

RESEARCH PAPER

## Effectiveness of Melatonin for Prophylaxis in Childhood Migraine: A Comparative Study with Propranolol

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### Abstract

**Background:** Migraine is a primary headache disorder which has debilitating effects on regular day to day activities. Melatonin is a well-recognized drug for maintaining the circadian sleep cycle in children. The aim of this study was to assess the effectiveness of melatonin in pediatric migraine prophylaxis.

**Methodology:** This quasi-experimental study was conducted in Department of Pediatric Neurology, BMU. Children aged 5–16 years with diagnosis of migraine with or without aura were assigned to two groups. Intervention group received tab melatonin 0.3mg/kg at night (maximum 6 mg) and control group received tab propranolol at a dose of 2mg/kg/day (maximum 60 mg). The effectiveness of both drugs was measured by the reduction in headache frequency, severity, duration, and PedMIDAS score. Adverse effects were recorded during follow-up.

**Results:** A total of 46 patients were included in the study. Headache frequency, severity, duration, and Pediatric Migraine Disability Assessment score (PedMIDAS) were significantly reduced by both drugs (all  $P < 0.05$ ). Melatonin was more effective in reducing headache severity and duration, with duration decreasing from  $6.65 \pm 0.93$  h to  $3.52 \pm 1.62$  h ( $P < 0.05$ ). Subjects taking melatonin had higher odds of achieving  $>50\%$  reduction in headache severity and duration compared to propranolol. Somnolence was the most common adverse effect, occurring in 43.5% of the melatonin group and 34.8% of the propranolol group.

**Conclusion:** This study showed that melatonin has a significant effect in the prophylaxis of pediatric migraine, particularly in reducing headache severity and duration.

**Key words:** Migraine prophylaxis, Propranolol, Melatonin.

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## INTRODUCTION:

Migraine is a primary headache disorder characterized by recurring attacks, usually lasting 2 to 72 hours. Attacks are often unilateral, pulsating in quality, moderate or severe in intensity, aggravated by physical activity, and associated with nausea, photophobia, or phonophobia (ICHD-3 beta).<sup>1</sup>

WHO stated in Global burden of Disease Survey 2010 that migraine is the 3rd most prevalent disorder and 7th highest specific cause of disability worldwide.<sup>1,2</sup>

It is the most common neurological problem in children with a prevalence ranging from 1.4% to about 11%.<sup>2</sup> The word migraine is a Greek word meaning ‘hemicranias’, used to describe unilateral headache. Migraine in children often causes disturbances in daily functioning, including sports, exercise, and academic activities. Chronic overuse of analgesics in migraine can lead to chronic daily headache.<sup>3</sup>

Once the diagnosis of migraine is established, a balanced, flexible, and individually tailored treatment plan should be made. Prophylactic therapy is indicated if headaches occur frequently (i.e., one or more attacks per week) and to reduce headache-related disability.<sup>4</sup>

Migraine preventive medications include a diverse group of drugs such as antiepileptics, antidepressants, antihypertensives, antihistamines, and nutraceuticals. In clinical pediatric practice, a variety of these agents are used based on adult data, but the available data on their efficacy and safety in the pediatric population are limited and insufficiently robust. Their use should be limited to those patients whose headaches occur with sufficient frequency or severity as to warrant a daily treatment. Some guidelines recommend daily prophylactic treatment when a patient has three or more severe migraine episodes per month that fail to respond adequately to symptomatic therapy.<sup>5</sup>

A clear sense of functional disability must be established before committing to a course of daily medication. Once preventive treatment is initiated, parents must be encouraged to permit enough time for the beneficial effects to be appreciated. Generally, 8 to 12-week course is necessary before success or failure can be determined.<sup>6</sup>

After a patient has achieved effective migraine control on a therapy, the timing of the medication wean is often guided by clinician experience and patient preference.<sup>7-8</sup>

