REVIEW ARTICLE

THERAPEUTIC HYPOTHERMIA (TH) IN NEONATAL HYPOXIC ISCHAEMIC ENCEPHALOPATHY (HIE)

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ABSTRACT

Therapeutic hypothermia is considered as a standard of care in the treatment of moderate to severe hypoxic ischaemic encephalopathy in neonates ≥36 weeks of gestation and is considered safe and effective. The time period to initiate it is critical as it should start before the onset of secondary brain injury. This article reviews the criterion to initiate therapeutic hypothermia in hypoxic ischaemic encephalopathy, management and neuroimaging related to it and adjuvant treatment options for HIE.

Keywords: Ischaemic encephalopathy, Therapeutic hypothermia.

INTRODUCTION

Hypoxic ischaemic encephalopathy (HIE) remains a devastating condition with about 60% risk of death or severe disability in survivors of moderate and severe HIE. It occurs in 1.5 per 1000 live full term births but can vary in different population groups[1]. Infants without motor impairment may have poor cognitive outcomes, poor scholastic achievements and often require special educational needs long term.

Evidence from numerous multicentre randomised controlled studies shows that mild hypothermia (33-34 °C) can improve neurological outcome by reducing death and disability at 18 months of age and improve neurological outcomes in survivors and is now recognised as the standard of care. Recent meta-analyses have demonstrated that hypothermia is effective and safe[2,3] and magnetic resonance imaging of the brain has clearly demonstrated neuroprotection associated with hypothermia[4,5]. The principle to postnatal therapeutic hypothermia (TH) is the concept of secondary injury. After delivery and resuscitation, the neonatal brain undergoes partial recovery, and then enters into a latent period which lasts till 6 hours. Following this the neonatal brain enters into the phase of secondary injury with clinical deterioration often with seizures associated with mitochondrial energy production failure, cytotoxic oedema, cell death, lasting about 6-15 hours[6]. It is clear from available clinical and preclinical evidence that moderate therapeutic hypothermia should be implemented in this therapeutic window period, before onset of secondary injury and continued until this period of secondary energy failure has resolved.

When to Initiate Therapeutic Hypothermia

Cooling should be started as soon as possible after the decision is made. Established current evidence states that hypothermia is most effective when commenced within 6 hours of birth[7]. Hypothermia is unlikely to be beneficial if commenced after 12 hours of age. The infant rectal temperature should reach the target of 33.5 ± 0.5°C in a safe and controlled manner. This should be achieved in 2 hours from commencing TH and within 6 hours of birth. This is achieved by putting the baby on servo controlled cooling mattress. Infants cooled within 3 hours of birth have better neurodevelopmental outcomes compared with infants whose cooling commences between 3-6 hours. So any infants suspected to have HIE should be considered for TH when the A and B criteria are met[8].

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Criteria A - Infants >36+0 weeks gestation who are less than 6 hours of age with Apgar score of <5 at 10 minutes after birth or continued need for resuscitation, including endotracheal or mask ventilation, at ten minutes after birth or acidosis within 60 minutes of birth (defined as any occurrence of umbilical cord, arterial, venous or capillary pH <7.00 or base deficit greater than or equal to 16 mmol/l in umbilical cord or any blood sample (arterial, venous or capillary) within 60 minutes of birth.

Criteria B - Moderate to severe encephalopathy, consisting of seizure which may be clinically evident (rhythmic limb movements, lip smacking etc.) or may only be detected with a Cerebral Function Monitor (CFM), or altered state of consciousness (reduced response to stimulation or absent response to stimulation) and abnormal tone (focal or general hypotonia, or flaccid) and abnormal primitive reflexes (weak or absent suck or Moro response).

Management During Active Therapeutic Hypothermia

Neonates with HIE may suffer from varing severity of multiorgan dysfunction. Diving reflex will preserve blood flow to vital organs at the expense of blood flow to kidneys, liver, splanchnic vessels and the skin. Hepatic and renal damage along with syndrome of inappropriate antidiuretic hormone are common. It is challenging to maintain blood glucose level due to restrictive parenteral fluid administration. Glucose concentrations ≤40 mg/ dL may aggravate the severity of perinatal brain injury in neonates with HIE.

Coagulopathy

Coagulopathy due to hypoxic-ischaemic injury is multifactorial. Altered blood supply to the liver have negative impact on the synthesis of clotting factors[9] and also causes abnormal synthesis of platelets due to its effect on bone marrow. So clotting studies are routinely performed by serial monitoring of a PTT, PT/INR, Fibrinigen levels and PLT counts. Transfusion to maintain platelet counts >130×10^9/L, fibrinogen >1.5 g/L and INR <2 may prevent clinical bleeding[10].

Ventilation

TH does not have any deleterious effect on respiratory function. Acidosis and hypoxia should be corrected to avoid additional brain injury. Hyperoxia and hypocarbia should be avoided as they are detrimental to long-term outcome[11]. PPHN (persistent pulmonary hypertension) and meconium aspiration may coexist, however infants receiving high oxygen in the first few hours have predicted poor outcome[12].

