

# Comparison between selective head cooling and whole-body cooling in neonatal therapeutic hypothermia

Guilherme Rangel e Souza<sup>1</sup>, Letícia de Oliveira Zambeli<sup>1</sup>, Vinícius Parma Ruela<sup>1</sup>, Anna Carolina Bovarêto Silveira<sup>1</sup>, Maria Eduarda Dias Maia<sup>1</sup>, Geandra Martins de Freitas<sup>1</sup>, Julia Machado Vieira<sup>1</sup>, Vitor Fernandes Alvim<sup>2</sup>

<sup>1</sup>Faculdade de Ciências Médicas e da Saúde de Juiz de Fora (FCMS/JF) – Juiz de Fora (MG), Brazil

<sup>2</sup>Departamento de Pediatria, Faculdade de Ciências Médicas e da Saúde de Juiz de Fora (FCMS/JF) – Juiz de Fora (MG), Brazil

## ABSTRACT

**Introduction:** Experimental evidence, as well as improved clinical studies of the reduction of brain injury and, improves the neurological outcome, in newborns with hypoxic-ischemic encephalopathy (HIE) occurring in therapeutic hypothermia (TH). **Objective:** To verify the potential of hypothermic hypoxic-ischemic encephalopathy (HIE) therapy in neonatal asphyxia, based on literature data, comparing the benefits between selective head cooling (SHC) and whole-body cooling (WBC), see that the use of TH as a standard treatment in newborns with moderate or severe HIE has been adopted. **Methods:** A search was performed in the PubMed and SciELO databases of human studies, using the keywords “Therapeutic Hypothermia”, “Induced Hypothermia”, and “Hypoxic-Ischemic Encephalopathy”, “Selective cooling of the head”, “Total body cooling” and its variables. **Results:** Eleven articles were selected to compose the review, after detailed reading. There is a consensus, that the reduction of the risk of death or disability at 18 months of life in neonates with moderate to severe HIE, occurs to TH through the techniques of WBC or SHC. It was found in the studies that there is no difference in terms of adverse effects between the two methods. As for radiological changes, such as hypoxic-ischemic injuries and the incidence of seizures after cooling, they are more frequent with SHC. **Conclusion:** Both WBC and SHC demonstrated neuroprotective properties, although WBC provides a broader area of brain protection. However, no significant differences were found between the methods in terms of adverse effects and beneficial short or long-term results.

**Keywords:** hypothermia, induced; brain diseases; hypoxia-ischemia, brain; infant, newborn.

## INTRODUCTION

The hypoxic-ischemic encephalopathy (HIE) is one of the most alarming conditions in newborns worldwide, with an incidence ranging from 2 to 6 per 1,000 live births, being higher in less developed countries<sup>1</sup>. In Brazil, it is the second cause of neonatal mortality when considering the first day or the first week of life<sup>2</sup>. HIE leads to death in 60% of affected infants<sup>3</sup>, with at least 25% of survivors having long-term neurological sequelae<sup>2,4</sup>. The severity of the insult varies with gestational age, with the most severe

How to cite this article: Souza et al. Comparison between selective head cooling and whole-body cooling in neonatal therapeutic hypothermia. ABCS Health Sci. 2023;48:e023301 <https://doi.org/10.7322/abcshs.2021015.1742>

Received: Feb 11, 2021

Revised: May 27, 2021

Approved: Jun 22, 2021

Corresponding author: Guilherme Rangel e Souza - Faculdade de Ciências Médicas e da Saúde de Juiz de Fora - Alameda Salvaterra, 200 – Salvaterra – CEP: 36033-003 - Juiz de Fora (MG), Brazil - Email: [guir006@hotmail.com](mailto:guir006@hotmail.com)

Declaration of interests: nothing to declare



This is an open access article distributed under the terms of the Creative Commons Attribution License  
© 2023 The authors

newborns being those with a high degree of cerebral vascular immaturity and subjected to a longer time of aggression<sup>2</sup>. Since 2010, neonatal resuscitation guidelines have recommended the use of therapeutic hypothermia (TH) as standard treatment in newborns with moderate or severe HIE<sup>5,6</sup>.

