Therapeutic Whole Body Cooling for Hypoxic Ischemic Encephalopathy

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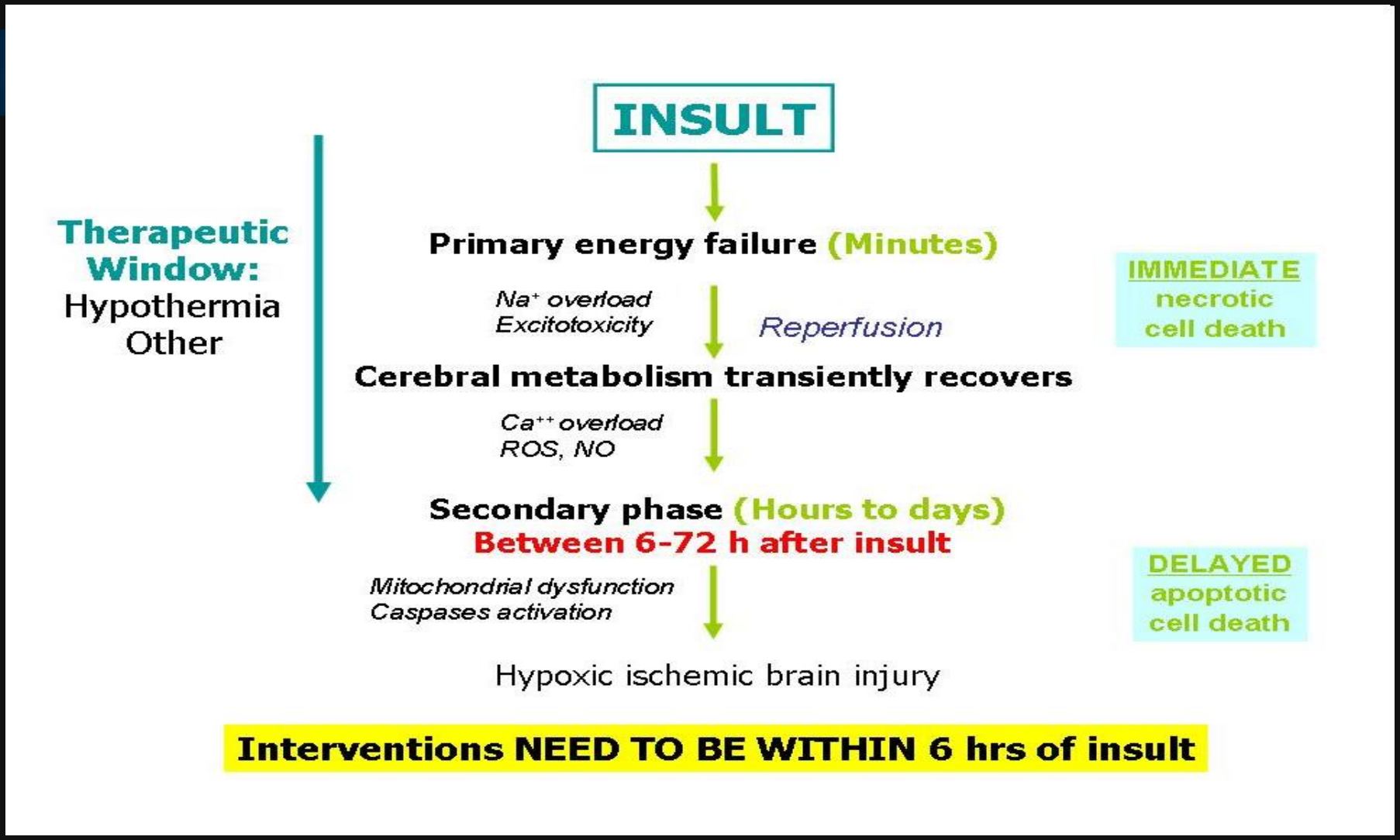
Objectives

- Brief background on cell physiology and effects of asphyxia
- Describe the pathophysiology and stages of HIE
- Discuss the effects of cooling on HIE
- List eligibility criteria for therapeutic whole body cooling
- Examine current data on clinical whole body cooling and data on clinical trials.
- Review nursing implications, interventions to anticipate
- Discuss needs of the family

Cell Physiology and Effects of Asphyxia

- Cell Physiology:
  - Oxygen is used by the cells in production of energy (ATP)
  - Hypoxia is the single most common cause of cellular injury
- Effects of Asphyxia:
  - SNS stimulation, which causes:
    - Decreased cardiac output and cerebral perfusion
  - Anaerobic metabolism causes
    - Decreased ATP, cytotoxic edema and electrical failure of neural tissue
  - Reperfusion injury (6-15 hours after insult) causes:
    - Irreversible cell death

