Author's response to reviews

**Title:** Appropriate sevoflurane concentration to stabilize autonomic activity during intubation with rocuronium in infants: a randomized controlled trial

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**Author's response to reviews:** see over
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Dear Dr. Marco Gemma,

We are submitting the revised version of our manuscript entitled “Appropriate sevoflurane concentration to stabilize autonomic activity during intubation with rocuronium in infants: a randomized controlled trial”, for publication in *BMC Anesthesiology*.

We are most grateful to you and the reviewers for the helpful comments on the previous version of our manuscript. We have taken all these comments into account and prepared a revised version of our paper. We have addressed all the comments from the editors and reviewers as indicated on the attached pages and hope that the explanations and revisions are satisfactory. We have highlighted the changes in red color in the revised manuscript.

Our manuscript has not been published in another journal and is not currently submitted or accepted for publication elsewhere. The authors declare that they have no competing interests. The manuscript has been read and approved by all the co-authors. We are submitting the manuscript as a “Research article”.

We hope that the revised version of our manuscript is now suitable for publication in *BMC Anesthesiology* and we look forward to hearing from you at your earliest convenience.

We are grateful to referee #1 for the critical comments and useful suggestions that have helped us improve our paper. As indicated in the responses that follow, we have taken all the comments and suggestions into account in the revised version of our paper.

Comments by referee 1

Comment 1

Abstract, page 2, line 18: you write: Heart rate and mean arterial pressure were measured. You should probably specify: 5 times in the 150 seconds after intubation.

Response: We added the recommended information in the abstract. (Page 2, Line 18)
Background: pag 4 line 16: intubating conditions
Response:
We changed the description from “intubation condition” to “intubating condition”.
(Page 4, Line 16)

Comment 3
Study protocol, pag 6 lines 9-13: it is unclear whether you use those ventilation parameters, derived from a preliminary study and used in mechanical ventilation via a tracheal tube, also for the mask ventilation before intubation.
Response:
As the respiratory condition might influence HRV, we applied the same ventilation settings before and after intubation. The parameters used were dependent on the anesthesia machine. A comment about end tidal CO$_2$ has been added in the discussion section.
We added the following sentence to facilitate understanding of the Methods section.
“As respiratory condition might influence HRV, we applied the same ventilator settings before and after intubation.” (Page 6, Lines 14-15)

Comment 4
Pag 6, line 17: were the RAE tubes cuffed or uncuffed? This can alter the patient selection, since you state a few lines later that an important leak lead to tube replacement and exclusion of the patient from the study.
Response:
We used an uncuffed tube. We added this word in the Methods section of the revised manuscript. (Page 7, Line 3)

Comment 5
Discussion, pag 12, line 3: please specify better why you could not use the up-and-down- method.
Response:
Since a cutoff value for ANS activity was not available, we could not use the up-and-down- method to assess MAC. We understand that HRV is usually assessed using relative changes, due to the inter-individual variability in HRV values. We added the following comment in the discussion section. “HRV is usually assessed using relative changes.” (Page 12, Lines 11-12)
Comment 6
Page 12, line 18: please specify why anesthetist should refer to the 95% effective dose of MAC-TI rather than MAC-TI.

Response:
To reduce the stress during intubation for almost all patients, ED 95 rather than ED 50 is useful and helpful. We added a statement explaining this, as “to achieve effective reduction of the stress associated with intubation in almost all patients”, in the discussion section. (Page 13, Lines 9-10)

Comment 7
Page 13 line 1-3: I wonder if a comparison to MAC-TI makes sense, considering that in the study vecuronium was used to facilitate tracheal intubation and MAC-TI refers to an intubation performed merely with anesthetic gas. Please explain better your idea.

Response:
We agree that comparison of sevoflurane concentration during intubation with a muscle relaxant and MAC-TI might not strictly make sense. However, there is no appropriate index for assessing volatile anesthetic use during tracheal intubation with muscle relaxants. Although we used HRV, its cutoff value is not known. Therefore, we only compared the effect of 3%, 4% and 5% sevoflurane in this study. We compared our results with MAC-TI for the purpose of discussion.

We are grateful to referee 2 for the critical comments and useful suggestions that have helped us improve our paper. As indicated in the responses that follow, we have taken all the comments and suggestions into account in the revised version of our paper.

