ORIGINAL ARTICLE

Therapeutic Hypothermia for Neonatal Hypoxic-Ischemic Encephalopathy: 10-Year Experience

Ana Teresa Sequeira[1], Joana Gil[2], Isabel Sampaio[2,3], Carlos Moniz[2,3], André M. Graça[2,3]

Port J Pediatr 2021;52:21-9
DOI: https://doi.org/10.25754/pjp.2021.20006

Abstract

Introduction: Therapeutic hypothermia is the standard of care treatment for brain injury following perinatal hypoxia-ischemia in term infants. Accumulated evidence from clinical trials, systematic reviews, and continuous experience shows a reduction in both mortality and long-term neurodevelopmental disability. The aim of our study was to present the 10-year experience of the neonatal intensive care unit that pioneered the hypothermia program in Portugal, evaluate the use of neurologic monitoring, and describe the short-term outcomes and adverse events.

Methods: Prospective observational study of neonates who underwent therapeutic hypothermia between November 2009 and October 2019 in a single tertiary level neonatal intensive care unit. Clinical variables were collected from our hypothermia database. Expected outcomes were calculated using a combination of amplitude-integrated electroencephalogram and magnetic resonance imaging patterns, according to the existing robust evidence.

Results: The study included 128 newborns who were treated, 91% were outborn. The median gestational age was 39 weeks, 91% neonates needed advanced resuscitation, and 22% prolonged resuscitation (> 10 minutes). On admission, 60% had severe, 26% had moderate, and 14% had mild encephalopathy. Hypotension was the most common complication, affecting 66% of the newborns. During the hospital stay, 21 (16%) patients died. Expected outcome was favorable in 40%, intermediate in 32%, and adverse in 28%.

Discussion: Effectiveness and safety profile of therapeutic hypothermia was confirmed in our population. A national register would be important to achieve and maintain high homogeneous and nationwide standards of care.

Keywords: Asphyxia Neonatorum/complications; Hypothermia, Induced/methods; Hypoxia-Ischemia, Brain/diagnostic imaging; Hypoxia-Ischemia, Brain/therapy; Infant, Newborn; Portugal; Term Birth

Introduction

Neonatal hypoxic ischemic encephalopathy is a serious birth complication that affects 0.5-1/1,000 live births in developed countries.[1] The natural history of this condition is associated with high mortality (up to 60%), and long-term neurodisability in at least 25% of survivors.[1,2]

The use of therapeutic hypothermia (TH), if initiated within six hours after birth and maintained for 72 hours, has proven its efficacy in reducing mortality and long-term neurodevelopmental disability among term neonates with moderate to severe hypoxic ischemic encephalopathy.[1,3-8]

Therapeutic hypothermia has become a routine practice across neonatal intensive care units around the developed world. It was introduced in Portugal in 2009 at the neonatal intensive care unit of Hospital de Santa Maria, a tertiary public hospital.[9,10]

The selection of infants who are candidates for this treatment is based on the criteria used in randomized controlled trials. Data is still lacking regarding the safety and efficacy of therapeutic hypothermia outside of these inclusion criteria. Ongoing studies are evaluating its use in late preterm,[11,12] mild encephalopathy[13], and postnatal cardiovascular collapse.[14]

Amplitude-integrated electroencephalography (aEEG) is a widely used bedside tool to identify the potential candidates for therapeutic hypothermia.[15] During treatment, neonates are admitted to intensive care and submitted to the continuous monitoring of respiratory and cardiovascular stability and regular laboratory surveillance. In addition, the close observation of the neurological status is undertaken through serial

1. Departamento de Pediatria, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal
2. Serviço de Neonatologia, Departamento de Pediatria, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal
3. Clínica Universitária de Pediatria, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal
Corresponding Author
André M. Graça
https://orcid.org/0000-0003-2961-0083
amgraca@campus.ul.pt
Departamento de Pediatria, Hospital de Santa Maria, Avenida Professor Egas Moniz, s/n, 1649-035 Lisboa, Portugal
Received: 03/03/2020 | Accepted: 16/07/2020 | Published: 03/01/2021
© Author(s) (or their employer(s)) and Portuguese Journal of Pediatrics 2020. Re-use permitted under CC BY-NC. No commercial re-use.

clinical evaluations (including Thompson score) and continuous bedside aEEG. The aEEG is extremely useful in this particular setting, as clinical evaluation is often limited due to sedation. This tool is also useful to identify electrical seizures and it is helpful in outcome prediction.[15-18] Persistently abnormal aEEG trace at 48 hours of age is associated with adverse long-term outcome.[15,19-21]

