

Research Article

Comparison of Efficacy and Safety of Melatonin in Improving Total Duration of Night-Time Sleep In Children with Neurodevelopmental Disorders: A Placebo Controlled Study

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Abstract:

Background: Poor sleep is known to have adverse impact on a child's attention, memory and learning behaviors. Inappropriate sleep is also linked to affect a child's non-verbal intelligence and communication. Moreover, insufficient sleep is also known to impact social skills among children.

Objective: To compare the efficacy and safety of melatonin and placebo in improving total duration of night-time sleep in children with neurodevelopmental disorders (NDDs).

Methods: This placebo controlled randomized trial was conducted at the Department of Pediatric Neurology, The Children's Hospital and Institute of Child Health, Multan from January 2021 to June 2021. A total of 160 children (80 in melatonin group and 80 in placebo group) aged 3-12 years with NDDs having sleep problems were enrolled. Oral melatonin was started as 1mg/day while melatonin was advised to be administered 45 minutes prior to child's usual bedtime. Parents were asked to follow up at 4-week interval. Final outcome in shape of total sleep time according to sleep diaries was recorded at 12 week time.

Results: Mean night sleep time at the time of enrollment was calculated to be 501+83 minutes. There was a significant improvement in total sleep time with the use of melatonin as total sleep time increased from 494+78 minutes at baseline to 555+94 at 12 weeks ($p < 0.0001$). In comparison to placebo, melatonin also proved to significantly increased the total sleep time duration at night (555+94 vs. 528+81, $p = 0.0340$). No significant difference was noted in terms of adverse events in between study groups ($p > 0.05$).

Conclusion: Melatonin was found to improve total sleep time significantly during the course of this study among children with NDDs having sleep problems. No major side effects of melatonin were reported among children with NDDs having sleep problems.

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Introduction:

Poor sleep is known to have adverse impact on a child's attention, memory and learning behaviors.^{1,2} Inappropriate sleep is also linked to affect a child's non-verbal intelligence and communication. Moreover, insufficient sleep is also known to impact social skills among children.³ As per “American Academy of Sleep

Medicine”, children aged 1 to 2 years sleep between 11-14 hours normally while those aged 3-4 years normally spend 10-13 hours sleeping.

Children suffering from neurodevelopmental disorders (NDDs) have an increased incidence of sleep disturbances in comparison to those who are unaffected which is thought to have an adverse effect on the

learning and behavioral aspects of these children.⁵ Literature points out towards prevalence of sleep disturbances among children with NDDs ranging between 25 to 86%⁶ while the exact burden in Pakistan is still unknown. Sleep problem is a big and common problem in children with NDDs and it needs to be addressed as not only the baby but also whole family is in distress condition.

Melatonin is known to be a neurohormone that regulates circadian sleep-wake rhythm while its plasma concentration follows circadian rhythm as its levels are low during the day time and high at night.⁷ Peak secretion of melatonin usually occurs around 2 AM that explains why it is called “darkness hormone”. Melatonin is also known to have other actions like a potent anti-oxidant, protection of organisms from carcinogenesis as well as helping immune modulatory effects.⁸ Research conducted on melatonin regarding its benefits among children suffering with sleep disorders have usually been on small set of patients and projected variations in results. A study from UK by Gringras P et al evaluating role of melatonin for sleep problems among children with NDDs found melatonin to increase mean total sleep duration of 40.5 ± 71.8 minutes from baseline to 12 weeks of treatment while this was 12.5 ± 52.5 minutes with placebo from baseline to 12 weeks.⁹ Scarcity of local data exists about role of melatonin in sleep disorders among children. Some studies have highlighted melatonin to improvement in total sleep time (TST) and time to sleep onset while number of awakenings have also been observed to reduce.^{10,11} Many of the children with NDDs experience sleep problems and might benefit from melatonin treatment but not much work is seen to evaluate these aspects of melatonin among children. The present study was aimed to compare the efficacy and safety of melatonin and placebo in improving total duration of night-time sleep in children with NDDs. The findings of this study will provide local evidence about the role of melatonin among children with NDDs aiming effectiveness in terms of improvement in night-time sleep. Our hypothesis was that melatonin results in significantly better improvement in night-time sleep in comparison to placebo.

Methods:

This randomized controlled trial was conducted in the

Department of Pediatric Neurology, Children's Hospital and Institute of Child Health, Multan” from January 2021 to June 2021.

A minimum sample size of 146 (73 in each group) was calculated considering 2-sided confidence interval of 95%, power 80%, ratio of sample size in 2 groups as 1:1, anticipated net mean increase of total night sleep in melatonin group as 40.45 ± 71.8 minutes and in placebo group as 12.52 ± 52.5 minutes.⁹ An additional 10% sample size was also recruited considering possible drop outs so total number of children enrolled in the present study were 160 (80 in each group) at the start of the trial.

