Adnyana *et al.*
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REVIEW Open Access

Melatonin as a treatment for migraine sufferers: a systematic review

I Made Oka Adnyana, Clarissa Tertia*, I Putu Eka Widyadharma and Ni Putu Ayu Putri Mahadewi

Abstract

Background: Migraine is a primary headache with a prevalence of 12–20% in the world. Approximately 38% sufferers were indicated for prophylactic therapy, but only a small proportion (3–13%) received prophylactic therapy. The role of melatonin in migraine is to protect the brain against toxins through anti-free radical activity, inhibition of the release of inflammatory factors and neurotransmitters.

Results: This review uses the PRISMA protocol and uses source from Pubmed. A total of 142 articles were found according to the search strategy. 5 articles were collected with a randomized-controlled trial design that matched the inclusion criteria. Of the 5 articles, there were only 2 articles that proved significant where melatonin gave better results compared to placebo in migraine sufferers, especially in the frequency of attacks, duration, and reduction in the use of other analgesics. Based on the dose and duration of melatonin administration, although most use a dose of 3 mg melatonin with a duration of 2–3 months, this still needs to be investigated further because the available data are not sufficient. In addition, the use of melatonin before going to bed at night is said to be better because it is associated with the majority of side effects that occur, namely sleepiness.

Conclusion: Studies on melatonin and migraine with a randomized-controlled trial design are still limited so there is not enough evidence to support the administration of melatonin as a treatment for migraine sufferers, including the safety and side effects, especially for a long period of time.

Keywords: Migraine, Melatonin, Therapy, Systematic review

Background

Migraine is a primary headache that interferes with the patient's activities with a prevalence of 12–20% in the world, 3–5% in children and 18% in adults with a dominance in women (2–3 times more than men) [1–10]. Migraine is the second leading cause of disability according to the 2016 Global Burden of Disease Study [4].

Approximately 38% sufferers were indicated for prophylactic therapy, but only a small proportion (3–13%) received prophylactic therapy. Whereas the provision of prophylactic therapy is very useful, especially in chronic migraine sufferers by obtaining a decrease in the severity and frequency of attacks so as to improve the quality of the sufferer. In addition, prophylactic therapy is expected to reduce the use of migraine abortive therapy [1, 3, 5, 11]. Migraine, especially if it becomes chronic, will cause a decrease in the quality of life of the sufferer. Management for chronic migraine is still very limited, even though preventive/prophylactic therapy can prevent episodic migraine from developing into chronic migraine [5].

Based on guidelines from the American Academy of Neurology and the American Headache Society, the recommended prophylactic therapy is anti-epileptic therapy such as sodium valproate, topiramate, beta blockers such as propranolol, metoprolol and timolol with Level A. Level B includes antidepressants such as amitriptyline, venlafaxine, and other beta blockers such as nadolol [6, 11–15]. There are several integrative therapies

*Correspondence: clarissa_tertia@yahoo.com

Department of Neurology, Faculty of Medicine, Udayana University/Sanglah General Hospital, Denpasar, Bali, Indonesia

used to prevent migraines such as vitamin D, melatonin, coenzyme Q10, riboflavin, and polyunsaturated fatty acids (PUFA). In migraine sufferers, low levels of melatonin and melatonin metabolites in urine are found. In addition, migraine sufferers are often associated with disturbed sleep patterns, so that studies have begun to examine the relationship between melatonin and migraine with activation of melatonin receptors in the hypothalamus [1–3, 16].

Melatonin (*N*-acetyl-5-methoxytryptamine) is a tryptophan derivative that plays role in regulating circadian rhythms and pathophysiology of migraine. Melatonin is synthesized in the pineal gland (the amino acid tryptophan), where the suprachiasmatic nucleus located in the hypothalamus plays a role in regulating the synthesis and secretion of melatonin, especially at night. The light signal will be transmitted through the retinal ganglion cells [2, 7, 16–20].

