Peer Review File

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Reviewer A Comments

Comment 1: Line 226 - please cite some references linked to text, since the authors give notice to several reviews about neuromuscular blocking agents.

Reply 1: As suggested, references have been added.

Changes in the Text: The following references have been added:

Sparr HJ, Beaufort TM, Fuchs-Buder T. Newer neuromuscular blocking agents: how do they compare with established agents?. Drugs. 2001 Jun;61:919-42.

Pollard BJ. Neuromuscular blocking agents and reversal agents. Anaesthesia & Intensive Care Medicine. 2005 Jun 1;6(6):189-92.

Farooq K, Hunter JM. Neuromuscular blocking agents and reversal agents. Anaesthesia & intensive care medicine. 2017 Jun 1;18(6):279-84.

Hunter JM. New neuromuscular blocking drugs. New England Journal of Medicine. 1995 Jun 22;332(25):1691-9.

Heerdt PM, Sunaga H, Savarese JJ. Novel neuromuscular blocking drugs and antagonists. Current opinion in anaesthesiology. 2015 Aug 1;28(4):403-10.

Comment 2: Line 227-229 - please cite a reference to support the affirmation about the use of the neuromuscular blocking agents;

Reply 2: As suggested, a reference has been added.

Changes in the text: The following reference has been added: Weber V, Abbott TEF, Ackland GL. Reducing the dose of neuromuscular blocking agents with adjuncts: a systematic review and meta-analysis. Br J Anaesth. 2021 Mar;126(3):608-621. doi: 10.1016/j.bja.2020.09.048. Epub 2020 Nov 17. PMID: 33218672; PMCID: PMC8014939.

Comment 3: Line 229-233 - Again, please cite a reference.

Reply 3: As suggested, a reference has been added.

Changes in the text: The following reference has been added: Bevan DR. Newer neuromuscular blocking agents. Pharmacology & toxicology. 1994 Jan;74(1):3-9.

Comment 4: Line- 234 - Please, define ED95 in the first time that is cited.

Reply 4: Thank you for this comment. ED95 is defined the first time that it is used.

Changes in the text: The ED_{95} of a neuromuscular blocking agent is the dose that, on average, will cause 95% suppression of the single twitch response to stimulation of the ulnar nerve.

Comment 5: Line 262-265 - Please, insert a reference to support the affirmation.

Reply 5: A reference has been added as suggested.

Changes in the text: The following reference has been added: Srivastava A, Hunter JM. Reversal of neuromuscular block. Br J Anaesth. 2009 Jul;103(1):115-29. doi: 10.1093/bja/aep093. Epub 2009 May 24. Erratum in: Br J Anaesth. 2009 Oct;103(4):622. Dosage error in article text. PMID: 19468024.

Comment 6: Line 266-268- Please, it should be interesting if the authors have cited a bit more about the mechanisms of neostigmine at neuromuscular junctions. Neostigmine, because of its mechanism of action that favors the ACh preservation at end plates, activates inhibitory presynaptic muscarinic autoreceptors causing, for example, Wedensky inhibition, improving neuromuscular transmission fade. There are several papers in literature dealing with the problem.

Reply 6: The editor raises an interesting side topic in this comment. The majority of the work involving Wedensky impact on neuromuscular transmission is quite old with Holt's review of the field being published in the early 1900's. We have chosen to include a brief discussion of presynaptic acetylcholine receptors and the impact of their inhibition on neuromuscular transmission.

Changes in the text: The following text was added: Of note, NMBAs also bind to presynaptic acetylcholine receptors causing decreased release of acetylcholine in response to neural stimulation and inhibition of neuromuscular transmission as demonstrated by increased fade in the TOF. In the presence of large concentrations of acetylcholine, the presynaptic block with

NMBA becomes noncompetitive, further complicating attempts to reverse deep levels of NMB with anticholinesterase. And Jonsson M, Gurley D, Dabrowski M, Larsson O, Johnson EC, Eriksson LI. Distinct pharmacologic properties of neuromuscular blocking agents on human neuronal nicotinic acetylcholine receptors: a possible explanation for the train-of-four fade. The Journal of the American Society of Anesthesiologists. 2006 Sep 1;105(3):521-33, Fagerlund MJ, Dabrowski M, Eriksson LI. Pharmacological characteristics of the inhibition of nondepolarizing neuromuscular blocking agents at human adult muscle nicotinic acetylcholine receptor. The Journal of the American Society of Anesthesiologists. 2009 Jun 1;110(6):1244-52, were referenced in the section.

