PORTUGUESE JOURNAL OF PEDIATRICS

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ORIGINAL ARTICLE

Therapeutic hypothermia in mild neonatal hypoxic-ischemic enencephalopathy: the experience of a single center in Portugal

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Abstract

Introduction and Objectives: Therapeutic hypothermia (TH) is the standard of care for neonates with moderate and severe hypoxic-ischemic encephalopathy (HIE). There is a growing trend toward the use of TH in mild HIE, although current evidence regarding optimal management is lacking. This study aims to evaluate the incidence of newborns with mild HIE undergoing TH over the last 14 years, and to describe the severity of brain injury and short-term results. **Methods:** We conducted a retrospective, descriptive study of neonates admitted with mild HIE (Sarnat stage 1 encephalopathy) and treated with TH in a level III Neonatal Intensive Care Unit in Portugal, from January 2010 to June 2024. The data collected included information on birth details, clinical factors, and short-term outcomes. **Results:** A total of 176 neonates with HIE were treated with TH in the studied period. The sample included 12 neonates (6.8%) with mild HIE. The main results showed that: a sentinel event was identified in 58% of cases; the aEEG background was mainly classified as normal or moderately abnormal (83%); abnormal brain Magnetic Resonance Imaging was identified in five neonates (41.6%); the neurological examination at discharge was normal in 92% of the neonates; and none had epileptic activity on the EEG at discharge. **Discussion:** Brain injury may be identified in some neonates with mild hypoxic-ischemic encephalopathy. However, the clinical significance of these findings and the potential benefit or harm of hypothermia in this population remain uncertain. Larger, multicenter case-control studies are needed to clarify the impact of therapeutic hypothermia on brain injury patterns and neurodevelopmental outcomes in mild HIE.

Keywords: Therapeutic hypothermia. Mild hypoxic-ischemic encephalopathy. Neonatal intensive care.

Hipotermia terapêutica na encefalopatia hipóxico-isquémica neonatal ligeira: experiência de um centro em Portugal

Resumo

Introdução e Objetivos: A hipotermia terapêutica (HT) é a terapêutica padrão em recém-nascidos com encefalopatia hipóxico-isquémica (EHI) moderada e grave. Há uma tendência crescente na utilização da HT na EHI ligeira, no entanto a evidência disponível é insuficiente para determinar a abordagem ideal. Os objetivos do estudo são avaliar a incidência de recém-nascidos com EHI ligeira submetidos a HT nos últimos 14 anos, descrever a gravidade da lesão cerebral e os resultados a curto prazo. **Métodos:** Estudo retrospetivo e descritivo de recém-nascidos internados com EHI ligeira (estadio um de Sarnat)

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Received: 14-01-2025
Accepted: 07-10-2025
https://pjp.spp.pt

Available online: 30-01-2026
Port J Pediatr. 2026;57(3):130-138
DOI: 10.24875/PJP.25000003

tratados com HT numa Unidade de Cuidados Intensivos Neonatais nível III em Portugal, de Janeiro de 2010 a Junho de 2024. Foram colhidos dados relativos ao nascimento, fatores clínicos e resultados a curto prazo. **Resultados:** Um total de 176 recém-nascidos com EHI foram tratados com TH no período estudado. A amostra incluiu 12 recém-nascidos (6,8%) com EHI ligeira. Os principais resultados mostraram que: em 58% foi identificado um evento sentinela; o aEEG foi predominantemente classificado como normal ou moderadamente alterado (83%); a ressonância magnética craniana mostrou alterações em cinco casos (41,6%); o exame neurológico na alta foi normal em 92% dos recém-nascidos; nenhum apresentou atividade epilética no EEG na alta. **Discussão:** A lesão cerebral pode ocorrer em alguns recém-nascidos com encefalopatia hipóxico-isquémica ligeira. No entanto, o significado clínico destes achados, bem como o potencial benefício ou risco da hipotermia terapêutica nesta população, permanecem incertos. São necessários estudos multicêntricos, de maior dimensão e com grupos de controlo, para esclarecer o impacto da hipotermia terapêutica nos padrões de lesão cerebral e nos resultados do neurodesenvolvimento na EHI ligeira.

