Prophylactic use of Immediate Release Melatonin for Decreasing Occurrence, Severity, and Duration of Migraines in the Adult Population

Robert Barnes

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Prophylactic use of Immediate Release Melatonin for Decreasing Occurrence, Severity, and Duration of Migraines in the Adult Population

Abstract

Background: Research has begun to uncover the likely role of melatonin in primary headache disorders such as migraine. The pineal gland produces the hormone melatonin and is largely influenced by environmental stimuli. Migraines often have environmental triggers with research starting to show lower levels of circulating melatonin found in migraineurs. Melatonin is an inexpensive, easily procured, and natural hormone with a minimal side effect profile compared to current pharmacologic migraine treatments. It is thought that migraine treatment with melatonin can decrease migraine occurrence, severity, and duration.

Methods: Exhaustive search of available medical literature was conducted on MEDLINE-PubMed, Clinical Key, CINAHL-EBSCO host using the keywords: melatonin and migraine. Inclusion criteria consisted of studies on the adult population, using immediate release melatonin, and on patients with classic migraines with and without aura. Quality assessment was conducted using GRADE.

Results: The search resulted in two studies. When comparing from baseline to month 3 of treatment with melatonin, a greater than 50% reduction in headache frequency was seen in 53% (32/60) of patients in one study and 78% (25/32) of patients in the other study. Reduction of migraine frequency (in migraine days) was 2.7 and 4.6 fewer days per month, respectively. Reduction in migraine intensity (0-10 scale) was 3.5 and 3.8, respectively. Reduction in migraine duration per episode was 7.2 and 11 hours, respectively. All reductions were observed comparing baseline to month 3 of treatment with melatonin.

Conclusion: Prophylactic use of 3mg of melatonin daily for migraine prevention and symptom reduction was found to significantly reduce frequency, intensity, and duration of attacks when comparing patients baseline and after 3 months of treatment.

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Prophylactic use of Immediate Release Melatonin for Decreasing Occurrence, Severity, and Duration of Migraines in the Adult Population

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A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
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Hillsboro, OR
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Faculty Advisor: Jennifer Van Atta PA-C
PA Student, Pacific University. Robert Barnes, PA-S
Biography

[Redacted for privacy]
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Acknowledgements

[Redacted for privacy]
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Table 1: Quality Assessment of Reviewed Studies
Table 2: Summary of Findings

List of Abbreviations

SCN: Suprachiasmatic Nucleus
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BACKGROUND

Roughly 24 million individuals in the US suffer from migraine headaches. Of those seeking treatment only 3-5% report adequate preventative therapy while roughly half stop seeking care due to dissatisfaction. Further research on migraine causation and novel treatment options are needed for this majority of patients receiving what they view as inadequate care. Though current treatment has been shown to provide symptomatic relief, the side effect profile of such medications often impede treatment adherence. A correlation between the pineal gland and migraines has been hypothesized due to a congruency of environmentally triggered melatonin release from the pineal gland from similar causative/exacerbative stimuli on migraine symptomatology. Melatonin has been shown to be well tolerated even at high doses with a mild to no side effect profile in patients. Evidence for the use of melatonin to treat migraine has been increasing.

Several avenues pointed towards the exploration of melatonin as a factor in primary headaches. Melatonin release is directly influenced by environmental factors. Best known of these factors is light (photo) stimulation on the eyes. As Joel J. Gagnier described in his study, the pineal gland is considered a photoendocrine transducer, translating information from the environment to directly influence the amount of melatonin released. In addition, the suprachiasmatic nucleus (SCN) releases N-Acetyltransferase which synthesizes melatonin from serotonin based on photic-stimulation by the environment. Thus a possible link may exist between light stimulation on the eye and decreased melatonin release from the pineal gland.
leading to worsening migraine symptoms. Additionally, smell, temperature, and noise influence both melatonin release and the worsening of migraines.\textsuperscript{5}

