PERSPECTIVE

Can progesterone be a better alternative to dexamethasone for use in routine brain surgery?

Can progesterone be a better alternative to dexamethasone for use in routine brain surgery? Surgical brain injury (SBI) is a form of brain trauma caused by various forms of neurosurgical interventions including brain tumor excision, evacuation of intracerebral hemorrhage and brain lobectomy (*e.g.*, in epilepsy surgery). Cerebral edema and brain swelling typically occurs soon after SBI and commonly peaks on post-operative days 3 to 7. SBI may cause secondary damages due to disruption of the blood-brain barrier (BBB), release of inflammatory cytokines (*e.g.*, tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, toll-like receptor (TLR-2) and TLR-4) as well as increased expressions of Fas and Fas-L, free radical overload, dysfunctions of membrane ionic pumps and many other pathophysiological changes (Pan et al., 2007). Severe cerebral edema may eventually lead to elevated intracranial pressure (ICP), neurological deterioration or even death. Other long-term effects in survivors include sensori-motor and cognitive dysfunctions due to secondary, delayed degenerative changes. Given the large number of routine neurosurgical operations performed worldwide on a day-to-day basis, the prevention of SBI is just as important as the treatment of accident-related traumatic brain injury (TBI). The latter differs from SBI in that it is not amendable to pre-emptive therapy whereas SBI can theoretically be prevented, at least during routine elective surgery. The issue of using the best way to prevent cerebral edema and secondary damages in these situations are critical and deserve our research effort.

Glucocorticoids in neurosurgical clinical practices: Traditionally, dexamethasone (DEXA) and other glucocorticoids (GCs) have been used as adjunctive agents during neurosurgical operations to reduce brain edema, maintain BBB integrity and minimize inflammatory responses. It has also been used in TBI patients since 1960s. However, several major studies conducted between 1979 and 2004 demonstrated that the use of GCs in severe TBI had no beneficial effect and may in fact be deleterious (Guidelines for the Management of Severe Traumatic Brain Injury, 2007). Given that SBI is essentially a form of brain trauma also, there is no logical reason why GCs should be beneficial in SBI. In this respect, our group has been investigating alternative strategies for the treatment of SBI.

The early use of DEXA and other synthetic GCs as neurosurgical adjuncts began with a series of preclinical investigations which reported encouraging experimental results in the treatment of cerebral edema (Guidelines for the Management of Severe Traumatic Brain Injury, 2007). GCs were found to have the abilities to restore BBB integrity and to prevent further leakage of intravascular fluid into the cerebral intercellular space. These were thought to be particularly important findings because cerebral edema in TBI is commonly vasogenic in origin that represents one of the key underling mechanisms of subsequent brain swelling (Bebawy, 2012). These favorable experimental results prompted the use of GCs as a "standard treatment" for TBI patients. Later studies, however, did not show consistently positive results and it was found that GCs would have no effect on cytotoxic brain edema, which is another important mechanistic process underlying the development of post-traumatic edema. Other investigators soon concluded that there was no evidence to support the routine use of GCs in regulating ICP and improving the overall outcome of TBI patients (Guidelines for the Management of Severe Traumatic Brain Injury, 2007). Moreover, due to its pharmacological properties, GCs have many side effects, including glucose intolerance, immunosuppression, osteoporosis, myopathy, gastric erosion and neuropsychiatric problems, all of which can cause post-operative morbidities or even mortalities (Bebawy, 2012). One of the latest clinical trials has also established that the use of GCs is detrimental and contraindicated in patients with TBI (Guidelines for the Management of Severe Traumatic Brain Injury, 2007). A search for alternative agents is needed and progesterone has emerged as a potential promising candidate.