TH aims to reduce brain metabolism by approximately 5% for every 1°C reduction. Such procedure has been proven to have neuroprotective properties by modifying cells programmed for apoptosis, leading to survival by reducing the metabolic rate of the brain, attenuating the release of excitatory amino acids (glutamate, dopamine), ameliorating ischemic damage by glutamate uptake, and decreasing nitric oxide and free radical production, thus reducing neuronal death. Other strategies involved are reduction of reactive oxygen species production, a decrease of

metabolic rate with the decay of oxygen consumption and carbon dioxide production, and some endogenous neuroprotective effect<sup>2,7</sup>. The moment of transition from the recovery period to the second phase of the injury is what allows a potential window for neuroprotection or reduction of this injury, so treatment with TH should be initiated in the first 6 hours of life and continued for 72 hours<sup>2,8-19</sup>. Some criteria should be followed for the application of TH (Table 1).

The interventions are primarily used in two methods: selective head cooling (SHC) and whole-body cooling (WBC)<sup>2</sup>. Olympic Cool-Cap, which provides selective head cooling with mild systemic hypothermia, was the first cooling method approved by the FDA in 2006 to be used in newborns with HIE<sup>5</sup> WBC cools the brain uniformly, while SHC cools the superficial brain more intensely

**Table 1:** Main characteristics of the selected articles.

Title	Journal	Author	Conclusions
Whole-Body Hypothermia for Neonates with Hypoxic–Ischemic Encephalopathy.	N Engl J Med	Shankaran et al. <sup>4</sup>	Whole-body cooling to a temperature of 33.5 degrees, started within 6h and maintained for 72h reduced deaths and moderate or severe disabilities in full-term infants
The TOBY Study Whole Body Hypothermia for the Treatment of Perinatal Asphyxial Encephalopathy: a Randomised Controlled Trial	BMC Pediatr	Azzopardi et al. <sup>8</sup>	The maximum benefit of hypothermia occurs when started within 6 hours, limited neuroprotection was observed when started within 12h. Treatment for 72 hours is suggested if body cooling of 3 to 4 degrees is followed. Uncertainty about the benefit of selective head cooling over whole body cooling
Distribution and Severity of Hypoxic-Ischaemic Lesions on Brain MRI Following Therapeutic Cooling: Selective Head versus Whole Body Cooling	Arch Dis Child Fetal Neonatal Ed	Sarkar et al. <sup>9</sup>	Hypoxic-ischemic lesions seen on NMR after therapeutic cooling are more frequent in selective head cooling compared with whole-body cooling
Comparison of Selective Head Cooling Therapy and Whole Body Cooling Therapy in Newborns With Hypoxic Ischemic Encephalopathy: Short Term Results.	Turk Pediatri Ars	Atici et al. <sup>10</sup>	There is no difference between selective head cooling and whole-body cooling methods in terms of adverse effects and short-term results.
Selective Head Cooling with Mild Systemic Hypothermia After Neonatal Encephalopathy: Multicentre Randomised Trial	Lancet	Gluckman et al. <sup>13</sup>	Except in severe encephalopathies, selective cooling of the head early after birth can be an effective procedure in reducing the development of long-term sequelae and disability
A Systematic Review of Cooling for Neuroprotection in Neonates with Hypoxic Ischemic Encephalopathy - Are We There Yet?	BMC Pediatr	Schulzke et al. <sup>14</sup>	Cooling neonates with moderate to severe hypoxic-ischemic encephalopathy reduces the risk of death or sequelae by 18 to 22 months without significant adverse effects.
Pulmonary Dysfunction And Therapeutic Hypothermia in Asphyxiated Newborns: Whole Body Versus Selective Head Cooling	Am J Perinatol	Sarkar et al. <sup>15</sup>	Pulmonary dysfunction in newborns with asphyxia during therapeutic hypothermia is common but not severe. Any of the established cooling protocols can be adopted without concern for worsening pulmonary dysfunction
Hypothermia Therapy for Newborns with Hypoxic Ischemic Encephalopathy.	J Pediatr (Rio J)	Silveira & Procianny <sup>16</sup>	Therapeutic hypothermia significantly reduces morbidity and mortality in many newborns with moderate encephalopathy. However, it emphasizes the need for association with other neuroprotective strategies.
Moderate Hypothermia to Treat Perinatal Asphyxial Encephalopathy	N Engl J Med	Azzopardi et al. <sup>17</sup>	It showed no significant reduction in the combined rates of death and severe disability with cooling, but it did show significant improvement in several secondary neurological outcomes among survivors.
Effects of Therapeutic Hypothermia on Multiorgan Dysfunction in Asphyxiated Newborns: Whole-body Cooling Versus Selective Head Cooling	J Perinatol	Sarkar et al. <sup>18</sup>	The components of organ dysfunction in newborns with asphyxia during cooling are similar to the cooling techniques. Concerns regarding different effects on multiple organ dysfunction should not be considered when selecting one method over the other.
Therapeutic Hypothermia in Asphyxiated Newborns: Selective Head Cooling vs. Whole Body Cooling — Comparison of Short Term Outcomes	Ginek Pol	Gulczynska et al. <sup>5</sup>	Both cooling methods were equally effective, with similar short-term outcomes and risk of adverse events.