Palavras-chave: Hipotermia terapêutica. Encefalopatia hipóxico-isquémica ligeira. Cuidados intensivos neonatais.

Keypoints

What is known
- Current evidence is insufficient to recommend routine therapeutic hypothermia in mild neonatal hypoxic-ischemic encephalopathy.
- Brain injury and neurodevelopmental impairments occur in neonates with mild hypoxic-ischemic encephalopathy.
- Treatment rates with therapeutic hypothermia in newborns with mild hypoxic-ischemic encephalopathy are increasing.

What is added
- This is the first report describing the use of therapeutic hypothermia in mild hypoxic-ischemic encephalopathy in Portugal.
- The proportion of neonates with mild hypoxic-ischemic encephalopathy receiving therapeutic hypothermia is lower than that reported internationally.
- The profile of treated patients did not change as significantly over time compared with trends described in other cohorts.

Introduction

Hypoxic-ischemic encephalopathy (HIE) remains a leading cause of neonatal mortality and morbidity worldwide, occurring in one to two per 1000 live births and accounting for 23% of neonatal deaths.[1,2] It accounts for 20% of cerebral palsy cases and is the most significant neonatal disorder after preterm birth.[3] The clinical presentation of HIE is variable and depends on the severity, timing, and duration of hypoxemia or ischemia. At birth, HIE is classed as mild, moderate, or severe according to the Sarnat classification or Thompson score for HIE. These stages are based on clinical features that can be dynamic and subtle.[4] Therapeutic hypothermia (TH) is recommended as the standard of care for newborns over 36 weeks of gestational age presenting with moderate or severe HIE as it significantly decreases mortality and improves survival rates without disability during infancy and childhood.[5]

Current guidelines exclude neonates with mild HIE from TH due to insufficient evidence of any benefit.[5,6] While observational studies suggest improvements in MRI biomarkers,[7,8] systematic reviews and meta-analyses of neurodevelopmental outcomes have not confirmed a clear advantage, although small sample sizes limit definitive conclusions.[5,6] Pre-clinical data further suggests that TH may even lead to apoptosis in uninjured brain regions.[9] Moreover, the risks of TH may outweigh its potential benefits in this population, including adverse events such as bradycardia, thrombocytopenia, and coagulopathy, as well as the burdens of invasive ventilation, central access, sedation, prolonged hospitalization, and the disruption of breastfeeding and maternal-infant bonding.[6,7] Despite this uncertainty, and alongside the growing evidence of less favorable outcomes,[5] the use of TH in mild HIE is increasing, accounting for up to 20% of all cases receiving TH in some series[1,2,5,10,11] and is reported in 50% of US[12] and 60% of UK centers.[10] Unresolved questions include how to accurately classify HIE within the first six hours after birth to identify infants at risk of adverse neurodevelopmental outcomes, and whether TH in mild HIE improves or worsens long-term prognosis.

Our study aims to describe the current use of hypothermia in this population in a level III neonatal intensive care unit in Portugal and to evaluate the alignment of practice with international recommendations.

Methods

A retrospective observational cohort study was conducted on neonates with HIE who underwent TH in the

Table 1. Resuscitation characteristics, Apgar scores, and cord pH at birth in neonates treated with therapeutic hypothermia during the study period