Progesterone for SBI: The therapeutic effect of progesterone in TBI has been extensively studied over the last 25 years. Progesterone is a pleiotropic agent that is commonly known as a gonadal hormone but is now also recognized as an important neurosteroid. Progesterone is synthesized in the central nervous system (CNS) where it performs many important biological functions (Melcangi et al., 2008). It displays fewer systemic side effects and a wider therapeutic window than GCs in patients with TBI (Xiao et al., 2008). Preclinical experiments have also demonstrated encouraging results of progesterone's effects in the reduction of brain edema and in providing neuroprotection by means of its anti-inflammatory, anti-apoptotic, antioxidant and anti-excitatory properties (Stein, 2008).

Our laboratory group has conducted two related pilot studies. In the first study, we investigated the effect of systemic progesterone on the brain's cellular inflammatory response to electrocautery-induced injury. Electrocautery is a standard hemostatic technique in neurosurgical practice. It uses thermal energy to stop bleeding but can at the same time cause additional brain trauma due to heat dissipation. Progesterone was found to significantly reduce astrocytic hypertrophy and macrophage infiltration following electrocautery (Un et al., 2013). In our second study, we compared progesterone with DEXA in their effects on brain edema and inflammatory responses following experimental brain resection (Xu et al., 2014). The experimental model involved a partial frontal lobectomy in male rodents that mimicked a common situation in daily neurosurgical procedures for elective brain tumor excision or the treatment of severe TBI. Two escalating dosages (10 and 20 mg/kg) were used and compared with the therapeutic effects of DEXA in terms of subsequent BBB disruption, brain water content and cellular inflammation around the resection area. Our results demonstrated greater beneficial effects of progesterone. Progesterone resulted in a significant reduction of brain water content and extravasation of Evan's Blue (EB) dye, indicating higher integrity of BBB, in all treatment groups than control. The expression levels of glial fibrillary acidic protein (GFAP), ionized calcium-binding adapter molecule 1 (IBA1) and matrix metalloproteinase (MMP)-9 in all hormone-treated groups were significantly lower than those in the control group. With respect to the dosage and time window for progesterone administration, the lower dose was found to be more effective than high dose in relieving acute cellular inflammatory responses when the treatment was given at 1 hour after operation. Although no difference was found between progesterone and DEXA, the study showed that progesterone should be considered as a non-inferior alternative to DEXA as an adjunctive agent for the protection against SBI in daily neurosurgical practices. When compared with other neuroprotective agents, progesterone has the advantages of being inexpensive and readily accessible, and can therefore be readily applied in clinical practice.

Further studies are clearly needed to understand the underlying mechanisms of progesterone's action in SBI and how they may differ from the situation of TBI. Many preclinical investigations have reported that progesterone could up-regulate the expression of p-glycoprotein, leading to an increase in efflux pump activities along the BBB, thereby reducing brain edema. In TBI, Guo et al. (2006) showed increased water content in pericontusional regions that were accompanied by an increase in aquaporin (AQP)-4 gene expression. After the treatment of progesterone, the expression of AQP4 decreased and there was a reduction in brain water content in the ipsilateral hemisphere. Our studies suggested that a similar mechanism might also be at play in SBI. Another interesting issue concerns gender differences due to physiological fluctuations of serum progesterone level in female animals. According to the pioneering study by Stein et al. (2008) in rodent TBI, male rats developed more severe cerebral damages and brain edema than female rats at 24 hours post-injury. Female rats also recovered faster than male ones. Furthermore, female rats with higher serum progesterone levels demonstrated remarkably little cerebral edema when compared with female rats with lower serum progesterone levels. The introduction of exogenous progesterone to male rats resulted

in a reduction of cerebral edema, lesion volume and neuronal loss, as well as improved cognitive outcomes in the Moore water maze test. Stein's group also suggested that the therapeutic window for progesterone would be up to 24 hours after TBI (Stein, 2008). This is likely to be related to the time taken for the onset of acute cellular inflammatory responses. In clinical practice, this therapeutic window allows surgeons to give treatment when inadvertent injures have been inflicted during an otherwise uneventful operation.

