Moderate systemic hypothermia for the treatment of neonatal hypoxic ischaemic encephalopathy (HIE)

HIE: Incidence

Hypoxic ischaemic brain injury is a serious perinatal event with significant risk of long term adverse consequence. The incidence of intrapartum hypoxia varies between countries, with lower rates in developed countries. In 1986, Levene et al[1] reported a rate of 3 to 5 per 1000 live births with subsequent moderate or severe HIE in 0.5 to 1 per 1000 live births. Wu et al reported a declining rate of birth asphyxia in California, with rates falling from 14.8 to 1.3 / 1000 live births between 1991 and 2000.[2] In 1992, Hull and Dodd reported an incidence of moderate or severe HIE of 1.8/1000 live birth.[3] Of babies who develop moderate or severe HIE, between 10-60% die and at least 25% of the survivors have neurodevelopmental sequelae.[4] A published review of outcomes after moderate HIE at RPA Hospital showed a one year disability rate of 36%.[5] Hypothermia is the most promising and, currently, the only clinically feasible manoeuvre to decrease brain damage from this cause by providing neurological rescue for neonates with HIE.

Therapeutic hypothermia - background

Pathophysiology of hypoxic-ischaemic encephalopathy

Mechanisms of neuronal death: Following a reversible hypoxic-ischaemic global insult, neuronal death occurs in two major phases, each characterised by distinct pathophysiological processes influenced by the nature and severity of the insult.[6, 7, 8] There may be immediate neuronal death if the insult is severe. After a latent period the secondary phase of delayed neuronal death is initiated and accounts for a significant proportion of final cell loss even after very severe insults.

Primary neuronal loss is related to cellular hypoxia, which leads to exhaustion of high-energy metabolism (primary energy failure) and cellular depolarisation. However, many neurons do not die during this primary phase of injury. Rather, a cascade of pathologic processes is triggered leading to further loss of neurons starting after some hours and extending over days.

This secondary loss of neurons, termed secondary or delayed neuronal death, is associated with marked encephalopathy occurring 6 to 100 hours after the injury.[9] The mechanisms involved include hyperaemia, cytotoxic oedema, mitochondrial failure, accumulation of excitotoxins, active cell death (analogous to developmental apoptosis), NO synthesis and cytotoxic actions of activated microglia.[10] The delayed phase is associated with increased seizure activity, which in itself may further deplete energy reserves. Magnetic resonance spectroscopy studies in infants with moderate to severe HIE have confirmed normal cerebral oxidative metabolism shortly after birth followed by evidence of secondary energy failure. This was predictive of both mortality and neurodevelopmental outcome at both one and four years of age.[11, 12]

Therefore a therapeutic window of opportunity exists in the interval following resuscitation of the asphyxiated newborn, before the secondary phase of impaired energy metabolism and injury is fully established.

Evidence for neuroprotection by hypothermia:

For some time, deep hypothermia to less than 28^0C has been shown to be valuable for neuroprotection

during cardiac surgery requiring bypass. Recent studies, in a variety of models of perinatal hypoxia-ischaemia, have shown a beneficial effect with induced hypothermia of a few degrees below normal, i.e. mild hypothermia.[13, 14, 15]

There are a number of postulated mechanisms by which hypothermia may be neuroprotective. It may modify cells programmed for apoptosis. In neonatal piglets, 12 hours of mild hypothermia after resuscitation significantly decreased the number of apoptotic cells, but not the number of necrotic cells.[16] Other mechanisms may include reduced cerebral metabolic rate, attenuated release of excitatory amino acids (glutamate, dopamine), amelioration of the ischaemia-impaired uptake of glutamate and lower production of nitric oxide and free radicals.