Variable	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Total, n	14	19	11	14	12	11	13	11	9	16	6	10	10	12	8
Resuscitation, n (%)															
Intubation	100	95	100	93	100	100	100	82	78	100	100	80	80	92	100
Chest compressions	43	32	45	50	67	27	46	18	44	50	50	60	70	33	25
Epinephrine	71	32	82	50	58	36	38	9	22	50	67	60	70	25	13
Apgar score (median)															
1 minute	1	2	1	1	0	1	1	2	0	2	5.5	1	0	2.5	0.5
5 minutes	4	4	4	4	3	3	4	5	4	4	7	2	3	5	4
10 minutes	4	5	5	5	5	4	4	6	6	5	7	4	5	6	5
pH at birth (mean)	6.91	6.95	6.98	6.94	6.94	6.89	6.92	6.88	6.98	6.97	6.73	6.9	6.86	7.02	6.80

neonatal intensive care unit (NICU) of a tertiary public hospital in Portugal. The study period extended from January 1, 2010 (the date of TH implementation) to June 30, 2024.

Data was obtained from a local NICU TH database, with prior approval from the institutional ethics committee. To identify neonates with mild HIE treated with TH, we included those with a Thompson score of ≤ 10 and classified with mild HIE based on clinical records. Mild HIE was defined as the presence of any abnormality in at least one of the six categories of the modified Sarnat scoring system, with no more than three categories classified as moderate or severe.[4] The exclusion criteria were: (i) the presence of electrographic seizures within the first 12 hours of life, as infants were maintained in passive cooling during this period to guide eligibility for the TH protocol, and (ii) postnatal collapse.

Whole-body TH was administered following the same standards used for neonates with moderate and severe HIE, in accordance with the updated national protocol.[13]

Collected variables included perinatal and neonatal data (pregnancy, delivery, and resuscitation), clinical course, and short-term outcomes, namely brain magnetic resonance imaging (MRI) findings and neurological examination at hospital discharge. Neonatal brain MRIs were assessed by a single pediatric neuroradiologist using the Weeke score.[14] The sequences analyzed included T1- and T2-weighted images, diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) maps, and T2*/susceptibility-weighted imaging; spectroscopy was not performed.

Statistical analysis was performed using Microsoft Excel® (Redmond, WA, USA). Simple and conditional frequencies were calculated. Continuous variables were expressed as means with ranges, and categorical variables as percentages.

Results

Study population

We reviewed 176 neonates with HIE who were treated with TH during the study period. The resuscitation characteristics, Apgar score, and pH at birth are presented in table 1.

According to the Sarnat classification, 19 neonates (10.8%) were classified as having mild HIE. We excluded seven neonates initially classified as mild HIE who presented with documented electrical seizures within the first 12 hours of life, leaving a sample of 12 neonates (6.8%). The total number of treated neonates decreased over the studied period; however, the number of treated neonates with mild HIE remained stable (Fig. 1).

All mild HIE neonates were outborn: nine were born in the Lisbon region, two in the Algarve, and one in the Azores islands.

Demographic and clinical characteristics

Most of the mothers were healthy and no complications during pregnancy were observed. All pregnancies were singleton. All neonates were born over 36 weeks of gestational age, and no significant prenatal problems were detected. A perinatal sentinel event was identified in seven cases. Additional birth-related variables are described in table 2.

All neonates required resuscitation at birth. Epinephrine was administered during resuscitation in five cases. One neonate underwent prolonged resuscitation (> 10 minutes). The median Apgar scores at one, five, and ten minutes were one, four, and seven,

