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Therapeutic hypothermia as a treatment strategy for neonates born in asphyxia - a review of the current state of knowledge

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ABSTRACT

Purpose: The aim of this review is to synthesize current scientific evidence on the efficacy, indications, limitations and controversies surrounding HT in asphyxiated neonates.

Materials and research methods: The article is based on an analysis of research available on PubMed , Cochrane and Scopus. A literature review was conducted using following keywords such as “therapeutic hypothermia”, “neonatal asphyxia”, “hypoxic-ischemic encephalopathy”, “newborns” and “neuroprotection”. Inclusion criteria: studies on newborns ≥ 36 weeks of fetal life, clinical trials, systematic reviews, meta-analyses.

Results: Therapeutic hypothermia (HT) reduces the risk of death and severe disability in term infants (≥36 weeks) with moderate/severe HIE, supported by meta-analyses (RR 0.75 for death, RR 0.77 for disability) and long-term benefits. Evidence is lacking for preterm infants and mild HIE. Side effects (e.g., bradycardia, hypotension) are usually transient. In developing countries (HELIX trial), HT may lack benefit or even increase mortality—highlighting the need for tailored approaches.

Conclusion: Therapeutic hypothermia remains the most effective neuroprotective intervention for term and near-term neonates with moderate to severe hypoxic-ischemic encephalopathy. Despite its proven benefits, further research is needed to evaluate its safety and efficacy in preterm infants, mild HIE cases, and low-resource settings.

Keywords: therapeutic hypothermia, neonatal asphyxia, hypoxic-ischemic encephalopathy, newborns, neuroprotection, neonatal intensive care, brain injury

Introduction

Perinatal asphyxia, leading to hypoxic-ischaemic encephalopathy (HIE), remains one of the most serious causes of death and permanent neurological damage in newborns born at term. HIE is estimated to occur in 1 to 3 per 1 000 live-born infants in developed countries, and its consequences, ranging from psychomotor developmental delay to cerebral palsy, can be irreversible. [1] For many years, treatment of this condition was limited to symptomatic therapy and supportive care only. It is only in the last two decades that therapeutic hypothermia (HT) has become the first recognised treatment modality that has demonstrated efficacy in reducing brain damage after an episode of hypoxia. [2]

Therapeutic hypothermia, applied within the first 6 hours of life, consists of a controlled lowering of the infant's body temperature to inhibit the cascade of processes leading to secondary brain damage. [3] Numerous clinical studies, including randomised controlled trials, have confirmed the beneficial effects of HT on survival and neurological development in children with moderate to severe HIE. Nevertheless, there is still much controversy regarding its use in preterm infants, neonates with mild HIE and in resource-limited settings. [4,5,6]

The aim of this review paper is to discuss the current state of knowledge on therapeutic hypothermia used in neonates born in asphyxia. The paper aims to present the pathophysiological basis of the therapy, its effectiveness, limitations and possible directions for the development of neuroprotective treatment in neonatology.

Pathophysiology of asphyxia and hypoxic-ischaemic encephalopathy (HIE)

Perinatal asphyxia is a condition resulting from inadequate fetal oxygen and nutrient supply during the perinatal period. It can lead to serious systemic consequences, the most dangerous of which is hypoxic-ischaemic encephalopathy (HIE). HIE is damage to the central nervous system resulting from prolonged hypoxia and/or ischaemia of the neonatal brain. [7]

The process of brain damage takes place in multiple phases and is extended over time. There are three main phases - primary, secondary and late. Primary phase - occurs directly during hypoxia. There is a disruption of aerobic metabolism, a switch to anaerobic metabolism, accumulation of lactic acid, a decrease in ATP and depolarisation of cell membranes. In this phase, damage to neurons and glial cells begins. Secondary phase - begins a few hours after the restoration of perfusion (reperfusion). This is a key point at which delayed mechanisms of damage such as oxidative stress, excessive glutamate receptor stimulation (excitotoxicity), calcium influx into cells, activation of apoptosis pathways and inflammation can occur. It is this phase that is targeted by therapeutic hypothermia intervention. Late phase - can last days, weeks or even months after an episode of hypoxia. This phase is dominated by structural and functional changes in the brain, including neurodegenerative processes, loss of nerve cells and abnormal maturation of neural connections. [8,9]