Comments by referee 2

Comment 1
This study is not a dose-finding study to determine the optimal sevo concentration for intubating condition as you mentioned in the discussion. You designed this study to find appropriate sevo concentration providing stable autonomic responses during intubation. Thus, it is recommended to change this title appropriately such as, ~stable hemodynamic/autonomic status during intubation~

Response:
Thank you for your useful suggestion. Accordingly, we changed the title to, “Appropriate sevoflurane concentration to stabilize autonomic activity during intubation with rocuronium in infants: a randomized controlled trial” (Page 1, Lines 1-3)

Comment 2
Background of this study must be clarified more than this. Your hypothesis that "laryngoscopy or intubation ..." is vague and nothing special. You have to emphasize the part that you mentioned in the discussion (page 13, line 4~) in here.
"Although NMB facilitates the tracheal intubation, light sevoflurane anesthesia during intubation induces SNS activation and may results in hemodynamic instability. Therefore, appropriate anesthetic depth is recommended to prevent ANS imbalance"... ANS activity can be evaluated by measuring heart rate variability (HRV) indices. Spectral analysis of HRV is widely used as a non-invasive method to assess cardiac sympathetic and parasympathetic system functions.
Response:
We added the following sentences as you suggested. “Although muscle relaxants facilitate tracheal intubation, their use may result in intubation under a lighter depth of sevoflurane anesthesia, which would induce sympathetic nervous system activation and result in the possibility of hemodynamic instability. Therefore, appropriate anesthetic depth during intubation is recommended to prevent ANS imbalance. ANS activity can be evaluated by measuring heart rate variability (HRV) indices. Spectral analysis of HRV is widely used as a non-invasive method to assess cardiac sympathetic and parasympathetic function [8, 9].” (Page 4, Line 16-Page 5, Line 3) Moreover, we added the abbreviation of autonomic nervous system (ANS) as you provided. (Page 17, Lines 18)

Comment 3
Page 11, Line 1~9; , you did not mention your result of HFnu and LF/HF ratio. You mentioned that you used the relative value of HFnu. So, what you tried to explain with it?
Response:
We added the following comments about our results. “In the present study, we estimated that increase in sympathetic activity and decrease in parasympathetic activity occurred 30 seconds after intubation, as indicated by the increase in LF/HF
and decrease in HFnu, respectively. The increase in LF/HF and decrease in HFnu were smaller in the E_{Sevo}-5\% group than in the E_{Sevo}-3\% group. Therefore, we estimated that the autonomic responses to intubation were reduced by sevoflurane in a dose-dependent manner.” (Page 11, Lines 15-19)

Comment 4
Line 12: You mentioned that you excluded the data from the time of laryngoscopy to 30 seconds after the start of ventilation in order to avoid the effects of apnea based on a study by Nakatsuka et al. (ref 14). However, they obtained the apnea data during mechanical ventilation after 15 minutes something of tracheal intubation. The situation was different from your time point of apnea and theirs. The hemodynamic changes are usually peak-up at 1~2 minutes after intubation. Thus, you don't need to comment the "apnea thing" of reference 14, I think. It is recommended to remove the sentences (line 10~17).
Response:
Thank you for your helpful comment. As you mentioned, the situation regarding the apnea time point in the previous study was different from that in our study. However, our study protocol was established to minimize the influence of apnea. We think that Nakatsuka's study is excellent because they focused on heart rate variability before and after intubation. Although our study is not complete, we are convinced of the importance of the respiratory effects. Therefore, we decided to retain the sentences despite your suggestion to remove them.

Comment 5
Line 19: You described that your study is the first report of ANS response to intubation evaluated by HRV, but Janda et al. reported the study “Comparison of heart rate variability response in children undergoing elective endotracheal intubation with and without neuromuscular blockade: a randomized controlled trial” in Pediatric Anesthesia 2013. Please remove the sentence or re-describe it.
Response:
Thank you for the useful information. We opted to delete the sentence because it is confusing.

Conclusion
Comment 6
As a result of your study, the conclusion may be rewrite as "In infants, sevo 4% or 5%
is appropriate to prevent sympathetic hyper-activation and obtain ANS balance rather than 3% for intubation even though NMB is co-administered. Please clarify the description of your results in discussion.

Response:

We changed the conclusion, as you suggested, to “In conclusion, during tracheal intubation in infants, 4% or 5% sevoflurane is appropriate for prevention of sympathetic hyperactivation and maintenance of autonomic nervous balance as compared to 3% sevoflurane, when a muscle relaxant is co-administered.” (Page 16, Lines 12-14) We also similarly changed the last sentence in the abstract. (Page 3, Lines 12-14)

We hope that our manuscript will now be suitable for publication in your journal.

Sincerely yours,

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