# Addition of melatonin to hypothermia therapy for neonatal hypoxic-ischemic encephalopathy

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**Citation** Meza V. V, Toso M. P. Adición de melatonina a terapia con hipotermia para encefalopatía hipóxico-isquémica neonatal. *Medwave* 2022;22(8):e2568

**Doi** 10.5867/medwave.2022.08.2568

**Submission date** 26/01/2022
**Acceptance date** 13/08/2022
**Publication date** 30/09/2022

**Origin and peer review** Not commissioned. Externally peer-reviewed by two reviewers, double-blind.

**Competing interests** The authors declare that they have no conflicts of interest with the subject matter of this article.

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**Keywords** Hypoxic-ischemic encephalopathy, Melatonin, Induced hypothermia, Epistemonikos, GRADE.

## Abstract

### Introduction

Neonatal hypoxic-ischemic encephalopathy is caused by perinatal asphyxia, resulting in an acute neurological dysfunction of variable severity. It occurs in one to six of every 1000 full-term newborns and is associated with high neonatal morbimortality and adverse neurological outcomes. The use of hypothermia is considered the standard therapy for this condition. However, different adjuvant therapeutic options have been proposed due to limited clinical efficacy, including drugs like melatonin. There is controversy about whether combined therapy with melatonin is superior to monotherapy with hypothermia.

### Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, and Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of the findings table using the GRADE approach.

### Results

We identified two systematic reviews that included two primary studies, both randomized trials. The two randomized trials were included in the analysis of the present work.

### Conclusion

It is not possible to establish whether the addition of melatonin decreases mortality or the probability of alterations in brain magnetic resonance imaging because the certainty of the existing evidence has been assessed as very low. On the other hand, the addition of melatonin to hypothermia therapy, compared to hypothermia monotherapy, may increase the probability of normal neurological examination at six months and the probability of normal cognition at 18 months. Finally, adding melatonin to hypothermia therapy likely reduces the probability of seizures.

## Problem

Hypoxic-ischemic neonatal encephalopathy is characterized by acute neurological dysfunction of variable severity caused by perinatal asphyxia [1]. In these episodes, hypoxia generates excitotoxicity and the accumulation of free radicals, nitric oxide, cytokines, and intracellular calcium, resulting in neural necrosis [2]. Clinically, it is possible to classify this pathology into three stages according to the modified Sarnat Classification to assess prognosis [3].

Hypoxic-ischemic neonatal encephalopathy incidence is estimated to be one to six per 1000 term newborns [4] and is associated with high neonatal mortality. Mortality rates are close to 10% in patients with moderate disease and up to 60% in cases of severe neonatal disease [5]. Moreover, about 30% of surviving patients with moderate and virtually all patients with severe neonatal hypoxic-ischemic encephalopathy have severe neurological sequelae, including cerebral palsy [5]

Currently, the standard therapy for neonatal hypoxic-ischemic encephalopathy is based on hypothermia treatment, consisting of the controlled reduction of body temperature by two to four degrees Celsius during the first six hours of life. Multiple studies have validated this therapy due to its neuroprotective capacity [6]. However, it has been shown that approximately half of the cases do not obtain significant clinical benefits from hypothermia as monotherapy [7].

In this context, new adjuvant treatments have been studied, highlighting the therapeutic potential of using melatonin – a neurohormone with antioxidant and anti-inflammatory properties – and its ability to cross the blood-brain barrier [8]. Other therapeutic options currently under study include erythropoietin, magnesium, allopurinol, and xenon [1].

Although the therapeutic addition of melatonin could decrease mortality and improve neurological outcomes [9], there is currently no consensus on whether hypothermia monotherapy or combination therapy with the addition of melatonin should be used [9-12]. For this reason, it is essential to provide a summary of the evidence that allows a comparison of both treatments.

