Therapeutic Hypothermia

How Can We Optimize This Therapy to Further Improve Outcomes?

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KEYWORDS

• Hypoxic-ischemic encephalopathy • Cooling • Neonate

KEY POINTS

- Therapeutic hypothermia to 33.0°C to 34.0°C for moderate to severe hypoxic-ischemic encephalopathy has been demonstrated to be safe and efficacious in reducing death and disability.
- In addition to the biochemical criteria, evidence of moderate or severe encephalopathy on neurologic examination is a prerequisite to cooling; serial examinations have prognostic utility.
- Avoidance of hypocarbia, hyperoxia, and glucose derangements and detection and control of seizures during cooling are important to optimize outcomes in neonatal encephalopathy.

CURRENT RATES OF MORTALITY AND DISABILITY FOLLOWING HYPOTHERMIA THERAPY

Neonatal encephalopathy is a condition of disordered neonatal brain function and is associated with many risk factors. The incidence of neonatal encephalopathy is estimated to be 3.0 per 1000 live births. Neonatal encephalopathy due to hypoxic-ischemic events is a subset of neonatal encephalopathy and occurs in 1.5 per 1000 livebirths. About 15% to 20% of affected newborns die in the postnatal period, and

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an additional 25% will sustain childhood disabilities.[1] Six randomized clinical trials of induced therapeutic hypothermia (TH) at 33.0°C to 34.0°C for 72 hours for neonatal moderate or severe hypoxic-ischemic encephalopathy (HIE) have demonstrated a decrease in death or disability up to 24 months of age.[2–7] This neuroprotection continues to childhood.[8–10] TH is currently the standard of care for term neonates with encephalopathy due to hypoxia-ischemia.[11] The rate of death or disability in the cooled group ranged from 44% to 55% in these clinical trials. In the most recent Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network's (NICHD NRN) randomized clinical trial of standard cooling at 33.0°C to 34.0°C for 72 hours compared with deeper or longer cooling, the rate of death or disability in the usual care group following neonatal moderate or severe HIE was 29%.[12] This lower rate may be due to fewer infants with severe HIE in the recent trial (23% compared with 38% in the cooled group of the first NICHD NRN trial[3]), lower acuity of neonates, and earlier initiation of cooling.

HOW EFFECTIVE IS THERAPEUTIC HYPOTHERMIA?

TH is an effective therapy to reduce death or disability at 18 months of age after moderate or severe neonatal HIE (typical relative risk [RR] 0.75, 95% confidence interval [CI] 0.68–0.83).[11] TH was also associated with significant reduction in mortality and in disability in survivors.[11] The number needed to treat (NNT) to prevent one case of death or disability is 7,[11] much lower than the NNT of adults receiving statins to prevent cardiovascular disease (n = 72)[13] or that of neonates receiving surfactant to prevent complications of respiratory distress syndrome (n = 25)[14]; thus, TH for moderate or severe HIE is a very robust therapy.

SELECTION OF NEONATES FOR THERAPEUTIC HYPOTHERMIA

It is important to select the appropriate neonates for hypothermia therapy; the safety and efficacy of this therapy has been demonstrated only for neonates with moderate or severe HIE.[11,15] All the clinical trials have had a 2-step process of selection, initially with biochemical evidence of hypoxia-ischemia followed by evolving moderate or severe encephalopathy. In the NICHD NRN trials,[3,12] acidosis was required at birth on cord pH or the first blood gas within 1 hour of age (pH <7.0 or base deficit >16 mmol/L). If a blood gas was not available or the pH was between 7.01 and 7.15 and the base deficit was between 10.0 and 15.9 mmol/L, additional criteria were required, including a history of an acute perinatal event and either a 10-minute Apgar score of 5 or less or assisted ventilation initiated at birth and continued for at least 10 minutes. The second parameter was evidence of moderate or severe encephalopathy on the neurologic examination.

THE NEUROLOGIC EXAMINATION FOR MODERATE OR SEVERE ENCEPHALOPATHY

The clinical trials of hypothermia for neonatal HIE have required 3 or more out of 6 abnormalities in the moderate or severe categories of the neurologic examination or clinical seizures within 6 hours of age for trial eligibility. The CoolCap and TOBY (Total Body Hypothermia for Neonatal Encephalopathy) trials mandated that one of the abnormal categories of the neurologic examination needed to be level of consciousness, and they both also required an abnormal amplitude integrated electroencephalogram (aEEG).[2,4] The NICHD NRN has standardized the examination to minimize examiner variability and promote enrollment of appropriate infants. The examination is challenging because it is subjective and the one performed within 6 hours of age