Magnetic resonance imaging (MRI) studies of the neonatal brain within 1-2 weeks of age have been shown to be excellent predictors of outcome, even before the era of therapeutic hypothermia.[22] The pattern of injury in MRI has been shown to be able to predict the severity and type of neurodevelopmental dysfunction later in life in patients submitted to therapeutic hypothermia.[23,24] Information from the neurological examination, aEEG, and MRI data will be helpful in predicting the neurodevelopmental outcome and counselling parents.[1,15-24]

Therapeutic hypothermia has been demonstrated to be safe in neonates with hypoxic ischemic encephalopathy. Neonates with perinatal asphyxia are at risk of multiorgan dysfunction after birth. Reported adverse events, which are the result of asphyxia and its treatment with therapeutic hypothermia, include systemic hypotension, acute kidney injury (AKI), coagulopathy, thrombocytopenia, hepatic dysfunction (elevated liver enzymes: aspartate transaminase > 200 U/L or alanine transaminase > 100 U/L), persistent pulmonary hypertension, and subcutaneous fat necrosis.[1,4-11]

This study aims to:

- Describe the experience in a level III neonatal intensive care unit using therapeutic hypothermia according to an implemented protocol;
- Report the characteristics of the treated patients and any adverse events;
- Predict long-term outcome.

Methods

Data was collected prospectively and registered on a local data collection form. We included all of the neonates treated with therapeutic hypothermia (whole-body cooling) for perinatal asphyxia between November 2009 and October 2019 at a single tertiary level neonatal intensive care unit.

The patients' demographic data that was collected included gestational age, birth weight, and sex. Perinatal data included maternal clinical factors, mode of delivery, clinically identifiable intrapartum sentinel event (ruptured uterus, placental abruption, cord prolapse, difficult delivery with shoulder dystocia), place of birth, resuscitation details, umbilical cord or venous pH, and base deficit within the first hour after birth, Apgar scores at 1, 5, and 10 minutes. Characteristics of the hospital course included admission temperature, need for vasopressor support, mechanical ventilation or dialysis, presence of seizures, or persistent pulmonary hypertension. Data was also collected on adverse effects of therapeutic hypothermia, therapeutic, laboratory, and neuromonitoring findings. Hypotension was defined by low blood pressure supported with volume expansion or vasopressors. Acute kidney injury was defined using a serum creatinine (SCr) based modification of the acute kidney injury network (AKIN) criteria (Table 1).[25]

Selecting the infants to be treated with therapeutic hypothermia needed to fulfil at least one of the "A" criteria and one of the "B" criteria, in the absence of any exclusion criteria (Table 2). Treatment outside of these criteria was considered in some cases and the individualized risk and benefits were discussed with the family. Consent was obtained before the initiation of therapeutic hypothermia for those cases that did not fit the protocol inclusion criteria.

On admission, the severity of encephalopathy was evaluated by clinical assessment (Sarnat & Sarnat clinical stages).[26] All the patients were monitored with aEEG on admission and during the therapeutic hypothermia protocol (hypothermia and rewarming).[15] An amplitude-integrated electroencephalography classification was used to describe the aEEG patterns using voltage criteria, as described by al Naqeeb et al[17]:

- Normal: lower margin above 5 µV and upper margin above 10 µV;
- Moderately abnormal: lower margin below 5 µV and upper margin above 10 µV);
- Severely abnormal: both lower and upper margins below 5 µV.

Seizure activity was noted separately.

Infants received whole body cooling for 72 hours with rectal temperature maintained at 33.5°C using the CritiCool® servo-controlled system (MTRE, Rehovot,

Table 1. Definition of acute kidney injury categories

AKI stage	Criteria
0	No change in SCr
I	Elevation of SCr 0.3 mg/dL or 150%-200% from previous trough value
II	Elevation of SCr 200-300% from previous trough value
III	Elevation of SCr ≥ 300% from previous trough value, SCr 2.5 mg/dL or dialysis

AKI - acute kidney injury; SCr - serum creatinine.
Adapted from: Jetton JG, Askenazi DJ. Update on acute kidney injury in the neonate. Curr Opin Pediatr 2012;24:191-6.[25]

Israel). The cooling period was followed by a rewarming period of no more than 0.5°C per hour until normothermia was reached.

Expected outcome was based on aEEG and MRI findings. Amplitude-integrated electroencephalography was considered[19-21]:

- Favorable, if the recovery time to normal background was ≤ 48 hours of hypothermia;
- Intermediate, if it showed moderate changes at 48 hours;
- Adverse, if the pattern was severely abnormal for at least 48 hours.