Since the beginning of modern migraine treatment,  $\beta$ -blockers have been used for prophylaxis; however, several other drugs have also shown efficacy in double-blind, placebo-controlled trials.<sup>9</sup>

This has been considered by treatment guidelines for migraine such as the European guidelines, the American guidelines, which differentiate between drugs of first, second and sometimes even third choice in the prophylaxis of migraine.<sup>10-11</sup>

Propranolol has been a prophylactic agent since 1966 after Rabkin et al discovered its effectiveness in migraine coincidentally.<sup>12</sup>

Since then several clinical trials have confirmed its effectiveness and safety in pediatric population. Propranolol can cause side effects such as bradycardia, hypotension, bronchospasm, and dizziness.<sup>13</sup>

Moreover, it should be used cautiously in children with asthma, exertional dyspnea, or diabetes. Recently, several studies have found melatonin to be effective in migraine prophylaxis in the adult population.<sup>14</sup>

Melatonin is an endogenous indole compound which is secreted from pineal gland and it modulates circadian rhythm of sleep. Therefore, it may reduce migraine frequency by maintaining normal sleep patterns. Its efficacy in migraine headache is due to anti-inflammatory, hypnotic, analgesic, cytokine upregulation and neurovascular regulation.<sup>15</sup>

In a study, Gelfand found both high and low dose of melatonin is effective in acute treatment of migraine.<sup>16</sup>

Fallah et al compared the efficacy of melatonin with amitriptyline in 5-15 years old children and found melatonin is effective and safe in children.<sup>17</sup>

In another study, Miano S et al found melatonin is effective in primary headache in children.<sup>18</sup>

Thus, melatonin can be considered for migraine prophylaxis due to its favorable side-effect profile and its sleep-modulating and analgesic properties. In our country there is no study regarding use of melatonin in migraine in children. Therefore, the

aim of this study was to assess whether melatonin is more effective than propranolol in pediatric migraine prophylaxis.

## **Materials And Method:**

This quasi-experimental study was conducted in the Outpatient Department (OPD) of the Department of Pediatric Neurology, Bangladesh Medical University (BMU), over a one-year period from January 2022 to December 2022.

### **Inclusion criteria:**

Children aged 5–16 years who were clinically diagnosed with migraine with or without aura according to the ICHD-3 $\beta$  criteria and in whom prophylactic therapy was indicated were included.

### **Exclusion criteria:**

Children were excluded from the study if they had other types of primary or secondary headaches. Patients with bronchial asthma, cardiorespiratory compromise, or those already receiving migraine prophylaxis were also excluded. In addition, children with a known history of allergy or adverse reactions to either melatonin or propranolol were not included in the study.

Study participants were divided into two groups by alternating assignment:

Intervention group: Received tablet melatonin 0.3 mg/kg at night (maximum dose: 6 mg).

Control group: Received tablet propranolol 2 mg/kg/day in divided doses (maximum dose: 60 mg).

The study procedure and objectives were explained to the parents (in person or over the phone), and written informed consent and assent were obtained in both English and Bengali.

Each child underwent detailed history-taking and clinical examination, including assessment of headache frequency per month, location, pain quality, aura status, intensity, aggravating/relieving factors, and family history of migraine. The Pediatric Migraine Disability Assessment (PedMIDAS) score was obtained by summing the responses to six questions. Vital signs (pulse, heart rate, blood pressure, temperature) were recorded. A detailed neurological examination was performed by a pediatric neurologist. Weight, height, and occipitofrontal circumference (OFC) were plotted

on growth charts.

Investigations such as X-ray PNS (occipitomenthal view), CT scan of the brain, and ophthalmologic evaluation for refractive errors were performed when secondary causes were suspected based on history or clinical examination.

According to the selection criteria, a total of 50 patients were enrolled in the study. Participants were allocated into two groups: the control group, which received tablet propranolol, and the intervention group, which received tablet melatonin, for a duration of 12 consecutive weeks (3 months). During this period, acute migraine attacks were managed with oral paracetamol at a dose of 15 mg/kg every 8 hours.