Melatonin is associated with regulation of circadian rhythms and sleep, in addition, because of its availability in almost all countries, affordable prices and minimal side effects, melatonin is being investigated as a treatment for migraine [7]. In a study in Colorado, melatonin compared with amitriptyline gave an improvement in headache frequency > 50% (54% and 39%), and melatonin gave a much greater effect than placebo (54% and 20%), with a sleep-stimulating effect [11, 19]. In a Brazilian study by Gonçalves et al., melatonin 3 mg was superior to either amitriptyline 25 mg or a placebo. Amitriptyline has side effects such as dry mouth, somnolence, dizzy, weight gain and fatigue. In the study of Alkhaffaf et al., topiramate had more side effects than melatonin such as paresthesias, impaired attention and concentration, and anorexia. Melatonin can reduce body weight in some patients through the mechanism of inhibiting the change of preadipocytes into adipocytes thereby reducing visceral adipose tissue and triglyceride levels, increasing metabolism by converting white adipose tissue into brown adipose tissue. In addition, melatonin can lower blood pressure and glucose levels, so it needs attention and monitoring in people with hypertension and diabetes [1, 3].

The role of melatonin in migraine is to protect the brain against toxins through anti-free radical activity, inhibition of the release of inflammatory factors (anti-inflammatory effect), regulate neurotransmitters and neuronal pathways by inhibiting the formation of nitric oxide, inhibition of dopamine and glutamate release, modulation serotonin and CGRP (calcitonin gene-related peptide). Melatonin also plays a role in membrane stabilization so that it can maintain the structural integrity and function of the brain. In addition, melatonin has analgesic properties by inhibiting prostaglandins and other substances that can produce pain, increasing the release of β-endorphins and stimulating GABAergic (γ-aminobutyric acid). In addition, in animal studies, melatonin plays a role in cortical spreading depression by decreasing trigeminal nociceptive activation [1, 3, 16–24]. In migraine sufferers, sleep disturbances are more pronounced, which were found to be five times higher than healthy person [25].

In addition, there is a relationship between melatonin levels and mood disorders. In a study conducted by Kozak et al. Beck anxiety inventory and Pittsburgh sleep quality index scores were found to be higher in migraine sufferers than healthy controls. Sleep disturbances and anxiety can be factors that trigger migraine [16] Besides, studies have shown that people with insomnia have an increase in the hypothalamic–pituitary–adrenal axis, adrenocorticotropic hormone, cortisol, inflammatory cytokine IL-6 (interleukin-6) and TNF-α (tumor necrosis factor-α), which are associated with pain [26]. Overall, melatonin secretion is associated with migraine, sleep and human psychology [4, 16].

Based on these studies, a theory was formed that melatonin can play a role in the management of headaches, namely the relationship between the hypothalamus and melatonin in improving sleep quality and no serious side effects were found on melatonin administration [27, 28]. The aim of this study was to provide a systematic review of the administration of melatonin as a treatment for migraine sufferers both in terms of attack frequency, intensity, duration, severity of headache attacks and also the side effects produced.

Methods

This study was conducted in January 2022 using a search from Pubmed according to the PRISMA protocol. The search strategy was carried out from 2010 to 2022 using 2 keywords, "migraine" AND "melatonin". This study aims to find research based on randomized clinical trials that examine the use of melatonin as a therapy in migraine sufferers, including as prophylaxis.

The inclusion criteria were an English-language study, a randomized clinical trial, and a complete manuscript. Articles in the form of case reports, descriptive studies, cross-sectional studies, cohort studies and case–control studies were excluded. Then the titles and abstracts were screened manually according to the eligibility criteria (Table 1).

In this study, through our search strategy, we found 142 articles, then 130 were excluded because they were not randomized-controlled trials. Of the 12 articles, further screening was carried out, namely by year, where this study used studies from 2010 to 2022 and excluded 4 articles. A total of 8 articles were attained and screened

Table 1 Eligibility criteria

	Inclusion criteria	Exclusion criteria
Population	People (human) with migraine	Animal model
Intervention	Melatonin	Do not use melatonin
Control	Placebo and/or other drugs	–
Outcomes	Migraine improvement with specific criteria	Do not measure migraine improvement
Study design	Randomized-controlled trial	Case–control, descriptive study, cross-sectional study, cohort study, case–control study
Language	English	Non-English
Statistics	There is an analytical statistics	Only descriptive, no analytical statistics
Full text	Available	Unavailable

further either by title, content and availability of complete manuscripts. A total of 1 article was found to assess rTMS (repetitive transcranial magnetic stimulation) for migraine and did not assess melatonin in that study, 1 article was not available in full text, and 1 article was conducted on people with epilepsy not migraine sufferers, therefore these three articles were excluded so that in the end 5 articles were collected that matched with the inclusion and exclusion criteria of researchers (Fig. 1).

