ORIGINAL ARTICLE

Efficacy of Melatonin Administration in Reducing Headaches in Children with Migraines without Sleep Disorders

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ABSTRACT

Objectives

Migraine is one of the common diseases of children, which can disrupt their quality of life. Some studies have shown the effect of melatonin in reducing migraine headaches. This study aims to investigate the effect of melatonin administration in reducing headaches in children with migraine without sleep disorders.

Materials & Methods

In this clinical trial study, fifty-five children aged five to 15 years with migraines who had no sleep disorder were enrolled. The control group (twenty-seven patients) was treated with propranolol tablets, and the intervention group (thirty patients) was treated with propranolol tablets plus melatonin tablets for three months. Patients were visited before, one month, and three months after the start of treatment, and their data was collected and recorded.

Results

The number of headache attacks decreased significantly in the intervention group compared to the control group three months after the treatment (P=0.006). The number of patients with a good response to treatment in the intervention group was significantly more than the control group (p=0.023). Parents' satisfaction with the treatment in the intervention group was significantly higher than the control group (P=0.026). There was no significant difference in the intensity of disability caused by headaches after treatment in the two groups. No significant drug side effects were seen in any of the two groups.

Conclusion

Adding melatonin to the treatment of children with migraine without sleep disorders significantly reduces the frequency of headache attacks and increases satisfaction with the treatment.

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Introduction

Migraine is one of the most common causes of headaches in children and adults, which can disrupt the quality of life of patients and must be controlled with proper management. (1). The brains of migraine sufferers are more sensitive to neurochemical changes due to genetic reasons. These neurochemical changes reduce the excitability threshold of the trigeminal nerve and cause neuronal inflammation, and then the sensory stimuli of the trigeminal nerve stimulate the somatosensory and limbic cortex (2, 3). The prevalence of migraine in children aged three to seven is 1% to 3%, which increases to 8% to 23% in 15-year-olds (4). About 18% of children referred to the emergency have symptoms related to migraine (5). In about 25% of migraine patients, the number of headache attacks is one or less per month, but about 61% of patients experience more than four serious headache attacks per month that require migraine prophylaxis therapy (6). Migraine prophylaxis treatments include lifestyle modification and drug treatments (7). Lifestyle modification includes sleep pattern modification, diet, stress management, physical activity, and avoidance of irritants (8). For drug treatments, beta-blockers, calcium channel antagonists, antiepileptics, and antidepressants are mostly used (9)(8). Previous studies have shown a reciprocal relationship between sleep quality disorder and headache incidence (10). Sleep deprivation lowers the pain threshold and makes patients prone to headache attacks. In fact, sleep deprivation increases the response to pain stimuli (11). In addition, sleep deprivation is one of the most common triggers of migraine headache attacks, and the severity of headaches is inversely related to the duration of sleep (12) (13). Melatonin is secreted from the pineal gland to regulate the sleep and wake cycle. Melatonin secretion is regulated by the suprachiasmatic nucleus of the hypothalamus gland, and its secretion increases during darkness and sleep (14). The effect of melatonin in treating primary headaches, including migraines, can be due to neurotransmitter changes such as inhibiting the production of nitric oxide, inhibiting the release of dopamine, and also antagonistic effects on glutamate function (14). Some previous studies have shown the effectiveness of melatonin as a preventive treatment for migraine headaches in adults (15, 16, 17). This study aims to investigate the direct effect of melatonin in preventing migraine headaches in children; therefore, children who did not have underlying sleep disorders were studied.

Materials & Methods

In this clinical trial study, sixty-five children aged five to 15 years with migraine without sleep disorders referred to the children's neurology clinic of Be'sat Hospital in Hamadan, Iran (2017 – 2018) were included. After removing ten cases (three cases due to a change of diagnosis and seven due to lack of satisfaction with the study), fifty-five children were randomly divided into two groups by simple random sampling method.