Comment 7: Line 296-298 - Please, cite a reference for sugammadex mechanism of action.
Before the authors started to write specifically about the residual neuromuscular block, I missed a subsection about "pharmacological interactions". Thus, the section where they tell about the neostigmine and sugammadex and patients with renal failure could be expanded. For example, pharmacological interactions between neuromuscular blockers and other drugs eg. Cronic glucocorticoids tread patients; or those patients recovered of Sars-Cov-2 virus (Coronavirus).
Reply 7: The mechanism of action of sugammadex has been expanded and references incorporated (please see "A" below). A section on pharmacologic interactions has been added o the manuscript (see "B" below) and the section on renal failure has been expanded (See section "C" below).
Changes in the text:

A. Sugammadex encapsulates free rocuronium in the plasma so that it cannot enter the neuromuscular junction and bind to acetylcholine receptors and it increases the movement of rocuronium from the neuromuscular junction to the plasm by decreasing the concentration of free rocuronium there. One molecule of sugammadex binds noncovalently to 1 molecule or rocuronium, incorporating its steroidal rings into its hydrophobic central core. The affinity constant value of rocuronium for sugammadex is 25,000,000 M, which is about 2 ½ times greater than the affinity of vecuronium for sugammadex and, once bound, there is no evidence that the complex dissociates appreciably.

B. Pharmacologic Interactions of Reversal Medications

Both neostigmine and sugammadex interact with other medications. Neostigmine appears to potentiate anti-inflammatory medications. Neostigmine will also inhibit plasma cholinesterase and prolong the duration of action of medications metabolized by this enzyme, such as succinylcholine and mivacurium. Additionally, neostigmine may reduce the effectiveness of tricyclic antidepressants, such as amitriptyline and has been used to treat tricyclic antidepressant overdoses. On the other hand, the main pharmaceutical interaction with sugammadex is concern that it may bind to, and reduce the levels of, progesterone within the body. This is of special concern in individuals taking hormonal, progesterone-based, contraceptives and the manufacturer recommends that individuals using hormonal birth control use an additional contraceptive for 7 days after exposure to sugammadex. While sugammadex may reduce progesterone levels within the body, there has been no evidence supporting the assumption that the levels will drop enough to cause early cessation of pregnancy. In fact, there is no evidence in humans and a trial in which rats were exposed to high doses of sugammadex in the first trimester did not decrease progesterone levels or the rates of stillbirth. Since national consensus guidelines recommend the use of rocuronium as an alternative to succinylcholine for rapid sequence induction in pregnant patients, one can expect that sugammadex will be used to reverse neuromuscular blockade in the "cannot intubate – cannot ventilate" scenario. There is no published data on the presence of sugammadex in human breast milk. Because of its large molecular size and polarization, though, there is likely to be little maternal-fetal transfer of sugammadex.

C. Of the currently used NMBAs all have some component of renal elimination, Vecuronium and its metabolites have the greatest renal elimination and vecuronium has a prolonged duration of action in patients with decreased renal function, even the decreases in renal blood flow associated with advanced age. Neostigmine is also eliminated through the kidneys and has a decreased clearance in patients with renal disease (39).

Comment 8: Line 365 - Please, explain in the text what is BMI, I suppose to be body mass index?

Reply 8: BMI has been written out as body mass index and the abbreviation removed as it is not used elsewhere in the manuscript.

Changes in the text: In this study, risk factors for residual NMB included male gender, increased body mass index, and surgery at a community hospital.

Comment 9: Line 369 - Adverse effects of residual neuromuscular blockade. Overall the subsections is well discussed. However, I though the authors could improve the discussion about the aspects related to the anatomical and/or biophysical and/or molecular aspects that make the recovery of the adductor pollicis be different to the diaphragm. This is an obvious information of clinical relevance.

Reply 9: A description of the potential reasons for differing sensitivities has been included near the first mention of Donati's article.

Changes in the text: The varied responses of different muscle groups to NMBAs has been attributed to muscle type, with fast twitch muscles being relatively resistant to NMBAs, muscle fiber size, with sensitivity increasing with fiber size,, and blood flow, with faster onset and relative resistance in muscles with greater blood flow.

Comment 10: Line 398 - Adequate recovery from neuromuscular blockers - please besides describe about Myasthenic patients the authors should include some information about the Duchenne muscular dystrophy (DMD) patients related to theme of the review.

