

Effect of melatonin in children with neurodevelopmental disabilities and sleep disorders

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ABSTRACT

Objectives: The aim of this study is to assess the efficacy and side effects of melatonin use in a population of children with neurodevelopmental disabilities who had sleep disorders. **Methods:** This is a cross-sectional study conducted in the pediatric neurology clinic at King Abdulaziz Medical City. A designed questionnaire was given to the parents to inquire about the sleep characteristics of their children before and after using melatonin. The patients' demographic data were collected and different parameters before and after starting melatonin were compared. Categorical variables were summarized and reported in terms of frequency and percent (n%). Continuous variables were reported in terms of mean and standard deviation. **Results:** A total of 23 patients were enrolled in our study, of which 15 (65.22%) were male. The mean age was 5.83 ± 3.07 years. For melatonin dose, 9 (39.13%) received 1 mg, 8 (34.78%) received 2 mg, and 6 (26.09%) received over 3 mg. Regarding melatonin duration of use, 7 (30.43%) received melatonin for 0 to 6 months, 7 (30.43%) received it for 7 to 12 months, and 9 (39.13%) received it for over a year. Significant differences were observed in time taken to fall asleep ($P=0.046$), the number of times the child woke up at night ($P=0.071$), total sleep time within 24 hours ($P=.011$), and time taken to wake up ($P=.007$), while no significant difference was observed in the number of naps taken during the daytime ($P=.801$). There were no major side effects reported. **Conclusion:** Melatonin had a significant impact on total sleep time and quality during the pre and post assessment of children with neurodevelopmental disabilities and sleep disorders.

Keywords: Children, melatonin, neurodevelopmental disabilities, side effect, sleep disorders

Introduction

Sleep disorders are commonly seen in children diagnosed with neurodevelopmental disorders such as cerebral palsy, intellectual disabilities, and learning disabilities, among others. These children have different degrees of sleep disruption

or fragmented sleep, which are of high concern to their families given their effect on both the quality of life of the patients and their caregivers. Methods used to solve sleep problems vary with different degrees of response based on the particular details of a given case. Efforts made to improve sleep patterns in children with neurodevelopmental disorders are of substantial value. The role of the primary care physician is of great importance to this special group of patients to spot such issues and be comfortable handling them; eventually contributing to improve the quality of life for those patients.

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Melatonin, or N-acetyl-5-methoxytryptamine (Mel), is a neurohormone that is produced by the pineal gland in the brain from the amino acid tryptophan through its hydroxylation into 5-hydroxytryptophan. This part of the process is followed by decarboxylation to form serotonin, which undergoes a rate-limiting step within the pineal gland through the enzyme N-acetyl-transferase. The serotonin is then converted into N-acetyl serotonin and finally methylated into melatonin.^[1] It then moves into circulation and binds to high-affinity G-protein-coupled receptors, namely, the melatonin receptors MT1 and MT2, to exert its effect. Of most importance to the scope of this study is the regulation of the sleep-wake cycle, or the circadian rhythm.^[1,2] Melatonin also has other cardiovascular and immunological functions owing to its antioxidant and anti-inflammatory properties.^[1]

Naturally, melatonin secretion follows a diurnal rhythm, with minimal secretion during the daytime, onset of secretion as night falls, which is referred to as Dim-Light Melatonin Onset,^[3] and a peak after midnight between 2 and 4 am.^[1,3] It is released from the pineal gland in response to norepinephrine release from the retinal photoreceptors, which activates the retinohypothalamic-pineal system in response to dim/dark light, thus promoting sleep. While blue light or daylight inhibits melatonin production, dim light stimulates the suprachiasmatic nucleus in the hypothalamus to signal melatonin secretion from the pineal gland.^[2]

