PEER REVIEW HISTORY

ARTICLE DETAILS

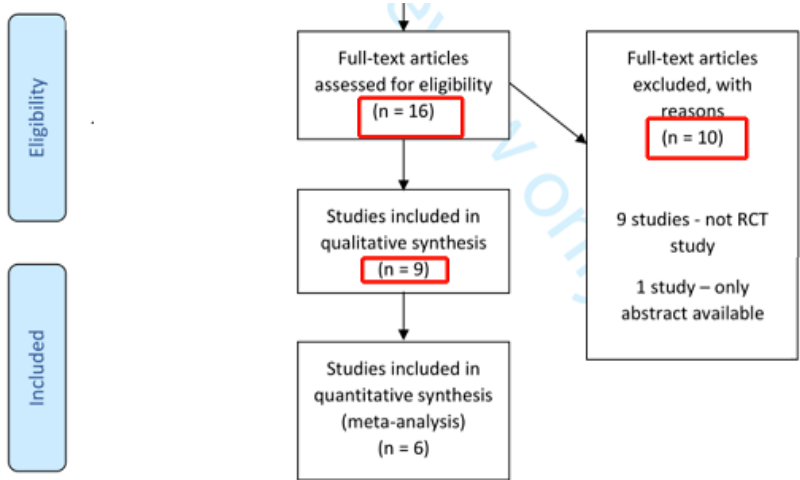|	
TITLE (PROVISIONAL)	COENZYME Q10 SUPPLEMENTATION FOR PROPHYLAXIS IN ADULT PATIENTS WITH MIGRAINE –A META-ANALYSIS
AUTHORS	Badrin, Salziyan; Sazali, Suhairul; Norhayati, Mohd Noor; Idris, Nur Suhaila

VERSION 1 – REVIEW

REVIEWER	Christine A. Ganzer, Ph.D. Hunter College, New York, USA
REVIEW RETURNED	17-Jun-2020

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript. Migraines are a debilitating condition that affects almost 15% of the general population and is ranked as the seventh most disabling of diseases. Supplements can offer some relief and this paper highlights the role of coenzyme Q 10 as a potential treatment. In reading your manuscript I would recommend the correction of grammatical tense throughout. Example, page 11 line 20, Six study should be studies. Page 10 line 37, "because all of it" -should be because all of the studies. Please check paper throughout. I would also inquire about the use of I statistic and how it relates to heterogeneity and effect size. How did you determine the percentages of heterogeneity? Was this done randomly? This is unclear as written.

REVIEWER	Xiaoshan Zhao School of Traditional Chinese Medicine, Southern Medical University, China
REVIEW RETURNED	24-Jul-2020

GENERAL COMMENTS	This is a potentially important area for a meta-analytic study. My concerns are as follows. 1.The literature search was potentially biased. In the Literature search part you only search the Cochrane Central Register of Controlled Trials CENTRAL and MEDLINE, so why not also search PsycINFO and Embase databases. 2.In Data Collection and analysis, the interpretation of heterogeneity is overlap and imprecision. 3. In Abstract and Results part the authors write, "We included six studies with a total of 723 participants", but in Effects of interventions part and Table 1, there are only 371 participants. 4. There are few indicators in Table 1, which do not describe the

number of people lost to follow-up, the reasons for loss, etc.

5. One of the strength of the article is the use of the GRADE approach for ebidence quality evaluation, but i can not find the figure, table or GRADE evidence profile that is a little bit more intuitive in Results part.

6. In the Identification of study part the authors write, "We excluded trials published other than English language", but in Potential biases in the review process part authors write, "searching multiple databases without language restriction". So I just wonder if there is a language restriction.

7. Women are more likely to have migraines, and most of the participants in the included studies are females. There may therefore be scope for carrying out a separate sub-analysis regarding this potential confounding variable.

8.There may be a small error in Figure 1

REVIEWER	Raffaele Ornello Department of Applied Clinical Sciences and Biotechnology, University of L'Aquila, L'Aquila, Italy
REVIEW RETURNED	23-Sep-2020

