

## Therapeutic hypothermia in neonatal hypoxic-ischemic encephalopathy: integrative review

*Hipotermia terapêutica na encefalopatia hipóxico-iscêmica neonatal: revisão integrativa*

*Hipotermia terapéutica en la encefalopatía hipóxico-iscémica neonatal: revisión integrativa*

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### ABSTRACT

**Objective:** to identify the evidence on safe use of therapeutic hypothermia in newborns. **Method:** integrative review of the literature, conducted between June and July of 2018, in electronic sources from the Virtual Health Library and PubMed, through the question: "What evidence can support nursing care aimed at reducing sequelae in newborns undergoing therapeutic hypothermia?". Analysis was conducted for nine selected articles, being eight from international literature and one from Brazilian national literature. **Results:** cooling should occur for 72 hours with mild hypothermia. Indications for inclusion in the protocol were: first six hours of life, gestational age greater than 35 weeks and acidosis in the first hour of life. Essential care includes hemodynamic monitoring, skin observation, rectal thermal control, Integrated Amplitude Electroencephalogram surveillance. **Conclusion:** the therapy has benefits, but its application depends on institutional protocol and team training focusing on potential complications.

**Descriptors:** Hypothermia, induced; hypoxia-ischemia, brain; infant, newborn; nursing; patient safety.

### RESUMO

**Objetivo:** identificar evidências acerca do uso seguro da hipotermia terapêutica em recém-nascidos. **Método:** revisão integrativa realizada entre junho e julho de 2018, em fontes eletrônicas da Biblioteca Virtual de Saúde e PubMed, por meio da pergunta: "Que evidências podem subsidiar o cuidado de enfermagem voltado para a redução de sequelas em recém-nascidos submetidos à hipotermia terapêutica?". Foram eleitos nove artigos para análise, sendo oito internacionais e um nacional. **Resultados:** o resfriamento deve acontecer por 72 horas, com hipotermia leve. As indicações para inclusão no protocolo foram: primeiras seis horas de vida, idade gestacional maior que 35 semanas e acidose na primeira hora de vida. São cuidados essenciais: monitoração hemodinâmica, observação da pele, controle térmico retal, vigilância do Eletroencefalograma de Amplitude Integrada. **Conclusão:** a terapêutica apresenta benefícios, porém sua aplicação depende de protocolo institucional e treinamento das equipes com foco nas potenciais complicações.

**Descritores:** Hipotermia induzida; encefalopatia hipóxico-iscêmica; recém-nascido; enfermagem; segurança do paciente.

### RESUMEN

**Objetivo:** identificar la evidencia sobre el uso seguro de la hipotermia terapéutica en recién nacidos. **Método:** revisión integradora de la literatura, realizada entre junio y julio de 2018, en fuentes electrónicas de la Biblioteca Virtual de Salud y PubMed, a través de la pregunta: "¿Qué evidencia puede apoyar la atención de enfermería dirigida a reducir las secuelas en los recién nacidos que sufren hipotermia terapéutica?". Se realizaron análisis para nueve artículos seleccionados, ocho de literatura internacional y uno de literatura nacional brasileña. **Resultados:** el enfriamiento debe ocurrir durante 72 horas con hipotermia leve. Las indicaciones para la inclusión en el protocolo fueron: primeras seis horas de vida, edad gestacional mayor de 35 semanas y acidosis en la primera hora de vida. El cuidado esencial incluye monitoreo hemodinámico, observación de la piel, control térmico rectal, vigilancia integrada de electroencefalograma de amplitud. **Conclusión:** la terapia tiene beneficios, pero su aplicación depende del protocolo institucional y del entrenamiento del equipo, enfocándose en posibles complicaciones.

**Descriptores:** Hipotermia inducida; hipoxia-isquemia encefálica; recién nacido; enfermería; seguridad del paciente.

## INTRODUCTION

Hypoxic-Ischemic Encephalopathy (HIE) is a manifestation secondary to asphyxia at birth, which raises neonatal morbidity and mortality indicators. About 60% of newborns (NBs) affected by this condition die and the vast majority have severe sequelae<sup>1</sup>.

