Treatment of Neonatal Hypoxic Ischemic Encephalopathy with Hypothermia; the Window of Opportunity

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Abstract

In this review we describe the pathogenesis of hypoxic-ischemic cerebral injury, the experimental data, and clinical studies that have evaluated the potential benefits of selective or whole body hypothermia in reducing the subsequent development of irreversible brain injury without untoward side effects.

Keywords: Hypoxic-ischemic encephalopathy; Neonate; Hypothermia

Introduction

Perinatal hypoxic-ischemic encephalopathy (HIE) is a common cause of brain damage and death in the newborn period. HIE occurs as a result of an injury to the brain from a combination of systemic hypoxemia; which refers to an arterial concentration of oxygen that is less than normal; and diminished cerebral perfusion that leads to ischemia or insufficient blood flow to the cells to maintain their normal function. The pathogenesis involves a sequence of cerebral insults that occur initially with hypoxemia, ischemia and next by oxygenation and reperfusion of the ischemic tissue. HIE may cause multi-system organ damage with significant aberrations in clotting, renal, and cardiac functions.

The incidence of HIE is 2-6 per 1,000 live birth and it appears to be much higher in the developing countries. It may occur as a result of prepartum, intrapartum, or perinatal causes, and is most commonly seen in full-term or post-term infants. Prenatal-intrapartum risk factors include fetal distress, abruptio placenta, placenta previa, maternal hypertension, prematurity, postmaturity, intrauterine growth retardation, prolapsed or nuchal cord, dystocia and precipitous or prolonged labor. Neurological sequelae usually occur in HIE in infants who experienced an associated occurrence of severe respiratory distress, persistent pulmonary hypertension, recurrent apnea, hypotension or septic shock.

Hypoxic-ischemic encephalopathy is an important cause of permanent damage to CNS cells that may result in neonatal death or be manifested later as with neurodevelopmental sequelae such as cerebral palsy or some degree of intellectual and/or motor impairment [1]. These Long-term outcomes depend on the degree of cerebral insult. Management of HIE is essentially supportive. Considerable attention is focused on optimizing management of newborns in the period immediately after resuscitation from perinatal asphyxia to minimize delayed neuronal death [2].

Early Experimental data show that mild selective head cooling combined with systemic hypothermia in term newborns after perinatal asphyxia is a safe method of reducing cerebral temperature. These initial studies showed safety and hinted at efficacy [3].

Animal studies on HIE and neurodevelopmental follow-up of newborn infants who have been treated with hypothermia provide some evidence that brain damage may be reduced if the brain temperature is decreased by a few degrees for a period of approximately 72 hours, beginning as soon as possible after birth.

The Pathophysiology of HIE

The Brain injury which occurs after a hypoxic ischemic insult is an evolving sequence of three phases:

The phase of impaired brain perfusion

The initial damage is related primarily to impaired cerebral blood flow which occur as a consequence of interruption in placental blood flow and gas exchange, which is referred to as asphyxia or severe fetal acidemia (defined as a fetal umbilical arterial pH $\leq$ 7.00) [4].

The reduction in cerebral blood flow and oxygen delivery initiates a cascade of potentially deleterious biochemical events including the depletion of high-energy phosphate reserves including ATP, accumulation of lactic acid, and inability to maintain cellular functions with resultant intracellular accumulation of Na^+, Ca^{2+}, and water. The membrane depolarization results in a release of excitatory neurotransmitters, specifically glutamate from axon terminals. There also is accumulation of free fatty acids within the cytoplasm that undergo peroxidation by oxygen free radicals. The end result of this process the disruption of essential components of the cell, resulting in its ultimate death [4,5]. Many other factors, including the duration or severity of the insult, influence the progression of the cellular injury.

The latent phase

This is the recovery phase that follows the delivery room resuscitation. During this phase the cerebral oxygenation and perfusion are restored. The concentration of phosphorus metabolites and the intracellular pH soon return to baseline.

