Objectives

- Review Pathophysiology of Hypoxic-Ischemic Encephalopathy (HIE)
- Identify Criteria for initiating Therapeutic Hypothermia for presumed HIE
- Review Therapeutic Hypothermia
- Discuss evidence supporting Therapeutic Hypothermia for HIE
- Application to Clinical Practice

What is Hypoxic-Ischemic Encephalopathy?

Hypoxic: diminished amount of oxygen
Ischemic: diminished blood perfusion
Encephalopathy: dysfunction of the brain

HIE is an abnormal neurological state as a result of a hypoxic-ischemic insult. HIE occurs when there is impaired cerebral blood flow, thus reducing oxygen delivery to the brain followed by cerebral dysfunction.

Factors that Affect Fetal Oxygenation that may contributing to the development of HIE

- Maternal factors
  - seizures, trauma, smoking, sepsis, vasculopathies, severe preecclampsia, antepartum hemorrhage
- Uteroplacental factors
  - placental abruption, placental infarction/dysfunction, oligohydramnios, abnormal doppler studies or chorioamnionitis
- Fetal Factors
  - cord compression, cord prolapse, entanglement, significant anemia (e.g. maternal-fetal hemorrhage)

Incidence of HIE

- 1 to 6 per 1000 live births
- It is often unanticipated
- HIE infants are often initially cared for in community hospitals

Pathophysiology Review

(The ACoRN Neonatal Society, 2010; Deacon & O'Neill, 1999; Fetus and Newborn Committee & CPS, 2012)
Hypoxic-Ischemic Encephalopathy & Therapeutic Hypothermia in the Newborn

Jan 28, 2015

HIE Pathophysiology

Primary Phase (primary neuronal death & energy failure)

Latent Period 6 hours

Secondary Phase (delayed neuronal death)

"reperfusion injury begins"

How does Therapeutic Hypothermia fit into this clinical picture?

If infant cooling is initiated within the 6 hour window, the extent of neuronal damage may be decreased.

Therapeutic Hypothermia is a neuroprotective intervention intended to prevent severe neurological sequelae.

How do we decide which infants should receive Therapeutic Hypothermia?

Canadian Pediatric Society (2012)

Practice Point

Infants > 36 weeks gestation with HIE who are <6 hours of age and who meet the following criteria:

Criteria A (any two):
- APGAR score <5 at 10 minutes of age
- Continued need for ventilation & resuscitation at 10 min. of age
- pH<7 or base deficit >16 mmol/L in cord blood OR arterial blood gases measured within 1 hour of birth.

AND

Criteria B:
- Moderate (Sarnat stage II) or Severe (Sarnat stage III) encephalopathy demonstrated by the presence of SEIZURES OR at least ONE SIGN IN AT LEAST THREE OF THE CATEGORIES shown in Table 1

Clinical Criteria for HIE

Exclusion Criteria

- < 36 weeks gestation based on CPS statement
- OR < 35 weeks gestation based on some current research
- Significant hemorrhage
- Major congenital or genetic abnormalities and no further aggressive treatment is planned

How do we decide which infants should receive Therapeutic Hypothermia?

Clinical Criteria for HIE

<table>
<thead>
<tr>
<th>Category</th>
<th>Seizures</th>
<th>Hypotonia</th>
<th>Increased muscle tone</th>
<th>Muscular hypotonia</th>
<th>Posture</th>
<th>Irritability</th>
<th>Poor tone</th>
<th>Oligomelia</th>
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* presence of seizures or at least one sign in at least three of the categories

[From: and Newborn Committee & CPS, 2012, pp. 3; modified from original Sarnat & Sarnat, 1976]

Hypoxic-Ischemic Encephalopathy &
Therapeutic Hypothermia in the Newborn

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How do you provide Therapeutic Hypothermia?

• Decreasing a newborn temperature to a rectal or esophageal temperature of 34 ± 0.5°C for 72 hrs.
• Head/whole body cooling.
• Provision at a Level III NICU/Paediatric Critical Care Unit with trained personal to diagnose and treating seizures, multi-organ failure, arrhythmias, coagulopathy and other complications that may develop.


What can be done until the transport team arrives?

• Initiate passive cooling in the peripheral hospital as per direction of accepting physician at tertiary centre
• Turn off the overhead warmer
• Remove infant hat, un-swaddle infant
• Monitor temperature very closely to avoid excessive hypothermia
• Establish venous/arterial access if possible prior to the cooling process
• Monitor vital signs & for signs of seizure activity
• Intervene as clinically indicated

*Update family prior to transport!*

Infant Cooling System

Possible Multi-organ Involvement: Pathophysiology Review

Multi-organ Involvement

• Cerebral edema, ischemia, cerebral hemorrhage, spinal cord injury
  • Monitor: seizures, altered suck, swallowing, gag, spontaneous breathing, neurological assessment, motor function
• Pulmonary Edema (related to cardiac dysfunction and increased pulmonary capillary permeability), RDS (surfactant deactivation), MAS, PPHN
  • Monitor: pulmonary hemorrhage, acidemia (may lead to pulmonary vessels remaining constricted thus leading to PPHN), hypoxemia
• Ischemia of cardiac muscle and reduced contractility
  • Monitor: hypotension, bradycardia, arrhythmia, decreased perfusion, cardiovascular shock

(Gomella 1999; The ACoRN Neonatal Society, 2010; Stackel, E. & Hendricks-Muñoz, K., 2011)

