New brain protection strategies for infants with hypoxic-ischaemic encephalopathy

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Abstract

Hypoxic ischaemic encephalopathy (HIE) occurs in 1.5–2/1000 births in developed countries and 26/1000 births in developing countries. Therapeutic cooling to a core temperature of 33.5°C for 72 h has become the mainstay of treatment for term infants with moderate and severe HIE with clinically proven improvements in both mortality and morbidity. This review article first explores current knowledge and limits of the use for therapeutic hypothermia, and then goes on to explore the potential new therapies that can provide additional neuroprotection. Currently researched neuroprotective treatments include pharmacological therapies (allopurinol, cannabinoids, erythropoietin, magnesium sulphate, melatonin, topiramate, and the noble gases xenon and argon), remote ischaemic post-conditioning, and the use of stem cells. The evidence available for these therapies and the current stage of their research are discussed.

Keywords hypoxic ischaemic encephalopathy; neonatal encephalopathy; neuroprotection; neuroprotective agents; newborn; therapeutic hypothermia

Introduction

Hypoxic ischaemic encephalopathy (HIE) is defined as a combination of a lack of oxygen and a lack of blood flow depriving the brain of essential nutrients which ultimately results in increased mortality and neurodevelopmental impairment. Unfortunately, this still occurs in 1.5–2/1000 births in developed countries and up to 26/1000 births in developing countries. HIE is thought to be responsible for around 23% of neonatal deaths globally each year.

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Pathophysiology

Injury following a hypoxic-ischaemic brain insult occurs in multiple phases (see Figure 1). Following a hypoxic-ischaemic insult with successful newborn resuscitation and restoration of the circulation, the neurons go through a *primary energy failure phase*, in which they are acutely deprived of oxygen and glucose. This results in a shift toward anaerobic metabolism with accumulation of lactic acid and decreased adenosine-tri-phosphate (ATP). Lack of ATP leads to failure of Na^+/K^+ pumps causing sodium influx into the neurons along with water. This causes cell oedema and eventually cell death.

At the same time mechanisms to maintain low intracellular calcium fail and lead to intracellular calcium accumulation. Glutamate, an excitatory neurotransmitter, is released into the synaptic crest, free radicals are released, and mitochondria start to fail, which takes us into the *secondary energy phase*. This phase occurs from around six hours following the insult, but this depends on the insult severity. This is also where the notion of a 'therapeutic window' for neuroprotection is based on. Glutamate binds to glutamate receptors leading to additional calcium influx through N-methyl-D-aspartate (NMDA) receptors. High intracellular calcium causes oedema, ischaemia, and eventually necrosis and apoptosis. In this phase there is continued delayed and programmed cell death in the absence of cerebral acidosis.

In the weeks to years following an insult there is ongoing inflammation, altered cell proliferation and synaptogenesis with reduced myelination, as well as epigenetic dysfunction. This phase is now labelled the *tertiary brain injury phase*. The main targets for neuroprotective intervention following an insult are in the six hours prior to the secondary energy failure phase, and through modulation of the changes during the secondary and tertiary phases.

Where are we now?

Therapeutic hypothermia is currently the only proven therapy which improves both mortality and long-term neurodevelopmental outcome in infants with moderate and severe HIE, and is now standard care in developed countries. Meta-analysis of the cooling trials has shown that 72 h of therapeutic hypothermia to a core temperature of 33.5°C is safe and effective in neonates ≥36 weeks gestation. The 2013 Cochrane review included 11 trials with 1505 neonates with moderate or severe HIE and confirmed a significant reduction in the combined outcome of death or major disability in survivors in the hypothermia arm of the trials. Sixty-one percent of the infants treated in the normothermia arm of the trials died or were disabled at 18–24 months; this was reduced to 47% in the infants in the hypothermia arm. The number needed to treat for one additional beneficial outcome was 7 (95% confidence interval 5–10). The most common side effects of hypothermia treatment include bradycardia and thrombocytopenia.

Most neonatal networks now use a standard set of cooling criteria to assess infants for therapeutic hypothermia, consisting of a combination of factors related to a perinatal hypoxic-ischaemic insult (need for resuscitation and acidosis in the first postnatal hour), neurological findings of encephalopathy, and an abnormal amplitude integrated electroencephalography (aEEG) trace. Table 1 summarises the criteria used in the

