v. 3, n. 41, 2023

International Journal of Health Science

USE OF THERAPEUTIC HYPOTHERMIA IN NEONATES WITH HYPOXIC ISCHEMIC ENCEPHALOPATHY: A LITERATURE REVIEW

Vinícius Schneider
Centro Universitário de Brusque, Brusque, Santa Catarina, Brazil.

Alison Losi Francisco
Centro Universitário de Brusque, Brusque, Santa Catarina, Brazil.

Larissa Gamba
Centro Universitário de Brusque, Brusque, Santa Catarina, Brazil.

Ana Sophia Petry Strobel
Universidade do Sul de Santa Catarina, Palhoça, Santa Catarina, Brazil.

Barbara Antônia Dups Talah
Pontifícia Universidade Católica do Paraná, Curitiba, Paraná, Brazil.

Davi Eduardo Simioni
Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil.

Natália de Souza
Centro Universitário Anhanguera de Marabá, Marabá, Pará, Brazil.

Sabrina de Araújo Nicoletti
Universidade de Gurupi (UNIRG), Paraíso do Tocantins, Tocantins, Brazil.

Bruno Augusto Lopes
Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Rio de Janeiro, Brazil.

Abstract: Objectives: Expose basic concepts of the existing literature on induced hypothermia in newborns who evolved with hypoxic-ischemic encephalopathy. Methods: A narrative literature review was carried out based on 22 articles, from February to April 2023, prioritizing articles published in the last 5 years. The articles were taken from the Lilacs, Pubmed, Scielo, Embase and Scopus databases. **Results**: Hypoxic-ischemic encephalopathy (HIE) consists of a series of cellular and molecular alterations resulting from a severe anoxic brain injury that occurred in the neonatal period. Current research reveals that even the condition in its mild form is not benign. Therapeutic Hypothermia (TH) is the most effective technique indicated for the management of newborns (NB) admitted to the Neonatal Intensive Care Unit (NICU) who present neuropathies secondary to asphyxia, accompanied by clinical signs of Hypoxic-Ischemic Encephalopathy. The therapy consists of exposing the newborn at term or late preterm to a temperature of 33.5º C from the first 6 hours of life and, over 72 hours of cooling, gradually rewarming the patient. Total body hypothermia, when compared with the control group to identify the outcome of neurological abnormalities, contributed to a 17% reduction. Concomitantly with these data, found at 18 months of age, there was also a 21% reduction in the risk of cerebral palsy and a 22% reduction in moderate or severe disability. **Conclusion**: It has been shown that induced hypothermia can be effective in reducing mortality and neurodevelopmental failures in these newborns.
Keywords: "induced hypothermia", "newborn" and "hypoxic-ischemic encephalopathy".

INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE) consists of a series of complex cellular and molecular physiological alterations as a result

of a severe anoxic brain injury occurring in the neonatal period (1). Initially, this condition presents with low APGAR, acidosis, seizures, changes in consciousness, respiratory failure, muscle hypotonia, metabolic disorders, among other signs and symptoms. In the long term, intellectual impairment, attention deficit, cerebral palsy, epilepsy, behavioral disorders, among others, may be noticed. The condition has variable severity, and may vary from the absence of neurological symptoms to the patient's death (2).

Acute hypoxic-ischemic encephalopathy at birth is a leading cause of death and disability throughout life and accounts for up to 23% of neonatal deaths worldwide (3). The incidence of newborns (NB) with HIE is 2-3 per 1,000 live births (4), with low- and middle-income countries having the highest occurrence of HIE, which is responsible for approximately one million deaths annually (4). Among the most common causes of HIE are placental abruption, umbilical cord prolapse and uterine rupture (5).

Studies carried out in the 1980s and 1990s showed that mild HIE did not result in neurological impairments. However, current research reveals that even the condition in its mild form is not benign and exposes infants to the risk of later ranking lower on the Intelligence Quotient (IQ) scale. Furthermore, it can contribute to changes in verbal development and performance at 5 years of age, in addition to problems in social behavior and memory between 8-10 years of age, including the need for educational support at school (6).

Hypoxemia in the brain was associated with an elevation in body temperature, probably caused by an increased metabolic demand and by inflammatory cytokines released after ischemic injury. Thus, it was found that regulating core body temperature by 1°C reflects a 6% to 10% decrease in the body's metabolic demands. This data shows that measures that reduce markers of oxidative stress, inflammation and cell apoptosis, such as HIE, have good relevance and prognosis in asphyxiated newborns (4).

