Author's response to reviews

Title: The impact of oral melatonin on critically ill adult patients with ICU sleep deprivation: study protocol for a randomised controlled trial

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Author's response to reviews: see over
Response Letter

Dear Editors and Reviewers:

We are very glad to know that our manuscript has been reviewed. We appreciate the reviewers’ constructive suggestions, which were helpful in improving the overall quality of our paper. We are now submitting the revised version titled “The impact of oral melatonin on adult critically ill patients with ICU sleep deprivation: study protocol for a randomised controlled trial” (MS: 1384773337124173). Point-by-point responses to the reviewers’ valuable comments are as follows.

Responses to the Editor’s comments:

1. Please ensure the title conforms to journal style for study protocol articles. The title should follow the format ?___________: study protocol for a randomized controlled trial.?

Response: As the editor suggested, we have modified the title format as follows: The impact of oral melatonin on adult critically ill patients with ICU sleep deprivation: study protocol for a randomised controlled trial.

2. Please remove the funding information and competing interests statement from your title page. This information should only be found at the end of your manuscript.

Response: As the editor suggested, we have removed the funding information and competing interests statement from the title page and have added them to the end of the manuscript.

3. Please include all author affiliations and email addresses on your title page.

Response: As the editor suggested, we have included all author affiliations and email addresses on the title page.
4. Please include the date your study was registered with your trial registration number at the end of your Abstract.

**Response:** This study was registered with ClinicalTrials (NCT) (number: ChiCTR-TRC-14004319) on 4 March 2013, and we have added the date of registration at the end of the abstract.

5. Please include a figure title and legend section after your reference list.

**Response:** As the editor suggested, we have included all figure titles after the reference list.

**Responses to the reviewers' comments:**

- **Major Compulsory Revisions**

  1. To allow replication, the main analysis and the main variable should be clearly and fully specified. Based on previous experience you should already know if your main variable can be (approximately) represented by the Normal distribution. Please, consider improving your power by adjusting for baselines in the final analysis (see, for example, chapter 7 in “Statistical Issues in Drug Development”, by Stephen Senn, Ed Wiley).

**Response:** Thank you for your suggestion. First, we have clearly and fully specified the main analysis and the main variable in the section entitled “Statistical analysis”. In addition, based on previous experience, we known that the main variable can be approximately represented by normal distribution. We have read the literature that you recommended in order to improve the power by adjusting for the baseline data in the final analysis. We will use the appropriate (linear, logistic, or Poisson) regression models, which will be generated for the identification of the determinants of outcomes and for the correction of baseline covariates.
2. In sample size, you correctly specify power and a two-sided alpha of 5%. But, instead of specifying the software, you should provide details about the statistical method and the expected difference (“delta”) under the alternative hypothesis (see Consort for examples). [Please, note that you open some further ambiguity because: (1) you employ median instead of mean to justify the expected effect; and (2) you specify 2 metrics, 5 hours and 59% percentage.]

Response: Thank you for this suggestion. In the sample size justification, we used the Power Analysis and Sample Size for Windows software (PASS2000, NCSS, Kaysville, UT, USA) to calculate the sample size. We have added the details about the statistical method and a 20% (0.7 h) difference in the nightly sleep time between the two study arms as the expected difference under the alternative hypothesis in the section entitled “Current sample size justification”.

In using 2 metrics (5 hours and 59% percentage), we created some ambiguity. Now, we have chosen the TST from nightly sleep as the main variable. In addition, based on previous experience, the main variable can be approximately represented by normal distribution. Thus, we have employed the mean TST from nightly sleep instead of the median to justify the expected effect, and have made some modifications to the section entitled “Current sample size justification”.

3. In the first lines of page 13, you specify “they are regarded as the protocol violation and should drop out”. As you later specify that your main analysis will be by ITT, please note that you will need to have an outcome determination for those patients, and so they have to finish the follow up. See, for example, http://www.nap.edu/catalog.php?record_id=12955 or http://www.nejm.org/doi/full/10.1056/NEJMsr1203730

Response: We are very sorry for making this mistake regarding the ITT. Per the reviewer’s suggestion, we have reviewed the literature and have modified the section entitled “Trial interventions”. In those cases, the patient should stop taking the study drug but remain
in the study and the investigator will perform the end-of-treatment assessment immediately and the end-of-study visit 28 days later.

-Minor essential Revisions
Following Spirit 2013, please consider specifying your dissemination policy (item31). Please, consider specifying that your final report will be written in accordance with the Consort statement.

Response: We have specified the dissemination policy in our report. In addition, we have made a statement that our final report will be written in accordance with the Consort statement.

- Discretionary revisions
Please, consider a statement like “a fully specified Statistical Analysis Plan will be provided prior to unmasking”. It should clarify all the details, such as, for example, the outcome imputation method for missing values (such as patients staying less than the full follow-up period).

Response: Thank you for your suggestion. We have made a related statement in the section entitled “Statistical analysis”.

We have tried our best to improve the manuscript, and changes have been made in the manuscript. These changes will not influence the content and framework of the paper. In addition, we did not list the changes here, but instead, marked them in red in the revised paper.

We earnestly appreciate the Editors/Reviewers’ careful work, and hope that the corrections will be met with approval. Thank you for your review, and we look forward to your reply.

Best regards.
Yours sincerely,
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