HYPOTHERMIA AND PERINATAL ASPHYXIA: EXECUTIVE SUMMARY OF THE NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT WORKSHOP

ROSEMARY D. HIGGINS, MD, TONSE N.K. RAJU, MD, JEFFREY PERLMAN, MD, DENIS VICTOR AZZOPARDI, MD, LILLIAN R. BLACKMON, MD, REESE H. CLARK, MD, A. DAVID EDWARDS, F MED SCI, DONNA M. FERRIERO, MD, PETER D. GLUCKMAN, MBCHB, FRS, ALISTAIR J. GUNN, MBCHB, PHD, SUSAN E. JACOBS, MD, DOROTHEA JENKINS EICHER, MD, ALAN H. JOBE, MD, PHD, ABBOT R. LAPTOOK, MD, MICHAEL H. LEBLANC, MD, CHARLES PALMER, MBCHB, SEETHA SHANKARAN, MD, ROGER F. SOLL, MD, ANN R. STARK, MD, MARIANNE THORESEN, MD, JOHN WYATT, MD, THE NICHD HYPOTHERMIA WORKSHOP SPEAKERS AND DISCUSSANTS*

The National Institute of Child Health and Human Development (NICHD) held a workshop on hypothermia as a potential treatment modality for perinatal hypoxic-ischemic encephalopathy (HIE) in May 2005. A panel of experts summarized the current evidence on the efficacy and safety of hypothermia and reviewed knowledge gaps. The panel concluded that mild, therapeutic hypothermia offered a potential for short-term benefits (up to 18 months of age) when used under strict experimental protocols in term infants. However, these findings have not been tested in preterm infants or severely growth-restricted infants with asphyxia. Many questions still remained about the optimal use of hypothermia for HIE in term infants, including the incidence of possible rare, short-, and long-term side effects. Moreover, the longer-term benefits in neurodevelopmental outcomes after hypothermia for HIE remain to be shown. Because of these and other reasons, the panel concluded that at the current time, therapeutic hypothermia for perinatal HIE should be considered an evolving therapy, the longer-term safety and efficacy of which are still to be established. The panel offered a framework for patient care emphasizing the need for standardized protocols for treatment and follow-up, including school-age outcome assessments. Research priorities were also recommended. The panel strongly urged that the ongoing hypothermia trials should be continued to enable assessment of its efficacy and safety. It recommended the formation of national and international HIE registries, so that scientific progress in this field can be assessed continuously to develop, refine, and optimize therapies for HIE.

BACKGROUND

There are no therapies other than supportive measures for perinatal HIE, a condition associated with high neonatal mortality rates and severe long-term neurologic morbidity. Although hypothermia was used for “asphyxia neonatorum” in 1955, only in the past decade have systematic studies been carried out to address the safety and efficacy of this therapy in HIE.2-16

Recently, 2 large trials have been completed providing the results of 18-month follow-up.17,18 Other trials are actively enrolling patients.19,20 Thus there seemed to be an urgent need to assess hypothermia as a potential neuroprotective strategy for perinatal HIE and to formulate a continuing research agenda. To address these, the NICHD organized a workshop in May 2005. The invited panel reviewed the available evidence, identified knowledge gaps, and suggested research priorities along with a framework for translating evidence into patient care. This article provides a summary of the major points discussed at the workshop.

AN OVERVIEW OF THE PATHOGENESIS OF HIE

The biochemical and molecular processes leading to brain injury after an hypoxic-ischemic (HI) insult have been studied in fetal sheep, newborn mice, rat pups, piglets, and nonhuman primates,2-12,21,22 as has been reviewed elsewhere.23,24 Despite the wide range of species and experimental paradigms used, a number of general conclusions can be drawn about this topic, as follows.

Brain injury after experimental H1 insult is an evolving process. The nature and severity

| aEEG | Amplitude-integrated electroencephalography |
| EEG | Electroencephalography |
| HI | Hypoxic-ischemic |
| HIE | Hypoxic-ischemic encephalopathy |
| NICHD | National Institute of Child Health and Human Development |
| TOBY | Total Body Cooling Trial |
of the injury dictates the magnitude of the initial damage. After the initial reperfusion period, brain oxidative metabolism often recovers partially or completely, a phase referred to as the "latent phase." However, in many cases, an ominous phase of secondary deterioration follows, also known as the "delayed phase of injury," during which neurons and oligodendroglia continue to die for longer periods. The processes of cell injury and death during the initial HI insult appear to be a predictable phenomenon: deprivation of oxygen and nutrients leads to a shift to anaerobic glycolysis, depletion of high-energy phosphate reserves, loss of cell membrane functions, accumulation of lactic acid, calcium, free radicals and neurotoxic, excitatory neurotransmitters such as glutamate in the extracellular milieu, and deterioration of cell function. If the insult is not interrupted, this cascade ultimately leads to acute or "primary" cell death.

