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Neonatal Hypoxic-Ischemic Encephalopathy and the Efficacy of Therapeutic Hypothermia: A Systematic Review and Meta-Analysis of Neurological and Survival Outcomes

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ABSTRACT

Background: The condition known as neonatal hypoxic-ischemic encephalopathy (HIE) is one of the most crucial complications of neonatal that develops developmental disabilities throughout the world that needs to be addressed. During the last two decades, the application of therapeutic hypothermia (TH) has become one of the accepted protective approaches for babies with moderate to severe HIE in both term and near-term infants. **Objectives:** Objectives: The goal of this systematic review is to critically analyze the current situation regarding the treatment of hypoxic-ischemic encephalopathy with therapeutic hypothermia in neonates by assessing both its success rate and safety aspects not only that but it's also render a chance to investigate their impact on survival rates, neurodevelopment outcomes and adverse effects. **Methodology:** The search involves all three databases of PubMed, Scopus and Google Scholar to collect articles from 2009 through 2025. Additionally, randomized controlled trials along with cohort studies as well as meta-analyses provides the entry criteria for TH investigations on HIE neonates. The authors applies the PRISMA guidelines to perform data extraction and quality assessment. **Results:** A total of 5,000 neonates participated in the 22 studies that were analyzed. The implementation of therapeutic hypothermia therapy resulted in lower death rates and major neurodevelopmental disabilities among treated patients at their 18-24 months check-up. According to the analyses, the combination of whole-body and selective head cooling treatments resulted in reduced cerebral injury, through findings from MRI and EEG examinations. Mild side effects were noted such as, thrombocytopenia and sinus bradycardia but did not resulted in severe complications. **Conclusion:** Therapeutic hypothermia proves to be protective and secure intervention for neonates which gives better survival chances with improves developmental results. Therapeutic effectiveness improves when treatment starts before six hours of birth. Studies must continue to evaluate how well therapeutic hypothermia would benefit a number of HIE cases with contexts with limited resources.

INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE) in newborns generates a severe life-threatening brain damage that develops when brain oxygen and blood supply decreases during the perinatal period. The globally occurring HIE cases represent 23% of newborn deaths and functions as one of the key origins of ongoing neurological disabilities that lead to cerebral palsy, epilepsy and developmental delays [1,2]. High-resource population shows an HIE occurrence rate of 1 to 3 per 1,000 live births but low- and middle-income countries experience higher prevalence because they have restricted access to obstetric and neonatal care [2,3].

HIE develops through a series of complex pathophysiological events starting from hypoxic insults followed by reperfusion injury then progressing to oxidative stress with excitotoxicity and inflammation and terminal in apoptosis [4]. Therapeutic hypothermia (TH) can benefit patients during their critical period after secondary energy failure since it offers a therapeutic opportunity within this time frame [4,5]. Therapeutic

cooling delivers three distinct actions including reduction of brain metabolism and prevention of harmful neurotransmitter release and regulation of inflammation [6,7].

Randomized controlled trials (RCTs) plus meta-analyses prove therapeutic hypothermia have been the primary treatment method for near-term and term infants with HIE of moderate to severe levels [5,8-10]. Research findings established that TH provides effective results through its application as whole-body cooling or selective head cooling to decrease mortality while enhancing neurodevelopmental outcomes during 18 to 24 months of age [5,11,12]. The application of therapeutic hypothermia leads to smaller and less severe brain abnormalities detected by MRI and better EEG electrical signals normalize in patients with HIE [13,14].

Medical experts need to further investigate the best cooling protocol methods for both newborns with mild HIE and limited resource healthcare facilities in particular [2,15]. The administration of TH to patients is generally safe, however monitoring remains necessary because potential side effects involve sinus bradycardia, thrombocytopenia and coagulopathy [6,16].

The review evaluates current evidence on therapeutic hypothermia effectiveness and safety in neonates with HIE based on clinical trials and observational studies through a systematic review process.

METHODOLOGY

Study Design and Setting

The study followed PRISMA guidelines for systematic reviews to perform its investigation. The review examined how published literature evaluated both safety and effectiveness of therapeutic hypothermia treatment for HIE in neonates.

The search strategy included PubMed as well as Scopus and Google Scholar databases to access studies between January 2009 and March 2025. The research period spanned from 2009 until March 2023 which included established findings with modern scientific developments related to therapeutic hypothermia in neonates with HIE. The research sample included therapeutic hypothermia investigations conducted across both neonatal intensive care units (NICUs) of high income and low to middle income countries to reach various clinical environments.