## Main messages

- It is not possible to establish whether the addition of melatonin decreases mortality or the probability of presenting alterations reflected in brain magnetic resonance imaging because the certainty of the existing evidence has been evaluated as very low.
- Adding melatonin to hypothermia compared to hypothermia monotherapy may increase the likelihood of normal neurologic examination at six months and normal cognition at 18 months (low certainty of the evidence).
- Adding melatonin to hypothermia compared to hypothermia monotherapy may likely decrease the likelihood of seizures (moderate certainty of the evidence).

## About the body of evidence for this question

| | |
|---|---|
| What is the evidence?<br><br>See the evidence matrix in Epistemonikos below. | We found two systematic reviews [9-10], which included two primary studies [13],[14], both randomized trials.<br><br>This table and the summary are based on both trials. |
| What type of patients did the studies include? * | One trial [13] included 30 term infants diagnosed with neonatal hypoxic-ischemic encephalopathy.<br><br>The other study [14] included 25 preterm or term infants diagnosed with neonatal hypoxic-ischemic encephalopathy.<br><br>Exclusion criteria were not reported in either trial [13],[14]. |
| What type of interventions did the studies include? * | Both trials [13],[14] compared melatonin and hypothermia therapy versus hypothermia monotherapy. |

## Métodos

We searched Epistemonikos, the largest database of systematic reviews in health, which is maintained by searching multiple information sources, including MEDLINE, EMBASE, and Cochrane, among others. We extracted and analyzed the data from the primary studies of the identified reviews and generated a structured summary called FRISBEE (Friendly Summaries of Body of Evidence using Epistemonikos). We followed a preestablished format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), a meta-analysis of all studies, when possible, a summary table of results with the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) method, and a section of other considerations for decision-making.

| | |
|---|---|
| | The doses of melatonin used in one trial [13] were 10 milligrams per kilogram of body weight per day by orogastric tube, completing five doses in total.<br><br>The doses of melatonin used in the other trial [14] were five milligrams per kilogram of body weight per day by the intravenous route, completing three doses in total.<br><br>Both trials [13],[14] used manual hypothermia controlled with ice packs for three days for both the intervention and control groups. |
| What type of outcomes were measured? | The trials reported multiple outcomes, which were grouped by the systematic reviews as follows:<br><br>• Mortality<br>• Normal neurological examination at six months.<br>• Neurodevelopment delay at six and 18 months.<br>• Seizures<br>• Alterations in brain magnetic resonance imaging.<br><br>The follow-up of one trial [13] was six months, while the follow-up of the other study [13] was 18 months. |

* Information on primary studies is extracted from the identified systematic reviews and not directly from the studies unless otherwise specified.

## Summary of results

Information on the effects of adding melatonin to hypothermia therapy for neonatal hypoxic-ischemic encephalopathy is based on two trials [13],[14] involving 55 patients. Both trials [13],[14] measured mortality, the presence of seizures, and brain magnetic resonance imaging alterations. One trial [13] measured neurological examinations at six months, while the other trial [14] assessed neurodevelopment at six and 18 months. None of the trials reported the presence of clinical adverse effects.

## The summary of the results is as follows:

- It is not possible to establish whether adding melatonin to hypothermia therapy compared to hypothermia monotherapy decreases mortality because the certainty of the existing evidence has been assessed as very low.
- It is not possible to establish whether adding melatonin to hypothermia therapy compared to hypothermia monotherapy decreases the likelihood of having brain magnetic resonance imaging alterations because the certainty of the existing evidence has been assessed as very low.
- Adding melatonin to hypothermia compared to hypothermia monotherapy may increase the likelihood of a normal neurologic examination at six months (low certainty of the evidence).
- Adding melatonin to hypothermia compared to hypothermia monotherapy could increase the likelihood of normal cognition at 18 months (low certainty of the evidence).
- Adding melatonin to hypothermia use compared to hypothermia monotherapy is likely to decrease the likelihood of seizures (moderate certainty of the evidence).

