OPEN PEER REVIEW

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Archives of Neuroscience
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Peer Review Report for "Melatonin as a Potential Prophylactic Therapy for Menstrual-Related Migraine Headache: A Randomized Clinical Trial"

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Review Timeline:

Submit Date: 26 May 2019
Revised Date: 11 Aug 2019
Accepted Date: 30 Jun 2020

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (0) 31 May 2019

Dear AE,
- Introduction needs to be written better. A very obscure introduction has been written.
- Materials and methods of the paper are inaccurate. Please more and fully explain. It is very important in the clinical trials. Sort your way. For example, write the type of study, the sample size, the entry and exit criteria, the questionnaire, the method of intervention, the ethics, and then the method of data analysis. Did you buy software version 22? If not, refer to version 16.
- In the findings, use the demographic profile table as well.
- Separate the chart, mean, and standard deviation.
Thanks.

REFEREE: Reviewer | **Revision** (0) 6 Jul 2019

Dear AE,
Comments for the authors:
1. One of the main factors in reducing bias when interpreting trial results is including a placebo arm. In the current research there is not any placebo group, but also the essential

factors in designing a randomized double-blind clinical trial have been neglected including the nature of blindness when prescribing naproxen in a different way compared to melatonin due to the differences in the timing, dosage, and frequency of taking drugs (i.e. it has been stated that 3 mg of melatonin was given overnight (30 minutes before bedtime) from 3 days before to 5 days after menstruation. Another treatment group prescribed 250 mg naproxen BID for the same time course).

2. In the introduction, please better clarify the aim and rationale of the trial. The current information provided in the abstract is not convincing enough. For example, it has been stated that “Despite the conflicting result, a systemic review of the current study suggests that melatonin could be a suitable and beneficial alternative for migraine prophylaxis with dose corresponding to 3mg and therapy duration about three months or more”. So it should clarify if the aim of this study is the response to drugs in menstrual-related attacks.

3. “Participants who experienced migraine attacks exacerbations two days before to three days after the onset of menses was considered as menstrual-related migraine.”

4. It seems the current trial cannot be considered as a double-blind, randomized clinical trial while in the methods section it has been declared that “This study is a phase 2 double-blind, randomized clinical trial.”

5. The age and BMI ranges of the included patients should be clarified in the methods.

6. The abbreviations should be clearly defined throughout both the abstract and manuscript (i.e. MIDAS).

7. Consider adding some updated statistics on migraine/headache epidemiology and burden.

8. Please be consistent in using variable names throughout the manuscript including “frequency of attacks” or “attacks days”.

9. It is not clear whether the authors studied menstrual related or menstrual migraine?

10. Number of sedative or abortive drugs? This should be clarified.

11. “the estrous cycle” this word is fused or other mammalians. The word for human is the menstrual cycle.

12. Ovarian cycle has different phases. Which of them is addressed here?

13. how did the authors choose fertile women? I think this is the wrong word here.

14. Some more explanations are necessary to show that the study population is menstrual-related migraineurs, though this is not clear in different parts of the manuscript and in the method part.

15. Naproxen is in the tablet format and melatonin might be a capsule or sublingual tablet. I wonder if a pharmaceutical manufactory produced both of them in the same shape and if this is the case please address that manufactory.

16. The method section is not well structured and very short. The trial should be reported in detail including the duration of intervention. Was it only during the menstrual cycle or it lasts 3-month?

17. It is not clear which reported side effects were experienced following either naproxen or melatonin consumption.

18. It is not clear how the patients were examined/followed up for the study.

19. The English language of the manuscript needs improving.

Thanks.

REFEREE: Associate Editor | **Revision** (0) 17 Jul 2019

Dear EIC,

The manuscript needs major revision.

Thanks.

REFEREE: EIC | **Revision** (0) 17 Jul 2019

Dear Authors,

Please revise based on reviewer comments.