There have now been 4 published randomised controlled trial of hypothermia as neuroprotection after HIE. The two largest of these studies are the CoolCap study of selective head cooling and the NICHD trial of systemic hypothermia.[17, 18] The CoolCap trial followed 218 infants to 18 months, and reported no significant difference in the primary outcome of death or severe disability in the infants treated with selective head cooling with mild systemic hypothermia after neonatal encephalopathy hypothermia (unadjusted: 55% vs 66%, p=0.10, OR 0.61 [95% CI 0.34-1.09]), or on any secondary outcome measures. Predefined subgroup analyses based on pre-randomization background aEEG amplitude abnormalities demonstrated no effect of delayed cerebral hypothermia on outcome in infants with severe aEEG abnormalities, but significant benefit in infants with intermediate (moderate) aEEG abnormalities (n=172: 48% vs 58%, P=0.021, OR 0.47 [95% CI 0.26-0.87]; adjusted P=0.009, OR 0.42 [95% CI 0.22-0.88]). The NICHD trial followed 205 infants to 18-22 months, and reported a reduction in the primary outcome of death or moderate/severe disability in infants treated with whole-body hypothermia (44% vs 62%, RR 0.72 [95% CI 0.54-0.95]; p=0.01).

The latest update of the Cochrane Review on this issue shows the statistically significant (p = 0.0006) therapeutic benefit of hypothermia after HIE on death and neurodevelopmental disability with a relative risk of 0.76 (95%CI, 0.65 - 0.89).[19] Because of this the two ongoing trials of hypothermia, the ICE trial based in Australia and the TOBY trial based in the UK have ceased recruitment during 2007. RPA Hospital was part of the ICE trial until recruitment ceased; therefore this guideline will follow closely that applied in the ICE trial.

Theoretical modelling of cooling investigating temperature distribution within the neonatal head implied that it is necessary to reduce systemic temperature to achieve deep brain cooling.[20] Evidence from the Cool Cap study is thus that there is benefit from head cooling, but it is not known if this effect may be from systemic cooling. Selective head-cooling requires expensive technology that is not currently commercially available in Australia and use of such a device precludes starting cooling at the birth hospital for infants requiring transport to a participating centre. Therefore, we will use whole body cooling to 33.0-34.0°C for 72 hours.

Hypothermia, when to start?

The evidence from animal studies is that the earlier the cooling can be started after the hypoxic ischaemic insult, the better the potential neuronal rescue, see figure.[21, 22] One additional problem in the clinical arena is that unless there is a clear sentinel event, we do not know the timing of the hypoxia that caused the brain injury. It may have preceded delivery by some time, so the imperative to try and commence cooling as soon as possible after birth is even greater. This creates the clinical need for early postnatal prediction of babies likely to develop moderate or severe encephalopathy. Many of the trials have used clinical criteria such as Apgar score, pH and early evidence of encephalopathy. The CoolCap study used early recordings of amplitude integrated EEG in addition to clinical criteria.
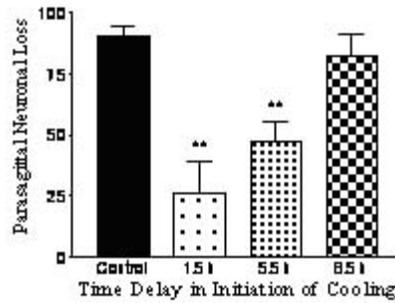
Figure 1: *Benefit of early initiation of hypothermia on outcome (% parasagittal neuronal loss) following global hypoxic-ischaemic brain injury in the term fetal lamb.*

Hypothermia, who to treat?

Clinical Selection Criteria: In a study of neonatal HIE,[1] a 10 minute Apgar score of 5 or less had a sensitivity of 96% and specificity of 78%. An Apgar score of 3 or less at 10 minutes was associated with a 23% risk of death or severe disability in the Collaborative Perinatal Project for the National Institutes of Health,[23] while a base deficit of greater than 12 mmol/L was associated with a 39% risk of adverse neurological outcome at one year of age.[24] Combinations of perinatal events have also been used to predict outcome. A 5 minute Apgar score of 5 or less in association with encephalopathy and seizures has been associated with a 70% risk of death or disability.[25] The triad of delivery room intubation with a 5 minute Apgar score of 5 or less and a cord pH of 7 or less and/or postnatal base deficit of 14 or more combined with early moderate or severe encephalopathy [at 3 (SD 2.5) hours of age] predicted 83% of deaths or abnormal neurological examinations at discharge (sensitivity 92%, specificity 50%).[26] BrainNZ monitor: Amplitude-integrated EEG (aEEG) recordings with a cerebral function monitor, such as the BraiNZ monitor, obtained continuously from two biparietal electrodes, have also been shown to be useful in the early prediction of the severity of brain injury. Of 35 infants with a moderately abnormal or suppressed tracing and/or seizures, 27 died or survived with neurological abnormalities on follow up at 18 to 24 months.[27] Of 21 babies with normal amplitude, 19 were normal on follow up.