All recruited children were aged 3 to 12 years. The NDDs were described as developmental delay with or without epilepsy, “autistic spectrum disorder (ASD)” and/or genetic/ chromosomal disorder. All enrolled children were having a minimum history of sleep impairment spanning at least 5 months. Sleep impairment was described as inability to sleep within one hour following switching off the lights. Children whose parents were willing and likely to complete sleep diaries were enrolled. Only children whose parents had completed sleep diaries for an average of 5 out of 7 nights at baseline (T0W) were included while enrolment continued until the desired sample size was recruited.

Exclusion criteria was children treated with melatonin within 5 months of screening, current use of beta-blockers, current use of sedative or hypnotic drugs, children with a known allergy to melatonin or with obstructive sleep apnoea syndrome.

Approval from “Institutional Ethical Committee” was taken. Written consent was sought from parents/guardians. All Children's age, weight and area of residence were recorded at the time of enrollment. Randomization was done through computer generated numbers. Oral melatonin was started as 1 mg per day while both melatonin and placebo were advised to be administered 45 minutes prior to child's usual bedtime. The dosage of melatonin was increased after 4-weeks of treatment to stepwise 2mg, 4mg and 6mg if the child had no serious adverse events, completed sleep diary for at least 5 days a week or if there was no increased seizure activity (doubling of seizure episodes in the preceding 4 weeks). All enrolled children were given sleep diaries to be filled by the parents (Figure 1) to note their child's

تاریخ														
دن														
صبح جاگنے کا وقت														
دن میں نیند (اگر کی تو)	Time	Duration	Time	Duration	Time	Duration	Time	Duration	Time	Duration	Time	Duration	Time	Duration
رات میں لائینس بند کرنے کا وقت														
رات میں نیند شروع ہونے کا وقت														
رات میں جاگنے کے اوقات (اگر ہوں تو)	Time	Duration	Time	Duration	Time	Duration	Time	Duration	Time	Duration	Time	Duration	Time	Duration

Figure 1: Sleep diaries filled by the parents

sleep patterns. All parents were asked to complete sleep diaries in terms of time when their child went to bed, fell asleep and woke up next morning. Parents were asked to follow up at 4-week interval. Final outcome in shape of total sleep time according to sleep diaries was recorded at 12 week time while data of all children was compared between baseline and at the end of the study period. During the follow ups, any adverse events of the advised melatonin were recorded.

SPSS version 26.0 was used for data analysis. Qualitative data like gender, area of residence, types of sleep disorder and adverse effects were represented as percentages and frequencies while quantitative data like age, weight total sleep time at night were shown as mean and standard deviation (SD). For quantitative variables, data from baseline to end of the study period within the same group was compared using paired sample t-test while comparison between two groups at a given time was made using independent sample t-test. Qualitative data was compared employing chi-square test. P value < 0.05 was considered as statistically significant.

Results:

Out of a total of 160 children, 106 (66.3%) were male. Majority of the children, 88 (55.0%) belonged to rural areas of residence. Overall, mean age was recorded to be 8.5 ± 3.6 years. Delayed sleep onset was the most frequent type of sleep disorder recorded in 62 (38.8%) children. Mean night sleep time at the time of enrollment was calculated to be 501 ± 83 minutes. Table 1 is showing baseline characteristics of all children enrolled in the present study while no significant

difference was recorded at baseline between children of both study groups ($p > 0.05$).

Table 1: Baseline Characteristics of Children ($n=160$)

Characteristics		Melatonin Group (n=80)	Placebo Group (n=80)	P-Value
Gender	Male	52 (65.0%)	54 (67.5%)	0.7381
	Female	28 (35.0%)	26 (32.5%)	
Area of Residence	Urban	38 (47.5%)	34 (42.9%)	0.5250
	Rural	42 (52.5%)	46 (57.1%)	
Age in Years (Mean+SD)		8.6 ± 3.1	8.4 ± 3.6	0.7106
Weight in kg (Mean+SD)		24.4 ± 4.9	23.8 ± 5.2	0.4537
Types of Sleep Disorder	Delayed Sleep onset	29 (36.2%)	33 (41.2%)	0.5277
	Poor Sleep Maintenance	13 (16.3%)	16 (20.0%)	
	Poor Sleep onset and maintenance	38 (47.5%)	31 (38.8%)	
Night Sleep Time at Baseline in minutes (Mean+SD)		494 ± 78	512 ± 88	0.1729