Thanks.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

August 10, 2019

Reference: Manuscript ID: 94375
Title: “Melatonin as a potential prophylactic therapy for menstrual-related migraine headache: a randomized clinical trial"

Dear Dr. Zahid Hussain Khan | Editor-in-Chief | Archives of Neuroscience

Thank you very much for your kind considerations and reviewing our manuscript. We appreciate all precious comments from all the esteemed reviewers and the editorial board. All of these comments were very valuable and improved our manuscript. Having carefully considered the comments and suggestions, we have made all the relevant changes to our manuscript as outlined below in an itemized, point-by-point manner.

We sincerely hope that these changes meet the approval criteria of the esteemed reviewers and the editorial board. Please do not hesitate to contact us if there is any question or comment.

With best regards,

Point-by-point description of the changes that are made in response to the referees' Suggestions:

Reviewer 1:

1. One of the main factors in reducing bias when interpreting a trial results is including a placebo arm. In the current research there is not any placebo group, but also the essential factors in designing a randomized double blind clinical trial have been neglected including the nature of blindness when prescribing naproxen in a different way compared to melatonin due to the differences in the timing, dosage, and frequency of taking drugs (i.e. it has been stated that 3 mg of melatonin was given overnight (30 minutes before bedtime) from 3 days before to 5 days after menstruation. Other treatment group prescribed 250 mg naproxen BID for the same time course).

Response: First of all thank you for your precious comment on methods section of the study. We corrected the design of trial to open label randomized clinical trial, and also add the limitation to the last paragraph of discussion:
“However, number of cases and lack of placebo arm are two limitation for the trial, and should be considered in future investigation for the role of melatonin as a potential treatment goal in women with menstrually related migraine headaches. “

2. In the introduction, please better clarify the aim and rationale of the trial. The current information provided in the abstract is not convincing enough. For example, it has been stated that “Despite the conflicting result, a systemic review of the current study suggest that melatonin could be a suitable and beneficial alternative for migraine prophylaxis with dose corresponding to 3mg and therapy duration about three months or more”. So it should clarify if the aim of this study is the response to drugs in menstrual related attacks.

Response: Regarding to your kind comment we over write the introduction and abstract sections. We add a paragraph, which describing role of hormonal change

in menstrual cycle which exacerbate the migraine headaches and potential role for melatonin in modulating this hormonal pathway.
Abstract:
“It has been shown that migraine attack rates change according to the hormonal changes during the menstrual cycle. A study showed reduced progesterone level especially during the end days of luteal phase and menstruation is associated with an increase episodes of attacks in more than half of migrainous patients. Moreover, another study suggested that the melatonin level changes are positively correlated to progesterone blood level. Previous studies indicated that the level of nocturnal urinary melatonin in patients with menstrual related migraine is lower than healthy subjects.”
Introduction:
The presence of specific receptors for progesterone have been reported in the bovine pineal gland(7). In addition, it has been shown that the circadian secretion of melatonin is modulated via native progesterone levels(8) and increased by progesterone administration(9) in healthy women. Then, it could be deduced that melatonin secretion is influenced by gonadal steroids. Although this relationship has not been consistently confirmed in reported studies. Murialdo et al reported significant decrease of nocturnal urinary melatonin during the ovarian cycle in common- type migrainous patients compared to healthy controls. They reported significantly decreased melatonin urinary excretion in migrainous subjects compared with control groups in all phases of the menstrual cycle. The melatonin levels during the luteal phase in both groups were higher than the follicular and menstrual periods. Although, there is no significant changes in melatonin level when the data were analyzed between different phases of the ovarian cycle (10).

3. “Participants who experienced migraine attacks exacerbations two days before to three days after the onset of menses was considered as menstrual-related migraine.”