Multi-organ Involvement

• Altered synthesis, excretory and detoxifying functions of the liver
  • Monitor: LFTs, ammonia levels (hyperammonemia), coagulopathies
• Necrotizing enterocolitis, delayed gastric emptying, ileus, GI bleed
  • Monitor: Abdominal status, stooling/stool, cautiously initiate of feeds
• Decreased GFR, acute tubular necrosis (ATN), impaired Na & H2O regulation, fluid shifts, SADI, CHF
  • Monitor: Electrolytes, BUN, Cr, accurate ins and outs

(Gomella 1999; The ACoRN Neonatal Society, 2010; Stackel, E. & Hendricks-Muñoz, K., 2011)
Multi-organ Involvement

- **Hematological**: Coagulopathy, impaired synthesis of clotting factors, thrombocytopenia
  - **Monitor**: CBC, Platelets counts, INR, Fibrinogen; may need volume replacement; blood products (e.g. platelets, PRBCs, cryoprecipitate)

- **Metabolic**: Hypokalemia, hypo/hypermagnesemia, Hypocalcemia, Hypoglycemia, Acidosis

Clinical Management Considerations:

- **Venous/Arterial Access**: venous/arterial access prior to the cooling process!
- **Fluid and Nutritional Requirements**: metabolic activity is reduced
  - prevention of excess fluids, TFI 40-70mls/kg/day
- **Analgesia / Sedative treatment**: indications for analgesia include agitation, pain or shivering response. Shivering leads to increased peripheral muscle oxygenation consumption.
  - **Remember** hypothermia may have reduced drug clearance, potentially toxic serum concentrations may occur with moderate hypothermia. (E.g. Morphine infusion rates should not be >10 mcg/kg/hr)
- **Therapeutic Drug Level Monitoring**: metabolism by the liver and pharmacokinetics may be significantly altered during the cooling process.

Possible Seizure Activity

**Peak time for seizure occurrence is 6-48 hrs**

- **Why do we monitor for this?** If seizures are untreated negative sequelae can occur
- **How?** Bedside Amplitude-integrated electroencephalography (aEEG)
  - e.g. Brain2
  - aEEG is a tool for monitoring both normal and severely abnormal background patterns and seizure activity
- Seizures detected by aEEG should be evaluated by a 40-60 min. 12–16 sensor Conventional Electroencephalography (cEEG) done by a cEEG technician.

What else do we monitor & when?

- **On Admission**: CBC, coagulation, electrolytes, LFTs, ammonia, urea & creatinine, calcium, glucose, phosphate and alkaline phosphatase, gas, lactate
- **1st 24 hours**: Arterial blood gas, electrolytes, glucose & lactate q6-8h
- **24 hours to end of cooling phase**: CBC, coagulation, electrolytes, LFTs, bilirubin, urea & creatinine, ammonia, calcium, phosphate and alkaline phosphatase
- **Lipid level if receiving IV lipid**
- **Arterial blood gas, electrolytes, glucose and lactate q6-8h**
- aEEG, 12 lead EEG, MRI
- Paediatric Neurology Consultation
- **Consider**: Echocardiogram if hemodynamically unstable

What supporting literature exists for Therapeutic Hypothermia?
Jacobs et al., 2007
The Cochrane Library, 4

- Cochrane Review included 8 RCTs (n=638) comparing hypothermia treatment to normothermia treatment for newborns with moderate or severe HIE.

- **Objective:** Determine the effect of therapeutic hypothermia on mortality, long-term neurodevelopmental disability (18 months) and clinical side effects.

Jacobs et al., 2007
The Cochrane Library, 4

- **Conclusion:** Death or major disability, mortality and neurodevelopmental disability in survivors are all reduced. It is important to note that there is some evidence of harm from therapeutic hypothermia. These risks include increased thrombocytopenia & hypotension, however the benefits on survival and neurodevelopment outweighed these short-term adverse effects.

Shah (2010)
Seminars in Fetal & Neonatal Medicine 15; 5

- A systematic review and meta-analysis was conducted to including 13 RCTs comparing hypothermia treatment to normothermia treatment for newborns with HIE. The Meta-analysis included n=1440 newborns >35 weeks gestation.

- **Objective:** To evaluate the effectiveness and safety of therapeutic hypothermia use in newborns with HIE.

Shah (2010)
Seminars in Fetal & Neonatal Medicine 15; 5

- **Conclusion:** Hypothermia is a safe and effective treatment of neonatal HIE in term and near-term newborn infants. Therapeutic hypothermia reduced mortality and neurological disability at 18-24 months of age.
Systematic Reviews Favour Therapeutic Hypothermia & Governing Bodies Endorse this Therapy.

- CPS, AAP

What do we do after 72 hours of cooling?

Rewarming after Therapeutic Hypothermia

Increase rectal temperature by 0.5°C every 1-4 hours.

The consensus is rewarm infant VERY SLOWLY!

Why do an MRI at 24-72 hrs post warming?

- Edema secondary to hypoxic ischemic insult usually subsides so patterns of injury that are reversible may be identified as restricted diffusion BEFORE lysis of cerebral cells occurs.
- Aids in prognostic counselling

Conclusions

Morality and neurodevelopmental disability are reduced when therapeutic hypothermia is utilized for moderate to severe HIE.

Mortality is $\downarrow$ without major disability
References