Table 2 is showing comparison of total sleep time (minutes) at baseline and at 12-weeks among and in between study groups. In melatonin group, 6 patients lost follow up so they were excluded from the final analysis. Likewise, 7 children lost follow ups in placebo group, so were excluded in the final analysis. There was a significant improvement in total sleep time with the use of melatonin as total sleep time increased from 494 ± 78

Table 2: Comparison of Outcome as Total Sleep Time (Mean±SD) between study groups

Outcome	Melatonin Group at Baseline (n=80)	Melatonin Group at 12 weeks (n=74)	P-Value
Total Night Sleep Time	494±78	555±94	<0.0001
Outcome	Placebo Group at Baseline (n=80)	Placebo Group at 12 weeks (n=74)	P-Value
Total Night Sleep Time	512±88	528±81	0.2452
Outcome	Melatonin Group at 12 weeks (n=74)	Placebo Group at 12 weeks (n=74)	P-Value
Total Night Sleep Time	555±94	528±81	0.0340

minutes at baseline to 555+94 at 12 weeks ($p < 0.0001$). In comparison to placebo, melatonin also proved to significantly increased the total sleep time duration at night (555+94 vs. 528+81, $p = 0.0340$).

Cough was the commonest type of adverse event reported in 40 (25.0%) children while mood swings were reported among 39 (24.4%) children. Table 3 is showing frequency and comparison of various adverse events during the study period.

Table 3: Adverse events noted among children of both study groups during the study period

Adverse Events	Melatonin Group (n=80)	Placebo Group (n=80)	P-Value
Cough	21 (26.3%)	19 (23.8%)	0.7150
Mood Swings	19 (23.8%)	20 (25.0%)	0.8539
Nausea & Vomiting	18 (22.5%)	19 (23.8%)	0.8513
Increased Excitement	15 (18.8%)	13 (16.3%)	0.6773
Rash	13 (16.3%)	9 (11.3%)	0.3585
Fatigue	9 (11.3%)	7 (8.8%)	0.5982
Headache	8 (10.0%)	8 (10.0%)	1
Dizziness	3 (3.8%)	2 (2.5%)	0.6496
Breathlessness	1 (1.3%)	1 (1.3%)	1

Discussion:

We noted children with NDDs and sleep problems were found to improve total sleep time significantly within

melatonin group from baseline to final outcome ($p < 0.0001$) as well as when compared to placebo at the time of final follow up ($p = 0.0340$). A placebo controlled trial done by Appleton RE et al among children having sleep problems along with NDDs from UK reported total sleep time to increase significantly among children using melatonin (mean increase of 22.4 minutes, $p = 0.04$) while sleep onset latency also improved ($p = 0.0003$).¹²

Some systemic reviews have tried to evaluate effects of melatonin on sleep problems and reported variation in findings from the “evidence to no effect”¹³ to “evidence of effect”¹⁴ while they have also advocated large multi-central trials to confirm the findings of randomized clinical trials conducted so far on melatonin. Differences in the measurement of sleep among children studied by different researchers could be one very important reason for reported variation in the trials. There is also a chance that night awakening could be missed by parents while there is also a probability that parents could have avoided vigorous check on sleep patterns due to disturbances in their own sleep. The increase in total sleep time reported in the present study is largely consistent with some of the studies conducted so far on melatonin aiming improvement in total sleep time among children with NDDs and sleep problems.^{13,15} Although, we were unable to measure sleep onset latency in the present study but some studies have highlighted role of melatonin on sleep onset latency as described clinically and statistically based upon sleep diaries and actigraphic measurements.^{9,16} Actigraphy is considered to be a major evaluating tool for sleep related research and it also helps in assessing clinical effectiveness of various sleep related interventions.

There is no consensus on dosage regimen for melatonin among children with NDDs having sleep problems. Studies have reported variation in dosage of melatonin ranging from 0.1 mg to 12mg while very similar to our study, some studies reported increase in dosage of melatonin following response.^{9,12,17} Variation in duration of melatonin treatment has also been reported by researchers ranging between 1 to 13 weeks.¹²

There were some limitations to the present study. As this was a single center study, our findings cannot be

generalized. Absence of comparator group warrants further local studies adopting randomized controlled designs are required to establish the role of melatonin among children having NDDs with sleep problems. We were unable to measure the sleep onset latency in the present study. As sleep diaries were maintained by parents, difference in educational background and socioeconomic patterns could have affected the outcomes.

Conclusion:

Melatonin was found to improve total sleep time significantly during the course of this study among children with NDDs having sleep problems. No major side effects of melatonin were reported among children with NDDs having sleep problems.

Ethical Approval: Given

Conflict of Interest: The authors declare no conflict of interest.

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