We add more explanation about menstrually related migraine to introduction part.
“Although true menstrual migraine occurs in 7-14% of the patients, which is defined as experiencing migraine attacks just 2 days before to 3 days after the onset of menses (4, 5). When menstrually related migraine is considered, more than 90% of the migraine attacks occur between the two days before menses and the first days of menses. Then, this distinction between "menstrual" and " menstrually related" migraine is important, it also should be considered that exacerbation of attack during the hormonal change has not been reported in all patients. Therefore, presence or absence of a definite relationship of pain to menses

may involve a different biochemical mechanisms in different subtype of the disease(6). “

4. It seems the current trial cannot be considered as a double-blind, randomized clinical trial while in the methods section it has been declared that “This study is a phase 2 double-blind, randomized clinical trial.”
Response: regarding your kind comment we corrected the explanation in method section:
‘This study is an open label, randomized clinical trial”
&
“Neither the patients nor the physicians were blinded to the patient’s groups.”

5. The age and BMI ranges of the included patients should be clarified in the methods.

Response: “Women, 18 years and older who were experiencing regular menstrual cycles that ranged from 28-35 days, with a BMI range 20-35 were included in the study.”

6. The abbreviations should be clearly defined throughout both the abstract and manuscript (i.e. MIDAS).
Response: Recommended explanations were provided for abbreviations, if needed.

7. Consider to add some updated statistics on migraine/headache epidemiology and burden.

Response: For further updated statistics of the text, we made corresponding changes
“Prevalence is increased between ages 12-40 years and reduce thereafter in both sexes. The severe headache attacks are reported to cause profound impairment and activities or require bed rest in 43% of the patients. One third of migrainous patient missed at least 1 day of work or school in the previous 3 months due to headaches, and 51% reported reduced productivity at work or school”

8. Please be consistent in using variable names throughout the manuscript including “frequency of attacks” or “attacks days”.

Response: We do understand and appreciate the concern pointed out by the respected reviewer about the variable names as far as possible. Based on different definition in other trials, in introduction or discussion section, we used the exact words based on what mentioned in each specific study results (i.e., attack rates).

9. It is not clear whether the authors studied menstrual related or menstrual migraine?

In fact we include both of them in this trial. The below explanation, based on International Classification of Headache Disorders [ICHD-III beta], added to method section to clarify the study population.
“they were assessed for eligibility with a previous definite history of migraine at least six months before the current outpatient visit and experienced menstrual related migraine attacks (according to International Classification of Headache Disorders [ICHD-III beta]).

Participants who were included in this study completed criteria for pure menstrual migraine or menstrually related migraine based on criteria proposed by ICHD-III beta. They fulfilled the criteria for Migraine without aura and prospectively recorded migraine attacks over at least three consecutive cycles exclusively on day 1 ± 2 (i.e. days -2 to +3) of menstruation in at least two out of three menstrual cycles. In addition, If they experienced migraine attack at no other time of the cycle, defined as “menstrual migraine”. And if additional attacks at other times of the cycle was reported classified as menstrually related migraine. Both subgroup was included in this study and labeled as “menstrual-related” migraine patient.”

10. Number of sedative or abortive drugs? This should be clarified.

Response: With respect to your kind comment we added a new table to revised manuscript “Table 2 shows the frequency and name of the sedative/analgesic drugs used during migraine attacks in patients enrolled in this study.”

11. “the estrous cycle” this word is fused or other mammalians. The word for human is menstrual cycle.

Response: We correct the mistake, and added the appropriate word.
“Migraine attacks distribution change in accordance with the hormonal changes during the menstrual cycle.”

12. Ovarian cycle has different phases. Which of them is addresses here?

Response: In fact, the author of the study reported the significant decrease of significant decrease of nocturnal urinary melatonin during the ovarian cycle in migrainous patients, and they failed to demonstrate significant changes regarding the different phases of the ovarian cycle compared to control. Regarding to your precious comment, some extra explanation were added to paragraph.