Two authors (IMAO and CT) screened the titles and abstracts of all studies that met the eligibility criteria, then proceeded to read and screen the full manuscripts of these studies. The discrepancy between the two authors will be resolved by the third and fourth author.

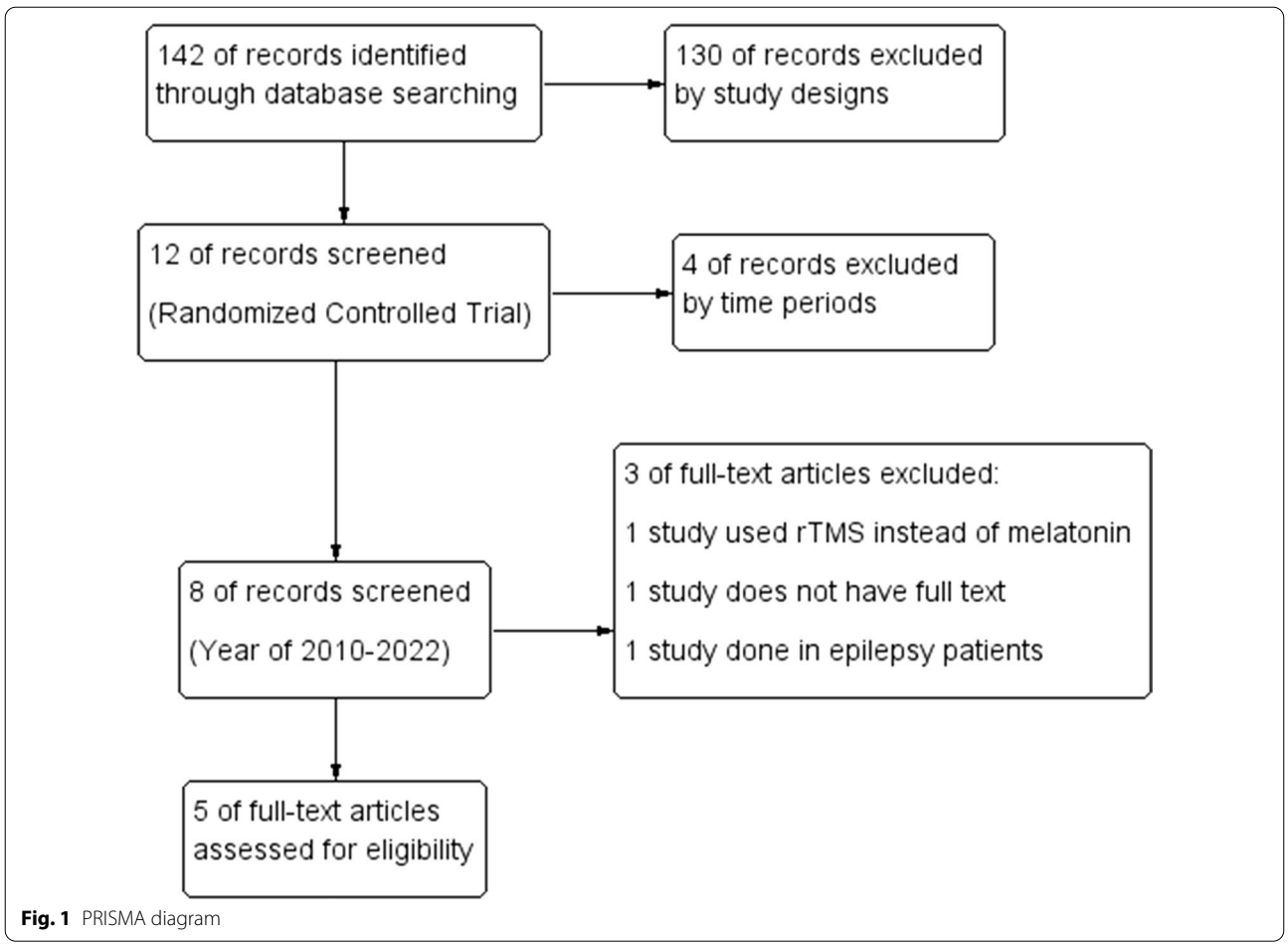

Fig. 1 PRISMA diagram

Quality assessment for randomized-clinical trial study is the JADAD scale. A score of 0–2 is considered low quality, while a score of 3–5 is of good quality. From the 5 studies that we got, in general, the quality of the studies is quite good. Most of the studies were randomized, blinded and there was an explanation for participants dropping out (Table 2).