Therapeutic hypothermia aims at neuroprotection against disorders of decreased brain metabolism, cytotoxic cerebral edema, intracranial pressure and inhibition of cell apoptosis. The therapy consists of exposing the newborn (NB) at term or late preterm (from 36 weeks) to a temperature of 33.5º C from the first 6 hours of life and, during the 72 hours of cooling, rewarm the patient slowly and gradually (7). Added to this, today there are several researches in search of new compounds that have effective use together with induced hypothermia (8).

Due to perinatal ischemic hypoxic brain damage, 62% of infants die or have moderate to severe disabilities between the ages of 18 and 22 months. The application of HI reduces this rate to 41% (4). As for mortality, the relative risk was approximately 26% lower when compared to newborns who did not have cooling therapy (6). Thus, the present study aims to expose basic concepts of the existing literature on induced hypothermia in newborns who evolved with hypoxic-ischemic encephalopathy.

METHODOLOGY

A narrative literature review was carried out based on 22 articles, from February to April 2023, prioritizing articles published in the last 5 years. The articles covered the Portuguese, English and Spanish languages, and were taken from the Lilacs, Pubmed, Scielo, Embase and Scopus databases. The descriptors used were "induced hypothermia", "newborn" and "hypoxic-ischemic encephalopathy".

RESULTS

DEFINITION AND ETIOLOGIES

Hypoxic-ischemic encephalopathy (HIE) is a neurological disorder that originates from perinatal asphyxia (9). As a consequence, there is oxygen deficit in brain cells, which can result in severe injuries (10). Moreover, these injuries may be associated with other metabolic alterations, generating serious metabolic and physiological disorders in the newborn (11). Neonatal encephalopathy syndrome presents itself as a condition in which there are neurological deficits that appear in the first days of life. Symptoms include difficulty breathing, reduced muscle tone and reflexes, lowered level of consciousness and seizures (12).

HIE is still one of the main causes of morbidity and mortality in newborns worldwide. In low- and middle-income countries, it affects about 20 out of every 1,000 live births, resulting in approximately 1 million deaths annually. Therefore, it can be considered a critical public and social health problem. Regardless of improvements in perinatal care in developed countries, the incidence of HIE remains high (9). The numbers about this disease indicate that hypoxic-ischemic episodes that occur before birth are around 20%, those that occur in the intrapartum period reach 30% of cases, those that appear before and during childbirth add up to 35% and only 10% of cases occur after the birth of the neonate (13).

Hypoxic-ischemic encephalopathy can be caused by maternal complications such as uterine rupture, placental abruption, maternal hypotension and hypoxemia, and severe maternal-fetal hemorrhage. The mode of delivery is also a risk factor. Examples include the use of forceps, cesarean delivery, and even vaginal delivery. The occurrence of HIE after birth can also have different origins, such as necrotizing enterocolitis, pneumonia, sepsis and bronchopulmonary dysplasia (13).

PATHOPHYSIOLOGY

The pathophysiology of HIE can be divided into 3 phases. In the first phase, due to the unavailability of oxygen in the first 6 hours, the cerebral anaerobic metabolism begins with an increase in lactate, free radicals and cerebral edema. In a second moment, between 6 and 72 hours, there is an increase in excitatory neurotransmitters and apoptosis. Finally, the chronic inflammation phase occurs 72 hours after the onset of the hypoxic-ischemic event, with repair or brain injury. Furthermore, harmful cytokines can lead to the formation of damaged axons, synapses and neurons in cases of extensive injuries (13).

THE THERAPEUTIC HYPOTHERMIA

Therapeutic Hypothermia (TH) is the most effective technique indicated for the management of newborns (NB) admitted to the Neonatal Intensive Care Unit (NICU) who have neuropathies secondary to asphyxia, which is accompanied by clinical signs of Hypoxic- Ischemic (3, 13, 14, 15). This procedure had its first applications reported 200 years ago through experiments on animals undergoing cardiac arrest (CRA), however it was not widely adhered to at the time due to complications such as infections, lack of resources and coagulopathies (3).

From 1930 onwards, narratives of its use in clinical trials returned, in which it was highly successful. In 1965, HT ended up being promoted to formal indication in international procedures for major brain injuries and Lowering of the Level of Consciousness (RNC) (11). In the 90's, TH had already become a routine procedure in the Emergency Departments (ED) for CA and in the NICU for HIE (3). However, in the Brazilian hospital setting, the HT recommendation only became a reality in 2012 (11).

