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Original Article

The Effect of Melatonin on Reducing the Frequency and Severity of Migraine Attacks: A Double-Blind, Randomized Clinical Trial

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Abstract

Background: There is no definite recommendation for melatonin supplementation in episodic migraine. This study aimed to evaluate the effect of melatonin on reducing the frequency and severity of migraine attacks.

Methods: This randomized, double-blind clinical trial was conducted at Golestan Hospital of Ahvaz, Iran, in 2021. A total of 60 patients with episodic migraine were randomly assigned into 2 groups of receiving 3 mg melatonin (intervention group; n=30) or the same dose of placebo (control group; n=30) along with baseline therapy (propranolol 20 mg, BID) for two months. The attack frequency, attack duration, attack severity (based on VAS), the number of analgesic intakes, drug complications, Migraine Disability Assessment score (MIDAS), and Pittsburgh sleep quality index (PSQI) were evaluated at baseline and in the first, second, third, and fourth months of follow-up. The independent *t* test, chi-square, and analysis of variance (ANOVA) with repeated measures were used to compare variables between the two groups.

Results: In both groups, the frequency, duration, and severity of attacks, taking analgesics, MIDAS, and PSQI scores during follow-up decreased significantly (P<0.001). After treatment, the mean frequency (P=0.032) and duration of attacks (P=0.001), taking analgesic (P<0.001), and MIDAS (P<0.001) and PSQI scores (P<0.001) in the melatonin group were lower than placebo. Only the attack severity was not significantly different between the two groups (P=0.126). Side effects were observed in two patients (6.7%) in the melatonin group and one patient (3.3%) in the placebo group (P>0.999).

Conclusion: Our study shows that melatonin was more efficacious than the placebo in the reduction of frequency and duration of migraine attacks. It was equally safe as the placebo and might be effective in the preventive treatment of episodic migraine in adults.

Trial registration number: IRCT20190107042264N5.

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Keywords ● Migraine disorders ● Melatonin ● Headache

What's Known

- Oral melatonin has been shown to be an effective prophylactic treatment for episodic migraine.
- Due to limited evidence, there is no conclusive recommendation for using melatonin supplementation in episodic migraine.

What's New

- Our findings support the safety and efficacy of melatonin in the preventive treatment of migraine. Melatonin is effective in reducing the frequency and duration of migraine attacks and improvement of migraine disability and sleep quality.
- Oral melatonin might be used for the preventive treatment of episodic migraine in adults.

Introduction

Migraine is one of the most common neurological problems in the primary clinical field with a one-year prevalence of about 12-20% in the general population.[1] Clinically, episodic migraine

is seen in the form of frequent headache attacks with a wide range of accompanying symptoms, including nausea, vomiting, lethargy, and sensitivity to light and sound.[2] It causes a significant disruption in patients' quality of life.[3]

Currently, preventive treatments are the standard of care for migraine patients.[3-5] First-line drugs include beta-blockers without sympathomimetic activity (i.e., ethanol, metoprolol, and propranolol),[6] and second-line medicines are flunarizine, amitriptyline, and sodium valproate.[5] However, most of these prophylactic drugs do not induce sufficient responses and cause side effects.[3, 5]

Although the mechanisms of migraine occurrence are unknown, several evidences have shown the role of the hypothalamus in the pathophysiology of migraine.[7, 8] On the other hand, insomnia is one of the common problems associated with migraine, and three out of four patients with episodic migraine have insomnia.[9, 10] Therefore, some neuropeptides related to hypothalamic axes have been considered for treating migraine.[11]

Among hypothalamic neuropeptides, melatonin and its role in circadian rhythms are well known. Oral melatonin has been approved for the treatment of chronic insomnia.[12] Melatonin is endogenously secreted from the pineal gland and plays a vital role in regulating the circadian cycle. Theoretically, melatonin can be helpful for migraine prophylaxis due to its biological properties, including antioxidant effects, regulation of dopamine-glutamine activity, and inhibition of calcitonin gene-related peptide (CGRP) release.[3, 13] Due to the involvement of circadian rhythms in migraine, a significant relationship between morning episodic migraine and insomnia, and the role of melatonin in regulating the activity of the suprachiasmatic nucleus (SCN) and circadian rhythms through the effect on the hypothalamus-pineal axis, melatonin is an option. Thus, melatonin has been considered for further investigation.[14]

This clinical trial was conducted to investigate the effectiveness of melatonin in preventing episodic migraine attacks in episodic migraine patients. Obtaining more evidence of the effectiveness or lack of effectiveness of melatonin could help to treat the disease more effectively.

