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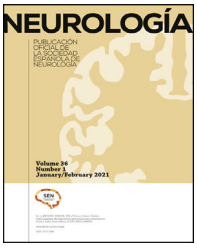

REVIEW ARTICLE

Ten years since the introduction of therapeutic hypothermia in neonates with perinatal hypoxic-ischaemic encephalopathy in Spain

A. Garcia-Alix[a,h,i,j,*], J. Arnaez[b,i,j], N. Herranz-Rubia[a,c,h], A. Alarcón[a,c,j], G. Arca[d,i,j], E. Valverde[e,i,j], D. Blanco[f,j], S. Lubian[g,i,j], Grupo Cerebro Neonatal[1]

[a] *Institut de Recerca Sant Joan de Déu, Hospital Universitario Sant Joan de Dèu, Barcelona, Spain*
[b] *Unidad de Neonatología, Hospital Universitario de Burgos, Burgos, Spain*
[c] *Servicio de Neonatología, Hospital Sant Joan de Dèu, Barcelona, Spain*
[d] *Departamento de Neonatología, Hospital Clinic, IDIBAPS, Barcelona, Spain*
[e] *Servicio de Neonatología, Hospital Universitario la Paz, Madrid, Spain*
[f] *Servicio de Neonatología, Hospital Gregorio Marañón, Madrid, Spain*
[g] *Servicio de Neonatología, Hospital Puerta del Mar, Cádiz, Spain*
[h] *Universidad de Barcelona, Barcelona, Spain*
[i] *Fundación NeNe, Spain*
[j] *Grupo Cerebro Neonatal*

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Abstract
Introduction: More than a decade has passed since therapeutic hypothermia (TH) was introduced in Spain; this is the only neuroprotective intervention that has become standard practice in the treatment of perinatal hypoxic-ischaemic encephalopathy (HIE). This article aims to provide a current picture of the technique and to address the controversies surrounding its use.
Development: In the last 10 years, TH has been successfully implemented in the vast majority of tertiary hospitals in Spain, and more than 85% of newborns with moderate or severe HIE currently receive the treatment. The factors that can improve the efficacy of TH include early treatment onset (first 6 h of life) and the control of comorbid factors associated with perinatal asphyxia. In patients with moderate HIE, treatment onset after 6 h seems to have some neuroprotective efficacy. TH duration longer than 72 h or deeper hypothermia do not offer greater neuroprotective efficacy, but instead increase the risk of adverse effects. Controversy persists around the sedation of patients during TH, the application of the treatment in infants with mild HIE, and its application in other scenarios. Prognostic information and time frame are one of the most challenging aspects.

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* Corresponding author.
E-mail address: alfredoalix@gmail.com (A. Garcia-Alix).
[1] All group members are listed in Appendix A.

Conclusions: TH is universal in countries with sufficient economic resources, although certain unresolved controversies remain. While the treatment is widespread in Spain, there is a need for devices for the transfer of these patients and their centralisation.

PALABRAS CLAVE
Asfixia perinatal;
Encefalopatía hipóxico-isquémica;
Encefalopatía neonatal;
Hipotermia terapéutica;
Neuroprotección;
Neonato;
Cuidado neurocrítico

Una década después de la implantación en España de la hipotermia terapéutica en el recién nacido con encefalopatía hipóxico-isquémica perinatal

Resumen
Introducción: Se cumple ahora más de una década del inicio de la hipotermia terapéutica (HT) en España, la única intervención neuroprotectora que ha venido a ser práctica estándar en el tratamiento de la encefalopatía hipóxico-isquémica perinatal (EHI). El objetivo de este artículo es ofrecer un panorama actual y presentar las controversias surgidas alrededor de la aplicación de esta terapia.
Desarrollo: En esta década se ha implantado con éxito la HT en la gran mayoría de los hospitales terciarios de España y más del 85% de los recién nacidos con EHI moderada-grave reciben esta terapia. Entre los aspectos que pueden mejorar la eficacia de la HT están su inicio precoz dentro de las primeras 6 horas de vida y el control de factores comórbidos asociados a la asfixia perinatal. En los pacientes con EHI moderada el inicio después de las 6 horas parece mantener cierta eficacia neuroprotectora. Una duración de la HT mayor de 72 horas o un enfriamiento más profundo no ofrecen mayor eficacia neuroprotectora y aumentan el riesgo de efectos adversos. Persiste la controversia acerca de la sedación durante la HT, la aplicación de esta intervención a los neonatos con EHI leve y en otros escenarios. La información pronóstica y su marco temporal es uno de los aspectos más desafiantes.
Conclusiones: La HT es universal en países con recursos económicos, aunque existen puntos de controversia no resueltos. Si bien es un tratamiento generalizado en nuestro país, falta disponer de dispositivos para el traslado de estos pacientes y su centralización.

