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IMPACT OF THERAPEUTIC HYPOTHERMIA IN THE TREATMENT OF NEONATAL ASPHYXIA: A SYSTEMATIC REVIEW OF CLINICAL AND NEUROLOGICAL OUTCOME

Luana Annicchino Cembranelli
Universidade Anhembi Morumbi (UAM)
Piracicaba - SP
https://orcid.org/0009-0001-3590-200X

Isadora de Paula Queiroz Barbosa
Universidad Nacional de Rosario (UNR)
Rosário - Argentina
https://orcid.org/0009-0003-9984-9759

Luiza Raquel Fernandes Silva Bucsky
Universidade Iguaçu - Campus V (UNIG)
Itaperuna - RJ
https://orcid.org/0009-0000-1208-8829

Carolina Telles de Sá Almeida
Universidade Cidade de São Paulo (UNICID)
São Paulo - SP
https://orcid.org/0009-0007-5088-3939

Elizandra Franciele Fernandes da Silva
Universidade do Oeste Paulista (UNOESTE)
Jaú - SP
https://orcid.org/0000-0003-1214-5496

Rebeca Rebouças Dias
Faculdade de Enfermagem Nova Esperança de Mossoró (FACENE), Mossoró - RN
https://orcid.org/0009-0001-1243-8806

Maria Luiza Ribeiro Pedrosa
Universidade de Itaúna(UIT)
Itaúna-MG
https://orcid.org/0009-0003-5830-6598

Ana Beatriz Guilherme Pupin
Centro Universitário Max Planck (UniMAX)
Indaiatuba - SP
https://orcid.org/0009-0000-1842-1856

Claudia Luiz Da Silva Teixeira Bastos
Faculdade Zarns - Medicina FTC
Salvador-BA
https://orcid.org/0000-0002-9960-9953

Mariana Araújo Coelho Saraiva de Sousa
Centro Universitário Uninovafapi (UNINOVAFAPI)
Teresina - PI
https://orcid.org/0009-0004-8668-1077

Isadora Amarys Cossa
Universidade São Francisco (USF)
Bragança Paulista - SP
https://orcid.org/0009-0006-6675-9820

Neidejany de Assunção do Sacramento
Universidad Nacional de Rosario (UNR)
Rosario - Argentina
https://orcid.org/0000-0001-7050-6697

Abstract: Objective: This study aims to analyze recent evidence on the efficacy, safety and impact of therapeutic hypothermia in the treatment of neonatal asphyxia, highlighting its effect on the clinical and neurological outcomes of newborns. Methodology: A bibliographic review was carried out using the PubMed database, with the descriptors "Perinatal asphyxia", "Neonatal hypoxic-ischemic encephalopathy" and "Birth hypoxia". Of the 461 articles initially found,14 were meticulously selected for detailed analysis. Results: The studies reviewed indicate that therapeutic hypothermia is an effective strategy for preventing hypoxic-ischemic encephalopathy in neonates. This therapy has been shown to significantly reduce adverse neurological events and mortality. Furthermore, factors were identified that can improve clinical interventions, substantially improving the prognosis for patients undergoing this therapy. Final considerations: Induced hypothermia is recognized as an essential preventive treatment for neonatal ischemic encephalopathy. However, the complexity of the topic requires additional studies to elucidate the long-term effects and develop more accurate prognostic tools that guarantee favorable clinical outcomes for this population.
Keywords: neonatal asphyxia; Newborn hypoxia; Therapeutic hypothermia.

INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE) is a serious condition that frequently occurs in the context of neonatal asphyxia and is a major cause of neonatal morbidity and mortality. Studies indicate an incidence of moderate to severe perinatal HIE of between 1 and 3 cases per 1,000 live births (Davies et al., 2019). The severity of this condition is evidenced by data showing that, of affected newborns, 15 to 20% die prematurely, and among survivors,

25 to 30% develop serious neurological complications (Ristovska, Stomnaroska, Danilovski, 2022).

Therapeutic cooling emerges as the main intervention available for the treatment of moderate to severe HIE in full-term newborns. This technique has been shown to significantly reduce mortality and brain damage associated with the condition (Davies et al., 2019). The mechanism by which therapeutic cooling exerts its protective effect involves attenuating the formation of free radicals and nitric oxide, reducing brain metabolism, and decreasing edema and inflammation, although specific details about these processes still require further clarification (Ristovska, Stomnaroska, Danilovski, 2022).