However, the biochemical processes involved in evolving cell death that develops after reperfusion are more complex. A series of interrelated mechanisms may be responsible for perpetuating the initial injury, some of which include the following: cytosolic accumulations of calcium and exposure to free radicals, including formation of nitric oxide, and toxic effects caused by accumulating iron; injury from inflammatory mediators; and mitochondrial dysfunction. These and other processes trigger apoptotic pathways contributing to continued neuronal and oligodendroglial injury and death, which may evolve over hours, days, or possibly weeks and months after an HI injury.

Although the sequence of evolution of the phases of energy failure and cellular damage and dysfunction after HI injury are strikingly consistent across animal species and among subjects, the duration of these phases (especially that of the latent and secondary deterioration) and the degree of continuing damage can vary considerably. The factors that might affect the length of the reperfusion and latent phases of injury are not well known but likely include the following: the nature, magnitude, and the pattern or repetition of the initial HI insult; the maturational stage of the brain; the subject's general health and nutritional status; regional cerebral blood flow and metabolic characteristics; and the species studied. These issues need to be considered when translating the results of animal experiments into clinical practice, since most experimental interventions have been designed to halt or reduce brain injury after timed insults in previously healthy animals during the reperfusion and latent phases.

HYPOTHERMIA AND NEUROPROTECTION

Studies in fetal sheep showed that brain cooling to about 32° and 34° C beginning 90 minutes or 5.5 hours after HI injury and continuing for 48 to 72 hours diminished the extent of parasagittal neuronal damage (the effect of cooling was observed in other regions of brain as well). Improved neurologic outcomes were confirmed by use of quantitative neuropathologic methods, imaging studies, and tests of learning and memory functions.

From the animal studies it could be concluded that brain cooling should be initiated as early as feasible after the brain injury, preferably within 2 hours, but not later than 6 hours; the rectal temperature should be reduced to between 32° to 34° C for effective brain cooling with whole-body hypothermia; smaller reductions in rectal temperature (34°–35° C) may be needed for head cooling; and cooling should be continued for about 48 to 72 hours. Although optimal methods for rewarming were not tested in newborn animals, adult animal studies indicated that slow rewarming was to be preferred.}

TRANSLATING THE RESULTS OF ANIMAL STUDIES TO HUMAN TRIALS

Many limitations had to be noted before extrapolating the potentially beneficial effects seen in animal models of HIE and hypothermia to human HIE. In human beings, "perinatal encephalopathy" is not a single disease entity, but a condition resulting from diverse causes manifesting signs of brain injury at different phases of its evolution. Despite the etiologic diversity, the clinical signs may be identical. The cause(s) of HIE is rarely obvious, and the timing, nature, or severity of the HI injury is almost never known. The underlying status of the human brain, such as its maturity, nutritional and hormonal status, inflammatory, and preexisting developmental abnormalities may alter the responses to acute insults.

Moreover, one can only offer therapy for HIE in human infants at a known postnatal age—not after a known interval from brain injury. However, in only about 25% of HIE cases can one discern signs of a sentinel event in the peripartum period indicating the time of injury. There is considerable variability in the neuronal (and other brain cellular) responses to HI injury and to hypothermia among the experimental species, and in human infants. Thus one cannot determine with precision how late after an ischemic injury one can provide cooling and still expect neuroprotection. Further, in only a few experimental animal models of HIE and hypothermia have there been attempts to characterize the frequency of multisystem organ injury and other organ responses to hypothermia. Because of this gap in knowledge, there is a concern that hypothermia in infants with very severe HIE might increase their survival but with severe disability, as well as increase the risk for systemic complications.

CLINICAL TRIALS

Pilot Trials

In 1955 Westin et al showed that hypothermia was beneficial in perinatal asphyxia. However, systematic pilot studies were not done until Gunn et al, Azzopardi et al, and Thoresen and Whitelaw described simple approaches to cooling the head and the whole body for up to 72 hours without serious, short-term adverse effects. The findings from these studies showed that although bradycardia occurred commonly, other acute complications, such as severe hypotension, acute deterioration in pulmonary function, increased rates of infection, or imbalances in blood viscosity, electrolytes, and clotting did not occur with mild therapeutic hypothermia for 72 hours.