Follow-up assessments were conducted at 1 month, 2 months, and at the end of treatment. Patients and his/her caregiver were instructed to maintain a headache diary to calculate frequency, severity and duration of headache after treatment. Headache severity was measured by visual analogue scale (VAS). PedMIDAS score denotes the headache related disability at both home and school.

The primary endpoint of the study was at 3 months after initiation of treatment, aimed at evaluating the efficacy and safety of both drugs. Tolerability and adverse effects were assessed through parental interviews conducted at each follow-up visit. Patients who were lost to follow-up were excluded from the final analysis. Treatment and follow-up were continued as per schedule even after completion of the study period in the BMU outpatient department, as part of routine clinical care.

### **Outcome measurement:**

Treatment outcomes were defined as follows: a good response was considered a  $\geq 50\%$  reduction in outcome variables (headache frequency, severity, duration, and disability), a fair response as a 20–50% reduction, and no response as a  $< 20\%$  reduction. A total of 50 patients were enrolled during the study period; among them, 4 were lost to follow-up. Therefore, data from the remaining 46 patients with migraine who completed the follow-up period were included in the final analysis.

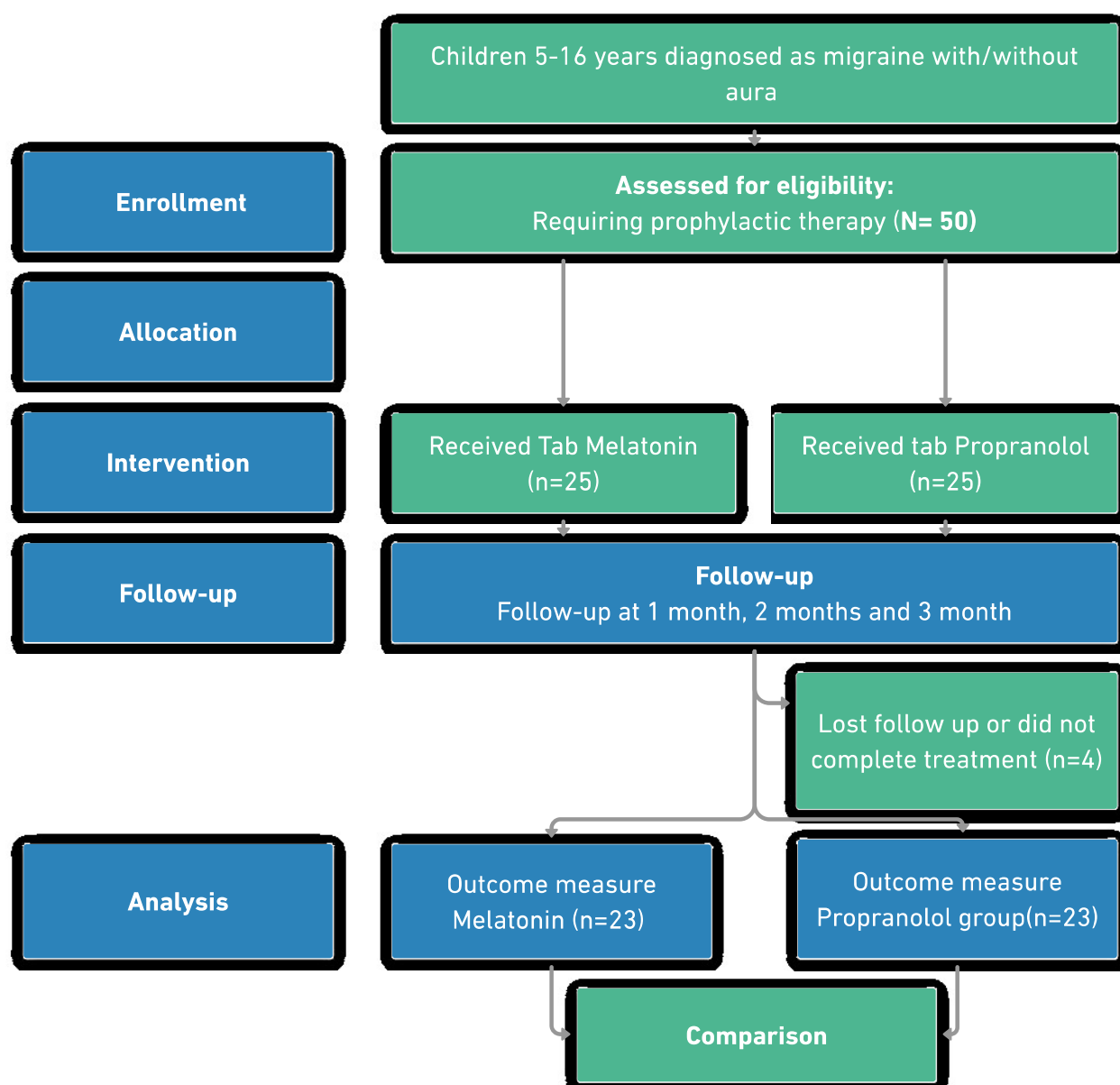


Figure 1: Flow chart of patient enrollment and their outcome comparison

## DATA ANALYSIS:

Data entry and analysis were performed using the Statistical Package for the Social Sciences (SPSS), version 22. Categorical variables such as sex, socioeconomic status, and residence were analyzed using the Chi-square test or Fisher's exact test, as appropriate. Continuous variables, including age,

weight, height, occipitofrontal circumference (OFC), headache frequency, and headache severity, were expressed as mean  $\pm$  standard deviation (SD) and compared using independent sample and paired t-tests. A p-value of less than 0.05 was considered statistically significant, with a 95% confidence interval.

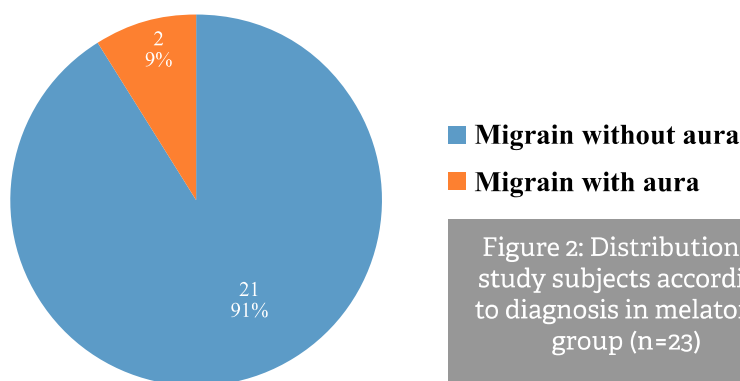
## RESULT:

