REVIEW

Therapeutic hypothermia for hypoxic–ischaemic encephalopathy in the newborn infant

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Purpose of review

This review examines recent findings from experimental models and clinical trials of induced hypothermia as treatment after cerebral hypoxia–ischaemia in term newborn infants.

Recent findings

Experimental hypothermia inhibits many steps in the biochemical cascade that produces severe brain injury after hypoxia–ischaemia. This is in contrast to pharmacological agents, which tend to target only one step in the process that leads to brain injury. In adult humans hypothermia initiated immediately after cardiac arrest has improved outcomes. Delayed cooling after brain trauma has also been effective in a subgroup of adult patients. Seventy-two hours of selective head cooling with mild systemic hypothermia (rectal temperature 34.5°C) in term infants with hypoxic–ischaemic encephalopathy (HIE) reduced death or disability in the infants with less severe electroencephalographic changes at entry (no benefit in those with advanced electroencephalographic changes). Cooling had no apparent adverse effects. A smaller randomized clinical trial of 48 h whole body cooling (rectal T 33°C) found a reduction in death and neurological impairment.

Summary

In term infants with HIE there is emerging evidence that both selective head cooling and whole body cooling are neuroprotective and safe. This is consistent with a wealth of experimental animal data and adult trials. Neuroprotection seems to be lost if cooling is started after 6 h. The challenge now is to complete ongoing trials. If meta-analysis confirms a therapeutic effect, then this may lead to selection criteria and treatment protocols for very early hypothermia in HIE at term.

Keywords

asphyxia, brain injury, hypothermia, neuroprotection, newborn, rewarming

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Abbreviations

aEEG	amplitude-integrated electroencephalography
HIE	hypoxic–ischaemic encephalopathy
TBI	traumatic brain injury

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Introduction

The financial and social burden of hypoxic–ischaemic brain injury in the newborn is huge because of the large number of quality life years lost and the severity of disability. With the observation that infants abandoned and exposed to cold often remained viable for prolonged periods, clinical interest in hypothermia began in the 1950s with observations and case reports of successful resuscitation and outcomes after immersing asphyxiated infants in a tub of cold water [1]. Drowning victims who were hypothermic after periods of up to 40 min under cold water were found to survive intact [2]. Therapeutic hypothermia at core temperatures of 28–30°C was used in patients following cardiopulmonary resuscitation 30 years ago, but this was discontinued because of side effects, uncertain benefit and management problems. However, interest in therapeutic hypothermia was rekindled in the early 1980s, when animal studies showed that benefits could also be obtained with mild (32–35°C) rather than moderate or deep hypothermia [3,4].

Important in the management of clinical situations such as traumatic brain injury (TBI), stroke, cardiac arrest and perinatal asphyxia is the appreciation that a substantial part of the neurological damage does not occur immediately but develops at later stages [5,6]. Postinjury treatment focuses on prevention or mitigation of this secondary injury [7].

Clinical trials of hypothermia after traumatic brain injury in adults

Although no overall treatment benefit was seen in the large trial of hypothermia after brain trauma conducted by Clifton *et al.* [8], subgroup analyses from that and other studies are promising. Studies of mild hypothermia (about 33°C body temperature) after TBI in those with moderate injury (Glasgow Coma Scale score 5–6 on admission) found that outcome was better in the patients

randomly assigned to hypothermia if hypothermia was long-lasting (on average 115 h), rewarming was slow, or the patients were hypothermic at trial entry [9]. It is also suspected that there is a learning curve, with the effect of therapeutic hypothermia being more apparent in single centres [10] managing large numbers of cases than in multicentre trials with hospitals each having small numbers of cases. This is equally important for the newborn.

Clinical trials of hypothermia after cardiac arrest in adults

Two randomized clinical trials of hypothermia after witnessed out-of-hospital cardiac arrest [11,12] both demonstrated improved survival and neurological outcome after 12 or 24 h of hypothermia at 33°C. Immediate onset of cooling after the arrest was possible because consent was waived [13]. These patients, like those in the TBI trials, were anaesthetized and paralysed during hypothermia. The cardiac arrest trials [11,12] led to changed guidelines for management after cardiac arrest [14].