Exogenous melatonin can be administered through different routes with variable bioavailability and dosages.^[4] The intranasal route has quick absorption and high bioavailability, yet more human studies are required to draw any conclusions regarding its use. Transdermal patches have slower to variable absorption and skin disposition rates. Oral transmucosal administration yields a high plasma concentration owing to the skipping of the first-pass metabolism. Another route is subcutaneous injection with a rapid absorption rate but no other specific benefit. The remaining routes are intravenous and oral administration, the most commonly used but with known variable bioavailability.^[4] Melatonin is mainly metabolized by the liver enzyme cytochrome P450, with the metabolites conjugating to sulfuric acid and then excreted through urine.^[5] Melatonin has been shown to be beneficial if used in sleep disorders in both adults and children.^[6] When compared with placebo, long-term melatonin use has some mild unwanted side effects, such as dizziness, sleepiness, and nausea, with no major side effects reported.^[7] However, the long-term effects and safety of melatonin have not yet been well studied.

To the extent of our knowledge, limited studies have been conducted to evaluate the efficacy of melatonin on sleep disorders in children with neurodevelopmental disorders in the Middle East and North Africa region despite the high prevalence of such disorders. Thus, we conducted this study to assess the efficacy and duration of melatonin use in our population of children with neurodevelopmental disabilities and sleep disorders.

If efficacy is proven in long-term use, melatonin will be of great help to children and their caregivers.

Methods

Study setting

This was a cross-sectional study conducted over 6 months in the pediatric neurology clinic at King Abdulaziz Medical City, a tertiary-care academic hospital in Riyadh, Saudi Arabia. The institutional review board approval was obtained from King Abdullah International Medical Research Center (KAIMRC) with an approval number of RR09/051. The caregivers of all children, 14 years old or younger, who had been diagnosed with neurodevelopmental and sleeping disorders for which they were on melatonin and following up in the clinics, were asked to fill out a designed questionnaire about the sleeping characteristics of their children before and after using melatonin. Patients who had normal neurodevelopment or a primary diagnosis of a sleep disorder were excluded from the study.

Cohort characterization

The initial focus of all analyses was the characterization of the sample under study. The characterization was given in terms of the demographics of the sampled subjects by running a comprehensive univariate analysis. The demographic data collected included age, gender, primary diagnosis, secondary diagnosis, developmental milestones, concomitant diseases, sleep medications and their dosages, duration of medication, side effects experienced, other medications, and type of sleep disorder. Categorical variables were summarized and reported in terms of frequency and percent (n%). Continuous variables were reported in terms of mean and standard deviation.

Pre and post melatonin comparison of sleep patterns

This study involved the assessment of sleep patterns twice for the same patient: once before and once after the introduction of melatonin. The pre and post melatonin comparison of sleep patterns (time taken to fall asleep, time taken to wake up, number of times the child woke at night, number of naps during the daytime, and total sleep time in 24 hours) was analyzed by utilizing Bowker's test. The results are reported in the tables in terms of n (%) and *P* values.

All analyses were conducted and reported using SAS V9.2, SAA Institute, NC.

Results

Cohort and clinical characteristics

The total number of patients enrolled in this study was 23. The mean age of the study population was 5.83 ± 3.07 years, with 15 (65.22%) males and 8 (34.78%) females. The majority of the patients used a melatonin dose of 0 to 1 mg, as seen in 9 (39.13%) children, while 8 (34.78%) children had received a higher dose of 2 to 3 mg, and 6 (26.09%) had received over 3 mg of melatonin.