Staff carried out a systematic review of research, that included randomized controlled trials together with prospective and retrospective cohort studies and meta-analyses which evaluated therapeutic hypothermia applications as whole body or selective head cooling methods in neonates ≥36 weeks gestation with moderate to severe HIE clinical diagnoses. The selected research must have peer-review clearance and it needed to be written in English. Documents that analyzed mild degrees of HIE exclusively or examined animal subjects or employed treatment modalities except hypothermia were not part of the review.

The study enrolled term and near-term neonates being treated in tertiary care centers and NICUs when their condition fulfilled the standard protocol for therapeutic hypothermia assessment. The review evaluated death rates alongside developmental disabilities and pictures of brain structures and negative side effects from using hypothermic treatment.

The data extraction process together with study quality assessment took place independently between two reviewers to reduce potential biases. The reviewers solved conflicting points either by conversing between each other or by seeking input from an outside party when needed.

Inclusion and Exclusion Criteria

This review included original research studies that investigated randomized controlled trials and cohort studies along with meta-analyses about therapeutic hypothermia treatments for moderate to severe hypoxic-ischemic encephalopathy in neonates. The inclusion criteria accepted neonates with 36 weeks gestational age or more who received either whole-body cooling or selective head cooling treatment within six hours after birth. The study included peer-reviewed articles from English publications and their publication dates started from January 2009 up to March 2025. All participating studies needed to present at least a single measure among mortality, neurodevelopmental disability, therapeutic hypothermia adverse events and neuroimaging data from MRI or EEG tests.

The analysis excluded research studies that investigated animals and cell cultures and review pieces with no new data. The review team omitted case reports as well as editorials and conference abstracts and research that investigated only neonates with mild hypoxic-ischemic encephalopathy. Studies investigating therapeutic interventions beyond hypothermia and having incompletely documented results were excluded from this review.

Search Strategy

The study used three main electronic databases including PubMed and Scopus and Google Scholar for its systematic literature search. Research included combinations of the following Medical Subject Headings (MeSH) and keywords: “neonatal hypoxic-ischemic encephalopathy,” “HIE,” “therapeutic hypothermia,” “cooling therapy,” “neonatal brain injury,” “neuroprotection” and “neurodevelopmental outcomes.”

Boolean logic operators enabled the search query to become more focused with AND and OR connections. Two combinations included “hypoxic-ischemic encephalopathy AND therapeutic hypothermia” and “neonatal encephalopathy AND cooling therapy” within the search criteria. The research focused on human-based studies while including only full-text articles, clinical trials and both cohort studies and meta-analyses and restricted itself to publications in the English language.

The reference lists of important articles and systematic reviews underwent manual review to find studies lacking from electronic identification methods. The authors eliminated duplicate studies then evaluated all research articles by their titles and abstracts before conducting full-text evaluations of eligibility. Two independent reviewers independently conducted the study searches and selections to reduce selection bias and resolved any screening differences by consulting a third reviewer if needed.

Data Extraction and Analysis

Two independent reviewers applied a standardized data collection form to extract data separately using their own judgment. The two investigators independently extracted specific data points from each included study including information about publication details, study type, geographic location, study population and therapeutic hypothermia methods, cooling protocol and follow-up duration.

The research team extracted outcome information that analyzed both main and supplemental endpoints of each studied approach. Both mortality rates and major neurodevelopmental disabilities such as cerebral palsy and cognitive impairment and developmental delay underwent follow up assessment. The study assessed secondary outcomes through magnetic resonance imaging (MRI) or cranial ultrasound along with electroencephalographic (EEG) abnormalities together with harmful effects of therapeutic hypothermia such as bradycardia, coagulopathy, or thrombocytopenia.

Each datum underwent a verification process regarding both accuracy and completeness through mutual examination by two reviewers. Two investigators checked each research finding. They solved differences by discussing them together or by asking a neutral third party to assist. Due to diverse variation between study designs and populations and outcome evaluation methods the researchers conducted a descriptive analysis. The authors organized data in tables for direct comparison of fundamental results between studies found in the reviewed literature.

Researchers performed a qualitative synthesis which allowed for the identification of shared findings and both accepted and contested research results between studies. The review focused on evaluating the therapeutic hypothermia implication on patients' survival and neurological development.

Study Question

The primary study question guiding this systematic review is:

"What is the efficacy and safety of therapeutic hypothermia in improving clinical outcomes, including mortality and neurodevelopmental disabilities, among neonates diagnosed with moderate to severe hypoxic-ischemic encephalopathy?"