than its deeper structures<sup>9</sup>. Although WBC is more popular and more commonly explored today, SHC is still used because it is believed to minimize the potential side effects of hypothermia<sup>5,10</sup>.

Given the above, given the severity of HIE and the importance of early therapy in these patients, the article aims to verify the potentiality of hypothermic HIE therapy in neonatal asphyxia, based on literature data, comparing the benefits between WBC and SHC.

## METHODS

The primary endpoint of this study was the systematic evaluation and characterization of the distinct methods of TH application, particularly WBC and SHC techniques, applied in the management of pediatric cases of HIE. The primary analysis focused on the gestational age of newborns, gender, clinical manifestations at birth, presence of criteria for the diagnosis of HIE, application of induced hypothermia therapy and other adjuvant treatments, taking into consideration the time of treatment and its techniques, outcomes and adverse events directly associated with the therapeutic tools employed.

An extensive search strategy was designed to retrieve all articles published by November 30, 2020, describing the different methods of application of TH and its effectiveness and inherent safety in the treatment of HIE by combining the generic terms “Therapeutic Hypothermia,” “Induced Hypothermia,” “Hypoxic-Ischemic Encephalopathy” in PubMed and SciELO databases. Following the quality standards for reporting observational studies, seven independent researchers reviewed the 36 articles found. The same researchers independently evaluated the full texts of the records deemed eligible for inclusion. Any discrepancies were resolved by discussion and consensus.

The risk of bias for eligible observational studies (cross-sectional and case-control) was assessed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline<sup>11</sup>. Two investigators independently assigned an overall risk of bias to each eligible study, and if they disagreed, a third reviewer was consulted. Studies with a risk of bias were excluded. Inclusion criteria were observational studies originating from worldwide human-based perinatal care centers and pediatric intensive care units and assigned to newborns with a gestational age of 35 weeks or older who met the diagnostic criteria for HIE, as seen in American College of Obstetricians and Gynecologists criteria<sup>12</sup>. Exclusion criteria were studies not based on humans and involved in their sampling cases that did not meet the diagnostic criteria for HIE or with congenital malformations, life-threatening abnormalities and extremely poor prognosis (Apgar score 0 for more than 10 minutes of life) or inability to initiate treatment within the first six hours of the life of the newborn or refusal of consent by a parent or responsible neonatologist.