In 2014, asphyxia/hypoxia was the third leading cause of mortality among NBs, whether on the first day or the first week of life. It was responsible for 18% and 15% of deaths in these periods, respectively<sup>2</sup>.

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HIE resulting from an injury to the fetus or NB occurs in two stages. In the first, the neonatal brain responds by converting to anaerobic metabolism. In the second phase of HIE, there is an accumulation of excitatory neurotransmitters and cell apoptosis. If the second phase begins, any brain injury is considered irreversible<sup>3,4</sup>.

The latency phase of the injury occurs between 6 to 15 hours after the hypoxic injury, allowing a phase of deterioration that leads to the definitive brain injury. This secondary phase can last for days and is characterized by the appearance of seizures, secondary cytotoxic edema, accumulation of excitatory cytotoxins, mitochondrial failure and cell death. It is in this latency phase, before the start of irreversible secondary deterioration (called "therapeutic window"), that it is possible to interrupt the process of neuronal injury and recovery of the penumbra zone through the application of therapeutic hypothermia (TH)<sup>4</sup>.

TH is a technique used for neuroprotection, through mechanisms to decrease cerebral metabolism, reduce cytotoxic cerebral edema, intracranial pressure and inhibition of cell apoptosis. It consists of subjecting the newborn to term or late preterm (from 36 weeks onwards) at a temperature of 33.5°C within the first 6 hours of life and, during 72 hours of cooling, reheat him slowly and progressively<sup>3,4</sup>.

The use of this technology is still incipient in Brazil, impacting low production on the subject. In international publications, the positive effects of TH stand out: the increase in NB survival and the decrease in neurological sequelae in asphyxiated NBs<sup>1</sup>. Thus, it is necessary to carry out more research on the topic at the national level, in order to contribute to the generation of evidence that can collaborate for improvements in the scope of health care, teaching and research.

The use of TH started approximately 200 years ago, where first reports on post-cardiopulmonary arrest (CPA) treatment are described, in experiments with canine animals<sup>5</sup>.

Due to operational/resource problems and complications such as infection and coagulopathy, the technique was not widely used. Thus, from the 90s, the use of TH returned to emergencies in CPA and in the Neonatal Intensive Care Unit (NICU) for the treatment of HIE<sup>6</sup>.

In view of the still incipient scenario of the use of hypothermia as a therapeutic tool in asphyxiated NBs, with this study we aim to identify the main evidence that can support nursing care aimed at reducing neurological sequelae in NBs undergoing TH.

## METHODOLOGY

It is an integrative literature review with a descriptive and exploratory approach. This method includes the analysis of relevant researches that support decision making and the improvement of clinical practice, thus enabling the synthesis of the state of knowledge of a given subject<sup>7</sup>. The construction of the integrative review followed six distinct stages, which are: First stage - identification of the theme and selection of the hypothesis or research question for the elaboration of the integrative review; Second stage - establishment of criteria for inclusion and exclusion of studies/sampling or literature search; Third stage - definition of the information to be extracted from the selected studies/categorization of the studies; Fourth stage - evaluation of the studies included in the integrative review; Fifth stage - interpretation of results; Sixth stage- presentation of the knowledge review/synthesis.

The search was carried out in June and July 2018, in the electronic sources of the Virtual Health Library (VHL) and Pubmed, being used as descriptors (DeCS): "hypoxic-ischemic encephalopathy", "induced hypothermia", "newborn" and "nursing". English correspondents from the National Library's *Medical Subject Headings* (MeSH) were also crossed: "Hypothermia, Induced", "Encephalopathy", "Hypoxic Ischemic", "Newborn"; and "Nursing". The descriptors were combined in pairs and trios, using the Boolean AND operator.