**The addition of melatonin to hypothermia therapy compared to hypothermia monotherapy in neonatal hypoxic-ischemic encephalopathy**

**Patients** Newborns with neonatal hypoxic-ischemic encephalopathy
**Intervention** Addition of melatonin to hypothermia therapy
**Comparison** Monotherapy with hypothermia

| Outcomes | Absolute effect size* | | Relative risk (95% CI) | Certainty in evidence (GRADE) |
|---|---|---|---|---|
| | **WITHOUT melatonin** | **WITH melatonin** | | |
| | Difference: patients per 1000 | | | |
| Mortality | 179 per 1000 | 77 per 1000 | RR 0.43 (0.08 to 2.23) | ⊕◯◯◯[I] Very low |
| | Difference: -102 (Margin of error: -164 to 220) | | | |
| Normal neurological examination at six months ** | 273 per 1000 | 715 per 1000 | RR 2.62 (0.94 to 7.27) | ⊕⊕◯◯[II] Low |
| | Difference: 442 (Margin of error: -16 to 1710) | | | |
| Neurodevelopment at 18 months *** | One trial [14] found a significant increase in the composite cognitive score in the intervention group compared to the control group without describing its magnitude. No significant differences were observed in the other neurodevelopmental components.<br>In the other trial [13] this outcome was neither measured nor reported. | | - | ⊕⊕◯◯[II] Low |
| Seizures† | 375 per 1000 | 139 per 1000 | RR 0.37 (0.14 to 0.99) | ⊕⊕⊕◯[III] Moderate |
| | Difference: -236 (Margin de error: -323 to -4) | | | |
| Brain magnetic resonance imaging alterations †† | Neither of the two studies [13-14] found significant differences in the percentages of gray matter and basal ganglia alterations in the intervention group compared to the control group.<br><br>One trial [13] found a lower percentage of white matter alterations in the intervention group compared to the control group: zero of 14 patients versus four of 11 patients, respectively (relative risk: 0.9; 95% confidence interval: 0.01 to 1.49); while the other study [14] mentions no significant difference between the two groups, without describing the frequencies or percentages of each group. | | - | ⊕◯◯◯[I] Very low |
| Adverse effects | The clinical outcome of adverse effects was not reported. | | - | - |

**Margin of error:** 95% confidence Interval (95% CI).
**MD:** Mean difference.
**RR**: Relative risk
**GRADE:** Levels of evidence from GRADE *Working Group* (see below).
*The mean **WITHOUT melatonin** is based on the study's average of the control group. The mean **WITH melatonin** (and its margin of error) is calculated from the mean difference (and its error margin).

** The outcome "neurological examination" was measured by performing a clinical neurological assessment in addition to using the Denver Developmental Screening Test II (DDST-II) scale [15]. This scale assesses four major categories (gross motor, adaptive fine motor, language, and personal-social) using multiple items or 'tasks'. A test with at least two failures in the 'tasks' is considered 'abnormal', and a test with at least two categories with a single failure in any 'task' is considered 'borderline'.

*** The outcome "neurodevelopment" was measured using the Bayley III scale [16], which measures cognitive, language, motor, adaptive and socio-emotional levels. In turn, some of these areas are divided into subtests, as in the case of the motor area: fine motor and gross motor. The standardized mean score on this scale is 100 (standard deviation of 15); scores below 85 indicate mild impairment, and below 70 indicates moderate or severe impairment. The Cognitive Composite Score corresponds to the score obtained in the cognitive area of the scale. The Gross Motor Function Classification System (GMFCS) and the Tardieu Scale [17] were also used.

† The outcome "seizures" was measured by 16-channel electroencephalogram, bipolar montage, in 10/20 position, considering as abnormalities paroxysms of more than 10 seconds duration, in the absence of artifacts.