Patients and Methods

The present study is a double-blind controlled clinical trial conducted on patients with migraine complaints referred to the neurology clinic of Golestan Hospital in Ahvaz, Iran in 2021. This study was approved by the Clinical Studies Ethics Committee of Ahvaz University of Medical Sciences, Ahvaz, Iran (Ethics code: IR.AJUMS.HGOLESTAN.REC.1401.022) and Iranian Registry of Clinical Trials (IRCT registration number: IRCT20190107042264N5). The study protocol conformed to the provisions of the Declaration of Helsinki, and informed consent forms were obtained from all patient participants.

The sample size was determined based on α error of 0.05 and power (1-β error) of 0.90 and the results of a pilot study (n=15) in which at the end of 2 months of treatment, the mean number of migraine attacks in melatonin and placebo group was 2.6±1.1 and 4.5±2.8, respectively. The sample size was calculated using G*Power program version 3 (Heinrich Heine University, Düsseldorf, Germany), based on the statistical test of the difference between two independent means as described below, and was determined to be 28 subjects in each group. Finally, assuming 15% sample dropouts, the sample size was considered 32 patients in each group.

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \left({S_1}^2 + {S_2}^2\right)}{(\bar{X}_1 - \bar{X}_2)^2}$$

Inclusion criteria were: patients with confirmed chronic migraine based on the criteria of the International Headache Society (IHS) by ICHD-3 diagnostic criteria,[15] no primary internal and neurological complaints and no other reason for their headache, at least one year of migraine history, and willing to enter the study. Exclusion criteria were: severe and debilitating migraine (to eliminate the therapeutic effects of analgesic overuse), chronic daily headache, using any drugs other than propranolol to prevent attacks, using hypnotics medications, treatment-resistant migraine, history of abnormal use of analgesics and Medication-overuse headache (MOH), significant psychological disorders (mental illness leading to chronic drug use for at least 6 months), pregnancy and lactation, underlying medical and surgical conditions, those requiring medical interventions (including contraindications to beta-blockers), multiple headaches diagnosed other than migraine with or without medical treatment such as tension, history of melatonin allergy or complication, and patient request to withdraw from the study.

Grouping and Intervention

At the beginning of the study, the basic characteristics of the patients, including demographic information (i.e., age, sex, marital status, and occupation) and the clinical data on the characteristics of their migraine headaches,

were collected through the general migraine headache questionnaire. The questionnaire was based on the International Headache Society criteria for migraine diagnosis.[16] The patients were asked to complete the migraine attack registration questionnaire that was provided to them, which includes attack information such as the number of attacks, time of onset, symptoms before the onset of the attack, symptoms during and after the migraine attacks, possible triggers, and amount of analgesic drugs. They were also asked to complete the migraine disability assessment and the sleep quality questionnaires.

Patients were assigned into two groups by a simple randomization method. Allocating patients into two groups was done by random number generation using Excel 2016 (Microsoft Corporation, US). A member of the hospital staff who had no role in patient registration and treatment allocation performed the randomization. The implementation of the random allocation sequence was done without any knowledge about the patient's treatment.

In the case group, 3 mg melatonin tablets (Razak Company, Iran) were given to the patients. In the control group, placebo tablets with the same shape and packaging were prescribed. The placebo tablets contained starch and were prepared at the Faculty of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. Moreover, propranolol 20 mg (Abidi Co., Iran) twice a day was used as a standard anti-migraine treatment in both groups of patients. The method of taking the intervention drugs was 1 hour before going to sleep. The intervention continued for 2 months. To eliminate the bias caused by the knowledge of physicians, patients, and statistical analyzer and its possible impact on the research result, the study was conducted in a double-blinded manner. Medicine packaging, intervention, and patient evaluation were carried out by a physician blinded to both treatment groups. The patients and the statistical analyzer did not know about patient grouping as well. For blinding patients involved in the study, the melatonin and placebo tablets were provided to patients in similar and indistinguishable packages where only the title of the research and serial number were displayed on them. At the end of the study, the serial numbers were converted to groups A and B in the Excel software; and after performing statistical analysis, it was determined which group was melatonin or placebo.