Currently, the NB under suspicion of HIE must be subjected to constant monitoring in the ICU, especially through Electroencephalogram (EEG) and Magnetic Resonance Imaging (MRI). Together with laboratory tests, they provide the necessary evidence to prove the diagnostic hypothesis, which is essential for starting treatment (16). Monitoring during therapy is also recommended via the use of a rectal thermometer, due to the risk of seizures in 50% and intracranial hemorrhage in 38% of cases (3, 11, 15, 16, 17).

Treatment with Therapeutic Hypothermia consists of suppressing the inflammatory elements arising from hypoxia that lead to activation of the coagulation cascade that causes ischemia (3, 11, 13, 14, 15, 16). This technique is applied 6 hours after delivery, during the latency period of EIH, when blood flow returns to the affected region (13, 18, 19). Therefore, this is the ideal moment for interference and interruption of the neuropathological process within the objective of recovering the patient's penumbra zone, since there has not yet been a complete depletion of the cellular metabolism of blood hypoperfusion (3, 11, 13, 18).

The success of this event is registered at RM. In particular, there is a promising recovery from lesions involving the Thalamus and Basal Ganglia, which are the most frequent sequelae in non-premature NBs, due to the selective nature of their neuronal necrosis for the cortical region, while in premature NBs there is a predisposition to demyelination of the substance white (13, 15, 16).

HT is divided into 3 main stages: passive hypothermia, cooling and warming. The passive hypothermia step is a measure of preparation for the next phase. It occurs in cases where the NB presents clinical signs that indicate the demand for treatment in the first 10 minutes of life or when there is a need to wait for tertiary care. This phase allows for the removal of heat sources around the neonate, such as clothing and blankets, in addition to turning off the radiant heat crib in the delivery room or heated incubator in the NICU. The NB only wears diapers so that there is a natural loss of heat until the incubator is ready to start the next phase, and the waiting time varies according to the availability of the equipment (18, 19).

Then, the Hypothermia stage itself occurs in the 6th hour of life, providing a slight cooling of the patient's body within the change range of 0.5°C per hour until reaching 33.5°C, which is the temperature maintained for the next 72 hours. hours (3, 11, 15, 16, 17, 20). This procedure can be applied using 2 modalities: localized hypothermia of the head and total body (3, 13, 14). These methods are distinguished by factors related to the maximum temperature and the body territory affected by the therapy.

Head-focused hypothermia turns out to be a more limited option both in terms of temperature, which operates up to 34.5° C, and in territory restricted to the cerebral cortex (3, 11, 13, 15, 19). At first, it may seem disadvantageous, but there is currently a debate about the implementation of this modality in newborns that do not fit the selection criteria consistent with gestational age (GA) greater than 35 weeks, to avoid systemic effects, which are harmful to the these premature neonates (3, 11, 15, 17, 19).

On the other hand, total body hypothermia allows an extension of the temperature up to 33.5° C, being able to encompass also the white matter regions along with the rest of the fetal organism (3, 11, 13, 15, 18, 19, 20). Furthermore, this modality allows access for monitoring with the electroencephalogram, which is why it is more used in NICUs than hypothermia focused on the head (16, 17, 19).

The last stage is the warm-up, in which the

patient receives 0.5°C of heat per hour so that he slowly reaches a temperature of 36°C (3, 15, 17, 18, 20). This phase is monitored by the rectal thermometer for up to 24 hours after the completion of the process to ensure the safety of the NB (3, 11, 17, 18). This happens due to the exacerbated probability that the sudden variation in temperature carries to trigger episodes of severe hemorrhages due to vasodilation (3, 18). This way, it is possible to interrupt the process in the face of the appearance of prodromal signs and symptoms of this syndrome, as is the case of seizures that must be stopped before continuing the therapy (17).

Selection criteria for HT include gestational age greater than 35 weeks; weight greater than 1.8 kg; classification of moderate or severe EHI by Thompson score above 8 or Sarnat at stage greater than or equal to 2; indicators of acute perinatal distress marked at the 10th minute and 1st hour of life, where the first includes an APGAR greater than 5 or a convulsive event, while the second refers to an episode of acidosis defined by a pH lower than 7 or a base excess (BE) less than –10 (3, 11, 13, 14, 15, 16, 17, 19).