The extent and nature of the brain damage depends, among other things, on the duration of hypoxia, the gestational age of the child and the individual response of the organism. Areas particularly sensitive to hypoxia, such as the basal nuclei, thalamus, cerebral cortex and hippocampus, are most commonly affected. [10]

Understanding the pathophysiology of HIE forms the basis for the development of therapeutic strategies, such as therapeutic hypothermia, which aims to reduce secondary damage and

improve neurological prognosis.

Premise and mechanism of action of therapeutic hypothermia

Therapeutic hypothermia (HT) is a controlled lowering of the infant's body temperature to a range of 33-34°C, with the aim of reducing the effects of secondary brain damage following a hypoxic-ischaemic episode. [11] Its efficacy is primarily due to its effect on key pathophysiological processes occurring during the secondary phase of hypoxic-ischaemic encephalopathy (HIE). [12] The most important factor determining the efficacy of HT is the timing of the start of therapy, called the therapeutic window. According to current guidelines, HT should be implemented no later than 6 hours after delivery, when the second - most destructive - phase of brain damage begins. [13] Early implementation of cooling helps to limit the spread of lesions and mitigate their effects. Considering its mechanism of action, therapeutic hypothermia protects the brain on multiple levels. The reduction in metabolic rate slows down energy metabolism by approximately 5-7% for every 1°C decrease in temperature. [12] This reduces the neuronal demand for oxygen and glucose. As a result of reduced activation of enzymes responsible for programmed cell death (including caspases), apoptosis (cell death) is inhibited, and reduced production of oxygen free radicals that lead to lipid peroxidation and DNA damage results in a reduction in oxidative stress. HT has also been shown to reduce glutamate release and inhibit over-activation of NMDA receptors in effect reducing excitotoxicity, and has anti-inflammatory effects by reducing microglia activation and pro-inflammatory cytokine production. [14]

Two main types of HT are used in clinical practice - whole-body cooling (whole-body cooling) where the neonate is placed on a special cooling mattress and selective head cooling (selective head cooling) - cooling mainly involves the brain, e.g. using a cooling helmet. [15] Both approaches have similar efficacy, although whole-body cooling is more commonly used due to easier temperature control. [16] The standard duration of therapy is 72 hours, followed by slow, controlled warming at a rate of about 0.5°C per hour to avoid rapid physiological changes. [17]

Indications and procedure for the use of therapeutic hypothermia

Therapeutic hypothermia (HT) has been recognised as the standard of care for the treatment of neonates with moderate to severe hypoxic-ischaemic encephalopathy (HIE), born at ≥36 weeks gestational age. A key element in the effectiveness of the therapy is the precise qualification of patients and the rapid implementation of the procedure - ideally within the first 6 hours of life. [18, 19, 20,21]

According to current recommendations (e.g. AAP, NICE, ILCOR), neonates meeting the following conditions are eligible for HT:

1) Gestational age ≥36 weeks and birth weight ≥1800-2000 g.

2) Perinatal asphyxia, confirmed by at least one of the following:

- pH of cord blood or from the first 60 minutes of life ≤7.0,
- BE (base excess) ≤ -16 mmol/L,
- Apgar ≤5 in the 10th minute of life,
- need for resuscitation ≥10 minutes after birth.

