NEONATOLOGY GIVES BACK WHAT OBSTETRICS TAKE AWAY

I. Introduction

It is well-known that hypoxic and/or ischemic events during labor and delivery can cause injury to the baby's brain. The mechanisms at first blush appear to be reasonably straightforward. On closer examination, the pathophysiology of such injuries is actually quite complex. To be sure, the primary energy failure associated with lack of oxygen during labor and delivery can and does cause injury to fetal brain tissue. It may well be, however, that the greatest amount of injury to the neonatal brain occurs over time through a complex series of mechanisms put into motion by the initial insult. This being the case, it is possible that all or a substantial part of the injury to the brain can be avoided if the appropriate steps are taken to interrupt the process.

For years, nurses and neonatologists were in agreement that it was bad to let a sick baby get cold. Accordingly, protocols developed to quickly dry newborns and put them in an infant warmer. By the same token, for thousands of years, medical practitioners have attempted to relieve all sorts of maladies by cooling. Throughout the world, there were numerous accounts of people who survived tragic events intact, apparently as a result of cold conditions. For

example, most have heard of accounts where a near drowning victim survived intact in icy water. The development of the use of cardioplegia during open-heart surgery demonstrated that a lengthy post hypoxic cascade of molecular and cellular processes could be interrupted to protect the human body from ultimate cell death. This raised serious questions as to whether hypothermia after hypoxia could possibly reduce brain injury.

Throughout the 90's, numerous studies demonstrated that hypothermia had potential as a neuroprotective therapy following a hypoxic event. This culminated first in pilot clinical trials, and then large randomized trials, establishing the efficacy of hypothermia as a neuroprotective treatment following a hypoxic ischemic insult during labor and delivery. In December 2006, the FDA granted pre-market approval to the Olympic Cool Cap Device, setting forth the criteria for selective cooling with mild hypothermia to prevent or reduce the severity of neurologic injury associated with hypoxic ischemic encephalopathy. The criteria for the therapy included physiologic evidence of intrapartum hypoxia. Since then, both head cooling and whole body cooling have become standard throughout the United States. Most hospitals which provide therapeutic hypothermia use essentially the same criteria as were used in the initial studies. Importantly, it is a

widespread belief that to be effective, the therapy must be initiated within six hours of birth, the earlier the better.[1]

II The Studies

The initial studies were not surprisingly animal studies, primarily pigs, rats and sheep. And the studies showed promise. The following table (Levene, 2002) summarizes many of the studies throughout the 1990's:

Model	**Hypothermic Treatment**	**Outcome after hypothermia**	**References**
7-day-old rats, unilateral carotid artery ligation + 8% O_2 for 3 h	Environmental temperature was reduced from 37 to 34 or 31˚C for 3 h; hypothermia induced either during the hypoxia or immediately after hypoxia	Brief reductions in temperature of 3 - 6˚C had neuroprotective effects if initiated during, but not after, the insult. Percentage damage in the ipsilateral hemisphere was reduced from 45.5 to 0% in hypothermic animals	Yager et al. (1993)
7-day-old rats, unilateral carotid artery ligation + 8% O_2 for 3 h	30˚C vs 37˚C started immediately after insult	Percentage damage in the ipsilateral hemisphere was reduced from 45.5 to 0% in hypothermic animals	Saeed et al. (1993)
9- day-old piglets, neck compression + hemorrhagic	Intraischemic temperature reduced from 38 to 35˚C (rectal temperature)	Partial neuroprotection with reduced damage in areas of cerebral cortex and caudate	Laptook et al. (1994)

