

Efficacy of an Oral Melatonin Suspension in Idiopathic Nocturnal Irritability among Infants Older than 6 Months: A Randomized, Single-blind, Quasi-experimental Trial

Elham Safdarian¹, Hossein Saneian², Majid Khademian², Erfaneh Ghassami³, Farnaz Ebrahimi⁴,
Sayed Ahmad Sajjadi-Sureshjaani⁴, Ali Mohammad Sabzghabae^{5,6}

¹Students' Research Committee, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran

²Department of Pediatrics, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

³Department of Pharmaceutics, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran

⁴Department of Clinical Pharmacy and Pharmacy Practice, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran

⁵Isfahan Clinical Toxicology Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

⁶Department of Pharmaceutical Care, Imam Hossein University Children's Hospital, Isfahan University of Medical Sciences, Isfahan, Iran

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ABSTRACT

Objective: Excessive or frequent night waking in infants can cause significant parental distress, maternal fatigue, family dysfunction, and increased risk of depression and anxiety. Melatonin, a hormone secreted in response to darkness, regulates the sleep-wake cycle. Infants with sleep difficulties may have low melatonin levels; therefore, melatonin supplementation may help improve sleep. This study evaluated the efficacy of an oral melatonin suspension in infants with idiopathic nocturnal irritability. **Methods:** In this randomized, single-blind quasi-experimental clinical trial, infants aged 6–24 months with idiopathic nocturnal restlessness were assigned to receive either oral melatonin (0.1 mg/kg nightly) or a matching placebo for 14 days. Sleep parameters were recorded by parents at baseline and reassessed after treatment. Infants with organic causes of restlessness, sedative medication use, hypersensitivity, or poor adherence were excluded. Data were analyzed using appropriate statistical tests with a significance level of $P < 0.05$. **Findings:** Sixty-seven infants were enrolled; 60 completed the study (30 melatonin and 30 placebo). After 14 days, the melatonin group showed significant reductions in nocturnal awakenings, sleep onset latency, and total nocturnal wakefulness, along with significant increases in longest continuous sleep duration and total sleep time. No significant changes occurred in the placebo group. **Conclusion:** Melatonin at 0.1 mg/kg appears to be effective and safe as an adjunctive therapy for idiopathic nocturnal restlessness in infants. Further studies with larger samples and longer follow-up are recommended.

KEYWORDS: Infant, melatonin, nocturnal insomnia, nocturnal irritability

INTRODUCTION

Suboptimal sleep in mothers has been linked to daytime fatigue and functional impairment,

Address for correspondence: Prof. Ali Mohammad Sabzghabae, E-mail: sabzghaba@pharm.mui.ac.ir

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disturbances in family dynamics and mother–infant bonding, and an increased risk of psychological symptoms such as depression and anxiety.^[1] Reduced endogenous melatonin secretion has been reported in infants with sleep problems, supporting the potential benefit of melatonin supplementation.^[2]

Night-time awakenings are frequently observed during early infancy and tend to decrease as sleep regulation matures over the 1st months of life. By approximately 6 months of age, the majority of infants are capable of maintaining more consolidated nocturnal sleep. Nevertheless, distinguishing normal age-related sleep patterns from clinically meaningful sleep disturbances remains challenging for clinicians. Total sleep duration shows a gradual decline with increasing age, averaging approximately 14.2 h at 6 months and decreasing to around 8.1 h by 16 years of age. While sporadic episodes of insomnia in children are generally benign, persistent or recurrent sleep disturbances warrant careful evaluation to identify potential underlying causes. Insufficient sleep, in terms of both duration and quality, may negatively affect daytime functioning and contribute to irritability, behavioral difficulties, cognitive impairment, and mood-related disturbances.^[3] Moreover, sleep difficulties in young children can disrupt parental sleep, adversely affecting parents' mood and daily performance.^[1]