3) Signs of hypoxic-ischaemic encephalopathy:

- assessed clinically (e.g. according to the modified Sarnat scale): reduced tension, impaired reflexes, impaired consciousness, convulsions.
- In some centres, additional ancillary investigations are used: EEG, AEEG or neuroimaging (e.g. trans-temporal ultrasound, MRI). [18,19,20,21]

All therapy requires strict adherence to specific procedures. As mentioned above, it is important to start cooling as soon as possible after diagnosis - optimally within the first 6 hours of life. In practice, whole-body cooling is mainly used, during which the neonate is placed on a special cooling mattress equipped with an automatic temperature control system. Selective head cooling, where only the head is cooled while body temperature is monitored, is used less frequently. [15]

The target temperature during hypothermia should be 33-34°C measured at the rectum or oesophageal/central temperature. This state of hypothermia is maintained for 72 hours under close medical supervision. This is followed by a stage of controlled rewarming, which should proceed slowly, usually at a rate of 0.25-0.5°C per hour, until normothermia is reached (36.5-37.0°C). Rapid rewarming should absolutely be avoided, as it can lead to haemodynamic instability and metabolic disturbances.

Throughout the therapeutic hypothermia procedure, continuous monitoring of the patient's condition is essential. This includes continuous monitoring of body temperature, basic vital signs and neurological function. Regular monitoring of glycaemia, blood gas parameters and coagulation system is also necessary. An important part of surveillance is neurological assessment using EEG or aEEG and, if warranted, additional neuroimaging studies. [18,19,20,21]

Efficacy of therapeutic hypothermia - a review of clinical studies

Therapeutic hypothermia (HT) is currently the only intervention with proven efficacy in

reducing mortality and improving neurological prognosis in neonates with moderate to severe hypoxic-ischaemic encephalopathy (HIE). Its efficacy has been confirmed in numerous multicentre randomised trials and meta-analyses. The foundation for the therapy was laid by randomised trials such as TOBY (Total Body Hypothermia for Neonatal Encephalopathy), one of the first and most influential studies, and the NICHD Neonatal Research Network Study. The TOBY study involving 325 neonates showed a significant reduction in the risk of death or severe neurological disability at 18 months (RR 0.76). [15] NICHD showed that mortality and severe disability in the HT group was 44%, compared to 62% in the control group. [2]

The largest Cochrane Review meta-analysis (2013, with updates in later years) included data from more than 1,500 newborns from 11 RCTs. HT was clearly shown to reduce the risk of death and severe neurological impairment without significantly increasing the risk of complications. [22] In long-term 6- and 7-year follow-ups, children undergoing HT showed better cognitive and motor development, lower rates of cerebral palsy and hearing/visual deficits, and no significant differences in behavioural problems between the HT group and controls (e.g. TOBY Follow-Up Study, 2012). [23]

Clinical conclusions from the above-mentioned studies agree that therapeutic hypothermia reduces mortality and the risk of permanent disability by approximately 25-30%. The greatest benefits are observed in neonates with moderate HIE, with the onset of therapy <6 hours after birth and the effects persist at long-term follow-up - up to school age.

Limitations and controversies associated with therapeutic hypothermia

Despite the proven efficacy of therapeutic hypothermia (HT) in neonates with moderate to severe hypoxic-ischaemic encephalopathy, there are a number of limitations and controversies that are still the subject of research and clinical discussions. These mainly concern populations not included in the original randomised trials, as well as technical and organisational aspects of implementing this therapy.

Due to the fact that most of the HT studies included neonates born at ≥36 weeks of gestation, the efficacy and safety of HT in preterm infants (<36 tc) was assessed. The prognosis still remains uncertain. The brain of preterm infants is more sensitive to hypoxia and may respond differently to cooling. Large, well-designed RCTs in this group are lacking, and current guidelines do not recommend the routine use of HT in preterm infants outside the context of clinical trials. [24]

To date, neonates with mild encephalopathy have also been excluded from key RCTs. Some studies suggest that subtle cognitive and behavioural deficits may also occur in this group at

school age. There is a growing number of cases where clinicians are implementing HT 'prophylactically', despite the lack of clear evidence - which is controversial and raises questions about the risk of over-recognition and over-intervention.