The studies assessed were conducted in Norway, Iran, Brazil and 2 studies in the USA. The number of participants ranged from 26 to 178 participants with a range of study periods varying from 2 to 4 months. The age of the participants in 2 studies was teenagers while the other 3 studies were over 30 years old (Table 3). 2 studies compared melatonin with placebo in migraine sufferers, 2 in addition to comparing melatonin with placebo, also compared with other drugs, while 1 study compared melatonin doses without the use of other drugs or a placebo. In most studies, a melatonin dose of 3 mg was used (Table 4).

Results

Based on our search strategy, the first study was conducted by Alstadhaug et al. in 2010 with randomization, double-blind and crossover. There were 2 groups, namely the group with 2 mg melatonin and the placebo group. Melatonin extended-release (Circadin) 2 mg given 1 h before bedtime. Then after being evaluated in 8 weeks, each group will be washed out. After 6 weeks of washout period, crossover will be carried out. There are 48 total participants with 24 participants in each group, and 2 participants dropped out. There was a decrease in the frequency of migraine attacks in the two groups, 1.4 and 1.3 in the melatonin and placebo groups, respectively, but not statistically significant ($p=0.75$). In evaluating sleep quality using the Pittsburgh Sleep Quality Index (PSQI), there were significant differences in participants with baseline PSQI > 6, in the melatonin group 6.8 ± 4.0 and 9.4 ± 4.0 in the placebo group ($p<0.05$). However, melatonin did not make a difference in PSQI scores compared to placebo, with the mean PSQI being 4.7 ± 3.2 and 5.6 ± 4.1, respectively ($p=0.09$). In the study there were several side effects such as nightmares, nervousness, night sweats, fatigue, and so on but no further analysis was conducted [31].

In 2016, Gonçalves et al., conducted a randomized, double-blind study using placebo as a control and comparing melatonin 3 mg and amitriptyline 25 mg which are often used to treat migraine. Of the 196 participants, it turned out that there were 18 participants who lost to follow-up, so that the total participants analyzed were 178 participants who were followed for 3 months. 60 participants received melatonin, while 59 participants received a placebo and 59 participants received amitriptyline. The main result of this study was that the melatonin and amitriptyline group had fewer migraine attacks

Table 2 JADAD scale

JADAD scale	Gelfand et al. [22]	Gelfand et al. [29]	Ebrahimi-Monfared et al. [30]	Gonçalves et al. [1]	Alstadhaug et al. [31]
Was the study described as random?	1	1	1	1	1
Was the randomization scheme described and appropriate?	1	1	1	1	1
Was the study described as double-blind?	0	1	1	1	1
Was the method of double blinding appropriate? (were both the patient and the assessor appropriately blinded?)	0	0	1	1	0
Was there a description of dropouts and withdrawals?	1	1	1	1	0
Total score	3/5	3/5	5/5	5/5	3/5

Table 3 Baseline characteristics studies

Authors	Country	Study design	Periods	Mean age (years)	Total participants
Gelfand et al. (2020)	USA	Randomized 1:1 Not blinded Home-based trial	4 months	11.8	84
Gelfand et al. (2017)	USA	Randomized, double-blind, placebo-controlled pilot	3 months	12–17	26
Alstadhaug et al. (2010)	Norway	Randomized, double-blind, placebo-controlled, crossover	2 months	41.9 ± 9.2	48
Ebrahimi-Monfared et al. (2017)	Iran	Randomized, double-blind, placebo-controlled clinical trial	2 months	38.9 ± 9.2	105
Gonçalves et al. (2016)	Brazil	Randomized, double-blind, placebo controlled	3 months	36.9 ± 10.1	178