In most cases, nonpharmacologic approaches including parental education and attention to proper sleep hygiene should be implemented before considering pharmacological treatment. However, in situations where sleep disturbances impose significant challenges for the child or disrupt family functioning, pharmacotherapy may be introduced in conjunction with behavioral interventions. A range of internal (such as hunger and boredom) and external factors (such as noise and light exposure) can either facilitate or inhibit sleep. Awareness of these determinants enables caregivers to better understand the complexity of the sleep–wake regulatory system and highlights the importance of behavioral strategies as a valuable adjunct to medication. Recommended educational measures include modifying the sleep environment, such as minimizing screen use before bedtime, ensuring low light exposure, and providing an optimal room temperature.^[4]

There is limited empirical evidence regarding the efficacy, safety, and tolerability of pharmacological treatments for sleep disturbances in pediatric populations. To date, no hypnotic agent has been approved by the US Food and Drug Administration for the management of insomnia in children younger than 16 years.^[4] Consequently, the clinical use of pharmacotherapy in this age group

requires cautious consideration of potential benefits, associated risks, and alternative treatment options. Among the over-the-counter medications, antihistamines and melatonin remain the most commonly administered agents for pediatric insomnia.^[5]

Antihistamines may be considered for short-term or occasional use in younger children, especially those with underlying atopic conditions. However, tolerance to antihistamines often necessitates dose escalation, and their adverse effect profile substantially limits long-term administration. First-generation antihistamines, such as diphenhydramine and hydroxyzine, readily cross the blood–brain barrier and exert pronounced central nervous system effects, including sedation. In addition, their anticholinergic properties can lead to several side effects such as dry mouth, blurred vision, and urinary retention. Rare but serious adverse events have also been reported in children, including seizures, aggression, respiratory distress, persistent rashes, and central anticholinergic syndrome. Due to their interaction with multiple receptor types (histaminergic, serotonergic, cholinergic, and dopaminergic), first-generation antihistamines carry a risk of fatal overdose, with cases of severe toxicity and death documented in pediatric populations. In contrast, second-generation antihistamines, which do not cross the blood–brain barrier, lack sedative effects.^[5]

Melatonin is an endogenous hormone synthesized by the pineal gland in the brain,^[6] primarily responsible for regulating the body's circadian rhythm and the sleep–wake cycle.^[7] It is widely used as a sleep aid in the management of insomnia and related disorders. Taken approximately 2 h before bedtime, melatonin has been shown to reduce sleep onset latency, increase total sleep duration, and improve overall sleep quality.^[8,9] Compared with other sleep medications, melatonin is generally well tolerated and associated with a lower incidence of adverse effects.^[8,10] Circulating melatonin levels demonstrate marked age-related variation. During early infancy, melatonin secretion remains very low before approximately 3 months of age and then increases gradually as circadian regulation matures. By around 3 years of age, the sleep–wake rhythm becomes relatively stable. Nocturnal melatonin concentrations reach their highest levels between 4 and 7 years of age, after which a gradual decline is observed.^[11] Melatonin is considered safe and nonaddictive for both short and long-term use.^[10] Furthermore, despite theoretical concerns regarding suppression of endogenous production, several studies have demonstrated no such inhibitory effect.^[12] The most frequently reported side effects include nausea, headache, dizziness, and daytime drowsiness.^[10]

Therefore, this study aimed to evaluate the efficacy and safety of oral melatonin suspension in improving idiopathic nocturnal irritability and sleep quality among infants aged 6–24 months.

METHODS

This was a single-blind, randomized, placebo-controlled quasi-experimental clinical trial conducted at the Pediatric Specialty Clinic of Imam Hossein Hospital, Isfahan, Iran.

This was a single-blind study in which parents were unaware of treatment allocation, while the investigators preparing the study medications were not blinded.

The study population comprised all eligible infants brought to the clinic by their parents during the study period. Patient selection, prescription of the study medication, and clinical management were carried out by two associate professors of pediatrics from the research team, who were also responsible for participants' follow-up and safety monitoring.