Figure 2:
This study classified aEEG findings into three groups:

A. Normal amplitude, where the upper margin of the aEEG band was > 10µV and the lower margin > 5 µV.

B. Moderately abnormal amplitude , where the upper margin of the aEEG band was > 10µV and the lower margin = 5 µV
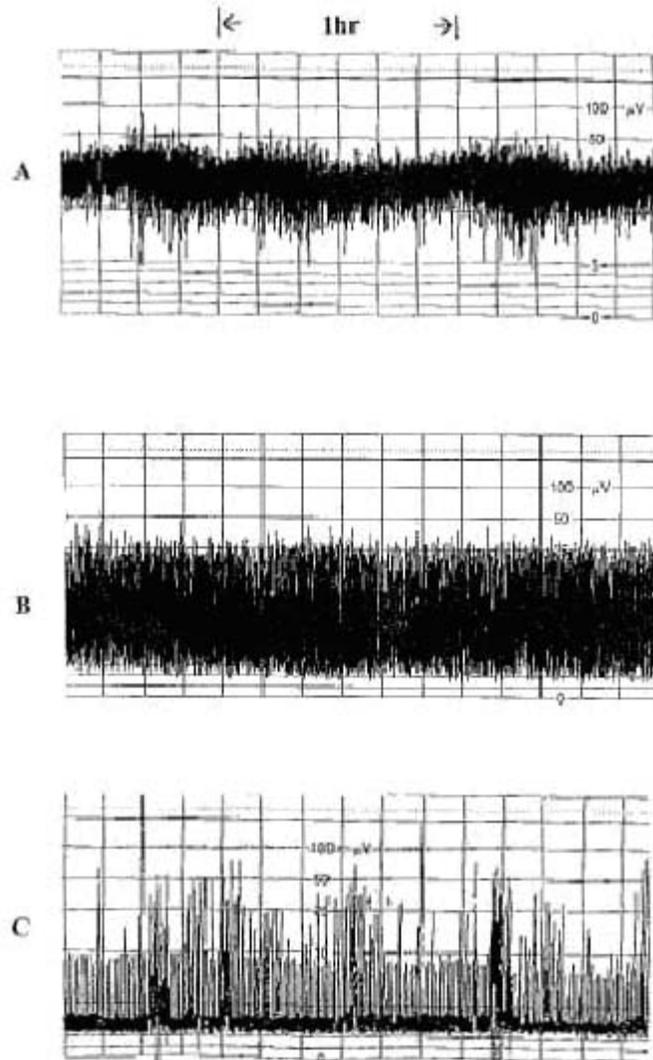
C. Suppressed

amplitude. where the upper margin of the aEEG band was < 10µV and the lower margin < 5 µV, usually accompanied by bursts of high voltage activity (burst suppression).

Hypothermia, for how long should infants be cooled?

There is a minimum period of hypothermia necessary for protection (5 hours in the rat),[28] and it should be continued throughout the period of secondary energy failure for maximum effect. In the fetal sheep model, 72 hours of cerebral hypothermia provided by a water-cooling cap, resulted in a significant decrease in neuronal injury;[29] thus the ICE study administered cooling therapy for 72 hours. This was consistent with the other concurrent international infant cooling trial protocols (17,18).[17, 18] 72 hours cooling will thus be used in this guideline.

Practical Guidelines to Therapeutic Hypothermia.