Outcome Evaluation

The patients were followed up for 4 months from the beginning of the treatment. The study outcomes included the migraine attack frequency (number of migraine headache days during the month), attack duration (duration of each migraine episode), migraine attack severity based on the visual analog scale (VAS), number of analgesic intakes, and drug complications. Migraine Disability Assessment score (MIDAS) and Pittsburgh Sleep Quality Index (PSQI) were evaluated at baseline and during follow-up in the second and fourth month after the start of intervention.

The MIDAS includes seven questions related to headaches during the past 3 months and divides the level of pain and disability caused by headaches into four groups: Little or No disability (MIDAS grade I: score 0-5); Mild disability (MIDAS grade II: score 6-10); Moderate disability (MIDAS grade III: 11-20); Severe disability (MIDAS grade IV: score≥21).[17]

The PSQI is a 19-item questionnaire designed to measure sleep quality and disturbance over the past month. This questionnaire has seven components that are graded on a scale of zero to three, including sleep duration, sleep disturbance, sleep latency, daytime dysfunction due to sleepiness, sleep efficiency, overall sleep quality, and sleep medication use. Finally, the sleep component scores are summed to yield a total score ranging from 0 to 21, with a higher total score (referred to as the global score) indicating worse sleep quality.[18]

Statistical Analysis

SPSS (SPSS Inc., Chicago, IL, U.S.A.) version 22 was used for statistical analysis. In quantitative variables, mean, standard deviation, frequency, and percentage were used to describe the data. The normality of the data was checked by the Kolmogorov-Smirnov test. The independent *t* test and Chi square (or Fisher's exact test) were used to compare quantitative and qualitative variables between the two groups, respectively. The analysis of variance (ANOVA) with repeated measures was used to compare the mean of the variables during the follow-up period. The Bonferroni *post hoc* test was used to compare the groups. The significant level in the tests was considered 0.05.

Results

In this study, 60 patients with migraine headaches with a mean age of 32.78±7.83 years (between 20 and 57 years) participated (table 1). The diagram of the study process and participants' exclusion are shown in figure 1.

Table 1: Basic characteristics of the participants

Variable	Group	Melatonin (n=30)	Placebo (n=30)	P value
Age (year), mean±SD		33.77±6.89	31.80±8.67	0.335 *
Age group, n (%)	≤25 y	3 (10.0)	5 (16.7)	0.735 **
	26-35 y	17 (56.7)	16 (53.3)	
	36-45	6 (20.0)	7 (23.3)	
	>45	4 (13.3)	2 (6.7)	
Sex, n (%)	Male	11 (36.7)	14 (46.7)	0.601 ***
	Female	19 (63.3)	16 (53.3)	
Marital status, n (%)	Married	12 (40.0)	15 (50.0)	0.713 **
	Single	15 (50.0)	13 (43.3)	
	Divorced	3 (10.0)	2 (6.7)	
Occupation, n (%)	Housewife /Unemployed	7 (23.3)	8 (26.7)	0.758 **
	University student	8 (26.7)	6 (20.0)	
	Employee	6 (20.0)	4 (13.3)	
	Self-employee	9 (30.0)	12 (40.0)	
Underlying disease, n (%)		5 (16.7)	4 (13.3)	0.739 **
Family history of headache, n (%)		12 (40.0)	14 (46.7)	0.795 ***
Duration of disease, n (%)	1-2 y	5 (16.7)	7 (23.3)	0.711 **
	3-4 y	8 (26.7)	9 (30.0)	
	≥5	17 (56.7)	14 (46.7)	

*Independent *t* test; **Chi square test; ***Fisher's exact test; P<0.05 is statistically significance.

