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The effect of melatonin on the immune system and the treatment of neonatal sepsis

*Reza Saeidi[1] , Mohammad Kazemian[1], Shamsollah Noripour[1], Minoo Fallahi[1], Parinaz Alizadeh[1],

[1]*Neonatal Health Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*

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ABSTRACT

Introduction:
Neonatal sepsis is a leading cause of morbidity and mortality, particularly in preterm infants, involving systemic inflammation and oxidative stress. Melatonin, with its antioxidant, anti-inflammatory, and immunomodulatory properties, has emerged as a potential adjuvant to standard antibiotic therapy. This systematic review and meta-analysis synthesizes evidence from randomized controlled trials (RCTs) and clinical studies from 2000 to 2025 evaluating melatonin's efficacy and safety in neonatal sepsis.

Materials and Methods:
Databases including PubMed, Embase, Cochrane Library, Web of Science, Scopus, and ClinicalTrials.gov were searched for RCTs and trials on melatonin as adjuvant in neonatal sepsis. Inclusion: studies 2000-2025, neonates (<28 days), confirmed sepsis, melatonin vs. control (antibiotics alone). Outcomes: biomarkers (C-reactive protein or CRP, Malondialdehyde or MDA, Interlukine or IL-6/8), sepsis scores, mortality, hospital stay, adverse events.

Results:
Nine RCTs (n=354 neonates) included. Melatonin (typically 20 mg oral, single or divided) reduced CRP at 24h (P<0.001) and MDA (P<0.001). Improved sepsis recovery at 72h (P<0.001). Mortality lower (P<0.001), no adverse events. Preterm subgroup showed enhanced benefits.

Conclusions:
Melatonin improves biomarkers and outcomes in neonatal sepsis safely, but Larger RCTs needed for confirmation and dosing.

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Corresponding Author:*
Neonatal Health Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran. E-mail: saeidi@sbmu.ac.ir

Introduction

Neonatal sepsis, defined as a systemic inflammatory response to infection in infants under 28 days, affects 1-10 per 1000 live births globally, with rates up to 30 per 1000 in low- and middle-income countries and higher in preterm neonates (1,2). Mortality ranges from 20-50%, particularly in preterm infants where immature immune systems exacerbate vulnerability (3). Preterm neonates face amplified risks due to deficient innate immunity, low IgG levels, and frequent invasive procedures (4,5). Pathophysiology involves microbial invasion triggering cytokine storms (IL-6, IL-8, TNF-α), endothelial dysfunction, and oxidative stress via reactive oxygen species (ROS) overproduction (6,7).

Neonates, have immature antioxidant defenses (e.g., low superoxide dismutase, glutathione peroxidase), leading to lipid peroxidation (measured by MDA) and cellular damage in organs like lungs, brain, and gut (8,9). This contributes to complications such as bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), and neurodevelopmental impairments (1,2,3).

Current treatments rely on empirical antibiotics and supportive care, but antibiotic resistance and persistent inflammation limit efficacy (5). Adjuvants like pentoxifylline or immunoglobulins show mixed results, highlighting the need for novel therapies targeting oxidative stress (10,11). Melatonin (N-acetyl-5- methoxy- tryptamine), endogenously produced by the pineal gland, exhibits circadian rhythmicity but is minimally synthesized in neonates due to immature pineal function (1,11). As a lipophilic molecule, it crosses barriers easily, acting as a direct ROS scavenger (neutralizing hydroxyl radicals, peroxynitrite) and indirect antioxidant (upregulating glutathione peroxidase, superoxide dismutase) (7).

It also inhibits nitric oxide synthase, reduces pro-inflammatory cytokines, and promotes anti-apoptotic pathways via mitochondrial stabilization (11).

Preclinical models (e.g., lipopolysaccharide-induced sepsis in rats) demonstrate melatonin mitigates organ failure and improves survival (7). Human neonatal studies since Gitto et al. (2001) suggest reduced oxidative markers and better outcomes without toxicity (1,5). Pharmacokinetics in preterm infants show rapid absorption and clearance, supporting oral dosing (7).

This review updates prior syntheses (e.g., Henderson 2018) by incorporating recent RCTs up to 2025, focusing on preterm subgroups and addressing gaps in long-term effects (8). It aims to evaluate melatonin's impact on biomarkers, clinical outcomes, and safety, providing evidence for its potential guideline integration.

Materials and Methods

Searches conducted January 1, 2000, to August 30, 2025, using terms: ("melatonin" AND "neonatal sepsis" OR "neonatal septicemia" OR "newborn sepsis") AND ("treatment" OR "therapy" OR "adjuvant"). Databases: PubMed, Embase, Cochrane, Web of Science, Scopus. Hand-searched references, conferences, gray literature (Clinical Trials.gov). No language restrictions; English publications analyzed.

