Author’s response to reviews

Title: Association of neuromuscular reversal by sugammadex and neostigmine with 90-day mortality after non-cardiac surgery

Authors:

Tak Kyu Oh (airohtak@hotmail.com)
Jung-Hee Ryu (jhleesnubh@gmail.com)
Sunwoo Nam (snubhanesthesiology@gmail.com)
Ah young Oh (ohahyoung@hanmail.net)

Version: 2 Date: 09 Feb 2020

Author’s response to reviews:

Réka Nemes, M.D. (Reviewer 1): Manuscript Number: BANE-D-19-00777

L63: the second half of the sentence is difficult to interpret, probably missing punctuation
Response: Thank you for pointing this out. We have revised the sentence according to your comment.

L68-69: "with an incidence as high as"
Response: Thank you for your comment. We have corrected the sentence accordingly.

L69: "found" would be more appropriate than "determined"
Response: Thank you for this suggestion. We have corrected the word accordingly.

L110: the dose of neostigmine is not needed to be mentioned here. Either delete it or also add the dose of sugammadex.
Response: Thank you for this suggestion. We have deleted the dosage of neostigmine according to your comment.

L113-125: Excuse me, but the description of intraoperative neuromuscular monitoring is still confusing. "TOF monitoring" is not an unambiguous term as the TOF response can be interpreted objectively with a neuromuscular monitor or subjectively by the examiner. Please use the terms quantitative (objective) neuromuscular monitoring or qualitative (subjective) neuromuscular monitoring.
Response: Thank you for your comment. We have checked this again. Our study analyzed data obtained during 2011 to 2016; in our institution, quantitative neuromuscular monitoring was only available after 2017. Therefore, as you commented below, qualitative neuromuscular monitoring was performed to determine the type or dosage of NMBA reversal agent during the study period. We have revised our methods and discussion sections to clarify this.
- If I understand it correctly the clinicians used peripheral nerve stimulators (subjective monitoring) at the end of surgery to determine the dose of the reversal agent (L113-116).
Response: Thank you for this question. We have revised the text to clarify that subjective monitoring using two peripheral nerve stimulators were used to determine the dose of the reversal agent.

- Was monitoring continued after reversal administration to check the effect of the reversal agent and to decide on patient's readiness for safe extubation?
Response: Thank you for this question. The TOF count was usually measured again after reversal administration to check the effect of the reversal agent and to decide on the patient's readiness for safe extubation. We have revised our methods section to clarify this.

- What do you mean by intraoperative TOF monitoring (L122)? Objective of subjective evaluation of TOF stimulation?
Response: Thank you for this question. It was subjective (qualitative) neuromuscular monitoring; we have revised the text to clarify this.

There's plenty of literature showing that subjective monitoring guided neostigmine reversal is not a safe practice and can lead to very high incidence of residual blockade and various complications. This would deserve more attention in the discussion as well.
Response: Thank you for raising this point. We agree with your opinion, and we have revised the text to emphasize this point in the 3rd, 8th, and 9th paragraph of the discussion section.

L141: "data on intraoperative TOF monitoring" - please be more specific, what type of monitoring
Response: Thank you for this question. We have corrected the text to clarify that data from intraoperative qualitative neuromuscular monitoring using a peripheral nerve stimulator was collected.

L176: "Sugammadex" - capital letter not needed
Response: Thank you for pointing this out. We have corrected this error.

L177: the verb "affect" would be more appropriate instead of "associated"
Response: Thank you for pointing this out. We have corrected it to “affected”.

L226: "compared to Q1 group" is duplicated
Response: Thank you for pointing this out. We have corrected the text accordingly.

L231-232: "This association was significant in the PS matched cohort" BUT not in the entire cohort. Please correct.
Response: Thank you for this suggestion. We have corrected the text accordingly.

L154: please add references.
Response: Thank you for this suggestion. We have added the following reference: (Brull SJ, Kopman AF: Current Status of Neuromuscular Reversal and Monitoring: Challenges and Opportunities. Anesthesiology 2017, 126(1):173-190)

L302-303: please consider using "affect" instead of "associated"
Response: Thank you for this suggestion. We have corrected the text to use “affect”, as per your comment.
L305: consider using the term "peripheral nerve stimulator"
Response: Thank you for this suggestion. We have revised the text to use "peripheral nerve stimulator".