Introduction

Hypoxic-ischaemic encephalopathy (HIE) affects approximately one in every 1000 live births in our setting[1], representing the leading cause of death, severe neurological morbidity, and seizures in full-term neonates worldwide, and explaining 20% of cases of cerebral palsy[2].

After preterm birth, HIE is the most significant neonatal disorder according to the estimated number of disability-adjusted life years (DALY) attributed to this entity[3]. The health, socioeconomic, and legal implications of this entity constitute a major healthcare problem[4].

Preclinical studies conducted over the second half of the 1990s showed that brain hypothermia starting within 6 hours of perinatal hypoxic-ischaemic injury significantly reduces brain damage and improves recovery[5]. During the first decade of the 21st century, several randomised clinical trials (RCT) were conducted with neonates presenting moderate-severe HIE. These trials showed that therapeutic hypothermia (TH), that is, a decrease in body temperature by 3-4°C, started in the first 6 hours of life and maintained for 72 hours, decreases mortality and disability in these patients[6,7]. The efficacy and safety of neuroprotection with TH was confirmed by several meta-analyses; since then, it has been considered a cost-effective intervention in high-income countries, where 6-9 neonates are needed to treat to prevent one case of death or severe disability[8,9].

The purpose of this review is to provide an overview of the current situation of this treatment and the controversies surrounding the application of TH in neonates with HIE.

Development

Therapeutic hypothermia in our setting

In Spain, TH began to be used in 2008; in 2011, the Spanish Society of Neonatology published a series of guidelines standardising the application of hypothermia[10]. In 2014, a group of experts drafted clinical practice guidelines for the Spanish Ministry of Health, Social Services, and Equality based on the available evidence on the management of neonates with HIE[11]. TH was quickly implemented in Spanish hospitals, with 57 of the 90 public tertiary hospitals (60%) offering this treatment in 2015; over 85% of neonates with moderate/severe HIE received this treatment, although resource centralisation and optimisation remain a problem[12].

Improving the efficacy of therapeutic hypothermia

Although TH is the main successful treatment for HIE and its usefulness in neuroprotection has been confirmed, this strategy only reduces the absolute risk of death or severe disability by approximately 15% as compared to not receiving TH (61% vs 46%)[9,13].

To improve the neuroprotective efficacy of TH, several factors must be controlled; these include comorbid factors, time of onset, duration and depth of hypothermia, rewarming, sedoanalgesia, and concomitant treatments.

Comorbid factors

In clinical practice, the effectiveness of TH seems to be greater than reported in the early RCTs[14]. Among the factors contributing to this difference are those occurring in the first hours of life: adequate resuscitation in the delivery room, early administration of TH with passive cooling following stabilisation of the neonate, and comprehensive control of comorbid factors that may aggravate hypoxic-ischaemic injury before and during TH (eg, hyperthermia, hypoglycaemia, hypo- or hypercarbia, hypo- or hyperoxia, hypocalcaemia, and hypomagnesaemia in the first hours). Strategies aimed at controlling these factors are known as the ''brain neuroprotection chain'' and constitute a fundamental pillar in optimising neuroprotection during the first hours of life[15].

Establishing the severity of encephalopathy

Neurological examination enables rapid screening of neonates with HIE. Determining the severity of HIE within 6 hours after birth is a key element in the brain neuroprotection chain; severity is determined with clinical scales[15]. Most scales are nominal, establishing 3 degrees of severity: mild, moderate, or severe[16–19]. One difficulty of determining HIE severity lies in the fact that most scales do not provide a working definition for their items. However, accurately establishing the severity of HIE is essential to indicating TH and drawing robust conclusions in observational studies and RCTs.

Time of onset

In preclinical studies, TH has been found to confer greater neuroprotection when started immediately after hypoxic-ischaemic injury, and within the first 6 hours of life[20]. However, the therapeutic window may narrow according to the severity of hypoxic-ischaemic injury[21].

Clinical data have shown a correlation between the time of TH onset and outcomes: the treatment should ideally be started within the first 3 hours of life[22,23]. This suggests that an effective way to improve the outcomes of TH is to diagnose and determine the severity of HIE as quickly as possible, with a view to starting treatment early.