Hypothermia And Perinatal Asphyxia: Executive Summary Of The NICHD Workshop
ran et al\textsuperscript{16} also confirmed the feasibility of providing whole-body cooling for 72 hours without major short-term complications. In a pilot study of whole-body cooling to a rectal temperature of 33° ± 0.5°C for 48 hours in infants with severe HIE, Eicher et al\textsuperscript{19} reported a higher incidence of bradycardia and a greater use of inotropic agents during cooling in the hypothermia group (n = 33) compared with in the control subjects (n = 32). The hypothermia group also had longer prothrombin times and lower platelet counts than the control subjects, but all of the values were within normal range.

Thus the cumulative evidence from numerous animal studies and the reassuring conclusions about the short-term safety and feasibility of providing therapeutic hypothermia in human infants led to the development of larger randomized controlled trials.

Large-Scale Clinical Trials

In the second large randomized controlled clinical trial (CoolCap) conducted in 25 centers in New Zealand, Great Britain, and the United States, 234 infants with acute perinatal HIE were enrolled.\textsuperscript{17} The stepwise biochemical/clinical, neurologic, and electroencephalography (EEG) criteria for entry were as follows: >36 weeks gestation; an Apgar score <5 at 10 minutes after birth or a continued need for resuscitation at 10 minutes after birth; or a pH <7.0 or base deficit > 16 mmol/L in the umbilical blood or venous blood sample within 60 minutes of birth; and a modified Sarnat score and amplitude-integrated EEG (aEEG) criteria consistent with a diagnosis of moderate to severe HIE.

Infants in the experimental group (n = 116) received selective head cooling with mild systemic hypothermia induced with a cooling cap device in which cold water was circulated. The rectal temperature was maintained between 34° to 35° C for 72 hours, and the infants were rewarmed at a rate <0.5°C per hour. Conventional intensive care with normal body temperature was provided for 118 infants in the control group.

On intention to treat analysis, the incidence of death or severe disability was 55% in the cooled infants and 66% in the control subjects. Outcome information was known for 205/208 (98%) infants; death or moderate/severe disability occurred in 44% (45/102) of the hypothermia group and 62% (64/103) of the control group (risk ratio 0.72; 95% CI, 0.54–0.95, P = .01), indicating 6 infants need to be treated on average to result in 1 infant with a better outcome. The mortality rate was 24% in the hypothermia group and 37% in the control group (risk ratio 0.68, 95% CI: 0.43–1.01, P = .08). The risk ratio for death or disability after moderate HIE was 0.69 (95% CI, 0.44–1.07) and after severe HIE was 0.83 (95% CI 0.64–1.13). For the hypothermia group versus the control group, respectively, the risk of disabling cerebral palsy was 19.2% and 30.0% RR 0.68 (0.38–1.22), blindness 7% versus 14% RR 0.50 (0.17–1.44) and hearing impairment requiring a hearing aid was 4% and 6%, RR 0.54 (0.10–3.02). The frequency of adverse event rates during cooling was similar: 19% in the hypothermia group and 15% in the control group.

Other Ongoing Trials

In the Total Body Cooling Trial (TOBY) from England,\textsuperscript{19} infants with moderate-to-severe HIE are randomized to receive whole-body cooling or standard intensive care. Thus far, 206 of the planned 239 (86%) infants (as of January 26, 2006) have been enrolled, and the study is continuing. The trial design features and the entry criteria for the TOBY trial are similar to those of the CoolCap trial.\textsuperscript{17} Thus, upon completion, the findings from the TOBY trial can be effectively compared with those of CoolCap to assess the relative benefits from whole-body versus selective head cooling in HIE. Such comparisons would be of great value, since these trials will constitute 2 of the largest cohorts of infants studied under an identical enrollment protocol.

The ICE (Infant Cooling Evaluation) trial aims to enroll infants from a wide geographic region, using simplified protocols.\textsuperscript{20} Hypothermia is achieved by turning off the ambient heating systems and by applying “Hot-Cold” gel packs (at 10°C) around the infant’s head and over the chest, so that the rectal temperature is reduced to 33° to 34°C. After
demonstrating the feasibility of this approach in 17 infants, the investigators have enrolled 96 of the planned 276 infants from 15 participating centers in Australia, New Zealand, and Canada in this ongoing trial.

**MAJOR GAPS IN KNOWLEDGE**

In spite of rapidly accumulating clinical and laboratory data related to hypothermia as a neuroprotective strategy for HIE, the speakers and discussants at the workshop underscored numerous gaps in knowledge in this field. They noted that with only 2 completed studies providing information on follow-up for only up to 18 months of age, the longer-term impact of hypothermia for HIE remains unknown. This, they concluded, should lead to an overall measure of caution in applying the new therapy of hypothermia indiscriminately for all cases of HIE. Some components of the panel’s discussion are outlined in the Table, and briefly highlighted below.