[1] See generally Edwards, et al., Neonatal Neural Rescue: A Clinical Guide, 2013. The authors have been the leaders in therapeutic hypothermia research

hypotension (15 min)		nucleus	
7-day-old rats unilateral carotid artery occlusion + hypoxia	Focal cooling with ipsilateral scalp temp of 22-35˚C vs. 37˚C for 2 h during the hypoxia	Cooling of less than 28C completely protected the brain from damage, neuropathology 3 – 4 days after insult	Towfighi et al. (1994)
1-day-old piglet, bilateral carotid artery occlusion + hypoxia	34.9˚C vs. 38.5˚C (tympanic membrane temperature) for 12 h, initiated immediately after resuscitation	No difference in necrotic cell numbers, but the number of apoptotic cells was reduced	Edwards, et al. (1995)
Newborn piglet, transient bilateral carotid artery occlusion + hypoxia (45 – 98 min)	Hypothermia (35˚C, tympanic) initiated at the time of resuscitation and maintained for 12 h	Energy ratios 24 – 48 h after insult were maintained at a similar level to sham control animals, no pathology	Thoresen, et al. (1995)
21-day-old rats, unilateral carotid artery ligation + 8% O_2 for 15 min	Animals were treated with post-ischemic environmental hypothermia (22˚C) for either 0 – 6 h, 6 – 72 h or 0 – 72 h. This resulted in a 2˚C reduction in brain temperature (38 - 36˚C)	Neuroprotection was only seen after prolonged (0 – 72 h) post-ischemic hypothermia. Protection was still evident after 3 weeks.	Sirimanne et al. (1996)
7-day-old rat, bilateral carotid artery ligation + 80% O_2 for 2 h	Hypothermia (from 38˚C vs. 32˚C, rectal temperature) for 3 h, started immediately, after hypoxia-ischemia	Hypothermic animals had a 65% reduction in histological brain damage	Thoresen et al. (1997)
Piglets (<2 weeks old), 15 min hemorrhage	Hypothermia 36˚C vs. 38˚C (rectal) for 1 h, started immediately	Reduced neuronal damage at 72 h in temporal and occipital	Laptook et al. (1997)

and four-vessel occlusion	after the insult	cortex and caudate nucleus	
Newborn piglets	Hypothermia: 35˚C vs. 39˚C, initiated on resuscitation	Reduced release of excitatory amino acids and NO in the cortex after hypothermia	Thoresen et al. (1997)
Newborn piglets, Fi_{o2} 6% or higher, depending on arterial pressure and pulse rate aiming at low-voltage EEG. Total hypoxic duration approximately 45 min	Cooling for 3 h (35˚C vs. 39˚C), started immediately after the insult	After 3 days, there was no overall improvement in histological outcome. Hypothermia was, however, protective after adjustments for differences in severity of insult and post hypoxic seizures. Hypothermia improved neurologic score and recovery of EEG at some time-points	Haaland et al. (1997)
7-day-old rats, unilateral carotid artery ligation + 8% O_2 for 75 min	32˚C vs. 35˚C vs. 38˚C for 3 h started immediately after HI	The brain damage was delayed but was similar to normothermic animals after >1 week recovery	Trescher et al. (1997)
Newborn piglets, bilateral carotid artery ligation + hypoxia (31 – 98 min)	Cooling (rectal temperature 35˚C) began at the time of resuscitation and was maintained for 12 h	Reduced rise of lactate during secondary phase as measured by MRS	Amess et al. (1997)
7-day-old rats, bilateral carotid artery occlusion + 7.7% O_2 for 70 min	Hypothermia (rectal temperature 32˚C) was induced for 6 h immediately after hypoxia-ischemia	Long-term (6-week) 30% reduction of injury was observed in cerebral cortex, hippocampus, basal ganglia and thalamus. No effect on sensory-motor function	Bona et al. (1998)
Fetal sheep, 30 min bilateral carotid artery	Delayed cooling from either 1.5-72 h or from 5-22 h after	Reduction in neuronal loss in cerebral cortex from 40 to 99%	Gunn et al. (1997) Gunn et al.

occlusion	ischemia, i.e. hypothermia started before postischemic seizures. Extradural temperature reduced from 39 to 30-33˚C		(1998)
Fetal sheep, 30 min bilateral carotid artery occlusion	Delayed cooling from I to 72 h after ischemia, i.e. hypothermia started after postischemic seizures. Selective head cooling 39˚C vs. 30-33˚C (extradural temperature)	No neuroprotective effects were observed	Gunn et al. (1999)