GENERAL COMMENTS	Authors performed a systematic review and meta-analysis to assess the efficacy of coenzyme Q10 for the prevention of migraine. Authors found that coenzyme Q10 decreases migraine frequency and duration, but not its intensity. Several points of the paper should be clarified. Please find my observations below. 1) Authors state that the total number of patients included in the meta-analysis was 723. However, in Table 1 the total is less than 723. Please explain. 2) The studies included in the meta-analysis assessed the efficacy of coenzyme Q10 in migraineurs compared with "controls". However, it is unclear whether controls were actively treated, treated with placebo, or untreated. I suggest clarifying this issue. 3) The characteristics of migraine are important for patient selection. Were the treated patients naïve with respect to migraine prevention? Had they been treated with other preventatives in the past? Did they

	have previous treatment failure? Which was their mean/median migraine duration? These data should be reported and discussed.
	4) The duration of treatment with coenzyme Q10 and the timepoints for outcome assessments in the included studies should be sspecified. They are also a potential source of heterogeneity.
	5) The doses of coenzyme Q10 used in the included trials were very different. This point should be taken into account. I suggest performing a meta-regression analysis according to coenzyme Q10 dose. That would be useful to determine the optimal coenzyme Q10 dose to prevent migraine.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Thank you for the opportunity to review this manuscript. Migraines are a debilitating condition that affects almost 15% of the general population and is ranked as the seventh most disabling of diseases. Supplements can offer some relief and this paper highlights the role of coenzyme Q 10 as a potential treatment. In reading your manuscript I would recommend the correction of grammatical tense throughout. Example, page 11 line 20, Six study should be studies. Page 10 line 37, "because all of it" -should be because all of the studies. Please check paper throughout. I would also inquire about the use of I statistic and how it relates to heterogeneity and effect size. How did you determine the percentages of heterogeneity? Was this done randomly? This is unclear as written.

Author's response:
Thank you for your comments.
1. We have checked the grammatical errors and amendments have been made.
2. We assessed the presence of heterogeneity, first, by face value and second, by I2 statistic. The assessment was based on the recommendation by Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019), as follows:
"We assessed the presence of heterogeneity in two steps. First, we assessed obvious heterogeneity at face value by comparing populations, settings, interventions and outcomes. Then, we assessed statistical heterogeneity by means of the I2 statistic. We interpreted the heterogeneity as: 0% to 40% represent might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity and 75% to 100% would be considerable heterogeneity (11)."

Reviewer 2
1. The literature search was potentially biased. In the Literature search part you only search the Cochrane Central Register of Controlled Trials CENTRAL and MEDLINE, so why not also search PsycINFO and Embase databases.
Author's response:
Thank you for your comments. We have added the databases, search terms and Boolean operators that we used as follows:
We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Psychological Information Database (PsycINFO) from inception till December 2019. We used the search terms "coenzyme Q10", "ubiquinone" and "migraine" with Boolean operators of AND and OR.

2. In Data Collection and analysis, the interpretation of heterogeneity is overlap and imprecision.
Author's response:

We assessed the presence of heterogeneity, first, by face value and second, by I2 statistic. The assessment was based on the recommendation by Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019), as follows:
"We assessed the presence of heterogeneity in two steps. First, we assessed obvious heterogeneity at face value by comparing populations, settings, interventions and outcomes. Then, we assessed statistical heterogeneity by means of the I2 statistic. We interpreted the heterogeneity as: 0% to 40% represent might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity and 75% to 100% would be considerable heterogeneity (11)."

3. In Abstract and Results part the authors write, "We included six studies with a total of 723 participants", but in Effects of interventions part and Table 1, there are only 371 participants.
Author's response:
There was a writing error. The number of 732 was the total number of participants in the 16 trials, including the excluded trials. There was a total of 371 participants in six included trials as presented in Effects of interventions part and Table 1. Amendment has been made.

4. There are few indicators in Table 1, which do not describe the number of people lost to follow-up, the reasons for loss, etc.
Author's response:
The indicator regarding loss to follow-up was stated under the Risk of bias subheading as follows:
"All six studies had less than 20% lost to follow-up and the reasons such as major protocol violation(23), refused to continue the study(25, 26), failed to return to clinic(21, 22), pregnancy(21, 22, 24) and failed to keep diary(21, 22) and there were balanced between both groups."

5. One of the strength of the article is the use of the GRADE approach for ebidence quality evaluation, but i can not find the figure, table or GRADE evidence profile that is a little bit more intuitive in Results part.
Author's response:
The GRADE table was not included in the manuscript during initial submission. GRADE table has been added.

6. In the Identification of study part the authors write, "We excluded trials published other than English language", but in Potential biases in the review process part authors write, "searching multiple databases without language restriction". So I just wonder if there is a language restriction.
Author's response:

We excluded trials other than English. The statement under the subheading Potential biases in the review process was amended.

7. Women are more likely to have migraines, and most of the participants in the included studies are females. There may therefore be scope for carrying out a separate sub-analysis regarding this potential confounding variable.

Author's response:
That is a good idea. However, the trials only mentioned the overall number of male and female participants. They did not identify the number of males and females for each intervention and control groups.

8. There may be a small error in Figure 1 (see attached).

Author's response:
Amendment has been made.