Seizure Treatment

Seizures are common with HIE and can be extremely subtle to the extent of being not clinically observable in nearly half of neonates[13]. The first line anticonvulsant drug to treat seizures in HIE is phenobarbitone[14], however local practices may vary. Common second line agents include phenytoin, benzodiazepines and lidocaine. A Cochrane review demonstrated that there is no evidence to support the use of prophylactic anticonvulsants after perinatal asphyxia.

Cardiac Support

Hypotension is noted in up to 62% of infants with HIE; necessitating inotropic support[15]. Markers of myocardial ischaemia i.e troponin I[16] and troponin T are monitored in HIE with troponin T levels peak on day 1, remain elevated for the first week and correlate with the severity of HIE. TH hypothermia reduces cardiac output by 67% and an increase in support will usually be required during the cooling period. However current evidence does not show that giving inotropic drugs improves outcome.

Infection

HIE can coexists with perinatal infections. Early diagnosis of infections is increasingly important as the combination of hypothermia and infection has been shown to result in worst outcomes in animal models[17].

Use antibiotics as per local unit policy. Aminoglycosides and Penicillin are >75% meta-

bolised via the kidneys which are less affected by hypothermia than liver metabolism. Gentamicin levels should be checked according to the standard protocol and be withheld with high creatinine level. Hearing impairment has been associated with high levels of gentamicin in infants who have received therapeutic hypothermia.

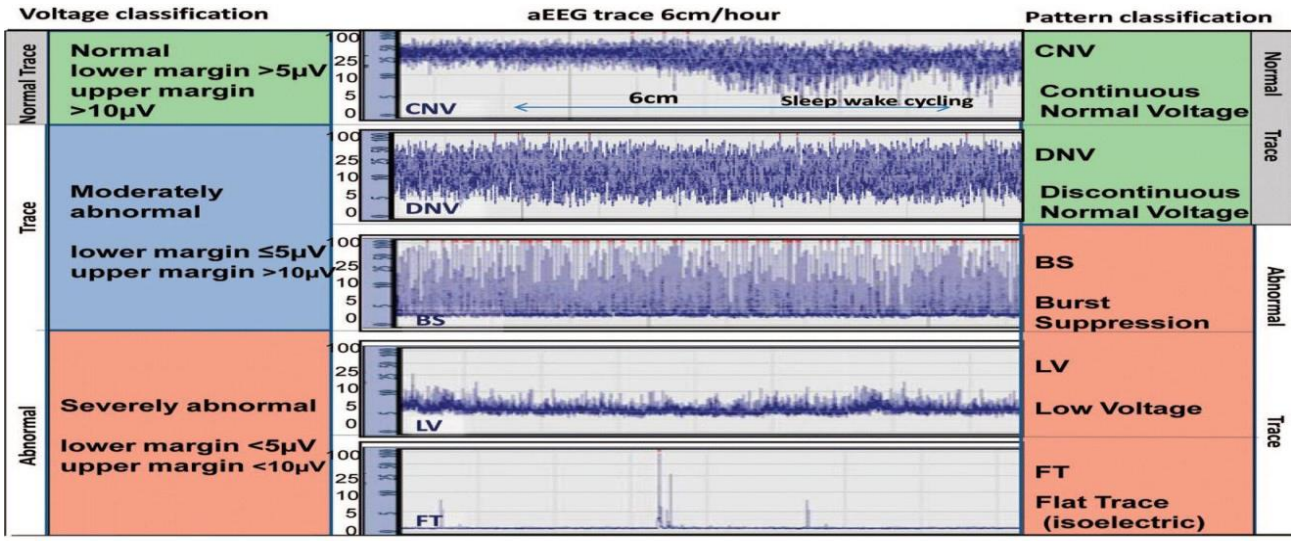
Sedation and Paralysis

There is experimental evidence that hypothermia is not neuroprotective if in stress[18].

Start morphine and use heart rate as a good proxy marker for adequate sedation. At 33.5°C, the average heart rate is ~90bpm. Heart rate changes by 10bpm for every 1 degree C change in temperature but when on inotropic drugs this is less sensitive. If the infant is not ventilated then chloral hydrate can be used.

Fluid and Electrolytes Management and Feeding

Renal damage along with syndrome of inappropriate antidiuretic hormone is common in HIE. Parenteral fluids should be restricted to 40 ml/kg/24 hours until the urine output increases however it is sometimes difficult to deliver enough glucose on 40 ml/kg - can increase to 60 ml/kg if hypoglycaemic on day 1. Hyper-glycaemia and hypoglycaemia should be avoided, as both are associated with long-term disability[18] or death in infants with moderate to severe HIE[19]. Commencing enteral feeds in infants during therapeutic hypothermia should be considered on an individualised basis taking into account the overall clinical status however trophic feeding with breast milk can be done[20], however enteral feeds should not be given in infants with significant multisystem involvement. Feed intolerance is common as gut circulation may have been compromised, this may increase the risk for necrotising enterocolitis. Hypocalcemia and hypomagnesemia are common in asphyxiated neonates and may lower the seizure threshold. Hence, electrolytes should be monitored regularly and maintained in the normal range for HIE patient except that the magnesium level may be maintained within the high normal range[21]. Keep Mg levels >1 mmol/L.