**Table I: Demographic characteristics of study population (n=46)**

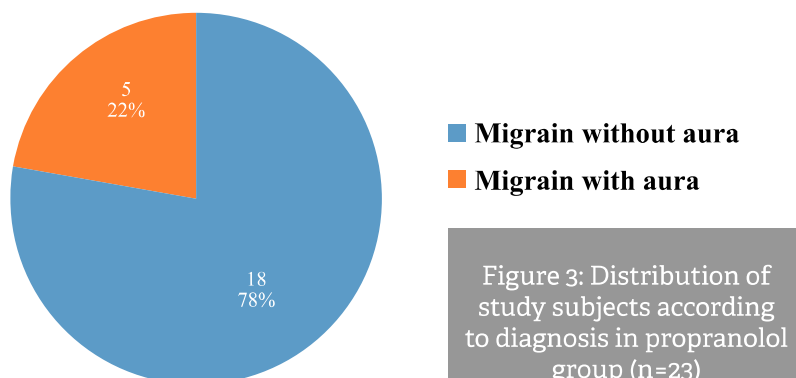
Parameter	Melatonin n=23 (%)	Propranolol n=23 (%)	P value
<b>Age of study patients (year)</b>	10.96±2.70 (7-15)	11.39±2.85 (8-16)	0.816 <sup>a</sup>
<b>Gender</b>			
Male	14 (60.9)	09 (39.1)	0.140 <sup>b</sup>
Female	09 (39.1)	14 (60.9)	
<b>Residence</b>			
Rural	07 (30)	13 (56.5)	0.074 <sup>b</sup>
Urban	16 (70)	10 (43.5)	
<b>Socio economic status</b>			
Lower	01 (4.4)	01 (06)	0.750 <sup>b</sup>
Middle	09 (39.1)	08 (34)	
Upper	13 (56.5)	14 (60)	
<b>Educational qualification</b>			
Pre-primary	01 (4.4)	01 (4.4)	0.955 <sup>b</sup>
Primary	12 (52.2)	11 (47.8)	
Secondary	10 (43.4)	11 (47.8)	
<b>Age of onset of headache(year)</b>	8.00±2.158	8.52±2.192	0.420 <sup>a</sup>
<b>Family history of headache</b>	11 (47.8)	12 (52.1)	0.768 <sup>b</sup>

Independent T test<sup>a</sup> and Chi-square<sup>b</sup> test was done.

## Melatonin Group



## Propranolol Group



**Table II: Distribution of the study patient's characteristics before and after treatment in melatonin group (n=23)**

Parameter	Before treatment (Mean±SD)	After treatment (Mean±SD)	P value
Headache frequency	16.43±2.55	12.74±3.82	0.003 <sup>s</sup>
Headache severity by VAS score	7.61±0.66	3.39±1.85	0.040 <sup>s</sup>
Headache duration in hours	6.65±0.93	3.52±1.62	0.001 <sup>s</sup>
PedMIDAS	26.74±4.11	14.0±4.43	0.007 <sup>s</sup>

s =significant

<sup>a</sup>p value reached from paired t-test

Mean headache frequency per month was significantly reduced by melatonin. Other parameters such as headache severity by VAS score, headache duration in hour and headache related disability by PedMIDAS score were also reduced by melatonin significantly. (*P-value*<0.05)

**Table III: Distribution of the study patients characteristics before and after treatment in propranolol group (n=23)**

Parameter	Before treatment Mean±SD	After treatment Mean±SD	P value
Headache frequency	15.30±2.86	11.65±4.83	0.004 <sup>s</sup>
Headache severity by VAS score	7.22±0.8	4.78±2.35	0.04 <sup>s</sup>
Headache duration in hours	6.26±0.92	4.65±1.87	0.001 <sup>s</sup>
PedMIDAS	25.09±3.91	13.65±5.12	0.001 <sup>s</sup>

s =significant

<sup>a</sup>p value reached from paired t-test

Here, mean headache frequency/month, headache duration, headache severity, and PedMIDAS were significantly reduced in the study patients of propranolol group. (*P-value*<0.05)

**Table IV: Distribution of study population by treatment outcome comparison. (n=46)**

Parameter	Melatonin n(%)	Propranolol n(%)	P value
Headache frequency			
Good ≥50%	7 (30.43%)	10 (43.47%)	0.310 <sup>ns</sup>
Fair 20-50%	14 (60.86%)	12 (52.17%)	
No response	2 (8.69%)	1 (4.34%)	
Headache severity by VAS score			
Good ≥50%	13 (56.6%)	06 (26.08%)	0.04 <sup>s</sup>
Fair 20-50%	10 (43.4%)	12 (52.17%)	
No response	0	5 (21.73 %)	
Headache duration			
Good ≥50%	15 (65.21%)	04 (17.39%)	0.02 <sup>s</sup>
Fair 20-50%	8 (34.78%)	17 (73.91%)	
No response	0	2 (8.69%)	
PedMIDAS score			
Good ≥50%	06(26.08%)	10 (43.47%)	0.805 <sup>ns</sup>
Fair 20-50%	15 (65.21%)	12 (52.17%)	
No response	2 (8.69%)	1 (4.34%)	