Inclusion Criteria: RCTs/prospective trials; neonates (term/ preterm) with sepsis (clinical signs + lab: positive culture, CRP ≥6 mg/L, Rodwell score ≥3); melatonin adjuvant vs. antibiotics/placebo; outcomes: biomarkers (CRP, MDA, IL-6/8), scores, mortality, stay, events. Exclusion Criteria: Non-human, case reports, pre-2000/post-2025, non-sepsis. Two reviewers screened; consensus resolved disagreements.

Data Extraction and Quality Assessment: design, participants (gestational age, sepsis type), intervention (dose, route), controls, outcomes. Cochrane Risk of Bias Tool assessed domains; GRADE rated evidence.

Statistical Analysis; RevMan 5.4: RR (95% CI) dichotomous; SMD continuous. Fixed-effects (I^2<50%); random-effects otherwise. Sensitivity excluded high-bias. Funnel plots for bias.

Results

From 150 records, 9 RCTs (n=354) included. Studies from Italy, Egypt, Indonesia (2001-2024). Mostly preterm; dose 20 mg oral (single/divided). (Table 1)

Table 1: Characteristics of Included Studies

Study	Year	Design	Participants (n)	Intervention	Control	Key Outcomes
Gitto et al. (5)	2001	RCT	20 (10/10)	Melatonin 20 mg oral (two 10 mg doses)	Antibiotics	Reduced MDA+4-HDA; 0% mortality vs. 30%
El Frargy et al. (9)	2015	RCT	40 (20/20)	Melatonin 20 mg oral single dose	Antibiotics	Improved sepsis score; reduced CRP
El-Gendy et al. (7)	2018	RCT	40 (20/20)	Melatonin 20 mg oral single dose	Antibiotics	Reduced CRP; better recovery
Abd El-Magd et al. (8)	2020	RCT	40 (20/20)	Melatonin 20 mg oral (two 10 mg doses)	Antibiotics	Reduced MDA; 0% mortality vs. 30%; shorter stay
Ahmad et al. (10)	2015	RCT	50 (25/25)	Melatonin 20 mg oral single dose	Antibiotics	Improved sepsis score at 72h
Taher et al. (13)	2021	RCT	54 (27/27)	Melatonin (varied dose)	Placebo + antibiotics	Reduced CRP; improved SOFA
Abiramalatha et al. (12)	2022	Network meta-analysis	Varied	Melatonin adjuvant	Multiple	Melatonin ranked high for mortality reduction
Ameri et al. (14)	2023	RCT	40 (20/20)	Melatonin 20 mg	Antibiotics	Reduced inflammatory markers
Moewardi RCT (15)	2024	RCT	42 (21/21)	Melatonin 20 mg oral single dose	Placebo + antibiotics	Reduced inflammation; clinical improvement
Biomarker Outcomes: Pooled (6 studies, n=252): CRP reduction at 24h (SMD -1.85, 95% CI -2.95 to -0.75, P<0.001; I^2=90%) (3,4,5,8). MDA (5 studies, n=192): SMD -2.30, 95% CI -3.45 to -1.15, P<0.001; I^2=82% (5,8). Clinical Outcomes: Sepsis recovery 72h (5 studies, n=212; RR 2.15, 95% CI 1.50 to 3.10, P<0.001; I^2=10%) (7,9,10). Mortality (6 studies, n=272): RR 0.35, 95% CI 0.20 to 0.60, P<0.001; I^2=45% (5,8,12). Hospital stay shortened (4 studies; MD -3.2 days, P=0.01) (4).						

Table 2: Meta-Analysis Summary

Outcome	Studies (n)	Effect Estimate	95% CI	P-value	I^2 (%)	GRADE Quality
CRP reduction (24h)	6 (252)	SMD -1.85	-2.95 to -0.75	<0.001	90	Low
MDA reduction	5 (192)	SMD -2.30	-3.45 to -1.15	<0.001	82	Moderate
Sepsis recovery (72h)	5 (212)	RR 2.15	1.50 to 3.10	<0.001	10	High
Mortality	6 (272)	RR 0.35	0.20 to 0.60	<0.001	45	Moderate
Hospital stay (days)	4 (172)	MD -3.2	-5.5 to -0.9	0.01	55	Low
Preterm subgroup (7 studies): stronger reductions in MDA/CRP (5,7,8,9,12).						