HIE is therefore a time-dependent emergency in terms of both diagnosis and treatment. In many cases, TH must be started in the referring hospital prior to the patient's arrival at the reference centre, which means that a stable temperature must be maintained during transfer[24]. Ten years after the introduction of TH programmes for neonates with HIE in our setting, cooling during transfer continues to be exclusively passive, as no servo-controlled cooling equipment is available[24,25]. In addition to this, no standardised guidelines have been issued on the management of these patients during transfers, and healthcare teams are rarely trained for this scenario[15].

Duration and depth of hypothermia

A duration of 72 hours and a cooling depth of 33-34°C have been established, based exclusively on the results of preclinical studies[26]. However, this approach has been found to be adequate, since experimental and clinical studies using longer and deeper cooling have not obtained better outcomes but do report higher systemic morbidity rates[27–29]. In preclinical studies, shorter durations (48 hours) have been associated with progressive deterioration over the rewarming phase, with histological findings suggesting reactivation of the inflammatory process associated with injury and rewarming[30].

Rewarming

Rewarming is a critical stage, and must be slow (0.2-0.5°C/h)[10]. This strategy was used in the first RCTs due to concern that rapid rewarming may lead to cardiovascular instability and uncoupling of brain oxygen supply and consumption. In animals and adult humans, rapid rewarming is associated with poorer prognosis, whereas slow rewarming preserves the benefits of cooling[31,32].

Rewarming occasionally triggers seizures, which may be subclinical, underscoring the need for continuous monitoring of brain electrical activity during this stage. When this occurs, rewarming should be slowed or even temporarily suspended. TH may reduce such proinflammatory responses as the release of complement and cell adhesion molecules, as well as oxidative stress and the release of excitotoxic amino acids; these processes may be reactivated during rewarming. Furthermore, increases in body temperature increase brain energy metabolism and, consequently, oxygen and glucose consumption.

Although little information is available, the evidence described above suggests that rewarming is a critical phase for neuroprotection; it has been suggested that slower rewarming following TH may result in greater neuroprotection[32].

Sedoanalgesia in neonates during therapeutic hypothermia

Although it is unclear whether sedoanalgesia, which aims to minimise pain or stress responses during TH, increases the efficacy of the procedure, the practice is used based on the observation that stress and/or pain seem to counteract the neuroprotective benefits of TH in preclinical models[33].

In a retrospective study of neonates with HIE, patients treated with opioids presented less severe brain damage on MRI and better long-term neurological outcomes[34]. A Euro-

pean multicentre RCT evaluating the efficacy of TH revealed greater efficacy than that reported in previous clinical trials (number needed to treat of 4, vs 6-9); this improvement was attributed to the fact that neonates receiving TH had been sedated[35].

Unsolved questions include the suitability and dosage of the drug, and the clinical scales and neurophysiological tools used to assess distress. Dexmedetomidine is an attractive alternative to opioids as it is less detrimental to respiratory function and intestinal motility, and has potential neuroprotective effects; however, it may also play a role in cardiovascular instability[36,37].

Pending further evidence, we recommend systematic sedation of neonates undergoing TH, above all due to the ethical imperative to minimise the discomfort and stress associated with the procedure.

Therapeutic hypothermia starting beyond 6 hours after birth

To guarantee the efficacy and safety of TH, the RCTs conducted to date establish age > 6 hours as an exclusion criterion[7]. This cut-off point is mainly based on experimental research, with secondary cerebral energy failure, beginning 5.5-8 hours after injury, marking the end of the therapeutic window[20]. Both in animal models and in humans, the neuroprotective effects of hypothermia after a hypoxic-ischaemic event seem to decrease over time[20,23].

Treatment onset may be delayed due to several factors, including difficulty determining HIE severity in the first hours, patient transfer to a tertiary centre, lack of availability of cooling equipment, or severe patient instability in the first hours[1]. However, a recent well-designed study showed that onset of TH between 6 and 12 hours after birth has neuroprotective effects in neonates with moderate HIE (but not in those with severe HIE)[38]. Another study found that TH starting 6 to 24 hours after birth may have some therapeutic benefit[39]. Although the benefits are more modest than when TH is started within 6 hours after birth, these data support the use of TH beyond the 6-hour mark in neonates with moderate HIE.

Controversies around therapeutic hypothermia in mild hypoxic-ischaemic encephalopathy

RCTs on the efficacy of TH for HIE did not include neonates with mild HIE, as the available evidence at the time suggested that these patients do not present relevant neurodevelopmental alterations[16,40—42]. In the era of TH, 2 RCTs that incidentally included a small number of neonates with mild HIE reported no neurodevelopmental alterations as compared to the control group[43,44].