The animal studies led to human trials (Azzopardi, et al, *Pediatrics* 2000). The first large randomized trial was the Cool Cap Study, which looked at selective head cooling for 72 hours for enrolled babies with asphyxia, signs of encephalopathy and abnormal aEEG's. This trial showed a reduction in death or disability at 18 months for babies with less severe EEG changes at the time therapy was initiated (Gluckman, et al, *The Lancet*, 2005). The next study was conducted by the U.S. National Institute of Child Health and Development Network. It used whole body cooling, showing significant reduction in death or disability (Shankaran, et al., N Eng J Med, 2005). The total body hypothermia trial (TOBY) was another whole body cooling study. It showed a significant increase in survival and decrease in neurologic injury (Azzopardi, et al., N Eng J

Med 2009). All three of these early trials have been followed and have established evidence that the protection at 18 months lasts into the school years. A meta-analysis of the trials has confirmed that hypothermia works. It reduces both disability and death in babies who have suffered a hypoxic ischemic event during birth (Jacobs, et al., Cochran Data Base Syst. Rev. 2013).

III The Criteria

The criteria for therapeutic hypothermia are reasonably straightforward. It should be noted that the criteria for treatment are far different from what ACOG has tried to sell as the necessary criteria to establish HIE during labor and delivery. And the criteria are essentially the same throughout the country. In the main, they have remained unchanged. Not surprisingly, the criteria are often suggested by the manufacturer's recommendation. In granting pre-market approval for the Olympic Cool-Cap, the FDA set forth the following criteria in 2006 (FDA letter to Olympic Medical, December 20, 2006):

> Clinical evidence of moderate to severe HIE is defined as meeting criteria A, B and C below:
>
> A. Infant at greater than or equal to 36 weeks gestational age (GA) and *at least one* of the following
>
> - Apgar score less than or equal to 5 at 10 minutes after birth
> - Continued need for resuscitation, including endotracheal or mask ventilation, at 10 minutes after birth.
> - Acidosis defined as either umbilical cord pH or any arterial pH within 60 minutes of birth less than 7.00.

- Base Deficit greater than or equal to 16 mmol/L in umbilical cord blood sample *or* any blood sample within 60 minutes of birth (i.e., arterial or venous blood).

B. Infant with moderate to severe encephalopathy consisting of altered state of consciousness (as shown by lethargy, stupor or coma) and ***at least one*** of the following:

- Hypotonia
- Abnormal reflexes, including oculomotor or papillary abnormalities
- Absent or weak suck
- Clinical seizures

If the infant is paralyzed, assume an abnormal evaluation for criteria B and proceed to criteria C.

C. Infant has an amplitude-integrated electroencephalogram/cerebral function monitor (aEEG/CFM) recording of at least 20 minutes' duration that shows *either* moderately/severely abnormal aEEG background (score of 2 or 3) *or* seizures.

Note: The aEEG/CFM should be performed after one hour of age and should not be performed within 30 minutes following intravenous (IV) anticonvulsant therapy as this may cause suppression of EEG activity.

The aEEG/CFM score is determined as follows:

1a Normal: Lower margin of band of aEEG activity above 7.5 microVolts (µV); sleep-wake cycle present. (Cool only if seizures are present)

1b Mildly abnormal: Lower margin of band of aEEG activity above 5 microVolts µV; sleep-wake cycles absent. (Cool only if seizures are present)

2. Moderately abnormal: Upper margin of band of aEEG activity above 10 µV and lower margin below 5 µV.

3. Severely abnormal: Upper margin of band of aEEG activity below 10 µV and lower margin below 5 µV,

S. Seizures: Seizures on the aEEG are characterized by a sudden increase in voltage accompanied by narrowing of the band of aEEG activity and followed by a brief period of suppression.

If all three criteria are met, cooling should be started within six hours of birth.

