Original Article

# Comparison of Efficacy and Tolerability of Melatonin and Amitriptyline in Children Suffering with Migraine



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## ABSTRACT

**Objective:** To compare the efficacy along with tolerability of melatonin and amitriptyline in children suffering with migraine.

**Study Design:** Randomized clinical, parallel group trial study.

**Place and Duration of the Study:** This study was conducted at the Department of Pediatrics, Sahara Medical College, Narowal from July 2018 to December 2018.

**Materials and Methods:** A total of 90 children (45 in each group), with age 5 to 15 years, having migraine were enrolled. Frequency of headache along with its severity and the duration and pedMIDAS were noted on monthly bases, and compared after 3 months of treatment with studied drugs. A good response was labeled if reduction of 50% in headache frequency on a monthly basis was recorded.

**Results:** Out of a total of 90 children, 47 (52.2%) were male and 43 (47.8%) female. Mean age of the study participants was 9.28 years. At the end of the treatment period when both groups were compared, good response, monthly frequency of headache, severity and duration, and headache disability pedMIDAS, all turned out to significant better in amitriptyline group (P value < 0.05). A total of 32 (35.6%) children experienced some kind of side effects. No children experienced any serious adverse event during the study period.

**Conclusion:** Melatonin and amitriptyline have both been found to produce good response in children for prophylaxis of migraine. Both drugs have nominal and manageable side effects. In comparison to melatonin, amitriptyline significantly better good response for migraine prophylaxis.


**Key Words:** Melatonin, amitriptyline, migraine, good response.

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## INTRODUCTION

In children, migraine is known to be a common problem. It is estimated that around 28% of teenagers are affected with migraine.[1] About 30% of children are said to meet criteria regarding drug prophylaxis. Experts are advocating advise prevention therapies for migraine if children are experiencing 3 to 4 episodes of headache monthly with an aim to reduce this frequency frequency to 2 or less attacks in a month. Pediatric migraine Disability Assessment Score (pedMIDA) is the focus while looking at the control of migraine in children, therapies achieving a score of less than 10 are rated good in children.[2]

Wide variety of drugs including antihistamines, antidepressants as well as antiepileptics have been in practice for migraine prophylaxis in children while no generalized guidelines exist.[3] Recently, topiramate got FDA approval for use in children but data is scarce regarding its use.[4] Amitriptyline is a tricyclic antidepressants, known to have minimum side effects and considered very common for managing migraine in children.[5] However, amitriptyline is not recommended for children who have irregular heartbeat and/or prolonged QT syndrome.[6] Melatonin is known to be an indole compound, produced in the pineal gland. Its major function is adjustment of the circadian rhythm related to sleep while during migraine, its levels might be reduced that is suppose to play an important role in the pathophysiology of migraine.[7] Melatonin is said to exhibit anti-inflammatory, hypnotic, analgesic as well as antioxidative properties while it is also hypothesized

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to inhibit the release of dopamine along with neurovascular modulation.[8]

Efficacy of melatonin as 3 mg daily at bedtime has been studied in children from 6 to 16 years of age[8] but not data is available in Pakistan comparing the use of melatonin with amitriptyline regarding migraine prophylaxis that could give us a better insight in to both these drugs for our use in the local population. The aim of current study was to compare the efficacy along with tolerability of metatonin and amitriptyline in children suffering with migraine.

# MATERIALS AND METHODS

This was a randomized clinical trial, conducted at The Department of Pediatrics, Sahara Medical College, Narowal, from July 2018 to December 2018. A total of 90 children (45 in each group), with age 5 to 15 years, having migraines with or without aura, who had fulfilled the criteria for migraine prevention therapy as described by 2nd edition of the International Classification of Headache Disorders criteria[9] as per clinical evaluation, exhibiting> 1 headache attack weekly, stating moderate or severe headache disability pedMIDA> 20, and no history of using migraine prevention therapies, were enrolled in this study.

Informed consent was sought from parents/guardians of all the study participants before starting them drugs, assessed in the study. The study was approved by institute's ethics and research committee while no funding was asked from pharmaceutical companies.

Those children who had secondary headaches or who accompanied any systemic illness (renal or hepatic impairment, heart disease, hematological disorders or any other endocrine disorder) were not enrolled in this study. As per physical, clinical and laboratory evaluation, children with raised intracranial pressure or those who were not able to complete 3 months period of treatment, were also excluded from the study.

