

Summary Proceedings From the Neurology Group on Hypoxic-Ischemic Encephalopathy

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ABSTRACT

Hypoxic-ischemic cerebral injury that occurs during the perinatal period is one of the most commonly recognized causes of severe, long-term neurologic deficits in children; it is often referred to as cerebral palsy. Despite improvements in perinatal practice during the past several decades, the incidence of cerebral palsy attributed to intrapartum asphyxia has remained essentially unchanged, primarily because management strategies were supportive and not targeted toward the processes of ongoing injury. Two processes of neuronal injury can be demonstrated after hypoxia-ischemia: neuronal necrosis and apoptosis. Because the mechanisms of these processes likely differ, strategies to minimize brain damage in an affected infant after hypoxia-ischemia likely will have to include interventions that target both processes. The goals of management of a newborn infant who has sustained a hypoxic-ischemic insult and is at risk for evolving injury should include (1) early identification of the infant at highest risk for evolving to the syndrome of hypoxic-ischemic encephalopathy, (2) supportive care to facilitate adequate perfusion and nutrients to the brain, and (3) consideration of interventions to ameliorate the processes of ongoing brain injury. Although the neurology group was unable to develop a definitive framework for the study of neuroprotective strategies for neonatal encephalopathy, it (1) listed key questions to be addressed before exploring possible study designs for managing hypoxic-ischemic encephalopathy in neonates, (2) identified important study-design issues, (3) determined general principles and key elements for neuroprotective-treatment strategies, (4) identified potential treatment strategies, (5) proposed a clinical-trial framework, and (6) identified key elements for a potential clinical-trial framework comparing hypothermia with hypothermia “plus” for moderate-to-severe encephalopathy.

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Key Words

hypoxic-ischemic encephalopathy, neuroprotective strategies, hypothermia, seizures

Abbreviation

EEG—electroencephalogram

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HYPOXIC-ISCHEMIC CEREBRAL INJURY that occurs during the perinatal period is one of the most commonly recognized causes of severe, long-term neurologic deficits in children; it is often referred to as cerebral palsy.^{1,2} The brain injury that develops is an evolving process that is initiated during the insult and extends into a recovery period, the latter referred to as the “reperfusion phase” of injury. Clinically, it is the latter phase that is amenable to potential intervention(s). Until recently, current management strategies were supportive and not targeted toward the processes of ongoing injury.³ Thus, it should not be surprising that, despite improvements in perinatal practice during the past several decades, the incidence of cerebral palsy attributed to intrapartum asphyxia has remained essentially unchanged.¹ However, novel exciting strategies aimed at preventing ongoing injury are being clinically evaluated and offer an opportunity for neuroprotection.

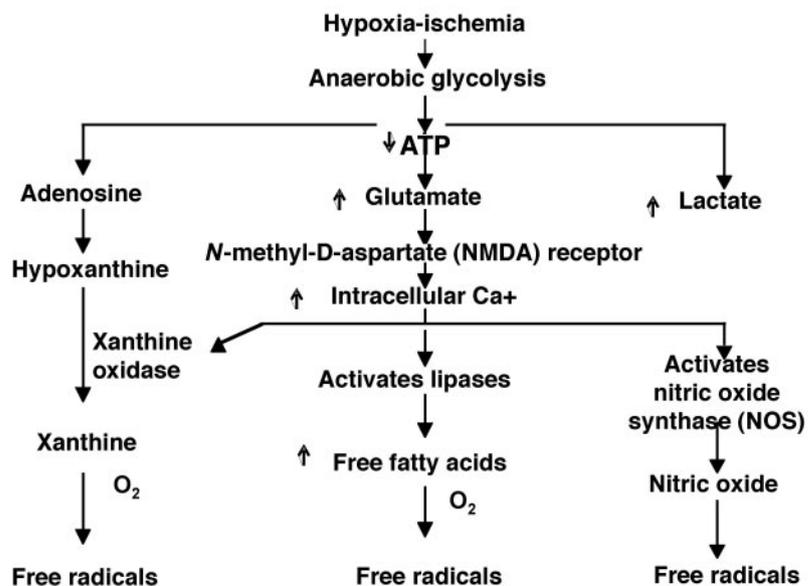
The principal pathogenetic mechanism underlying most of the neuropathology attributed to intrapartum hypoxia-ischemia is impaired cerebral blood flow, which is most likely to occur as a consequence of interruption in placental blood flow and gas exchange; it is often referred to as “asphyxia” or severe fetal acidemia. The latter is defined as a fetal umbilical arterial pH level of ≤ 7.00 .¹