The inclusion criteria were: articles available in full and *online*, published in Portuguese, English and Spanish. The target audience aged 0 to 28 days and the period between 2014 to 2018 was used as a filter. The research question, based on the PICO<sup>8</sup> strategy, was the following: "What evidence may support nursing care aimed at reducing sequelae in newborns undergoing TH?". Thus, it was considered: P (patient) = NB; I (intervention) = Therapeutic Hypothermia; C (Context) = Care strategies and O (outcome) = reduction of neurological sequelae. Repeated articles, incomplete texts, theses, dissertations and articles that did not answer the research question were excluded.

The search captured 1,769 publications and, after applying the inclusion, eligibility and exclusion criteria, 9 (nine) studies were selected for analysis. The articles were obtained in full for categorization, evaluation and synthesis of the studies, as provided in the Selection Diagram, as shown in figure 1.

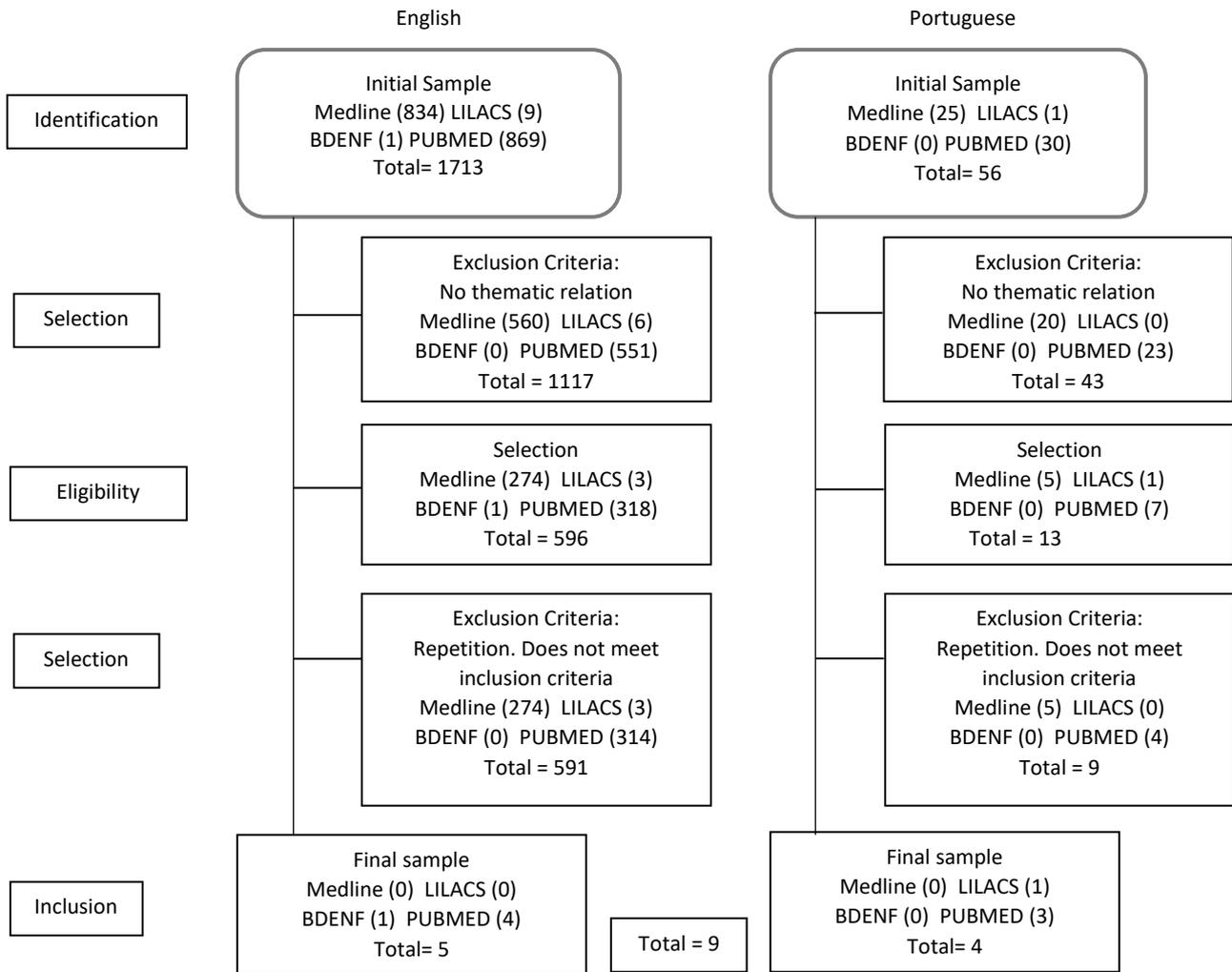


FIGURE 1: Diagrama de seleção dos estudos de acordo com Fluxograma de PRISMA<sup>9</sup>. Rio de Janeiro- RJ, Brasil, 2018.

## RESULTS AND DISCUSSION

The articles selected for review are shown in Figure 2. Of the 09 studies, 08 were found in international magazines and 01 in a national magazine. Of the selected studies, 06 were in the medical category and 03 in the nursing category. There is a tendency for North American publications (05) followed by Canadians (02) and only a Brazilian production.

The articles present the clinical bases that underlie TH. In short, we can say that the therapy consists of interrupting the evolution of the brain injury process induced by ischemia. In the initial phase of the lesion neuronal necrosis occurs due to hypoxia and, after resuscitation and reperfusion of the central nervous system, there is a latency period of up to 6 hours, followed by the late phase, characterized by neuronal apoptosis<sup>6</sup>.

The technique consists of lowering the core temperature between 33 to 34°C during a 72h period in order to reduce neurological sequelae and improve the prognosis in asphyxiated babies<sup>10,11</sup>.

Two randomized controlled clinical trials, one American and one Canadian, were conducted showing TH as a clinically viable strategy to minimize brain damage and mortality in newborns after acute asphyxia that evolve with moderate to severe HIE<sup>1,12</sup>.