†† In the outcome "brain magnetic resonance imaging abnormalities", the posterior limb of the internal capsule (PLIC), basal ganglia, and thalami were evaluated. Abnormalities were classified as (1) mild if there were focal lesions involving the posterior lentiform nuclei or ventrolateral nuclei of the thalami and (2) moderate-severe if there was an involvement of the PLIC or widespread abnormalities in the thalami and/or all regions of the basal ganglia. White matter imaging was classified as (1) normal/minimal, indicating no abnormalities or only minimal lesions affecting a small focus; or (2) moderate-severe, if there were larger lesions, with involvement of subcortical areas or with the presence of hemorrhage, infarcts and/or loss of gray/white matter differentiation [18]. Magnetic resonance imaging was performed during the first week of life in one trial [14], while in the other trial [13], it was performed at two weeks of life. In both trials [13-14], the percentages of alterations in the control and intervention groups were compared, considering the gray matter, basal ganglia, and white matter.

No meta-analysis was performed because the systematic reviews included in the present study only reported the frequencies of white matter alterations from one study.

[I] Three levels of certainty of evidence were downgraded for risk of bias, inconsistency, and imprecision. For the mortality outcome, the confidence interval limits are wide, favoring one therapy or another at each confidence interval limit.
[II] Two levels of certainty of evidence were downgraded for imprecision and risk of bias. For the outcome of normal neurologic examination at six months, the confidence interval limits range from a value close to no effect to one that favors the use of combination therapy.
[III] One level of certainty of the evidence was lowered due to the risk of bias.

## About the levels of evidence (GRADE)*

⊕⊕⊕⊕
**High:** the research provides a very good indication of the likely effect. The probability that the effect is substantially different† is low.

⊕⊕⊕◯
**Moderate:** the research provides a good indication of the likely effect. The probability that the effect is substantially different† is moderate.

⊕⊕◯◯
**Low:** research provides some indication of the likely effect. However, the probability that the effect will be substantially different† is high.

⊕◯◯◯
**Very low:** research does not provide a reliable estimate of the likely effect. The probability that the effect is substantially different† is very high.

*This is also called 'quality of evidence' or 'confidence in the effect estimate'.

†Substantially different = a difference large enough to affect a decision.

## Otras consideraciones para la toma de decisión

### To whom this evidence applies and to whom it does not apply

The evidence presented applies to patients diagnosed with neonatal hypoxic-ischemic encephalopathy who have not received treatment for this pathology.

### About the outcomes included in this summary

Mortality, normal neurological examination at six months, and adequate neurodevelopment at 18 months were included as these are the most critical outcomes for patients and their caregivers, according to the authors of this review.

The outcomes of seizures and brain magnetic resonance imaging alterations were evaluated, despite being secondary outcomes, since they are associated with worse response to treatment and worse neurological prognosis in the medium and long term.

The outcomes included in the summary are those considered relevant for decision-making by the authors, coinciding with those reported by the systematic reviews.

### Harm/benefit balance and certainty in evidence

When comparing the benefits and risks between the two therapies, it is not possible to establish whether the combined treatment decreases mortality or the probability of presenting alterations reflected on brain magnetic resonance imaging because the certainty of the existing evidence has been evaluated as very low. In addition, melatonin use may increase the likelihood of normal neurologic examination at six months (low certainty of the evidence), normal cognition at 18 months (low certainty of the evidence), and probably decreases the likelihood of seizures (moderate certainty of the evidence).

On the other hand, no adverse effects associated with the combination of both therapies are reported compared to hypothermia monotherapy.

However, it is not possible to perform a correct harm/benefit balance analysis regarding the use of melatonin, given the current uncertainty in the evidence, so other aspects should be considered for decision-making.

### Costs

The included systematic reviews did not perform a cost-effectiveness analysis between the two treatments.

Melatonin is a drug with low cost and wide availability. It is available in various presentations, including three, five, and 10-milligram tablets and in one milligram per milliliter solution for intravenous application.

Therefore, a cost-effectiveness analysis of the two therapies is essential.