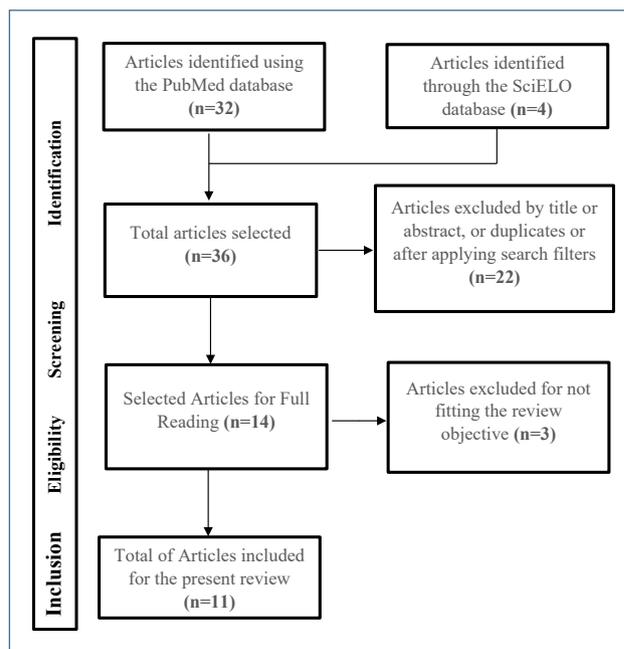
Two independent reviewers extracted data from each eligible study using a standardized data extraction spreadsheet and then cross-referenced the results. Disagreements between the reviewers regarding the extracted data were resolved through discussion and consensus by a third reviewer. The following information was extracted: first author’s name, publication date, study type, and origin, gestational age of the newborns evaluated, therapies administered, adverse events derived from the therapeutic modalities applied, and short- and long-term outcomes.

We found 36 studies that met at least one of the recorded inclusion criteria. After applying the exclusion criteria, 22 pieces of evidence were excluded because they presented studies based on animals or were not directly related to the theme. Subsequently, three articles were excluded for not meeting the review objectives. Based on the inclusion criteria, 11 studies were selected, see the flow demonstrating the search strategy used (Figure 1).

## RESULTS

Eleven studies that met the recorded inclusion criteria were selected. Table 1 summarizes their main characteristics (Table 1).

Evidence from randomized clinical trials indicates a reduction in the risk of death or disability at 18 months (delayed neurodevelopment) in neonates with moderate to severe IHN undergoing TH, which is a relevant option for neuroprotection. This positive effect has been demonstrated with cooling (33.5 °C to 34.5 °C), up to six hours after birth, and in neonates with a GA greater than 35 weeks, using the WBC and SHC techniques<sup>4,13</sup>.



**Figure 1:** Flow chart to demonstrate the search strategy used, excluded, and included studies.

In a systematic review study, a subgroup analysis of the studies by Gluckman et al.<sup>14</sup> and Shankaran et al.<sup>4</sup> regarding the cooling technique indicated no significant reduction in mortality after SHC. However, WBC did have a protective effect. This is due to the different ways of sample selection, with Gluckman et al.<sup>14</sup> having selected a higher proportion of neonates with lower Apgar scores, integrated amplitude electroencephalogram (aEEG) background activity, and severe encephalopathy, leading to a less favorable outcome.

A clinical trial involved newborns older than 35 weeks, diagnosed with moderate or severe HIE, randomly assigned to the SHC and WBC methods, intending to maintain a rectal temperature between 33 and 34°C in the WBC method and between 34 and 35°C in the SHC method for 72 hours. There was no significant difference in terms of adverse effects related to cooling therapy between the two groups. As for short-term outcomes, it was found that the average length of hospital stay was 34 days in the SHC group and 18 days in the WBC group, without, however, showing statistical significance ( $p=0.097$ ). At the end of the study, it was found that there is no difference between the methods in terms of adverse effects and short-term outcomes<sup>10</sup>.