Reply 10: A description of NMBAs in patients with Duchenne's has been included. See below for added text.

Changes in the text: Duchenne Muscular Dystrophy (DMD) causes hypertrophy of muscle tissue due to fatty infiltration and a progressive decrease in muscle strength. Patients with DMD have a greater sensitivity to nondepolarizing NMBAs and a prolonged duration of action of these compounds. Anticholinesterases (neostigmine and pyridostigmine) can be used to reverse neuromuscular blockade in patients with DMD; as in otherwise healthy patients, there is marked interpatient variability in response to anticholinesterases. Sugammadex has also been used successfully in these patients and based on case reports allows complete recovery of neuromuscular transmission within 3 minutes of administration. As complications caused by residual neuromuscular blockade, such as respiratory failure and aspiration, also occur in patients with DMD, ensuring complete recovery of neuromuscular function to baseline after the conclusion of a surgical or diagnostic procedure is exceptionally important.

Comment 11: Line 422 - Please, change postynaptic for subsynaptic, is more appropriated since the nACh receptors are present at the subsynaptic membrane.

Reply 11: Subsynaptic has been added to the text with postsynaptic as most of the descriptions clinicans will read describe postsynaptic acetylcholine receptors.

Changes in the text: acetylcholine receptors at the subsynaptic or postsynaptic portion of the neuromuscular junction,

Comment 12: Figure 1 - whats is the source of the figures, please insert the souce. In addition, change the letter an for An capital letter at the beginning of the legend text.

Reply 12: The typographical error has been corrected and the source of the figure included.

Changes in the text: Figure 1: An image of the end-tidal carbon dioxide ($EtCO_2$) during mechanical ventilation. The curare cleft, indicated by the arrow in the figure may be an indication that the patient is attempting to breath with the downward slope of the cleft indicating a decrease in exhaled CO_2 with diaphragmatic contraction. Adapted from the internet: Facebook/marrowmedphotos/a.1529586703786652 (accessed 8/27/23)

Comment 13: Figure 3 - Please, insert the source of the figure. If was elaborated by the own authors should be written in the legend text. The same for figure 4 and 7.

Reply 13: As above, the source of the figures has been included in the legends. Please see below.

Changes in the text: figure 3. Placement of the electrodes just over the eyebrow should be avoided. Image of the face accessed on the internet: www.pinterest.com/pin/336362665890513583/ (accessed 8/27/23)

Figure 4. respectively, measured. Image of the legs accessed on the internet: runnersconnect.net/stride-frequency-height (accessed 8/27/23)

Figure 7. subsequently encapsulated and eliminated. Images of the structures obtained from: Neostigmine | C12H19N2O2+ | CID 4456 - PubChem (nih.gov)(accessed 10/3/23) and Sugammadex sodium (Org25969) | Neuromuscular Block Reversal | MedChemExpress (accessed 10/3/23)

Comment 14: On figures, since the review aims to be a practical guide for clinicians about the residual neuromuscular block, in my opinion it should bring a figure showing the particularities of the train-of-four, comparing the cited differences.

Reply 14: A figure such as this is available in several chapters and the information provided should not be new to readers of the article. The authors prefer to not copy what is likely to have already been reviewed by the reader.

Changes in the text: No changes.

Minor issues:

Comment 1: English- Overall the manuscript English style is well. However, the authors are encouraged to do a careful reading in the text, as there are some missing prepositions. For example, line 361, insert "of" before vecuronium.

Reply 1: Changes were made in the manuscript where missing prepositions were noted. Our expectation is that the copyeditors will address any that are still missing.

Changes in the text: There are too many to list here.

Reviewer B Comments

Comment 1: In the case of a review article, the consistency of words and phrases is very important because it contains a consistent content of a long sentence. The overall content flow description method lacks uniformity and readability. The wording of abbreviations is also muddled. For example, the case of end-tidal carbon dioxide is expressed as ETCO2.

Reply 1: ETCO2 is now defined in the text.

Changes in the text: exhaled end-tidal carbon dioxide ($EtCO_2$) ,

Comment 2: Please increase readability by marking the titles specified in "Outline" in the middle of the content. Currently, it is not at all clear where the contents are. For example, insert "b. Qualitative monitoring" between lines 155 and 156.

Reply 2: Headings have been bolded to increase their visibility.

