REVIEW ARTICLE

# Selective head cooling and whole body cooling as neuroprotective agents in severe perinatal asphyxia

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## SUMMARY

INTRODUCTION: *The possibility that hypothermia has a therapeutic role during or after resuscitation from severe perinatal asphyxia has been a longstanding focus of research. Studies designed around this fact have shown that moderate cerebral hypothermia, initiated as early as possible, has been associated with potent, long-lasting neuroprotection in perinatal patients.*

OBJECTIVES: *To review the benefits of hypothermia in improving cellular function, based on the cellular characteristics of hypoxic-ischemic cerebral injury and compare the results of two different methods of cooling the brain parenchyma.*

METHODS: *Medline, Lilacs, Scielo, and PubMed were searched for articles registered between 1990 and 2019 in Portuguese and English, focused on trials comparing the safety and effectiveness of total body cooling with selective head cooling with HIE.*

RESULTS: *We found that full-body cooling provides homogenous cooling to all brain structures, including the peripheral and central regions of the brain. Selective head cooling provides a more extensive cooling to the cortical region of the brain than to the central structures.*

CONCLUSIONS: *Both methods demonstrated to have neuroprotective properties, although full-body cooling provides a broader area of protection. Recently, head cooling combined with some body cooling has been applied, which is the most promising approach. The challenge for the future is to find ways of improving the effectiveness of the treatment.*

KEYWORDS: *Brain Diseases. Hypothermia, Induced. Asphyxia Neonatorum. Hypoxia-Ischemia, Brain. Neuroprotection.*

## INTRODUCTION

In the presence of neonatal asphyxia, the fetus uses a variety of adaptive mechanisms, which include increased blood flow to the brain, heart, and adrenal glands, and diversion of the pulmonary, intestine, liver, kidneys, and skeletal muscle flow, culminating in a slight blood pressure increase and a small change in

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cardiac output. Severe hypoxia and acidosis lead to a decrease in cardiac frequency and cardiac output and a drop in blood pressure, with consequent reduction of the cerebral flow, ischemia, and cellular necrosis.[1,2]

Hypoxic-ischemic injuries of asphyxiated neonates cause Hypoxic-Ischemic Encephalopathy (HIE). This injury is due to hemodynamic changes associated with the prenatal period, during childbirth, and even neonatal events, which can selectively affect vulnerable areas of the central nervous system. The severity of the insult varies with gestational age, and the most serious are those with a high degree of brain-vascular immaturity, in addition to the time of the aggression.[3,4]

Hypoxic-Ischemic Encephalopathy is one of the most significant worldwide problems regarding newborns, leading to death in 10-60 percent of the children affected, and at least 25 percent of the survivors will present long-term neurological sequelae. In Brasil, this is the second cause of neonatal mortality when the first day or the first week of life are considered. HIE is responsible for 18.3 percent and 16.7 percent of deaths in these periods, respectively. HIE is also the most frequent cause in the etiopathogenesis of cerebral palsy, a chronic childhood encephalopathy characterized by non-progressive motor disorders, leading to motor, tonus, and posture disorders, which may or may not be associated with cognitive and sensory deficits.[5,6]

Reports of experiments with hypothermia began to be described around 1964, in a study that suggested a better neurological outcome in newborns (NB) victims of hypoxic insult who were cooled in cold-water baths for 10 minutes after birth.[7]

In order to minimize the high prevalence of HIE, the therapeutic hypothermia procedure is performed worldwide, but the great challenge lies in obtaining conclusions about the effect of hypothermia since there are multiple ways to administer the treatment. Interventions are mainly used in two methods: selective cooling of the head or cooling of the whole body and with further complexities, such as varying temperature variation and cooling time.

## OBJECTIVES

The main objective is to verify the hypothermic therapy potentiality of HIE in neonatal asphyxia, based on literature data, to find the evidence level available comparing the benefits between whole-body cooling or selective head cooling

### Methodology and selection criteria

Medline, Lilacs, Scielo and PubMed were searched for articles registered between 1990 and 2019 in Portuguese and English. We focused on trials comparing the safety and effectiveness of total body cooling with selective head cooling with HIE. The inclusion criteria were clinical trials comparing whole-body cooling with selective head cooling. The exclusion criteria were studies that compared temperatures or standard treatment methods since the goal was to determine which cooling method is best.