## Adverse Effects

Potential adverse systemic effects, including cardiovascular, pulmonary, hematological, and metabolic complications appear to be proportional to the degree of cooling<sup>15</sup>, occurring most commonly when the temperature was below 30°C<sup>16</sup>.

In a multicenter randomized study, Azzopardi et al.<sup>17</sup> when performing the Total Body Hypothermia for Neonatal Encephalopathy Trial (TOBY) protocol, observed adverse effects presence of venous thrombosis, renal failure requiring dialysis, pneumonia, air leak syndrome, longer hospital stay, intracranial hemorrhage, persistent arterial hypotension, pulmonary hemorrhage, persistent pulmonary hypertension of the newborn (PPHN) prolonged blood clotting time, culture-confirmed sepsis, and thrombocytopenia.

Thrombocytopenia is one of the main adverse effects of TH, probably due to the different settings and platelet counting times<sup>5</sup>. When comparing cooling techniques, no significant differences were detected between the methods regarding the increased risk of thrombocytopenia<sup>5,10</sup>.

## Multiple organ dysfunction

The multiorgan dysfunction is a consequence of the circulatory adaptation that occurs after the asphyxia process, with the adverse effects of PH being superimposed by the hypoxic-ischemic syndrome. The cardiac output is redistributed aiming to preserve perfusion of the noblest areas (heart, central nervous system, and adrenals) to the detriment of other organs. TH can cause vasoconstriction, hemoconcentration, and hyperviscosity, leading to pulmonary dysfunction<sup>15,16</sup>. The important events of multiple organ dysfunction<sup>18</sup> are defined in Table 2.

It is hypothesized that by effectively cooling the brain, with less systemic hypothermia, SHC may cause less systemic adverse effects<sup>18</sup>. On the other hand, there are also doubts as to the real benefit of SHC on organs other than the brain, since this method aims to adequately cool the brain with a small reduction in head temperature, while the rest of the body is heated<sup>15</sup>.

Sarkar et al.<sup>15,18</sup> conducted nonrandomized observational studies comparing the effects of multiorgan dysfunction and pulmonary dysfunction specifically, in the different techniques (SHC and WBC) in two separate publications, but evaluating the same sample of neonates. Demographic characteristics, and clinical and laboratory evidence of an intrapartum hypoxic-ischemic event were similar across groups. Of the 59 newborns in the sample, 28 of them received WBC and 31 of them received SHC. Dysfunctions during cooling were similar between the two methods, and it was not possible to establish a safer technique in this respect.

About pulmonary dysfunction specifically, its incidence was 96% of the neonates with HIE submitted to TH. Despite the high incidence, it was of low intensity and did not vary during the procedure, regardless of the method, except for 15% who developed PPHN, with more severe repercussions<sup>15</sup>.

When compared to control groups (without TH) with moderate to severe encephalopathy from other studies, the incidence of PPHN was lower or equal. Regarding the different techniques, there were no significant differences ( $p=0.72$ ), having low incidence in both (WBC 17.8% x SHC 12.9%). This suggests that the occurrence of PPHN is not related to moderate therapeutic hypothermia nor the cooling methods, it probably occurs due to perinatal stressors, for example, meconium aspiration or pulmonary hemorrhage<sup>14</sup>.

**Table 2:** Defining the important events of multiple organ dysfunction. Sarkar et al.<sup>18</sup>

1. Cardiac dysfunction (mean arterial pressure <40 mm Hg treated with vasopressors for > 24 h);
2. Renal dysfunction (oliguria with urine output <0.5 ml kg<sup>-1</sup>h<sup>-1</sup> for >24 h after birth, or increased serum creatinine with peak serum creatinine >0.9 mgdl<sup>-1</sup>);
3. Pulmonary dysfunction (presence of clinical respiratory distress along with the need for positive pressure ventilatory support and supplemental oxygen);
4. Coagulopathy (disseminated intravascular coagulation or hepatic coagulopathy, with or without associated clinical bleeding);
5. Suppression of bone marrow (platelet count <100,000 µl<sup>-1</sup>);
6. hyponatremia (serum sodium <130 mmol l<sup>-1</sup>);
7. hypokalemia (serum potassium <3.5 mmol l<sup>-1</sup>);
8. hypocalcemia (serum calcium <8 mg dl<sup>-1</sup>).