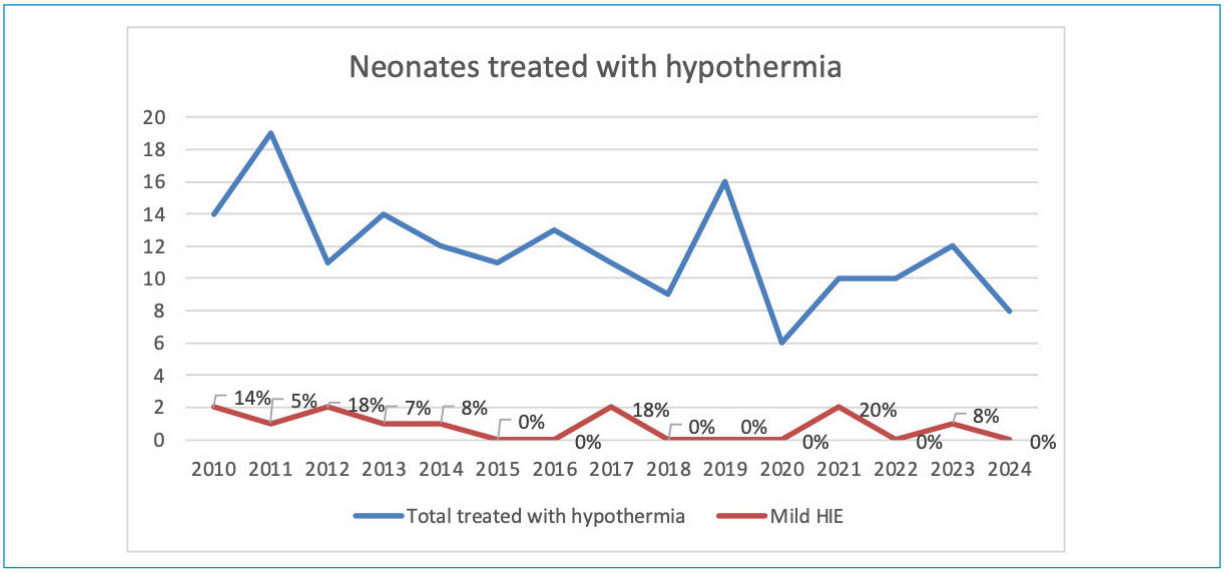

Figure 1. Annual distribution of neonates with HIE treated with therapeutic hypothermia.

respectively. The mean pH in the first hour of life was 6.91 (range: 6.74-7.08). The base deficit ranged from unmeasurable (one case) to 27 mmol/L. Additional data relating to respiratory and cardiovascular support, complications, and medications administered during and after the TH protocol is presented in table 3. We point out that the protocol for empiric coverage for early-onset neonatal sepsis was changed during the studied period (the ampicillin plus cefotaxime regimen was changed to ampicillin plus gentamicin).

Cooling characteristics

Most neonates were started on passive hypothermia within the first hour of life (median: one hour; range: 1-5 hours), and all were started on active hypothermia within the first 12 hours of life (median: 7.5 hours; range: 3-11 hours).

Neurological findings and neuromonitoring

In our center, the Thompson score is applied on admission and daily during TH to describe encephalopathy. The Sarnat classification was retrospectively estimated from available records. The median Thompson scores at admission, 24 hours, 48 hours, and at the end of rewarming were five, six, seven, and eight, respectively. All neonates were treated with morphine, and in two patients, midazolam or dexmedetomidine were also administered (Table 4). The morphine infusion dose had to be titrated to 15 mcg/kg/hour in two patients and up to 20 mcg/kg/hour in seven patients.

Three infants had suspected clinical seizures at the referring hospital. In one infant, TH was initially considered not indicated; however, seizures occurred 12.5 hours after birth during rewarming, leading to the reinstatement of TH.

Electrical seizures were documented in three additional infants during treatment. In total, seven infants received anticonvulsants, with phenobarbital administered in every case, and a combination of phenobarbital and midazolam in one case.

On admission, the aEEG was normal in most neonates, while four had a moderately abnormal background. In each of the patients with an altered aEEG, the background normalized during TH (in two at 48 hours, one at 60 hours, one at 14 hours, and one at 16 hours). In one case, the aEEG pattern worsened during treatment, progressing to a burst-suppression pattern before eventually normalizing (Table 4).

Cranial ultrasound

The cranial ultrasound showed evident or equivocal grey-white matter differentiation in four neonates, a resistive index of < 0.55 in three, and no signs of cerebral edema in any of the cases.