### Action mechanisms of therapeutic hypothermia

Therapeutic hypothermia aims to reduce brain metabolism by approximately 5 percent for each 1 °C of body temperature decreased.[8,9]

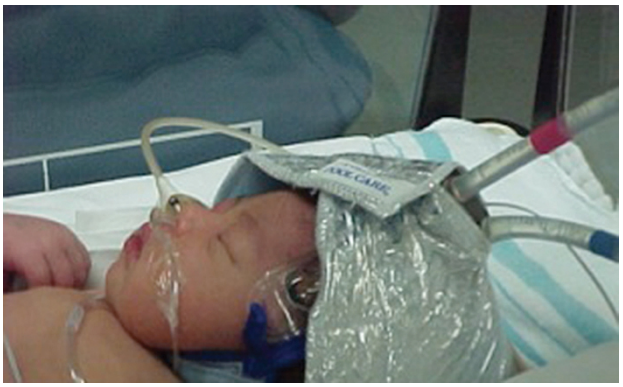

**FIGURE 1.** INFANT ON SELECTIVE HEAD COOLING USING THE COOL-CAP(R).[26]

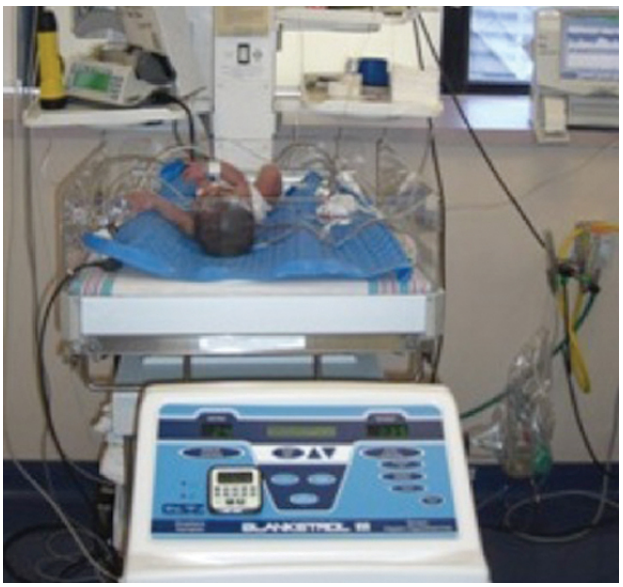

**FIGURE 2.** INFANT ON WHOLE BODY COLLING USING THE BLANKETROL III BY CINCINNATI SUB-ZERO [26]

Basically, such procedure has proved 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), improving ischemic damage by the absorption of glutamate, and decreasing the production of nitric oxide and free radicals, thus reducing neuronal death.[5,10]

Other strategies involved are the reduction of the production of reactive oxygen species, reduction of the metabolic rate with reduction of oxygen consumption, and production of carbon dioxide, and some endogenous neuroprotective effect.[5,11-14] The inhibition of the inflammatory reaction, which always accompanies the ischemic process, was demonstrated by Prandini et cols. with the use of hypothermia in brains of rats that were submitted to an inflammatory process induced by the application of a potent inflammatory substance. The reduction of brain temperature to 30ºC during 120 minutes was demonstrated to be effective in reducing the inflammatory reaction.[15,16]

### Criteria for the application of cooling

Meet both criteria:

1. Evidence of perinatal asphyxia:

- Arterial blood gas analysis of cord blood or in the first hour of life with pH <7.0

or BE <-16

- Or a history of acute perinatal event (abrupt placental abruption, prolapse

of cord)

- Or Apgar score of 5 or less at the 10th minute of life
- Or a need for ventilation beyond the tenth minute of life

2. Evidence of moderate to severe encephalopathy within 6 hours of life: convulsion, level of consciousness, spontaneous activity, posture, tonus, reflexes, and autonomic system. (Table 1)

### Contraindications

Gestational age less than 35 weeks and 0/7 days
Birth weight less than 1800 grams.[8,17]

## RESULTS

Based on the inclusion criteria, five comparative clinical trials were selected, totaling 323 hypoxemic infants.

In the prospective randomized study conducted at the Intensive Care Unit of Newborns of the Mersin University of Medicine, the selective head cooling (SHC) and whole body cooling (WBC) methods were compared. Thirty patients with hypoxic-ischemic encephalopathy born after 35 weeks of gestation were selected. The groups were randomized, with 17 patients assigned to the selective head cooling group and 13 to the whole-body cooling group.

In both groups, the temperature was measured every thirty minutes. The WBC the goal was to keep the actual temperature at 33ºC for 72 hours, and the SHC group goal was to maintain the actual temperature at 34-35ºC for 72 hours. After cooling for 72 hours, the temperature in both groups was increased to 36.5ºC at less or equal to 0.5ºC/h.

