Outcomes of Hypoxic-Ischemic Encephalopathy in Neonates Treated with Hypothermia

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KEYWORDS

• Encephalopathy • Neonatal • Hypothermia • Outcome • Predictors

KEY POINTS

- Hypothermia for neonatal hypoxic-ischemic encephalopathy is safe and effective in reducing death and disability at 18 months of age.
- This neuroprotection continues into childhood, as demonstrated by a reduction in mortality and major disability at 6 to 7 years of age.
- Outcome at 18 months of age is a good predictor of childhood outcome.

OUTCOMES OF CHILDREN WITH BIRTH DEPRESSION/ENCEPHALOPATHY BEFORE HYPOTHERMIA THERAPY

Before the advent of neuroprotective therapy with hypothermia, studies evaluating outcomes of children born at term with birth depression or encephalopathy were generally cohort studies, each having unique inclusion criteria, evaluation methods, and duration of follow-up. Among these studies, the outcome of children with acute perinatal asphyxia and/or neonatal encephalopathy was a disability rate of 6% to 21% in children with moderate encephalopathy and 42% to 100% in those with severe encephalopathy.[1–5] Among nondisabled children who were able to undergo psychometric and behavioral testing, lower executive function and delays in school readiness (reading, spelling, and arithmetic) and lower scores in language, memory, and sensorimotor perception have been noted.[1,3,6] The possibility of an increase in the rate of symptoms associated with attention-deficit/hyperactivity disorder, including anxiety, depression, attention regulation, time perception, and thought problems, as well as an increased risk of autism has been noted in children with encephalopathy or depression at birth.[6–9] A recent systematic review of long-term neurodevelopmental outcomes after intrauterine and neonatal insults, especially in low- and middle-income countries (LMIC), noted that the 27 studies evaluating 2708 infants reported sequelae

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in 1002 (37%) children. Cognitive, general developmental delay or learning difficulties were noted in 45%, cerebral palsy (CP) in 29%, deafness/hearing loss in 9%, impaired vision/blindness in 26%, gross motor coordination problems in 17%, epilepsy in 12%, and behavioral problems in 1% of children. Multiple impairments were reported in 20.5% of children while at least 1 impairment was noted in 44%, and severe sequelae in at least 1 domain in 27%.[10]

OUTCOMES OF CHILDREN WITH MODERATE OR SEVERE ENCEPHALOPATHY AT 18 MONTHS OF AGE FOLLOWING HYPOTHERMIA THERAPY

All of the randomized controlled trials (RCTs) of neuroprotection with hypothermia for neonatal hypoxic-ischemic encephalopathy (HIE) have had very similar inclusion criteria ($\geq$36 weeks gestational age, severe acidosis or birth depression, moderate or severe encephalopathy with or without an abnormal amplitude-integrated electroencephalogram [aEEG]) and cooling initiated within 6 hours of age. The exclusion criteria were infants of age greater than 6 hours, those with major congenital or chromosomal abnormalities, or those with severe intrauterine growth restriction. The neurodevelopmental assessment tools evaluating 18-month outcome were similar and comparable between trials. Details of the results of the primary outcomes, components of the primary outcome, and predefined secondary outcomes are summarized herein. Predictors of 18-month outcomes are also presented, as this information may be helpful in discussions with families of infants with HIE.

CoolCap Trial

The CoolCap Trial was the first large RCT of hypothermia to be published.[11] Selective head cooling to a target temperature of 34° to 35° for 72 hours, or intensive care alone following moderate or severe encephalopathy and an abnormal aEEG or seizures, was compared among 234 neonates, 116 infants assigned to cooling and 118 to conventional care. Eight infants were lost to follow-up in each group. The primary outcome was mortality or severe neurodevelopmental disability at 18 months. Severe disability was defined as gross motor function level (GMF) of 3 to 5, Bayley Scales of Infant Development (BSID II) with either Mental Development Index (MDI) or a Psychomotor Development Index (PDI) less than 70 (2 standard deviations [SD] below normal), or bilateral cortical visual impairment. Nine survivors did not have MDI scores and 4 of 9 were missing visual outcome data, but all had GMF scores of 3 or higher. Death or severe disability was noted in 59 of 108 (55%) cooled infants versus 73 of 110 (66%) control-group infants, odds ratio (OR) 0.61 (95% confidence interval [CI] 0.34–1.09); with mortality rates of 33% versus 38%, OR 0.81 (0.47–1.41) and severe disability in 14 of 72 (19%) versus 21 of 68 (31%), OR 0.54 (0.25–1.17) in the cooled and control groups, respectively. A Bayley MDI score of lower than 70 occurred in 21 of 70 (30%) versus 24 of 61 (39%), and visual impairment in 7 of 72 (10%) versus 11 of 64 (17%) cooled and control infants (*P* not significant).

Predictors of 18-month outcome in the CoolCap RCT[12]:

1. The primary outcome was lower among infants who received hypothermia.
2. Primary outcome was also lower among infants with a less severe aEEG pattern at study intervention.
3. A worse outcome was noted among infants with severe HIE in comparison with infants with moderate HIE.
4. The absence of seizures by aEEG was associated with better outcome.
5. Elevated temperature in control-group infants was associated with worse outcomes.