## Intrinsic brain changes and imaging examinations

Although experimental evidence has shown that SHC can be effective, there is the possibility of damage to deeper structures of the brain, and it is uncertain whether SHC alone is effective in reducing the temperature of these areas. Another factor of concern is the lack of accurate, non-invasive methods to measure the temperature of brain regions, thus a major drawback regarding this method<sup>8</sup>.

In a study in which nuclear magnetic resonance (NMR) scans of 83 cooled infants were analyzed, hypoxic-ischemic lesions were evidenced in 47 of them. Hypoxic-ischemic lesions on brain NMR after therapeutic cooling were found to be more frequent with SHC compared to WBC. The mean score used to assess the severity of NMR brain lesions is also higher in infants who received SHC. In addition, although no brain NMR findings were reported, this study described a higher incidence of seizures requiring anticonvulsants in neonates treated with SHC compared to WBC<sup>9</sup>.

A clinical trial involving 34 newborns evaluated whether hypothermia alters the patterns of injury commonly identified in neonates with HIE. In particular, lesions in the basal ganglia, thalamus, and posterior part of the internal capsule are predictive of paralysis in neonates with HIE. Less commonly, neonates who sustain lesions primarily in the white matter are subject to cognitive changes and later disabilities; the more extensive the abnormalities in the white matter, the more pronounced the impairments. There were no unusual patterns of injury in the neonates treated with hypothermia, and the prevalence of hemorrhage was similar in all groups. The patterns of brain injury documented in the neonates who underwent cooling were similar to those seen and reported previously and after HIE. Cortical abnormality often accompanies the classic lesions seen in the basal nuclei and thalamus after acute ischemic hypoxia. These cortical abnormalities are most often seen along the central sulcus and the medial portion of the interhemispheric fissure. No differences were shown in the imaging patterns of cortical abnormalities in infants who were cooled or uncooled<sup>9</sup>.

## DISCUSSION

To have experimental clinical evidence that the use of TH causes a reduction in brain injury and better neurological outcomes for newborns submitted to it, randomized studies have been conducted for more than a decade, focused on this investigation. Most clinical trials are based on one form of hypothermia, either head hypothermia alone or body hypothermia, compared to the standard treatment (normothermia)<sup>19</sup>. The current challenge is due, in part, to the different ways in which TH is applied, in a quest to designate which presents the best infant outcome<sup>20</sup>.

Based on the evidence, WBC provides homogeneous cooling that covers the brain in a generalized way, peripheral and central regions. Whereas SHC provides cooling that is more selective for

the cortical region of the brain than for the central structures. The adverse effects in the articles studied were not significantly different concerning vital organ dysfunction<sup>2</sup>. Peripartum asphyxia remains an important cause of long-term neurosensory disabilities and impairments. TH improves survival and neurodevelopment in newborns with HIE by both SHC and WBC. Although TH has better outcomes in moderate compared to severe HIE, current evidence supports initiating TH as soon as possible after birth for newborns with moderate to severe HIE<sup>21</sup>.

Cooling should be performed as soon as possible after the ischemic hypoxic event and started within at least 6 hours for the therapy to have the desired effect<sup>19,21</sup>. The cooling temperature should be throughout the hypothermia period above 33°C; temperatures below 32°C are less neuroprotective and below 30°C severe systemic adverse effects have been observed in addition to increased mortality<sup>4</sup>.