The time of the study was twelve months, and at this time, it was possible to observe that there was no significant difference in adverse effects when comparing the two groups. During the period, seven patients in the SHC group and four in the WBC group died; a nonsignificant difference. Adverse effects related to therapy were hypotension, bradycardia, abnormalities in coagulation tests, renal malfunction, hyponatremia, hypokalemia, thrombocytopenia, hypocalcemia, hypoglycemia, high blood concentration, sepsis, and elevated liver enzymes. The complications among patients who survived after twelve months of treatment were severe deficiencies (six in the SHC group and four in the WBC group). The final results of the number of survivors at the end of the study were three survivors in the SHC group and

**TABLE 1.** CRITERIA FOR DEFINING MODERATE AND SEVERE ENCEPHALOPATHY

| Category | Moderate encephalopathy | Severe Encephalopathy |
|---|---|---|
| Level of consciousness | lethargic | Stupor or coma |
| Spontaneous activity | Decreased activity | No activity |
| Posture | Distal flexion, complete extension | Decerebrate |
| Tone | Hypotonia ( focal or general) | Flaccid |
| Primitive reflexes:<br>Suck<br>Moro | <br>Weak<br>Incomplete | <br>Absent<br>Absent |
| Autonomic System:<br>Pupils<br>Heart Rate<br>Respiration | <br>Constricted<br>Bradycardia<br>Periodic Breathing | <br>Deviated, dilated or nonreactive to light<br>Variable<br>Apnea |

Source: Shankaran et al.17

four in the WBC group. Therefore, we can conclude that there were no significant differences between the two treatments, both related to complications and related to death. [18]

Sakar et al.[19] at the University of Michigan conducted a randomized study on therapeutic hypothermia as a neuroprotective factor in neonates with hypoxic-ischemic encephalopathy. Both selective cranial cooling (CSR) and total body cooling (WCT) were used in infants of gestational age greater than or equal to 36 weeks and who had significant hypoxic-ischemic encephalopathy. A total of 59 infants were enrolled, 28 children who received total body cooling and 31 children who received selective head cooling. Hypotension, urinary output <0.5 ml/kg/h for> 24 hours after birth, and electrolyte abnormalities (hyponatremia, hypokalemia, hypocalcemia) were also observed in the groups. Coagulopathy, thrombocytopenia, hypotension. This study suggests that none of the cooling methods offers a lower risk of organic dysfunction[19].

In the non-randomized retrospective study conducted by the University of Michigan, the authors hypothesized that hypoxic-ischemic lesions observed on brain magnetic resonance imaging after cooling were able to differentiate both cooling modalities. The objective was to compare the frequency, distribution, and severity of hypoxic-ischemic lesions between SHC and whole-body cooling WBC. Ninety-eight newborns were selected, but it was possible to use magnetic resonance imaging in 83, of which 34 were subjected to SHC and 49 to WBC. All of them underwent magnetic resonance imaging between 7 and 10 days of life. The classification of brain lesions included two patterns of images in infants with asphyxia: primary lesion of the nucleus of the gray matter, and primary lesion in the areas of vascular borders. Hypoxic-ischemic lesions were observed on MRI after cooling in 47 of 83 infants. The distribution of the lesions was: BGT in 7, cortical not extending beyond the areas of hydrocephalus in 16, cortical not extending beyond the areas of hydrocephalus and basal nuclei in 5, and cortical extending beyond hydrocephalus and basal nuclei in 19. Magnetic resonance imaging was more frequent in patients with CRS, and they still presented more severe lesions.

When comparing the two methods, they observed that during SHC, a relatively better protective effect could be achieved on the cortex. However, no differences were observed between isolated lesions of the cortex. The cortical lesions may not be seen immediately after the examination so they may have been missed because they were examined very early. Another limitation they found was that, because of the retrospective design, it was impossible to rule out the possibility that babies in the SHC group may have had a worse prognosis because of the more severe initial brain lesions.[20]

In another perspective on the differences in hypothermia application, Sakar et al.[21] assumed that SHC allows effective cerebral cooling with less systemic hypothermia and potentially fewer systemic adverse effects. Based on this, they proposed to evaluate pulmonary dysfunction and the potential adverse systemic effects of neuroprotection compared to WBC. Sixty-three infants with gestational period greater than or equal to 36 weeks were selected to receive neuroprotective hypothermia in cases of moderate or severe hypoxic-ischemic encephalopathy. Among these, 33 NB met the clinical, laboratory, and amplitude integrated electroencephalography (aEEG) criteria for the Cool Cap protocol, and received SHC. Another 28 newborns with clinical conditions and similar laboratory criteria received WBC. They observed that the incidence of persistent pulmonary hypertension of the newborn (HPPN) was similar in the WBC and SHC groups and that pulmonary mechanics and gas exchange did not differ with the method of obtaining hypothermia. [21]

Hoque et al.[22] conducted an observational study with four groups who received hypothermia in different ways to determine the differences in temperature and hemodynamic stability between the groups. A total of 73 newborns with HIE were subdivided into four groups: selective head cooling (n = 20), whole-body cooling with manually controlled mattress (n = 23), whole-body cooling with control-wrapped body wrap (n = 28). Hemodynamic changes in mean arterial pressure (MAP) and central temperature in maintenance and rewarming were higher in the whole group, compared to the whole-body servo-controlled group. This means that the difficulty in minimizing maximum variation manually can lead to possible systemic changes, which could compromise the long-term goal of hypothermia.[22]