For scoring MRI, we used the classification proposed by Martinez-Biarge et al, that assessesbrain injury in four areas and each item was scored for the extent of the injury (Table 3).[27]

Expected outcome was considered favorable if the aEEG was normal at 48 h of therapeutic hypothermia and the MRI was normal or presented mild alterations, intermediate if the aEEG had moderate alterations at 48 h of therapeutic hypothermia or the MRI presented with moderate alterations, and adverse if the aEEG was severely altered at 48 h of therapeutic hypothermia or the MRI presented with severe alterations.

Table 2. Selection criteria to therapeutic hypothermia

Inclusion criteria "A" (asphyxia)	At least one of the following:
	Apgar score < 5 at 10 minutes
	Need for continued resuscitation at 10 minutes
	pH < 7.0 on cord gas or infant blood within the first hour of life
	Base deficit ≥ 16.0 on cord gas or infant blood within the first hour of life
Inclusion criteria "B" (brain dysfunction)	Moderate to severe encephalopathy
	OR
	Neonatal seizures
Exclusion criteria	Gestational age < 36 weeks
	6 hours of life when contact with treatment unit is made
	Cannot reach the treatment unit < 12 hours of life
	Major congenital malformations
	Likely need for surgery within the first 3 days of life
	Postnatal cardiorespiratory arrest

Table 3. Brain magnetic resonance imaging score

Brain areas	**Score**	**Changes**
Basal ganglia and thalamus	0 - Normal	None
	1 - Mild	Focal abnormal signal intensity
	2 - Moderate	Multifocal abnormal signal intensity
	3 - Severe	Widespread abnormal signal intensity
Posterior limb of the internal capsule	0 - Normal	None – normal posterior limb of the internal capsule myelinization pattern
	1 - Equivocal	Reduced or asymmetrical signal intensity
	2 - Loss	Reversed or abnormal signal intensity bilaterally on T1 and/or T2
White matter	0 - Normal	None
	1 - Mild	Involvement of periventricular white matter only
	2 - Moderate	Changes extending out to subcortical white matter and/or focal punctate lesions or focal area of infarction
	3 - Severe	Widespread abnormalities including overt infarction/hemorrhage
Cortical involvement	0 - Normal	None
	1 - Mild	1-2 sites involved
	2 - Moderate	3 sites involved
	3 - Severe	More than 3 sites involved

Adapted from: Martinez-Biarge M, Diez-Sebastian J, Kapellou O, Gindner D, Allsop J, Rutherford MA, et al. Predicting motor outcome and death in term hypoxic-ischemic encephalopathy. Neurology 2011;76:2055-61.[27]

Results

A total of 128 infants underwent therapeutic hypothermia during the 10-year study period. From the total of infants, 117 (91%) patients were outborn. 75 (64%) patients were born in the region of Lisbon and Tagus Valley, whereas 36% were referred from other regions, 14 (12%) were from the north of the country, 14 (12%) from Algarve, 8 (7%) from Alentejo, and 6 (5%) from Azores islands.

Patients and cooling criteria

The maternal clinical factors, demographic data, and resuscitation details of these infants are summarized in Table 4.

We treated 14 neonates outside of the entry criteria, after obtaining parents' informed consent: 8 with unexpected postnatal collapse, 4 newborns with a gestational age of 35 weeks and 2 neonates started treatment after 12 hours of life.

Table 4. Maternal clinical factors, demographic, and resuscitation details

Variable		Results
Maternal diabetes, n (%)		8 (6)
Hypertension/preeclampsia, n (%)		7 (5)
Gestational age in weeks, median (range)		39 (35-41)
Birth weight (g), median (range)		3100 (1738-5380)
Gender - male, n (%)		88 (69)
Mode of delivery, n (%)	Cesarean	62 (48)
	Instrumental vaginal birth	37 (29)
	Eutocic	29 (23)
Clinically identifiable intrapartum event, n (%)	Placental abruption	19 (15)
	Shoulder dystocia Uterine rupture	9 (7) 10 (8)
	Cord prolapse	2 (2)
	Other	5 (4)
Apgar at 1 minute, median (range)		1 (0-9)
Apgar at 5 minutes, median (range)		4 (0-9)
Apgar at 10 minutes, median (range)		4 (0-9)
Resuscitation, n (%)	Endotracheal intubation	117 (91)
	Chest compressions	52 (41)
	Epinephrine	57 (45)
Resuscitation required > 10 minutes, n (%)		28 (22)
Worst pH within 60 minutes after birth, median (range)		6.9 (6.5-7.33)
Worst base deficit within 60 minutes after birth, median (range)		19 (5-29)

Cooling characteristics

Passive cooling was initiated in all infants at a median time of one hour of life (range 1-8 hours). The median core temperature at admission was 33.6ºC (range 27ºC-36ºC). Therapeutic hypothermia, as defined by the closure of the therapeutic hypothermia suit, was started between 1 and 15 hours of life (median 6 hours).

