

## Systemic Hypothermia — A “Cool” Therapy for Neonatal Hypoxic–Ischemic Encephalopathy

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Hypoxic–ischemic encephalopathy is an important cause of death and disability in full-term infants. The incidence of moderate or severe hypoxic–ischemic encephalopathy has remained essentially unchanged over the past 20 years, at 1.5 to 2 per 1000 live births in the United States. Approximately 15 to 20 percent of these infants will die, and 20 to 25 percent of those who survive will be disabled.<sup>1,2</sup> Prevention is problematic, as the initiating event may occur before the onset of labor, and there are no proven effective therapies.

Brain injury is a process that begins with a hypoxic–ischemic event and evolves after resuscitation. Studies in human infants and animal models indicate that there is an interval of several hours after resuscitation during which a therapeutic intervention might effectively reduce the severity of the ultimate brain damage.<sup>3–5</sup> Brain cooling is one possible therapy and has been studied extensively in newborn animal models of hypoxia–ischemia. Pilot trials of brain cooling achieved by either selective cooling of the head or systemic hypothermia suggested that applying this therapy to neonates with hypoxic–ischemic encephalopathy is feasible and potentially beneficial.<sup>6–9</sup>

In a recently published, large, randomized clinical trial of brain cooling for neonatal encephalopathy, there was no significant reduction in the rate of death or severe disability at 18 months of age in neonates assigned within 6 hours of birth to selective brain cooling with mild systemic hypothermia for 72 hours.<sup>10</sup> Infants were enrolled in the trial if they had severe acidosis or required resuscitation at birth, clinical signs of moderate or severe encephalopathy, and abnormal results of amplitude-integrated electroencephalography (aEEG), a technique that permits the continuous monitoring of cerebral electrical background activity at the bedside. The method used to cool the brain included fitting a cooling cap around the head and maintaining the rectal temperature at 34°C to 35°C. In a prespecified subgroup analysis there was no effect of treatment on the outcome in infants with the most severe changes on an aEEG at the time of enrollment, but infants with less severe changes showed significant benefit. However, the study had insufficient power to assess subgroup effects definitively.

In this issue of the *Journal*, Shankaran et al. report the results of a large, randomized clinical trial of brain cooling by means of systemic hypothermia as a treatment for neonatal hypoxic–ischemic encephalopathy.<sup>11</sup> Infants with clinical signs of moderate or severe encephalopathy who were six hours of age or younger and had either severe acidosis or perinatal complications and a need for resuscitation at birth were included. Systemic hypothermia was accomplished by placing infants on a water blanket precooled to 5°C and regulating the temperature of the blanket to maintain an esophageal temperature of 33.5°C for 72 hours. The use of a second cooling blanket minimized fluctuations in esophageal temperature. Systemic hypothermia resulted in a significant 18 percent reduction in the rate of death or moderate or severe disability at 18 to 22 months of age. Potential adverse consequences of whole-body hypothermia, such as cardiac arrhythmias, were rare and not clinically significant, confirming the findings of the earlier trial that brain cooling is safe under controlled conditions. In addition, there was a reduction in both death and moderate or severe disability, allaying concern that head cooling would increase the number of surviving infants with disabilities.

How might the positive findings of the present report be reconciled with the lack of significant benefit overall in the earlier trial? The current trial used systemic hypothermia, whereas the previous study used selective head cooling with mild systemic hypothermia. However, both provide adequate brain cooling in studies in animals.<sup>12</sup> Because the protective effects of brain cooling depend on the timing of the onset of cooling, an important consideration is how quickly brain cooling is achieved.<sup>13</sup> In the current report by Shankaran et al., randomization took place at a mean age of 4.3 hours and brain cooling was achieved in less than 1 hour, as compared with a mean age of 4.8 hours and cooling within 1 to 2 hours in the previous trial. Enrollment at an earlier age and faster achievement of brain cooling with systemic hypothermia may have contributed to the greater benefit observed in the present study. However, there is insufficient information to decide whether one method is more effective. Another possible explanation for the discrep-

ant results is that the severity of brain injury may have differed in the two reports. The current trial included infants with clinical signs of moderate or severe encephalopathy, whereas the previous trial required additional evidence of an abnormal aEEG.

Overall, the benefit of hypothermia in the current report was relatively small. In studies in animals, the beneficial effects of brain cooling require the onset of cooling within 5.5 hours of the hypoxic-ischemic event.<sup>5,14</sup> Because the timing of the hypoxic-ischemic event in most neonates is unknown, the onset of cooling in the current study may have been too late to benefit some infants.

It is also possible that the inclusion in the study of infants who could not benefit from hypothermia because of irreversible brain injury, as well as infants whose encephalopathy was not caused by hypoxia-ischemia, resulted in an underestimate of the possible benefit of this therapy with a better selection of candidates. A neurologic examination in combination with aEEG may be more discriminating.<sup>15</sup> More information regarding the value of aEEG as a screening tool is expected in the next year or two, when additional large, randomized clinical trials of brain cooling are completed.

In the United States, neonates with hypoxic-ischemic encephalopathy are frequently born in community hospitals to women whose pregnancies are uncomplicated, and they are subsequently referred to a neonatal center; transfer to a center that can provide brain cooling within the time frame required may not be possible in many cases. These births are rarely predictable, so in order for the use of brain cooling to have widespread application, it will be necessary to determine the feasibility of applying this therapy before transfer to a neonatal center.

The results reported by Shankaran et al. suggest that a useful therapy for neonatal hypoxic-ischemic encephalopathy is a real possibility. However, effective translation of this suggestion into clinical practice will require confirmation of these findings in ongoing randomized trials, as well as a better understanding of which infants are most likely to benefit, how to achieve brain cooling quickly, and the feasibility of applying this technique in the field. Because neurodevelopmental outcome in infancy is an imprecise predictor of later performance, fol-

low-up of treated infants at school age is needed before brain cooling can be considered a beneficial therapy.<sup>2</sup> Until more data are available, this treatment is best considered an experimental technique for which informed parental consent should be obtained. Widespread application of brain cooling in the care of neonates with hypoxic-ischemic encephalopathy would be premature.

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