Author’s response to reviews

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

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Author’s response to reviews:

Dear editor,

We would like thank our reviewers in providing in depth review of our article and helping make it make better.

We would like to inform that we had used varying criteria for definition of AMS in our initial meta-analysis (All studies except the one by Berger et al used LLS ≥ 3 with headache as AMS criteria. Berger et al. used AMS diagnostic criteria as LLS ≥ 5 with an AMS-C score ≥0.7). However, on thorough exploration, we found that Berger et al. had also performed analysis using LLS ≥ 3 with headache as AMS criteria. For uniformity, as suggested by reviewer 2, we used result of later criteria to perform meta-analysis of mild AMS in this revision.

Berger et al. did not classify severe AMS in their study. However, all other studies used LLS ≥ 5 as criteria for severe AMS. Therefore, LLS ≥ 5 with an AMS-C score ≥0.7 criteria set by Berger et al. was included for analysis of severe AMS.

Further, Berger et al. included two different doses of BUD i.e. 200 μg and 800 μg. However, for uniformity and analysis we only included data of 200 μg group.
Point – to – point response to reviewer’s comments:

1. “altitude” or “altitudes” should be carefully checked throughout this manuscript. 
   Response: This has been addressed.

2. Line 49 in page 5, “HAI” should be defined.
   Response: This has been addressed.

3. Line 5 in page 8, the diagnostic criteria of AMS should be clarified, because new score system of AMS was published in 2018.
   Response: All the studies included in our metaanalysis were conducted before 2018, when new LLS score was introduced. Hence, it was not possible to modify data based on new criteria and is perhaps one of the major limitations of our study and has been mentioned in the text.

4. Typically the Lake Louise Score is abbreviated as LLS; the word “system” is not usually included.
   Response: This has been addressed.

5. Include a sentence in the background section that explains the potential role of BUD in treatment of AMS, such as mechanisms of BUD action.
   Response: Included: It has been hypothesized that signals arising from hypoxic lungs causes inflammation and oxidative damage and increase capillary permeability in lungs and brain, which is thought to be responsible for development of AMS. Budesonide probably suppresses this signal from hypoxic lungs to brain and prevent oxidative damage. Inhaled budesonide has been shown to blunt the response of aldosterone to renin elevation by suppression of Angiotensin Converting Enzyme, by preserving the integrity of pulmonary endothelial membrane.

6. Format of secondary titles should be uniform. Some was italic while others not.
   Response: The uniform format has been maintained throughout.

7. Line 12 in page 12, “however” should be “However”, and format error also should be checked throughout this manuscript.
   Response: this has been corrected.

8. Maybe comment on the different populations and the effects that the inclusion of varied populations in one genetic study could have.
   Response: Sorry, we could not understand this comment.

9. In figure 3, 5, and 7, I2 and analysis model should be clarified.
   Response: This has been mentioned in the text.

10. The figure legends are not detailed enough for the reader to understand the graphs. Please explain in better detail.
    Response: Thank you. We explained it in this revision.
Marc Moritz Berger (Reviewer 2): 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.
  Response: We have modified the text 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).
  Response:

- 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 $\geq 5$ with an AMS score $\geq 0.7$, while in the other studies a Lake Louise score $\geq 3$ was used. How can the results of these studies be mixed if the definition of the endpoint varies? This should be addressed.
  Response: we have maintained uniform criteria throughout as mentioned in the introduction section of this response.

- How did the authors deal with the significant data heterogeneity that was observed as reported on page 12, line 39. This should be addressed.
  Response: Some degree of heterogeneity is expected in any metaanalysis due to differences in study designs, differences in variables of study population, rate of ascent and altitude at which study was conducted. We were able to reduce the heterogeneity by maintaining uniform criteria for definition and endpoints and have reduced the heterogeneity but it still exists.

- 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.
  Response: This has been addressed.

- 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.
  Response: According to wilderness medical society guidelines, both acetazolamide and dexamethasone are effective for prophylaxis of AMS. However, the use of acetazolamide for
emergent ascent has not found to be beneficial. In such cases, dexamethasone may be used as a priority drug but has many systemic side effects. (wilderness medical society guidelines) This has been already mentioned in the text. (page 6)

- In the methods, page 8, it should be explained what it means that duplicate patient cohorts were excluded. What are duplicate study cohorts?
Response: The word “duplicate” may have been misleading. By duplicate cohorts, we meant individuals who were acclimatized prior to enrollment in study and hence excluded as this would lead to false positive results (fewer cases of AMS in this cohort would have lead us to conclude budesonide is effective in emergent prophylaxis). This line has been removed as it is self-understood.

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).
Response: Both these issues has been addressed in the text.

- Methods, page 8: Definition of AMS. The cut-off values of the AMS-scoring tools that were applied should be provided here.
Response: this has been mentioned in the text.

- It remains unclear what the "Z-value" in the figures is. This should be explained.
Response: Will be explained in text.

- In Figure 7 it remains unclear which direction of the midline indicates what effect.
Response: We have tried our best to explain figures in this revised manuscript.