A melatonin suspension with a concentration of 1 mg/mL was prepared for each patient. To prepare 60 mL of the suspension, twenty 3-mg melatonin tablets were completely crushed and finely ground in a mortar, then mixed with 300 mg of hydroxypropyl methylcellulose (HPMC) to obtain a uniform powder. Separately, 51 g of sucrose was dissolved in approximately 40 mL of water, and the resulting viscous solution was added to the mortar containing the powder mixture and mixed thoroughly until a homogeneous paste was obtained. This paste was then diluted to a final volume of 60 mL with water, transferred to a light-resistant bottle, and stored in a refrigerator until use. The placebo suspension was prepared using the same procedure, except that melatonin was omitted. HPMC (0.5%) served as a suspension stabilizer and thickening agent, and sucrose (85%) was used as a sweetener to improve palatability. Melatonin suspensions were prepared on demand for each patient and prescription, and were stable during the short usage period, considering our advice to the parents to keep the drug in the refrigerator (4°C–6°C).

Infants aged 6–24 months were eligible if they had a clinical diagnosis of idiopathic nocturnal restlessness without underlying causes, as defined in the 19th edition of *Nelson Textbook of Pediatrics* and confirmed by a pediatric specialist. Additional inclusion criteria included:

- Absence of organic causes for restlessness/insomnia such as fever or teething
- No use of other medications for restlessness/insomnia (e.g., antihistamines)

- Written informed consent provided by parents or legal guardians.

Infants meeting any of the following conditions were excluded:

- Parents' request to withdraw the infant from the study
- Development of any hypersensitivity reaction related to the study medication
- Nonadherence to treatment for more than four nights per week for 2 consecutive weeks.

All eligible participants were enrolled until each group included at least 30 infants. Using a random numbers table and the order of enrollment, participants were assigned to either the intervention group (melatonin suspension) or the control group (placebo suspension). Random allocation continued until the target sample size was reached for both groups.

Participants were randomly assigned to the intervention (melatonin) or control (placebo) group as described above. The intervention group received oral melatonin suspension at a dose of 0.1 mg/kg,^[13] prepared as a pediatric-friendly oral formulation (1 mg/mL suspension), while the control group received a placebo with identical appearance and packaging. Participants were evaluated using insomnia/restlessness indices at two time points: Before the initiation of the study and 14 days after the administration of the suspension. To ensure accurate administration of the medication, in addition to initial training provided to parents, the remaining volume of the suspension was measured during follow-up visits. Infants showing a discrepancy >40% between the expected and actual remaining volume were excluded from the study.

The primary outcomes of our study are listed in Table 1. The secondary outcome was to document any safety issues and adverse effects of melatonin use in infants, as reported by the parents.

Data were analyzed using the SPSS software (version 26, IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was applied to assess the data normality. Within-group comparisons were performed using the paired-sample t-test or Wilcoxon signed-rank test, depending on data distribution, while categorical baseline characteristics were compared between groups using the Chi-square test, as appropriate.

The study was conducted in accordance with the principles outlined in the Charter of Patients' Rights and the 31 articles of the Tehran Ethical Guidelines for Clinical Trials involving human participants. Written

informed consent was obtained from all parents or legal guardians. Participants who withdrew from the study were not deprived of standard care. All the collected data were treated confidentially. Ethical approval was granted from the Ethics Committee of Isfahan University of Medical Sciences (IR.ARI.MUI.REC.1401.244). This trial was registered in the Iranian Registry of Clinical Trials (IRCT20090808002306N8).

RESULTS

A total of 67 infants meeting the inclusion criteria were enrolled between autumn 2022 and autumn 2023 and were randomly assigned to the melatonin and placebo groups [Figure 1]. Of these, 60 participants completed the study. One infant in the melatonin group discontinued treatment due to mild stumbling as reported by parents (adverse effect), while six infants in the placebo group discontinued participation because of lack

of efficacy within the first 2 weeks of intervention. Each participant was followed for 2 weeks after initiation of treatment. The final analysis was conducted on 60 infants (30 per group) using a per-protocol approach. No other adverse events were reported.

The presence of two groups, melatonin and placebo, necessitated statistical verification of baseline similarity. According to the demographic data, there were 19 boys and 11 girls in the melatonin group and 17 boys and 13 girls in the placebo group, with no statistically significant differences between groups [Table 2].

