Reviewer's report

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

Version: 0 Date: 16 Aug 2017

Reviewer: Marcel Smits

Reviewer's report:

This manuscript describes a very important often overlooked issue, i.e. sleep disturbances in TBI.

1. The study concludes that long-acting melatonin helps to improve sleep quality and its consequences for daily functioning. However these conclusions are based on statistically found differences. They are not supported by clinical impression of the patients. Especially only 28 - 47 % correctly guessed their treatment. In placebo-controlled melatonin studies about 95 % of the participants correctly guess their treatment!. Furthermore Clinical Global impression was not assessed. These items should be commented in the discussion.

2. Melatonin is a chronobiotic drug with some hypnotic properties. This study mainly concerns the hypnotic properties, without placing these in the general perspective of melatonin. Timing of melatonin administration is crucial for its effects, i.e. 5-6 hours before (delayed) Dim Light Melatonin Onset(1). This is important because several studies suggest that DLMO is delayed in TBI(2-4). In the present study DLMO was hardly not measured. Maybe the lack of effect of circadin at sleep onset could be caused because circadin was not timed adequately. This is also the explanation for the finding that a meta-analysis with melatonin administered at a time related to DLMO showed that melatonin improved sleep(5), while a meta-analysis with melatonin, administered before bedtime ( just like in the present study) did not improve sleep(6). The discussion should mention that circadian rhythmicity should be studied in TBI preferentially by measuring DLMO, eventually by estimating DLMO.

3. In sleep literature there is a firm discussion going on about the usefulness of long acting melatonin compared to fast release melatonin(7). This should be mentioned in the discussion. Further it should be recommended that comparative studies between long-acting en fast release melatonin are needed.

4. Nowadays the basic treatment for insomnia is Cognitive Behaviour Therapy for insomnia (CBT-I). This also applies for insomnia in TBI. This should be mentioned placing drug treatment in a broad treatment perspective for insomnia in TBI.

5. In this cross over trial the wash out period was only 48-h. It could be possible that melatonin improves sleep (wake rhythm) and that this improvement remains after stopping melatonin.
treatment. Consequently when the participant is first treated with melatonin and later with placebo, the effect of placebo treatment could be identical with that of melatonin. This should be mentioned in the discussion. Therefore parallel studies should be recommended in stead of cross over studies.

6. Time of administration of circadin should be mentioned, more than 2 hours before initiating sleep. If not known this should be commented in the discussion.

7. It could be possible that severity of the TBI correlates with the effect of treatment. This should be studied and commented in the discussion.

8. The time at which the diary is completed each day should be mentioned.

9. How many days the participants wore the actigraph?

10. Both in the results section and in the methods section duration of the study (august 2011 - august 2016 is mentioned. One is sufficient.

Reference List


(2) Smits MG. Whiplash injury may deregulate the biological clock. J Neurol Neurosurg Psychiatry 2005 Aug;76(8):1044.


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

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