Author’s response to reviews

Title: Usefulness of intra-operative neuromuscular blockade monitoring and reversal agents for postoperative residual neuromuscular blockade: a retrospective observational study

Authors:

Gonzalo Domenech (gonzalo.domenech@hospitalitaliano.org.ar)
Matias Kampel (matias.kampel@hospitalitaliano.org.ar)
Maria Eugenia Garcia Guzzo (mariae.garcia@hospitalitaliano.org.ar)
Delfina Sanchez Novas (delfina.sanchez@hospitalitaliano.org.ar)
Sergio Terrasa (sergio.terrasa@hospitalitaliano.org.ar)
Gustavo Garcia Fornari (gustavo.garciafornari@hospitalitaliano.org.ar)

Version: 1 Date: 09 Jul 2019

Author’s response to reviews:

Editor Comments

BMC Anesthesiology operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.
Reviewer reports:

Anthony Kovac (Reviewer 1): The authors report a study evaluating the occurrence of residual NMB when neuromuscular monitoring is or is not used. They also report any associated outcomes.

Abstract: The authors repeat their primary and secondary outcomes in the Methods that was also previously stated in the background section of the abstract. Please be more succinct and brief and delete the primary and second outcomes in the methods section.

Response: Thank you for your suggestion. We have deleted the primary and secondary outcomes from the methods section of the abstract.

page 4, line 40: Please explain or site references for the authors statement of the "high incidence of RNMB."

Response: We have now added specific references regarding our statement of the “high incidence of RNMB”.

Page 5, line 30-33: Have the authors published their results of 20-30% RNMB in their hospital?

Response: We have not previously published our results of an incidence of 20-30% RNMB in our institution, since this is an estimate based on observations during clinical practice in the PACU. The primary aim of this study was to establish the real incidence of RNMB at our PACU.
Please explain potentially related variables?

Response: The potentially related variables which have been analysed for existing associations are now enumerated in the text; these include the use of NMB monitoring, duration of surgery, type of NMBD, type of reversal agent, and time between the last NMBD administration and the presence of a TOFR in the PACU.

Why was sugammadex unsuccessful to reverse blockade. 16% failure rate seems far too high. Was the incorrect dose of sugammadex used?

Response: Our results show that administering sugammadex in the absence of NMB monitoring is not an effective strategy to avoid RNMBs, revealing an RNMB incidence of 16% and accounting for 3 of 19 non-monitored patients. The mean sugammadex dose used among patients who presented RNMB at the PACU was 3.22 ± 1.23 mg/kg; unfortunately, we cannot be sure if this was the appropriate dose since NMB monitoring was not applied.

Although Kotake et al. and other authors have reported a lower incidence than noted in the present study for reversal failure with sugammadex use in non-monitored patients (4.3%; interquartile range: 1.7% to 9.4%), we believe this is related to an insufficient dosage and a lack of NMB monitoring.

Please explain why the rate of quantitative NMB monitoring so low in their hospital, a major hospital in Argentina and that the availability of monitors was so high?

Response: The low rate of NMB monitoring usage (26%) in our institution shows an underestimation of the clinical danger that RNMB represents. The lack of awareness among some anaesthesiologists regarding the need for NMB monitoring and the high incidence of RNMB when NMB monitoring is not used may be 2 reasons why available monitors are not used routinely in our institution. We believe that awareness of the clinical implications of RNMB remains limited in our country, probably because respiratory complications in the PACU have multifactorial etiology, such as opioid and benzodiazepine use, and are usually not confirmed to be related to RNMB.
Page 13, lines 16-19: Why such a low use of reversal agents in your hospital?

Response: The low rate of NMB monitoring usage is probably related to the low use of reversal agents. Individuals who were monitored received a reversal agent in 81% of cases, while only 13% of non-monitored patients received such an agent. This shows that the same group of anaesthesiologists who do not use monitoring despite its availability probably do not consider the need for NMB reversal agents. On the contrary, the group of anaesthesiologists who use NMB monitoring routinely are more likely to consider peri-operative NMB management as an important aspect of patient safety and quality of care. These physicians likely administer reversal agents, whenever needed, always following NMB monitoring results.

Page 13, lines 43-46: Because this is a retrospective study, a major weakness and flaw in this reviewers opinion is that the authors did not have access about the depth of paralysis at which a reversal agent such as neostigmine was administered.

Response: As the reviewer stated, a major limitation of this study is that we do not have the data regarding the depth of block at which neostigmine was administered in monitored patients. Neostigmine administration at an inadequate depth of NMB may account for the reversal failure with this drug; this is why the conclusion of this study focuses on reinforcing the importance of unexceptional use of NMB monitoring and highlights it as the most important factor associated with avoidance of RNMB.