Pathophysiology of HIE:



Hypoxic Ischemic Encephalopathy

- Definition:
  - Encephalopathy: brain injury resulting from hypoxic insult
  - Can occur due to prenatal, intrapartum or postnatal insults

Maternal and placental infections

Cord Compression/ Prolapse, Nuchal Cord, Abruption,

CPR at birth, cardiac failure, severe respiratory disease

Stages of Hypoxic Ischemic Encephalopathy

- **Stage 1 - Mild**
  - Hyper alert, normal tone and activity
  - No seizure activity
  - Exaggerated response to stimulus
  - Reactive pupils

- **Clinical Manifestations**
  - During the first few days the infants tone may be slightly increased and their deep tendon reflexes may be brisk
  - May observe poor feeding, excessive sleepiness or crying
  - These manifestations normalize by 3-4 days of life

- (Zanelli, 2012)

Stages of Hypoxic Ischemic Encephalopathy

- **Stage 2 - Moderate**
  - **Clinical Manifestations:**

  - Hypotonia
  - Development of seizure activity and/or lethargy indicates deteriorated status
  - Constricted but reactive pupils
  - Periodic breathing or apnea
  - Decreased activity
  - Weak suck and incomplete moro
  - Bradycardia

  - (Zanelli, 2012)

Stages of Hypoxic Ischemic Encephalopathy

- **Stage 3 – Severe**
  - **Clinical Manifestations:**

  - Stupor/Coma
  - Absent reflexes
  - Non reactive pupils
  - Seizures
  - No spontaneous activity
  - Requires mechanical ventilation
  - Decerebrate posture
  - Flaccid tone
  - Deviation/dilation/Non-reactive to light

- (Zanelli, 2012)

Effects of Therapeutic Hypothermia on HIE

- Preserves brain energy state
- Slows the release of excitotoxic neurotransmitters and nitric oxide
- Decreases apoptosis
- Reduces inflammatory cascade
- In sum, these slow the extent of secondary energy failure following a hypoxic insult and reduce extent of brain injury

(Parikh, 2007)

Eligibility - vs – Ineligibility

- **Eligibility**
  - Gestational age ≥ 36 weeks and ≤ 6 hours of life
  - Need for resuscitation at birth secondary to poor respiratory effort or diagnosis of encephalopathy
  - Presence of moderate to severe encephalopathy
  - Any one of the three:
    - Cord or arterial blood gas with pH ≤ 7and base excess (BE) ≥ 16 mEq/L
    - Acute perinatal event and Apgar ≤ 5 at 10 minutes of life
    - Initiation of assisted ventilation at birth for ≥ 10 minutes in response to an acute event
- **Ineligibility**
  - Infant ≥ 6 hours of life
  - Known chromosomal anomaly
  - Known congenital anomalies
  - Severe intrauterine growth restriction with birth weight ≤ 1800 grams
  - Infant extremis (at the point of death)

Neurological Exam

- Upon arrival to NICU:
  - MD/NNP should perform neuro exam prior to initiation to cooling.
  - Points are given according to the physical exam. 1 to 3 points for each of the categories.
    - 1 is always normal and 3 is the worst score.

Category	Signs
1) Level of Consciousness	1-3
2) Spontaneous Activity	1-3
3) Posture	1-3
4) Tone	1-3
5) Primitive reflexes	
Suck	1-3
Moro	1-3
6) Autonomic System	
Respiration	1-3
Pupils	1-3
Heart Rate	1-3
Clinical Seizures	Y/N
Sedated/Paralyzed	Y/N