For the duration of melatonin use, 7 (30.43%) children had received melatonin for 0 to 6 months, 7 (30.43%) had received it for 7 to 12 months, and 9 (39.13%) had received it for over a year. Regarding the primary diagnosis, 10 (43.48%) children had cerebral palsy, 5 (21.74%) had hypoxic-ischemic encephalopathy, 5 (21.74%) had developmental delay, 2 (8.70%) were diagnosed with attention deficit hyperactivity disorder, and one (4.35%) was diagnosed with Sjogren–Larsson syndrome. As a secondary diagnosis, 14 (60.87%) children had a seizure disorder, 2 (8.70%) had a speech delay, 2 (8.70%) were diagnosed with Joubert syndrome, 1 (4.35%) had hydrocephalus, and 1 (4.35%) had a mass in the right mesial temporal lobe. Finally, as concomitant diseases, 5 (21.74%) children were diagnosed with bronchial asthma, 5 (21.74%) were diagnosed with gastroesophageal reflux disease, 3 (13.04%) had undergone fundoplication and gastrostomy tube insertion, 3 (13.04%) had poor vision, 1 (4.35%) had undergone a tonsillectomy, and 1 (4.35%) had a resolved case of partial deep vein thrombosis in the left bronchial vein. The baseline demographics and clinical characteristics are shown in [Table 1].

Sleep characteristics and sleep medications

The sleep patterns for 19 (82.61%) children were indicative of insomnia, 1 (4.35%) child had interrupted sleep, and 3 (13.04%) children had no clear description to fit a specific sleep disorder. For melatonin-related side effects, 2 (8.70%) children had developed a tolerance, 1 (4.35%) had experienced vomiting, 1 (4.35%) had difficulty swallowing, and 19 (82.60%) had no reported side effects. Apart from melatonin, 3 other sleep medications were used in 8 (34.78%) children, and multiple other medications were also used, the data for which are included and summarized in [Table 2].

Pre and post melatonin comparison of sleep patterns

A pre and post melatonin comparison of sleep patterns was conducted for the 23 patients. The patients' parents were questioned about their children's sleep-related behavior. Significant differences were observed in time taken to fall asleep ($P = 0.046$), the number of times the child woke at night ($P = 0.071$), total sleep time within 24 hours ($P = .011$), and time taken to wake up ($P = .007$), while no significant difference was observed in pre and post numbers of naps taken during the daytime ($P = .801$). The pre and post melatonin comparison is shown in [Table 3].

Discussion

The efficacy of melatonin use in children with neurodevelopmental and sleep disorders has not been well established in practice or implemented in treatment guidelines despite the high prevalence of sleep disorders in this patient population. Primary care physicians and family physicians would benefit from clear management guideline as patients and their families are likely to seek their medical advice first, and most of those patients have regular follow-ups in their clinics, allowing for continuity

Table 1: Demographics and clinical characteristics of the study cohort

Variables	n (%)
Age, Mean±SD	5.83±3.07
Gender	
Male	15 (65.22)
Female	8 (34.78)
Medication Dosage	
1 mg	9 (39.13)
2-3 mg	8 (34.78)
Over 3 mg	6 (26.09)
Duration of Medication	
0-6 months	7 (30.43)
7-12 months	7 (30.43)
Over 1 year	9 (39.13)
Primary Diagnosis	
Cerebral Palsy	10 (43.48)
Hypoxic Ischemic Encephalopathy	5 (21.74)
Developmental Delay	5 (21.74)
Attention Deficit Hyperactivity Disorder	2 (8.70)
Sjogren-Larsson Syndrome	1 (4.35)
Secondary Diagnosis	
Seizure Disorder	14 (60.87)
Speech Delay	2 (8.70)
Joubert Syndrome	2 (8.70)
Hydrocephalus	1 (4.35)
Mass in the Right Mesial Temporal Lobe	1 (4.35)
Concomitant Diseases	
Bronchial Asthma	5 (21.74)
Gastroesophageal Reflux Disease	5 (21.74)
Post Fundoplication and Gastrostomy Tube Insertion	3 (13.04)
Poor Vision	3 (13.04)
Post-Tonsillectomy	1 (4.35)
Resolved Left Bronchial Vein Partial Deep Vein Thrombosis	1 (4.35)

of care and treatment response assessment. Our study aimed to assess the efficacy and duration of melatonin use in children with neurodevelopmental disabilities and sleep disorders. Our study concluded that melatonin was safe and effective in managing sleep disorders in children with neurodevelopmental disabilities if given before bedtime in terms of total sleep time and sleep quality, with no major side effects detected. Thus, melatonin could improve the quality of life of both the affected children and their caregivers.