For the control group (twenty-seven patients), propranolol (Razak company) at a dose of 1 mg/Kg/daily, and for the intervention group (twenty-eight patients), propranolol (Razak company) at a dose of 1 mg/Kg/daily plus a 3 mg melatonin tablet (Razak company), was prescribed. The treatment period of the patients was three months. Patients were visited before, one month, and three months after the start of treatment, and their data was recorded. In case of severe drug side effects or lack of adequate clinical response until one

month after the start of treatment, alternative drugs were prescribed.

Inclusion criteria included children from five to 15 years old with migraine, eligibility to receive migraine prophylaxis treatment due to frequent or disabling headaches (headache attacks more than once a week or debilitating headache attacks leading to absence from school or interruption of daily activities or having a PedMIDAS score above 20), and absence of sleep disorder based on CHSQ checklist.

Exclusion criteria included change in diagnosis and non-satisfaction of parents or children to cooperate in the study.

The diagnosis of migraine was according to the International Classification of Headache Disorders, 3rd edition (ICHD-3 beta).

PedMIDAS scale, Likert scale, CHSQ checklist, and parent-patient questionnaire were used to investigate the disabilities related to migraine headaches, parents' satisfaction with treatment, sleep disorder, and frequency of headaches.

Parents' satisfaction was evaluated with a 5-rank Likert scale. A good response to treatment was considered when the frequency of headache attacks decreased to two times or less per month, and the PEDMIDAS decreased to less than 10.

Migraine was diagnosed by a pediatric neurologist based on the criteria of the International Headache Society.

This study used analysis of variance and the Chi-square test to analyze and compare the findings between the groups. Data were analyzed using SPSS 16 software. P value < 0.05 was considered statistically significant.

This study was conducted with the approval of the Ethics Committee of the Hamadan University of Medical Sciences with the ethics code, the Deputy of Research and Technology ID IR.UMSHA.REC.1398.517, IRCT IRCT20120215009014N345

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

Results

Out of sixty-five children aged five to 15 who were evaluated, after removing ten cases (three cases due to a change of diagnosis and seven due to lack of satisfaction with the study), fifty-five children were enrolled the study in the two groups, control group (twenty-seven cases), and intervention group (twenty-eight cases). Both groups did not have statistically significant differences in demographic and clinical variables (Table 1).

Three months after treatment, the severity of disability (according to the Ped MIDAS scale) showed a significant decrease compared to before treatment in both groups, but this decrease was not significantly different between the two groups (Table 2).

The numbers of headache attacks per month before the start of treatment in the control and intervention groups were 10.1 ± 7.2 and 8.8 ± 4.6, respectively, which significantly decreased in both groups in the first and third months after treatment (Table 3). The decrease in the number of headache attacks per month in the first month of treatment was not significantly different between the two groups, but the decrease in the number of headache attacks in the third month of treatment compared to the first month was significantly more in the intervention group than in the control group (Table 3).

Twenty-five patients (89.3%) from the intervention group and 17 patients (63%) from the control group had a good response to treatment (two or fewer headache attacks per month), which was significantly more in the intervention group than

the control group (p = 0.023.)

According to the Likert scale, the parents' satisfaction with the treatment was significantly higher in the intervention group than in the control group (P=0.026) (Table 4).

Regarding headache severity, there was no significant difference between the two groups (P=0.74) (Table 5).

