Author’s response to reviews

Title: A Systematic Review and Meta-Analysis of the Use of Oral Zinc in the Treatment of Hepatic Encephalopathy

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Author’s response to reviews: see over
Dear Editors,

We have read the interesting comments from the reviewers. All of the suggestion were important to improve the quality of our manuscript. Here he describe all the modifications according the suggestions.

**Reviewer 1. Marzia Lazzerini**

Abstract – methods “Only prospective randomized clinical trials”: remove “prospective” (RCT cannot be retrospective)

*According the suggestion we change the abstract.*

Abstract - results: reorganize this section. First describe what outcomes are reported (“A limitation of this analysis is that there was heterogeneity in the outcomes reported in the included trials”); Then put the sentence “a significant improvement in performance on the number connection test, etc…”. Remove the following sentence “which precluded evidence-based analysis of significant outcomes of hepatic encephalopathy.”

*The abstract was modified, and the last sentence was replaced by “Other clinical significant (mortality, liver related morbidity, quality of life) outcomes were not reported”. This shows the real limitation of the meta-analysis, the lack of hard outcomes to assess benefits from the intervention.*

Abstract - “with a significant improvement in performance on the number connection test (SMD –0.54; 95% CI –0.90 to –0.18) but not with reduction in encephalopathy recurrence (RR 0.64; 95% CI 0.26 to 1.59). -Add in brackets the number of studies and number of patients in each comparison

*This information was modified to include the information requested, and now appear in this way “Oral zinc supplementation was associated with a significant improvement in performance on the number connection test (SMD –0.54; 95% CI –0.90 to –0.18) reported in four trials (n=268), but not with reduction in encephalopathy recurrence (RR 0.64; 95% CI 0.26 to 1.59) reported in two trials (n=169)”*

Methods - Search methods for identification of studies: add the search strategy

*The search strategy was included as additional table.*
Synthesis of results - Start by saying that meta-analysis on primary outcomes was not possible, due to the few existing studies and the heterogeneity in reporting outcomes.

The sentence at the beginning of synthesis of results section is “The synthesis of primary outcomes was not possible due to lack of information and heterogeneity to report data in the trials.”

Risk of bias within studies: All trials included were at risk of bias. Add if the risk was medium or low risk.

The risk of bias was unclear in all trials due to lack of information, and was not possible to assess if the trials were on high or low risk of bias.

The risk of bias was assessed as the Cochrane Handbook suggests and most of the articles did not report the elements to assess the risk of bias. We change the sentence to be clear in this issue “The risk of bias was unclear in all trials due to lack of information, and was not possible to assess if the trials were on high or low risk of bias.”

Results, line 203 “The quantitative analyses was performed only for secondary outcomes” substitute in “the meta-analysis”

This phrase was changed.

Table 1 – In the raw describing outcomes I suggest to list what outcomes are considered in the study (so that to provide an immediate view of what types of outcomes are reported by literature). Results of the studies are reported in the text (or you could add another raw).

We include only the primary outcome reported in the original trial. The outcomes remain in the text.
Reviewer 2. Toru Ishikawa

This is an interesting review of Meta-Analysis of the Use of Oral Zinc in the Treatment of Hepatic Encephalopathy. However, meta-analysis as also, somewhat less paper, poor on a comparison of the contents of each paper. Unfortunately, it is not acceptable.

We appreciate the comments from the reviewer and the information described is the available nowadays. This systematic review and meta-analysis highlight the need of more RCT in this topic.
Reviewer 3. Eamonn Quigley

Please comment on the dose equivalency/comparability of the different products used.

This is an interesting question because there is limited data about the equivalence of different sources of Zinc supplementation [Biol Trace Elem Res. 2006 Sep;112(3):247-62] [Yakugaku Zasshi. 2005 Oct;125(10):829-32]. But apparently experimental data suggest no significant differences in cirrhosis [Res Commun Mol Pathol Pharmacol. 1999 Feb;103(2):167-76]. Considering this, was added a new sentence as limitation of our manuscript “Additionally there is few data regarding the clinical importance of the different zinc formulation used in the trial”.

On page 10, lines 231-239, please clarify the biology of zinc in relation to brain function. The data presented here seems contradictory with zinc being both deleterious and beneficial. I think I can understand what you are getting at but it will be far from clear to most readers.

Effectively the message is not clear, the paragraph was modified to show the cause-effect relationship between insult and zinc deficiency. Now appears as “Cytokines or lipopolysaccharides could induce the formation of nitrogen oxide species and triggers the release of zinc from the metallothioneins, the principal protein store for zinc. A fluctuation in intracellular zinc level modulates signal transduction, transcription factor activity, and gene expression, ultimately causing hepatic encephalopathy symptoms. Zinc deficiency is associated with disturbances in learning, memory, and emotional stability and is accompanied by hyperammonemia. Zinc supplementation reduces ammonia level in experimental animals and humans as consequence of a stimulation of hepatic urea synthesis and glutamine synthesis in skeletal muscle”

3. Table 1. What are the asterisks referring to?

The table was incomplete, without foot legends, we refer to mean ± standard deviation (the table was completed with the foot legends)

4. Table 1. Are these baseline zinc levels? These should be commented on in the text.

The baseline zinc levels were included.