Effect of longer, deeper cooling for newborns with neurological condition

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Among full-term newborns with moderate or severe hypoxic ischemic encephalopathy (damage to cells in the central nervous system from inadequate oxygen), receiving deeper or longer duration cooling did not reduce risk of neonatal intensive care unit death, compared to usual care, according to a study in the December 24/31 issue of *JAMA*.

Hypoxic ischemic encephalopathy is an important cause of childhood neurodevelopmental deficits among infants born at full-term. Hypothermia (reduced body temperature) at 33.5°C for 72 hours reduces death or disability, according to background information in the article. Longer cooling and deeper cooling has been found to be neuroprotective in animal models.

Seetha Shankaran, M.D., of Wayne State University, Detroit, and colleagues conducted a study in which full-term infants were randomly assigned to four hypothermia groups: 33.5°C for 72 hours, 32.0°C for 72 hours, 33.5°C for 120 hours, and 32.0°C for 120 hours, to examine if longer duration and deeper cooling would improve outcomes at 18 to 22 months. Infants admitted to the neonatal intensive care until within 6 hours of birth were candidates for the study when seizures or moderate or severe encephalopathy was present. The trial was closed for safety and futility issues and included 364 infants (of 726 planned).

Mortality in the neonatal intensive care unit (NICU) was 7 percent for the 33.5°C for 72 hours group, 14 percent for the 32.0°C for 72 hours group, 16 percent for the 33.5°C for 120 hours group, and 17 percent for the 32.0°C for 120 hours group.

Among neonates with moderate hypoxic ischemic encephalopathy, death in the NICU occurred in 4 percent in the 72 hours group; 8 percent in the 120 hours group; 7 percent in the 33.5°C group; and in 5 percent in the 32.0°C group. Among neonates with severe hypoxic ischemic encephalopathy, deaths in the NICU occurred in 34 percent in the 72 hours group; 42 percent in the 120 hours group; 31 percent in the 33.5°C group; and in 44 percent in the 32.0°C group.

Safety outcomes were similar between the 120 hours group vs 72 hours group and the 32.0°C group vs 33.5°C group, except major bleeding occurred among 1 percent in the 120 hours group vs 3 percent in the 72 hours group. Futility analysis determined that the probability of detecting a statistically significant benefit for longer cooling, deeper cooling, or both for NICU death was less than 2 percent.

"Among neonates of at least 36 weeks' gestational age with moderate or severe hypoxic ischemic encephalopathy, deeper cooling or longer duration of cooling compared with hypothermia at 33.5°C for 72 hours

did not reduce NICU death. These results have implications for patient care and the design of future trials," the authors conclude.

In an accompanying editorial, Nicola J. Robertson, M.B.Ch.B., Ph.D., and Neil Marlow, D.M., F.Med.Sci., of University College London, United Kingdom, comment on the findings of this study.

"Therapeutic hypothermia would not be a safe and effective therapy in neonatal care if not for the willingness and enthusiasm of neonatologists to take on the extra work needed to enter neonates into clinical trials. In the trial by Shankaran et al, clinical practice did not bear out preceding preclinical studies. However, the persistent high mortality and morbidity found with perinatal asphyxial encephalopathy encourages continuing efforts to improve the efficacy of treatment and minimize intercurrent and subsequent complications from this unpredictable and often devastating condition. The current focus is on adjunct therapies that can augment 72 hours of hypothermic neuroprotection at 33°C to 34°C."

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