The supposed greater systemic protection in SHC has not proven true, studies have obtained similar organ dysfunction results between the cooling techniques, suggesting that concerns regarding a differential effect of SHC versus WBC on systemic protection, should not determine the choice of TH method<sup>18,20</sup>. Regarding the long-term neurodevelopment of those treated with TH, most evidence favored the hypothermia group over the control group, although the differences are modest<sup>22</sup>.

Follow-up evaluation at 18 months and then at 7 to 8 years of age is important in determining prognosis. Children with encephalopathy who were treated with hypothermia shortly after birth were significantly more likely to survive with an Intelligence Quotient (IQ) score of 85 or higher at six and seven years of age than children who did not have this therapy. When compared with the control group, there was a higher proportion of survivors in the TH group with an IQ score of 85 or higher, and the frequency of moderate to severe disability was lower<sup>23</sup>.

Hypothermia is safe and has become the standard of care for neonatal HIE, and it is important to establish extended multidisciplinary follow-up to assess cognitive, motor, and psychoeducational outcomes to contribute to the discovery of further future benefits<sup>19</sup>.

## Conclusion

TH is a neuroprotective technique indicated for newborns with perinatal asphyxia and HIE. Both WBC and SHC have demonstrated neuroprotective properties, although WBC provides a wider area of brain protection. WBC constitutes the most widely used technique today, evidence suggests that there is no superiority of one method over the other, as no significant differences have been found regarding adverse effects and short- and long-term beneficial outcomes. Therefore, randomized studies with larger samples are needed, as well as trials that aim to discover more advantages related to the evolution of patients, to determine the best method and safety of TH.