Table 4 Results

Authors	Drugs and doses	Statistics	Outcomes					
			Measurements	Baseline	Melatonin	Placebo	*p* value	Conclusion
Gelfand et al. (2020)	Melatonin Group 1: Low dose 1-2 mg (n = 42) Group 2: High dose 4-8 mg (n = 42)	Independent T-test, Fisher exact	•Change in pain intensity in cm, mean (SD) •Pain-free rate, n (%) •Pain-relief rate n(%) •Adverse events Napped Nausea	Group 1: 5.1(1.8) Group 2: 5.6(1.8) NA NA NA NA	•Group 1: 2.3 (2.1) Group 2: 2.7 (2.1) •Group 1: 4/15 (27) Group 2: 7/17 (41) •Group 1: 12/15 (80) Group 2: 16/17 (94) •Group 1: 9/19 (47) Group 2: 4/21(67) •Group 1: 1 Group 2: 0	NA NA NA NA NA	0.581 0.415 0.482 0.209 NA	•There is no difference in outcomes between Group 1 and Group 2
Gelfand et al. (2017)	Group 1: melatonin 3 mg (n = 13) Group 2: placebo (n = 13)	Mann–Whitney, χ^2, and Fisher exact	Mean migraine days	NA	3.6 (0.9)	4.9 (1.7)	> 0.05	•There is no difference in mean migraine days between Group 1 and Group 2
Alstadhaug et al. (2010)	Group 1: melatonin 2 mg (n = 46) Group 2: placebo (n = 48)	Paired t-test	Migraine attack frequency Mean PSQI PSQI at baseline > 6 (n = 16) Adverse events	4.2 ± 1.2 6.3 ± 3.8 10.5 ± 2.8 NA	2.8 ± 1.6 4.7 ± 3.2 6.8 ± 4.0 Fatigue and dizziness = 2 Nervousness and nightmares = 1	2.9 ± 1.4 5.6 ± 4.1 9.4 ± 4.0 Eczema = 1 Night sweat 1 Abnormally high dream activity = 1 Dry mouth and irritability = 1	0.75 0.09 < 0.05 NA	•Poorer sleep quality based on PSQI with baseline > 6 was found higher in Group 2 than Group 1 •There is no difference in frequency of migraine attacks and mean PSQI between Group 1 and Group 2
Ebrahimi-monfared et al. (2017)	Group 1: melatonin 3 mg (n = 35) Group 2: valproate 200 mg (n = 35) Group 3: placebo (n = 35)	Post hoc test	•Attack frequency •Attack duration •Attack severity •Number of analgesics •MIDAS score •Adverse events	4.2 ± 1.2 19.7 ± 18.5 7.4 ± 1.4 7.33 ± 3.2 15.8 ± 5.1 NA	2.5 ± 1.3 8.7 ± 12.4 3.5 ± 2.6 2.1 ± 2 8.9 ± 2.2 Fatigue = 2 Drowsiness = 1	3.8 ± 1.1 14.1 ± 8.1 6.0 ± 3.2 4.1 ± 1.1 12.1 ± 4.2 Dry mouth = 1	< 0.05 < 0.05 < 0.05 < 0.05 < 0.05 NA	•There is no difference in outcomes between Group 1 and Group 2 •Group 1 is superior in decrease of frequency, duration, severity, number of analgesics usage, and MIDAS score than Group 3

Table 4 (continued)

Authors	Drugs and doses	Statistics			Outcomes			
			Measurements	Baseline	Melatonin	Placebo	*p* value	Conclusion
Gonçalves et al. (2016)	Group 1: melatonin 3 mg (n = 60) Group 2: amitriptyline 25 mg (n = 25) Group 3: placebo (n = 59)	ANOVA	•Number of headache days •Intensity •Duration •Number of analgesics •Improvement > 50% in headache frequency •Adverse event Sleepiness Pruritus Dizziness Epigastralgia Weight gain Constipation	7.3 ± 2.8 6.9 ± 1.8 17.8 ± 14.5 4.4 ± 1.6 NA NA NA NA NA NA	4.6 ± 2.3 3.6 ± 3.5 10.9 ± 9.5 2.9 ± 1.7 54.4% 11/60 1/60 0/60 2/60 0/60 1/60	6.2 ± 2.5 4.8 ± 3.3 16.2 ± 15.3 3.6 ± 1.2 20.4% 7/59 0/59 1/59 0/59 1/59 4/59	< 0.05 < 0.05 < 0.05 < 0.05 < 0.05 NA NA NA NA NA NA	•There is no difference in outcomes between Group 1 and Group 2 •Group 1 is superior in decrease of number of headache (days),intensity, duration, number of analgesics usage than Group 3