Consider therapeutic hypothermia in babies that fulfil the following criteria:

1. Infants born after 34 completed weeks of gestation and with a birth weight more than 1800g.
2. Evidence of intrapartum hypoxia: at least two of:
   - Apgar score of 5 or less at 10 minutes;
   - Mechanical ventilation or need for continued resuscitation at 10 minutes;
   - Cord pH < 7.00, or an arterial pH < 7.00 or base deficit of 12 or more within 60 minutes of birth.
   - If there is no cord gas or early arterial blood gas then an additional criterion indicating an intrapartum event should be sought:

- A sentinel intrapartum event (eg cord prolapse, abruption, shoulder dystocia etc);
- Abnormal fetal heart rate or fetal scalp pH < 7.2 detected intrapartum; or
- Clinical appearance of terminal (pallid) apnea at birth (pale, floppy and apneic).

3. Early clinical evidence of moderate or severe encephalopathy: To a degree, this assessment is subjective and experiential and for this reason it must be made by the attending consultant. The NICHD trial used a clinical alogorithm which is useful as a guideline to selecting babies for therapeutic hypothermia.[18] In Figure 3 below, babies eligible for hypothermia needed to have one or more signs in at least three of the six categories: Level of consciousness, spontaneous activity, posture, tone, primitive reflexes and autonomic system signs.

Table 1. Criteria for Defining Moderate and Severe Encephalopathy.		
Category	Moderate Encephalopathy	Severe Encephalopathy
Level of consciousness	Lethargic	Stupor or coma
Spontaneous activity	Decreased activity	No activity
Posture	Distal flexion, complete extension	Decerebrate
Tone	Hypotonia (focal or general)	Flaccid
Primitive reflexes		
Suck	Weak	Absent
Moro	Incomplete	Absent
Autonomic system		
Pupils	Constricted	Deviated, dilated, or nonreactive to light
Heart rate	Bradycardia	Variable
Respiration	Periodic breathing	Apnea

Figure 3: *Criteria for defining moderate and severe encephalopathy*

4. If uncertain or the above clinical criteria are on the borderlines, apply Brainz monitor and consider hypothermia if aEEG shows moderately abnormal or suppressed amplitude.

In the following situations, therapeutic hypothermia may not be beneficial:

1. When cooling cannot be started within 6 hours of birth.
2. When birth weight is < 1800g
3. When there are major congenital abnormalities including:
   - Suspected neuromuscular disorders.
   - Suspected significant chromosomal abnormalities.
   - Life threatening abnormalities of the cardiovascular or respiratory systems.
   - Severe coagulopathy despite treatment.
4. Infant is requiring inspired oxygen over 80%.
5. Infant is in extremis and not expected to survive.

Cooling, how to:

Target Temperature:

The target rectal temperature is 33.5°C, with an acceptable range of 33 to 34 °C. Cooling should be started as soon as possible after birth and commencing cooling at a referral hospital should be considered after consultation with the local paediatrician and NETS.

Equipment and monitoring:

- All infants will be nursed under a radiant warmer in Servo Mode with the skin probe attached.
- All infant will have venous and arterial catheters inserted as soon as possible.
- Temperature will be measured continuously by a thermistor inserted 5 cm into the rectum. These

rectal thermistors are kept in the NICU medication room on the top shelf.
- Four Cool Paks, which are kept in the fridge in the NICU medication room.
- Usual thermometer for intermittent checking of axillary temperature.

How to cool.

The aim is to achieve the target temperature by 60 minutes of commencing cooling. Hypothermia will be targeted initially with passive cooling but, if that does not reduce the rectal temperature to < 35 oC within 30 minutes of starting, then active cooling should be used.

Passive Cooling:

1. Switch off radiant heater
2. Nurse the baby naked. Do not use nappies or wraps, do not nurse on a sheepskin and do not use Glad Wrap.