However, 3 recent prospective studies have indicated that neonates with mild HIE are at considerable risk of presenting neurodevelopmental alterations[45—47]. A systematic review found that 25% of neonates with mild HIE presented unfavourable outcomes, defined as death or severe disability (cerebral palsy, blindness, or sensorineural deafness), developmental delay, or cognitive impairment[48]. However, the working definition of mild HIE was not homogeneous.

A recent multicentre, prospective study including 63 neonates and using a clear, uniform working definition of mild HIE found that 7 of 43 patients presented disability at the age of 18-22 months[46]. Only one of these 7 patients presented cerebral palsy, and the most frequent alteration was scoring < 85 on the Bayley-III Cognitive Scale. These data are consistent with the results of 2 studies reporting lower cognitive scale scores (mean difference of 6 points) in children with mild HIE than in patients with history of perinatal asphyxia but not presenting HIE, both at ages 2 and 5 years[45,47]. It is unclear whether clinical data or biomarkers may help us to identify the subgroup of neonates with mild HIE who will subsequently develop neurodevelopmental alterations, particularly cognitive scale scores < 85. This question should be addressed in future studies.

In conclusion, it is unclear whether the benefits of TH in neonates with mild HIE outweigh the costs. This treatment is associated with a number of difficulties and complications, as it requires transfer of the patient to a tertiary centre, involves the administration of sedatives and respiratory support, and results in considerable family distress and healthcare costs[49]. As mentioned previously, the HIE assessment tools currently available do not accurately reflect the continuous spectrum of clinical severity; as a result, differentiating between mild and moderate HIE is difficult in some cases. Although it is currently accepted that TH should not be indicated for neonates with clearly mild HIE, it should be administered when it is unclear whether HIE is mild or moderate.

Use of therapeutic hypothermia in other scenarios

The first RCTs applied strict inclusion criteria in order to gather robust evidence and to avoid confounding factors. In clinical practice, however, up to 22% of neonates undergoing TH do not meet these criteria[50]. TH has been applied to neonates with HIE associated with such other conditions as: *1)* congenital heart disease, *2)* need for surgery, *3)* intra- or extracranial bleeding, *4)* ischaemic stroke, *5)* encephalopathy following postnatal collapse, and *6)* late preterm infants (32-36 weeks of gestational age)[50—52]. In these situations, TH is used as a compassionate treatment and should be carefully evaluated on a case-by-case basis after ruling out pre-existing conditions that may be exacerbated by TH; the limitations of the available evidence should always be discussed with patients' families[52].

However, not all these potential indications for TH are equally accepted. While TH is more widely accepted in patients with encephalopathy following postnatal collapse[51,53], its use in the context of HIE and extracranial (subgaleal haematoma) or intracranial haemorrhage is more controversial: the limited data available suggest that these patients present a high risk of complications, as TH may worsen the bleeding. Therefore, this treatment should not be started until haemorrhage and coagulation are under control, and only mild hypothermia should be applied (rectal temperature of 35°C, rather than 33°C)[54].

Furthermore, indication of TH is controversial in premature infants younger than 36 weeks, as the treatment may cause more severe adverse events in these patients than in

full-term infants, including coagulation disorders, immunosuppression, a leftward shift of the oxygen-haemoglobin dissociation curve, and alterations in the pharmacokinetic properties of drugs metabolised by the liver. These effects suggest an increased risk of intracranial haemorrhage, nosocomial infections, and poor oxygenation in these patients.

Although preclinical data from preterm animal models suggest that TH has neuroprotective effects[55], 2 observational studies addressing the safety profile of this therapy do not report promising results[56,57]. A study including 31 preterm infants (34-35 weeks of gestational age) and 32 full-term infants revealed that preterm infants undergoing TH presented more complications associated with the procedure (hyperglycaemia, leukopaenia, and a trend toward greater frequency of coagulopathy). They also presented more frequent and more severe brain lesions, particularly white matter alterations and cerebellar lesions. Lastly, 13% of premature infants died, whereas no deaths were recorded in the full-term birth group[57]. The second study included 30 premature infants (33-35 weeks of gestational age); although it did not include a control group of full-term infants, it reports a prevalence of hypothermia-related complications (77%) similar to that of the previous study, with 75% of infants presenting neuroimaging alterations (which were moderate or severe in 35% of the sample) and 50% dying or presenting neurological disability[56].