* *NA* not available, *PSQI* Pittsburgh Sleep Quality Index, *MIDAS* Migraine Disability Assessment Score

than the placebo group and a statistically significant difference with a difference of 2.7 days more in the frequency of migraine attacks on the placebo, compared to the melatonin group and 2.2 days more on the frequency of migraine attacks on the placebo, compared with the amitriptyline group. In addition, Gonçalves et al. also analyzed the mean intensity of attacks, the mean duration of attacks and the amount of analgesics used by the participants. The mean attack intensity in the melatonin group was 3.6 ± 3.5 less than the placebo (4.8 ± 3.3) with differences from the baseline data, 3.5 and 1.8, respectively. In the melatonin group, there was a significant difference in the mean duration of attacks, namely 10.9 ± 9.5 compared to placebo 16.2 ± 15.3. In this study there were some side effects, but no serious side effects. Side effects in the melatonin and placebo groups were almost similar ($p > 0.05$) but there were more side effects in the amitriptyline group when compared to the placebo and melatonin groups ($p > 0.03$). The majority of side effects were drowsiness, in addition to epigastralgia and constipation in small amounts, especially in the melatonin group [1].

The next randomized study found in this search was the study conducted in Iran by Ebrahimi-Monfared et al. in 2017 in a double-blind and placebo as a control. In addition to melatonin 3 mg, Ebrahimi-Monfared et al. also analyzed the administration of valproate 200 mg. Each group consisted of 35 participants and was matched by age, sex, and clinical characteristics. Then participants will be evaluated twice, at the end of the first and second months. The mean age of the participants was 38.9 ± 9.2 years of which 51.42% were women. Based on this study, the majority of migraine experienced by participants occurred in the morning with the most characteristic being throbbing. About 65.57% were triggered by stress and pain complaints improved with sleep (70.47%). In the post hoc test analysis, significant results were obtained in terms of attack frequency, duration, severity, and MIDAS (Migraine Disability Assessment Score). In the melatonin group, the frequency of attacks was lower (2.5 ± 1.3) when compared to the placebo group (3.8 ± 1.1) with a difference of 1.7 and 0.4 from the baseline, respectively. In terms of duration and severity of attacks, the placebo group was much higher than the melatonin group (14.1 ± 8.1, 6.0 ± 3.2 and 8.7 ± 12.4, 3.5 ± 2.6). Changes in MIDAS were also found in the melatonin and valproic acid groups with $p = 0.005$ and $p = 0.001$, respectively. This change in MIDAS was not found in the placebo group ($p = 0.44$). In the melatonin group there were 2 participants who experienced side effects, fatigue and confusion, but only 1 participant experienced side effects on the placebo, namely dry mouth. However, there are no analytical data for side effect outcomes in this study [30].

The study conducted by Gelfand et al. was a randomized, double-blind study comparing melatonin and placebo. This study consisted of 31 participants, but 5 participants experienced fewer migraine attacks so that only 26 participants were continued in this study. The first group consisted of 13 people and was given melatonin 3 mg, while the second group consisted of 13 people and was given a placebo. The baseline characteristics in the two groups were almost the same except that headache-related disability was higher in the melatonin group. Headache-related disability was calculated using the Pediatric Migraine Disability Assessment scoring. Of the 26 participants, there were 3 participants who withdrew (2 people from the first group, and 1 person from the second group). The mean migraine attack day by day was 3.6 ± 0.9 in the melatonin group compared with 4.9 ± 1.7 in the placebo group. These results suggest that migraine attacks were fewer in the melatonin group, but not statistically significant (difference 1.3 with 95% KI − 5.1 to 2.6). No serious side effects were found on giving melatonin 3 mg, namely the effect of daytime fatigue in 2 people in the first group [29].