Other factors such as mean age, preterm birth status, and the educational level of the parent were also statistically comparable between the two groups with the two groups with no statistically significant differences [Table 2]. The mean age of infants in both groups was approximately 13 months [Table 2].

Table 1: Comparison of sleep parameters before and after the intervention between the melatonin and placebo groups

Variable	Intervention group				Control group			
	Mean	SD	Median	P	Mean	SD	Median	P
Number of nocturnal awakenings before intervention	3.37	1.098	3	0.000	3.23	1.040	3	0.180
Number of nocturnal awakenings after intervention	1.23	1.194	1		3.07	1.258	3	
Sleep onset latency before intervention	116.6	48.14	120	0.000	117.5	50.49	120	0.194
Sleep onset latency after intervention	55.83	51.74	30		110.8	55.52	120	
Longest continuous nocturnal sleep duration before intervention	178.3	87.69	180	0.000	189.6	88.63	180	0.181
Longest continuous nocturnal sleep duration after intervention	371.6	133.4	345		203.1	108	180	
Total nocturnal sleep duration before intervention	454.6	88.21	462.5	0.000	455.8	91.46	462.5	0.180
Total nocturnal sleep duration after intervention	555.8	69.19	570		463.5	99.45	467.5	
Total nocturnal wakefulness duration before intervention	47.67	25.88	45	0.000	48	25.33	40	0.285
Total nocturnal wakefulness duration after intervention	14.83	18.95	7.5		46	27.60	38.5	

$P < 0.05$ were considered statistically significant. Paired *t*-test or Wilcoxon signed-rank test was used for within-group comparison. SD=Standard deviation

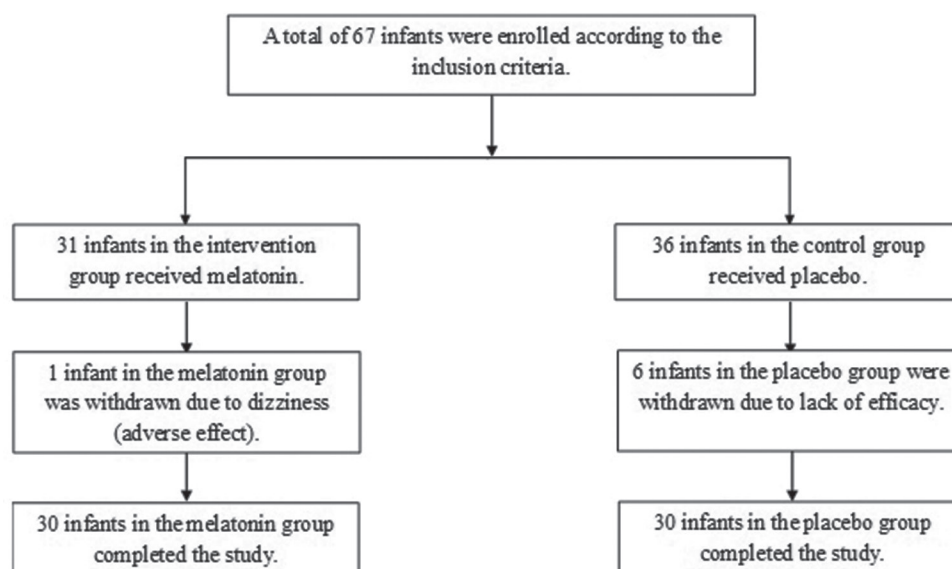


Figure 1: Flow diagram of participant recruitment, randomization, and follow-up

Table 2: Baseline demographic and clinical characteristics of participants in the intervention and control groups

Variable	Group	n	Mean	Frequency (%)	P
Sex	Intervention				0.605
	Female	11	-	36.7	
	Male	19	-	63.3	
	Control				
	Female	13	-	43.3	
Age (months)	Intervention	30	13.07	-	0.852
	Control	30	12.80	-	
	Intervention				
	Yes	1	-	3.3	
	No	29	-	96.7	
Preterm birth status	Control				0.561
	Yes	2	-	6.7	
	No	28	-	93.3	
	Intervention				
	Below high school diploma	1	-	3.3	
Parental educational level	High school diploma	8	-	26.7	0.848
	University education	19	-	63.3	
	Postgraduate education	2	-	6.7	
	Control				
	Below high school diploma	1	-	3.3	
	High school diploma	10	-	33.3	
	University education	16	-	53.3	
	Postgraduate education	3	-	10	
	Intervention				
	Below high school diploma	1	-	3.3	