ns =not significant

<sup>a</sup>pvalue reached from chi-square test

s = significant

Table IV shows the comparison of efficacy between the two drugs in reducing baseline headache frequency, severity, duration, and headache-related disability as measured by the PedMIDAS score. A higher percentage of patients in the propranolol group experienced more than a 50% reduction in baseline headache frequency, whereas a greater proportion of patients in the melatonin group showed less than a 50% response. However, melatonin was found to be more effective in reducing both the severity and duration of headaches, and these differences were statistically significant.



**Table V: Distribution of the study patients by adverse effects. (n=46)**

Side effect	Melatonin n=23(%)	Propranolol n=23(%)	P value
Somnolence	10(43.5)	8(34.8)	0.545 <sup>ns</sup>
Vertigo	0(0.0)	4(17.4)	0.036 <sup>s</sup>
Vomiting	1(4.3)	0(0.0)	0.312 <sup>ns</sup>
Nausea	0(0.0)	1(4.3)	0.312 <sup>ns</sup>
Weight gain	0(0.0)	3(13.0)	0.073 <sup>ns</sup>
Fatigue	0(0.0)	4(17.4)	0.036 <sup>s</sup>
Respiratory distress	1(4.3)	3(13.0)	0.295 <sup>ns</sup>
Other SE	0(0.0)	1(4.3)	0.312 <sup>ns</sup>

ns= not significant

s= significant

p value reached from Chi-square test

Table V shows more than one third (34.8%) patients reported somnolence in propranolol group and about half of the patients in melatonin group. Among the side effects vertigo and fatigue were only seen in propranolol group. Respiratory distress, weight gain were more prevalent in propranolol group.

## DISCUSSION

In our study, the mean age of participants was between 10 and 11 years in both groups. The prevalence of migraine tends to increase to adult levels during the late teenage years. The relatively late childhood onset observed in this study could be attributed to factors such as menarche in females and academic stress affecting both sexes during adolescence.<sup>19,20</sup> The mean age of onset of headache was  $8.52 \pm 2.19$  years in the propranolol group and  $8.00 \pm 2.16$  years in the melatonin group. These findings are comparable to those of Fallah et al., who reported mean ages of onset of  $8.59 \pm 1.56$  years and  $8.34 \pm 2.45$  years in two respective groups.<sup>17</sup>

In this study, a family history of headache among first-degree relatives was present in 12 (52.1%) participants in the propranolol group and 11 (47.9%) in the melatonin group. Eidlitz-Markus et al. (2015) reported that children with a positive family history of migraine tend to have an earlier age of onset and longer migraine duration compared to those without such a history.<sup>21</sup> This finding supports the notion that a genetic predisposition increases susceptibility to migraine earlier in life.

Most of our study participants belonged to an upper socioeconomic background, likely reflecting greater health awareness and better financial capacity to maintain regular follow-up. Both melatonin and propranolol significantly reduced headache frequency, duration, severity, and headache-related disability. However, when efficacy was evaluated in terms of  $\geq 50\%$  reduction in headache frequency, propranolol was effective in 43% of cases, while melatonin showed a 30% response rate. Although the mean difference between the two drugs was not statistically significant ( $p > 0.05$ ), our findings align with previous studies reporting the beneficial role of melatonin in migraine management.