Clinical trials of hypothermia after stroke in adults

No results from larger clinical trials of hypothermia after stroke are available; only pilot trials of hypothermia in anaesthetized stroke patients have been reported [15]. Following the recognition of the devastating effect of secondary hyperthermia after acute stroke [16], the clinical guidelines were changed avoiding hyperthermia after stroke [17]. Whether fever itself exacerbates neurological injury, or whether it is simply a co-marker of severity of injury is not clear. However, in animal experiments induction of even mild hyperthermia [18] significantly increases the extent of neurological damage and leads to greater morbidity and mortality, independent of initial severity. This also relates to the newborn [19]; current guidelines advocate thermal care of all newborn infants at 37°C after birth whether asphyxiated or not. By using efficient incubators and radiant warmers to counteract the physiological response to hypoxia [20], which is to reduce metabolism and core temperature, one adds significant risk for secondary hyperthermia. We believe that this form of management can increase brain injury.

Interestingly, in the ongoing 'Nordic Cooling trial after Stroke' [21], early hypothermia is achieved by cooling mildly sedated self-ventilating patients to 35°C. The investigators avoid the use of anaesthesia and manage to maintain the rectal temperature at about 35°C without causing shivering by using drugs that lower the thermoregulatory set point. This design is relevant to the newborn because these patients are often self-ventilating and anaesthesia is not standard clinical practice after perinatal asphyxia.

Animal work leading to clinical trials of hypothermia after perinatal asphyxia

We and others have conducted a sequence of experiments using different species, models, survival times, and degrees, modes, and duration and delay of cooling. We have shown that posthypoxic hypothermia is neuroprotective in the neonatal rat [22–25], newborn pig [7,26,27,28••] and near term foetal sheep [29,30]. Many of the studies used quantitative neuropathology. Magnetic resonance spectroscopy has been used to measure energy status and other studies used long-term survival and functional testing to demonstrate neuroprotection from hypothermia.

Cerebral metabolism is reduced by between 5 and 7% for each degree centigrade reduction in body temperature [31]. The protective effect of cooling appears to be much greater than can be explained by changes in metabolism alone. Thus, although reduction in metabolism probably plays a role, other mechanisms are more important.

Posthypoxic hypothermia has been shown to reduce apoptosis more than necrosis [32], to reduce production of the free radical nitric oxide, to reduce excitatory amino acids [33] and, importantly, to reduce the duration of seizures [28••,34]. Hypothermia reduces disruption to the blood–brain barrier, thereby reducing oedema formation [35]. Mainly based on Gunn's work in foetal sheep [36], it was decided that the first clinical pilot cooling trials should last for 72 h and cooling should start with a maximum delay of 5.5 h after birth [37,38]. This design has been followed, irrespective of the mode of cooling, by all subsequent large trials [39••] (one smaller trial used 48 h [40••]), thus making future meta-analysis easier.

Hypothermia and seizures

Experimentally, if drug-induced seizures are added after a hypoxic–ischaemic insult, the injury is aggravated [41]. In our more physiological piglet model, which spontaneously develops posthypoxic seizures, the brain injury is more severe after seizures [42]. Unlike Eicher *et al.* [40••], we found in controlled studies [28••,34] that both pigs and humans had shorter duration of seizures if they were hypothermic after the hypoxia–ischaemia. Currently, phenobarbital is first-line treatment against neonatal seizures. Experimental data suggest that topiramate combined with hypothermia is an effective anticonvulsant and neuroprotective strategy that is worth trying out clinically [43].

Hypothermia and drugs

Many classes of drugs are likely to increase the neuroprotection if they are combined with hypothermia. Previously, before scientists controlled body temperature carefully during neuroprotective studies, the neuroprotection found was often due to the fact that the drug

induced hypothermia *per se*. Administration of drugs that reduce the temperature regulatory set point to 33–35°C meant that there was no shivering until the temperature dropped below these thresholds and neuroprotection would result. This concept is used in a current ongoing adult stroke trial [21], in which drugs reduce the shivering threshold to about 35°C, thus allowing an early start to cooling without the resources and risks associated with full anaesthesia.