$P < 0.05$ was considered statistically significant. Between-group comparisons were performed using the Chi-square test

Before statistical analysis, data normality was assessed using the Kolmogorov–Smirnov test. The results indicated that most variables were nonnormally distributed, except for sleep onset latency in both groups before the intervention and in the control group after the study, as well as the longest continuous sleep duration before and after the intervention in both groups, total nocturnal sleep duration in the intervention group after the study, and total nocturnal wakefulness duration after intervention in control group ($P > 0.05$). Therefore, nonparametric tests were applied for variables with nonnormal distributions.

Baseline comparisons of insomnia/restlessness indices showed no significant differences between the melatonin and placebo groups prior to intervention.

Based on the results of the Wilcoxon signed-rank test and paired t -test, there was a statistically significant

reduction in the number of nocturnal awakenings, sleep onset latency, and total nocturnal wakefulness duration, along with significant increases in both the longest continuous nocturnal sleep duration and total nocturnal sleep duration in the melatonin group ($P < 0.05$ for all parameters). In contrast, no statistically significant differences were observed in the placebo group ($P > 0.05$ for all parameters) [Table 1].

Therefore, the observed improvement in sleep indices among infants receiving melatonin can be attributed to the therapeutic effect of melatonin supplementation rather than random variation or parental behavioral factors [Figure 2].

Only one case of mild stumbling (probably due to dizziness) was reported by parents of a 23-month-old baby in the melatonin group, leading to withdrawal. No serious or unexpected adverse reactions were recorded.

DISCUSSION

In this randomized controlled trial, we evaluated the efficacy and safety of melatonin compared with placebo for the management of idiopathic insomnia and nocturnal restlessness in infants aged 6–24 months. The findings demonstrated significant improvements in all sleep parameters – sleep onset latency, nocturnal awakenings, total nocturnal wakefulness, and total and continuous sleep duration – in the melatonin group compared with placebo. These results support the hypothesis that melatonin supplementation is effective in improving sleep quality in infants experiencing idiopathic nocturnal irritability.

Melatonin is a neurohormone produced by the pineal gland and is widely recognized for its role in circadian rhythm regulation. Numerous studies have demonstrated its capacity to influence the sleep–wake cycle, particularly when administered with appropriate timing and dosing. As a result, melatonin has become one of the most frequently prescribed interventions by pediatricians for sleep-related conditions in children and adolescents, including sleep onset difficulties (89%), delayed sleep phase syndrome (66%), and nocturnal awakenings (30%).^[14] Its use has been reported both in typically developing children and in those with neurodevelopmental and behavioral conditions, such as autism spectrum disorder, developmental delay, and attention-deficit/hyperactivity disorder. Nevertheless, despite its endogenous nature, standardized clinical guidelines for melatonin use in pediatric populations with neurological disorders are currently lacking.^[14]

Recent pediatric recommendations suggest that melatonin should primarily be used on a short-term basis