Another rendition of the criteria for cooling eligibility is set forth. It is essentially the same (Mossali 2012):

> **Eligibility Criteria for Infant Cooling**
>
> Infants of gestational age greater than or equal to 36 weeks must meet both physiological and neurological criteria
>
> **Physiological Criteria**
>
> Evidence of intrapartum hypoxia, including at least two of the following:
>
> 1. Apgar score 5 or less at 10 min.
> 2. Needing mechanical ventilation and/or ongoing resuscitation at 10 minutes
> 3. Metabolic or mixed acidosis defined as arterial cord gas, or any blood gas within the first hour of life showing pH of 7 or less, or base deficit of ≥12 mmol/l.
>
> **Other qualifying criteria**
>
> If no cord blood gas is available and the initial blood gas within 60 min of birth shows a potential pH of <7.10 with a base deficit of ≥ 16 mmol/l, plus an acute perinatal event (abruption placenta, cord prolapse, or severe fetal heart rate (HR) abnormalities, variable or late decelerations) requires resuscitation, plus either (a) or (b).
>
> a) Apgar less than 5 at 10 min
> b) Continued need for ventilation initiated at birth and continued for at least 10 min.
>
> **Neurological criteria**
>
> One of the following:
>
> 1. The presence of seizures is an automatic inclusion
> 2. Evidence of encephalopathy suggested by amplitude-integrated EEG (a-EEG)
> 3. Physical examination consistent with moderate to severe encephalopathy

Hospitals offering therapeutic hypothermia available for treatment have their own criteria, which have little variation. These criteria are no secret. They

are often published on the hospital's website or even on their You-Tube presentations. These are for marketing purposes and worth viewing. They are often generous about the likely outcome from their therapy. Note also that most treating hospitals have sent correspondence to all of the referral hospitals in their catchment area. These letters are an effort to generate referrals and are worth getting if therapeutic cooling is an issue in a case.

All of the criteria reviewed include reference to Apgar scoring. Although cooling was not at issue in the 50's, when Virginia Apgar suggested the scoring system, it has been used in evaluating neonates as a standard part of newborn care for decades (Edwards 2013):

	0	**1**	**2**
Heart Rate (pulse)	No pulse felt	Less than 100	Greater than 100
Respiratory Effort	Apnoea	Irregular, shallow ventilation	Breathing/crying
Reflex irritability (grimace)*	No response to stimulation	Grimace/feeble cry when stimulation	Sneeze/cough/pulls away when stimulated
Muscle tone (activity)*	Flaccid	Good tone	Spontaneous movement
Colour (appearance)*	Blue/white	Partially pink	Entirely pink

*The Apgar mnemonic introduced as a teaching tool in 1963 by Dr. Joseph Butterfield

The degree of neurologic insult suggesting encephalopathy is another part of the criteria. It is determined through either an aEEG or through physical examination. The physical examinations typically refer to a moderate or severe encephalopathy. Typically, they are using the Sarnat grading scale for encephalopathy. It gives a consistent method of evaluation and is easy to apply. the Sarnat grading of encephalopathy (Edwards 2013):

Measure	**Sarnat grade**		
	1	2	3
Conscious level	Hypoalert	Lethargic	Stupor
Muscle tone	Normal	Hypotonic	Profound hypotonia
Posture	Mild distal flexion	Strong distal flexion	Decerebrate
Stretch reflexes	Normal	Overactive	Overactive
Moro reflex	Strong	Incomplete	Absent
Suck reflex	Normal	Weak	Absent
Tonic neck reflex	Slight	Strong	Absent
Pupils	Dilated	Constricted	Poorly reactive
Gut motility	Normal	Increased	Variable
Seizures	Uncommon	Focal or multifocal	Generalized

The outcome probabilities for cooling are often measured by whether the baby is mildly, moderately, or severely encephalopathic before and after treatment. Again, this

is typically measured by evaluating the child using the Sarnat Scale. As a general rule, the studies show the therapeutic hypothermia is potentially helpful. Importantly, if a baby is cooled in a timely fashion and is a Sarnat one or two at the time of cooling, more likely than not, the baby's outcome will be better. For example, the NICHD and Cool Cap Trials study show:

Proportion of Infants with Moderate and Severe Encephalopathy with Primary Outcome of Death and Disability in the NICHD and Cool Cap Trials (Shankaran, et al, **Optimizing Cooling for HIE**, NICHD Neonatal Network, 2010):