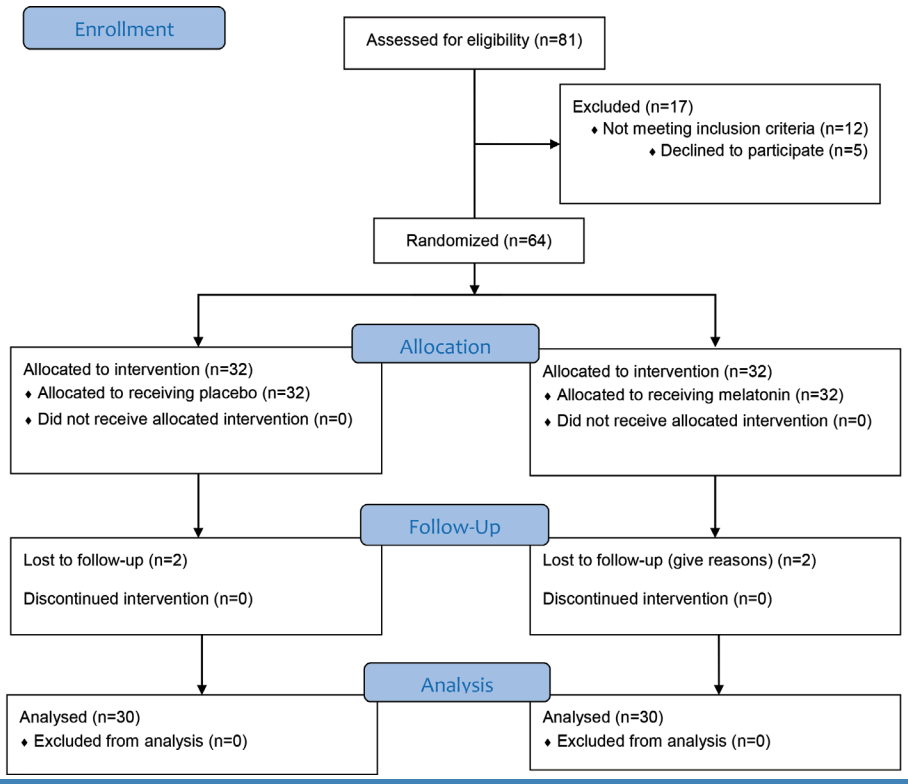

Figure 1: The figure represents the CONSORT flow diagram of the study.

The result of the independent *t* test showed that the frequency and duration of migraine attacks in the melatonin group were significantly lower than in the placebo group in the second, third, and fourth months (figure 2). The mean VAS in baseline and follow-up visits did not differ significantly between the two groups (P=0.645 and P=0.126, respectively). However, the number of analgesic intakes in the first, second, third, and fourth months after treatment was significantly less in the melatonin group than placebo (P=0.003 and P<0.001, respectively) (figure 2).

Based on the results of ANOVA with repeated measures, the mean frequency of migraine attacks (Power:0.984; F:17.526; P<0.001), duration of migraine attacks (Power:0.996; F:25.328; P<0.001), and the number of analgesic intakes (Power:0.960; F:14.230; P<0.001) in different time points were significantly different

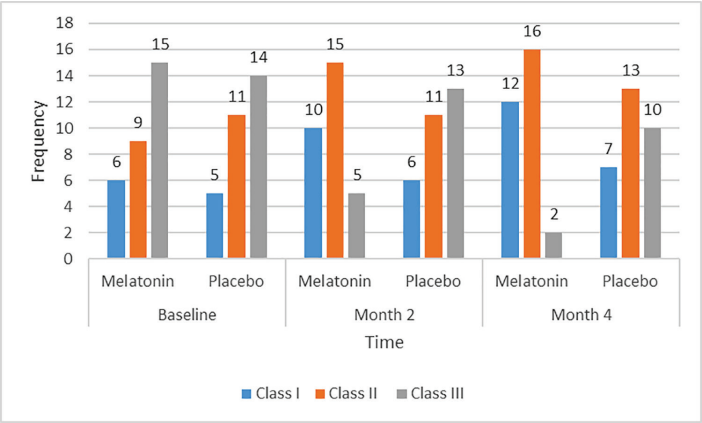

Figure 2: Characteristics of migraine attacks and the number of analgesics taken in the two groups. NS: Not significant; VAS: Visual analogue scale; P values are for independent *t* test. P<0.05 is significant.