It is recommended to carry out TH using proper equipment with the use of a thermal blanket and/or appropriate vest for neonatal clients. However, in the absence of servo-controlled cooling equipment, passive cooling by exposing

the naked NB to a radiant heat unit turned off, associated with the use of cold compresses or ice packs is an option. This alternative can be used up to six hours after the event and until the newborn is able to be transferred to a reference center in TH<sup>1,12</sup>.

Title	Ref	Estima	Qualis	Year	Country	Sample
Effect of depth and duration of cooling on deaths in the NICU among neonates with hypoxic ischemic encephalopathy: a randomized clinical trial	1	JAMA	A1	2014	Canada	364 randomized NBs. 185 for 72 hours and 179 for 120 hours of TH.
Electroencephalography Interpretation during therapeutic hypothermia: an educational program and novel teaching <sup>(c)</sup>	3	Neonatal Network/Journal of Neonatal Nursing	B3	2016	EUA <sup>(b)</sup>	13 studies: 1 meta-analysis, 5 randomized clinical trials, 1 control, 3 systematic reviews.
Cooling for newborns with hypoxic-ischemic encephalopathy <sup>(c)</sup>	4	REUOL	B2	2016	Brasil	Systematic Review
Obstetric antecedents to body-cooling treatment of the newborn infant	10	Am J Obst Gynecol	A1	2014	EUA <sup>(b)</sup>	98 children submitted to TH.
Effect of therapeutic hypothermia initiated after 6 hours of age on death or disability among newborns with hypoxic-ischemic encephalopathy arandomized clinical trial	11	JAMA	A1	2017	Canada	168 children 83 who received treatment with TH and 85 standard.
Effect of therapeutic hypothermia initiated after 6 hours of age on death or disability among newborns with hypoxic-ischemic encephalopathy arandomized clinical trial	12	JAMA	A1	2017	Canada	168 children 83 who received treatment with TH and 85 standard.
Neuroprotección en pacientes con asfixia perinatal	13	Arch Pediatr Urug	B5	2016	Uruguai	20 NBs submitted to TH.
The use of whole bodycooling in the treatment of hypoxic-ischemic encephalopathy. <sup>(c)</sup>	14	Neonatal Network/Journal of Neonatal Nursing	B3	2017	EUA <sup>(b)</sup>	44 primary studies, review, meta-analyzes and book chapters.
Predictive value of amplitude-integrated EEG (aEEG) after rescue hypothermic neuroprotection for hypoxic ischemic encephalopathy: a meta-analysis.	18	Journal of Perinatology	B1	2017	EUA <sup>(b)</sup>	9 meta-analysis studies.