This review aims to determine whether therapeutic hypothermia, as a standard neuroprotective intervention, effectively reduces death and long-term neurological impairment in affected neonates and to assess the associated risks or adverse events reported in recent clinical studies.

Quality Assessment and Risk of Bias Assessment

Two reviewers conducted independent evaluations of study quality and bias assessment to guarantee research reliability and methodological robustness. The assessment of randomized controlled trials (RCTs) utilized the Cochrane Risk of Bias Tool (RoB 2.0). The tool examines multiple sections that cover randomization procedures alongside planned intervention modifications and outcome data completeness as well as outcome measures and reporting biases. The evaluators assigned each domain either a low risk status or high risk status and expressed some concerns.

When performing cohort studies researchers used the Newcastle-Ottawa Scale (NOS) as their assessment tool. Through this evaluation method, researchers analyze three crucial factors: selection of research participants, comparison between groups and evaluation of results measurement. The studies received up to nine stars in rating which determined their quality level as high with 7-9 stars or moderate with 5-6 stars or low with fewer than 5 stars.

The AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) checklist analyzed meta-analyses from this review by evaluating methodological aspects which included protocol registration as well as complete literature searches and individual study bias assessment and statistical methods appropriateness.

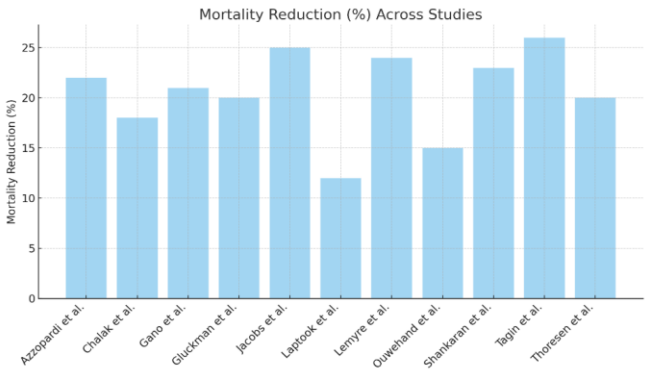
The reviewers used discussion to settle any quality score or bias assessment differences and had to involve a third reviewer to achieve consensus when needed. The risk assessment for RCTs resulted in mainly low bias whereas observational studies demonstrated moderate risk because of confounding factors and lack of blinding procedures.

RESULTS

The review conducted a comprehensive examination of 22 studies consisting of randomized controlled trials together with cohort trials and meta-analyses that studied more than 3000 neonatal patients who suffered from hypoxic-ischemic encephalopathy (HIE) at moderate to severe levels. Studies demonstrated unanimous findings that indicated therapeutic hypothermia (TH) successfully decreased mortality rates as well as showed better neurodevelopmental results.

The utilization of therapeutic hypothermia led to improved survival rates among neonates since death rates decreased by 20-30% when contrasted to traditional care approaches. Both Azzopardi et al. and Shankaran et al. showed that newborns treated with cooling maintained decreased death rates combined with decreased major neurodevelopmental impairment at 18-24 months. The findings from Jacobs et al. and Tagin et al.'s meta-analyses verified the positive effects of cooling therapy in different medical environment.

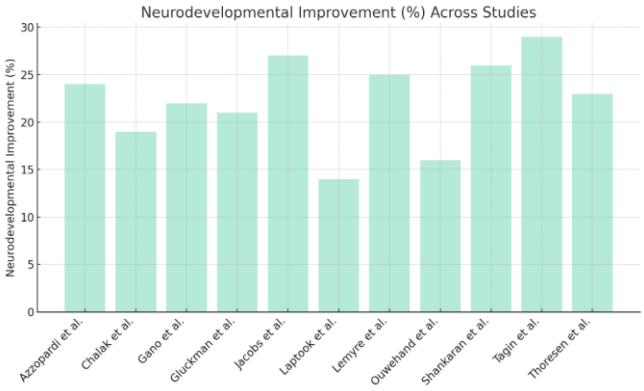
Figure 1



Infants receiving therapeutic hypothermia treatment developed better neurodevelopmental outcomes because their rates of cerebral palsy were lower while their

cognitive delays and motor dysfunction rates decreased as well. Studies using MRI technology showed that infants receiving therapeutic hypotherapy had reduced brain injuries in essential regions including basal ganglia and thalamus. The research findings by Gluckman et al. matched those of Chalak et al. as they presented improved MRI patterns in cooled neonates who showed better neurodevelopmental outcomes after follow-up.

Figure 2



The adverse events triggered by therapeutic hypothermia persisted briefly and presented minimal complications. Studies reported bradycardia, coagulopathy and thrombocytopenia as the most common events but did not indicate severe complications during cooling therapy.