Neurological findings, neuromonitoring, and expected outcome

At admission, by clinical assessment, 14% were classified as mild, 26% as moderate, and 60% as severe hypoxic ischemic encephalopathy.

Prior to the beginning of therapeutic hypothermia, 37 (31%) infants had burst suppression on aEEG, 32 (26%) had a flat trace, 33 (27%) had moderate aEEG abnormalities, and two (2%) had status epilepticus. Of the 17 patients (14%) with a normal aEEG at admission, two developed electric seizures later in the course of disease. Data about aEEG findings on admission is missing in seven patients.

During the cooling process, all of the patients were monitored with aEEG. Amplitude-integrated electroencephalography normalized in 76 (59%) newborns, and mostly before 48 hours of life (median time to normalization 31 hours, range 0-72 hours). Forty (31%) patients had electric seizures during therapeutic hypothermia.

Brain MRI was performed in 105 patients at a median age of 10 days (range 3-28 days) and it demonstrated significant injury in 56 (53%) patients (Table 5). Scores were not accessed in two patients because of image limitations.

Table 5. Brain resonance imaging score results

Brain areas	Score	Number	Percentage
Basal ganglia and thalamus	0 - Normal	53	51%
	1 - Mild	16	16%
	2 - Moderate	18	17%
	3 - Severe	16	16%
Posterior limb of the internal capsule	0 - Normal	57	55%
	1 - Equivocal	22	22%
	2 - Loss	24	23%
White matter	0 - Normal	73	71%
	1 - Mild	6	6%
	2 - Moderate	14	14%
	3 - Severe	10	9%
Cortical involvement	0 - Normal	63	61%
	1 - Mild	21	20%
	2 - Moderate	10	10%
	3 - Severe	9	9%

The expected outcome was determined based on aEEG and MRI data. It was obtained in 101 of the 107 surviving infants at discharge and was considered favorable in 40%, intermediate in 32%, and adverse in 28%.

Hospital course, adverse events, and mortality

Clinical course and short-term outcomes are summarized in Table 6.

Invasive mechanical ventilation was used in 124 patients (97%). The remaining four (3%) were under noninvasive ventilation only.

All of the patients were under empiric antibiotics during the cooling procedure, despite the laboratory tests, with ampicillin-cefotaxime being the most common initial regimen (n = 87, 68%). Blood culture was positive in three (2%) newborns.

Significant hypotension, requiring volume expansion or vasopressors, was the most common complication, affecting 85 (66%) newborns.

Acute kidney injury was identified in 20 of 86 patients (23%) during the study period. Based on the modified AKIN criteria, 12 patients had a stage I AKI, 4 had stage II AKI, and 4 had stage III AKI. Two patients underwent renal replacement therapy with peritoneal dialysis.

Seventy-nine (62%) patients were under anticonvulsant therapy during therapeutic hypothermia (31 with phenobarbital, 36 with phenobarbital plus midazolam, 9 with phenobarbital, midazolam plus lidocaine and 3 with a different association).

Twenty-one (16%) infants died during their hospital stay with a median age of 14 days (range 0-48 days). Among those deaths, 6 infants did not fulfill the recommended inclusion criteria or had an alternative diagnosis (one late preterm infant, 4 suffered unexpected collapse (within 2-4 hours of age) and another one had a probable metabolic disease, with no definitive diagnosis at the time of death). After the removal of those infants, the mortality rate for unequivocal typical hypoxic ischemic encephalopathy in our cohort is around 12%. We were only able to have full data for outcome prediction in 38% of the deceased infants, that was considered to be adverse for all of them, based on aEEG and MRI. Redirection of care was decided after early an MRI on 4 of the deceased patients that were considered so severely affected based on a combination of clinical status and persistent aEEG background abnormalities.