The relevance of early recognition and effective treatment of HIE is amplified by the long-term impact on affected children, who often face sequelae such as cerebral palsy, epilepsy, as well as cognitive and behavioral disabilities that affect their quality of life and social integration (Ristovska, Stomnaroska, Danilovski, 2022).

Recent European studies link the severe form of HIE to motor disorders and emotional problems, highlighting the complexity and severity of the disease's consequences (Hortigüela et al., 2024).

The diagnosis of HIE encompasses a combination of perinatal factors, including the need for resuscitation, neurological imaging, and biochemical markers. The most effective treatment involves combining therapeutic cooling with pharmacological therapies. Recently, inhalational gases such as xenon have been investigated as synergistic agents in treatment, due to their neuroprotective properties, which include the ability to block receptors involved in excitotoxicity (Tolaymat et al., 2020).

Given the persistence of this health problem, especially in developing countries where resources for obstetric care, monitoring, resuscitation and adequate treatment may be limited, it is essential to investigate and analyze the most recent evidence on the effectiveness, safety and impact of therapeutic hypothermia (Ristovska, Stomnaroska, Danilovski, 2022). Therefore, the objective of this study is to analyze the use of this therapy and its effects on the clinical and neurological outcomes of newborns, thus optimizing treatment practices and improving the chances of recovery and quality of life for these children.

METHODOLOGY

This study is a literature review structured according to the PVO approach, which defines Population or research problem, Variables and Outcome. The research was guided by the guiding question: "What is the role of therapeutic hypothermia in the treatment of neonatal asphyxia, and how is this approach influencing the clinical and neurodevelopmental outcomes of affected newborns?"

The searches were carried out in the PubMed - MEDLINE (Medical Literature Analysis and Retrieval System Online) database, using search terms in combination with the Boolean operators "AND" and "OR". This initial strategy identified 461 articles, of which, after a secondary analysis based on meticulously defined selection criteria, 45 articles were considered for further evaluation.

The inclusion criteria were: articles written in English or Spanish, published in the last five years, and that were available in full. Furthermore, articles must directly address topics related to the use of therapeutic hypothermia in the treatment of neonatal asphyxia and its consequences. Duplicate articles, those that did not directly correspond to the guiding question and objective of the study, as well as studies that did not meet the other inclusion criteria were excluded.

After applying the exclusion criteria, 14 articles were selected from the PubMed database to compose the collection of the present study. This careful selection allowed the creation of a comprehensive and updated review, focused on evaluating the clinical and neurodevelopmental impact of therapeutic hypothermia in neonates with asphyxia, offering a detailed view of current practices and their results.

DISCUSSION

MECHANISMS AND NEUROPROTECTIVE EFFECTS OF THERAPEUTIC HYPOTHERMIA

Birth asphyxia, a condition that causes oxygen deprivation in a newborn before and during birth, is a leading cause of hypoxic-ischemic encephalopathy. This brain injury, resulting from obstruction of oxygenated blood flow to the baby's brain, is one of the main causes of neonatal brain injury and global morbidity and mortality (Van BF et al., 2020).

Therapeutic hypothermia has been widely adopted as an effective treatment for hypoxic-ischemic encephalopathy (HIE), occurring in many experiments in both animals and humans (Wang, H. et al., 2012; Davies et al., 2019).). In developed countries, specialized body cooling devices are commonly used to treat neonates with HIE. These devices, although effective, are expensive and require regular maintenance, as well as generating recurring costs. In contrast, low-cost, labor-intensive cooling techniques can cause temperature fluctuations and shivering, potentially compromising the neuroprotective efficacy of the treatment (Higgins, RD et al., 2011). In developing countries, these devices are often unavailable or accessible to a very limited extent.

According to Packer, Hersh, Sargent and Caughey (2020), therapeutic hypothermia is defined as the reduction of body temperature by 3 to 4°C in the first six hours of life, maintained for 72 hours. Studies such as that by Wang et al. (2021) highlight the importance of classifying HIE between moderate and severe to determine whether the therapy is cost-effective. In cases of moderate HIE, treatment significantly reduces mortality and morbidity.