At the cellular level, the reduction in cerebral blood flow and oxygen delivery initiates a cascade of deleterious biochemical events. Depletion of oxygen precludes oxidative phosphorylation and results in a switch to anaerobic metabolism, which is an energy-inefficient state resulting in (1) rapid depletion of high-energy phosphate reserves including adenosine triphosphate, (2) accumulation of lactic acid, and (3) the inability to maintain cellular functions.⁴ Transcellular ion-pump

failure results in the intracellular accumulation of Na^+ , Ca^{++} , and water (cytotoxic edema). The membrane depolarization results in a release of excitatory neurotransmitters and specifically glutamate from axon terminals. The glutamate then activates specific cell-surface receptors resulting in an influx of Na^+ and Ca^{++} into postsynaptic neurons. Within the cytoplasm, there is an accumulation of free fatty acids secondary to increased membrane phospholipid turnover. The fatty acids undergo peroxidation by oxygen free radicals that arise from reductive processes within mitochondria and as byproducts in the synthesis of prostaglandins, xanthine, and uric acid. Ca^{++} ions accumulate within the cytoplasm as a consequence of increased cellular influx as well as decreased efflux across the plasma membrane combined with release from mitochondria and endoplasmic reticulum. In selected neurons, the intracellular calcium induces the production of nitric oxide, a free radical that diffuses into adjacent cells that are susceptible to nitric-oxide toxicity. The combined effects of cellular energy failure, acidosis, glutamate release, intracellular Ca^{++} accumulation, lipid peroxidation, and nitric-oxide neurotoxicity serve to disrupt essential components of the cell, which ultimately lead to cell death (Fig 1).^{2,5} Many factors, including the duration or severity of the insult, influence the progression of cellular injury after hypoxia-ischemia.

After resuscitation, which may occur in utero or postnatally in the delivery room, cerebral oxygenation and perfusion are restored. During this recovery phase, the concentrations of phosphorus metabolites and the intracellular pH return to baseline. However, the process of cerebral energy failure recurs from 6 to 48 hours later in a second phase of injury. This phase is characterized by a decrease in the ratio of phosphocreatine/inorganic

FIGURE 1
Potential pathways for brain injury after hypoxia-ischemia.



phosphate, with an unchanged intracellular pH and stable cardiorespiratory status, and contributes to additional brain injury.^{4,6} In the human infant, the severity of the second energy failure is correlated with adverse neurodevelopmental outcomes at 1 and 4 years.⁷ The mechanisms of secondary energy failure may involve mitochondrial dysfunction secondary to extended reactions from primary insults (eg, calcium influx, excitatory neurotoxicity, oxygen free radicals, nitric-oxide formation). Recent evidence suggests that circulatory and endogenous inflammatory cells/mediators also contribute to ongoing brain injury.⁸

The mechanism of neuronal cell death in animals and humans after hypoxia-ischemia includes neuronal necrosis and apoptosis. The intensity of the initial insult may determine the mode of death, with severe injury resulting in necrosis, whereas milder insults result in apoptosis.⁹ Necrosis is a passive process of cell swelling, disrupted cytoplasmic organelles, loss of membrane integrity, and eventual lysis of neuronal cells and activation of an inflammatory process. By contrast, apoptosis is an active process distinguished from necrosis by the presence of cell shrinkage, nuclear pyknosis, chromatin condensation, and genomic fragmentation, which are events that occur in the absence of an inflammatory response.¹⁰ These 2 processes of neuronal death can be demonstrated after hypoxia-ischemia in both animals and humans.^{2,5,10} Because the mechanisms of neuronal necrosis versus apoptosis likely differ, strategies to minimize brain damage in an affected infant after hypoxia-ischemia likely will have to include interventions that target both processes.

The goals of management of a newborn infant who has sustained a hypoxic-ischemic insult and is at risk for evolving injury should include (1) early identification of the infant at highest risk for evolving injury, (2) supportive care to facilitate adequate perfusion and nutrients to the brain, and (3) consideration of interventions to ameliorate the processes of ongoing brain injury.

