Author’s response to reviews

Title: Does burst-suppression achieve seizure control in refractory status epilepticus?

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Dear Professor Aidan Neligan
Ref: Reply to Reviewer’s Comments

Thank you for considering our paper for publication. We have now made a number of changes as the reviewers have suggested. These are detailed below according to the numbered comments.

Reply to Athanasios Covanis’s Comments

1. Your paper will improve by including in your discussion the following publication: Hernandez OH et al 2014. Refractory Status Epilepticus: Experience in a Neurological Intensive Care Unit. Hindawi Publishing Corporation. Journal of Critical Care Medicine. Volume 2014, Article ID 821462, 9 pages. http://dx.doi.org/10.1155/2014/821462. These authors also preferred midazolam and burst suppression was achieved in 78.8% of the 80 cases with RSE and their cases were assessed using cVEEG.

We have added the publication in the discussion.

2. 1st paragraph: 6 patients with static lesion (11.7% instead of 76%) Discussion

   We have made corrections according to the comment.

3. 3rd paragraph: withdrawal seizure occurred in 21 cases (41.2%) and not in 21%.

   We have made corrections according to the comment.

Reply to Alain Lekoubou’s Comments

1. The purpose of the study is not clearly enunciated.

   We rewrote the purpose of the study and have made corrections according to the comment.
2. Can the author clarify for the reader what pre-compiled causal diagram mean?

We have given further explanation in the Statistical analysis subsection of the Methods.

3. Please add a subtitle for Introduction

We have made corrections according to the comment.

4. Please correct the typo in the sentence "Midazolam has been shown to have a wide margin of safety, a board therapeutic index, and be easy to use…"

We have made corrections according to the comment.

5. The sentence "The fact is that no study has established the effects of EEG-BS in midazolam-treated RSE patients" may sound contemptuous and offending to authors who have addressed this question in the past. I suggest changing it to "There is a scarcity of study assessing the effects of EEG-BS in midazolam-treated RSE patients…"

We have made corrections according to the comment.

6. The following sentence "Our study was conducted using systematically-collected retrospective data to analyze the effect of midazolam-induced BS on the occurrence of..." should appear in the methods section. Also the authors may want to explain how data can be systematically collected retrospectively?

We have made corrections according to the comment and expanded the sentence in the methods section.
7. Please provide a brief description of the guidelines cited in the methods section.

   We have made corrections according to the comment and expanded the sentence in the methods

8. It seems that definition of seizure freedom was based on EEG and clinical findings. This needs to be clearly stated. The authors may want to provide references from the literature to support the definitions of breakthrough seizure and withdrawal seizure provided here.

   We have added the reference.

9. I imagine that some of the outcomes were observed more than once i.e. a patient will have a breakthrough seizure and placed back on burst suppression and later have another breakthrough seizure. The same is true for withdrawal seizure. The authors would like to clarify how these outcomes were counted.

   We agree with this point. We have added information in the Statistical analysis section.

10. Inclusion criteria may be redundant. Patients fulfilling criteria 2) automatically fulfill criteria 1)

    We rewrote this section and have made corrections according to the comment.

11. A selection tree/diagram would be useful in summarizing the selection process.

    We have made corrections according to the comment.
12. The relationship between the outcome variables and the burst-suppression are presented as
incidence rate ratio. The use of incidence rate ratio is misleading in this case. Incidence rate ratio
is the ratio of the incidence rate between the exposed group and the non-exposed group in the
cohort. The incidence rate is the number of event divided by the unit-time of exposure. It seems
that the authors did not compute these estimates to be able to derive an incidence rate ratio. It
rather appears that the authors have reported on the cumulative incidence rate during the period
of hospitalization extending from June 2005 through April 2016. The incidence rate ratio is
likely the incidence risk ratio which is the ratio of the cumulative incidence in the exposed group
vs. the control group.

It is not clear if the measure of association provided is adjusted or not.

We agree with this point. The parameter is indeed the incidence risk ratio. The values in
Table 2 were adjusted for confounding and/or intermediate variables as required by the directed
acyclic graph.

13. A word should be say on the exclusion of anoxic brain injury.

We have made corrections according to the comment.

14. The significance of some results may also be due to random variations in this small sample.

The authors consider that the probability of the “statistically significant” results being due to
random error is already accounted for in the use of a type I error of 0.05 (i.e., the use of 95%
confidence interval for each IRR). We wish, therefore, to be allowed not to include this
suggested amendment.

15. The manuscript has to be reviewed by someone with an excellent grasp of the English
language as there are frequent grammatical errors throughout the manuscript.

We have rewritten this manuscript and it has been edited by an English speaker.
Please find enclosed the revised article of the resubmitted manuscript “Does burst-suppression achieve seizure control in refractory status epilepticus?” for your consideration.

Yours sincerely,

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