In a Brazilian study, Gonçalves et al. found that melatonin was more effective than placebo in reducing headache frequency among adults aged 18–65 years. The proportion of patients achieving  $\geq 50\%$  reduction in migraine attacks was significantly higher in the melatonin group ( $p = 0.009$ ) compared to amitriptyline ( $p = 0.19$ ) or placebo.<sup>22</sup> Similarly, Miano et al. reported that 14 out of 21 patients experienced  $\geq 50\%$  reduction in baseline headache frequency with melatonin.<sup>18</sup>



Mehramiri et al. conducted an RCT with 60 episodic migraine patients using 3 mg/day melatonin, assessing frequency, duration, severity, and analgesic use. Both groups improved significantly ( $P < 0.001$ ), but the melatonin group showed greater reductions in attack frequency ( $P = 0.032$ ), duration ( $P = 0.001$ ), analgesic use ( $P < 0.001$ ), MIDAS, and PSQI scores ( $P < 0.001$ ).<sup>23</sup> These results align closely with our findings.

In our study, a  $\geq 50\%$  reduction in headache severity and duration was observed in 56.52% and 65.21% of children, respectively, in the melatonin group. Melatonin demonstrated superior efficacy compared to propranolol in both parameters, and the difference was statistically significant. Headache severity, being a subjective symptom, was assessed using a visual analogue scale (VAS). The exact duration of headache episodes in children is often difficult to quantify and was therefore estimated indirectly based on parental interpretation of the child's activity level. Alstadhaug et al. also reported that melatonin significantly reduced headache severity in their study.<sup>14</sup> Similarly, Fallah et al., in a single-blinded randomized controlled trial comparing amitriptyline and melatonin, found that melatonin reduced headache severity, duration, and headache-related disability, although amitriptyline was superior across all parameters.<sup>17</sup>

In our study, there was a significant improvement in quality of life, as reflected by a decrease in PedMIDAS scores in both the propranolol and melatonin groups. However, the comparison between the two drugs did not show any statistically significant difference ( $P > 0.05$ ). The PedMIDAS is an objective tool that evaluates headache-related disability through questions regarding school attendance and activity levels at home. In many cases, decreased activity or missed school days may be perceived by parents as leisure or rest time rather than disability. Therefore, the overall assessment of headache-related disability can sometimes be challenging. Interestingly, disability scores reported by children are often slightly higher than those reported by their parents.<sup>24</sup>

Regarding adverse effects, somnolence or daytime sleepiness was the most common side effect observed in the melatonin group (43.5%). Vomiting and respiratory distress were reported in 4.3% of

cases. In the propranolol group, the most frequently observed adverse effects included somnolence (34.8%), vertigo (17.4%), fatigue (17.4%), weight gain (13%), and respiratory distress (13%). Gelfand et al., in a randomized controlled trial involving 72 participants, reported that melatonin was generally well tolerated with no serious adverse events.<sup>16</sup> Similar findings were observed in other RCTs conducted by Fallah et al. (2018), Ebrahimi et al. (2017), and Gonçalves et al. (2016).<sup>17, 22, 25</sup>

All patients in both study arms continued their respective medications, as the adverse effects were generally mild and tolerable. Treatment and follow-up were conducted on an outpatient basis. A notable strength of this trial is that the outcome analysis was based on participants who completed the full follow-up period.

## CONCLUSION

Our study demonstrates that melatonin has a significant effect in migraine prophylaxis by reducing headache severity and duration. Furthermore, melatonin appears to be better tolerated than propranolol in the pediatric population due to its lower incidence of adverse effects.

## LIMITATIONS:

The study had a relatively small sample size and a short duration of prophylactic treatment. There was a chance of recall bias, as the diagnosis, severity, and frequency of headache were predominantly based on patient history. In addition, randomization was not performed

## RECOMMENDATIONS:

Melatonin may be considered as a prophylactic agent in pediatric migraine, as it can reduce the severity and duration of headache and has a favorable side-effect profile. We also recommend multicenter, double-blinded studies with larger sample sizes and longer durations, including participants from diverse ethnic groups. Furthermore, a longer observation period is necessary to assess long-term outcomes and to determine the optimal duration of prophylactic treatment.

## Declarations

### Funding

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### Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Authors' contributions

### Ethics approval and consent to participate

This study was approved by the Institutional Research Board (IRB) of BMU (Registration no-3695)

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