Author’s response to reviews

Title: Rocuronium blockade reversal with sugammadex vs. neostigmine: randomized study in Chinese and Caucasian subjects

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Author’s response to reviews: see over
Dear Dr Rowles,

Thank you to you and the reviewers for taking the time to review our manuscript. Please find enclosed a revision of the manuscript, with the additions marked in red and deletions in blue and struck through. Our specific responses to the comments are shown below. We hope that the revised version of the manuscript will be acceptable for publication.

With kind regards,

Professor Xinmin Wu

Editor’s comments: “Both reviewers found the manuscript to be a well written report of a well designed study. The findings are important as they verify the efficacy of sugammadex in Chinese subjects and catalog some adverse effects.

Both reviewers have some minor questions that should be addressed.

Dr. Lee thought that the manuscript should be examined by a statistician. I looked at the power analyses myself. I found that they are appropriate. If anything, they may underestimate the power of the study (it was not clear to me whether the analysis was based on the arithmetic or geometric means). At any rate, the study is highly powered.

Authors’ response: Thank you. No further action required.

Dr. Lee thought it would be appropriate to quantify the adjunctive analgesics used. Given the high power of the study (among Chinese subjects in particular), it might be possible to make definitive statements about the possible effects of opioids on recovery from block. However, I am not aware of any previous evidence for an opioid effect.

Authors’ response: Administration of opioids has now been quantified in Table 1. Administration of opioids was generally similar between treatment groups, and between Chinese and Caucasian patients, and we do therefore not feel there is any evidence of an opioid effect.
BMI can be added to Table 1.

**Authors’ response:** BMI has now been added to Table 1, as requested.

I do not think the title of the manuscript has to be changed.

**Authors’ response:** We have left the title as it is.

I agree with Dr. Lee that paragraph 3 of the Introduction repeats the specific doses of the drugs too often.

**Authors’ response:** We have removed superfluous mention of drug doses from paragraph 3 of the introduction on Page 5.

As suggested by Dr. Carron, you should note whether the depth of anesthesia was monitored.

**Authors’ response:** Please see our response to Dr Carron’s comment below.

In addition, you should comment on the other issues raised by Dr. Carron, especially with regard to Collins et al [PMID: 11094012].

**Authors’ response:** We have now commented on the issues raised by Dr Carron, in the Results and Discussion, and the Collins et al (2000) paper has been discussed on Page 22.

**Reviewer 1 (Dr Carron) comments:**
Major Compulsory Revisions. None

Discretionary Revisions:
1. Methods - Study Procedure.
   a. “...IV propofol according to the clinical needs of the subject”. Was deep anesthesia monitored (bispectral index or entropy monitoring)? The use of the bispectral index monitoring resulted in less complications (i.e. intraoperative awareness, postoperative nausea and vomiting) (Klopman MA, Curr Opin Anaesthesiol 2011).
Authors’ response: Anesthetic practices such as use of bispectral index (BIS) or entropy monitoring for measuring depth of anesthesia were to be performed according to routine practices at the individual study sites. This has now been clarified on Page 8 of the Methods. As such, the use of these techniques varied between sites. Monitoring of anesthesia depth (by BIS) was confirmed to have taken place at two out of the ten sites (one site in Denmark and one in Norway). Investigators from these two sites confirmed that BIS was used in the majority of their patients, and that it was aimed for the BIS index values to be maintained between 40 and 50 in all cases. No further updates to the manuscript considered necessary.

b. “…use of oxygen in air or nitrous-oxide”: May the choice of nitrous-oxide have had an influence in the incidence of AEs in the study (es. high incidence of nausea and vomiting)?

Authors’ response: In line with study protocol, anesthetic practices such as use of nitrous-oxide were to be performed according to routine practices at the study site. However, there are no documented cases of patients having actually received nitrous oxide in this study. We have therefore deleted the text regarding nitrous oxide from Page 8 of the Methods to avoid confusion.

