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Commentary: Progesterone the protector?

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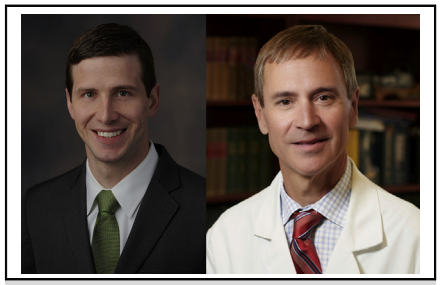

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CENTRAL MESSAGE

Progesterone is a promising therapy for neuroprotection in states of hypoxia in small animals, but further studies in man are needed to confirm its clinical applicability to cyanotic heart disease.

Neurodevelopmental delay and deficits remain among the most feared consequences of surgery in children with cyanotic congenital heart disease. With improving survival rates of surgical correction and palliation has been an increasing focus on neurodevelopmental outcomes—particularly because the majority of these children are expected to survive to adulthood.[1,2] Whereas most previous investigations have targeted the surgical contributions to neurodevelopmental outcomes, Lui and colleagues[3] provide a refreshing and novel experimental model exploring the potential neuroprotective effects of progesterone on brain development.

The authors clearly identify a mechanism for poor neurologic outcomes in cyanotic heart disease and eloquently identify and explore a therapeutic intervention to potentially reverse the insult. The investigation is thorough, exploring the effects of progesterone at the gross pathological level down to the subcellular level, and the results are promising. By comparing 3 groups (control, hypoxia, and hypoxia with progesterone), the authors were able to demonstrate that chronic hypoxia significantly increases the size of the ventricles, increases white matter loss, and is associated with lower brain weights and worse performance on Rotarod experiments (evaluating motor skill and coordination) compared with controls. Remarkably, all these effects were significantly mitigated with the daily administration of progesterone. These beneficial effects of progesterone were also redemonstrated at the cellular level by showing a significant increase in the number of mature oligodendrocytes and increased myelin basic protein expression. Furthermore, the authors identified a potential mechanism of protection by confirming that progesterone significantly increased the levels of the anti-inflammatory microglia phenotype M2.

Other groups have recently evaluated the neuroprotective benefits of progesterone, and their results are similarly promising. Fabres and coinvestigators[4] recently studied the effects of progesterone administration before, during, and after hypoxia. Importantly, they demonstrated that progesterone reduces the loss of brain tissue, reduces activity of apoptotic enzymes, and reduces reactive gliosis when administered at all 3 time points.

Although the results of this study and others are promising, we are still far from clinical applicability. Many questions remain unanswered: is it safe, when and how long should it be given, and perhaps most importantly, are the results reproducible in man. The difficulty in answering these questions lies in the challenges in experimental design of testing it in humans. In particular, outcome measures of gliosis, apoptosis, microglial phenotype, and white matter loss are extremely challenging if not impossible to assess clinically. Nonetheless, the authors should be commended on their well-designed study, and their promising results have paved the way for further investigation.

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