Randomization was done through lottery method as slips containing 90 numbers were mixed while 1stforty five slip drawn containing numbers were considered as children to be given oral melatonin (0.3mg/kg, maximum 6mg) whereas remaining were given oral amitriptyline as 1mg/kg/day (maximum 50mg) for 3 months at bedtime.[10]

Follow up visits were planned at an interval of 2 weeks up till a period of 3 months. Parents were enquired regarding frequency of headaches, its severity along with the duration and the disability score.[11] Adverse events regarding both treatment groups were also noted along with physical examination and assessment of vital signs. In the form any serious adverse event, parents or guardians of the children were asked to reach nearest emergency healthcare facility for the appropriate management. Routine laboratory studies were done during follow up visits in children who experienced any adverse effects during the study period. All children were allowed to use acetaminophen or ibuprofen (if needed) for the relief of moderate to severe headache episodes during the study period. Visual analog scale (VAS) was used to assess the intensity of headache. Children were asked to rate most of headache pain on VAS on a 10 point scale as zero indicated no pain whereas a score of 10 on VAS highlighted most severe pain.[12]

Frequency of headache along with its severity and the duration and pedMIDAS were noted on monthly bases, and compared after 3 months of treatment with studied drugs. A good response was labeled when reduction of 50% in headache frequency on a monthly basis was recorded.

A predesigned proforma was made to record all the study information while SPSS version 21 was used for data entry and analysis. Chi square test was used for comparing qualitative variables between the groups while independent sample t test was applied for comparing means between the two study groups. P value < 0.05 was taken as of statistical significance.

# RESULTS

Out of a total of 90 children, 47 (52.2%) were male and 43 (47.8%) female. Mean age of the study participants was 9.28 years with a standard deviation of 2.92.

In terms of baseline characteristics between the both groups, gender, age, recent monthly frequency of headache, severity and duration, types of migraine or family history of migraine had no statistical difference between the two groups (p value > 0.05).

At the end of the treatment period when both groups were compared, monthly frequency of headache, severity and duration, and headache disability pedMIDAS, all turned out to significant better in amitriptyline group.

After three months of treatment, good response (more than 50% reduction in monthly headache frequency) was noted in 30 (66.7%) children using melatonin whereas 39 (84.4%) showed good response in amitriptyline group. Although both groups showed good response but the statistical comparison between two groups was significantly better in amitriptyline in its comparison to melatonin with a significant p value of 0.04.

In terms of side effect, a total of 32 (35.6%) children experienced some kind of side effects. Daily sleepiness was noted as the commonest side effect in both the (n=17, 17.9%), while other frequent side effects were as 6 (6.7%) had constipation, body aches and pain in 4 (4.3%) and weakness in 3 (3.3%). When both groups were compared for side effects, no statistical difference was found amongst the both study groups (p value > 0.05). No children experienced any serious adverse event during the study period.

**Table No.1: Baseline Characteristics of Children Between Both the Study Groups**

| Study Characteristics | | Groups | | P Value |
|---|---|---|---|---|
| | | Melatonin (n=45) | Amitriptyline (n=45) | |
| Gender | Male | 25 | 22 | 0.67 |
| | Female | 20 | 23 | |
| Age in years (Mean+SD) | | 9.78 + 2.3 | 9.48 + 2.7 | 0.55 |
| Onset Age of Migraine (Mean+SD) | | 7.46 + 2.5 | 7.83 + 2.9 | 0.50 |
| Recent Monthly Frequency of Headache (Mean+SD) | | 18.47 + 5.8 | 17.24 + 6.4 | 0.31 |
| Severity of Headache (Mean+SD) | | 7.12 +1.9 | 7.65 + 1.5 | 0.13 |
| Recent Duration of Headache in hours (Mean+SD) | | 2.34 + 1.3 | 2.49 + 1.5 | 0.59 |
| pedMIDAS: Headache Disability | | 38.47 + 11.9 | 41.68 + 13.4 | 0.21 |
| Migraine Type | With Aura | 19 | 15 | 0.51 |
| | Without Aura | 26 | 30 | |
| Family History of Migraine | Yes | 36 | 32 | 0.46 |
| | No | 9 | 13 | |