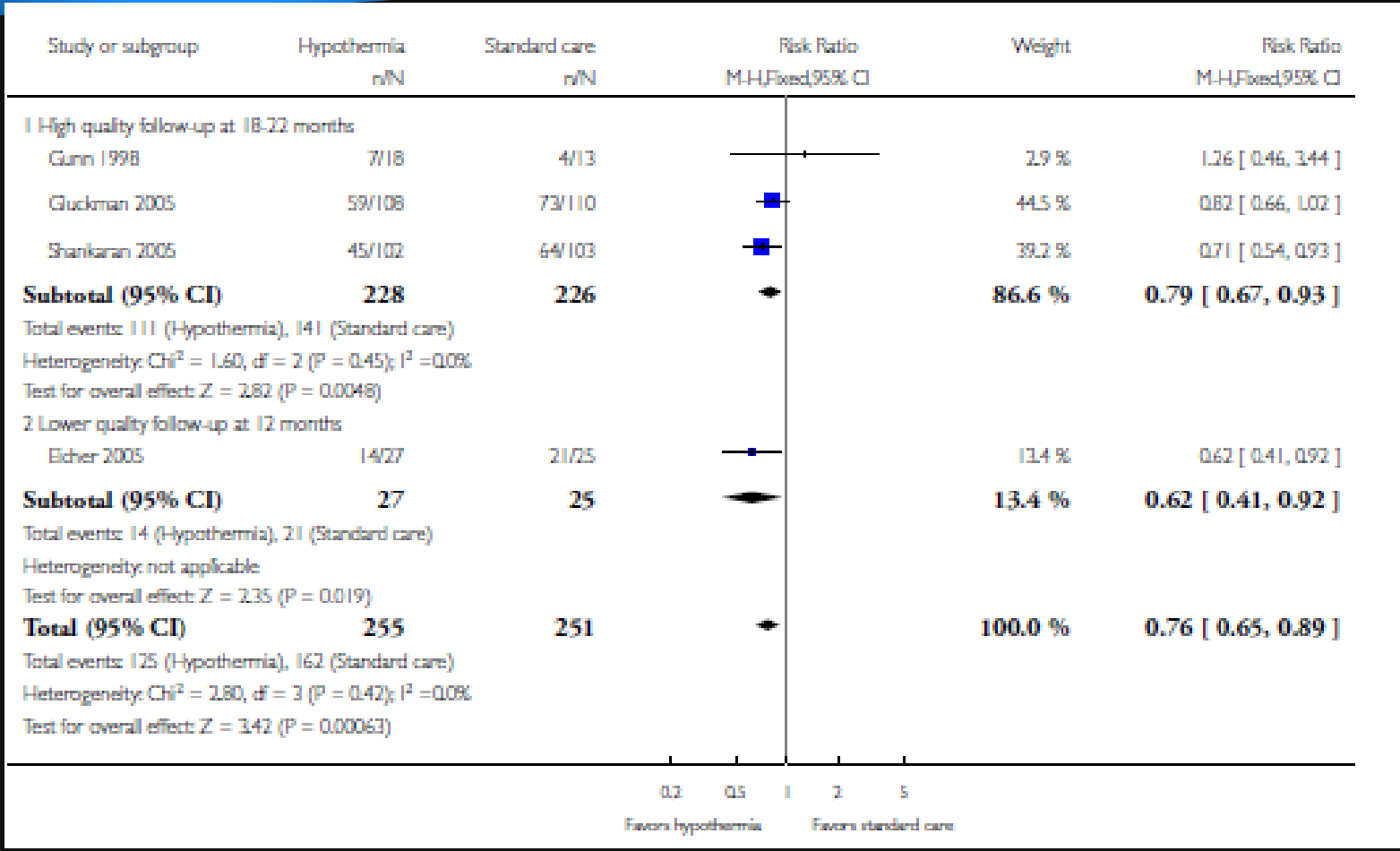
Clinical Trials

- There are 5 published randomized controlled trials of hypothermia in newborn infants whose primary outcome was death or disability at 18 months:
  - **Cool Cap**: used selective head cooling with mild systemic hypothermia for infants with moderate to severe encephalopathy and an abnormal aEEG. It showed a protective effect on primary outcome of death and disability at 18 months
  - Selective head cooling or usual care was evaluated in an RCT in China where 256 infants were enrolled with encephalopathy. The primary outcome occurred in 49 % control and 31 % hypothermia group infants, OR 0.47 (0.26–0.84, *P*=0.01).
  - **NICHD**: utilized whole body cooling, revealed significant reduction in death and moderate to severe disability at 18 months
  - **TOBY**: whole body cooling and did not show a significant effect on the primary outcome, however, there was improvement in the neurological outcomes in the survivors of the hypothermic group.
  - The European Network RCT enrolled 129 infants with moderate or severe encephalopathy and an abnormal aEEG. Death or severe disability occurred in 51 % of the hypothermia group and 83 % in the normothermia group.

(Chakkarapani & Thoresen, 2010)(Shankaran, 2013)

Evidence for therapeutic hypothermia:

Death or Major Disability



Attempted Clinical Trials

- A RCT by NICHD looking into the effect of longer duration and deeper cooling was initiated from 10/2010 to 11/2013. Pre-clinical animal studies showed the potential for greater neuroprotection. Eligible neonates were randomized to a 33.5 or 32 degree Celsius and to either 72 hours or 120 hrs. The trial was stopped on 11/2013 due to futility and safety concerns.