It is important to emphasize that the presentation of all the criteria for the introduction of the treatment is negligible. On the other hand, contraindications for HT are GA less than 35 weeks, weight less than 1,500 grams, carriers of expressive congenital or genetic abnormalities in which there is no ability to withstand aggressive therapy, and neonates with clinical signs of severe coagulopathy. However, as previously mentioned, it is possible to perform TH in these patients under specific restrictions and authorized consent of the family, affirming awareness of the precariousness of therapeutic success (17, 19).

The physiological and biochemical mechanism of neuroprotection carried out by TH is not fully ratified by the scientific community, although it is associated with a multifactorial pattern in which TH causes a reduction in metabolism, energy expenditure and release of free radicals, as previously discussed (13). Despite this, according to a cohort study published in Original Research Pediatrics in 2022, brain temperature and the MRI Apparent Diffusion Coefficient (ADC) in cortical regions have a directly proportional relationship during and after treatment with hypothermia in newborns with EHI, confirming a reduction in the kinetics of water molecules that accompanies the decrease in temperature (16).

OUTCOMES

Although HT is the main effective treatment for hypoxic-ischemic encephalopathy and its usefulness in neuroprotection has been confirmed, this strategy only reduces the absolute risk of death or severe disability in approximately 15% of cases. In order 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 (21).

Scholars have shown that the onset of TH between 6 and 12 hours after birth has neuroprotective effects in neonates with moderate HIE. Eleven randomized clinical trials of selective head and whole body cooling, initiated within 6 hours of birth, were performed involving 1505 newborns aged 35 weeks or older. From this, a reduction in mortality and in the risk of neurodevelopment failure was identified (22). Extending the procedure to 24 hours after birth may also have some therapeutic advantage (21).

Total body hypothermia, when compared with the control group to identify the outcome of neurological abnormalities, contributed

to a 17% reduction. Added to this, IQ scores equal to or greater than 85 increased by 13%. Concomitantly with these data, found at 18 months of age, there was also a 21% reduction in the risk of cerebral palsy and a 22% reduction in moderate or severe disability (22).

The complications that HIE can cause in the newborn are numerous and include functional alterations such as delay in motor development, cognitive and behavioral deficit, cerebral palsy, hyperactivity, among others (9). Disorders resulting from TH include arrhythmias, bradycardia (heart rate below 40 beats per minute), thrombocytopenia, inhibition of coagulation factors, intracranial hemorrhage, anemia, leukopenia, hypoglycemia, hypocalcemia, oliguria and pulmonary hypertension. In some cases, it can also lead to ischemic necrosis caused by hypoxia and hypothermia (7).

It is important to highlight that before the use of hypothermia as a therapeutic proposal, hypoxic-ischemic encephalopathy did not have any treatment protocol and/or therapeutic mediation. After the implementation, its use was limited to an attempt to mitigate worse damage and improve the prognosis, however, with the execution of the practice and obtaining positive results, it is noticed how HT is a therapy of great and favorable impact in cases of hypoxic-ischemic encephalopathy (1).

CONCLUSION

Induced hypothermia in newborns with HIE is a technique that aims to reduce the baby's body temperature for a few hours after birth in order to decrease brain damage caused by hypoxia during delivery. Newborns are selected based on gestational age, birth weight, Thompson classification, APGAR, pH, indicators of perinatal distress and the presence of a seizure event. It has been shown that induced hypothermia can be effective in reducing mortality and neurodevelopmental failures in these newborns. However, the technique is not risk-free and must be performed in a hospital environment with trained staff and adequate equipment to monitor the baby's temperature and health status.

It is worth mentioning that induced hypothermia can have side effects and complications, such as cardiac arrhythmias, respiratory and metabolic disorders. Also, it is not effective in all cases and may not completely reverse the brain damage caused by hypoxic-ischemic encephalopathy. It's not a cure for EHI, but it can help slow brain damage and improve long-term immune outcome in some cases. Thus, the present study has restrictions that may be complemented by future investigations, since the availability of experimental research with recognizable methodological quality, referring to the Brazilian reality in relation to this therapy, is extremely lacking.

REFERENCES

1. ABATE BB, et al. Effects of therapeutic hypothermia on death among asphyxiated neonates with hypoxic-ischemic encephalopathy: A systematic review and meta-analysis of randomized control trials. PLOS ONE, 2021; 16(2):1-20.

