

The search continues: neuroprotection for all neonates with hypoxic-ischemic encephalopathy

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Provenance: This is an invited Editorial commissioned by Section Editor Dr. Ming Zhong (Department of Critical Care Medicine, Zhongshan Hospital, Fudan University, Shanghai, China).

Comment on: Shankaran S, Laptook AR, Pappas A, *et al.* Effect of Depth and Duration of Cooling on Death or Disability at Age 18 Months Among Neonates With Hypoxic-Ischemic Encephalopathy A Randomized Clinical Trial. *JAMA* 2017;318:57-67.

Submitted Aug 25, 2017. Accepted for publication Sep 08, 2017.

doi: 10.21037/jtd.2017.09.64

View this article at: <http://dx.doi.org/10.21037/jtd.2017.09.64>

Hypoxic-ischemic encephalopathy (HIE) from peripartum complications is a leading cause of neonatal brain injury. Inducing therapeutic hypothermia within 6 hours of birth to 33.0–34.0 °C for 72 hours is the standard of care for moderate to severe encephalopathy in many developed countries. The protection afforded by hypothermia is incomplete, however, as nearly half of hypothermia-treated survivors suffer persistent moderate to severe neurologic disabilities (1,2). Therefore, we continue to search for therapeutic strategies that can provide full neuroprotection in all neonates with HIE.

Dr. Shankaran *et al.* report their findings from a multicenter randomized trial to test deeper, longer, or deeper and longer cooling for neonates with HIE in “Effect of Depth and Duration of Cooling on Death or Disability at Age 18 Months Among Neonates with HIE: A Randomized Clinical Trial”. After determining that the predicted probability of detecting a decrease in in-hospital mortality was less than 2% with longer or deeper cooling, the study was stopped for safety and futility. Bradycardia, inhaled nitric oxide use, extracorporeal membrane oxygenation use, and longer duration of oxygen therapy were more common in neonates cooled to 32.0 °C than in those cooled to 33.0–34.0 °C. The risks of arrhythmia, anuria, and longer hospital stay were also greater in neonates cooled for 120 hours than in those cooled for 72 hours (3). In the more

recent report of outcomes at 18 months, deeper cooling to 32.0 °C or longer cooling for 120 hours did not reduce rates of death or disability. Additionally, a significant interaction between cooling depth and cooling duration raised concerns about increased mortality when these interventions were combined (4). Preclinical studies also have shown that cooling to lower temperatures does not provide additional neuroprotection (5) and might be detrimental (6).

Hypothermia is the primary and most widely available brain-focused treatment for HIE. Until the advent of hypothermia, no other targeted therapies for HIE reached wide-scale clinical investigation. Hypothermia opened the door for neurotherapeutic clinical trials and stimulated the development of modern neonatal neurocritical care. Though we do not know precisely how hypothermia protects the brain, decades of preclinical studies have demonstrated that it reduces hypoxia-induced inflammation, oxidative stress, cytotoxic edema, excitotoxicity, energy failure, and the resulting neural cell death. The rationale for clinically testing hypothermia depth and duration was based on data from small and large-animal studies (7) coupled with the incomplete neuroprotection observed in a high proportion of infants cooled for HIE. Dr. Shankaran's study (4) suggests that improving neurologic outcomes after HIE will require approaches beyond hypothermia.

Limited evidence suggests that hypothermia's failure to

fully protect the brain could be due, in part, to potential adverse effects of hypothermia and rewarming on the developing brain (8,9). Therapeutic hypothermia for HIE usually involves rewarming at 0.5 °C/h (10), and the Therapeutic Hypothermia After Pediatric Cardiac Arrest trial (11) rewarmed children at approximately 0.25 °C/h. Research supporting either rewarming rate after neonatal or pediatric global hypoxia is limited. Seizures may occur during rewarming at 0.5 °C/h (12), and rapid rewarming promotes cortical apoptosis in a piglet model of HIE (13). It is unclear whether potential benefits from slow rewarming are due to the rewarming rate or the longer duration of hypothermia that occurs with slow rewarming.