**Legend:** <sup>(a)</sup>Ref. – reference, <sup>(b)</sup>USA- United States of America, <sup>(c)</sup>Nursing Publication

**FIGURE 2:** Table showing the publications included in the study, in chronological order of publication. Rio de Janeiro-RJ, Brasil, 2018

There are two equally effective techniques for body cooling: selective head hypothermia with temperatures reduced to 34.5°C and total body hypothermia with temperatures reduced to 33.5°C for 72 hours. However, regardless of the technique used, the reheating phase should be slow and gradual, over 4 to 5 hours, with an increase of 0.5°C per hour until reaching a temperature of 36.5°C. This recommendation aims to avoid complications from sudden rewarming after hypothermia. It is noteworthy that abrupt fluctuations in cerebral blood flow are associated with cerebral hemorrhage<sup>11,12</sup>.

All studies used mild hypothermia and the criteria for inclusion of newborns with HIE differed in terms of gestational age at  $\geq 35$  and  $\geq 36$  weeks.

Core temperature control is indicated by means of a rectal thermometer, which must be inserted from 5 to 6cm<sup>1,12</sup>. A study indicates the use of an esophageal thermometer with a temperature of 33.5°C (33-34°C)<sup>11</sup>.

The control of mild hypothermia by means of a central thermometer to effectively interrupt the evolution of the brain injury process induced by ischemia is essential, since large variations in temperatures can trigger new neurological injuries in the newborn.

Three studies<sup>1,12,13</sup> highlight recommendations inherent to the procedure: first 6 hours of life for gestational age (GA)  $\geq 35$  weeks, with moderate or severe HIE defined by Thompson score  $\geq 8$ , with an Apgar score  $\leq 5$  in the 10th minute of life, need for resuscitation at 10 minutes of life and/or acidosis in the first hour of life, with pH  $< 7.0$  or baseline deficit of 16 or more within 60 minutes after birth and do not weight  $< 1800$ g or congenital malformations incompatible with life.

Another randomized study showed that more intense cooling (32.0°C) or longer cooling duration (120 hours) compared to hypothermia at 33.5°C for 72 hours did not reduce NICU mortality, thus indicating the need for further clinical research<sup>11</sup>.

The TOBY<sup>12</sup> study, multicentre and randomized, carried out with 325 NBs registered in several hospitals in the United Kingdom aimed to monitor them up to 18 months of age in order to evaluate the late benefits of therapeutic hypothermia in childhood. It concluded that although the reduction in the combined rate of death and severe disability was not significant among babies which were submitted to cooling or not (RR: 0.86 [95% CI 0.68-1.07];  $p = 0.17$ ), cooled babies had an increased survival rate without neurological abnormalities (RR 1.57 [95% CI 1.16-2.12];  $p = 0.003$ ). At 18 months of follow-up, of the 325 newborns recruited, 44% survived without neurological abnormalities compared to 28% in the group which was not cooled<sup>12</sup>.

Regarding long-term brain protection, studies are still scarce. Results of the first clinical trials of total body hypothermia for HIE among 6 to 7-year-old patients have recently been reported. The data show a decrease in mortality and a better result of neurodevelopment in childhood in the cooled group<sup>12</sup>.

An American retrospective cohort<sup>10</sup> sought to assess obstetric history of newborns undergoing therapeutic hypothermia, showing maternal age of 15 years old or less, low parity, diabetes, pre-eclampsia, induction, epidural analgesia and chorioamnionitis as associated factors. This study shows a direct relation of maternal history in the incidence of complications in childbirth and birth such as perinatal asphyxia.

Cooling the entire body has physiological effects on other systems. Some of these effects are beneficial, while others can complicate the hemodynamic condition of the newborn undergoing cooling. A study found cardiovascular, respiratory, metabolic, hematological and dermatological effects<sup>14-15</sup>.