between the two groups. However, there was no significant difference in migraine pain intensity between the two groups at different times (Power:0.142; F:0.345; P=0.554). According to the Bonferroni *post hoc* test, the frequency, duration, and intensity of migraine attacks in the first, second, third, and fourth months of follow-up decreased significantly compared to baseline in both groups (P<0.001). In the melatonin group, there was a significant difference in attack frequency between months 1 and 2 (P=0.001). Moreover, a significant reduction in attack duration between the first and second months of follow-up (P=0.009), and the second and third months (P=0.023) was reported. Additionally, a significant decrease in the number of analgesics used was also observed between the first and second months (P=0.001), and a significant difference in pain intensity between the first and second months of the follow-up (P=0.009). In other comparisons, there was no significant difference between follow-up visits. However, in the placebo group, no significant difference was observed between frequency, duration, severity of attacks, and use of analgesics in different follow-up visits (between months 1 and 2 (P=0.435), months 2 and 3 (P=0.234), and months 3 and 4 (P=0.123).

The frequency of subjects with insignificant and mild disability (Class I and II) in the second and fourth months of follow-up in the melatonin group was higher than in the placebo group (P=0.001 in both) (figure 3).

Based on the results of repeated measures analysis, the mean MIDAS and PSQI scores showed a significant difference between the two groups (P<0.001) (table 2). According to the results of the Bonferroni test, the MIDAS score in melatonin and placebo groups decreased significantly in the second and fourth months compared to baseline (P<0.001 in both). However, there was no significant change between

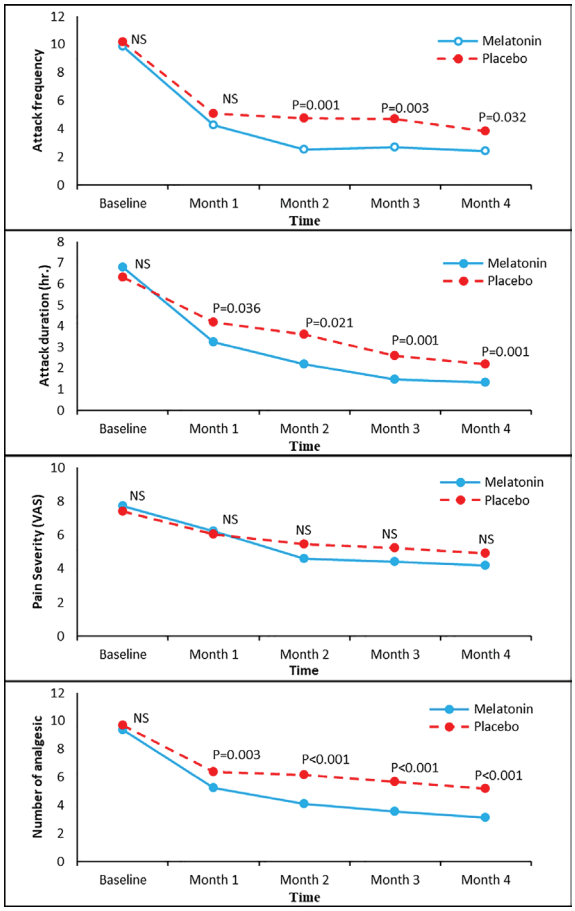

Figure 3: The comparison of different levels of MIDAS in two groups during the study. MIDAS: Migraine Disability Assessment; Class I refers to not significant disability; Class II refers to mild disability; and Class III refers to moderate disability.

the second and fourth months (P=0.345 and P=0.651, respectively). Furthermore, the sleep quality score in the melatonin group decreased significantly in the second and fourth months compared to baseline (P<0.001 in both), but in the placebo group, there was no significant change in the sleep quality score during follow-up (P=0.331 and P=0.308, respectively).