From Thoresen M, et al. Effect of hypothermia on amplitude-integrated electroencephalogram in infants with asphyxia. Pediatrics. 2010 Jul;126(1):e131-9. PMID:9563847 Reprinted with permission of The American Academy of Pediatrics

Figure: Effect of hypothermia on amplitude-integrated electroencephalogram in infants with asphyxia.

Polycythaemia and Hyperbilirubinaemia

For polycythemia in therapeutic hypothermia use the same cut off as in normothermic infants (dilution exchange at Hct 70% if no symptoms or at 65% if symptomatic). Low temperature makes the blood flow more slowly

so the combination of high PCV and hypothermia may lower the threshold hence some centres lower the threshold for exchange by 5% in hypothermic infants. There is no published data on this phototherapy can be used with hypothermia.

Neurophysiology

Cerebral Function Monitoring

Electroencephalogram (EEG) and amplitude-integrated electroencephalogram (aEEG) shown in figure are commonly used for assessment of extent of HIE, monitoring treatment and for recognition of seizures. aEEG is classified according to voltage and pattern. It can detect 30-60% of seizures, but those that are short lasting (<30 s) or distant from the electrodes may be missed[22]. Forty-eight hours is an optimal time to assess the aEEG for prognosis. The continuous or discontinuous normal voltage trace is linked with good prognosis especially if sleep wake cycling is present. The age in hours when the aEEG trace has recovered to a normal pattern is the best aEEG predictor. Also the age when sleep wake cycling appears is predictive of outcome but with cooling the predictability has altered[23]. While a normal aEEG record in the first 6 hours of life indicates a high probability of normal outcome, the results should be interpreted with caution as they can still be associated with poor outcome if features of encephalopathy exist. Improvement of aEEG at 6 hours of age is not an indication to discontinue therapeutic hypothermia.

EEG

A formal EEG provides information on regional background cerebral activity and can detect some seizures and other abnormalities not seen using aEEG.

The most useful prognostic information can be obtained once the infant has been rewarmed and is off anticonvulsant medication.

Cranial Ultrasound Imaging

Cranial ultrasound (Cr USS) is a simple, non-invasive and convenient initial imaging assessment for infants with HIE. Cerebral oedema may be evident, with sparkly echo reflectance of the parenchyma, obscuration of the sulcal markings and closure of the fissures. The diagnosis of HIE can be complicated, and other disease processes like neonatal stroke may present in a similar way. Scans should be performed at 24 hrs after commencing hypothermia and then daily for the first three days of life if possible. During the first 72 hours the Resistance Index measure should be recorded daily. Resistant Index in infants receiving therapeutic hypothermia is a less predictive outcome measurement than in normothermic infants[24].

Magnetic Resonance Imaging

MRI is the imaging modality of choice for assessing the distribution of injury and likely prognosis and to support a diagnosis of hypoxic ischaemic encephalopathy.

The most accurate prognostic information can be obtained at 10 days of age as severity of injuries may be underestimated during the first few days after birth[25].

Abnormality seen in the PLIC is an excellent predictor of abnormal neuromotor outcome. More chronic hypoxia-ischaemia is associated with cortical and subcortical abnormalities.

Rewarming

Following 72 hours of cooling, infants should be slowly rewarmed (<0.5°/hour). This is based on animal data showing increased seizures and increased cortical apoptosis with rapid rewarming. Longer or deeper cooling to <33.5° and/or for >72 hours has not been shown to be of benefit, and is harmful[26,27]. Rewarm at a speed of 0.2-0.3°C/h (18 hours) but stop rewarming if seizures occur, treat the seizures and ensure the infant has no seizures for at least 2 hours before you resume rewarming and consider a slower speed. Peripheral vasodilatation occurs during rewarming and the blood pressure may drop. Give volume as 0.9% sodium chloride or other fluids as appropriate.

Adjuvant Treatment Options

There are still significant number of infants for whom hypothermia is ineffective[28]. Adjuvant treatment options are being studied i.e. neuro-protective effects of allopurinol, erythropoietin, inhaled xenon and argon, melatonin, stem cells, magnesium and cannabinoids[29,30].

CONCLUSION

Newborn infants born at ≥36 weeks of gestation with evidence of evolving moderate to severe HIE should be treated with therapeutic hypothermia. It should be started within 6 hours of birth and preferably within first 3 hours and should maintain a core body temperature of about 33.5 ± 0.5°C for 72 hours, followed by rewarming at a rate of ≤0.5°C/h. The babies then need long term follow up.

CONFLICTS OF INTEREST

The author has no conflicts of interest or personal financial relationships relevant to this article.

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