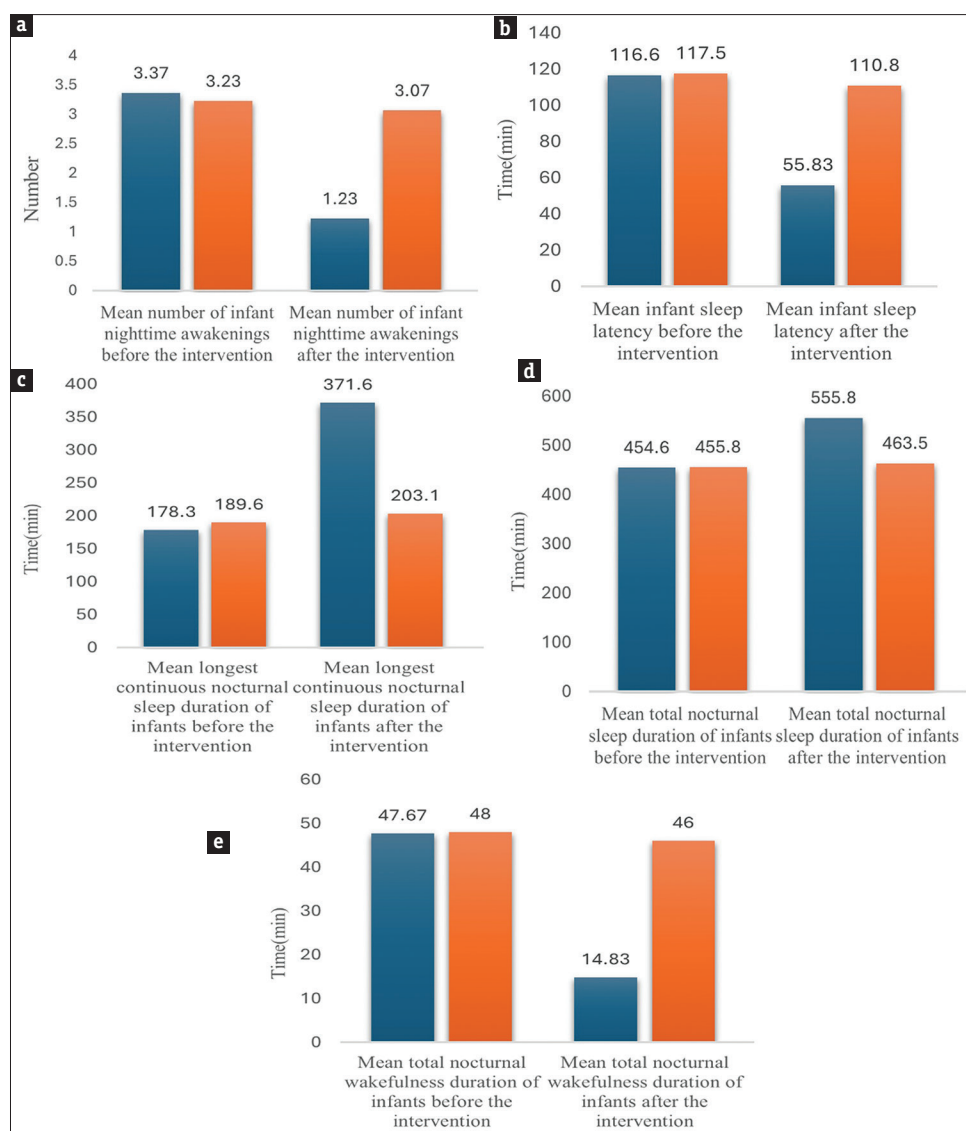


Figure 2: Comparison of sleep parameters before and after the intervention between the melatonin and placebo groups. (a) Number of nocturnal awakenings, (b) sleep onset latency, (c) longest continuous nocturnal sleep duration, (d) total nocturnal sleep duration, and (e) total nocturnal wakefulness duration. ■ Intervention group ■ control group

in carefully selected children, with careful consideration of appropriate indications, timing of administration, and conservative dosing. Nonpharmacological approaches, including behavioral interventions and proper sleep hygiene, continue to represent first-line management strategies, while pharmacotherapy should be employed as an adjunct rather than a substitute for these measures.^[15]

The absence of a circadian melatonin rhythm during the 1st months of life results in a transient deficiency of this hormone in infants, which may underlie sleep disturbances in this age group.^[16] While the pharmacokinetic profile of melatonin is well characterized in adults – with secretion typically initiating around 9 p. m. and peaking at 3 a.m.^[17] – such patterns differ substantially in infants. Nevertheless, existing evidence indicates that

melatonin therapy remains remarkably safe, even at pharmacological doses. Furthermore, a clinical study evaluating melatonin for the treatment of sleep disorders in pregnant and breastfeeding women demonstrated that, despite its placental transfer and secretion into breast milk, melatonin use is likely safe in humans during pregnancy and lactation.^[18] Recent pharmacokinetic analyses in pediatric populations have also demonstrated that immediate-release oral formulations achieve more rapid sleep induction compared with extended-release forms. These findings support the use of oral suspension preparations – such as the one applied in our study – as they allow flexible dosing and faster onset of action in young children.^[19]

