Author's response to reviews

Title: High Dose Erythropoietin Increases Brain Tissue Oxygen Tension in Severe Vasospasm after Subarachnoid Hemorrhage

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Author's response to reviews: see over
Re: Re-re-submission of the manuscript: “High Dose Erythropoietin Increases Brain Tissue Oxygen Tension in Severe Vasospasm after Subarachnoid Hemorrhage“

by Dr. Helbok et al. as “Research Article”

Sir,

please find enclosed the re-revised manuscript “High Dose Erythropoietin Increases Brain Tissue Oxygen Tension in Severe Vasospasm after Subarachnoid Hemorrhage.“

This study has been carried out in compliance with the Helsinki Declaration as stated in the Methods section.

**Point-by-point description of the changes:**

Thank you for these valuable comments, which are addressed point by point:

- **Descriptions of patients characteristics:**
We made appropriate changes as recommended by the reviewer: **Page 6 Line 4-5:** “84% were female” was changed to “six of seven were female”.

- Thank you for this valuable comment. As the reviewer correctly mentioned, a difference in \( P_{btO_2} \) was evident at trial start with a mean brain tissue oxygen tension of 29 mmHg, IQR: 22-32mmHg. All patients showed an increase in \( P_{btO_2} \) at some time during the 24 hours following EPO treatment. This information is now given in the results section: **Page 6 Line 23:** “All patients had an increase in \( P_{btO_2} \) at a certain point during the follow up time of 24 hours.” GEE analysis of absolute values resulted in the same significance level of the EPO effect. However, we believe, that the change in \( P_{btO_2} \) is more interesting when studying pathophysiologic processes underlying this treatment.

There are limitations due to the effect size as stated in the Limitations section in the manuscript. Increasing the number of variables lowers the power of the model. The variable “EPO treatment (EPO dose given per patient: i.e. day1, day2, day3)” did not change the model or effect on \( P_{btO_2} \), and showed that the effect of EPO an day 3 may be higher than on day 1 (P<0.05), however, I would be very cautious due to the limited number of patients in giving this result in the manuscript. We added the following information in the results section **Page 6 Line 22:** “Accounting for the EPO dose given per patient did not affect the observed result.”

- **Effect of EPO on \( P_{btO_2} \) in all patients:**
  Yes, \( P_{btO_2} \) increased in every patient at some point during the observation period following EPO treatment. This is now added as previously mentioned: **Page 6 Line 23:** “All patients had an increase in \( P_{btO_2} \) at a certain point during the follow up time of 24 hours.”

- We agree with the author that the number of authors is inconsistent with the number of patients/interventions described in the article. We would like to leave this decision to the discretion of the editor and would like to add the following comments: Multimodal neuromonitoring of complex SAH patients includes multiple disciplines and the clinical care by many neurointensivists. RH, RB, BP, ES and MS are neurointensivists at the Department of Neurology in Innsbruck and took care of all patients described in the study. ES was a research fellow responsible for data acquisition and primary analysis. AC is our interventional neuroradiologist and CT and FS our neurosurgeons responsible for coiling/clipping of the bleeding aneurysm and application for neuromonitoring devices. AZ
did all the TCDs on the patients enrolled in the study. PL is our statistician and MB our study nurse involved in all ongoing clinical trials since 6 months.

- Typo: this is corrected.

All persons who have made substantial contributions to the work reported in this manuscript (eg, data collection, writing or editing assistance) fulfill the authorship/coauthorship criteria and are named in the manuscript. No other persons have made substantial contributions to this manuscript. All authors have read and approved submission of the manuscript.

All authors have read and approved the submitted manuscript, the manuscript has not been submitted elsewhere nor published elsewhere in whole or in part, except as an abstract (NNC 2011 15:S1-S283).”

There is neither a relationship nor a support which might be perceived as constituting a conflict of interest of any of the authors. The authors have nothing to disclose.

Ethical clearance for advanced neuromonitoring was obtained by the institutional review board.

We would like to thank you for judging this revised manuscript.

With many thanks and best regards

Raimund Helbok, MD