There are numerous studies that have explored serotonin, the SCN, and melatonin in relation to migraines. In one study,\textsuperscript{7} migraine symptoms were found to alleviate in patients given serotonin and serotonin derivatives with symptoms made worse by serotonin synthesis inhibitors.\textsuperscript{7} It is also worth mentioning there is increased concurrence of migraines and depression which likely has something to do with decreased serotonin. Three studies\textsuperscript{6,8-9} looking at menstrual linked migraines found significant evidence for decreased urine melatonin levels in migraneurs as compared to control populations. An even greater decrease in urine melatonin levels was found in those experiencing acute migraine attacks.\textsuperscript{8-9} Observational studies\textsuperscript{10} found that migraneurs have lower melatonin levels on migraine days compared to symptom free days. Those suffering from chronic migraines were found to have lower melatonin levels compared to episodic migraine sufferers.\textsuperscript{10} Two studies\textsuperscript{11-12} evaluated prolonged release melatonin of 2 and 4mg from the medication Circadin. Both studies used headache frequency as their primary outcome when comparing melatonin treatment to non-treatment baseline. The study utilizing 2mg of Circadin found no significant decrease in number of headaches compared to placebo. However, the study using 4mg Circadin did find a significant decrease in headache days per month of the study. It is worth noting that the study with 2mg of medication was double-blind placebo controlled while the study using 4mg was a double-blind cross-over pilot study.

Though evidence supports the role of melatonin in migraines, the mechanism of action is not fully understood and likely multifaceted. Melatonin has been known to increase sleep hygiene, have anxiolytic and analgesic properties, inhibit nitrous oxide production, and has
strong antioxidant characteristics. Cerebral vasodilation has been thought to be a factor in migraine causation. Melatonin inhibition of nitrous oxide may help to prevent cerebral vasodilation. Melatonin has several analgesic mechanisms. Svogler et al goes on to describe melatonin as structurally similar to the NSAID indomethacin. Further, like indomethacin, melatonin has anti-inflammatory properties by inhibiting prostaglandin E that mainly targets the trigeminovascular system. It also inhibits up-regulation of pro-inflammatory cytokines. Evidence also suggests that melatonin potentiates opioid and GABA receptors increasing analgesic response.

METHODS

A systematic search of electronic databases was conducted utilizing MEDLINE-Pubmed, CINAHL-EBSCOhost, and Clinicalkey. The search strategy involved a methodological filter for abstract and full text human trial studies. Subject specific terms were limited to migraines and melatonin. Studies with a close match for migraines and treatment with melatonin were used to further find sources out of the reference section. Exclusion criteria was used to refine the myriad of studies returned pertaining to migraines and prophylactic treatment with melatonin. Criteria was used to select studies pertaining to the adult population between 18 and 65 years, males and females suffering from migraines with and without auras, and use of immediate release melatonin. Exclusion was applied to studies using prolonged release melatonin (Circadin), studies looking only at menstrual migraines, studies that included other primary headaches like tension and cluster, and studies looking specifically at the pediatric population. Quality assessment of the studies was conducted using GRADE. Inconsistency, indirectness, bias, and
imprecision was analyzed. The studies were rated low in GRADE quality as referenced at http://www.gradeworkinggroup.org.

RESULTS

The search yielded 371 articles. Applying eligibility criteria yielded two studies with similar design: *Randomised clinical trial comparing melatonin 3 mg, amitriptyline 25 mg and placebo for migraine prevention*, by Leite Goncalves et al,\textsuperscript{14} and *Melatonin, 3 mg, is effective for migraine prevention*, by Peres et al.\textsuperscript{15} (See Table 1.) Both of the studies\textsuperscript{14-15} used a nearly identical design with similar end points. The study by Goncalves et al\textsuperscript{14} included a placebo and amitriptyline group in addition to the melatonin treatment group. Peres et al\textsuperscript{15} only used a melatonin treatment group. Thus only the melatonin treatment group in each study was analyzed. Both studies\textsuperscript{14-15} occurred over 4 months with a month long baseline period. Migraine frequency, intensity (1-10), and duration were recorded for each month resulting in data points for: baseline, month 1, month 2, and month 3. Of these data points, only baseline, month 1, and month 3 were analyzed in this review. Primary endpoint analyzed for each study was the percentage of patients that experience a greater than 50% reduction in migraine frequency when comparing baseline to month 3 of treatment.