In support of the use of melatonin for the treatment of sleep disturbance in pediatric patients diagnosed with neurodevelopmental disorders, one study by Jan^[8] was conducted at King Abdulaziz University Hospital with similar doses and results to ours. They included 10 children who were handicapped and had a severe circadian rhythm sleep disorder and found that 3 mg of melatonin at bedtime was effective and well-tolerated in 80% of their study group with no major side effects. Similarly, Ross *et al.*^[9] carried out their study in a large pediatric neurology clinic where 49 mothers agreed to give melatonin to their children diagnosed with cerebral palsy, autism, and learning disabilities. After melatonin use, all aspects of sleep were significantly improved in 93% of the patients with no major side effects from the medication; therefore, Ross *et al.* also concluded that

Table 2: Sleep characteristics and sleep medications

Variables	n (%)
Type of Sleep Disorders	
Insomnia	19 (82.61)
Interrupted Sleep	1 (4.35)
Nonspecific	3 (13.04)
Side Effects	
No Side Effect	19 (82.60)
Tolerance	2 (8.70)
Vomiting	1 (4.35)
Difficulty Swallowing	1 (4.35)
Sleep Medications	
Clonazepam	6 (26.08)
Imipramine	1 (4.35)
Mannitol	1 (4.35)
Other Medications	
Phenobarbital	10 (43.48)
Valproic Acid	5 (21.74)
Lamotrigine	5 (21.74)
Carbamazepine	4 (17.39)
Levetiracetam	4 (17.39)
Topiramate	3 (13.04)
Phenytoin	3 (13.04)
Vigabatrin	1 (4.35)
Citalopram	1 (4.35)
Imipramine	1 (4.35)
Biotin	1 (4.35)
Pyridoxine	1 (4.35)
Baclofen	10 (43.48)
Dantrolene	6 (26.09)
Glycopyrrolate	2 (8.70)
Ranitidine	2 (8.70)
Domperidone	1 (4.35)
Lactulose	2 (8.70)
Salbutamol	1 (4.35)
Prednisolone	1 (4.35)
Nystatin	1 (4.35)

Table 3: Pre and post melatonin comparison of sleep patterns

Variables	Pre	Post	P
	Melatonin n (%)	Melatonin n (%)	
Time taken to fall asleep (h/min)			
0-5 h	11 (47.83)	19 (82.61)	0.046
6-10 h	3 (13.04)	0	
>10 h	6 (26.09)	1 (4.35)	
Time taken to wake up (h/min)			
0-6 h	17 (73.91)	8 (34.78)	0.007
7-12 h	1 (4.35)	12 (52.17)	
>12 h	2 (8.70)	0	
Number of times a child woke at night			
0-2 times woke at night	7 (30.43)	14 (60.87)	0.071
3-5 times woke at night	9 (39.13)	2 (8.70)	
>5 times woke at night	4 (17.39)	2 (8.70)	
Number of naps during daytime			
0-1 naps a day	14 (60.87)	16 (69.57)	0.801
1-2 naps a day	2 (8.70)	2 (8.70)	
2-3 naps a day	1 (4.35)	0	
Total sleep time in 24 h			0.011
0-6 h	15 (65.22)	5 (21.74)	
7-12 h	4 (17.39)	15 (65.22)	
13-24 h	1 (4.35)	0	

melatonin was effective in children with special needs who had sleep problems.

Multiple randomized, double-blinded, placebo-controlled trials have been conducted to assess melatonin use for children diagnosed with neurodevelopmental disorder who are having sleep problems,^[10-14] with conclusions supporting its use just as our results suggest. Nevertheless, it is important to keep in mind the different study types.