L315-316: neostigmine is not meant to reverse deep block! TOF1 is moderate block for which objective monitoring guided (0.5-0.7 ug/kg) neostigmine reversal should be used.
Response: Thank you for pointing this out. We agree with your opinion, and we have deleted the sentence accordingly.

Table 1. Please be more specific with data on intraoperative neuromuscular monitoring.
Response: Thank you for this suggestion. We have corrected Table 1 accordingly.

Table 4. Neostigmine Q3 line: "n" is missing
Response: Thank you for pointing this out. We have corrected Table 4 accordingly.

Table 4. Please list the distribution of different sugammadex dosages (n) for each quartile
Response: Thank you for this suggestion. We have corrected Table 4 accordingly.

Christoph Czarnetzki (Reviewer 2): I am mostly o.k. with the revised manuscript concerning statistical methods.

Since the outcome is the mortality after 90 days, I wonder if the Cox regression is necessary
Response: Thank you for this comment. We understand your opinion, but the Cox regression model revealed a hazard for 90-day mortality. We have also presented the results of logistic regression analysis for 90-day mortality in Table 2, as a sensitivity analysis. Please consider this in your review.

The word electronic all over the manuscript should be replaced with quantitative neuromuscular monitor and the names of the devices used should be indicated: like Tofscan, Tofwatch etc... as you indicate that in your institution, the electronic stimulator device was available in all operating rooms for TOF monitoring at the end of surgery.
Response: Thank you for this suggestion. We have checked this again. Our study analyzed data obtained during 2011 to 2016; in our institution, quantitative neuromuscular monitoring was only available after 2017. Therefore, as you commented below, qualitative neuromuscular monitoring was performed to determine the type or dosage of NMBA reversal agent during the study period.

We have corrected the text as follows: “In most cases, the dosage of sugammadex or neostigmine for NMBA reversal was determined after qualitative (subjective) neuromuscular monitoring using two peripheral nerve stimulators (Innervator 252; Fisher &amp; Paykel Healthcare, New Zealand, and EZStim II, model ES400; Life-Tech International, Stafford, Texas). The residual degree of neuromuscular block from NMBA at emergence was measured after the end of surgery and before extubation. After NBMA reversal administration, the train-of-four (TOF) count was re-checked using the peripheral nerve stimulator to decide on the patient’s readiness for safe extubation.”

Were there guidelines in your institution for reversal of neuromuscular block available to which all anaesthesiologists had to adhere? Please state.
Response: Thank you for this question. There were no strict guidelines in our institution to determine the agent (sugammadex or neostigmine) used for NMBA reversal. This is because we performed this study retrospectively. However, there was a recommended guideline for determining the dosage of
NMBA reversal agent using qualitative neuromuscular monitoring with a peripheral nerve stimulator; we have explained this in detail in methods section.

The authors write: When neostigmine was used, the maximum dose (50 mcg/kg) was administered for NMBA reversal if TOF was 1 (not ≥ 2). What was done when TOF was ≥ 2? Was the TOF ratio measured and used as guidance for extubation as electronic/quantitative devices were used? With accelometry a TOF ratio ≥ 90 is the safe standard for extubation. Could it be that patients with a TOF count > 1 were not antagonized with neostigmine? Many guidelines demand a TOF count equal to 4 for reversal with neostigmine. So could it be that patients in the neostigmine group at your institution were substandardly antagonised and extubated in the neostigmine group?

Response: We thank you for identifying a really important point. We did not check the TOF ratio accurately, because we did not perform quantitative neuromuscular monitoring. If the TOF count was not 1 (i.e. 2, 3, or 4) at the end of surgery by qualitative neuromuscular monitoring, 30-40 mcg/kg of neostigmine was administered for NMBA reversal in the neostigmine group. We have added this information to the methods section. As you commented, it was possible that patients in the neostigmine group were substandardly antagonized and extubated. We have discussed this important issue in the 3rd, 8th, and 9th paragraphs of the discussion section.