Table 2: MIDAS and PSQI scores in two groups

Parameter	Time	Melatonin (n=30)	Placebo (n=30)	P value*
MIDAS, (mean±SD)	Baseline	16.10±3.59	14.98±3.78	0.281
	Month 2	8.64±2.68	11.71±3.28	<0.001
	Month 4	7.21±2.28	10.98±2.89	<0.001
PSQI, (mean±SD)	Baseline	9.63±4.24	10.28±4.76	0.176
	Month 2	5.42±3.52	8.91±3.42	<0.001
	Month 4	4.61±2.63	8.24±3.75	<0.001

MIDAS: Migraine Disability Assessment; PSQI: Pittsburgh Sleep Quality Index; *P values are for Independent *t* test. P<0.05 is significant.

In this study, no severe side effects leading to withdrawal from the study or requiring immediate treatment were found in any of the participants. Only mild side effects, including daytime sleepiness and dizziness, were observed in two patients (6.7%) in the melatonin group and one patient (3.3%) in the placebo group (P>0.999).

Discussion

The results of this study showed that taking melatonin 3 mg 1 hour before bedtime for 2 months reduced the frequency and duration of migraine attacks and the amount of analgesic intake during the treatment period (in the first and second month) compared to placebo, and these positive effects were continued until the fourth month after treatment.

In the past decade, several randomized controlled trials have investigated the benefits of melatonin in patients with migraine, most of which were episodic.[3, 19] The results of a meta-analysis by Liampas and colleagues showed that melatonin was more effective than placebo for preventing migraine attacks in adults with equivalent safety as the placebo. In terms of reducing the number of attacks, the duration of attacks, and the severity of headache attacks, it showed similar effectiveness to amitriptyline, sodium valproate, or propranolol, and had better effectiveness than pizotifen.[19] A meta-analysis by Tseng and colleagues reported taking oral melatonin 3 mg before bedtime significantly reduced the number and severity of migraine attacks compared to the placebo and had no side effects.[3]

Three clinical trials conducted by Ebrahimi and others,[20] Gonçalves and colleagues,[21] and Ali and others,[22] in line with the present study, showed that melatonin is more effective than placebo in reducing the frequency and duration of migraine attacks and reducing the number of analgesics used in patients with episodic migraine. In the study of Ebrahimi Monfared and others, adding melatonin to the treatment of nortriptyline and propranolol for 8 weeks reduced the number of migraine attacks compared to placebo, while it had the same effectiveness as valproate.[20] Gonçalves and colleagues showed melatonin caused a significant reduction in pain intensity, duration of headache, and reduction of analgesic consumption compared to the placebo, and had the same effectiveness as amitriptyline. In contrast, it had better tolerability than amitriptyline.[21]

On the other hand, a clinical trial by Gelfand and colleagues[23] showed that at the end of 4 weeks of treatment, there was no difference between the melatonin and placebo in terms of the frequency of migraine attacks. However, in this study, only 13 children were examined in each group, which could affect the results. In the study of Alstadhaug and others,[14] the results showed that the reduction of migraine attacks was not significantly different between the two groups of melatonin and placebo after 8-week treatment. However, it should be noted that Alstadhaug and colleagues[14] used 2 mg of slow-release melatonin, while the present study and the other three mentioned trials, used 3 mg of immediate-release melatonin. In general, heterogeneity in patient characteristics and methodology (i.e., patient's age, prescription regimens, and outcome measurement methods) causes some differences in the results.

In another study, it was reported that melatonin (3 mg before bedtime) reduced the frequency and intensity of migraine attacks, and the number of analgesics intake, and improved sleep quality in patients with menstrual-related headaches.[24] Moreover, in a prospective observational study on patients with tension-type headache (TTH), the effectiveness (i.e., reduction in frequency, duration, intensity of attacks, and improvement of sleep quality), and safety of 3 mg melatonin before bedtime for 8 weeks were reported.[25]

In the present study, no serious side effects leading to withdrawal from the study or requiring immediate treatment were observed. Only one case of daytime sleepiness and one case of dizziness were observed, which did not require special treatment. In general, no severe side effects of oral melatonin have been reported

in previous studies.[13, 20] Despite variations in doses of melatonin,[14, 21] usages of adjuvant treatment with nortriptyline and propranolol,[20] or pizotifen[22] or inclusion of children in the study design,[23] all previous studies showed that the safety of melatonin in the preventive treatment of migraine was similar to placebo. Therefore, due to its favorable safety profile, melatonin can be a beneficial adjunctive therapy for patients with primary headache disorders.