Then there was a more recent randomized study conducted in 2020. However, this study did not compare melatonin with a placebo or other drugs. This study compared high doses of melatonin (4–8 mg) with low doses (1–2 mg). A total of 84 participants were randomized by stratification based on body weight, namely body weight above equal to 40 kg and body weight less than 40 kg. Because the average age of the participants was 11.8 years, and there were children, the melatonin in this study used milk chocolate-based melatonin. In addition to being edible, this formula has a faster onset of action than tablets, so it is hoped that headache relief will occur more quickly. This study was conducted by giving headache diaries to participants so it is a home-based trial. Participants will be observed every 2 weeks with pain improvement if there is a change in the scale ≥ 3 cm. A total of 38 participants were excluded (loss to follow-up = 10; withdrew = 10 in the low-dose melatonin group and loss to follow-up = 12; withdrew = 6 in the high-dose melatonin group). The basic characteristics in both groups were almost the same, both for pain intensity, photophobia, phonophobia, nausea and vomiting. At 2 h of melatonin administration, there was a change in pain intensity of 2.3 ± 2.1 in the low-dose group, and 2.7 ± 2.1 in the high-dose group, with a p value of 0.581. In these two groups there was only a difference of 0.4 cm with a 95% KI value: − 1.17 to 1.92 which was not statistically significant, so there was no significant difference between the administration of low doses of melatonin and high doses. This study also evaluated side effects with the majority of participants sleeping after 2 h of high-dose

melatonin (81%) and 68% in the low-dose group (p value = 0.352) [22].

Of the 5 studies, only 2 studies state that melatonin is better for migraine treatment than placebo. In both studies, a dose of melatonin of 3 mg was used and the results obtained that melatonin was superior to placebo in terms of attack frequency, attack duration, intensity and severity of attacks. In addition, based on a study conducted by Ebrahimi-Monfared et al. there was a significant decrease in MIDAS scores with the use of 3 mg melatonin. In addition, in 2 studies comparing melatonin with other drugs, melatonin did not give significantly better results than valproic acid and amitriptyline.

Of the 5 studies, only 3 studies discussed the side effects of giving melatonin and placebo. Side effects that occur vary from drowsiness, nausea, pruritus, dizziness, weight gain and constipation with the majority of side effects being drowsiness. However, only 1 study (Gelfand et al.) analyzed the incidence of drowsiness, but found no significant results ($p = 0.209$) (Table 4). General view of this systematic review can be seen in Fig. 2.

Discussion

The aim of this study is to provide a systematic review of melatonin as a treatment for migraine sufferers. One of the strengths of this systematic review study is that all five articles analyzed were randomized studies. Of the five studies, there were studies that only compared melatonin doses but did not compare placebo or other therapies. In this study, it appears that the group given high doses of melatonin (4–8 mg) had more changes in pain intensity, pain free, pain relief than the group with low doses of melatonin (1–2 mg). However, based on statistical analysis, the results were not significant with $p = 0.581$, 0.415, and 0.482, respectively. This is probably due to the high drop-out rate from participants, which is around 50% of the initial participants [22].

Based on studies, melatonin in animal models can modulate trigeminal activation after the cortical spreading depression stage in migraine pathogenesis through melatonin receptors 1 and 2. In addition, melatonin receptors are also present on retinoid Z receptors. Melatonin modifies cyclooxygenase 2 and opioid transmission so that it can reduce pain through the modulation stage [22].

Melatonin dose in 3 out of 5 studies were 3 mg, 1 study with melatonin 2 mg, and 1 study with variations of low (1–2 mg) and high (4–8 mg) doses. After statistical analysis, no significant results were found in either the 2 mg melatonin dose study or the low and high-dose variations, but in 2 studies using the 3 mg melatonin dose there were significant results compared to placebo. This is in accordance with several previous studies that melatonin at a dose of 3 mg given before bedtime has the best improvement in the frequency of migraine attacks so that it can be given as prophylaxis in episodic migraine. Melatonin has several biologic effects in the management of migraines, namely as an anti-inflammatory by reducing free radicals, as an anti-nociceptive by modulating descending pathways in the brainstem via MT2