MRI

Brain MRI was performed at a median age of 11.5 days (range: 7-16). Six neonates showed normal findings or only a small subdural hemorrhage (Weeke score 0-1). One patient showed signs of a left-sided

Table 2. Pregnancy and delivery characteristics of neonates with mild HIE treated with therapeutic hypothermia

Variable	Case											
	1	2	3	4	5	6	7	8	9	10	11	12
Gender	M	M	F	F	F	M	F	M	M	M	F	F
BW (g)	3530	3535	3450	2436	2070	3680	2046	3170	4070	3100	3145	2460
GA (w)	38	40	41	39	37	40	39	37	38	40	40	37
Mode of delivery	Vacuum	Vacuum	Forceps	Eutocic	C-section	Eutocic	Vaginal breech	C-section	C-section	C-section	Vacuum	C-section
CTG	Normal	-	Suspicious	Normal	-	Suspicious	-	-	Suspicious	Suspicious	Normal	-
Amniotic fluid	Clear	Meconium	Meconium	Clear	-	Clear	Clear	Bloody	Meconium	Meconium	Clear	-
Sentinel event	Shoulder dystocia	None	Nuchal cord	Placental abruption	Placental abruption	Nuchal cord	None	Placental abruption	None	None	None	Placental abruption
DR resuscitation	I	I	I + CM + RD	I + CM + RD	I + CM + RD	I + CM + RD	I	I	I	I + CM + RD	I	I
Apgar score	5-5-7	1-4-8	2-5-7	0-4-7	1-4-5	1-2-4	-	2-6-8	2-4-7	1-2-5	1-3-4	3-6-8
pH*	7.00	7.08	6.75	7.05	-	6.90	6.74	6.8	6.8	6.97	7.07	6.8
Base deficit (mmol/L)*	20	14	22	20	-	24	27	24.6	19.8	15	23.6	Unmeasurable

*Worst pH and base deficit in the first hour of life.
BW: birth weight; CM: cardiac massage; CTG: cardiotocography; DR: delivery room; F: female; g: grams; GA: gestational age; M: male; RD: resuscitation drugs; w: weeks.

Table 3. Respiratory and cardiovascular support, complications, and medications administered in neonates with mild HIE during therapeutic hypothermia

Variable	Case											
	1	2	3	4	5	6	7	8	9	10	11	12
Respiratory support*	NIV only	IV	IV	IV	IV	IV	IV	NIV only	IV	IV	IV	NIV only
Antibiotics	Other regimen	AMP + CEF	AMP + CEF	AMP + CEF	AMP + CEF	AMP + CEF	AMP + CEF	AMP + GEN	AMP + CEF	AMP + GEN	AMP + GEN	AMP + GEN
Cardiovascular support	Inotrope(s)	Inotrope(s)	Inotrope(s)	None	Inotrope(s)	None	Inotrope(s)	Fluid bolus	Inotrope(s)	None	Inotrope(s)	Inotrope(s)
Acute kidney injury	Yes	No	No	No	No	No	No	No	No	No	No	No
Hypoglycemia	No	No	No	No	No	No	No	No	No	No	No	No
Coagulopathy	Yes	No	No	No	Yes	No	Yes	No	Yes	No	No	No
Length of stay (days)	24	20	11	14	17	12	19	13	22	-	11	11

*IV occurred any time during hospitalization, prior and/or subsequent to NIV.
AMP: ampicillin; CEF: cefotaxime; GEN: gentamicin; IV: invasive ventilation; NIV: non-invasive ventilation.

ischemic infarct. Another patient exhibited cortical highlighting (Weeke score 1), and two showed equivocal myelination of the posterior limb of the internal capsule (PLIC) (Weeke score 1-2). One neonate showed basal ganglia lesions, Rolandic cortical highlighting, and equivocal PLIC (score 5). No MRI results were available for one patient.