**Table. Unresolved issues.**

**Implementing hypothermia for HIE**

- At the present time, hypothermia for HIE lacks long term safety and efficacy data. Institutions choosing to offer hypothermia should implement studied and reported protocols from existing or ongoing trials, and incorporate longer-term follow up plans.
- If hypothermia is offered to infants with HIE, the parents should be appraised about the knowledge gaps in this field and the uncertain nature of longer-term outcome.
- The ongoing TOBY, ICE, and other trials need be to be completed.
- National and international registries need to be organized for ongoing assessment of the global burden of HIE, its treatment and outcomes.
- International interest groups of scientists, practitioners, and others involved in public policy need to be formed for continued evaluation of accumulating evidence in this field.
- The role of therapeutic hypothermia in HIE for children born in countries with limited resources needs to be studied in the context of regional issues of feasibility, risks and potential benefits.

**Identification of infants for offering hypothermia**

- The value of standardized clinical examinations, scoring systems (e.g., modified Sarnat score), and aEEG should be studied to assess eligibility for hypothermia.
- Although it has been tested in term infants and to a lesser extent in late preterm, (>35 weeks gestation) infants; the value of hypothermia in premature infants, and in those with severe intrauterine growth restriction has not been studied. The risk benefit ratio for these infants cannot be assessed at this time due to lack of data.
- The severity of HIE at which the risk versus benefit ratio favors hypothermia remains unknown. Whether developmental outcomes are affected by the type and timing of hypoxic-ischemic injury needs to be studied.
- The latest postnatal age at which initiation of therapeutic hypothermia might still be effective (“how late is not too late”) is unknown.
- The potential beneficial or deleterious effect of hypothermia during resuscitation and transfer needs to be studied.

**Cooling and rewarming**

- Although it is postulated that deeper, longer, and earlier therapy with hypothermia is to be preferred, the optimal degree and duration of cooling is unknown. Whether the degree and duration of therapy should be based on the cause, severity, stage of brain injury, and the age at starting of hypothermia is unknown.
- The optimal mode of cooling (whole body or selective head) is unknown, especially with regard to their differential protective effects, if any, on various regions of the brain (generalized cortical versus deep brain nuclei), has not been established. The optimal/safe pace of re-warming is unknown.
- The frequency of uncommon and rare systemic side effects, and the method of monitoring for these need to be studied.

**Long-term outcome**

- The role of MRI or other anatomic or functional imaging modalities in prognosis and during follow-up remains to be studied.
- The duration of follow-up and the appropriate tests to assess outcome should be similar so that outcomes under differing protocols can be compared.
- Longer-term follow-up of infants who participated in the completed and ongoing and future hypothermia trials should be strongly supported.

**IMPLICATIONS FOR CLINICAL PRACTICE**

The workshop participants suggested some salient points as a framework for consideration by practicing clinicians.

- Based on the available evidence and the known gaps in knowledge, at the current time, therapeutic hypothermia should be deemed as an evolving therapy, the long-term safety and efficacy of which need to be established.
- Perinatal HIE is not a single disease from a single cause, with great diversity in the timing and magnitude of brain injury. It is therefore unreasonable to expect any single intervention will provide uniformly favorable outcome.
- The known heterogeneity in neuropathologic changes after perinatal HIE combined with potential regional heterogeneity of treatment effects will lead to marked differential effects on outcomes among survivors of HIE (eg, physical disability versus cognitive deficits). This underscores the
SUMMARY AND CONCLUSIONS

Based on the available data and large knowledge gaps, the expert panel suggested that although hypothermia appears to be a potentially promising therapy for HIE, long-term efficacy and safety are yet to be established. Clinicians choosing to offer this treatment should therefore understand all of the limitations of the available evidence, be prepared to keep up-to-date on evidence on this topic as it evolves, and counsel parents and family about the limitations of the current evidence.

Addendum: Following the workshop, it was brought to the attention of the participants that another whole-body cooling trial is ongoing and can be found at http://www.neonatal-research.at/php/detail.php?artnr=H11005.

We acknowledge the support of NIH Office of Rare Diseases; the American Academy of Pediatrics; Royal College of Pediatrics and Child Health; British Association of Perinatal Medicine; and the Canadian Academy of Pediatrics for their support for the workshop.