2. Methods - Efficacy analyses. “…TOF ratio to 0.9 was >6 min… classed as a prolonged recovery time”. Could the Authors explain why >6 min? Generally, sugammadex allows a recovery to a TOF ratio #0.9 in #3 min (Groudine SB, Anest Analg 2007; Sorgenfrei IF, Anesthesiology 2006; Schaller SJ, Core Evid. 2013). For this reason, some Authors believe adequate a time less than 3 min for a safe reversal and risky a time greater than 3 min (Le Corre F, Can J Anaesth 2011; Llauradó S, Anesthesiology 2012; Schaller SJ, Core Evid. 2013). A reversal time of about 5 min was associated to recurarization (Le Corre F, Can J Anaesth 2011)

Authors’ response: The cut-off point for prolonged recovery times was in line with the mean data from studies included in the Merck-sponsored sugammadex clinical trial programme. This has been added to Page 9 of the Methods. Recovery times were considered to be outlying when recovery to TOF ratio 0.9 was slower than the 95th percentile of recovery times observed in Phase 2 and 3A subjects from the clinical trial program. A recovery time of > 6 min was thus pre-specified as a prolonged recovery time.
3. Results - Efficacy analyses.

a. As for the Caucasian population, the Authors should report the fastest and slowest times to recovery following neostigmine administration in Chinese population

Authors’ response: This information has now been added to Page 13 of the Results.

b. Comparable median times in the recovery of TOF to 0.9 following sugammadex administration were observed in Chinese and Caucasian subjects (1.6 vs 1.4 min, respectively). On the contrary, the median times to recovery to TOF 0.9 following neostigmine administration were different (9.1 vs. 6.7 min, respectively). It appears an important difference. The Authors should comment.

Authors’ response: We have commented on this finding in the Discussion on Page 22 as follows:

Importantly, the results of the present study have excluded any clinically relevant differences in the effectiveness of sugammadex 2 mg/kg in Chinese compared with Caucasian subjects. However, geometric mean times to recovery to TOF 0.9 following neostigmine administration were 1.37 (95% CI: 1.05–1.78) times longer in Chinese versus Caucasian subjects. This result is statistically significant; however, it is unclear why this difference occurred. While there is no known race effect for neostigmine, Chinese subjects have previously been shown to be more sensitive to effects of atropine versus Caucasian subjects [26], and this may have potentially played a role. Furthermore, spontaneous recovery from rocuronium has previously been shown to be somewhat slower in Chinese versus Caucasian patients [30], with the authors concluding that reasons for the observed interethnic difference were likely to be multifactorial.

4. Results - Safety.

a. In the Methods–Safety section, the Authors considered the “treatment-related AEs” those “related…to sugammadex or neostigmine administration”. The Authors should better specify if some of the AEs reported, such as “incision site pain, procedural pain, wound complication, vaginal hemorrhage” are really related to reversal drug administration. In particular, the vaginal haemorrhage appears unlikely related to study drug. Any influences
of the other factors (i.e. surgery)? This may be important if one considers that sugammadex led to prolonged activated partial thromboplastin time (aPTT) and prothrombin time (PT) or international normalized ratio (INR) for a short time (below 30 minutes) (Schaller SJ, Core Evid. 2013). These effects were not found to be clinical relevant. So, in my opinion, it's important to exclude a possible role of sugammadex in bleeding.

Authors’ response: We have reworded the text in the paragraph on treatment-related AEs (Results, Page 15-16) as follows: “Treatment-related AEs considered by the investigator to be possibly or probably treatment-related were reported for 9% and 3% of sugammadex-treated Chinese and Caucasian subjects, respectively, and for 18% and 35% of corresponding neostigmine-treated subjects”. We have also clarified that the AEs listed in Table 3 are regardless of possible relation to the study drug. We have not listed out all AEs considered possibly or probably treatment-related as there are a considerable number (29) of different event types; however, the most frequently reported drug-related AEs are stated on Page 15-16. Furthermore, we have added further information regarding bleeding events to the Results, clarifying that none of the events associated with bleeding were considered related to study medication (Page 17-18), and discussion regarding bleeding events has now been added to Page 20-21.

b. Anesthetic cardiac complications. This point appears not very clear. The Authors should better specify in what they consist and, possibly, comment.