Many steps are needed before a treatment that is effective in rats can be tested in humans. For instance, the promising neuroprotective antibiotic minocycline, which is significantly neuroprotective in rats, was recently found to increase injury in the mouse using the same type of neonatal model [44].

Both hypoxia–ischaemia and low temperature reduce drug metabolism, in particular for those that are eliminated by the liver. Drug levels should therefore be checked to avoid overdosing. A case report [45] raised concern regarding the combination of hypothermia and phenytoin. We recently reported that the half-life of phenobarbital is twice as long in children treated with 72 h hypothermia as in normothermic infants [46].

Hypothermia as a neuroprotective intervention after perinatal asphyxia: first trial results

Eicher *et al.* [40••] conducted a small randomized trial in 65 infants of 35 or more weeks of gestation with abnormal neurological signs together with two of the following: foetal bradycardia <80 beats/min for 15 min, pH <7.1, base deficit >13, Apgar score <6 at 10 min, and postnatal desaturation <70% for 20 min. Within 6 h of birth, the infants were randomly assigned to either normothermia (37°C) or a cooling blanket to a rectal temperature of 33°C for 48 h. Six sites took part and neurodevelopmental assessment was conducted at 12 months. Of the infants included, 17% were lost to follow up. Of the 32 infants who were cooled 10 (31%) died, and 14 (42%) of the normothermic infants died. Among the normothermic infants with known outcome, 84% were dead or had severe motor disability, whereas among those treated with cooling 52% were dead or had severe motor disability ($P = 0.019$).

The first large multicentre trial to be published was the Cool Cap trial [39••]. Infants of 36 or more weeks of gestation were selected if they had evidence of perinatal asphyxia (pH <7.0, base deficit 16, Apgar score <6, or need for resuscitation at 10 min); abnormal neurological signs; and amplitude-integrated electroencephalography (aEEG) showing moderately or severely depressed amplitude or seizures. Randomization had to be completed by 5.5 h and infants were allocated to either normothermia (rectal temperature 37°C) or selective head cooling for 72 h via a cap through which water was circulated at a controlled temperature with mild systemic hypothermia (rectal temperature 34.5°C). A total of 234 infants were recruited in 25 centres and follow-up data at 18 months were available for 218 (93%). Of the normothermic infants 66% were dead or disabled versus 55% of the hypothermic infants ($P = 0.1$). However, the investigators had hypothesized *a priori* that hypothermia would be ineffective in the infants with the most severe aEEG changes (severe depression and seizures) before randomization. When these infants (21%) were excluded, only 48% were dead or disabled in the hypothermic group versus 66% in the normothermic group ($P = 0.02$), and severe neuromotor disability was reduced from 28 to 12% ($P = 0.03$).

Neither the Cool Cap trial [39••] nor Eicher *et al.* [40••] found an increase in serious adverse events in the cooled infants. Sinus bradycardia, transient elevation in plasma glucose and temporary scalp oedema (in the Cool Cap group) were not clinically significant. Eicher *et al.* reported lower platelet counts, longer prothrombin times and more dependence on pressors in the hypothermic group, but in the Cool Cap trial platelet counts, prothrombin times and hypotension were similar in the two treatment groups.

Shankaran *et al.* (unpublished data) used a cooling blanket technique in a large multicentre trial of whole body cooling. This trial included 208 infants selected by gestational age 36 or more weeks, and signs of hypoxic–ischaemic encephalopathy (HIE) following evidence of perinatal asphyxia but without the use of electroencephalography. Infants were randomly assigned to normothermia or whole body cooling to a rectal temperature of 33.5°C for 72 h. Those investigators reported no increase in serious adverse events in the cooled infants. In December 2004, at the Hot Topics Conference (Washington DC), Shankaran *et al.* presented outcome data showing that death or neurological impairment was reduced in the cooled infants.

Improving the neuroprotective effect of hypothermia

It is impressive that all three completed neonatal trials of hypothermia for HIE have shown a therapeutic effect despite the presence of two factors that would reduce the chances of showing such an effect. After resuscitation all trial infants were kept at or warmed to 37°C, in accordance with existing guidelines. Because of the logistics of diagnosing HIE and obtaining informed parental consent, cooling was started on average nearly 5 h after birth. It is likely that brain injury can be further reduced and neurological outcome improved by not rewarming the asphyxiated child, who is naturally cold, as well as by

starting to cool earlier. The infant can be gradually rewarmed to 37°C if neurological assessment is normal. When Westin *et al.* [1] rewarmed infants they had immersed in the cold tub, they emphasized that they had to be 'rewarmed slowly and by the pace of their own metabolism', without any active heating source except being dried, wrapped and swaddled, because it was natural for asphyxiated babies to be cold for the first 24 h [47].