In this sense, among the complications inherent to the treatment, the following stand out: arrhythmias, bradycardia (FC  $< 80$ bpm), hypotension (PAM 40mmHg), thrombocytopenia, inhibition of coagulation factors, intracranial hemorrhage, anemia, leukopenia, hypoglycemia, hypocalcemia, oliguria and pulmonary hypertension. Hypoxic insult and hypothermia also cause vasoconstriction and can lead to degradation and necrosis of the skin and subcutaneous tissue<sup>1,11</sup>.

Dermatological effects are noted in newborns treated with whole body cooling. The body tries to conserve heat by responding to therapy with peripheral vasoconstriction. Hypoxic insult also causes vasoconstriction, the diversion of blood from the skin to the vital organs. This vasoconstriction causes decreased tissue perfusion and can lead to skin degradation. In rare cases, decreased tissue perfusion may result in necrosis of subcutaneous fat. Subcutaneous fatty necrosis occurs more frequently due to cooling down<sup>16</sup>.

Descriptive study carried out in Colombia showed the occurrence of seizures and stridor among NB submitted to TH<sup>15</sup>. In this study, of the 34 neonates submitted to TH, 12 (35.3%) had stridor. Stridor cases in patients without airway manipulation suggest that it is not exclusively due to an inflammatory process, but is secondary to changes in the physiological conditions of the airways due to changes in central temperature and water redistribution<sup>15</sup>.

The multidisciplinary exchange in an NICU can significantly contribute to the quality and safety of care for asphyxial NBs, since they are vulnerable and susceptible to health problems, mainly because they present the risk of compromising vital organs after HIE. Nursing care aimed at preventing HT-related incidents can be considered a goal of care and contributes to the safety of newborns in the NICU.

For the application of the TH technique in newborns with HIE, it is recommended that NICUs that do not yet have an established protocol, establish and implement clearly defined protocols similar to those used in randomized, published clinical trials and in facilities with the capacity for multidisciplinary care and longitudinal monitoring<sup>17</sup>.

In this perspective, a North American study<sup>3</sup> created an educational program and a new teaching tool for the interpretation of the Integrated Amplitude Electroencephalogram (aEEG) seeking to provide nurses with evidence based on justification for the use of the interpretation of the exam during TH. The aEEG is a brain function monitor that compresses time, rectifies and filters the conventional electroencephalogram (cEEG)<sup>18</sup>, where it can be viewed and interpreted by the professional on the bedside. Monitoring is an important complement in predicting long-term neurological outcomes for babies with HIE. The use of aEEG allows the professional to identify seizure activity, which is not always recognized by visual assessment<sup>16</sup>.

## CONCLUSIONS

AHT é indicada nas primeiras 6 horas de vida; entretanto, novos estudos estão avaliando RN submetidos à hipotermia iniciada entre 6 e 24 horas após o nascimento. Os resultados têm demonstrado que pode ser benéfica, mas ainda há incertezas quanto à sua eficácia.

Conclui-se que, apesar dos riscos, a HT apresenta substanciais benefícios. Contudo, a aplicação do protocolo de hipotermia terapêutica no RN com EHI com segurança exige meses de treinamento da equipe multidisciplinar, com ênfase na compreensão do comprometimento multisistêmico que envolve a asfixia perinatal, associado às potenciais complicações inerentes à essa modalidade de tratamento.

Como assistência de enfermagem podemos destacar a importância da monitoração hemodinâmica do RN em HT, o controle térmico retal, observação da pele e a vigilância do Eletroencefalograma de Amplitude Integrada para captação de atividade convulsiva precoce.

O estudo apresenta como limitação a busca nas fontes de dados selecionadas, podendo haver estudos mais recentes em outras fontes de informação não apresentadas nesta revisão. Recomenda-se, assim, a ampliação da busca e novos estudos que possam conferir um corpo mais robusto de conhecimentos que garanta a utilização de diretrizes clínicas seguras em unidades neonatais.

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