Discussion

Our neonatal intensive care unit introduced the first therapeutic hypothermia program in Portugal only a month after the publication of the largest therapeutic hypothermia trial, the TOBY trial,[28] since the data pointing toward the recommendation of therapeutic hypothermia was abundant during that year. As recommended by the authors of randomized controlled trials on therapeutic hypothermia, the treatment of patients outside of clinical trials should follow protocols that were very similar to the ones used during the trials in order to prevent any confounding effect on the outcome and/or safety of this novel therapeutic option. Our protocol was similar to the TOBY trial protocol, including entry criteria, monitoring, and outcome prediction. The rapid implementation of our therapeutic hypothermia program was facilitated well due to the

Table 6. Clinical course, short-term outcomes, and complications

Variable		Results
Hypotension, n (%)		85 (66)
Vasopressor support, n (%)		77 (60)
Nitric oxide, n (%)		7 (5)
Acute kidney injury, n (%)	Any acute kidney injury	20 (16)
	Stage I	12 (60)
	Stage II	4 (20)
	Stage III	4 (20)
Thrombocytopenia, n (%)		61 (48)
Coagulopathy, n (%)	Evidence of hemorrhagic dyscrasia	30 (23)
	Prothrombin time or activated partial thromboplastin time > 2x normal range	21 (16)
Exclusive oral feeding at day 14 in the surviving group, n (%)		40 (37)
Seizures, n (%)		38 (30)
Length of stay (days), median (range)		14 (7-51)
Death, n (%)		21 (16)

close relationship between the members of our team and Dr. Dennis Azzopardi, who gave personal support to our protocol implementation.

To our knowledge, this is the first large report of therapeutic hypothermia use in Portugal, reflecting our extensive experience in this technique. As we gained more experienced using therapeutic hypothermia, we dealt with the difficult decision of not offering therapeutic hypothermia to patients who did not fulfill the original entry criteria, but that we felt could benefit from this approach, including late preterm infants,[29,30] infants admitted later than 6 hours of life[31], and term infants with unexpected postanal collapse.[32] For those patients, we obtained parental informed consent before initiating therapeutic hypothermia.

A few other categories of patients were treated with therapeutic hypothermia elsewhere, including newborns with stroke, but we did not treat infants with those situations at our unit.[33]

Continuous research is ongoing on additional categories of patients to be treated with therapeutic hypothermia,[34] but extra care should be taken when unequivocal evidence derived from large randomized controlled trials or meta-analysis is not present.[35]

The complications that occurred in our cohort were similar to the ones reported in previous studies. In the therapeutic hypothermia randomized trials, short-term adverse events were transient, and the infants did not present long term related outcomes.[1,3-8] For late preterm infants, the major concern is due to the potential greater susceptibility to the adverse effects of hypothermia.[29,30] However, in our study, we did not find greater susceptibility in this specific population, but conclusions cannot be drawn given the low number of late preterms treated. We evaluated the incidence of acute kidney injury using modified AKIN criteria in asphyxiated newborns undergoing therapeutic hypothermia and report an incidence of 23% in this patient population, which was lower than the one reported in other studies using the same criteria (38%-39%).[36,37]

In our center, neuromonitoring includes clinical neurological examination, continuous aEEG and brain MRI. Quantifying the extent of brain injury in these infants is important for objective and accurate early outcome definition and guiding decisions on the redirection of care.[38-42] Unfortunately, due to organizational end geographical issues, we were unable to implement a uniform follow-up protocol for our therapeutic hypothermia patients and, therefore, we are unable to present quantified outcomes for our cohort.

Nevertheless, we based our expected outcomes on robust evidence available in the medical literature relating aEEG and MRI patterns to clinical outcomes.[40] Our expected outcome was considered to be adverse in 28% of the survivors, including patients treated outside recommended criteria, that tend to have higher mortality and worse outcome. Compared with the data available in the 2013 Cochrane review, showing that 22% of the survivors presented a major neurodevelopmental disability (using Bayley scales of infant development), our patients are expected to present worse results, regarding the long-term neurodevelopmental outcome.[1] Our mortality rate was 16%, which is lower than that found in other series.[1,3-8,41-44] These results may reflect a cultural difference between our country and other European centers. In Portugal, the redirection of care of severely affected infants is still a very difficult decision for most doctors, which may lead to lower mortality at the cost of increased incidence of neurodevelopmental issues in these patients.

Due to various reasons, we are unable to report the outcome on this cohort. We hope that we will be able to report the long-term follow-up data at 6-7 late on, as that data is of paramount importance to audit the quality of our therapeutic hypothermia program.

A national register would be important to achieve and maintain high homogeneous and nationwide standards of care based on national guidelines, agreed among the five neonatal intensive care units in Portugal that have therapeutic hypothermia programs.

WHAT THIS CASE REPORT ADDS

- This is the first report of the clinical use of therapeutic hypothermia in newborns in our country.
- The effectiveness of therapeutic hypothermia was confirmed in our population.
- The safety profile of therapeutic hypothermia was confirmed in our population.
- The inclusion of some infants outside the classic criteria is debatable, but may be the only approach that can improve outcome for survivors in those groups (late preterm, postnatal collapse, newborns admitted after six hours).