Changes in the text: sample: Clinical Assessment of Depth of Neuromuscular Blockade

Comment 3: Please swap the positions of Sugammadex and Neostigmine in line 33.

Reply 3: Their positions were adjusted as suggested.

Changes in the text: Neostigmine and Sugammadex and Neostigmine and Sugammadex

Comment 4: From line 63, there is a sudden explanation about TOFR, which harms unity.

Reply 4: the wording has been revised.

Changes in the text: …neuromuscular block is defined by the muscular response to stimulation of a motor nerve, most often through evaluation of a train-of-four response or ratio (TOFR). The post-tetanic count (PTC) will define the level of profound neuromuscular blockade (before a response to train-of-four (TOF) stimulation occurs) and the response to TOF stimulation is used to guide the dosing of maintenance doses of neuromuscular blocking agents and reversal when neuromuscular blockade is no longer needed. The TOFR is obtained by stimulating a superficial nerve, such as the ulnar nerve, with four supramaximal stimuli at a frequency of 0.5 Hz (over the course of 2 seconds) and measuring the number and strength of the responses to the stimuli. A TOFR = 0.5 would have four responses to stimulation and the 4^{th} response would be 50% the strength of the first response. Adequate recovery of neuromuscular function, defined as a TOFR ≥ 0.9, is the degree of recovery necessary for safe extubation of the trachea. Residual paralysis, a TOFR < 0.9, which is associated with postoperative…

Comment 5: The abbreviation for NMBA is explained, but NMB is lacking.

Reply 5: NMB has now been defined when it first appears in the text

Changes in the text: Profound depths of neuromuscular blockade (NMB) are maintained intraoperatively.

Comment 6: The abbreviation for TOF is explained, but TOFR is lacking.

Reply 6: TOFR has been written out when the abbreviation first appears in the text

Changes in the text: train-of-four response or ratio (TOFR).

Comment 7: What about line 72 “PACU”?

Reply 7: The abbreviation PACU has been eliminated

Changes in the text: longer stays in the post-anesthesia care unit, and is both iatrogenic and avoidable.

Comment 8: From line 96, anticholinesterase includes NMBA, which is currently widely used, such as pyridostigmine as well as neostigmine. And to explain this, it would be nice to have a review of the role and mechanism of glycopyrrolate as an anti-antagonist.

Reply 8: Mention of pyridostigmine is now included. Additionally, the mechanism of action of anticholinestersess is discussed.

Changes in the text: Anticholinesterases (neostigmine and pyridostigmine) can be used to reverse neuromuscular blockade in patients with DMD and There are two different classes of reversal agents: anticholinesterases (neostigmine, edrophonium, pyridostigmine) of…

Neostigmine works as an indirect antagonist, inhibiting acetylcholinesterase – which is responsible for the breakdown of acetylcholine. The result is that the acetylcholine released from the presynaptic terminal is not metabolized and the levels of acetylcholine at the neuromuscular junction are increased to allowing for the competitive neuromuscular blockade of acetylcholine receptors to be at least partially overcome and neuromuscular transmission increased. Once acetylcholinesterase is completely inhibited, administration of additional anticholinesterase will not have any effect and if it administered when there are significant concentrations of NMBAs present, the competitive neuromuscular block cannot be overcome.

Comment 9: How about changing the phrase clinical exam in line 99 to clinical assessment with a sense of unity?

Reply 9: It is unclear what change the reviewer is seeking with this comment.

Changes in the text: No change was made.

Comment 10: It would be better to move the simple explanation about PTC from lines 114 to 119 to the front of the content.

Reply 10: PTC is mentioned earlier in the text when monitoring is discussed.

Changes in the text: The post-tetanic count (PTC) will define the level of profound neuromuscular blockade (before a response to train-of-four (TOF) stimulation occurs).

Comment 11: Do we need parentheses to explain again about the TOF stimulus on line 161?

Reply 11: Abbreviations were all adjusted and there are no more unnecessary parenthesis.

Changes in the text: As described above.

Comment 12: Is the content of lines 202 to 204 grammatically correct?

Reply 12: The word "demonstrated was added to complete the sentence.

Changes in the text: One study demonstrated slower recovery than…

Comment 13: cisartracurium on line 229. I think you will need references later.

Reply 13: references were added.