These discouraging findings may be explained by greater vulnerability to hypoxic-ischaemic injury in this population, but underscore the need to conduct further RCTs before TH can be indicated for preterm neonates. However, as this treatment has been shown to be safe for neonates with HIE born at 34-35 weeks of gestational age[50], we support its indication on an individual basis for neonates of that gestational age, but not for those born before week 34.

On the other hand, asphyxiated neonates with clinical signs of HIE who present respiratory failure and severe pulmonary hypertension (eg, meconium aspiration syndrome) and require extracorporeal membrane oxygenation (ECMO) have traditionally been excluded from TH protocols due to the high risk of haemorrhagic complications. Although some small series suggest that applying hypothermia in conjunction with ECMO is feasible and does not increase the risk of complications[58], an analysis of prospective data from 8 hospitals from the Collaborative Pediatric Critical Care Research Network revealed increased rates of intracranial haemorrhage in neonates receiving TH and recommended that this neuroprotective technique be used with caution in neonates with HIE who require ECMO[59].

Given the wide range of reasons why neonates with HIE may not meet the classic inclusion criteria, and the small number of patients with other conditions, it is challenging to conduct RCTs with sufficiently large samples and to determine the safety and effectiveness of this therapeutic strategy in these contexts. However, as the use of TH in contexts other than the condition for which it was originally conceived must be thoroughly documented, the difficulties mentioned above may be surpassed by conducting proof-of-concept studies using reliable biomarkers of ischaemic damage with high predictive capacity, such as magnetic resonance spectroscopy (lactate—to—N-acetyl aspartate ratio) or biochemical markers[51,60]. This strategy may yield efficacy data faster and using fewer patients, which would be particularly beneficial in this context.

Prognosis and time window

Healthcare professionals involved in the management of neonates with HIE are faced with the challenge of establishing a prognosis and informing patients' families. Over the last decade, significant prognostic information has been obtained for each of the tests used to estimate the likelihood of long-term disability or death[61]. However, informing families remains one of the most difficult aspects in the management of these patients. Establishing a prognosis in such a narrow time window is another source of stress for the physicians attending these patients. This time window is vitally important in determining each patient's needs and the onset of palliative care in the most severe cases. Delays in therapeutic decision-making may result in severe disability and dependence in cases of severe brain damage. These decisions should be based on high standards, ethical responsibility, and coherence, and based on a thorough analysis of prognostic data and the values of the patient's family[62]. Healthcare professionals in our setting perceive and acknowledge this complexity. In our study, conducted in Spain, only half of tertiary centres had adequate resources for proper communication, and many reported difficulties developing interdisciplinary collaboration including nursing staff[1,63]. This constitutes a key challenge for improving teamwork when administering TH and establishing a therapeutic relationship with families to help them face this difficult situation.

New coadjuvant treatments

Given the poor outcomes in nearly half of neonates undergoing TH, the development of new coadjuvant therapies to improve the neurodevelopmental outcomes of these infants is a top priority. Several therapies with endogenous products (erythropoietin, melatonin, cannabidiol, stem cells) are currently under study[64]. Other studies are focusing on such exogenous products as xenon, allopurinol, and topiramate; however, insufficient evidence is currently available to support their use in clinical practice[64,65]. In any case, we hope that some of these therapies will eventually be incorporated into clinical practice, extending the therapeutic window of TH and providing additional protection, which would ultimately decrease the rates of neurological disability associated with HIE.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Appendix A. Neonatal Brain Research Group

Thais Agut (Hospital Sant Joan de Déu, Barcelona); María Arriaga-Redondo (Hospital Universitario Gregorio Marañón, Madrid); Isabel Benavente-Fernández (Hospital Universitario Puerta del Mar, Cádiz; Fundación NeNe); Nuria Boronat (Instituto de Investigación Sanitaria La Fe, Hospital Universitario La Fe, Valencia); Nuria Carreras (Hospital Sant Joan de Déu, Barcelona); Malaika Cordeiro (Hospital Universitario La Paz, Madrid); María Garrido-Barbero (Hospital Universitario de Burgos, Burgos); Miriam Martínez-Biarge (Hammersmith Hospital, London); José Martínez-Orgado (Hospital Universitario Clínico, Madrid); María Teresa Moral (Hospital Universitario 12 de Octubre, Madrid); Sonia Caserio (Hospital Universitario Rio Hortega, Valladolid); Begoña Loureiro (Hospital Universitario de Cruces, Bilbao); Cristina Uria (University College, London), and María Teresa Montes (Hospital Universitario La Paz, Madrid).

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