Evaluation at discharge

The median NICU stay was 14 days (range: 11-24). Three neonates were transferred back to their original NICU and the remainder were discharged home. Neurological examination at discharge was normal in all but one infant with hypotonia and hyporeflexia. No seizures or anticonvulsant therapy were reported at discharge. Most neonates had a normal EEG and auditory evoked potentials. By day 14, only three required tube feeding, but all were discharged on oral feeding (Table 4). No deaths occurred. One neonate was diagnosed with ischemic cerebral infarct on MRI, and no other alternative diagnoses were identified.

Discussion

In this study, we describe our 14-year experience with therapeutic hypothermia in neonates with mild HIE in a level III NICU in Portugal. Although the overall profile of treated infants remained relatively stable, we observed a trend toward including neonates with mild symptoms or requiring only respiratory resuscitation. This pattern is consistent with international reports, reflecting both increasing awareness of the potential risks of mild HIE and growing confidence in the safety of TH in routine practice. Nevertheless, the proportion of mild HIE infants who underwent TH in our cohort was substantially lower than the 22% reported in a meta-analysis from seven high-income countries.[2,10]

A sentinel event was identified in 58% of our cases, higher than the one-third typically reported.[15] This may have influenced the decision to include some infants with mild symptoms in the TH protocol. Cardiovascular and respiratory support requirements were notable, with invasive ventilation needed in 75% and inotropic support in 67% of cases. Non-invasive ventilation was successfully used in several infants, in line with the current trend toward less invasive strategies to reduce complications.

Sedation was also a relevant challenge: nine out of 12 infants required high-dose morphine or a second agent, likely reflecting milder encephalopathy and greater discomfort associated with cooling. The need for higher opioid doses raises concerns about toxicity and highlights the potential risks of TH in mild HIE, including maternal separation, breastfeeding interference, and increased susceptibility to nosocomial infection. These factors may partly explain why current studies have not demonstrated a clear benefit.

Table 4. Neuromonitoring, neurological findings during therapeutic hypothermia, and short-term neurological outcomes in neonates with mild HIE

Variable	Case											
	1	2	3	4	5	6	7	8	9	10	11	12
TS at admission	0	0	5	5	6	6	4	3	5	5	6	3
Sedation/analgesia (ug/kg/h)	MOR (< = 10)	MOR (> 10)	MOR (> 10)	MOR (> 10)	MOR (> 10)	MOR (> 10)	MOR (< = 10)	MOR (> 10) + MDZ	MOR (> 10)	MOR (> 10)	MOR (> 10) + DEX	MOR (< = 10)
Anticonvulsants	None	PHE	PHE	None	PHE	PHE	PHE	PHE	None	None	PHE + MDZ	None
aEEG*	Normal	Normal	Normal	Normal	Moderately abnormal	Moderately abnormal	Moderately abnormal	Suppression	-	Normal	Moderately abnormal	Normal
Electrical seizure on aEEG	No	Yes	Yes	No	Yes	No	No	No	No	No	Yes	No
Exclusive oral feeding at day 14	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes
Auditory evoked potentials	Normal	-	Normal	Normal	Normal	Normal	Normal	Normal	-	Normal	Normal	Normal
EEG at discharge	Normal	-	Abnormal	Normal	-	Normal	Normal	Abnormal	-	Normal	Abnormal	-
Clinical seizures at discharge	No	No	No	No	No	No	No	No	No	No	No	No

*Worst aEEG during hospitalization.
DEX: dexmedetomidine; MDZ: midazolam; MOR: morphine; PHE: phenobarbital; TS: Thompson score.