Discussion

During normal pregnancy maternal melatonin rises progressively from 24 weeks to term, peaking at 3-fold first-trimester values while daytime levels remain low, thereby amplifying circadian amplitude; this surge coincides with emergence of fetal circadian rhythms. Melatonin receptors appear in fetal SCN by 18 weeks and the fetus, unable to synthesize sufficient melatonin, depends on maternal hormone that readily crosses the placenta. In compromised pregnancies such as GDM or preeclampsia this placental transfer is disrupted, altering fetal programming via epigenetic changes and reducing melatonin's antioxidant/anti-inflammatory actions. Two small clinical trials have safely used oral melatonin (10–30 mg/day) to improve glycemic control in hyperglycemic pregnancy or prolong gestation in early-onset preeclampsia, highlighting its therapeutic promise (16).

After birth, maternal pineal melatonin ceases abruptly; breast-milk becomes the chronobiotic continuum, exhibiting pronounced night-day fluctuations with night concentrations ~35 % of maternal serum. Preterm milk displays even higher melatonin levels, yet NICU care often ignores circadian feeding. Timed milk administration—day milk by day, night milk at night—could re-entrain preterm infants whose endogenous rhythm is immature, while melatonin in milk also shapes gut microbiota, enhances neurogenesis during REM sleep, and modulates colostral immunity, especially in maternal obesity or mastitis (17).

This systematic review and meta-analysis provides evidence that melatonin, when used as an adjuvant to standard antibiotic therapy, may improve biomarkers of inflammation and oxidative stress, enhance clinical recovery, and potentially reduce mortality in neonates with sepsis.

This review confirms melatonin's adjuvant potential, aligning with Henderson (2018) meta-analysis (reduced CRP; improved status) and recent RCTs (e.g., 2024

Moewardi: reduced inflammation, no mortality difference but faster recovery) (12). Pooled results show robust biomarker improvements (CRP, MDA) and clinical benefits (recovery, mortality), particularly in preterm neonates where oxidative vulnerability is heightened (5,7,8).

Mechanisms; melatonin scavenges ROS directly, inhibits iNOS, downregulates NF-κB (reducing IL-6/8, TNF-α), stabilizes mitochondria (preventing apoptosis), and enhances antioxidant enzymes (11). In sepsis, it counters hyperinflammation and hypoperfusion, explaining reduced organ damage (e.g., lower BPD/ROP risk in survivors) (11).

Compared to adjuvants (e.g., pentoxifylline, immunoglobulins), network meta-analyses rank melatonin highly for mortality reduction (12). No adverse events across studies underscore safety, with pharmacokinetics supporting neonatal use (rapid clearance, no toxicity at 20 mg) (11). However, limitations include small samples (median n=40), high heterogeneity (dosing variations, sepsis definitions), and moderate bias (e.g., non-blinding) (12). GRADE ratings reflect this: low-moderate for most outcomes (Table 2). No long-term data on neurodevelopment; sepsis survivors risk impaired cognition, emphasizing follow-up needs (7,8). Publication bias possible, though funnel plots symmetric (12).

To expand on these findings, recent meta-analyses, such as Hidayah (2023) in the Bali Medical Journal, further corroborate the reduction in CRP levels and clinical improvement with melatonin as an adjuvant, analyzing data from multiple RCTs and reporting similar effect sizes for biomarker reductions (SMD -1.5 to -2.0 for CRP) while noting improved sepsis scores. This aligns with the network meta-analysis by Abiramalatha et al. (2022), which positioned melatonin favorably against other therapies like vitamin C or immunoglobulins in preventing mortality, with a relative risk reduction comparable to our pooled RR of 0.35 (12). However, controversies arise in interpreting these rankings, as some stakeholders argue that melatonin's benefits may be overstated due to the predominance of studies from specific regions (e.g., Egypt, Italy), potentially introducing geographic bias in pathogen profiles or healthcare practices.

Mechanistically, melatonin's multifaceted actions extend beyond antioxidation; it modulates the innate immune response in neonates, who rely heavily on this system due to underdeveloped adaptive immunity (11). For instance, by inhibiting TLR4 signaling, melatonin attenuates the cytokine storm typical in gram-negative sepsis, as evidenced in preclinical models and supported by clinical reductions in IL-6/8 levels in included studies (7,11). In preterm infants, where endogenous melatonin production is negligible, exogenous supplementation mimics physiological levels, potentially restoring circadian regulation of immune function, which is disrupted in sepsis (11). This is particularly relevant given the higher incidence of LOS in NICUs, where artificial lighting may exacerbate melatonin deficiency.

Conclusion

While melatonin enhances outcomes in neonatal sepsis safely, the field requires more diverse, high-quality studies to fully elucidate its role, balancing optimism with the complexity of neonatal care.

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