The initial step in management is early identification of those infants who are at greatest risk for evolving to the syndrome of hypoxic-ischemic encephalopathy. This is a highly relevant issue, because the therapeutic window (ie, the time interval after hypoxia-ischemia, during which interventions might be efficacious in reducing the severity of ultimate brain injury) is likely to be short. On the basis of experimental studies, the therapeutic window is estimated to vary from 2 to 6 hours. Given this presumed short window of opportunity, these infants must be identified as soon as possible after delivery to facilitate the implementation of early interventions. There are increasing data to indicate that the highest-risk infant can be identified shortly after birth by a constellation of findings. These findings include evidence of a sentinel event during labor (eg, fetal heart rate abnormality), a severely depressed infant (low extended Apgar

score), the need for resuscitation in the delivery room (ie, intubation, chest compression with or without epinephrine administration), and evidence of severe fetal acidemia (cord umbilical artery pH < 7.00 and/or base deficit ≥ 16 mEq/L)¹¹ followed by evidence of an early abnormal neurologic examination and/or abnormal assessment of cerebral function, that is, from an integrated electroencephalogram (EEG).¹¹⁻¹⁴

KEY QUESTIONS

Several key questions need to be addressed before exploring possible study designs for the management of hypoxic-ischemic encephalopathy in neonates.¹⁵ These questions include:

- Which pathways predominate in brain injury?
- What mechanisms contribute to fetal resistance with hypoxia-ischemia?
- How can infants at highest risk for brain injury be identified early?
- What animal models of hypoxia-ischemia are appropriate for study?
- What neuroprotective strategies should be implemented?

STUDY-DESIGN ISSUES

Any study design needs to incorporate the following key issues.

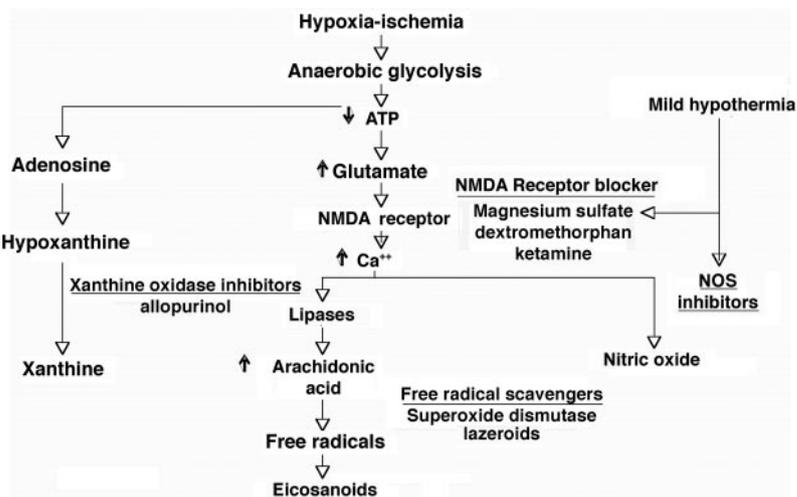
- Hypoxic-ischemic cerebral injury occurs in no more than 1 in 1000 live term deliveries in developed countries. As a consequence, a multicenter trial design will be necessary to explore any novel intervention.
- Early identification of infants at highest risk for evolving brain injury is critical. The therapeutic window for intervention is short (considered to be <6 hours).¹⁶
- Novel therapies carry the potential for significant adverse effects.

GENERAL PRINCIPLES FOR NEUROPROTECTIVE-TREATMENT STRATEGIES

The neurology group discussed the following general principles that need to be considered in developing neuroprotective-treatment strategies.

- Treatment strategies will likely depend on the severity of the findings during the initial examination.
- Multiple interventions may be necessary.
- Potential genetic and gender influences are likely and will require delineation.
- The contribution of any placental abnormality (eg, inflammation or thrombosis) to the evolving brain injury remains unclear but is likely to be an important variable.

FIGURE 2
Potential therapeutic intervention strategies.



- The potential contribution of other factors such as ischemic preconditioning needs to be considered.

KEY ELEMENTS OF A NEUROPROTECTIVE STRATEGY

The neurology group identified the following key elements of a neuroprotective strategy.

