Author's response to reviews

Title: Interventions provided in the acute phase for mild traumatic brain injury: A systematic review

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Author's response to reviews: see over
Dear Dr. Moher,

Thank you for your revision of our manuscript entitled “Interventions provided in the acute phase for mild traumatic brain injury: A systematic review.” The reviewers’ comments were appreciated and we have made improvements to the manuscript according to them. We would like to resubmit our manuscript to *Systematic Reviews* with the modifications suggested by the reviewers. The following paragraphs include our answers to their specific comments. We also provide a revised manuscript using the “tracked changes” mode to highlight all the modifications.

Hopefully, these modifications will be satisfactory.

Sincerely yours,

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**Comments of reviewer #1**

This is a well conducted and well written systematic review of literature relevant to the timely issue of rehabilitation for mTBI. A strength of the paper includes the clear reporting of systematic review methods, presented according to PRISMA guidelines. I am not aware of any RCTs on cognitive rehabilitation for mTBI that the authors did not include in their review, and therefore I believe the findings to be a comprehensive summary of existing literature.

**Major compulsory revisions:**

1. More information should be provided about risk of bias in the included studies, and this quality assessment should be better accounted for in the data synthesis.

   For example, the authors describe 5 of the 15 included studies as having “potential” risk of bias, though do not discuss the other 10 studies, 5 of which were rated as having “unclear” risk of bias (“unclear” ROB should generally not be weighted similarly to “low” ROB studies).

   **Response:** Table 1 was modified to include more information about RoBROB. While revising the manuscript, we concluded that one of the studies that was initially classified as “potential” could have been classified as “unclear”. We added the following sentences at the end of the paragraph discussing the RoB: “The risk of bias was unclear for six studies. Most of them had
unclear information about multiple components of the Risk of Bias tool. The more problematic components were sequence allocation and concealment.”

Though Figure 2 is a helpful summary of overall risk of bias across the studies, it would help to know specific areas of risk of bias in individual studies to facilitate comparison across studies (this could be added to Table 1 in addition to the “low, unclear, potential” descriptors).
Response: The information was added to Table 1.

Was study quality considered in the qualitative or quantitative analysis of results? I would recommend consideration of study quality in the data synthesis (both quantitative and qualitative). Having reviewed the quality ratings of the included studies and the results, I don’t imaging there would be a great impact on results; however, weighting the otherwise considering quality in the synthesis warrants mention.
Response: We added information about study quality in our analysis for the different interventions.

2. More information is needed in the introduction and discussion on other systematic reviews of cognitive rehabilitation effectiveness. For example, the recent IOM review (2011, by Cicerone & colleagues) is the most up to date systematic review of the literature through 2008 (see http://www.archives-pmr.org/article/S0003-9993(10)00950-0/abstract). Similarly, ECRI completed a review in 2009 with similar results as the IOM report, and an older AHRQ report by Carney and colleagues was not mentioned (see http://www.ncbi.nlm.nih.gov/pubmed/10381980). A more comprehensive summary of past reviews and comparison to the current findings should be presented. The authors provide a good summary of findings from the 2004 WHO report on mTBI, and should be aware that the same WHO group is in the process of completing an update to that report, to be published soon (per communication from a lead author, Linda Carroll).
Response: Cicerone’s systematic review evaluated rehabilitation in the context of stroke or neurological deficit secondary to TBI. This is not the study population we wanted to study. The study by Carney et al. includes only patients with moderate to severe TBI or patients with mild TBI who consulted a rehabilitation clinic for persistent symptoms. Once again, this is not our study population.
These studies are now mentioned in the discussion.

Minor essential revisions: Instead of referring to “victims of mTBI” change to individuals with mTBI or other more neutral language (e.g., in the abstract).
Response: This was modified throughout the manuscript.

In spite of the points that I recommend be revised, overall, I saw this paper as a concise, well-written, well-conducted systematic review of literature related to mTBI, and therefore I would recommend that the paper be resubmitted following revision.

Comments of reviewer #2
Thank you for the opportunity to review this interesting manuscript. This is a well designed systematic review and meta-analysis of published randomized controlled trials testing interventions for mild TBI delivered in the acute care
setting. The results are similar to other past reviews pertinent to treatment for mild TBI; however, this paper provides a unique contribution given its focus on the acute care setting.

I have no criticisms that require major compulsory revisions.

Minor essential revisions include the following:

1. My primary criticism of the paper is that the Discussion section does not do enough to push the field forward. The current focus on comparing the results of this review with detailed results of prior reviews is not all that interesting and does not do much to extend readers' knowledge. What I would rather see is a very brief comparison with past work, and then more depth into the authors' interpretation of these findings and suggestions for next-steps in the field. For example, how do the findings inform the delivery of care to patients with mTBI in the acute care setting? And, if they do not, what research should be done to inform healthcare delivery? The authors begin to do this in their final paragraph of the Conclusion section, where they introduce the concept of a composite score index, improved timing of outcomes measurements, and solicitation of 'patient-centered' outcomes. I would like to see these concepts introduced earlier in the Discussion section and expanded upon, so that the reader can follow along and understand what the authors are suggesting, and form their own conclusions.  
Response: According to the comments, we expanded the discussion section regarding the impact of the results of our study. We added a new paragraph on the impact of our study.

2. Another thought regarding the Discussion section: the authors focus on the discrepancies in outcome measures and how this impedes the ability to compare or meta-analyze results of RCTs. The NIH NINDS 'Common Data Elements' effort, which addresses this, should be incorporated into this discussion. More info can be found here: http://www.commondataelements.ninds.nih.gov/#page=Default and in this paper: http://www.ncbi.nlm.nih.gov/pubmed/21044708  
Response: Information about the NINDS was added in the discussion.

3. Also regarding the Discussion section, there is a lot of focus on the lack of RCTs to test new pharmacologic interventions for mTBI. Some more in-depth discussion of this would be nice. Do the authors think this is because RCTs simply haven't been conducted? Is there reporting bias? Are there any promising interventions out there that just haven't made it to the RCT stage? Or is there perhaps a lack of early-phase proof-of-concept research for pharmacologic interventions, and therefore little on which to build future RCTs? Where do the authors think the break-down is occurring in the mTBI research life cycle?  
Response: This was added in the same paragraph as our revisions for comment #1.

4. In the abstract, background, and throughout the paper, the authors use language that implies that those who experience mTBI are 'suffering' from mTBI. However, we know that the vast majority of patients who experience an mTBI will fully recover. The authors cite this in their Background, but I would recommend that they also be careful with their wording throughout the paper so as to reflect this expected recovery.  
Response: This was modified throughout the manuscript.
5. The authors should spell out and describe what "DDAVP" is, reported in the Interventions section.
Response: DDAVP is now spelled out.

6. There is theoretical reason to stratify or exclude RCTs involving children from those involving adults. They are combined in the authors' meta-analysis. If the RCTs involving children had been excluded, would the meta-analysis results have been any different? Suggest addressing this to some extent and considering reporting the children's studies separately.
Response: We comment on this in the results section.

7. Finally, the paper is well-written, but there are places where the English should be carefully edited to ensure the authors are conveying the appropriate concept and to rid the paper of small typos.
Response: The manuscript was revised and edited accordingly.