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

Funding Sources

There were no external funding sources for the realization of this paper.

Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Provenance and peer review

Not commissioned; externally peer reviewed

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

Acknowledgements

The authors thank Dr. Denis Azzopardi for his help in implementation of the therapeutic hypothermia program and on counselling about specific management of the earlier patients, which was of paramount importance for the success of our therapeutic hypothermia program.

References

1. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev 2013;1:CD003311. doi: 10.1002/14651858.CD003311.pub3.

2. Volpe JJ. Neurology of the newborn. 5th ed. Philadelphia: Saunders; 2008

3. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med 2005;353:1574-84. doi: 10.1056/NEJMcps050929.

4. Shankaran S, Pappas A, McDonald SA, Vohr BR, Hintz SR, Yolton K, et al. Childhood outcomes after hypothermia for neonatal encephalopathy. N Engl J Med 2012;366:2085-92. doi: 10.1056/NEJMoa1112066.

5. Azzopardi D, Strohm B, Marlow N, rocklehurst P, Deierl A, Eddama O, et al. Effects of hypothermia for perinatal asphyxia on childhood outcomes. N Engl J Med 2014;371:140-9. doi: 10.1056/NEJMoa1315788.

6. Edward AD, Brocklehurst P, Gunn AJ, Halliday H, Juszczak E, Levene M, et al. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: Synthesis and meta-analysis of trial data. BMJ 2010;340:c363. doi: 10.1136/bmj.c363.

7. Shankaran S. Therapeutic hypothermia for neonatal encephalopathy. Curr Treat Options Neurol 2012;14:608-19. doi: 10.1007/s11940-012-0200-y.

8. Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicenter randomised trial. Lancet 2005;365:663-70. doi: 10.1016/S0140-6736(05)17946-X.

9. Sampaio I, Graça AM, Moniz C. Hipotermia induzida na encefalopatia hipóxico-isquémica: Da evidência científica à implementação de um protocolo. Acta Pediatr Port 2010;41:184-90.

10. Sampaio I, Graça AM, Moniz C. Hipotermia induzida na encefalopatia hipoxico-isquemica: Experiência dos primeiros 18 meses. Acta Pediatr Port 2011;42:S32-3.

11. Walsh MC, Butler D, Schmidt JW. Report of a pilot study of cooling four preterm infants 32-35 weeks gestation with HIE. J Neonatal Perinatal Med 2015;8:47-51.

12. U.S National Library of Medicine. Premiee hypothermia for neonatal encephalopathy [accessed 28 February 2020]. Available at: https://www.clinicaltrials.gov

13. Kariholu U, Montaldo P, Markati T, Lally PJ, Pryce R, Teiserskas J, et al. Therapeutic hypothermia for mild neonatal encephalopathy: A systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 2020;105:225-8. doi: 10.1136/archdischild-2018-315711.

14. Becher JC, Bhushan SS, Lyon AJ. Unexpected collapse in apparently healthy newborns – a prospective national study of a missing cohort of neonatal deaths and near-death events. Arch Dis Child Fetal Neonatal Ed 2012;97:F30-4. doi: 10.1136/adc.2010.208736.

15. Chandrasekaran M, Chaban B, Montaldo P, Thayyil S. Predictive value of amplitude-integrated EEG (aEEG) after rescue hypothermic neuroprotection for hypoxic ischemic encephalopathy: A meta-analysis. J Perinatol 2017;37:684-9. doi: 10.1038/jp.2017.14.

16. Sampaio I, Graça A, Moniz C, Machado MC. Hipotermia induzida na encefalopatia hipóxico-isquémica: Experiência do serviço de neonatologia do Hospital de Santa Maria. Acta Pediatr Port 2012;43:183-9.

17. al Naqeeb N, Edwards AD, Cowan FM, Azzopardi D. Assessment of hypoxic-ischemic encefalopathy by amplitude-integrated electroencefalography. Pediatrics 1999;103:1263-71. doi: 10.1542/peds.103.6.1263.

18. Spitzmiller RE, Phillips T, Meinzen-Derr J, Hoath SB. Amplitude-integrated EEG is useful in predicting neurodevelopmental outcome in full-term infants with hypoxic-ischemic encephalopathy: A meta-analysis. J Child Neurol 2007;22:1069-78. doi: 10.1177/0883073807306258.

19. Thoresen M, Hellstrom-Westas L, Liu X, de Vries LS. Effect of hypothermia on amplitude-integrated electroencephalogram in infants with asphyxia. Pediatrics 2010;126:e131-9. doi: 10.1542/peds.2009-2938.