In the present study, melatonin significantly improved the MIDAS score compared to placebo. Moreover, in the follow-ups of the second and fourth month after treatment, the frequency of people with little or mild disability (class I and II) was higher in the melatonin group than in the placebo. Reduction of migraine disability score, following melatonin consumption has been reported in other studies.[20, 21, 26] Ebrahimi and colleagues reported that the use of melatonin in patients with episodic migraine caused a significant reduction in the migraine disability score compared to placebo, so after 8 weeks of treatment, the MIDAS score in the melatonin group was significantly reduced, but it did not decrease in the placebo group.[20]

Based on the results of the present study, in the second and fourth months after treatment, melatonin caused a significant improvement in the overall sleep quality score compared to placebo. It has been shown that the relationship between headache and sleep is bidirectional, such that poor sleep habits could worsen the migraine frequency and duration, and migraine attacks could reduce sleep quality as well.[4] Exogenous melatonin supplementation could regulate the activity of the SCN by acting on the hypothalamic-pituitary axis, thereby correcting the abnormal circadian rhythm.[27]

Improvement of sleep quality in patients with migraine following the use of immediate-release formulations of melatonin has been supported in previous studies[13, 25] Although, in a randomized trial, Alstadhaug and colleagues showed that administration of 2 mg slow-release melatonin before bedtime for 8 weeks did not lead to improvement in sleep quality (PSQI score) compared to placebo in migraine patients. However, in a comparison of PSQI in subjects with insomnia (PSQI score>6), melatonin performed better than placebo.[14]

Overall, the present study showed that melatonin is effective in reducing the frequency and duration of migraine attacks, has no serious complications, and could be used as a cost-effective and safe drug for the prevention of episodic migraine. Several hypotheses provide an adequate explanation for the beneficial effects of melatonin on migraine. First, melatonin has an anti-nociceptive nature due to its action on opioid, Gamma-Aminobutyric Acid (GABA), adrenergic, serotonergic, and cholinergic receptors, as well as its role in melatonergic receptors (MT).[27, 28] In addition, sleep disorders and anxiety are considered possible triggers for primary headache disorders. Therefore, it is suggested that improvement of the mentioned disorders by melatonin has a positive indirect effect on migraine.[9, 28] Finally, there is a hypothesis that neurogenic vasodilation and inflammation play a role in migraine.[29, 30] Melatonin decreases the production of vasoactive substances, including CGRP and nitric oxide (NO),[31] while it also has anti-inflammatory properties.[30] Therefore, melatonin could improve migraine attacks through multiple pathophysiological mechanisms.

The present study has some limitations, such as studying only the short-term effects of melatonin, and the relatively small number of study subjects. In this study, only melatonin 3 mg was prescribed, and the effect of different doses was not investigated. Furthermore, the melatonin dose was not titrated based on patient response or side effects. As a result, the actual lowest effective dose was not determined. It also could not clarify whether a more significant therapeutic effect (with minimal side effects) could be achieved with higher doses. Therefore, more beneficial results can be achieved by conducting a multicenter trial with a larger sample size.

Conclusion

The results of this study showed taking oral melatonin 3 mg one hour before bedtime for eight weeks is better than the placebo in decreasing the frequency and duration of migraine attacks, reducing migraine disability, and improving sleep quality. Additionally, no serious side effects were observed. Therefore, melatonin is a safe tolerable, available, and affordable choice for migraine prophylaxis in adults. Melatonin could be used in clinical practice for the preventive treatment of episodic migraines to reduce possible complications caused by acute treatments besides improving effectiveness.

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Authors' Contribution

A.M: Conceptualization, Methodology and design, Investigation/ data collection, Data Analysis, Editing the manuscript, Project Administration, Funding Acquisition; D.Sh: Conceptualization, Investigation/ data collection, Resources, Data Curation, Writing the manuscript draft, Supervision, Project Administration; S.E.M: Methodology and design, Editing the manuscript; L.K: Methodology and design, Data Curation, Editing the manuscript, Supervision; Y.H: Investigation/ data collection, Resources, Data Analysis, Writing the manuscript draft; All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None Declared.

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