ORIGINAL ARTICLE

Administration in Efficacy of Melatonin Reducing Headaches in Children With Migraines and Sleep Disorders
A Randomized Clinical Trial Study

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Abstract

Objectives

Migraine headache after tension headache is the most common primary headache in children, and sleep disorders can aggravate the symptoms. Melatonin has been proposed in some studies for prophylaxis of migraine headaches. This study aimed to evaluate melatonin's effect on migraine symptoms in children with migraine headaches and sleep disorders.

Materials & Methods

In this randomized clinical trial study, all 30 children aged 5 to 15 years with migraine headaches and sleep disorders were referred to the Pediatric Neurology Clinic and enrolled. Patients were randomly divided into two equal groups; the intervention group was treated with melatonin (3 mg daily) and propranolol (1 mg/kg daily), and the control group was treated with propranolol alone (1 mg/kg daily). The severity of the migraine headaches was assessed with PEDMIDAS and a five-point Likert scale. The children's sleep habits questionnaire (CSHQ) assessed children's sleep disorders. The ANOVA and linear regression methods were used to analyze and compare the findings between the groups.

Results

Out of 30 children participating in the study, 9 were girls, and 21 were boys.

The number of daily headaches one month ($P = 0.02$) and four months ($P = 0.03$) after treatment was significantly lower in the melatonin group compared to the control group.

Regarding sleep quality, there was no significant difference between the two groups.

Conclusion

Melatonin and propranolol could better alleviate migraine headaches than propranolol alone in children.

Keywords: Headache; Migraine; Children; Melatonin; Propranolol
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Introduction

Headache is an important symptom of various diseases in pediatrics. 2-6% of all emergency visits of children and adolescents are due to headaches. Migraine headaches are the most common type (after tension headaches) that occur in children in different forms and need timely diagnosis and treatment (1-5). According to the international community definition of headache, migraine headaches are recurrent with or without aura lasting 1-72 hours (6). They are unilateral, pulsating, moderate or severe in intensity, are intensified by daily routine activities, and are associated with anorexia, nausea, vomiting, and photophobia (7-9). Migraine headaches in children are often without aura, bilateral, and with a shorter duration than in adults (9-11). Several studies have shown that in 20% of adults with migraines, the onset of symptoms had been before 10 yrs. (10).

Sleep is one of the basic human needs essential for maintaining energy, physical condition, and well-being. Sleep deprivation has many adverse effects on the human mind and body (12).

Sleep is one of the body's biological rhythms and a stage of rest accompanied by a decrease in consciousness and brain function, during which the response to environmental stimuli is reduced (13). Sleep plays a vital role in children's development, stimulating physical, behavioral, and emotional development, and is closely related to cognitive functions, academic achievements, and concentrations (14). Improving sleep quality and managing sleep disorders such as insomnia, bruxism, sleep apnea, and restless legs syndrome reduce the severity of migraine headaches.

In addition to the medication, improving children's lifestyles, including sleep hygiene, can play an important role in the overall success of migraine management. Therefore, sleep patterns in children with migraine headaches should always be identified and addressed to improve treatment outcomes and select the most appropriate treatment plan (15).

Various clinical evidence confirms the interaction between sleep and headache (18-16). Engstrøm M et al. (2013) showed that patients with migraines had a decreased sleep cycle pattern, and these sleep cycle changes were similar to those in patients with narcolepsy and sleep deprivation. Disruption of this mechanism makes patients with migraine more vulnerable to trigger stimuli during sleep. Partial sleep deprivation reduces the pain threshold and makes the patient more prone to headache attacks. Sleep deprivation may increase the response to pain stimuli (19). In addition, sleep deprivation is one of the most common triggers for migraine headache attacks (20). A study by Heng K et al. (2006) showed that the severity of headaches was inversely related to sleep duration. In other words, the shorter the sleep duration, the more severe the headaches will be (21). Regardless of the economic effects of drug costs and repeated treatments, the

recurrence and persistence of headaches in children affect their social and academic performance and daily functioning (22). Children who constantly suffer from pain are comparatively incapable of participating in everyday activities. Since sleep patterns affect pain, by examining the effect of sleep on pain, we can determine the level of disability in children and the degree to which they can adapt to pain (23). With the early recognition of stimuli and non-pharmacological prevention methods, the recurrence and severity of headache attacks can be reduced and help children with the disease to better adapt to chronic pain and improve their quality of life (24). Studies have shown that using information collected from a child to plan their care and applying professional standards such as protection and support can help reduce sleep problems and control the affected child's pain (23). This study of previous studies showed a positive effect of sleep on child growth and development. It was performed to evaluate the effect of melatonin on migraine severity in children with migraine and sleep disorders (14).