Upcoming clinical trials…Possibilities for the future!

- Stem cell based therapies in conjunction with clinical whole body cooling.
  - Currently, 6 trials listed on clinicaltrials.gov where stem cells derived from human umbilical cord blood cell (HUBC) or bone marrow are being assessed for safety and efficacy in hypoxic ischemic injury and CP.

- Erythropoietin for neonatal neuroprotection
  - Has cytoprotective effects on glial cells, endothelial cells and neurons. Prevents the cellular response to inflammation from spiraling out of control.
  - Two clinical trials, “Neonatal Erythropoietin and Therapeutic Hypothermia Outcomes in Newborn Brain Injury” (NEAT-O) and “Efficacy of Erythropoietin to Improve Survival and Neurological Outcome in Hypoxic Ischemic Encephalopathy (Neurepo) are ongoing.

Patient Management during Therapeutic Cooling

- The following are all possible cooling related issues:
  - Bradycardia (can be associated with esophageal probe location)
  - Hypotension - requiring inotropic support
  - Coagulopathy – leading to thrombosis or hemorrhage
  - Thrombocytopenia
  - Oliguria

There have been some small studies that have demonstrated the use of ECMO while receiving hypothermia is feasible.

(Massaro, Bahrami, Chang, Glass, Short, & Baumgart, 2010).

Nursing Interventions & Implications

- Provide necessary resuscitation at delivery
  - Establish/maintain an airway
    - The patient may not have a sufficient respiratory drive to sustain life, help will be needed.
  - Be prepared/thinking about the need for Epinephrine admin for bradycardia.
    - Can be given ETT or via emergent UVC placement
  - Maintain adequate thermoregulation
    - Want to avoid hyperthermia (~≥ 36◦ axillary/skin or 37◦C core) - likely as important as therapeutic cooling

Nursing Interventions & Implications

- Treatments to consider:
  - Volume expanders
    - PRBC's, Fresh Frozen Plasma, Platelets (if indicated)
    - Normal Saline – want to avoid aggressive fluid administration as this may increase cerebral edema
  - Vasopressors
    - Dopamine
    - Dobutamine
  - IV fluids
    - Central line access is preferred for cooling.
      - Cooling causes a constriction of the vessel and PIV placement difficult.
    - Frequent scheduled blood glucose levels
  - Anticonvulsants
    - Anticonvulsants will mask seizures on an EEG, it is best to not give them prior to this study
    - Ativan and Phenobarbital are the main anticonvulsants used in the NICU

Nursing Interventions & Implications

- Labs
  - CBC –
    - complete blood count with differential and platelet count
  - Coagulation studies
  - Electrolytes
  - Blood glucose
  - Lactic Acid
  - Blood gases – with lactic acid and ionized Ca++,
  - Blood Cultures
    - Lumbar puncture

Nursing Interventions & Implications

- Diagnostic Tests
  - EEG –
    - Anticonvulsants can alter the accuracy of the test
  - aEEG – Amplitude integrated encephalography
    - performed within a few hours of birth can help evaluate the severity of brain injury in the infant with HIE
  - MRI –
    - usually done 4-8 days of life, can be done on the cooling blanket but only if the insult is severe.
  - ECHO –
    - performed if an congenital heart defect is suspected to be the cause of the insult.

After cooling – Nursing Care Considerations

- PO feeding may be difficult due to an inadequate gag and suck reflex. Tube feedings may be required.
  - Parents need to learn how to administer G-tube feedings and give medications via G-tube.
- Neurological damage:
  - Can result in the need for Anticonvulsant medications.
  - May cause these kids to have temperature instability.
  - If the infant has had a severe insult, PT and OT may need to evaluate for contractures and ROM.
- CPR is good for all parents to have even if they have healthy kids.
- Stress the importance of infection control in the home and to keep all follow up appointments after discharge.

(Verklan, 2007)

Parent Teaching & Support

- Provide information to the parents about HIE.
  - Offer to them informative websites, remind them that Google is not always their friend.
- Offer services to them such as:
  - Chaplaincy services
  - Social Services
  - Lactation consultants
- Also be sure to share with them ways to set up meetings with the medical team to discuss the plan of care.

Summary

- Perinatal HIE dramatically increases risk of death or neurdevelopmental disabilities
- Time is of the essence when managing a patient with HIE
- ILCOR now recommends cooling for acutely asphyxiated encephalopathic newborns in larger tertiary care centers
- Prompt transfer to such facilities should result in improved outcomes for affected high risk newborns
- Parent teaching needs to be ongoing and reinforced. Referrals for long term care or ECI should be considered.

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