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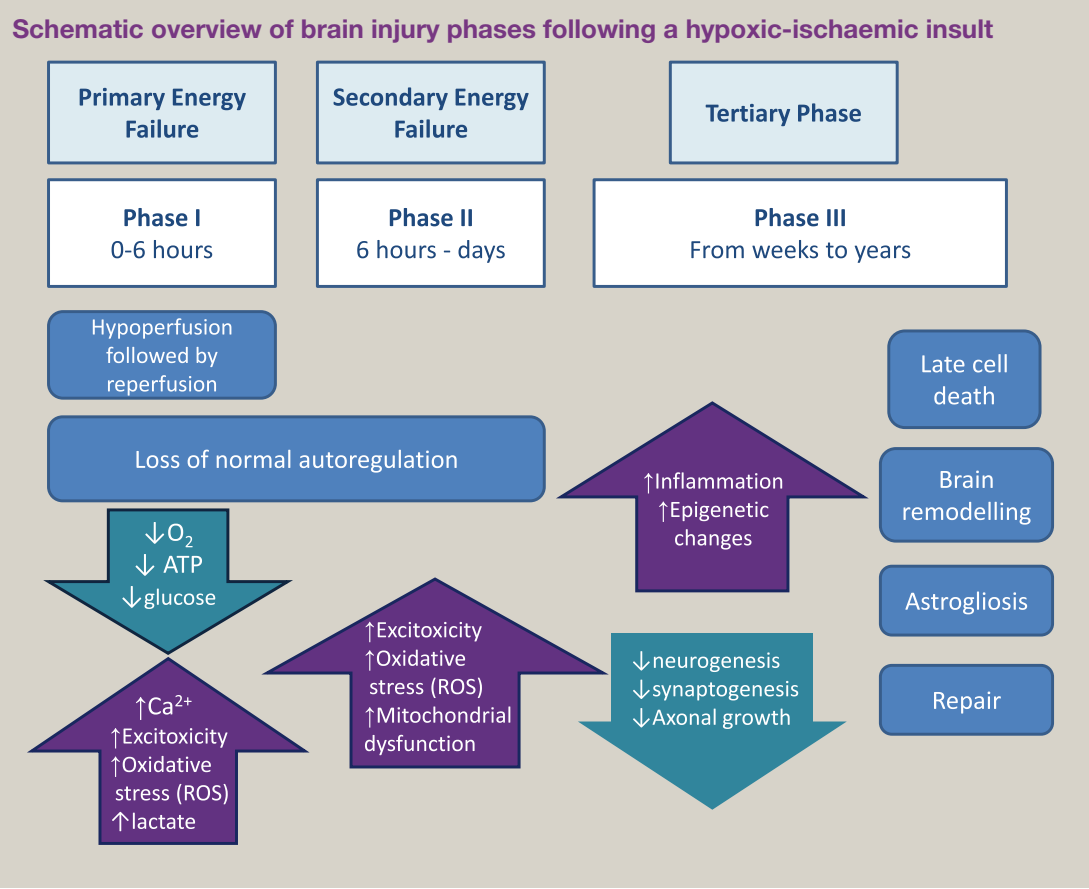

Figure 1

'Total Body Hypothermia for Neonatal Encephalopathy Trial' (TOBY).

Therapeutic hypothermia should be initiated in the first 6 postnatal hours; however evidence suggest that the earlier we initiate cooling and reach the target temperature of 33.5°C the greater the benefit conferred. Cooling initiated within 3 h has demonstrated an improved motor outcome in survivors in a single-centre study. Cooling in the United Kingdom is offered as a centralised service in tertiary neonatal intensive care units. Most newborn transport services therefore provide active cooling during transport to ensure early cooling prior to arrival in the tertiary centre.

Potential harm from cooling?

The 'Optimizing (longer, deeper) cooling for HIE trial' set out to find out if cooling for longer (5 days) and/or deeper (32°C) provided improved neuroprotection. The trial was halted in view of safety concerns and futility analysis after 50% of patients were recruited. Increased mortality was seen in the infants randomised to deeper cooling (14%), longer cooling (16%), and the longer plus deeper cooling arm of the trial (17%), compared to those in the standard arm of the trial (7%).

Animal studies have shown that in models of infection together with HIE, the neuroprotective effect from cooling was lost. The same loss of neuroprotection is seen when there is inadequate sedation during cooling in animal models of HIE.

Broadening the cooling criteria?

Following the establishment of benefit from therapeutic hypothermia for term infants with moderate and severe HIE, trials have continued to investigate whether additional groups of infants could benefit from cooling. A broadening of the entry criteria through cooling infants not fulfilling the standard cooling criteria has led to the following sub-groups of patients being considered for therapeutic hypothermia:

Preterm infants (33–36 weeks gestational age)

A difficulty with cooling preterm infants is that hypotonia, poor respiration and the need for resuscitation in view of immaturity, and a moderately abnormal aEEG trace can all be normal findings in preterm infants, making it difficult to directly apply the standard cooling criteria. Two of the original cooling trials included infants from 35 weeks onwards. In the Vermont Oxford Network Encephalopathy Register, 5% of infants who underwent cooling between 2006 and 2011 were less than36 weeks gestation. Small case series of cooling late preterm infants (34–35 weeks gestational age) show cooling is feasible and outcomes are similar to term infants. A randomised controlled trial (RCT) of 72 h of hypothermia versus normothermia in infants between 33 and 35 weeks gestational age is ongoing.

Late cooling (6–24 h)

In some cases the fact that an infant fulfilled the criteria for cooling may not be recognised within the first six postnatal

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