Active Cooling:

1. During initiation of cooling, only apply if rectal temperature is more than $35^{o}C$ by 30 minutes after commencing cooling.
2. From the refrigerator **(NEVER the freezer)** the temperature of the Cool Paks should be at around $10^{o}C$.
3. Use cotton covers as designed by Maria Spinola.
4. If necessary, up to 4 Cool Paks can be placed under the shoulders/upper back, under the head and/or across the chest/body:

Slowing down Active Cooling

1. Active cooling should be reduced when the rectal temperature falls below $34.5^{o}C$ and stopped when below $34.0^{o}C$.
   - When rectal temperature < $34.5^{o}C$, reduce active cooling by removing one/some Cool Paks.
   - When rectal temperature < $34^{o}C$, stop active cooling by removing all Cool Paks.
2. If the temperature falls below $33.5^{o}C$, the heater output on the radiant warmer will be set to Servo Control at the lowest temperature to maintain the target rectal temperature at around $33.5^{o}C$.
3. Consider reducing rate of active cooling if the inspired oxygen increases by more than 20% or if the infant is treated with anticonvulsants or muscle relaxants, until the temperature response to these is observed.

Duration of therapeutic cooling.

1. Normal therapeutic hypothermia should be continued for 72 hrs from the commencement of cooling.
2. Consider stopping cooling early if there is,
   - persistent hypoxaemia in 100% oxygen
   - life threatening coagulopathy despite treatment.
   - an arrhythmia requiring medical treatment (not sinus bradycardia)
   - after mutual discussion between parents and senior clinicians

Rewarming:

The primary goals in rewarming are to rewarm slowly over about 12 hours and to avoid making the baby hyperthermic.

1. Apply skin probe and turn the radiant warmer on with the servo set at $34.5^{o}C$.
2. Increase the set temperature by $0.5^{o}C$ every 2 hours until set at 36.2 to $36.5^{o}C$ and rectal

temperature is ?37°C. It should take up to 12 hours for rewarming.

3. Monitor with frequent axillary temperatures as the rectal temperature approaches the target range.

Tolerance to hypothermia:

In general babies tolerate hypothermia well, in our experience the babies that dont tolerate it well tend to be those in whom the encephalopathy has not progressed as expected or has improved faster than expected. In such babies, particularly if they are not ventilated, consideration should be given to ceasing the hypothermia early. If the babies are ventilated and have not been given anticonvulsants but appear uncomfortable and require sedation, then there is some data of better outcomes with the use of phenobarbitone.[30] So phenobarbitone should be used first line at a dose of 20 mg/kg. If phenobarbitone has already been used then consider morphine (if ventilated) or paracetamol (PR is fine when nil orally, even with rectal thermistor in-situ and even if not all retained in rectum).

Ongoing Monitoring:

- Continuous arterial blood pressure and rectal temperature.
- Brainz monitoring as indicated clinically by HIE.
- Blood Gas (arterial access is usually obtained); 4 hourly at least initially then as required by clinical state (includes glucose and lactate and ionised calcium)
- Electrolytes; 6-8 hourly initially then as required by clinical state but at least daily until day 5
- Full Blood count; 12 hrly initially then as required by clinical state but at least daily until day 5
- INR and APPT clotting studies; on day 1 and then, if abnormal, daily until day 5.
- LFT on day 2 and day 5

Risks of hypothermia:

Mild hypothermia appears well tolerated in multiple animal experimental models, as well as in adult human studies and there have been no reported serious adverse effects in the studies of hypothermia in human newborns. Adverse effects such as sinus bradycardia, decreased blood pressure and increased oxygen requirement seem to be transient and reversible with rewarming and are less likely to occur when the rectal temperature remained within 33.0°C- 34.0°C. The guideline is designed to avoid cooling below the target temperature. As there has been a median increase in FiO2 of 10-15% reported, infants with severe respiratory failure (oxygen requirement greater than 80%) should probably not be cooled unless at the senior clinicians discretion.[31] In the meta-analysis of the randomised trial the following effects were reported with significantly higher frequency in the cooled arm of the trial; sinus bradycardia, hypotension requiring inotropes and thrombocytopaenia.[19]

Key Points

1. Hypoxia ischaemia remains a significant cause of neonatal mortality and morbidity.	Level 2c evidence
2. Hypothermia to between 33°C and 34°C initiated as soon as possible after delivery reduces mortality and disability in babies with HIE.	Level 1a evidence
3. Adverse effects of hypothermia are physiological, transient and reverse with rewarming	Level 1a evidence

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