We must continue our search for adjuvant treatments that either improve hypothermia's neuroprotective efficacy or offer additional protection through mechanisms unrelated to hypothermia. Preclinical and early clinical trials have focused on xenon, allopurinol, topiramate, iminobiotin, umbilical cord blood transfusions, and other strategies. Erythropoietin is currently under phase III clinical investigation (NCT# 02811263). Numerous preclinical studies also show additive neuroprotection from combining hypothermia with adjuvant therapies.

Tailoring treatments to meet the needs of individual neonates might also improve outcomes. For example, it is possible that longer cooling might improve neuroprotection in a subset of patients with evidence of ongoing brain injury during hypothermia and rewarming. Brain injury biomarkers, such as circulating blood-based analytes (14,15) or physiologic measures of autonomic dysfunction (16,17), might be able to identify neonates at greatest risk of severe brain injury and provide real-time feedback on treatment efficacy. Optimizing cerebrovascular blood pressure autoregulation (18-20) with individualized hemodynamic goals and avoiding hypocapnia (21) might also improve outcomes. Moreover, current intrapartum fetal monitoring techniques do not sufficiently identify babies at risk of intrapartum hypoxia. Improving intrapartum monitoring to detect ongoing fetal hypoxia and identifying effective maternal-fetal interventions may enable a paradigm shift towards preventing HIE.

While Dr. Shankaran's study encourages future focus on neuroprotective strategies beyond hypothermia, ongoing studies will address important remaining questions about cooling. The risks and benefits of delayed hypothermia in those who cannot be cooled within 6 hours of birth will be answered shortly by the Neonatology Research Network Late Hypothermia for HIE trial (NCT00614744). Preclinical studies indicate that delaying the induction of hypothermia

reduces neuroprotection, and this trial will address whether this therapeutic window applies to clinical practice. Most HIE trials have enrolled only full-term or near-term gestation infants. Hypothermic treatment for premature infants with neonatal encephalopathy is now being studied (NCT01793129) (22). Active servo-controlled cooling (23) with full physiologic monitoring during transport may prevent delays in hypothermia induction and enable cooling for at risk neonates who cannot be transferred to a tertiary care hospital within 6 hours of birth. Though it is tempting to speculate that outcomes could be improved by initiating cooling immediately after birth in all newborns with intrapartum complications, the risks of hypothermia, such as cardiac arrhythmias, electrolyte abnormalities, coagulopathy, and leukopenia (22,24) generally necessitate that HIE be diagnosed prior to cooling.

Our basic science training and research grant systems encourage us to focus on specific neural injury and cell death pathways (25). For instance, we may become experts in inflammation or oxidative stress after neonatal hypoxia. We then test treatments oriented to that specific pathway using tools such as preclinical genetic knockdown models. Though research that focuses on specific mechanisms of injury is important, we must consider that effective clinical strategies will likely need to target multiple pathways simultaneously and use a combination of therapeutic approaches. The fact that hypothermia affects multiple mechanistic pathways is one of the primary reasons for its success in clinical medicine when numerous other more specifically targeted therapies have failed. We must ensure that our preclinical research remains translationally relevant and applicable to clinical HIE and therapeutic hypothermia, as this is the current standard of clinical care. Moreover, some mechanisms of neural injury in encephalopathic newborns may be unrelated to hypoxia-ischemia and unresponsive to hypothermia.

Dr. Shankaran should be commended for her tremendous contributions to neonatal resuscitation medicine as it relates to HIE and other neonatal brain injuries. She, along with many others, laid the groundwork for the only neuroprotective treatment clinically available for HIE today. We remain optimistic that the collective work of basic science, translational, and clinical researchers will one day improve the outlook for all neonates with HIE.

Acknowledgements

None.

Footnote

Conflicts of Interest: Dr. Lee and Dr. Northington received research support from Medtronic for a separate study. Dr. Lee was also a paid advisory board member for Medtronic. This arrangement has been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies.

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Cite this article as: Lee JK, Massaro AN, Northington FJ. The search continues: neuroprotection for all neonates with hypoxic-ischemic encephalopathy. *J Thorac Dis* 2017;9(10):3553-3556. doi:10.21037/jtd.2017.09.64