However, in cases of severe HIE, despite the reduction in mortality, there is no reduction in morbidity. Additionally, Abate et al. (2021) point out that cognitive impacts may not manifest themselves until adolescence, indicating the need for long-term follow-up after neonatal injury.

Zewdie et al. (2021) report a downward trend in the incidence of severe HIE in neonates, stabilizing at approximately 1/1000 births. Despite this, associated mortality did not decrease significantly, which can be attributed to the implementation of therapeutic hypothermia programs and the establishment of strict protocols that standardized management. However, especially in Ibero-American countries, the adoption of this therapy is still limited due to the lack of availability in many centers.

According to Jayasinghe, Wilcox and Schoonakker (2021), the S100B protein, found mainly in glial cells and some neuronal subpopulations of the CNS, can be used as a biomarker of hypoxia and to determine the ideal time window for cooling and rewarming during therapeutic hypothermia. The ease of obtaining urine samples for S100B analysis offers a safe form of monitoring that does not pose additional risks to the neonate.

IMPACT OF THERAPEUTIC HYPOTHERMIA ON CLINICAL AND NEUROLOGICAL OUTCOMES OF NEONATES

Therapeutic hypothermia has demonstrated a significant impact on reducing mortality in neonates with moderate to severe hypoxic-ischemic encephalopathy (HIE). A meta-analysis conducted by Abate et al. (2021) revealed that the relative risk of mortality for patients treated with therapeutic hypothermia is 26% lower compared to those who did not receive such treatment. This finding highlights therapeutic hypothermia as an effective neuroprotective strategy in the management of HIE. The technique, which involves controlled cooling of the neonate's body, not only significantly reduces mortality, but also has the potential to improve the long-term neurological prognoses of these patients. As described by Cawley and Chakkarapani (2020), the neuroprotective benefits of therapeutic hypothermia may extend into school age, including improvements in motor and cognitive development and reduced rates of cerebral palsy.

However, determining neurological outcomes in newborns undergoing therapeutic hypothermia involves significant challenges and is influenced by multiple factors. Additional complications such as sepsis, metabolic disorders, cardiac problems, or the need for surgical interventions may complicate accurate prognostic assessment. Furthermore, pharmacological sedation during treatment can obscure the accurate assessment of the newborn's neurological status (Cawley; Chakkarapani, 2020).

To date, it is not possible to fully guarantee the outcomes for each neonate after treatment, as each diagnostic tool has its own limitations and none is completely sensitive or specific.

The combined application of several diagnostic approaches, including a detailed neurological clinical examination, amplitude integrated electroencephalography (aEEG), brain MRI, serum biomarkers such as S100β protein and neurotrophins, as well as advanced neuroimaging techniques, can offer greater accuracy in prognosis long-term neurological outcomes. This integrated approach can more effectively guide clinical interventions with the goal of optimizing outcomes for patients undergoing therapeutic hypothermia (Walas et al., 2020).

Therapeutic hypothermia, involving controlled cooling of the neonate, has been shown to significantly reduce mortality and potentially improve the long-term neurological prognosis for patients with hypoxic-ischemic encephalopathy (HIE). According to Packer, Hersh, Sargent and Caughey (2020), the technique is defined by reducing body temperature by 3 to 4°C in the first six hours of life, maintained for a period of 72 hours. This approach has been associated with stabilization of the annual incidence of moderate to severe HIE at approximately 1/1000 births, as reported by Zewdie et al. (2021). However, despite this temporal trend of decreasing severity of HIE, a corresponding decrease in mortality was not observed. The authors suggest that this change is due to the widespread implementation of therapeutic hypothermia programs, which promoted the standardization of treatment protocols and more effective control of comorbid factors. Even so, there is an inconsistent use of this intervention in Ibero-American regions, where the availability of these services in many centers is still limited.

The study by Wang et al. (2021) highlights the importance of differentiating HIE from moderate to severe to assess the cost-effectiveness of the treatment. In cases of moderate HIE, therapeutic hypothermia is highly cost-effective, reducing both mortality and morbidity. However, in situations of

severe HIE, where the neonate presents severe symptoms such as stupor, flaccidity, pupils with photoreactive changes, decreased stretch reflexes, hypothermia and abolition of Moro reflexes, treatment reduces mortality but does not reduce morbidity. This distinction is crucial for treatment planning and delivery because it indicates that while therapeutic hypothermia can save lives, its impact on subsequent quality of life in severe cases may be limited.