Page 14, lines 28-58: There are major study limitations of which are very evident and that the authors themselves state.

Response: We have discussed the limitations in our manuscript and these will probably be addressed in future studies.

Page 14, line 45: Why were two different types of monitors used?

Response: The following explanation was included in the text.
Two different approaches to NMB monitoring were used due to the limited availability of monitors. Phillips IntelliVue NMT Modules (865383) are attached to multiparameter monitors in every operating room and are not portable. A different monitor, TOF-Watch® SX, was also available as a portable device for PACU measurements. Although both monitors use the same measuring principle (acceleromyography), there is no published evidence on the similarity of measurements between them.

Page 15, line 9: Did the patients experience any pain if they were conscious at the time the measurements were evaluated. This in spite that the authors state < 50 mA is acceptable in terms of patient comfort. Were that patients comfortable?

Response: Patient comfort was not recorded, so it was not assessed in the present study, but none of the patients complained of discomfort while TOF measurements were being acquired and TOF stimulation never had to be stopped due to the patient experiencing pain.

Conclusions, page 15: The authors seem biased in favor of the use of sugammadex. Are the authors mainly evaluating the use of NMB monitoring or the use of neostigmine and sugammadex. Some may argue that if neostigmine is given early enough the TOF ratio will still reach a level of 90%.

Response: The primary aim of this study was to estimate the incidence of RNMB in patients managed with or without the use of sugammadex or neostigmine as antagonists and quantitative NMB monitoring in the operating room. Multivariable analysis revealed that the use of intra-operative quantitative NMB monitoring and the use of sugammadex were associated with a lower incidence of RNMB, with calculated ORs of 0.04 (95% CI: 0.005 to 0.401) and 0.18 (95% CI: 0.046 to 0.727), respectively. Our conclusion, therefore, is that the optimal strategy for RNMB avoidance is the use of quantitative NMB monitoring and the eventual use of reversal agents, if needed, prior to emergence from anaesthesia. It has been established that neostigmine, if administered at correct doses and a TOF count of 4, is effective in reversing NMB. In the case of nonmonitored patients, complete recovery will not be achieved if neostigmine is administered below this count. Antagonism with not only neostigmine but also sugammadex without the use of NMB monitoring fails to prevent RNMB in the PACU, but in non-monitored patients reversal failure was lower for sugammadex (16%) compared to neostigmine (40%).
Table 1: There were unequal numbers of females and males in the unmonitored group while the smaller monitored group had similar numbers of males and females. Could the difference of muscle mass between males and females have been a factor in the non-monitored group?

Response: Differences regarding the number of males and females were not found to be statistically significant in monitored and non-monitored groups. Therefore, we do not believe this difference was a factor that affected our results.

Another confusing fact is the use of different types of NMB agents. Were all of the atracurium patients reversed with neostigmine? I would hope that none of the atracurium patients were reversed with sugammadex. As sugammadex is only effective for reversal of rocuronium and vecuronium.

Response: All patients who received atracurium as an NMBD were reversed with neostigmine and all patients who received sugammadex were under NMB after rocuronium or vecuronium use.

Why were sugammadex doses larger than 2 mg/kg used? Table 1 shows sugammadex doses of 3.22 and 3.9 mg/kg for the non-monitored and monitored groups, respectively.

Response: Table 1 shows average doses of 3.22 and 3.9 mg/kg for nonmonitored and monitored patients, respectively. We believe that average doses of sugammadex higher than 2 mg/kg were found in both groups because of the calculation of an average dose in each group using data from patients receiving 2 mg/kg and 4 mg/kg. Doses of 4 mg/kg were likely used for different reasons in both groups.

Monitored patients may have received higher doses of NMBDs so it could be expected that higher reversal doses were needed (average dose 3.9 mg/kg). When reversal administration is guided by NMB monitoring, doses are chosen according to the NMB depth.

Anaesthesiologists may be aware that the only reason for reversal failure of sugammadex when using rocuronium without NMB monitoring is insufficient reversal dosing. Therefore, when choosing to administer sugammadex without monitoring, we observed that some patients received 4mg/kg rather than 2 mg/kg, but not many since the average dose was 3.22 mg/kg for the nonmonitored group. According to the PACU results, these doses may also be insufficient or incorrect. Although non-monitored patients received an average of 3.22 mg/kg of sugammadex, we found a failure rate of 16%.
Table 3: It still confuses me why sugammadex was not successful in 3 of 19 patients who did not receive NMB monitoring. Please explain in your discussion section.

Response: An additional comment has been added to the fifth paragraph of the Discussion section regarding this matter.

