Reviewer's report

Title: Efficacy of Melatonin for Sleep Disturbance Following Traumatic Brain Injury: A Randomized Controlled Trial

Version: 0 Date: 31 Aug 2017

Reviewer: Jonathan Yabes

Reviewer's report:

Previous studies have shown that melatonin exhibited sleep promoting properties in insomnia and tetraplegia patients. Whether this will also hold in TBI patients is unknown. Hence, this study was conducted to determine the effect of melatonin supplementation on sleep disturbances in patients with TBI. It used a randomized, double-blind, 2x2 cross-over design, with each treatment period (melatonin or placebo) lasting 4 weeks separated by a 48 hour wash-out period to minimize carry-over effects. There were two primary endpoints (sleep quality and sleep onset latency), and several secondary outcomes. The reporting of the trial design, conduct, and results were generally adequate and clear. The CONSORT diagram was detailed enough to help understand study flow, and the mixed-model accounted for between- and within-subject variability. Effect estimates and precision were presented in terms of confidence intervals. However some aspects of the study needs clarification and further consideration:

- The manuscript can be improved by following reporting guidelines in the literature (eg, Li et. al. (2015) "Design, analysis, and reporting of cross-over trials for inclusion in a meta-analysis"; and Mills et. al. (2009) "Design, analysis, and presentation of crossover trials") including:

  --- stating the rationale for cross-over design

  --- justifying the washout period duration, and presenting relevant data to help understand whether or not potential carry-over effects exist

- In the title and abstract, safety appears to be one of the primary outcomes to evaluate, but the study was not designed to evaluate it. Safety was never discussed in the background section of the main article. Serious adverse events and symptoms were mentioned, but no specific safety outcome measure was defined nor tested.

- The operational definition of compliance needs to be stated more precisely. It was not clear what the percentages represent (eg, 100% median treatment compliance).
- In the mixed model, was the term "sequence" included in the model the interaction between treatment and period?

- On page 5 line 1-2, what does "regularly contacted" mean (daily, weekly?). Also, how frequently did deferring treatment happen? Was this similar between the melatonin and placebo period?

- There is a distinction between "effectiveness" and "efficacy", but the paper used these terms interchangeably. The article should pick whichever is more appropriate, and should use that term consistently. Based on the tightly controlled nature of the intervention (eg, within 2-hours of initiating sleep, text reminders, etc), "efficacy" seemed more appropriate.

- The authors should consider proof reading the article as several typographical errors can be found throughout the manuscript:

  --- page 7 line 41: alpha<0.05 should be alpha=0.05

  --- Table 1 footnote on PSQI

  --- Table 2 treatment effect estimate of sleep efficiency should be positive 0.32, and the confidence interval limits were reversed. Also, it is strange that the 95% CI includes 0, but the p-value was significant (p=0.04).

  --- Table 2 treatment effect estimate of MH score should be 2.51

  --- Figure 1 bottom boxes had "ITI" instead of "ITT"

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.
I am able to assess the statistics

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