The delayed injury phase

The delayed injury phase is a secondary deterioration that occurs in many cases after 6-48 hours following latent phase. During this phase neurons and oligodendroglia continue to die for extended periods. This phase is characterized by a decrease in the ratio of phosphocreatine to inorganic phosphate, despite an unchanged intracellular pH, and stable cardio respiratory status and contributes to further brain injury [6,7].

If the insult is not interrupted, this cascade ultimately leads to acute or "primary" cell death. The mechanisms of secondary energy failure seem to involve mitochondrial dysfunction secondary to extended reactions from primary insults. Mitochondria play a key role in determining the fate of neurons after hypoxia-ischemia. Translocation of apoptotic triggering proteins, such as cytochrome C from the mitochondria to the cytoplasm, can activate a cascade of proteolytic enzymes termed caspases or cysteine proteases that eventually trigger nuclear fragmentation [4,5].

More recent evidence suggests that circulatory and endogenous inflammatory cells and mediators also contribute to ongoing brain injury [4]. During this phase of injury, neuroprotective strategies are targeted.

The Mechanism of Protection with Hypothermia

They include inhibition of glutamate release, reduction of cerebral metabolism, which preserves high-energy phosphate compounds, decrease in intracellular acidosis and lactic acid accumulation, preservation of endogenous antioxidants, reduction of nitric oxide production; prevention of protein kinase inhibition, improvement of protein synthesis, reduction of leukotriene production, prevention of blood-brain barrier disruption and brain edema, and inhibition of apoptosis.

Answering the question of what is the optimal time to start hypothermia? Based on animal studies, brain cooling should be initiated as early as feasible after the brain injury, preferably within 2-6 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 48-72 hours. Data from adult animal studies indicated that slow rewarming is preferred [8,9].

Historical Review

The concept that hypothermia may have neuroprotective properties in human was first considered by Westin et al. in 1955 [10] who showed that hypothermia was beneficial in perinatal asphyxia. In 1962, Westin et al. [11] described improved survival in "asphyxia neonatorum" with the use of systemic hypothermia coupled with transfusion. In 1969, Westin [11] presented a larger consecutive series of 28 infants who successfully underwent brief systemic hypothermia (usually <5 minutes). A short-term favorable outcome was reported in 85% of the cases. The interest in the potential neuroprotective role of cerebral hypothermia waned following the studies by Silverman [12] and others [13,14] which revealed a potential deleterious effects of hypothermia. In 1980s, a renewed interest in the use of hypothermia as a neuroprotective strategy in human brain injury has emerged. In a variety of neonatal animal models, including sheep, piglets, and rats; modest systemic or selective cooling of the brain by 2°C to 4°C initiated before, during, and after a hypoxic-ischemic insult has been shown to reduce the extent of tissue injury, particularly if the cooling was implemented shortly after the insult (i.e, ≤ 6 hours) [15-38].

Recent Evidence Review

Recent experimental data were translated into clinical studies, initially pilot in design and culminating in two recently completed multicenter studies that have evaluated the feasibility, safety, and potential neuroprotective role of induced hypothermia administered in the form of selective head or total body cooling [39]. Further support for the use of hypothermia stemmed from randomized studies in adults that showed a neuroprotective effect after out-of-hospital cardiac arrest [40,41]. This neuroprotection was not seen when Hypotermia was used after traumatic brain injury [42-44].

Experimental studies

Most of the animal studies demonstrated diminished brain neuronal loss or cellular injury after treatment with cerebral hypothermia, although this is not a consistent finding [23,33-35] particularly if the injury is severe, the onset of cooling is delayed, the animal is not sedated, or seizures are present at the initiation of therapy [33,35].

Feasibility and safety studies

Gunn et al. [3] examined the safety of using selective head cooling to achieve minimal to mild hypothermia in the neonate. No adverse effect related to this degree of cooling was observed. Azzopardi et al. [46] used whole body cooling. All infants developed severe metabolic acidosis during the 48 hours of hypothermia, but this did not seem to be clinically relevant. Battin et al. [47,48] assessed the safety of selective head cooling coupled with mild systemic hypothermia. No differences in death, the need or extent of respiratory support, hypotension (MBP <40 mmHg), incidence of thrombocytopenia, hypoglycemia or renal failure were noted between the cooled and control groups. All cooled infants had a decrease in heart rate; however, no cardiac arrhythmias were seen.