With regard to specific sleep aspects, we found significant differences in time taken to fall asleep, the number of times the child woke at night, total sleep time within 24 hours, and time taken to wake up, while no significant difference was observed in pre and post melatonin numbers of naps. The results of Rossignol and Frye's^[15] systematic review were consistent with these findings. In contrast, in their systematic review published in 2004, Phillips and Appleton^[16] concluded that melatonin was specifically helpful in reducing sleep onset latency ($P < 0.05$), yet with no major difference in terms of total sleep time, night-time awakening, and parental opinions when compared with placebo. With melatonin efficacy in reducing sleep onset latency, Yuge *et al.*^[17] agrees that in their multicenter clinical trial, major difference was noted upon using melatonin for sleep issues in same patient population ($P < 0.0001$). Abdelgadir *et al.*^[18] also observed that melatonin was effective in reducing total sleep time and sleep onset latency in their systematic review, with no change in nocturnal awakening frequency. Similarly, Halstead *et al.*^[19] have found that although melatonin reduced the sleep onset latency, the patients had early wake-up times; questioning its efficacy in total sleep time and quality. Another recent systematic review and meta-analysis of randomized control trials conducted by Parker *et al.*^[20] concluded that evidence of melatonin use in the pediatric population with neuro disabilities and sleep disorders remains unclear despite its benefit and safety compared with placebo.

In terms of melatonin dosing, the benefits were observed in our study with doses not exceeding 3 mg. Ayyash *et al.*^[21] used a wider range of melatonin doses and found that even though dosages between 3 and 10 mg resulted in significant improvement in all sleep aspects ($P = 0.001$), 38% of the children responded to lower doses of 2.5 to 3 mg, as seen in this study, 31% responded to doses of 5 to 6 mg, and only a small percentage required high doses of 9 to 10 mg. On the contrary, Wasdell *et al.*^[22] started with 5 mg tablets and gradually increased the dose until an optimal response was achieved in their study of 51 children (aged 2 to 18 years) with neurodevelopmental disorders. However, they also noted that lower doses could have resulted in similar outcomes.

Despite the above-mentioned studies with similar conclusions to ours, melatonin use remains off-label for sleep disorders in children with neurodevelopmental disorders, with promising short-term effects and minimal side effects if any. Further research is warranted to assess its long-term efficacy and safety.

Our study has some limitations. Most importantly, as this was a one-center study, the study size was limited, and the nature of the

study type is associated with the possibility of recall bias from the children's caregivers. However, given the lack of clear guidelines for melatonin use in the pediatric population, our study adds important information to support its use, given the background ethnicity with insufficient existing data. Moreover, we included every patient with the inclusion criteria during the study period, which gives a justified reflection of our unique population. Finally, in comparing our study to other international studies, there is support that melatonin is safe and effective in the treatment of sleep disorders in children with neurodevelopmental disabilities, with benefits extending to caregivers and the quality of life of other involved persons.

We advise that a large, local, prospective, randomized, double-blinded, placebo-controlled, multi-center study be conducted to further assess melatonin efficacy and safety for sleep problems in children with neurodevelopmental disorders, and that both the short- and long-term effects on children and their caregivers be examined.

Conclusion

Melatonin was found to have a significant impact on the total sleep time and quality of sleep during the pre and post assessment of children with neurodevelopmental disorders, and its use was safe and accepted by the caregivers of those children with no major side effects.

Key points

1. Sleep disorders are common among children with neurodevelopmental disorders.
2. Melatonin use is not well-studied and incorporated in treatment guidelines for those children.
3. The use of melatonin has shown to be effective for this patient population on multiple studies globally.
4. No major side effects were reported while using melatonin; however, long-term safety in children remains lacking in literature.
5. Melatonin could improve the quality of life of this patient population and their caregivers.

Ethical approval

This study was approved by the institutional review board of King Abdullah International Medical Research Center (KAIMRC) with an approval number of RR09/051.

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Conflicts of interest

There are no conflicts of interest.

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