In a study that assessed the difference between temperatures and cerebral blood flow during selective head cooling and whole-body cooling in 17 pigs, it was observed that initial cooling of the head with constant rectal temperature resulted in an increase

in the temperature gradient in the brain from the warmest central structures to the periphery of the chiller (brain 2cm – dura temperature: 1.3 +/- 1.1 °C on the control to 7.5 +/- 3.5 °C during cooling). Hypoxia overlaid on head cooling decreased the temperature gradient by at least 50 percent. In contrast, body cooling was associated with an unchanged temperature gradient in the brain (brain 2 cm – dura temperature: 1.5 +/- 1.2 °C in the control up to 1.1 +/- 0.9 ° C during cooling).

Hypoxia overlaid on body cooling did not alter brain temperature. Both modes of brain cooling resulted in similar reductions in the overall uptake of cerebral blood flow (approximately 40 percent). This means that whole body cooling provides homogenous cooling to all brain structures, including the peripheral and central regions of the brain. Selective head cooling provides greater cooling to the periphery of the brain than to the central structures of the brain. [23]

## DISCUSSION AND CONCLUSION

Based on the evidence, full-body cooling provides homogenous cooling to all brain structures, including the peripheral and central regions of the brain. Selective head cooling provides a wider cooling to the cortical region of the brain than to the central structures. Adverse effects in the five studies analyzed were not significantly different regarding vital organ dysfunction.

Another important observation is that, in order to systematize the application, regardless of the methodology chosen for the cooling, the maintenance of the temperature must be done through servo-controlled monitoring, thus minimizing variations in temperature, blood flow, mean arterial pressure, and others parameters that should be evaluated with caution since the results of hypothermia may be affected.

For improved benefit, head cooling combined with some body cooling has been applied [24,25] and showed that it minimizes temperature gradients throughout the brain and facilitates cooling of the central regions. The association of both methods may be the most promising approach.

The main remaining problems are finding better ways to identify the babies most likely to be benefited, defining the ideal mode and conditions of hypothermia, and finding ways to improve treatment efficacy further and decrease sequelae and deaths.

The limitation of the present review was that most clinical trials are based on one hypothermia manner, SHC or WBC, compared to the standard treatment (normothermia). Clinical trials comparing the modalities of hypothermia between head and the whole-body are being conducted worldwide, so we should get its true benefits, better results, and the shortest negative impact on one of the modalities.

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### Author Contributions

[1] Mahara Nonato: Dissertation, interpretation and data analysis;

[2] Larissa Gheler: Dissertation, interpretation and data analysis;

[3] João Vitor Balestrieri: Dissertation, interpretation and data analysis;

[4] Marise Audi: Guidance and finalization;

[5] Mirto Prandini: Guidance and finalization


## RESUMO

INTRODUÇÃO: *A possibilidade de a hipotermia ter um papel terapêutico durante ou após a reanimação da asfixia perinatal grave tem sido um foco de pesquisa de longa data. Estudos desenhados em torno desse fato mostraram que a hipotermia cerebral moderada, iniciada o mais cedo possível, tem sido associada à neuroproteção potente e duradoura em espécies perinatais.*

OBJETIVOS: *Resumidamente, analisar os benefícios da hipotermia na melhoria da função celular, com base nas características celulares da lesão cerebral hipóxico-isquêmica e comparar os resultados de dois métodos diferentes de resfriamento do parênquima cerebral.*

MATERIAL E MÉTODOS: *Medline, Lilacs, SciELO e PubMed foram pesquisados para artigos registrados entre 1990 e 2019 nos idiomas português e inglês, com foco em estudos comparando segurança e eficácia do resfriamento corporal total com o resfriamento seletivo da cabeça com EHI.*

RESULTADOS: *Descobrimos que o resfriamento de corpo inteiro fornece resfriamento homogêneo para todas as estruturas cerebrais, incluindo as regiões periférica e central do cérebro. O resfriamento seletivo da cabeça fornece um resfriamento mais amplo para a região cortical do cérebro do que para as estruturas centrais.*

CONCLUSÕES: *Ambos os métodos demonstraram ter propriedades neuroprotetoras, embora o resfriamento de corpo inteiro forneça uma área mais ampla de proteção. Recentemente, o resfriamento da cabeça combinado com algum resfriamento corporal foi aplicado e essa é a maneira mais promissora. O desafio para o futuro é encontrar formas de melhorar a eficácia do tratamento.*

PALAVRAS-CHAVE: *Encefalopatias. Hipotermia induzida. Asfixia neonatal. Hipóxia-isquemia encefálica. Neuroproteção.*

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