USE OF S100B PROTEIN AND CHALLENGES IN THE ASSESSMENT OF NEUROLOGICAL OUTCOMES AFTER THERAPEUTIC HYPOTHERMIA

The S100B protein, a calcium ligand located predominantly in glial cells and neuronal subpopulations of the Central Nervous System (CNS), which is excreted mainly by the kidneys, has emerged as a potential biomarker of hypoxia. According to Jayasinghe, Wilcox and Schoonakker (2021), this protein can be used to identify the most appropriate time window for the cooling and rewarming phases during therapeutic hypothermia. The study highlights S100B due to the ease of obtaining it through urine samples, which does not represent an additional risk for the newborn.

However, determining neurological outcomes following the application of therapeutic hypothermia in newborns represents a significant challenge due to the complexity of the factors involved. Concomitant medical conditions, such as sepsis, metabolic and cardiac disorders, or the need for surgical interventions, can significantly complicate prognostic assessment (Cawley; Chakkarapani, 2020). Furthermore, the use of pharmacological sedation may obstruct the accurate assessment of the baby's neurological status.

To date, there is no method that guarantees the outcome for the newborn after treatment with absolute certainty. The available diagnostic tools have their limitations, and none are completely sensitive or specific. However, the combination of multiple diagnostic approaches can increase prognostic accuracy. These include detailed clinical neurological examination, amplitude-integrated electroencephalography (aEEG), brain MRI, serum biomarkers such as S100β protein and neurotrophins, as well as advanced neuroimaging tests (Walas et al., 2020).

These modalities, when used together, can provide a more accurate view of long-term neurological outcomes and guide clinical management with the goal of optimizing outcomes in patients undergoing therapeutic hypothermia. Such a multidisciplinary approach is critical to improving care and evidence-based decision-making in the treatment of neonates with hypoxic-ischemic encephalopathy.

ASSESSMENT OF BRAIN INJURY AND NEURODEVELOPMENTAL PROGNOSIS THROUGH MAGNETIC RESONANCE IMAGING AFTER THERAPEUTIC HYPOTHERMIA

Brain magnetic resonance imaging (CMR) is considered the gold standard imaging test for evaluating subacute brain injuries after treatment with therapeutic hypothermia. The severity and location of brain injury are critical determinants in the prognosis of childhood neurodevelopment, delineating the expected clinical phenotype for each case. When performed in the first week of life, CMR provides reliable results that predict the degree and extent of cognitive and motor impairments in patients (O'Kane et al., 2021). According to Aker et al. (2020), the application of the test to 46 patients with hypoxic-ischemic encephalopathy showed

a significant reduction in the number of moderate to severe abnormalities in patients undergoing therapeutic hypothermia (n=2, 9%) compared to those who did not receive the treatment (n=10, 43%), thus demonstrating the neuroprotective effect of this intervention.

Additionally, CMR is effective in quantifying changes in brain volume, a crucial factor in neurological outcomes and their long-term sequelae. Increased ventricular volume, often accompanied by a reduction in total brain tissue volume, is an important biomarker of the severity of hypoxic-ischemic encephalopathy, even after treatment with therapeutic hypothermia. Among 107 treated patients, 33.6% showed normal or minimally relevant results, while 66.4% showed significant abnormalities. Subsequent assessment of neurological, motor and linguistic impact was carried out at 18-24 months using the Bayley Scales of Infant and Toddler Development III (BSID III). This assessment revealed that 31 patients (29%) had neurodevelopmental delays, while the rest progressed normally (71%) (Im et al., 2024).

FINAL CONSIDERATIONS

Analysis of recent studies shows that therapeutic hypothermia, through the controlled reduction of body temperature, reduces mortality and morbidity in neonates, mitigating neuronal damage by reducing metabolic activity and brain inflammatory processes. However, challenges such as complications during the procedure and the accuracy in assessing neurological outcomes require additional research. The importance of this intervention is evident, especially in reducing fatalities in cases of neonatal asphyxia, which justifies continued investment in research to improve and develop more effective and safe methods.

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