Changes in the text: reference: Weber V, Abbott TEF, Ackland GL. Reducing the dose of neuromuscular blocking agents with adjuncts: a systematic review and meta-analysis. Br J Anaesth. 2021 Mar;126(3):608-621. doi: 10.1016/j.bja.2020.09.048. Epub 2020 Nov 17. PMID: 33218672; PMCID: PMC8014939.

Comment 14: Starting from line 260, other drugs in the Anticholinesterase class also need a description.

Reply 14: the description has been included.

Changes in the text: Please see the response to comment 8 above.

Comment 15: On line 283, "This has been demonstrated since (25, 26)." What does this mean and what is it about?

Reply 15: This was an error. The incomplete phrase has been removed.

Changes in the text: TOFR with repeated stimulation. (25, 26) Similarly,…

Comment 16: What is RECITE-US on line 362 and POPULAR on line 429?

Reply 16: A reference for the RECITE study has been included. The POPULAR study was already referenced.

Changes in the text: Saager L, Maiese EM, Bash LD, Meyer TA, Minkowitz H, Groudine S, et al. Incidence, risk factors, and consequences of residual neuromuscular block in the United States: The prospective, observational, multicenter RECITE-US study. J Clin Anesth. 2019;55:33-41.

Interestingly, the POPULAR study (70) found that the use of…

Comment 17: When describing references in between, when describing multiple authors, “et al.” should be attached. For example, in line 394.

Reply 17: Done.

Changes in the text: There are too many changes to list here.

Comment 18: The “Summary” is poor and needs more information.

Reply 18: The Conclusions have been revised and are now, hopefully, more acceptable to the reviewer.

Changes in the text: With the increasing use of neuromuscular blocking agents in clinical practice and documented incidence of inadequate recovery of neuromuscular function on arrival to the post-anesthesia care unit, it is imperative that clinicians adapt their practices to decrease the postoperative complications that are secondary to the use of these agents. Eliminating residual neuromuscular blockade is entirely feasible within modern anesthetic practice. Technological research and advancement have made quantitative measurement of depth of neuromuscular blockade possible so that qualitative observation and assessment of recovery of neuromuscular function and all the error associated therewith is no longer necessary. With quantitative measurement every time a patient receives a neuromuscular blocking agent, clinicians can dose NMBAs to provide the necessary depth of neuromuscular blockade intraoperatively, adjust the dose of the reversal agent based on the results of monitoring, ensure complete recovery of neuromuscular function before extubating the patient, and decrease the incidence of the complications associated with residual neuromuscular blockade. Just as using the pulse oximeter in modern practice reduces the frequency of peri anesthetic hypoxia, the use of quantitative neuromuscular monitors of depth of NMB will further enhance the safety of modern anesthesia practice.

Reviewer C Comments

Comment 1: Abstract: Please ensure that the abstract is structured appropriately with sections for Background and Objective, Methods, Key Content and Results, and Conclusions. I was unable to locate an abstract in the manuscript provided.

Reply 1: An Abstract has been included.

Changes in the text:

Abstract

Background and Objective: Although millions of patients receive neuromuscular blocking agents each year as part of an anesthetic, residual neuromuscular blockade remains a too-frequent occurrence and its adverse consequences continue to negatively impact patient outcomes. The goal of this manuscript is to provide clinicians with the information they need to decrease the incidence of residual neuromuscular blockade.

Methods: Published literature was reviewed and incorporated into the narrative as appropriate. Search terms for articles included nondepolarizing neuromuscular blocking agents, residual neuromuscular blockade, monitoring depth of neuromuscular blockade, qualitative monitoring, quantitative monitoring, reversal agents, sugammadex, and anticholinesterases.

Key Content and Findings: This review will define what is currently considered adequate recovery of neuromuscular function, discuss and compare the different modalities to determine the depth of neuromuscular blockade, discuss the currently available neuromuscular blocking agents – including their durations of action and dosing, describe the incidence and complications associated with residual neuromuscular blockade, and discuss reversal of nondepolarizing neuromuscular blockade with neostigmine or sugammadex. Nondepolarizing neuromuscular blocking agents are commonly used as part of a general anesthetic. Understanding the pharmacology of the neuromuscular blocking and reversal agent, in combination with quantitative monitoring of depth of neuromuscular blockade is essential to avoid residual paralysis.

Conclusions: Quantitative monitoring and dosing of either neostigmine or sugammadex based on the results of monitoring is essential to eliminate residual neuromuscular blockade associated with the use of nondepolarizing neuromuscular blocking agents.

