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Effect of Melatonin on Neonatal Asphyxia and Hypoxic-Ischemic Encephalopathy: A Systematic Review and Meta-Analysis (2000-2024)

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Abstract

Background: Neonatal asphyxia and hypoxic-ischemic encephalopathy (HIE) affect 1–3 per 1,000 term births and are associated with severe outcomes, including cerebral palsy, epilepsy, and developmental delays. Melatonin, a hormone with antioxidant, anti-inflammatory, and anti-apoptotic properties, has shown promise in reducing brain injury. This systematic review and meta-analysis aimed to assess the neuroprotective and therapeutic effects of melatonin in neonates with HIE, focusing on mortality, neurodevelopment, and biochemical markers of brain injury, and evaluating its efficacy and safety alone or in combination with therapeutic hypothermia (HT).

Materials and Methods: A systematic search was conducted in PubMed, Scopus, Web of Science, and Embase for studies published from January 2000 to December 2024. Search terms included "melatonin," "neonatal asphyxia," "hypoxic-ischemic encephalopathy," "neuroprotection," and "neonate." Eligible studies included randomized controlled trials (RCTs), observational, and preclinical studies examining melatonin's effects in neonatal HIE. Data were extracted on study design, population, dosage, timing, and outcomes. Random-effects models were used for meta-analysis, with heterogeneity assessed by I^2 and publication bias by funnel plots.

Results: A total of 42 studies were included (12 RCTs, 15 observational, 15 preclinical). Melatonin administered within 24 hours of birth improved neurodevelopmental outcomes and reduced oxidative stress and brain injury. The Bayley Developmental Score improved significantly (SMD = 0.65; 95% CI: 0.32–0.98; $p < 0.01$), and cerebral palsy risk decreased (RR = 0.72; 95% CI: 0.55–0.94; $p = 0.02$). No serious adverse events were reported.

Conclusion: Melatonin appears to be a safe and effective adjunct in treating neonatal HIE, improving outcomes and minimizing injury. Further large-scale trials are warranted to confirm efficacy and guide clinical use.

Key Words: Hypoxic-Ischemic Encephalopathy, HIE, Melatonin, Neonatal Asphyxia, Neuroprotection.

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1- INTRODUCTION

Neonatal asphyxia, defined as impaired gas exchange or blood flow during the perinatal period, can lead to hypoxic-ischemic encephalopathy (HIE), a significant cause of brain injury in newborns. HIE affects 1-3 per 1,000 live full-term births and is associated with severe outcomes, including cerebral palsy, epilepsy, and developmental delays (1). The pathophysiology of HIE involves a cascade of events, including energy failure, oxidative stress, inflammation, and apoptosis, which contribute to neuronal damage (2). Current treatments, such as therapeutic hypothermia (HT), are partially effective and must be administered within a narrow time window. Despite HT, approximately 48% of treated infants still experience adverse outcomes, highlighting the need for additional neuroprotective strategies (1,2).

Melatonin (N-acetyl-5-methoxytryptamine), a hormone secreted by the pineal gland, regulates circadian rhythms and possesses potent antioxidant, anti-inflammatory, and anti-apoptotic properties (3). Preclinical studies in animal models of HIE have demonstrated that melatonin reduces cerebral infarct size and improves neurobehavioral outcomes. It decreases cell death through multiple mechanisms, including scavenging free radicals, inhibiting the NLRP3 inflammasome, and modulating microglial activation (2,3).

The objective of this systematic review and meta-analysis is to synthesize clinical evidence on the neuroprotective and therapeutic effects of melatonin in neonates with HIE, focusing on mortality, neurodevelopmental outcomes, and biochemical markers of brain injury.

This study aims to evaluate the efficacy and safety of melatonin, alone or combined with therapeutic hypothermia, in neonates with HIE, and to identify gaps in current evidence to guide future research directions.

2- MATERIALS AND METHODS

A systematic search was conducted across PubMed, Scopus, Web of Science, and Embase for studies published between January 2000 and December 2024. Search terms included "melatonin," "neonatal asphyxia," "hypoxic-ischemic encephalopathy," "neuroprotection," and "neonate." Reference lists and grey literature were hand-searched for additional studies.

2-1. Inclusion and Exclusion Criteria

Studies were included if they:

1.Investigated melatonin in neonatal asphyxia or HIE (human or animal models).
2.Were published between 2000 and 2024.
3.Reported outcomes related to neurological function, oxidative stress, or brain injury.
4. Were randomized controlled trials (RCTs), cohort studies, case-control studies, or preclinical studies with robust methodology.

Studies were excluded if they:

1.Lacked a control group or clear outcome measures.
2.Focused on non-neonatal populations or unrelated conditions.
3.Were published in non-English languages without translations.
Studies with missing data were included only if sufficient information could be obtained from the authors or supplementary materials. Unpublished studies were searched through grey literature, but none met inclusion criteria.

2-2. Data Extraction and Analysis

Study selection and data extraction were performed independently by two

reviewers, and any discrepancies were resolved through discussion.

Data were extracted on study design, population, melatonin dosage, administration timing, and outcomes (e.g., neurodevelopmental scores, oxidative stress biomarkers, neuroimaging findings). Meta-analyses used random-effects models to calculate pooled effect sizes for continuous outcomes (e.g., Apgar scores, biomarker levels) and risk ratios for dichotomous outcomes (e.g., mortality, neurological deficits). Heterogeneity was assessed using the I^2 statistic, and publication bias was evaluated via funnel plots.

The quality of included studies and risk of bias were assessed using appropriate tools: the Cochrane Risk of Bias tool for RCTs and the Newcastle-Ottawa Scale for observational studies.

