric clinical trial of progesterone administration. The results of this research could lead to the development of a novel neuroprotective therapy with potential to reduce the profound long-term disability in head-injured children. This information could also contribute to the use of progesterone in the treatment of pediatric brain injury from other causes (cardiac arrest, stroke, and seizures).

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