"Although this relationship has not been consistently confirmed in reported studies. Murialdo et al reported significant decrease of nocturnal urinary melatonin during the ovarian cycle in common- type migrainous patients compared to healthy controls. They reported significantly decreased melatonin urinary excretion in migrainous subjects compared with control groups in all phases of the menstrual cycle. The melatonin levels during the luteal phase in both groups were higher than the follicular and menstrual periods. Although, there is no significant changes in melatonin level when the data were analyzed between different phases of the ovarian cycle."

13. How did the authors choose fertile women? I think this is a wrong word here.

Response: we changed the word with further explanation for selecting the study population: "Women, 18 years and older who were experiencing regular menstrual cycles that ranged from 28-35 days, with a BMI between 20-35 were included in the study"

14. Some more explanations are necessary to show that the study population is menstrual related migraineurs, though this is not clear in different parts of the manuscript and in the method part.

Response: Regarding to your precious consideration on explanation of study population as described in comment 3 and 9 we add two different paragraph to introduction and method section.

15. Naproxen is in the tablet format and melatonin might be capsule or sub lingual tablet. I wonder if a pharmaceutical manufactory produced both of them in a same shape and if this is the case please address that manufactory.

Response: with respect to your kind comment:

Considering that in this study, neither the patients nor the physicians were blinded to the patient's groups. We correct the mistake, and changed the study type to "open label".

16. The method section is not well structured and very short. The trial should be reported in details including the duration of intervention. Was it only during menstrual cycle or it lasts 3-month?

Response: We do understand and appreciate the concern pointed out by the respected reviewer about the bias. As mentioned in different part of method and result, In fact the eligible women with menstrual cycle range between 28-35 days were followed during the three month after thy enrolled for the study. Otherwise, if study prolonged for exact three menstrual cycle for each participant, the definition of some variable encountered to some bias regarding the increase course of follow up (i.e., migraine attack days).

17. It is not clear which reported side effects were experienced following either naproxen or melatonin consumption.

Response: As mention in result section, the side effect only collected and reported in melatonin group as a new potential treatment suggested in this trial.

"Side effects in the melatonin treatment group: The most reported side effect was dizziness (53.8 %). Other side effects in order of frequency were inattention (38.4%), daily fatigue (38.4%) and GI problems (15.38 %)."

18. It is not clear how the patients were examined / followed up for the study.

Response: Regarding to your precious consideration, we added some details to method: "Data regarding age, sex, body mass index (BMI), marital status were recorded for all cases. Patients were assessed for attacks and sleep problems, experienced through the previous month by a migraine dairy, Visual Analog Scale (VAS), and Berlin sleep Questionnaire by an external blinded research investigator. Data analysis was also assessed by an external investigator who was blinded to the intervention in each group. Reported side effects were assessed only for the melatonin group. Number of sedatives or analgesic drugs that were used for at least one month during migraine attacks was also recorded in each treatment group".

19. The English language of the manuscript needs improving.

Response: We asked an English literature editor to review and edit the text of the manuscript.

Reviewer 2:

Introduction needs to be written better. A very obscure introduction has been written.

Materials and methods of the paper are inaccurate. Please more and fully explain. It is very important in the clinical trials. Sort your way. For example, write the type of study, the sample size, the entry and exit criteria, the questionnaire, the method of intervention, the ethics, and then the method of data analysis. Did you buy software version 22? If not, refer to version 16.

In the findings, use the demographic profile table as well.

Separate the chart, mean, and standard deviation.

Response: Thank you for your kind consideration and comment to the manuscript .As mentioned in response to respected reviewer1, we modified the introduction and also materials and methods sections. With respect to your precious comments, we also provided a new table for describing demographic data as “Table 1”. Moreover, we changed the version for SPSS software to v. 16.0.

The figures were modified to depict both standard deviation and mean in each follow up for the treatment groups.

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Associate Editor | **Revision** (1) 30 Jun 2020

Dear EIC
Based on the authors' answers to the reviewers' comments, the reviewer(s) have recommended publication.
Kind regards.

REFEREE: EIC | **Revision** (1) 30 Jun 2020

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.