2. CÁNOVAS-AHEDO M, ALONSO-ALCONADA D. Terapia combinada frente a la encefalopatía hipóxico-isquémica neonatal. Anales de Pediatría, 2019; 91(1):59.e1-59.e7.

3. CONWAY JM, et al. Mild hypoxic ischaemic encephalopathy and long term neurodevelopmental outcome - A systematic review. Early human development, 2018; 120: 80-87.

4. CUNHA CR, et al. Hipotermia terapêutica em recém-nascidos com encefalopatia hipóxico-isquêmica: Revisão Integrativa. Revista da Sociedade Brasileira de Enfermeiros Pediatras, 2018; 18(1):37-42.

5. DAVIES A, et al. Can we further optimize therapeutic hypothermia for hypoxic-ischemic encephalopathy? Neural Regen Res., 2019; 14(10): 1678–1683.

6. FERREIRA BC, et al. Achados da ressonância magnética e desfechos neurológicos em recém-nascidos com Encefalopatia Hipóxico Isquêmica: revisão integrativa. Research, Society and Development, 2021; 10 (11): e356101119736.

7. GARCIA-ALIX A, et al. Ten years since the introduction of therapeutic hypothermia in neonates with perinatal hypoxic-ischaemic encephalopathy in Spain. Neurología, 2020; 22: 1-8.

8. GLASS HC. Hypoxic-Ischemic Encephalopathy and Other Neonatal Encephalopathies. Continuum, 2018; 24(1):57-71.

9. JESUS JHS, SANTOS PMM. Hipotermia terapêutica em recém-nascidos de unidades de terapia intensiva neonatal. Revista Eletrônica Atualiza Saúde, 2018; 7(7): 65-75.

10. LEITE PNM, et al. Hipotermia terapêutica na encefalopatia hipóxico-isquêmica neonatal: revisão integrativa. Revista Enfermagem UERJ, 2020; 28:1-7.

11. LEMYRE B, CHAU V. Hypothermia for newborns with hypoxic-ischemic encephalopathy. Paediatr Child Health, 2018; 23(4): 285–291.

12. MORAL Y, et al. Hipoxia-isquemia neonatal: bases celulares y moleculares del daño cerebral y modulación terapéutica de la neurogénesis. Revista de Neurología, 2019; 68(1): 23-36.

13. PAPAZIAN O. Encefalopatía hipóxica-isquémica neonatal. Medicina (Buenos Aires), 2018; 78(2):36-41.

14. PUGA GR, et al. Hipotermia terapêutica em recém nascidos com encefalopatia hipóxico isquêmica: Uma análise da primeira infância. Research, Society and Development, 2023; 12(2):, e16112240056.

15. RITSTOVSKA S, et al. Hypoxic Ischemic Encephalopathy (HIE) in term and preterm infants. PRILOZI, 2022; 43(1):77-84.

16. SAW CL, et al. Current Practice of Therapeutic Hypothermia for Mild Hypoxic Ischemic Encephalopathy. Journal of Child Neurology, 2019; 34(7):402-409.

17. SOUSA MTO, et al. Hipotermia terapêutica em neonatos: revisão narrativa. Revista Eletrônica Acervo Saúde, 2022; 15(9):1-8.

18. TORRES AR, et al. Factores predominantes de encefalopatía neonatal: hipoxia e isquemia, un problema global. Medicina (Buenos Aires), 2019; 79(3):15-19.

19. VALVASSORI BG, et al. Desfechos clínicos associados à hipotermia terapêutica em neonatos com encefalopatia hipóxico-isquêmica: uma revisão de metanálise. Revista UNILUS Ensino e Pesquisa, 2020. 17(48): 141-148.

20. WALAS W, et al. Methods for assessing the severity of perinatal asphyxia and early prognostic tools in neonates with hypoxic–ischemic encephalopathy treated with therapeutic hypothermia. Adv Clin Exp Med, 2020; 29(8):1011–1016.

21. WASSINK G, et al. Therapeutic Hypothermia in Neonatal Hypoxic-Ischemic Encephalopathy. Current Neurology and Neuroscience Reports, 2019; 19(2):1-10.

22. ZENOBI C, et al. Effects of Tissue Temperature and Injury on ADC during Therapeutic Hypothermia in Newborn Hypoxic-Ischemic Encephalopathy. American Journal of Neuroradiology, 2022; 43(3):462-467.