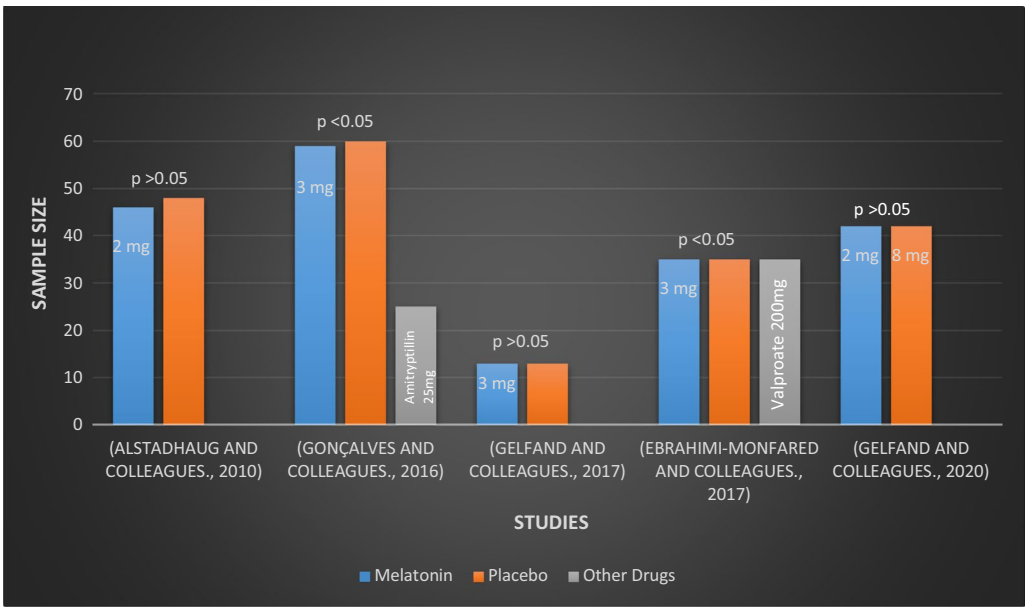

Fig. 2 Brief results of melatonin as a treatment for migraine sufferers

receptors, modulating neurotransmitters including dopamine, serotonin and glutamine and also directly modulating circadian rhythms [19].

Among these studies only 1 study did not provide information about the side effects of melatonin. However, from these 4 studies, no serious side effects were obtained from giving melatonin. The side effects of melatonin from these studies varied from nausea, fatigue, dizziness, pruritus, constipation, and so on with the majority mentioned being sleepy. Melatonin that binds to the MT1 receptor in the suprachiasmatic nucleus causes the opening of the nocturnal sleepiness canal and inhibits the circadian wakefulness mechanism that will stimulate sleep, especially at higher doses of melatonin with an immediate-release formulation, so that the patient will be sleepy. The desensitization of the MT1 receptor coupled G protein can reduce cAMP levels in the brain. So giving melatonin at night before going to bed is the most appropriate because melatonin can stimulate sleep, where sleep disturbances are one of the precipitating factors for migraines. However, in these studies no further analysis was carried out so that the safety of the use of melatonin as migraine therapy still needs to be investigated further [4, 19, 27, 32].

In addition, based on other studies, the side effects of giving melatonin were only mild and minimal [17, 21] In the study by Lyon and Langner, the side effects of giving melatonin were less than that of amitriptyline (18% vs 41%). However, there was no significant difference in side effects between melatonin and placebo [11]. The administration of melatonin doses, either larger or smaller doses, still needs to be investigated further.

Conclusions

In this systematic review, it was found that there are still very few studies on melatonin and migraine with a randomized-controlled trial design, so there is not enough evidence to support the administration of melatonin as a therapy in migraine sufferers. Further studies are still needed including the safety and side effects of giving melatonin as migraine therapy, especially for a long period of time.

Abbreviations

CGRP: Calcitonin gene-related peptide; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α; rTMS: Repetitive transcranial magnetic stimulation; PSQI: Pittsburgh Sleep Quality Index; MIDAS: Migraine Disability Assessment Score.

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Author contributions

IMOA and CT conceived the original idea of this research and proof outline. IMOA wrote the manuscript with support, help and input from CT, IPEW, and NPAPM. IMOA and CT collected and input the data. IMOA with help from CT, IPEW, and NPAPM analyzed the data. IMOA, CT, IPEW, and NPAPM also done the copyediting, proofreading and revised the final manuscript. All authors were involved in drafting the article or revising it critically for important intellectual content. All authors have read and approved the final manuscript to be published.

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Availability of data and materials

The data used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

None (the authors declare that they have no competing interests).

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