	Cooled Death/disability		Control Death/disability
MODERATE HIE			
Whole body Hypothermia NICHD trial (Shankaran 05)	32%		48%
Cool Cap trial (Wyatt 07)	45%		57%
SEVERE HIE			
Whole body Hypothermia NICHD trial (Shankaran 05)	72%		85%
Cool Cap trial (Wyatt 07)	70%		91%

IV. Pathophysiology

The primary mechanism of cell death from an asphyxia event is initiated by oxygen and glucose deprivation and an impairment in energy supplies. This primary or acute phase of injury typically begins within minutes. It includes the

depletion of energy metabolites and a switch to anaerobic metabolism with a rapid depletion of adenosine triphosphate (ATP). There is a rapid depolarization of cells, the initiation of cytotoxic edema, an increase in intracellular calcium, sodium overload, increase in extracellular glutamate and progressive acidosis, leading to cell injury and necrotic cell death.

Notably, the cascade of deleterious events that lead to cell death after a hypoxic ischemic insult that results in energy failure appears to occur following the termination of the insult during the reperfusion. After cerebral circulation and oxygenation are restored, there is a slow reduction of the metabolic acidosis. This is clinically shown by a reduction in cytotoxic edema and the reduction of the excitatory amino acids that are initially accumulated in the extracellular space. While cell death does occur during the primary phase after a sentinel event, it is often the later, latent phase of the insult which leads to global damage. Hours after the primary insult and restored perfusion, the secondary or latent phase includes secondary cytotoxic edema, inflammatory responses, an increase in free radical release and calcium overload. The accumulation of excitatory amino acids leads to neuronal cell death through apoptosis (Volpe, Neurology of the Newborn, 5th Ed; Edwards, et al., 2013).

As the precise mechanism of hypoxic ischemic cell death is not fully understood, nor is the precise mechanism of hypothermic neuroprotection. Pragmatically, it appears effective. Broadly, it seems well-established that cooling interrupts or at least suppresses many of the pathways leading to a hypoxic cell death. Hypothermia certainly reduces cellular metabolic demands. It

also reduces excessive accumulation of cytotoxin's and oxygen free radicals. It suppresses the post ischemic inflammatory process and seems to inhibit the intracellular pathway leading to apoptosis delayed programmed cell death (Edwards, et al. 2013).

V. Neuroradiologic Imaging.

Therapeutic hypothermia initiated within the first six hours of life is done so with the intent that it diminish or prevent acute brain lesions. The longer-term effects of cooling on the evolution of brain lesions have not been well studied. Predictably, some studies have reflected a decrease in both white matter and basal ganglia and thalamus lesions. But in the main these have not been controlled trials. An imaging study was performed within the TOBY trial. It showed that there was such a decrease (Rutherford 2010). At least one study has shown that cooling did affect the timing of the evolution of the injury, as reflected on MRI. It appears that therapeutic hypothermia delays the return of mean diffusivity ratios to normal, which is pseudo-normalization, until after the 10th day, as compared to the more typical 6 to 8 days. Accordingly, it appears that cooling slows the evolution of diffusion abnormalities as shown on MRI, (Bedrick 2012).

VI. Unanswered Questions.

There remain many unanswered questions as the science of brain injury and neuroprotection are evolving. In addition to finding the precise timing and temperature for therapeutic hypothermia, there are other potential therapies that

could be used in combination with hypothermia in an effort to optimize results. Obviously, antiepileptic drugs are used frequently to control seizures that attend an ischemic injury. Other adjuvant therapies show some promise, particularly given what we know now about the mechanisms of injury. For example, antioxidants, such as allopurinol and N-Actylcysteine are being studied.

Additionally, other therapies such as magnesium sulfate, Alpha 2 - adrenergic agonists, melatonin, and a variety of anesthetics are being looked at as well (Edwards, 2013). Implementation of clinical trials for future combination therapy has many practical problems, not the least of which is the expense. Moreover, it will be initially difficult to discern the incremental benefit from such adjuvant therapies. Another area of research is in the design of studies to determine “optimal" outcome. To be sure, using Sarnat scales and subsequent neuropsychological testing, hypothermia has been shown to yield “better" outcomes. To date, however, "better" defies a precise definition in a given case.

HEAD COOLING LITERATURE

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