On admission, four infants had a moderately abnormal aEEG, which likely influenced the decision to initiate TH, as our initial local guideline incorporated aEEG as a treatment criterion following the TOBY protocol.[16] aEEG has also been used in clinical trials and in practice to help select infants with mild HIE for cooling.[17–19] In this context, discontinuity, asymmetry, or a poor sleep-wake cycle may suggest an increased risk of an adverse outcome, although a normal aEEG does not exclude this.[7,20,21] In our cohort, background activity normalized within 48 hours in all but one infant, generally indicating a favorable prognosis, though less reassuring features were observed in four cases. Four infants had electrographic seizures; in one, the aEEG pattern deteriorated to burst-suppression before recovering, corresponding to the most severe MRI injury. Among the seizure group, one infant had an ischemic infarct, another had mild cortical highlighting, and two had normal MRI findings.

MRI abnormalities were present in 41,7% of infants, mostly mild, but one neonate showed a significant basal ganglia lesion (Weeke score 5). MRI is a reliable predictor of long-term neurodevelopment, and studies consistently report abnormalities in 34-66% of mild HIE cases, a rate comparable to moderate or severe HIE.[1,2,7,20–22] In mild HIE, injury patterns are usually less severe (periventricular edema, punctate white matter lesions, and minimal cortical highlighting) and may not translate into significant long-term poor outcomes, but misclassifying these subtle changes as abnormal can overestimate the prognosis of adverse outcomes. In fact, significant basal ganglia or thalamic injury on T1- and T2-weighted images is rare, occurring in < 4% of cases.[6,23]

The classification of HIE severity within the first six hours remains a major challenge. Neurological signs fluctuate over time, inter-observer variability is significant, and there is no universally accepted definition of perinatal hypoxia-ischemia or of the grading of encephalopathy. Reported progression rates from mild to more severe encephalopathy varies widely across studies (1.6% in PRIME, 12% in Gagne-Loranger et al., 26.7% in MARBLE, and up to 50% in ICE).[5,19,24] This uncertainty may explain why some infants with mild HIE and additional risk factors, such as an abnormal aEEG, seizures, or sentinel events, are cooled in clinical practice. In our cohort, most cooled infants with mild HIE had one of these features and international and national guidelines appear to be generally followed.

Ultimately, deciding which infants with mild HIE should receive TH is complex. Two ongoing randomized trials may soon provide crucial evidence. The COOL PRIME study (NCT04621279) is evaluating TH versus normothermia with neurodevelopmental outcomes at two years, while the COMET trial (NCT03409770) is testing normothermia versus TH for 48 or 72 hours, using magnetic resonance spectroscopy at two weeks as a surrogate outcome. These results will be critical to clarify the role of TH in this large group of infants.

Our study has limitations. Its retrospective design introduces variability in assessment and documentation, and the absence of a control group of untreated mild HIE infants prevents conclusions regarding efficacy or safety. Despite these limitations, our findings reflect real-world practice and highlight the importance of aligning clinical decisions with current evidence and guidelines, particularly given the risks of therapy.

In summary, the management of mild HIE remains an area of uncertainty. Early classification within the first six hours is complex and often unreliable, as some infants initially presenting with mild signs later evolve to more severe stages. Although increasing evidence links mild HIE with brain injury and adverse neurodevelopmental outcomes, current data does not justify routine use of TH in this group, which represents almost half of all HIE cases. The balance between potential benefit and possible harm is still unclear, highlighting the urgent need for well-designed clinical trials. Improving early risk stratification through refined neurological assessment, neurophysiological monitoring, and emerging biomarkers will be key. As the use of TH in mild HIE expands, studies such as ours add to the understanding of real-world practice and outcomes, and reinforce the importance of cautious, evidence-based decision-making.

Author contributions

J. Fortuna: design, data curation, formal analysis, methodology, software, visualization, writing of the original draft, review and editing; F. Proença: design, formal analysis, methodology, validation, review and editing; A. Graça: design, data curation, formal analysis, investigation, methodology, supervision, validation, visualization, review and editing; I. Sampaio: design, formal analysis, methodology, validation, review and editing.

Previous presentations

52º Congresso Português Neonatologia, Eurostars Oasis Plaza, Figueira da Foz. November 29, 2024.

Funding

None.

Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the drafting of this manuscript.

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