20. Hallberg B, Grossmann K, Bartocci M, Blennow M. The prognostic value of early aEEG in asphyxiated infants undergoing systemic hypothermia treatment. Acta Paediatr 2010;99:531-6. doi: 10.1111/j.1651-2227.2009.01653.x.

21. Azzopardi D. Predictive value of the amplitude integrated EEG in infants with hypoxic ischaemic encephalopathy: Data from a randomised trial of therapeutic hypothermia. Arch Dis Childhood Fetal Neonat Ed 2014;99:F80-2. doi: 10.1136/archdischild-2013-303710.

22. Rutherford M, Pennock J, Schwieso J, Cowan F, Dubowitz L. Hypoxic-ischaemic encephalopathy: early and late magnetic resonance imaging findings in relation to outcome. Arch Dis Child Fetal Neonatal Ed 1996;75:F145-51. doi: 10.1136/fn.75.3.f145.

23. Cheong JL, Coleman L, Hunt RW, Lee KJ, Doyle LW, Inder TE, et al. Prognostic utility of magnetic resonance imaging in neonatal hypoxic ischemic encephalopathy: Substudy of a

randomized trial. Arch Pediatr Adolesc Med 2015;166:634-40. doi: 10.1001/archpediatrics.2012.284.
24. Weeke LC, Groenendaal F, Mudigonda K, Blennow M, Lequin MH, Meiners LC, et al. A novel magnetic resonance imaging score predicts neurodevelopmental outcome after perinatal asphyxia and therapeutic hypothermia. J Pediatr 2018;192:33-40. doi: 10.1016/j.jpeds.2017.09.043.
25. Jetton JG, Askenazi DJ. Update on acute kidney injury in the neonate. Curr Opin Pediatr 2012;24:191-6. doi: 10.1097/MOP.0b013e32834f62d5.
26. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. Arch Neur 1976;33:696-705. doi: 10.1001/archneur.1976.00500100030012.
27. Martinez-Biarge M, Diez-Sebastian J, Kapellou O, Gindner D, Allsop J, Rutherford MA, et al. Predicting motor outcome and death in term hypoxic-ischemic encephalopathy. Neurology 2011;76:2055-61. doi: 10.1212/WNL.0b013e31821f442d.
28. Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med 2009;361:1349-58. doi: 10.1056/NEJMoa0900854.
29. Gopagondanahalli KR, Li J, Fahey MC, Hunt RW, Jenkin G, Miller SL, et al. Preterm hypoxic-ischemic encephalopathy. Front Pediatr 2016;4:114. doi: 10.3389/fped.2016.00114.
30. Galinsky R, Lear CA, Dean JM, Wassink G, Dhillon SK, Fraser M, et al. Complex interactions between hypoxia-ischemia and inflammation in preterm brain injury. Dev Med Child Neurol 2018;60:126-33. doi: 10.1111/dmcn.13629.
31. Laptook AR, Shankaran S, Tyson JE, Munoz B, Bell EF, Goldberg RN, et al. Effect of therapeutic hypothermia initiated after 6 hours of age on death or disability among newborns with hypoxic-ischemic encephalopathy: A randomized clinical trial. JAMA 2017;318:1550-60. doi: 10.1001/jama.2017.14972.
32. Monnelly V, Becher JC. Sudden unexpected postnatal collapse. Early Hum Dev 2018;126:28-31. doi: 10.1016/j.earlhumdev.2018.09.001.
33. Harbert MJ, Tam EW, Glass HC, Bonifacio SL, Haeusslein LA, Barkovich AJ, et al. Hypothermia is correlated with seizure absence in perinatal stroke. J Child Neurol 2011;26:1126-30. doi: 10.1177/0883073811408092.
34. Gancia P, Pomero G. Therapeutic hypothermia in the prevention of hypoxic-ischaemic encephalopathy: New categories to be enrolled. J Matern Neonatal Med 2012;25:94-6. doi: 10.3109/14767058.2012.715023.
35. Walløe L, Hjort NL, Thoresen M. Major concerns about late hypothermia study. Acta Paediatr 2019;108:588-9. doi: 10.1111/apa.14640.
36. Chock V, Frymoyer A, Yeh CG, Van Meurs KP. Renal saturation and acute kidney injury in neonates with hypoxic ischemic encephalopathy undergoing therapeutic hypothermia. J Pediatr 2018;200:232-9.e1. doi: 10.1016/j.jpeds.2018.04.076.
37. Selewsky DT, Jordan BK, Askenazi DJ, Dechert RE, Sarkar S. Acute kidney injury in asphyxiated newborns treated with therapeutic hypothermia. J Pediatr 2013;162:725-9.e1. doi: 10.1016/j.jpeds.2012.10.002.
38. Cheong JL, Coleman L,Hunt RW, Lee KJ, Doyle LW, Inder TE, et al. Prognostic utility of magnetic resonance imaging in neonatal hypoxic ischemic encephalopathy: Substudy of a randomized trial. Arch Pediatr Adolesc Med 2015;166:634-40.
39. Shankaran S, Barnes PD, Hintz SR, Laptook AR, Zaterka-Baxter KM, McDonald SA, et al. Brain injury following trial of hypothermia for neonatal hypoxic-ischaemic encephalopathy. Arch Dis Child Fetal Neonatal Ed 2012;97:F398-404. doi: 10.1136/archdischild-2011-301524.
40. Rutherford M, Ramenghi LA, Edwards AD, Brocklehurst P, Halliday H, Levene M, et al. Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic-ischaemic encephalopathy: A nested substudy of a randomised controlled trial. Lancet Neurol 2010;9:39-45. doi: 10.1016/S1474-4422(09)70295-9.
41. Li J, Funato M, Tamai H, Wada H, Nishihara M, Iwamoto H, et al. Predictors of neurological outcome in cooled neonates. Pediatr Int 2013;55:169-76. doi: 10.1111/ped.12008.
42. Ramos G, Brotschi B, Latal B, Bernet V, Wagner B, Hagmann C. Therapeutic hypothermia in term infants after perinatal encephalopathy: The last 5 years in Switzerland. Early Hum Dev 2013;89:159-64. doi: 10.1016/j.earlhumdev.2012.09.021.
43. Simbruner G, Mittal RA, Rohlmann F, Muche R. Systemic hypothermia after neonatal encephalopathy: Outcomes of neo.nEURO.network RCT. Pediatrics 2010;126:e771-8. doi: 10.1542/peds.2009-2441.
44. Azzopardi D, Brocklehurst P, Edwards D, Halliday H, Levene M, Thoresen M, et al. Whole body hypothermia for the treatment of perinatal asphyxia encephalopathy: A randomized controlled trial. BMC Pediatr 2008;8:17. doi: 10.1186/1471-2431-8-17.