- Who to treat: infants at highest risk as indicated by a combination of markers that includes evidence of a sentinel intrapartum event (eg, fetal bradycardia), the

need for delivery room resuscitation, a 5-minute Apgar score of ≤ 5 , cord arterial pH level of ≤ 7.00 , and/or base deficit ≥ 16 mEq/L, and postnatal evidence of moderate-to-severe encephalopathy as indicated by both an abnormal clinical examination and an abnormal EEG.¹¹⁻¹⁴

- When to treat: the earlier the better during the “short therapeutic window,” preferably <6 hours after reperfusion.¹⁶

FIGURE 3
Framework for the study of neonatal encephalopathy neuroprotective strategies.

Entry criteria

Term Infants >36 wk gestational age
Perinatal depression
Clinical + EEG criteria <6 h for moderate or severe encephalopathy

Intervention

Hypothermia
Hypothermia + (possibilities include earlier onset of hypothermia, prolonged duration of study, systemic vs selective cooling, other drugs such as phenobarbital)

Follow-up

18 mo and beyond to assess for motor, cognitive, visual, and hearing deficits

TABLE 1 Framework for the Study of Neonatal Encephalopathy Neuroprotective Strategies

Entry criteria: criteria for entry to the study would include

- Term infants >36 wk of age
- Perinatal depression
- Clinical plus EEG criteria at <6 h for moderate or severe encephalopathy

Intervention: hypothermia would be the first therapy used; the study would include the following 2 groups

- Hypothermia
- Hypothermia plus (possibilities include earlier onset of hypothermia; prolonged duration of study; lower temperature; systemic vs selective method of cooling; other drugs such as phenobarbital, magnesium, and allopurinol)

Risk factors: blood would be saved to examine for the following potential risk factors

- Male vs female
- Genetic polymorphisms
- Coagulation profile
- Follow-up at 18 mo

- How long to treat: optimal duration is unclear; 72 hours is recommended, but treatment may need to be extended beyond this time, depending on severity or other factors at the time of the initial presentation.
- What to treat with: hypothermia seems to be the most attractive initial strategy because of multiple effects at different levels within pathways that contribute to brain injury after hypoxia-ischemia.^{15,16}

POTENTIAL TREATMENT STRATEGIES

The neurology group identified certain potential strategies for preventing reperfusion injury in large part based on neonatal animal models of hypoxic-ischemic cerebral injury and recent clinical studies (Fig 2).¹⁶⁻¹⁸ With regard to the latter, data from a study of modest selective hypothermia in term infants at highest risk for perinatal hypoxic-ischemic brain injury suggests that this therapy may be neuroprotective with early moderate, but not severe, encephalopathy.¹⁷ In a second recent study, systemic hypothermia significantly reduced the incidence of death and moderate-to-severe neurodevelopmental deficits at 18 months.¹⁸ On the basis of current available data, the group identified the following treatment strategies for consideration during the workshop:

- Treatment for moderate encephalopathy (defined clinically and with amplitude EEG monitoring) should start with modest hypothermia. Possible adjunctive strategies could include phenobarbital, for infants with EEG-detected seizures, and other neuroprotective strategies.¹⁹⁻²⁴
- Treatment for severe encephalopathy (defined clinically and with an amplitude EEG) could include “deeper” hypothermia, more prolonged cooling, modest hypothermia plus other neuroprotective strategies including the possible use of phenobarbital even in the absence of seizures as an adjunctive strategy.²³⁻²⁹

PROPOSED CLINICAL-TRIAL FRAMEWORK

The neurology group was unable to develop a definitive framework for the study of neuroprotective strategies for neonatal encephalopathy. However, the group identified key elements for a potential clinical-trial framework comparing hypothermia with hypothermia “plus” for moderate-to-severe encephalopathy. These elements are listed in Fig 3.

The neurology group recognized that the clinical-trial framework needs to address the following additional considerations:

- drug interactions;
- effects of comorbid conditions;
- ethical issues;
- feasibility;
- treatment end points;
- outcome variables (eg, delay or reduce severity of EEG-detected seizures, death, cerebral palsy, mental retardation); and
- long-term outcomes at 18 months and beyond.

GAPS IN KNOWLEDGE

The neurology group identified the following questions regarding gaps in knowledge that still need to be addressed:

- What is the contribution of the fetal inflammatory response?
- Are there gender and genetic influences?
- Does ischemic preconditioning contribute to the resistance of the infant to hypoxia-ischemia, and can it be modulated in any way?
- How can all drugs be delivered effectively across the blood-brain barrier?
- What additional evaluations should be performed at the time of delivery to enhance therapy?
- What are potential treatment strategies for infants who initially present beyond 6 hours of age?

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