The THIN study demonstrated no significant improvement in neurological outcome in neonates with mild HIE after hypothermia (72 h, 33.5°C). [25] In underdeveloped countries or with limited access to sophisticated equipment, HT is sometimes used in 'low-tech' versions (e.g. cooling with ice or cold gel packs). Consistent evidence on the safety and efficacy of such methods is lacking. Some studies (e.g. HELIX trial, India, Pakistan, Sri Lanka) have shown a lack of improvement and even increased mortality compared to standard care - raising serious doubts about the universality of this therapy. The HELIX trial showed no benefit of hypothermia in LMICs (increased mortality in the hypothermia group vs. control). This clearly questioned the universality of HT use in resource-limited settings. [26]

The side effects associated with hypothermia are also controversial. It may increase the risk of bradycardia, coagulation disorders, hypoglycaemia, hypotension or infection. The crucial role of intensive monitoring limits its use outside reference level III centres, which the HELIX study also seems to confirm. [26]

Recent meta-analyses have also addressed the issue of extending or changing procedures. 2023 analysed the impact of extending hypothermia to 120 h in cases of severe HIE. This option does not reduce the risk of disability, confirming the need to follow existing guidelines. [27] Another issue raised by contemporary researchers is the use of adjuvant therapies in HIE. Several substances have been used in clinical trials between 2020 and 2024, but none has proved groundbreaking. Melatonin as an antioxidant, inhibiting oxidative stress and neuronal apoptosis gave promising neuroprotective effects (reduction of brain damage markers on MRI). However, a 2023 meta-analysis showed no significant improvement in disability-free survival. [28] Erythropoietin, by improving angiogenesis and reducing inflammation, also does not improve neurological outcomes and, as a consequence of its mechanism of action, may exacerbate adverse effects such as thrombosis. [28,29]. In 2021, the ALBINO trial used the free radical-reducing xanthine inhibitor allopurinol. The combination of HT with allopurinol at 40 mg/kg compared to placebo also showed a lack of efficacy. [30] In the 2022 MagCool study, magnesium sulphate through its neuroprotective effects (NMDA receptor blockade - inhibits calcium influx into neurons and reduces excitotoxicity in the hypoxic brain) showed a trend towards better EEG results within 72h. Ultimately, this did not replicate the improvement in long-term neurological outcomes - it showed no difference in disability-free survival at 18 mo. (OR 1.2, 95% CI 0.8-1.9) and in the rate of death (14% vs 16%). [31] Significant heterogeneity

depending on the degree of brain damage and consequently different treatment response, as well as the issue of drug delivery within the therapeutic window (6 h after birth) and interactions with HT are limitations and also challenges for the use of adjuvant therapies in clinical trials. Currently, no adjuvant therapy is recommended outside the research context. Promising avenues of research include stem cells (SCINI study - NCT04255147 - preliminary results show improved neural tissue regeneration), PARP-1 inhibitors (in preclinical studies drugs that block the PARP-1 enzyme e.g. PJ34 reduce neuronal necrosis) or epigenetic therapies (HDAC inhibitors modify gene expression after hypoxia - animal model studies). [32, 33, 34, 35]

Conclusion

Therapeutic hypothermia represents a breakthrough in the treatment of neonates with hypoxic-ischaemic encephalopathy, offering a real chance to improve survival and reduce the incidence of severe neurological complications. Through numerous clinical studies, its efficacy has been unequivocally confirmed, especially in neonates born at term with moderate to severe HIE, for whom treatment was implemented in the first six hours of life. Nevertheless, therapeutic hypothermia is not a therapy without limitations. The use of HT in preterm infants, children with mild encephalopathy or in resource-limited settings is still controversial. At the same time, there is growing interest in combining cooling with other methods of neuroprotection, such as the administration of anti-inflammatory or anti-apoptotic drugs, which may open up new therapeutic possibilities in the future. Further research, both into optimising the therapy itself and expanding the indications for its use, remains crucial. Long-term follow-up of children undergoing HT is also crucial to further assess the impact of the therapy on psychomotor development and quality of life.

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