3-RESULT

Forty-two studies were included: 12 RCTs, 15 observational studies, and 15 preclinical studies. Twenty studies involved human neonates with HIE, and 22 used animal models primarily rodents and piglets. Melatonin dosages ranged from 5 to 50 mg/kg in preclinical studies and 0.5 to 10 mg/kg in human studies, administered enterally or parenterally.

3-1. Clinical Outcomes

3-1-1. Neurodevelopmental Outcomes

RCTs showed that melatonin administration within 24 hours of birth improved Bayley Scales of Infant Development scores at 6–12 months (SMD= 0.65, 95% CI: 0.32–0.98, $p < 0.01$, I^2 =45%) (4,5). Observational studies reported a reduced incidence of cerebral palsy in melatonin-treated groups (RR= 0.72, 95% CI: 0.55–0.94, $p = 0.02$) (6).

3-1-2. Mortality

Melatonin was associated with a non-significant reduction in neonatal mortality (RR = 0.82, 95% CI: 0.66–1.02, $p = 0.07$, $I^2 = 30\%$) (7).

3-1-3. Brain Injury Severity

Neuroimaging (MRI, ultrasound) revealed reduced lesion volumes in melatonin-treated neonates (SMD = -0.48, 95% CI: -0.76 to -0.20, $p < 0.01$) (8,9).

3-1-4. Biochemical Outcomes

Melatonin significantly reduced oxidative stress markers, such as malondialdehyde (MDA) (SMD = -1.12, 95% CI: -1.45 to -0.79, $p < 0.001$) and increased superoxide dismutase (SOD) activity (SMD = 0.88, 95% CI: 0.54–1.22, $p < 0.001$) (10,11). Anti-inflammatory effects included decreased levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) (12).

3-2. Preclinical Findings

Animal studies demonstrated reduced neuronal apoptosis, preserved blood-brain barrier integrity, and attenuated microglial activation with melatonin (13,14). These effects were dose-dependent, with higher doses (20–50 mg/kg) showing greater neuroprotection (15).

3-3. Safety

No serious adverse events were reported in human studies. Mild side effects, such as transient sedation, occurred in less than 5% of cases (16). Preclinical studies confirmed no significant toxicity at high doses (17).

4- DISCUSSION

The findings of this systematic review and meta-analysis highlight melatonin's potential as a neuroprotective agent in neonatal asphyxia and HIE. The observed improvements in neurodevelopmental outcomes, particularly in Bayley scores and reduced cerebral palsy incidence, suggest that

melatonin may help mitigate long-term neurological deficits (4,6).

These benefits are likely driven by melatonin's multifaceted mechanisms, including scavenging free radicals, modulating inflammatory pathways, and inhibiting excitotoxicity (3,18). The significant reduction in oxidative stress markers, such as MDA, and the upregulation of antioxidant enzymes like SOD further support melatonin's role in counteracting the oxidative damage central to HIE pathophysiology (10,11).

The non-significant reduction in mortality ($p = 0.07$) may reflect the limited number of studies adequately powered to assess this outcome (7). Variability in melatonin dosing (0.5–10 mg/kg in humans) and administration timing (within 6–24 hours post-birth) introduces heterogeneity, complicating direct comparisons (5,8).

Preclinical studies provide valuable mechanistic insights, demonstrating melatonin's ability to preserve neuronal integrity and reduce inflammation in animal models of HIE (13,14).

The synergy between melatonin and therapeutic hypothermia is an area of growing interest. Preliminary studies suggest that combining melatonin with hypothermia may enhance neuroprotection by targeting complementary pathways, such as oxidative stress and apoptosis (19,20). However, the optimal timing, dosage, and administration route (enteral vs. parenteral) remain unresolved. For instance, early administration (within 6 hours) appears more effective in preclinical models, but human studies often initiate treatment later due to diagnostic delays (21). This discrepancy highlights the need for standardized protocols to maximize therapeutic efficacy.

Safety data are reassuring, with no serious adverse events reported in human trials (16). The mild sedation observed in some neonates may even be beneficial, potentially reducing metabolic demand during the acute phase of HIE (22). However, long-term safety data, particularly regarding repeated dosing, are sparse and warrant further investigation (23).

Limitations of this review include the small number of high-quality RCTs, with many studies having modest sample sizes (4,5). Observational studies, while valuable, are prone to confounding and selection bias (6). Heterogeneity in study populations (e.g., term vs. preterm infants) and outcome measures (e.g., different neurodevelopmental scales) complicates meta-analysis (24). Publication bias, as suggested by funnel plot asymmetry in some outcomes, may overestimate melatonin's effects (25). Additionally, most human studies were conducted in high-resource settings, limiting generalizability to low-resource environments where HIE is more prevalent (26).

Future research should prioritize large-scale, multicenter RCTs to establish optimal dosing regimens, timing, and combination therapies (27). Long-term follow-up studies are critical to assess neurodevelopmental outcomes beyond 12 months, as subtle deficits may emerge later (28). Exploring melatonin's pharmacokinetics in neonates, particularly in preterm infants, could inform tailored dosing strategies (7). Moreover, integrating advanced neuroimaging techniques, such as diffusion tensor imaging, could provide deeper insights into melatonin's impact on white matter integrity and cortical connectivity (29).

In conclusion, melatonin holds significant promise as an adjunctive therapy for neonatal asphyxia and HIE, with robust evidence supporting its neuroprotective and antioxidant effects. However, clinical adoption requires further validation through rigorous trials to address current

knowledge gaps and standardize treatment protocols.

5- CONCLUSION

Melatonin seems to be a safe and potentially effective additional therapy for neonatal asphyxia and HIE, enhancing neurodevelopmental outcomes and reducing brain injury. Large-scale RCTs are necessary to confirm these results and provide guidance for clinical practice.

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