Melatonin treatment data between the two studies was evaluated (see table 2) looking at the progression of three migraine factors over the course of 3 months for both studies (baseline, month 1, and month 3). Ninety-two patients were used in the analysis, 60 patients from Goncalves et al. and 32 from Peres et al. Patients experiencing a greater than 50% reduction between the two studies totaled 57/92 for 62% between the two studies. For the study of Goncalves et al., an average reduction in frequency of migraines (7.3 at baseline, 5.6 at month 1,
4.6 at month 3), intensity on a 0-10 scale (7.1 at baseline, 5.0 at month 1, 3.6 at month 3), and migraine length in hours (18.1 at baseline, 13.5 at month 1, 7.2 at month 3) was seen between baseline, month 1, and month 3 for both studies (see table 2). Similar results were seen in the study by Peres et al. with an average reduction in frequency of migraines (7.6 at baseline, 4.4 at month 1, 3.0 at month 3), intensity on a 0-10 scale (7.4 at baseline, 5.5 at month 1, 3.6 at month 3), and migraine length in hours (19.8 at baseline, 10.2 at month 1, 8.8 at month 3) was seen between baseline, month 1, and month 3 (see table 2).

DISCUSSION

The results of this review support the findings of both individual studies being analyzed. A significant decrease in frequency, severity, and length of migraine was observed by the first month of prophylactic treatment with 3mg of immediate release melatonin. Both studies had a significant primary endpoint finding with 78.1% of Peres et al patients compared to the 54.4% Goncalves et al patients experienced greater than a 50% reduction in migraine frequency by 3 months.

One of the most interesting findings is found in the study by Goncalves et al where 3mg melatonin is seen just as effective in treating migraines as amitriptyline 25mg. In fact number needed to treat was 3 with a relative risk of 2.67 and ARR of 34%. This suggests that melatonin may be as efficacious in treating migraines as a leading migraine medication with many patients receiving therapeutic benefit. This also highlights the benefits of treatment with melatonin compared to other leading migraine medications. Melatonin is very well tolerated with the adult and pediatric population while being extremely difficult to overdose on and inexpensive to obtain. This could likely increase patient satisfaction with treatment of their migraines and
decrease the number of those who have given up on seeking further treatment due to negative treatment side-effects.

There are limitations to this research. The primary author of *Melatonin, 3 mg, is effective for migraine prevention*, Dr. M.F.P. Peres, is also the sixth listed author for the other study, *Randomised clinical trial comparing melatonin 3mg, amitriptaline 25 mg and placebo for migraine prevention*, analyzed in this paper. It is possible that the initial study\(^\text{14}\) was a pilot study leading directly to the second study\(^\text{15}\) by the lead author Goncalves. A bias may exist due to this collaboration. The pilot study by Peres et al\(^\text{15}\) is an underpowered study that also lacks a placebo arm. The Peres et al study\(^\text{15}\) population reported higher baseline values and noticeably lower month 1 and 3 values compared to the Goncalves et al study\(^\text{14}\) population. This may partially be due to the fact that the Peres et al participants knew they were getting the study medication.

Research on melatonin and its role in migraines has been well documented and hypothesized for many years with research devoted to the topic going back more than 30 years. Evidence suggests the strong prophylactic nature of melatonin in preventing and diminishing the severity of primary headaches in a variety of patients but more studies are needed especially studies with a larger patient population that utilizes a randomized controlled double-blind design.

**CONCLUSION**

Prophylactic use of 3mg melatonin daily for migraine prevention and symptom reduction was found to significantly reduce frequency, intensity, and duration of attacks when comparing patients baseline and after 3 months of treatment. Of primary importance is the greater than 50% reduction in frequency of migraine attacks observed by 78.1% of Peres et al patients compared to the 54.4% Goncalves et al patients by the end of 3 months. More research is needed, but
preliminary findings are promising. Melatonin may be as effective as amitriptyline, one of the leading treatment options. In addition, it is safe, cheap, easily obtained, and easy to initiate. Most importantly, it can safely be used in conjunction with other treatment options.
References


Table 1: Quality Assessment of Reviewed Articles

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<tr>
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<td>RCT, Observational study</td>
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<tr>
<td>Migraine Duration</td>
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<td>Serious(^a)</td>
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<td>Not serious</td>
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</table>

\(^a\) Lack of blinding of both data collectors and patients in Peres et al study.\(^{15}\)
\(^b\) Small sample size
\(^c\) There are multiple authors that are part of both studies being used.

Table 2: Summary of Findings

<table>
<thead>
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<td></td>
<td>7.6(^*)</td>
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<td></td>
<td>7.4(^*)</td>
<td>5.5(^*)</td>
<td>3.6(^*)</td>
</tr>
<tr>
<td>Duration (hrs)</td>
<td>18.1</td>
<td>13.5</td>
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<td></td>
<td>19.8(^*)</td>
<td>10.2(^*)</td>
<td>8.8(^*)</td>
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</table>

Goncalves et al.
Peres et al.\(^*\)