Authors’ response: All subjects with anesthetic cardiac complication were reported to have bradycardia or decreased heart rate – this has been clarified on Page 16 of the Results, and included in the Discussion (Page 22).

Minor Essential Revisions:
1. Abstract (i.e. results) and main text (i.e. conclusions): please insert endotracheal before intubation.

Authors’ response: This update has been made as suggested.

Reviewer 2 (Dr Lee) comments: This is the study about the efficacy and safety of the sugammadex and neostigmine for reverse against the moderate neuromuscular blockade by rocuronium in Chinese and Caucasian subjects.
I'm impressed that this paper is well designed study.
The body text of the paper is well described.
The methods and results sections are very detailed and easy to understand.
Discussion is concisely summarized with appropriate references.

**Authors’ response:** Thank you very much for this positive summary of our paper.

I'd like to recommend some major concerns for improvement your manuscripts as follows.

1. There is no detailed descriptions about the anesthesia methods.

**Authors’ response:** We have added further detail where possible to the Methods (Page 8). However, while anesthesia was induced and maintained with IV propofol in all patients, other anesthetic practices (e.g. use of opioids, and oxygen in air or nitrous-oxide) were performed according to local routine practices at the individual study sites. Doses and agents used for anesthetic management were permitted to be adjusted when necessary to provide optimal patient care.

2. If you used the propofol as a main anesthesia, which drugs would be used as an adjunctive analgesics (ex, remifentanil, fentanyl, morphine etc.). Is there are any difference in frequency or doses of opioids between groups?

**Authors’ response:** Anesthesia was induced and maintained with propofol in all Chinese and Caucasian subjects. The most frequently administered opioid was remifentanil; received by 84% and 83% of Chinese subjects treated with sugammadex and neostigmine, respectively; and by 69% and 74% of Caucasian subjects treated with sugammadex and neostigmine, respectively. Administration of opioids was similar between groups. Information regarding anesthetic agents administered has now been added to Table 1.

3. Which body weight scale do you use for dosing the sugammadex or neostigmine? (ideal body weight / real body weight / lean body mass)
Authors’ response: Rocuronium, sugammadex and neostigmine were all administered based on actual body weight, on an mg/kg basis, in line current dosing recommendations. This information has been added to the Methods on Page 9.

4. There is no exceptional criteria for BMI (body mass index). This is an important point in related with above #3 and it can affect the postoperative residual curarization even after using sugammadex.

Authors’ response: Patients were not excluded from entering the study based on weight/BMI alone, in order to reflect a ‘real-world’ clinical scenario. Importantly, there was no evidence of residual NMB or recurrence of NMB, either clinically or based on neuromuscular monitoring, for any patient (stated on Page 17). BMI data have however now been added to Table 1.

Minor concerns
I’d like to recommend some minor concerns for improvement your manuscripts as follows:
1. Title of the manuscript may be inappropriate for summarizing your work. In this study, all reversal were done at moderate depth of blockade. More clear title should be needed.

Authors’ response: In line with the editor’s recommendations, we have left the title as it is.

2. In the "Introduction" section, the purpose of this study, some phrases are duplicated inappropriately. It would be better to describe shortly and concisely.

Authors’ response: Duplication has been removed from the introduction on Page 5.

3. In the “Methods” section, Efficacy analyses, if the time to recovery of the TOF > 0.9 was more than 6 min in the Sugammadex group, they would be classed as a prolonged recovery time. How many patients would be finally? and what is the cause of prolonged recovery?

Authors’ response: An outlying recovery time of 6.2 min was observed for one Chinese subject after receiving sugammadex. For this subject, TOF 0.7 and 0.8 were reached at 0.9 min and 1.4 min after sugammadex, respectively, and were thus within normal ranges. However, due to technical issues with neuromuscular monitoring, an unusually high first
twitch value affected the TOF ratio and caused the delay in reaching TOF 0.9. This is reported in the manuscript results on Page 14.

Thank you for the submission of interesting manuscript.

Authors’ response: Thank you for taking the time to review.