## REFERENCES

1. Elbahtiti A, Aly NY, Abo-Lila R, Al-Sawan R. Therapeutic hypothermia for infants with hypoxic ischemic encephalopathy: A five years' single center experience in Kuwait. *J Neonatal Perinatal Med.* 2016;19;9(2):179-85. <https://doi.org/10.3233/NPM-16915090>
2. Nonato M, Gheler L, Balestrieri JV, Audi M, Prandini M. Selective head cooling and whole body cooling as neuroprotective agents in severe perinatal asphyxia. *Rev Assoc Med Bras.* 2019;65(8):1116-21. <https://doi.org/10.1590/1806-9282.65.8.1116>
3. Long M, Brandon DH. Induced hypothermia for neonates with hypoxic-ischemic encephalopathy. *J Obstetr Gynecol Neonatal Nurs.* 2007;36:293-8. <https://doi.org/10.1111/j.1552-6909.2007.00150.x>
4. 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(15):1574-84. <https://doi.org/10.1056/NEJMcps050929>
5. Gulczynska EM, Gadzinowski J, Kesiak M, Sobolewska B, Caputa J, Maczko A. Therapeutic hypothermia in asphyxiated newborns: selective head cooling vs. whole body cooling - comparison of short term outcomes. *Ginekol Pol.* 2019;90(7):403-10. <https://doi.org/10.5603/GP.2019.0069>
6. Iwata O, Nabetani M, Takenouchi T, Iwaibara T, Iwata S, Tamura M. Hypothermia for neonatal encephalopathy: Nationwide Survey of Clinical Practice in Japan as of August 2010. *Acta Paediatr.* 2012;101:e197-202. <https://doi.org/10.1111/j.1651-2227.2011.02562.x>
7. Gunn AJ, Battin M, Gluckman PD, Gunn TR, Bennet L. Therapeutic hypothermia: from lab to NICU. *J Perinat Med.* 2005;33(4):340-6. <https://doi.org/10.1515/JPM.2005.061>
8. Azzopardi D, Brocklehurst P, Edwards D, Halliday H, Levene M, Thoresen M, et al. The TOBY Study Whole body hypothermia for the treatment of perinatal asphyxial encephalopathy: a randomised controlled trial. *BMC Pediatr.* 2008;8:17. <https://doi.org/10.1186/1471-2431-8-17>
9. Sarkar S, Donn SM, Bapuraj JR, Bhagat I, Barks JD. Distribution and severity of hypoxic-ischaemic lesions on brain MRI following therapeutic cooling: selective head versus whole body cooling. *Arch Dis Child Fetal Neonatal Ed.* 2012;97:F335-9. <https://doi.org/10.1136/fetalneonatal-2011-300964>
10. Atici A, Çelik Y, Gülaşi S, Turhan AH, Okuyaz Ç. Comparison of selective head cooling therapy and whole body cooling therapy in newborns with hypoxic ischemic encephalopathy: short term results. *Turk Pediatr Ars.* 2015;50(1):27-36. <https://doi.org/10.5152/tpa.2015.2167>
11. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol.* 2008;61(4):344-9. <https://doi.org/10.1016/j.jclinepi.2007.11.008>
12. Executive summary: Neonatal encephalopathy and neurologic outcome, second edition. Report of the American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy. *Obstet Gynecol.* 2014;123(4):896-901. <https://doi.org/10.1097/01.AOG.0000445580.65983.d2>
13. Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet.* 2005;365(9460):663-70. [https://doi.org/10.1016/S0140-6736\(05\)17946-X](https://doi.org/10.1016/S0140-6736(05)17946-X)
14. Schulzke SM, Rao S, Patole SK. A systematic review of cooling for neuroprotection in neonates with hypoxic ischemic encephalopathy - are we there yet? *BMC Pediatr.* 2007;5:7-30. <https://doi.org/10.1186/1471-2431-7-30>
15. Sarkar S, Barks JD, Bhagat I, Dechert R, Donn SM. Pulmonary dysfunction and therapeutic hypothermia in asphyxiated newborns: whole body versus selective head cooling. *Am J Perinatol.* 2009;26(4):265-70. <https://doi.org/10.1055/s-0028-1103154>
16. Silveira RC, Procianny RS. Hypothermia therapy for newborns with hypoxic ischemic encephalopathy. *J Pediatr (Rio J).* 2015;91(6 Suppl 1):S78-83. <https://doi.org/10.1016/j.jpeds.2015.07.004>
17. 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(14):1349-58. <https://doi.org/10.1056/NEJMoa0900854>
18. Sarkar S, Barks JD, Bhagat I, Donn SM. Effects of therapeutic hypothermia on multiorgan dysfunction in asphyxiated newborns: whole-body cooling versus selective head cooling. *J Perinatol.* 2009;29(8):558-63. <https://doi.org/10.1038/jp.2009.37>
19. Peliowski-Davidovich A, Canadian Paediatric Society, Fetus and Newborn Committee. Hypothermia for newborns with hypoxic ischemic encephalopathy. *Paediatr Child Health.* 2012;17(1):41-6. <https://doi.org/10.1093/pch/17.1.41>
20. Allen KA. Moderate hypothermia: is selective head cooling or whole body cooling better? *Adv Neonatal Care.* 2014;14(2):113-8. <https://doi.org/10.1097/ANC.000000000000059>
21. Tagin MA, Woolcott CG, Vincer MJ, Whyte RK, Stinson DA. Hypothermia for neonatal hypoxic ischemic encephalopathy: an updated systematic review and meta-analysis. *Arch Pediatr Adolesc Med.* 2012;166(6):558-66. <https://doi.org/10.1001/archpediatrics.2011.1772>
22. Guillet R, Edwards AD, Thoresen M, Ferriero DM, Gluckman PD, Whitelaw A, et al. Seven- to eight-year follow-up of the Cool Cap trial of head cooling for neonatal encephalopathy. *Pediatr Res.* 2012;71(2):205-9. <https://doi.org/10.1038/pr.2011.30>
23. Azzopardi D, Strohm B, Marlow N, Brocklehurst P, Deierl A, Eddama O, et al. Effects of hypothermia for perinatal asphyxia on childhood outcomes. *N Engl J Med.* 2014;371(2):140-9. <https://doi.org/10.1056/NEJMoa1315788>