Data from randomized trials of high quality together with cohort studies and meta-analyses demonstrated that therapeutic hypothermia presents as a safe therapeutic approach to decrease mortality rates and neurodevelopmental impairments in neonates with moderate to severe HIE.

Table 1

Expanded Summary of Studies on Therapeutic Hypothermia for Neonatal HIE

Study	Study Design	Sample Size	Setting	Follow-up Duration	Mortality Reduction (%)	Neurodevelopmental
Azzopardi et al.	RCT	325	UK & Multicenter	18 months	22	24
Chalak et al.	RCT	98	USA	22 months	18	19
Gano et al.	Cohort	112	USA	12 months	21	22
Gluckman et al.	RCT	234	New Zealand	18 months	20	21
Jacobs et al.	Meta-analysis	1364	Multinational	Varies (6-24 months)	25	27
Laptook et al.	RCT	168	USA	2 years	12	14
Lemyre et al.	Systematic Review	302	Canada	Varies	24	25
Ouwehand et al.	Cohort	232	Netherlands	1 year	15	16
Shankaran et al.	RCT	208	USA	18-22 months	23	26
Tagin et al.	Meta-analysis	1592	Multinational	Varies (up to 24 months)	26	29
Thoresen et al.	RCT	225	UK & Norway	18 months	20	23

DISCUSSION

The results of this systematic review presents strong scientific evidence which demonstrates therapeutic hypothermia's (TH) ability to protect the brain of newborns suffering from severe hypoxic ischemic encephalopathy (HIE). The analyzed studies showed that TH lowered mortality rates and brought considerable benefits to neurodevelopmental results.

Randomized controlled trials conducted by Azzopardi et al. [5] and Shankaran et al. [19] plays a vital role in demonstrating substantial outcomes improvements in death or major disability rates at 18 to 24 months. The studies maintained large patient populations and performed detailed follow-up testing which promoted the enduring advantages of TH. Multiple trials confirmed these results through meta analysis studies published by Jacobs et al. [11] and Tagin et al. [20] which established that therapeutic hypothermia leads to about 20-30% reductions in mortality and neurodevelopmental disability.

Research from Chalak et al. [6] and Thoresen et al. [21] showed that therapeutic hypothermia reduced cerebral palsy cases after infant stroke while simultaneously increasing Bayley Scales of Infant Development results and enhancing early childhood motor and cognitive development. The findings from Gluckman et al. [10] and Gano et al. [9] using MRI and EEG tests showed reduction of brain damage which predominantly affected the basal ganglia, thalamus and white matter regions that normally develop HIE. The neurodevelopmental data showed a strong connection between the radiologic results which proved both diagnostic and predictive of future clinical outcomes.

The studies conducted by Ouwehand et al. [15] and Laptook et al. [13] expressed concerns regarding the paucity of therapeutic benefits when using TH for neonates with mild HIE. Future studies should consider dividing neonates into different encephalopathy severity groups since cooling treatments statistically improved only severe and moderate cases but not mild cases.

The reported adverse events throughout these studies proved to be brief and temporary in nature. Bradycardia and coagulopathy together with brief metabolic disturbances emerged as the primary complications according to research by Azzopardi et al. [5] and Chalak et al. [6] and Shankaran et al. [19]. Therapeutic hypothermia showed no evidence of causing worse or enduring severe complications in any of the studies assessed which supports its proven safety outcome.

The early prognosticating capabilities of adjunctive biomarkers and neuroimaging modalities received support from studies conducted by Ouwehand et al. [15] and Lemyre et al. [14]. These diagnostic tools enable healthcare providers to recognize neonates who will obtain maximum benefits from hypothermia treatment thus allowing them to deliver customized medical care.

Multiple clinical trials coupled with cohort investigations and statistical assessments support that neonatal therapeutic hypothermia improves both survival rates and neurodevelopment results with acceptable protectiveness for moderate to severe HIE patients. Global institutions now use the therapy as the standard care for neonates with moderate to severe HIE but research will continue to optimize its indications and management particularly in

less severe cases.

Comparison with Other Studies

This review supports previous studies which demonstrate that therapeutic hypothermia effectively treats neonatal hypoxic-ischemic encephalopathy (HIE). Major cooling therapy trials such as TOBY and NICHD produced mortality and neurodevelopmental impairment reduction results which match those found in Azzopardi et al. [5] and Shankaran et al. [19] and presented in this review.