The effect of melatonin supplementation on the initiation of pineal melatonin secretion in infants has not yet

been studied. However, it is unlikely to interfere with this process, as suppression of endogenous melatonin has not been observed in older age groups receiving melatonin supplementation. Therefore, the treatment may be continued until the brain has matured sufficiently to regulate pineal function. The most convincing clinical evidence would be the persistence of a stable sleep–wake rhythm following a brief interruption of treatment.^[20] Contemporary reviews also reaffirm that while melatonin demonstrates favorable short-term efficacy and safety in pediatric insomnia, the long-term data remain limited. Therefore, clinicians are advised to use the lowest effective dose for the shortest necessary duration, while monitoring efficacy and adverse effects throughout treatment.^[21]

Notably, there are a limited number of clinical trials investigating the efficacy of melatonin in managing insomnia and nocturnal restlessness in infants. Given the significant adverse effects of conventional sedative–hypnotic drugs in this population, the treatment of sleep disturbances in infants remains particularly challenging.

In a study, melatonin was found to be safe and effective in the management of primary sleep disorders as well as sleep disturbances associated with various neurological conditions in children. However, further research is needed to identify infants most likely to benefit from melatonin therapy and to determine optimal dosing based on the type and severity of sleep disorders.^[22]

Another study investigating children aged 1–18 years with sleep disturbances secondary to atopic dermatitis reported that melatonin therapy significantly reduced sleep onset latency compared to placebo among 48 participants. No patients withdrew due to adverse effects, and no adverse events were reported during the study.^[23]

A separate investigation involving 100 children aged 1–6 years confirmed the efficacy and safety of liposomal melatonin in sleep induction. Liposomal melatonin demonstrated higher bioavailability compared to other formulations, ensuring a faster onset of action and allowing for lower dosing.^[24]

Furthermore, a study of 565 patients with epilepsy aged 1–17 years compared different sleep induction methods, including sleep deprivation, melatonin, and a combination of sleep deprivation plus melatonin. The results indicated that the combined approach was more effective.^[25]

In our trial, the comparable baseline characteristics between the melatonin and placebo groups confirmed adequate randomization and minimized confounding. High treatment adherence (89.5% completion rate) and

minimal adverse effects further enhance the internal validity and feasibility of this approach.

Study limitations

This study has several limitations that should be acknowledged. Parental noncompliance was observed in some cases due to concerns regarding potential dependency of the infant on the medication. In addition, the relatively short duration of the study limited the assessment of long-term efficacy and safety outcomes. Ethical considerations inherent to conducting randomized controlled trials in pediatric populations imposed certain constraints on study design and implementation. Furthermore, the lack of an available method for direct measurement of serum melatonin levels prevented objective evaluation of endogenous melatonin concentrations during the study period.

CONCLUSION

Our findings suggest that short-term melatonin supplementation may serve as a safe and effective therapeutic option in infants with idiopathic insomnia when behavioral interventions alone are insufficient. The significant improvements across all sleep parameters support its potential as a first-line adjunctive therapy. Given the natural origin and favorable tolerability of melatonin, it may offer an alternative to conventional sedative–hypnotic agents, which are associated with greater adverse effects in infants.

This randomized controlled trial provides evidence that melatonin is both effective and well tolerated in infants with idiopathic insomnia and nocturnal restlessness. The results contribute to the growing body of literature supporting melatonin as a promising therapeutic option in pediatric sleep medicine, with potential for incorporation into clinical practice guidelines following further validation.

AUTHORS' CONTRIBUTION

AMS proposed the research subject and designed the study, ES gathered clinical data, interviewed patients' parents and drafted the manuscript, HS and MKH guided for selecting eligible patients, EGH designed and formulated melatonin suspension and tested for quality control, FE and SASS analyzed the data and revised graphs and tables. All authors approved the final version of the manuscript and carry equal responsibility.

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Conflicts of interest

There are no conflicts of interest.

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