### What do patients and their caregivers think

Although many physicians favor combination therapy, uncertainty remains as to its potential superiority compared to hypothermia monotherapy.

In addition, the ideal route of administration, dosage, and duration of melatonin treatment has not yet been studied or defined.

Caregivers are likely to prefer melatonin addition over treatment with hypothermia alone as monotherapy, given the potential benefit of melatonin use, its low cost, and the absence of reports of adverse effects associated with its use.

### Differences between this summary and other sources

This summary's conclusions align with the two included systematic reviews [9-10] because, given the evidence's uncertainty, it is impossible to establish a treatment's superiority.

When comparing with international clinical guidelines, it is noted that both the Japanese Society of Neonatology [11] and the Spanish Clinical Practice Guideline [12] state that there is controversy about the superiority of combination therapy compared to monotherapy. Consequently, further studies are needed, which can be extrapolated to the results of this review.

### Could this information change in the future?

The likelihood that future evidence will change the conclusions of this summary is high due to current uncertainty.

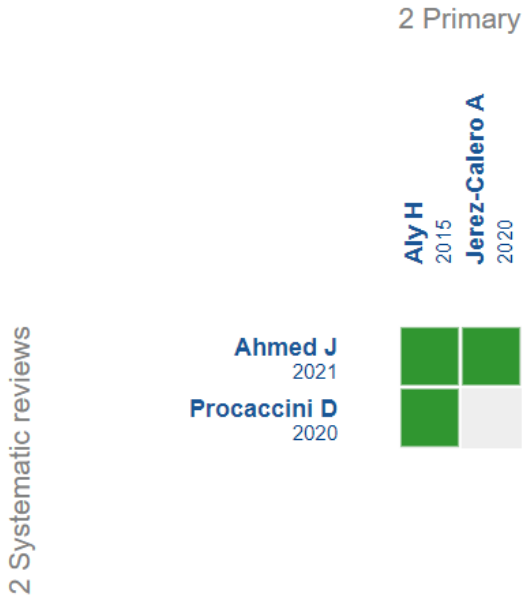
We identified a systematic review on the PROSPERO platform comparing combination therapy with hypothermia monotherapy for neonatal hypoxic encephalopathy that may shed new light on the topic [19].

Two trials were found on the National Institutes of Health (NIH) ClinicalTrials.gov platform comparing combination therapy versus hypothermia monotherapy for hypoxic neonatal encephalopathy [20-21]. Both studies are still in the recruitment phase and may shed new light on the topic once concluded.

In addition, further studies evaluating the optimal dose and additive effects of melatonin over a longer time frame are needed because of its potential influence on neuromodulation following asphyxiation.

## How we made this summary

Using automated and collaborative methods, we compile all the evidence relevant to the question of interest and present it in an evidence matrix.




Follow the link to access the **interactive version:**

Melatonin + hypothermia versus hypothermia monotherapy for neonatal hypoxic-ischemic encephalopathy.

## Notes

If new systematic reviews on this topic are published after the publication of this abstract, a "new evidence" notice will be displayed at the top of the matrix. While the project envisages regular updating of these abstracts, users are invited to comment on the Medwave website or contact the authors by e-mail if they believe there are evidence that warrants an earlier update.

After creating an Epistemonikos account, by saving the matrices, you will receive automatic notifications whenever there is new evidence that potentially answers this question.

This article is part of the Epistemonikos evidence synthesis project. It is elaborated with a pre-established methodology, rigorous methodological standards, and an internal peer review process. Each of these articles corresponds to a summary called FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence of a specific question in a friendly format for clinicians. Its main resources are based on the Epistemonikos evidence matrix and analysis of results using the GRADE methodology. Further details of the methods to elaborate this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997).

The Epistemonikos Foundation is an organization that seeks to bring information closer to health decision-makers through the use of technologies. Its main development is the Epistemonikos database (www.epistemonikos.org).

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