Reviewer’s report

Title: Efficacy of Inhaled Budesonide on Prevention of Acute Mountain Sickness during Emergent Ascent: A Meta-analysis of Randomized Controlled Trials

Version: 0 Date: 16 Nov 2019

Reviewer: Marc Berger

Reviewer's report:

This is a re-submission of a previously submitted manuscript. Some of the previous comments have been addressed and the manuscript has improved. Also the writing has improved. However, still major concerns remain as outlined below:

General Comments
- Throughout the manuscript the authors state that they compared individuals receiving inhaled budesonide to those receiving no intervention. This is misleading because in all the analysed studies subjects received placebo, and this is an intervention. The wording should be adapted accordingly.
- The authors found that inhaled budesonide did not reduce the incidence of AMS. They also found that budesonide was not effective in maintaining pulmonary function and oxygen saturation. I agree with these findings. However, to this reviewer it remains unclear how in this situation budesonide should have improved AMS symptomatology. This is unexpected and a clear explanation about a possible underlying mechanism should be provided. Otherwise the interested reader is lost when there is no mechanistic explanation how budesonide should improve AMS symptomatology without improving oxygen saturation (and without improving AMS incidence).
- An important aspect is the analysis of the budesonide effect on AMS incidence with the different cut-off values that were applied in the different studies to set the diagnosis of AMS. As the authors state, Berger et al. defined AMS as a Lake Louise score ≥5 with an AMS score ≥0.7, while in the other studies a Lake Louise score ≥3 was used. How can the results of these studies be mixed if the definition of the endpoint varies? This should be addressed.
- How did the authors deal with the significant data heterogeneity that was observed as reported on page 12, line 39. This should be addressed.
- It is stated that criteria for severe AMS were unavailable in the study from Berger et al. Was this study excluded from the analysis regarding the effect of budesonide on severe AMS? According to Figure 5 the data were included. This appears confusing to this Reviewer.
- Introduction page 6, line 6: The authors state that currently no gold standard exists for preventing AMS during emergency ascent. However, here the use of acetazolamide should be mentioned.
- In the methods, page 8, it should be explained what it means that duplicate patient cohorts were excluded. What are duplicate study cohorts?
Specific Comments
- Abstract, page 3, line 12: "Genetically" is misleading and should be deleted. There is no clear link between genetic polymorphisms and AMS susceptibility.
- Abstract, page 3, line 18: "acute mountain sickness" should be abbreviated as AMS once it is explained (as it is in line 10).
- Methods, page 8: Definition of AMS. The cut-off values of the AMS-scoring tools that were applied should be provided here.
- It remains unclear what the "Z-value" in the figures is. This should be explained.
- In Figure 7 it remains unclear which direction of the midline indicates what effect.

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

No

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.

No

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 recommend additional statistical review

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Needs some language corrections before being published

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