Neonatal Encephalopathy

Update on Therapeutic Hypothermia and Other Novel Therapeutics

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KEYWORDS

• Dexmedetomidine • Erythropoietin • Melatonin • *N*-acetylcysteine
• Neurodevelopment • Stem cells • Umbilical cord milking • Xenon

KEY POINTS

- Although limited in number, the available long-term follow-up studies of neonates with neonatal encephalopathy (NE) treated with therapeutic hypothermia (TH) demonstrate sustained benefits through middle childhood.
- Neonates with severe NE remain at high risk for death and disability despite treatment with TH, emphasizing the need for adjunctive neuroprotective treatments.
- Clinical trials of erythropoietin neuroprotection have raised no safety concerns, and suggest that erythropoietin treatment plus TH may improve neurologic outcomes in neonates with NE.
- Although preclinical trials seemed promising, the benefits of xenon, melatonin, and stem cell therapies in neonates with NE treated with TH need to be clarified.
- Studies investigating clinical management strategies in neonates with NE, such as umbilical cord milking and sedative, antiepileptics, and pressor medications are needed to optimize outcomes.

INTRODUCTION

Intrapartum hypoxic events are a major cause of neonatal mortality responsible for approximately 1 in 5 of all neonatal deaths worldwide, causing an estimated 717,000 deaths in 2010.[1] Intrapartum-related hypoxic events ("birth asphyxia") may result in neonatal encephalopathy (NE), defined as a disturbance of neurologic function evident in the first days after birth in a newborn, characterized by a subnormal level of consciousness and depressed tone and reflexes, with or without seizures and

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often with impaired respiration and feeding abilities (both of presumed central origin).[2] NE is characterized as mild, moderate, or severe based on the Sarnat scoring system.[3] Neonates with moderate to severe NE who survive are at risk for motor disabilities and long-term neurodevelopmental impairments, including cognitive, neuropsychological, educational, and behavioral problems.[4,5] Although preterm infants are at even higher risk of NE than term infants, this review is restricted to discussion of term and near term infants.

Throughout this article, we use the terms *NE* and *hypoxic ischemic encephalopathy* (HIE) interchangeably to describe the published studies discussed in this review. Although debate continues over which of these terms to use,[6,7] HIE specifically refers to encephalopathy associated with intrapartum injury from hypoxia and ischemia, mechanisms that can be difficult to prove, whereas NE is a broader term denoting a syndrome of neurologic disturbance owing to an intrapartum hypoxic insult or other causes.[2]

Considerable research has been conducted in the past decade on NE as demonstrated by the co-word analysis study by Huang and colleagues,[8] which identified 1892 scientific studies (1568 articles and 324 reviews) that included the cooccurrence of keywords related to HIE published between January 2005 to December 2014 in the Web of Science database. Multiple randomized controlled trials (RCTs) have investigated induced hypothermia for newborns with NE, which has led to therapeutic hypothermia (TH) becoming a standard treatment for newborns 36 weeks of gestation or greater with NE related to intrapartum hypoxic events.[9,10] Although TH seems to be effective at improving outcomes, neonates with severe NE remain at significant risk of death or severe neurodevelopmental impairment despite being cooled, emphasizing the urgent need for additional adjunctive treatment strategies.

This review discusses the evidence supporting TH for term or near term neonates with NE, including findings of recent long-term outcome studies. Clinical strategies and novel adjunctive therapies to augment neurodevelopmental outcomes for neonates with NE who receive TH are also discussed.

CLINICAL TRIALS OF THE BENEFITS OF THERAPEUTIC HYPOTHERMIA FOR NEONATAL ENCEPHALOPATHY

Numerous RCTs have investigated the benefit of TH for improving outcomes of newborns with NE.[11–21] TH methods for NE include whole body and selective head cooling, with both methods demonstrating similar effects regarding long-term neurologic outcomes based on metaanalysis.[22]

A recent Cochrane systematic metaanalysis review by Jacobs and colleagues[23] included 11 RCTs, comprising 1505 term and late preterm infants with moderate to severe encephalopathy and evidence of intrapartum asphyxia. This Cochrane review demonstrated that TH resulted in improvement of the primary outcome measure of less death and better neurodevelopmental outcomes for survivors. Findings from 8 of the 11 studies (1344 infants) demonstrated that TH decreased the combined outcome of mortality or major neurodevelopmental disability to 18 months of age (46% [312/678] vs 61% [409/666] in controls; typical risk ratio (RR), 0.75; 95% CI, 0.68–0.83; typical risk difference (RD) −0.15; 95% CI, −0.20 to −0.10).[11–18] The number needed to treat (NNT) to benefit 1 newborn is 7 (95% CI, 5–10).

Secondary outcomes of the Cochrane review included mortality, major neurodevelopmental disability, adverse effects of cooling, and additional indicators of neurodevelopmental outcome (eg, severity of electroencephalographic abnormality, seizures, MRI findings).