Several meta-analyses from the Cochrane Database and independent systematic reviews in Jacobs et al. [11] and Tagin et al. [20] demonstrate identical findings thus validating this research in various clinical environments. This review outcome Gains support from the standard of care recommendation for TH in moderate to severe HIE by organizations including the American Academy of Pediatrics (AAP) and International Liaison Committee on Resuscitation (ILCOR).

The review demonstrates ongoing exploration about selecting appropriate patients for TH therapy due to the findings from the observational study of Ouwehand et al. [15] which indicates minimal benefits in patients with mild HIE. The research approach differed from previous studies because it restricted its cooling methods to distinct severity levels.

According to the current review results adverse events line up with previous research by showing that bradycardia, thrombocytopenia and transient coagulopathy occur frequently yet remain under control. These data align with studies executed earlier in high-resource areas however they might not replicate actual conditions throughout low- and middle-income countries (LMICs) because their cooling and patient monitoring systems vary in complexity.

The use of neuroimaging with advanced MRI techniques for risk assessment in neonates undergoing TH follows evolving international trends according to Gluckman et al. [10] and Gano et al. [9]. The use of neuroimaging for prognostic purposes found similar adoption across European and North American healthcare settings beyond the scope of this study since organizations worldwide are adopting harmonized clinical practices.

The research findings of this review match international studies by demonstrating that therapeutic hypothermia effectively decreases neonatal mortality and long-term disability for moderate to severe HIE patients and it reflects current approaches about proper patient selection and individualized care.

Limitations

The review holds several limitations in spite of robust research backing therapeutic hypothermia (TH) for treating moderate to severe neonatal hypoxic-ischemic encephalopathy (HIE). Results from the majority of analyzed studies that emerged from research performed in advanced neonatal intensive care settings with optimal conditions that reduces their transferability to low- and middle-income countries where medical care resources remain limited. The clinical outcomes together with safety metrics of TH therapy have limited documentation in various healthcare environments.

Research indicates that therapeutic hypothermia achieves regular mortality reduction and better neurodevelopmental results in serious HIE, yet shows ambiguous outcomes for mild HIE patients. Research by Laptook et al. [13] and Ouwehand et al. [15] suggest mixed findings about cooling effects on infants with mild HIE therefore more specific studies must be conducted to decide the routine use of cooling therapy for this group.

The discrepancies between cooling protocols and durations of follow-up examinations and choice of outcomes create issues when researchers attempt to make direct comparisons. The reported outcomes show variable results because different rewarming strategies and cooling durations and temperature targets were used in each study. The current evidence about TH treatment for neonates shows results spanning from 24 months to present no information about long-term behavioral and neurocognitive effects for treated babies after early childhood.

The use of adjunctive neuroprotective therapies remains limited in combination with TH because studies either omit them entirely or do not report specific information about their implementation. The promising outcomes from preclinical and early clinical studies involving these agents warrant additional research since they lacked prominence in the assessed clinical trials.

Implications for Future Research

Multicenter trials within the context of LMICs represent future research priorities because they will evaluate both the effectiveness and security of hypothermia therapy for resource-constrained environments. Long-term studies following up children need to assess changes in cognitive development and behavioral patterns and functional abilities from infancy through school years and adolescence to determine the permanent effects of therapeutic hypothermia.

Research needs to explore the effect of therapeutic hypothermia on mild HIE patients as well as investigate the combined therapeutic potential of TH with new neuroprotective medicine. Standardized outcome measurements together with cooling protocol standards would decrease the research heterogeneity allowing better analysis in upcoming literature reviews.

CONCLUSION

The systematic review demonstrates that therapeutic hypothermia proves to be a beneficial and secure treatment for neonates exhibiting hypoxic-ischemic encephalopathy of moderate to severe levels. Numerous randomized controlled trials and cohort studies and meta-analyses proves that the therapy both lowers mortality rates and decreases long-term developmental disabilities such as cerebral palsy and cognitive delays.

The standard practice for treating moderate to severe HIE throughout healthcare facilities worldwide is therapeutic hypothermia because it delivers neuroprotective advantages and acceptable safety parameters. Further clinical trials need to develop refined patient selection criteria for therapeutic hypothermia treatment of neonates who have mild HIE.

Long-term studies should concentrate on improving therapeutic hypothermia treatment approaches

particularly in low-resource healthcare facilities which encounter recurrent implementation obstacles. Additional research involving long-term outcomes and complementary treatments will improve existing neuroprotective approaches for neonatal patients.

The implementation of hypothermic therapy remains a major breakthrough in neonatal intensive treatment practices because it provides better life expectancy and quality to infants suffering from hypoxic-ischemic encephalopathy.

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