Materials & Methods

In this randomized clinical trial study, 30 children aged 5 to 15 years who suffered from classic and common migraine headaches and had concurrent sleep disorders were referred to the pediatric neurology clinic of Besat Hospital in Hamadan between 2019 and 2020 were enrolled in the study. Patients were randomly divided into two equal intervention and control groups using random quadruple blocking.

Patients in the intervention group were treated with propranolol tablets (made by Razak company) at a dose of 1 mg/kg in 2 divided doses along with one melatonin tablet (made by Razak company) at a dose of 3 mg at 10 pm. Patients in the control group were treated only with propranolol tablets (made by Razak company) with the same dose as the intervention group.

Patients were evaluated before, 1, and 4 months after the commencement of the treatment, and the results were collected and recorded using a checklist. In case of complications or exacerbation of debilitating symptoms, alternative medications for patients were started, which were recorded on the list.

Inclusion criteria included

Children 5 to 15 years old who were diagnosed with migraine headaches by a pediatric neurologist.

- Having the indication for the commencement of migraine prophylaxis, including having more than one attack per week, more than one debilitating attack, and PEDMIDAS (pediatric migraine disability assessment score) of more than 20.
- Suffering from sleep disorders, including falling asleep late, waking up early, short sleep duration, and frequent awakenings at night.

Exclusion criteria include:

- Patients who did not cooperate
- Change in diagnosis.

Patients' sleep quality was assessed by the CHSQ questionnaire, which was designed and psychoanalyzed by Waumans RC et al. (2010) to determine the sleep habits of preschool and school-age children (25). The questionnaire contains 33 items in three-point Likert style, including eight domains: sleep resistance (6 items), sleep anxiety habits (4 items), parasomnia (7 items), respiratory disorders during sleep (3 items), night waking (3 items), daily drowsiness (8 items), disturbed duration of sleep (3 items), and delayed onset of sleep (1 item). The total score range was between 33 and 99. The higher the total score was (equal

to or greater than 41), the worse the child's sleep habits and quality were.

PEDMIDAS criteria measured the severity of symptoms and complications of migraine headaches, and a 5-point Likert Scale measured the parent's satisfaction with the treatment. Data were collected by SPSS 16 software, and ANOVA and linear regression were used to analyze and compare the findings between the two groups.

The Ethics Committee approved this study of the Hamadan University of Medical Sciences with the ethics code, the Deputy of Research and Technology IR.UMSHA.REC.1398.236, IRCT20190619043946N1

Informed consent was obtained from all the patients or their parents.

Results

Of the 30 children studied, 9 (30%) were girls. The mean and standard deviation of the study participants' ages were 10.28 and 3.34 years, respectively. Characteristics of the studied children show that the two groups were similar in all variables except migraine type (Table 1).

There were no significant differences in the number of daily headaches between the two groups before the treatment (P = 0.34). Still, the number of attacks decreased significantly in both groups one month and four months after the treatment. In terms of comparison between the two groups, in the intervention group, the number of daily headaches one month (P = 0.02) and four months (P = 0.03) after the treatment was significantly lower than in the control group (Table 2).

The two groups did not differ significantly regarding the PEDMIDAS index (Table 3).

There was no significant difference between parents' satisfaction with treatment by the Likert scale between the two groups one month (P = 0.25) and four months after treatment (P = 0.45).

In terms of CSHQ indices, the two groups did not differ significantly before the treatment. The mean CSHQ score decreased in the two groups after treatment, but there were no significant differences between the two groups (Table 4).

No significant drug side effects were observed in both group.

Table 1. Patient characteristics in intervention and control groups

Variable		Type of drug treatment				**P-value**
	Propranolol		Propranolol and Melatonin			
	Number	Percent	Number	Percent		
Gender	Female	4	44.4	5	55.6	0.690
	Male	11	52.4	10	47.6	
Age	<10 yrs	8	53.3	7	46.7	0.990
	10 yrs and more	7	46.7	8	53.3	
Family history of epilepsy	Yes	0	0	1	100	0.990
	No	15	51.7	14	48.3	
Type of headache	Pulsating	7	61.5	10	58.8	0.460
	Constant pressure	8	41.2	5	38.5	
Location of the headache	Frontal	10	52.6	9	47.4	0.690
	Temporal	2	66.7	1	33.3	
	Occipital	1	50	1	50	
	Frontal and temporal	2	33.3	4	66.7	
one-sided or two-sided headache	one-sided	7	43.8	9	56.3	0.460
	two-sided	8	57.1	6	42.9	
Migraine type	Classic	6	33.3	12	66.7	0.020
	Common	9	75	3	25	
Family history of headache	Father	1	25	3	75	0.480
	Mother	0	50	3	50	
	Other family members	3	0	1	100	
	Nobody	11	57.9	8	42.1	

Table 2. Number of daily headaches before and after treatment in two groups.