REFERENCES


50 Years Ago in The Journal of Pediatrics

A PSYCHOSOMATIC STUDY OF FIVE CHILDREN WITH DUODENAL ULCER


The understanding of duodenal ulcer (DU) pathophysiology, and much of gastric peptic disease, has been revolutionized in the last 50 years. Chapman and colleagues published descriptions of 5 children with symptomatic DU and associated the findings with detailed descriptions of the patient’s under-privileged living conditions and maladaptive psychological states. They correctly differentiated these cases of DU from those seen in patients with severe physiological stress, such as those with burns and major trauma. They reference other authors who also suggested associations between DU and various psychological conditions. However, new evidence has demonstrated something that these physicians could not have guessed and had no way to investigate—these patients with DU most likely had an infectious disease.

A myriad of basic science and clinical studies, since the first report by Warren and Marshall in 1983, have shown that 90-100% of DU cases in children are associated with, and are likely caused by, concurrent gastric infection with Helicobacter pylori. Although detailed knowledge of the pathophysiological cascade remains incomplete, it is evident that H. pylori can cause a chronic infection of the human gastric epithelium, incite an inflammatory response that produces a nodular, chronic gastritis, and elaborates toxins, which, in the presence of acid, are responsible of mucosal ulceration in the duodenum. H. pylori infection, which likely involves fecal-oral transmission, is known to be associated with poor sanitation, low socioeconomic conditions, infected family members, and residential institutions. The report by Chapman emphasizes many of these social problems; it also notes that parents with a history of DU live in the home. Studies of H. pylori-associated DU have shown a recurrence rate of at least 50% when H. pylori is not eradicated, but no recurrence when eradication is complete. The patients reported by Chapman, who were treated with antacids but not antibiotics, had chronic symptoms and long courses of recovery.

Given the knowledge that ulcer disease is infectious, we now have the perspective to question the role of chronic pain in the development of psychopathology. Although this has been incompletely addressed for ulcer disease, it is well known that patients with inflammatory bowel disease who are burdened with chronic pain and difficult gastrointestinal symptoms have higher rates of depression and other psychosocial problems. Let this be a cautionary tale to continue questioning the causes of our patients’ ills, even when we think we know the answer.

Jeffrey H. Teckman, MD
Associate Professor of Pediatrics
Chief, Pediatric Gastroenterology and Hepatology
St. Louis University
Cardinal Glennon Children’s Hospital
St. Louis, MO 63104

YMPD2045
10.1016/j.jpeds.2006.01.030
APPENDIX.

Workshop speakers, discussants, and moderators
Duane Alexander, MD, National Institute of Child Health and Human Development (NICHD), Bethesda, Maryland; Denis Victor Azzopardi, MD, FRCP, Imperial College London, London, United Kingdom; Lillian R. Blackmon, MD, FAAP, University of Maryland Medical School, Baltimore, Maryland; Kenneth Carr, PhD, Meridian Medical Systems, Ayer, Massachusetts; Reese H. Clark, MD, Pediatrix Medical Group, Inc., Sunrise, Florida; A. David Edwards, F Med Sci, Imperial College of London, London, United Kingdom; Donna M. Ferriero, MD, University of California, San Francisco, California; Peter D. Gluckman, MBChB, FRS, Liggins Institute, University of Auckland, Auckland, New Zealand; Alistair J. Gunn, MBChB, PhD, University of Auckland, Auckland, New Zealand; James Hanson, MD, NICHD, Bethesda, Maryland; Rosemary D. Higgins, MD, NICHD, Bethesda, Maryland; Susan E. Jacobs, MD, Royal Women's Hospital, Victoria, Australia; Dorothea Jenkins Eicher, MD, Medical University of South Carolina, Charleston, South Carolina; Alan H. Jobe, MD, PhD, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; Abbot R. Laptook, MD, Women & Infants Hospital, Providence, Rhode Island; Michael H. LeBlanc, MD, University Medical Center, Jackson, Mississippi; Charles Palmer, MB ChB, Milton S. Hershey Medical Center, Pennsylvania State University College of Medicine, Hershey, Pennsylvania; Jeffrey M. Perlman, MB ChB, Weil Medical College at Cornell University, New York, New York; Tonse N. K. Raju, MD, DCH, NICHD, Bethesda, Maryland; Seetha Shankaran, MD, Wayne State University School of Medicine, Detroit, Michigan; Roger F. Soll, MD, Fletcher Allen Health Care, Burlington, Vermont; Catherine Y. Spong, MD, NICHD, Bethesda, Maryland; Ann R. Stark, MD, Baylor College of Medicine, Texas Children's Hospital, Houston, Texas; Marianne Thoresen, MD, University of Bristol, St. Michael's Hospital, Bristol, United Kingdom; John Wyatt, MD, University College of London, London, United Kingdom.