Reviewer 3
1) Authors state that the total number of patients included in the meta-analysis was 723. However, in Table 1 the total is less than 723. Please explain.

Author's response:

There was a writing error. A total of 371 participants in the six included trials as presented in Table 1. The number of '732 participants' was the total number of participants in the 16 trials, including the excluded trials. Amendment has been made.

2) The studies included in the meta-analysis assessed the efficacy of coenzyme Q10 in migraineurs compared with "controls". However, it is unclear whether controls were actively treated, treated with placebo, or untreated. I suggest clarifying this issue.

Author's response:
The intervention methods used in the included studies summarized in the Table 1. This is explained in the Result section, third paragraph as follows:
All studies used placebo and one study added preventive medication to the placebo (21); however, the preventive medication was used for both the intervention and control groups in this study.

3) The characteristics of migraine are important for patient selection. Were the treated patients naïve with respect to migraine prevention? Had they been treated with other preventatives in the past? Did they have previous treatment failure? Which was their mean/median migraine duration? These data should be reported and discussed.

Author's response:
The characteristics of migraine in patient selection for the trials was added to the Result section, second paragraph as follows:
All six trials excluded any participants who on migraine preventive drugs in the last six months, who have history of using CoQ10 or other antioxidants supplementation for at least 3 months prior to the enrolment(21-26). One trial also excluded participants who failed to respond to the usage of more than two different prophylactic agents in the past or any patients who were resistant to all acute migraine drugs(23).

4) The duration of treatment with coenzyme Q10 and the timepoints for outcome assessments in the included studies should be specified. They are also a potential source of heterogeneity.

Author's response:
Duration of CoQ10 used in the included trial was mentioned in the 'Results' section as follows:
Duration of CoQ10 treatment differs among the trials and was reported at 8 weeks in one study(24), and at 3 months in five other studies(21-23, 25, 26).

5) The doses of coenzyme Q10 used in the included trials were very different. This point should be taken into account. I suggest performing a meta-regression analysis according to coenzyme Q10 dose. That would be useful to determine the optimal coenzyme Q10 dose to prevent migraine.

Author's response:

Thank you for the comment. We were aware of the possible differences. Therefore, we have decided to perform subgroup analyses based on the dosage of coenzyme Q10 of more and less 400 mg for the primary outcomes.

VERSION 2 – REVIEW

REVIEWER	Zhao Xiaoshan Southern Medical University, China
REVIEW RETURNED	12-Nov-2020

GENERAL COMMENTS	This study explored the effects of coenzyme Q10 (CoQ10) for reduction the severity, frequency of migraine attacks and duration of headache in adult patients with migraine. Meta regression analysis should be added to the analysis of publication bias.

REVIEWER	Raffaele Ornello University of L'Aquila, L'Aquila, Italy
REVIEW RETURNED	31-Oct-2020

GENERAL COMMENTS	Authors duly addressed the comments. The paper has now improved in my opinion. I have some further minor concerns: 1) All studies diagnosed migraine according to the ICHD criteria. That can be stated in the text and deleted from the Table, as it is the same for all studies. 2) The measure units for migraine duration and frequency are missing. For example, Authors state that coenzyme Q10 reduces migraine duration by -0.19; however, the meaning of that number is unclear. 3) The results of the present meta-analysis are still inconclusive with respect to the optimal dose of coenzyme Q10. This is a limitation to discuss.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2 comment:
This study explored the effects of coenzyme Q10 (CoQ10) for reduction the severity, frequency of migraine attacks and duration of headache in adult patients with migraine.
Meta regression analysis should be added to the analysis of publication bias.

Authors response:
Thank you for your suggestion. We are confident there is no publication bias. We have checked the protocol, and the consistency between objectives, methodology and results for each included trial therefore, meta regression analysis was not done in this meta-analysis.

Reviewer 3 comments:
Authors duly addressed the comments. The paper has now improved in my opinion. I have some further minor concerns:
1) All studies diagnosed migraine according to the ICHD criteria. That can be stated in the text and deleted from the Table, as it is the same for all studies.
2) The measure units for migraine duration and frequency are missing. For example, Authors state that coenzyme Q10 reduces migraine duration by -0.19; however, the meaning of that number is unclear.
3) The results of the present meta-analysis are still inconclusive with respect to the optimal dose of coenzyme Q10. This is a limitation to discuss.

Authors response:

Thank you for the comments.

1. Amendment has been made.

2. We have added the measure units for migraine duration and frequency in the Results section (effects of interventions) and Discussion section as follow:

"There was significant reduction in the duration by 0.19 hours of headache during attack per month and reduction in the frequency of migraine by 1.52 times per month."

3. We discussed the limitation in the Discussion section under conclusion part.