Groups		Mean	Standard deviation	P-Value
Propranolol	Before treatment	12.8	9.8	0.039
	1 month after treatment	9.4	5.1	
	4 months after treatment	4.1	3.2	0.003

Groups		Mean	Standard deviation	P-Value
Propranolol and Melatonin	Before treatment	8.9	5.4	0.001
	1 month after treatment	6	3.7	
	4 months after treatment	2.6	2.8	<0.001

Table 3. PEDMIDAS index in intervention and control groups.

Variable	Groups	Mean	Standard deviation	P-Value
PEDMIDAS three months after treatment	Control	36.2	33	0.100
	Intervention	17.3	22.7	

Table 4. CSHQ index in intervention and control groups.

Variable	Groups	Mean	Standard deviation	P-Value
CSHQ before treatment	Control	60.70	11.2	0.710
	Intervention	63.4	14.6	
CSHQ after treatment	Control	43.4	12.5	0.880
	Intervention	42.8	13.1	

Discussion

Migraine following tension headache is the most common cause of recurrent headaches in children (1). Recurrence of headache attacks and related complications can reduce the quality of life, disrupt daily activities, and impede personal communication, sleep, and wakefulness of the patients (22, 23). Previous studies have demonstrated an association between sleep patterns and migraine headaches, and sleep deprivation can exacerbate symptoms (16-20). This study's primary purpose was to evaluate melatonin's effect on improving sleep quality and its impact on the severity of migraine symptoms. Also, this study investigated whether the effect of melatonin is due to sleep pattern modification or whether melatonin has a direct preventive impact on the recurrence of migraine attacks. This study showed that propranolol alone and propranolol in combination with melatonin significantly reduced the number of daily headaches one month and four months after the commencement of the treatment in children aged 5 to 17 years with migraine headaches. The results of this study also confirmed the effectiveness of propranolol in preventing migraine in children, as shown in previous studies (26- 28).

The study also showed that adding melatonin to propranolol significantly reduced the number of headache attacks during the first four months after the treatment.

However, it did not improve children's sleep quality during this period. Therefore, it may be concluded that melatonin can directly affect the prevention of migraine attacks in children.

A study by Gonçalves AL et al. (2016) showed that

melatonin at the dose of 3 mg daily is effective in preventing migraine headaches in adults. (29). Also, a study by Long R et al. (2019) showed that melatonin is effective in the prevention of migraine attacks (30). Another study in 2004 showed that with the same dose of melatonin, insomnia caused by migraines could be prevented (31). In contrast, a study by Alstadhaug KB et al. found that if the dose of melatonin were reduced to 2 mg, the drug's effectiveness in preventing migraines would be diminished. (32). Liampas I et al. showed that melatonin effectively treats migraine in adults without any side effects. Still, in children, the effect of melatonin in the treatment of migraine was not significantly different from the placebo (33).

A study by Gelfand AA et al. showed that melatonin could effectively treat the acute phase of pediatric migraine (34).

A study by Mohammadinia et al. demonstrated a significant difference between the effects of melatonin and naproxen on menstrual migraine headaches (35). In our study, the effects of the two treatment regimens on sleep quality or CSHQ index of children in the two groups were not significantly different. Also, the results of our study showed that the effects of the two treatment regimens on sleep quality or the CSHQ index of children in the two groups were not significantly different. However, the effectiveness of melatonin in improving sleep quality has been shown in previous studies (36).

Considering that sleep habits and quality in children have different backgrounds and causes and establishing a sleep pattern in children requires the information and cooperation of parents (7), the ineffectiveness of the treatment programs used on the sleep quality of children in this study may be due to confounders such as propranolol consumption at night. After starting treatment, improving our patients' sleep quality did not improve the severity of headaches compared to patients with poor sleep. Still, some studies have shown a relationship between headaches and sleep quality in children and adolescents (37, 38).

Conclusion: Findings of this study showed that melatonin could be used to prevent migraine headaches in children without any significant side effects.

Study Limitations: Due to ethical considerations, it was impossible to compare melatonin and placebo separately in this study. It is recommended that the direct effect of melatonin on sleep quality and migraine prevention in children should be studied in more depth in future studies.

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Author's Contribution

Conception and design: Afshin fayyazi, Abassali Abdollahi, Hassan Bazmamoun. Analysis and interpretation: Afshin fayyazi, Hassan Bazmamoun, Abassali Abdollahi, Ali Moradi. Data collection: Afshin fayyazi, Abassali Abdollahi, Hassan Bazmamoun Writing the article: Afshin fayyazi, Hassan Bazmamoun Critical revision of the article: Afshin fayyazi, Hassan Bazmamoun. Final approval of the article: Hassan Bazmamoun Statistical analysis: Abassali Abdollahi, Ali Moradi Obtained funding: Afshin fayyazi, Abassali Abdollahi. Overall responsibility: Hassan Bazmamoun

Conflicts of Interest

The results of this study are not in conflict with the authors' interests

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