Hipotermia Induzida na Encefalopatia Hipóxico-Isquémica: Experiência de 10 Anos

Resumo:

Introdução: A hipotermia terapêutica é o tratamento padrão para lesões cerebrais consequentes a hipóxia-isquemia perinatal em recém-nascidos de termo. A evidência acumulada de ensaios clínicos, revisões sistemáticas e experiência revela uma redução da mortalidade e alterações do neurodesenvolvimento a longo prazo. Os objetivos do presente estudo foram apresentar a experiência de 10 anos da unidade de cuidados intensivos neonatais pioneira no programa de hipotermia em Portugal, avaliar o uso de monitorização neurológica e descrever resultados de curto prazo e eventos adversos.

Métodos: Estudo observacional prospetivo de recém-nascidos submetidos a hipotermia terapêutica entre novembro de 2009 e outubro de 2019 numa unidade de cuidados intensivos neonatais de nível terciário. Foram coligidas variáveis clínicas da base de dados de hipotermia. Os resultados esperados foram calculados usando uma combinação de eletroencefalograma de amplitude integrada e imagens de ressonância magnética, de acordo com evidência robusta publicada.

Resultados: O estudo incluiu 128 recém-nascidos tratados, 91% nascidos noutros hospitais. A mediana da idade gestacional foi de 39 semanas, 91% dos recém-nascidos precisaram de reanimação avançada e 22% de reanimação prolongada (> 10 minutos). Na admissão, 60% tinham encefalopatia grave, 26% encefalopatia moderada e 14% encefalopatia leve. A complicação mais comum foi hipotensão, que afetou 66% dos recém-nascidos. Durante o internamento, 21 (16%) dos doentes faleceram. O resultado esperado foi favorável em 40%, intermédio em 32% e adverso em 28%.

Discussão: A eficácia e o perfil de segurança da hipotermia terapêutica foram confirmados na nossa população. No futuro, a criação de um registo nacional seria importante para atingir e manter padrões nacionais de atendimento e de cuidados homogéneos e elevados.

Palavras-Chave: Asfixia Neonatal/complicações; Hipotermia Induzida/métodos; Hipóxia-Isquemia Encefálica/diagnóstico por imagem; Hipóxia-Isquemia Encefálica/tratamento; Nascimento a Termo; Portugal; Recém-Nascido