Table 1. Patient characteristics in intervention and control groups

Variable		Control group (n=27)		Intervention group (n=28)		P-value
Gender (Male)		14(52%)		14(50%)		0.690
Age (yrs)		9.6±2		10.6±2.1		0.160
Type of headache	Pulsating	13(48%)		16(57 %)		0.460
	Constant pressure	14(52%)		12(43%)		
Location of the headache	Frontal	17	52%	16	48%	0.690
	Temporal	4	67%	2	33%	
	Occipital	2	50%	2	50%	
	Frontal and temporal	4	33%	8	67%	
One-sided or two-sided headache	One-sided	14	44%	18	56%	0.460
	Two-sided	13	57%	10	43%	
Migraine type	Classic	11	48%	12	52%	0.670
	Common	16	50%	59%	25	
Family history of headache	Father	2	25%	4	75%	0.480
	Mother	4	40%	6	60%	
	Other family members	5	63%	3	38%	
	Nobody	16	52%	15	48%	

Table 2. Severity of disability caused by headache (PedMIDAS) in two groups before and after treatment

Control group	Before treatment	59.55±56.53	P<0.001
	After treatment	31.51±27.40	
Intervention group	Before treatment	51.96±44.19	P<0.001
	After treatment	31.14±28.06	
Comparison of PedMIDAS criteria between two groups 3 months after treatment			P=0.960

Table 3. The average number of headache attacks per month, before, one month, and three months after treatment in two groups

	Control group	Intervention group	P- value
Before treatment	10.1±7.2	8.8±4.6	0.852
One month after starting treatment	4.1±4	2.1±3.8	0.473
Three months after starting treatment	3.2±3.9	1.1±1.1	0.006

Table 4. Parents' satisfaction with treatment (Likert scale) in two groups

	Very satisfied	Satisfied	Effectless	Dissatisfied	Very Dissatisfied	P-Value
Control group	12(44.4%)	8(29.6%)	2(7.4%)	4(14.8%)	1(3.7%)	0.026
Intervention group	20(71.4%)	6(21.4%)	1(3.6%)	1(3.6%)	0(0%)	

Table 5. The severity of headaches before and after treatment in two groups

		Mild headache	Moderate headache	Severe headache	P-Value
Control group	Before treatment	4(14.8%)	11(40.7)	12(44.4%)	0.0001
	After three months of treatment	23(85.2%)	4(14.8%)	0(0%)	
Intervention group	Before treatment	2(7.1%)	10(35.7%)	16(57.2%)	0.0001
	After three months of treatment	25(89.2%)	2(7.1%)	1(3.7%)	

No significant drug side effects were seen in any of the two groups

Discussion

Migraine headache is a common disorder in children, and about 10% of children aged five to 15 suffer from it (18). The purpose of prophylaxis treatment in migraine is to improve the quality of life by reducing the frequency and severity of headache attacks, and it is used in cases of frequent headaches or headaches that lead to daily dysfunction (19).

Some previous studies have shown the effect of melatonin in preventing migraine headaches in adults (20, 15, 16). The study by Liampas et al. (2020) showed that melatonin may effectively prevent migraine headaches in adults, but the authors believe that more studies are needed to recommend its use (17). The results of a systematic review study by Long et al. (2019) showed that melatonin is likely beneficial in migraine prevention and has the same effect as other main migraine preventive drugs. According to this study, melatonin is ineffective in the treatment period of two months, but it may be effective in

the treatment period of three months or more, which is consistent with the results of the current study (14). Some studies conducted on children have shown the effect of melatonin in preventing migraine in children (21, 22). Gelfand et al.'s study revealed that melatonin effectively reduces headache attacks in children and adolescents in the acute phase of migraine (23).

Considering the association between migraine and sleep disorders (24) and the evidence that shows sleep disorders aggravate migraine attacks (25), melatonin may reduce the severity of migraine by improving the quality of sleep, but the present study showed that melatonin directly reduces migraine headaches in children without sleep disorders.

In Conclusion

The results of the present study showed that melatonin can be used as an effective drug without serious complications to prevent migraine headaches in children, although its maximum therapeutic effects may begin within a few weeks.

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Authors' Contribution

Conception and design: Afshin Fayyazi, Paria Abbasian, Seyed Mohammad Sadegh, Hosseini, Hassan Bazmamoun.

Conflicts of Interest

The authors have declared that no conflict of interest exist.

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