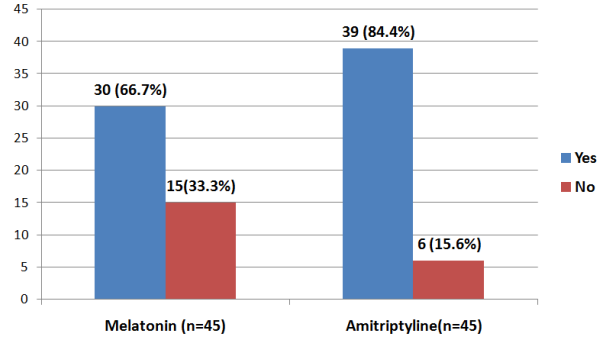


**Figure No.1: Good Response between the Study Groups**
P Value = 0.04

**Table No.2: Comparison of Study Parameters At The End of Treatment Between Both The Study Groups**

| Parameter | Groups | | P Value |
|---|---|---|---|
| | Melatonin (n=45) | Amitriptyline (n=45) | |
| Monthly Frequency of Headache (Mean+SD) | 8.03. + 3.7 | 4.7 + 3.9 | 0.0001 |
| Severity of Headache (Mean+SD) | 3.71 +1.7 | 2.37 + 1.3 | 0.0001 |
| Duration of Headache in hours (Mean+SD) | 1.27 + 0.9 | 0.74 + 0.65 | 0.59 |
| pedMIDAS:Headache Disability | 38.47 + 11.9 | 41.68 + 13.4 | 0.0019 |

# DISCUSSION

In children, headache is commonly reported in pediatric clinics. Migraine is known to be the commonest form of headaches in children while migraine with aura can sometimes accompany neurological symptoms (e.g. hemiparesis, visual disturbances or difficulty in speaking).[13]

Number of medicines are proposed for prophylaxis of migraine in children, and all have their own advantages and disadvantages. In the present study, we noted number of children reporting good response at the end of treatment period in both study groups but the difference between the study groups was turned out to be significant in favor of amitriptyline group in comparison to melatonin. Our results are aligned with another study conducted in Iran[10] where they found that 63% of childrenusing melatonin and 83% in amitriptyline group presented with good response at the end of the treatment period of 3 months with a significant difference (p value = 0.04) favoring amitriptyline group. On the other hand, in adult population in Brazil, less frequency of migraine headache along with improved tolerability in melatonin group was reported in comparison to amitriptyline.[14]

In the present study, we noted 66.7% children in melatonin group with good response (more than 50% reduction in monthly headache frequency) which is better than what was found from Italy[8] where they noted it to be 58%. Another study from Brazil[14] report good response of melatonin in children with migraine as 75% that could be due to different sample size, age group and dose of the drug.

Disturbance in sleep pattern have been noted to be linked with migraine while impaired production of melatonin has been connected with sleep disorders and headache episodes. Melatonin for the control of migraine can ultimately contribute to normal sleep patterns which has been also been documented.[15]

In the present work, amitriptyline group was recorded to have a good response rate of 84.4% which quite similar to what Hershey and colleagues[16] found (84%) while Lewis and coworkers[17] had also noted a good response rate of 83% in their research. A study from Bangladesh[18] report that amitriptyline was associated with very few side effects while common side effects with its use have been noted as daily sleepiness, constipation, malaise which are quite similar to what we found in the current study. Some previous researchers[19,20] also report side effects like dry mouth, dryness of eyes and cardiac arrhythmia but we did not observe anything similar in our study.In current study, no major adverse events related to any of the study drugs were noted while noted adverse events were pretty much similar to what has been found in earlier researches.[14-18]

The current study shows an overall good response rate of prophylactic migraine treatment that encourages all the clinicians considering these options more often when treating children with migraine. Efforts are

needed to be put to create more awareness and management options for migraine in children so that most children bearing this disease gather the benefits. In the current study benefits of amitriptyline were pronounced in for prophylaxis of migraine in children as compared to melatonin which again highlights the benefits of this tricyclic antidepressant that has been in the market sine 1970s.

There were few limitations of this current study like the duration of treatment was comparatively shorter while we could not follow the patients once treatment was completed. We did not have any data about the previous use of any herbal or homemade remedies commonly used for the treatment of migraine. Studies with bigger sample size having longer follow up details will further guide us about the benefits of both studied drugs.[19-20]

# CONCLUSION

Melatonin and amitriptyline have both been found to produce good response in children for prophylaxis of migraine. Both drugs have nominal and manageable side effects. In comparison to melatonin, amitriptyline significantly better good response for migraine prophylaxis.

**Author's Contribution:**

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|---|---|
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| Final Approval of version: | Khurram Shahnawaz |

**Conflict of Interest:** The study has no conflict of interest to declare by any author.

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