Thank you for all of your suggestions. We believe we have responded to them all thoroughly. The authors are willing to answer any further questions or concerns as well in the event that the reviewer does not feel all concerns have been addressed thoroughly.

Réka Nemes, M.D. (Reviewer 2): This study is retrospective analysis of neuromuscular monitoring and reversal habits in a tertiary referral university hospital.

The results of the study are alarming and draw the attention to the personal responsibility of anesthesia care providers to prevent RNMB. In this respect, the reviewer would like to highlight a recently published article by Naguib et al that elaborate on the role of human factor in neuromuscular blockade management [Anesthesiologists' Overconfidence in Their Perceived Knowledge of Neuromuscular Monitoring and Its Relevance to All Aspects of Medical Practice: An International Survey. Naguib M, Brull SJ, Hunter JM, Kopman AF, Fülesdi B, Johnson KB, Arkes HR. Anesth Analg. 2018 Aug 22.]

General questions to the authors:

- Was the dose of neostigmine fixed or adjusted to level of block?

Response: Due to the retrospective nature of this study, we cannot confirm at which depth of NMB neostigmine was administered or whether doses were fixed or adjusted to the depth of NMB in monitored patients.
- Do the authors have any information on how was the reversal chosen?
Response: The reversal strategy was chosen at the discretion of the consultant anaesthesiologist; no data were recorded regarding this matter.

- What kept people from transferring data to anesthesia records?
Response: Data from all monitors are automatically transferred to electronic anaesthesia records except for TOF measurements. Only some anaesthesiologists manually transfer data.

- Was hand adapter used intraoperatively or postoperatively?
Response: The same hand adapters were used intra-operatively and postoperatively in all patients.

Did the audit have any consequences with regard to neuromuscular monitoring and reversal practices?
Response: The Anesthesiology Department has provided several reinforcements involving residents and consultant anaesthesiologists regarding the significance of the unexceptional use of NMB monitoring whenever NMBDs are administered. Now, a new prospective audit is planned for the year 2020 to investigate if the rates of NMB monitoring have increased and whether the rates of RNMB have decreased.

P4L6-8 - Please rephrase the first sentence, it's confusing.
Response: We have rephrased the sentence as advised.

P4L52 - What do the authors mean by "measurements of TOFR in real time" - this is not a definition of quantitative neuromuscular monitoring.
Response: The phrase “measurements of TOFR in real time” has been deleted since it is not a definition of NMB monitoring and should not have appeared in the manuscript.
P5L1 - The sentence correctly: Several reports suggest that clinical evaluation and qualitative neuromuscular monitoring are not sensitive enough…

Response: We have rephrased the sentence as advised.

P5L30 - The authors here state that the estimated incidence of RNMB is 20-30%. However, the sample size calculation was based on an incidence of 45% (P8L28). Please clarify.

Response: Our sample size calculation, as mentioned in the Statistical analysis subsection of the Methods, was based on the study by Debeane et al., who found an RNMB incidence of 45% (TOFR < 0.9). The estimated incidence of 20-30% in our PACU should not have been expressed with the wording previously used and is only an observation from clinical practice.

P8L13 - Please omit the word "used"

Response: The word “used” was replaced.

P8L18 - What did the authors do if TOF counts were delivered?

Response: No patient showed TOF counts < 4 and TOF ratio results were determined for each patient. The mean TOFR in patients who exhibited RNMB was 0.68 ± 0.20 while that in patients without RNMB was 0.94 ± 0.03.

P8L25-38 - sample size calculation should go to statistical analysis section

Response: The paragraph explaining the sample size calculation was moved to the Statistical analysis subsection as recommended.

P10L37-43 - Did this patient receive reversal?

Response: This patient did not experience reversal, as mentioned in the Discussion section, and had presented with a TOFR > 0.9 prior to extubation, indicating no apparent need for reversal.
Please change word order: Intraoperative quantitative NMB monitoring
Response: The word order was fixed as suggested.

Did the authors examine the association between RNMB and the type of surgery or monitoring /reversal habits and the anesthesiologists?
Response: The present study did not examine these associations.

"A longer time since the last administration of NMBD and the time to TOFR in the PACU…” Please rephrase this sentence
Response: The indicated sentence has been rephrased.

I would move this passage to the limitations of the study section
Response: The passage was moved to the limitations paragraph of the manuscript as suggested.

How big was the variability of the TOFR triplets obtained postoperatively in this study?
Response: There were no alternative analyses of variability between the 3 measurements or average TOFR responses when the variability was high, so information regarding the amount of variability is not available.

This passage does not belong to the article.
Response: We eliminated this passage according to your suggestion. This was clearly not related to our study.