Progesterone for TBI: Although many preclinical studies and several early clinical trials have reported promising findings of using progesterone in TBI, the latest randomized controlled clinical trial had reported negative results (Wright el al., 2014). In the latter study, progesterone did not improve patient outcome over control. This was disappointing but not entirely unexpected since clinical TBI involves highly heterogeneous patient subgroups, each of which has complex and unique pathophysiologies and associated complications (*e.g.*, different degrees of vasogenic versus cytotoxic edema) (Schwamm, 2014). This contrasts with the situation in experimental laboratory studies where conditions are controlled and standardized. The failure to recapitulate preclinical findings has been a long-standing problem in TBI research. To overcome this would require detailed risk stratification, the use of relevant biomarkers as well as the testing of multiple therapeutic windows and treatment regimens, all of which can be very demanding to execute in clinical settings. Progesterone is a very versatile neuroprotective agent that can provide benefits in many neurological conditions other than TBI (Deutsch et al., 2013). When compared with TBI, SBI causes less heterogeneous pathological changes in the brain and may potentially show more consistent responses to progesterone. Whether the same problems with clinical translation would occur in using progesterone for SBI remains to be determined. It must be noted that the negative TBI trial did not include any comparison with GCs which is the main area of investigations in the present context of SBI.

Effects of progesterone on neurogenesis and neuroplasticity: The therapeutic effects of progesterone may extend beyond that provided by its neuroprotective properties. The abilities of progesterone to promote neurogenesis and neuroplasticity also deserve attention. In the peripheral nervous system (PNS), progesterone could promote the formation of myelin sheaths and axonal regeneration in rodent sciatic nerve following cryolesioning, and may also promote remyelination in peripheral neuropathies (Schumacher et al., 2012). For the CNS, the influence of progesterone has so far been under investigated, but it is known that progesterone plays critical roles in the development of the perinatal brain, and the expression of progesterone receptors is essential during the critical maturation phase of rodent forebrain (Wagner, 2006).

Anti-tumor effects of progesterone in malignant brain glioma: Many experimental studies have reported progesterone's significant anti-proliferative and cytotoxic effects in breast, endometrial, ovarian, colon and salivary gland tumors both *in vitro* and *in vivo*. The latest study of its anti-tumor effect in malignant brain glioma showed the involvement of the signaling pathways of PI3K, Akt, mTOR and p53 (Atif et al., 2015). Progesterone at high concentrations had an inhibitory effect in human glioblastoma cells, which is the commonest form of primary malignant brain tumor. Using a subcutaneous tumor xenograft model, supra-physiological dosages of progesterone could decrease tumor size by approximately 50% after 8 days of therapy. Progesterone treatment also prolonged animal survival time; systemic toxicity was minimal despite the high dosage used. This represents another important reason why progesterone should be considered as an alternative to DEXA, which is commonly used to reduce tumor-induced brain oedema in neurosurgical practice. We surmise that these properties of progesterone in malignant glioma will facilitate neurosurgical procedures and help to reduce postoperative complications by reducing tumor-induced edema as well as the potentially deleterious effects of tumor resection.

Conclusion: GCs have been widely used as adjunctive agents to reduce brain edema and control inflammation responses during routine brain surgery. However, their detrimental effects in TBI are now well established. SBI is a form of brain injury and it is only logical to hypothesize that GCs may also be potentially harmful in SBI. The neuroprotective effects and potential anti-tumor and pro-regenerative properties of progesterone suggest that it may be a better alternative to GCs. Further studies are needed to explore its use in the prevention and treatment of SBI.

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***Accepted:** *2015-06-16*
doi:** *10.4103/1673-5374.165221* **http://www.nrronline.org/*
Cheng SY, Leung GK (2015) Can progesterone be a better alternative to dexamethasone for use in routine brain surgery? Neural Regen Res 10(9):1379-1380.

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