Eicher et al. [49,50] studied 65 infants with neonatal encephalopathy in a multicenter safety randomized study. More infants in the hypothermia group developed bradycardia and overall lower heart rates, longer dependence on pressors to maintain blood pressure, hematuria, and pulmonary hypertension requiring nitric oxide administration. More patients in this group received platelet or plasma transfusions. Severe metabolic acidosis was found more frequently in the normothermic group. The combined outcome of death or severe motor scores was less in the hypothermia group (P=0.019).

Clinical efficacy trials

Gluckman et al. [51] reported the results of a multicenter randomized trial comparing selective head cooling coupled with mild systemic hypothermia with conventional treatment in infants with moderate-to-severe neonatal encephalopathy (Cool-Cap Trial). The primary outcome of the cool-cap trail was defined as death or severe neurological disability at 18 months of age. The data revealed no beneficial effect of head cooling, although predefined subgroup analysis suggested that induced head cooling could safely improve survival without neurodevelopment disability in infants with less severe encephalopathy at enrollment (Odd ratio 0.42; 0.22–0.80, p=0·009).

The second multicenter trial by Shankaran et al. [52] used whole body cooling compared with normothermia in infants with moderate-to-severe neonatal encephalopathy. Infants who underwent hypothermia had significantly less death or moderate-to-severe disability at 18 months (risk ratio, 0.72; 95% CI 0.54 to 0.95; P=0.01) without a clinically relevant difference in physiologic parameters or adverse events related to hypothermia.

The difference in the primary outcome between the two studies could be a result of study design or selection bias. Another important difference that may affect outcome was the degree of cooling used. The whole body study used a lower temperature of 33.5°C compare to 34-35°C in the cool

cap study. Additional unknown factors (i.e, use of sedation, the rate of rewarming) [53,54] also may have contributed to these differences. Both studies were relatively small, perhaps too small to examine all of the factors relevant to the use of cerebral hypothermia in neonatal encephalopathy.

Other Recent Trials

In the Total Body Cooling Trial (TOBY) from England, infants with moderate-to-severe HIE are randomized to receive whole-body cooling or standard intensive care, and the 18 months follow-up ended in 2008. The trial design features and the entry criteria for the TOBY trial are similar to those of the CoolCap trial [51]. The findings from the TOBY trial were published in 2009. The TOBY trial concluded that utilizing moderate hypothermia for 72 hours resulted in decreased neurologic adverse outcome in the survivors, even though it did not change the combined rate of death or severe disability significantly [55].

The ICE (Infant Cooling Evaluation) trial aimed at enrolling infants from a wide geographic region, using simplified protocols [56]. Hypothermia was 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 and safety of this approach in 17 infants.

The Neo.nEURO.network Hypothermia Randomized Controlled Trial, A total of 129 newborn infants were enrolled, and 111 infants were evaluated at 18 to 21 months. More than 65% of infants in this trial were out-born showed a strong neuroprotective effect in the severe HIE group [57].

Current Status and Implications for Clinical Practice

Perinatal HIE is not a single disease from a single cause. It has a great diversity in the timing and magnitude of brain injury. It is therefore unreasonable to expect that a single intervention will provide uniformly favorable outcome.

Now that the benefits of moderate hypothermia has been established in several randomized clinical trials; Moderate Hypothermia becomes the standard care as a rescue of neonates with HIE. NICUs around the world have established guidelines for the use of moderate hypothermia which include passive and active methods. In addition to eligibility criteria, a national registry was established in many centers to follow up the survivors. Long term follow up of these babies will provide key information about the efficacy and beneficial effects of this new therapy in decreasing the neurological sequelae following HIE injury in newborns.

Future Directions

Studies are ongoing to establish the optimal temperature for moderate hypothermia [58], and the duration of this therapy that produce maximum effects in improving long term outcomes in addition to finding the most effective adjunct therapy to potentiate the hypothermia effect in neuroprotection following HIE.

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