Avoiding stress and discomfort with hypothermia

Another way to improve further the effectiveness of hypothermia is to minimize stress by optimizing sedation. In piglets we found that hypothermia was only protective when the animals were anaesthetized [28••] and was not protective if they were awake and cold [48], with cortisol levels three times those found in those being nursed normothermic.

Duration of hypothermia

The duration of cooling necessary for neuroprotection if started immediately after the insult in acute animal experiments is much shorter than 72 h. However, in infants we rarely know the exact time of the insult, nor do we know whether the time course of the developing injury and processes of repair takes longer in humans. For both of these reasons one assumes that long-lasting hypothermia is likely to be more neuroprotective. In animal models the development of injury caused by focal ischaemia is significantly more rapid than in global ischaemia. At normothermia infarction is essentially complete by 24 h. Ischaemic oedema has a more protracted time course, peaking at approximately 48 h after injury. It has also been observed that seizures can recur during rewarming, and hence slow and passive rewarming seems preferable, but this needs further investigation.

Ongoing trials of hypothermia after perinatal asphyxia

There are several ongoing multicentre trials of total body cooling (UK, Europe and Australia) with similar 72 h cooling protocols. By 1 January 2005, together these trials had included approximately 270 patients over the preceding 3 years. Recruitment to target and follow up for these trials will take at least another 4 years. On average, the incidence of neonatal encephalopathy severe enough to meet the entry criteria has been 1/1000 deliveries. Mortality has been 30–40% and the combined risk for death or disability 60–70%. It is of the utmost importance to collaborate in recruiting patients into these trials; no single country can do this alone. If, as anticipated, the preliminary data presented by Shankaran *et al.* are confirmed in a peer-reviewed publication in 2005, there will be an important discussion as to whether the evidence is strong enough to remove equipoise in the minds of those seeking consent from parents in the ongoing trials. If three published trials all show evidence of a reduction in death or neurological impairment, then will it still be acceptable to have a normothermic control group? It is fortunate that the ongoing trials have similar protocols (all are body cooling to 33.5°C for 72 hours, with slightly different entry criteria). Meta-analysis should provide a way to extract maximum evidence from these trials if recruitment is cut short on ethical grounds. Future trials may focus on questions relating to technique and duration of cooling, as well as combining hypothermia with other neuroprotective strategies.

Conclusion

There is evidence from three published and presented randomized clinical trials that hypothermia for term infants with HIE is neuroprotective when applied at less than 6 h of age in centres with expertise and experience with this intervention. The physiological effects of hypothermia can be anticipated and safely controlled without adverse effects. Completion of all of the ongoing trials will be important in strengthening the evidence. What we do not know is whether hypothermia applied straight after birth will be as safe as hypothermia applied at 4–5 h. An important challenge is to develop the optimal treatment protocol for immediate hypothermia. The second challenge is to identify shortly after birth those infants who will benefit from hypothermic treatment. Some infants who would recover without hypothermia will be unnecessarily cooled. Theoretically, cooling the immature brain for a long period may have unknown adverse effects on brain development. There are no animal data on long-term survival after prolonged induced hypothermia to suggest that it is safe.

The aEEG in combination with clinical and biochemical assessment appears to be a useful tool for selection [49]. aEEG monitoring to predict outcome has mostly been done after 3 h of age [50]; hence, less is known of its predictability when applied within 1 h. One role for early aEEG may be in defining those infants who have a good prognosis regardless and do not need neuroprotection. Another role may be in defining infants who have such severe or advanced aEEG changes that cooling cannot help them. It would be valuable to have a register of patients treated with hypothermia (rather like surveillance of newly licensed drugs) to improve the protocol and detect any unforeseen adverse effects. Long-term follow up is also of the utmost importance.

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