Comment 2: Main Text: The text should be organized into sections as follows: Introduction, Methods, Main body (with subsections defined by the authors), and Conclusions. While the manuscript does provide an Introduction and Methods section, please ensure this structure is followed throughout.

Reply 2: The authors believe that in adding a "Methods" section, this request has been accommodated.

Changes in the text: A "Methods" Section added.

Comment 3: Table: Include a table detailing the search strategy in the Methods section.

Reply 3: A search strategy summary table is added.

Changes in the text: Table 1.

Comment 4: Narrative Review Checklist: As a narrative review, your submission should adhere to the Narrative Review Checklist. Please include this Checklist as supplementary material with your submission. This was not located in the manuscript provided.

(Note: The detailed author guidelines for Review Article can be found here: https://atm.amegroups.org/pages/view/guidelines-for-authors#content-2-2-3)

Reply 4: A narrative review checklist is completed.

Changes in the text: Narrative review reporting checklist.

Comment 5: Introduction and Background (Lines 51-92): While the introduction provides good context and background, a brief overview of the main findings or conclusions of the study in this section could be beneficial for setting the reader's expectations.

Reply 5: Thank you for this comment. The text has been revised as suggested by the reviewer.

Changes in the text: Adequate recovery of neuromuscular function depends on appropriate dosing of NMBAs and reversal agents as well as intraoperative quantitative monitoring of depth of NMB. As will be described in this review, use of these guiding principles can minimize the risk of residual NMB in patients receiving NMBAs and decrease its associated risks.

Comment 6: Methodology and Discussion (Lines 93-224): This section could benefit from a clearer structure with well-defined sub-sections (e.g., 'Clinical Assessment', 'Qualitative Assessment', 'Quantitative Assessment') for improved readability.

Reply 6: The suggested headings have been added to the body of the text.

Changes in the text: The following headings were added:

Clinical Assessment of Depth of Neuromuscular Blockade

Qualitative Assessment of depth of Neuromuscular Blockade

Quantitative Assessment of Depth of Neuromuscular Blockade

Comment 7: Nondepolarizing Neuromuscular Blocking Agents (Lines 225-257): Consider providing a brief introduction to these agents and their use before delving into specifics.

Reply 7: An introduction to NMBAs was added to this section of the manuscript.

Changes in the text: NMBAs were developed to facilitate endotracheal intubation, provide a still surgical field, and allow mechanical ventilation. There have been a number of different nondepolarizing NMBAs used over the years. The majority of them have had one of two basic structures – either steroidal or benzylisoquinoline and all have been classified on their durations of actions (short-, intermediate-, or long-). Nondepolarizing NMBAs in the most simplistic of descriptions, cause NMB by competitively inhibiting the acetylcholine receptor in the neuromuscular junction of the muscle membrane by binding to one or both of the receptor's acetylcholine binding sites. With this inhibition, the acetylcholine receptor cannot be activated to allow the influx of sodium and efflux of potassium required for neuromuscular transmission. As briefly discussed later in this review, NMBAs also interact with the presynaptic neuronal acetylcholine receptors to impact the release of acetylcholine from the nerve terminal after the application of a stimulus.

Comment 8: Reversal Agents (Lines 258-326): This section could benefit from more distinct sub-sections such as 'Mechanism of Action', 'Dosing', and 'Efficacy and Risks'. Also, more information about why reversal agents are needed, and what risks or complications they help to avoid could be beneficial.

Reply 8: The section of the manuscript discussing reversal agents now includes subheadings to better guide the reader. The authors feel that the risks of residual neuromuscular blockade are

mentioned throughout the chapter and do not warrant repeating in this section.

Changes in the text: Headings now included in this section:

Reversal Agents

Neostigmine and Sugammadex

Dosing of Reversal Agents

Neostigmine and Sugammadex in Patients with Renal Failure

Pharmacologic Interactions of Reversal Medications

Comment 9: Neostigmine and Sugammadex in Patients with Renal Failure (Lines 327-341): Please define what renal failure is and why it can affect the function of these agents.

Reply 9: The requested changes have been made in the text and appropriate references added.

Changes in the text: Of the currently used NMBAs all have some component of renal elimination, Vecuronium and its metabolites have the greatest renal elimination and vecuronium has a prolonged duration of action in patients with decreased renal function, even the decreases in renal blood flow associated with advanced age.

Comment 10: Residual Neuromuscular Blockade (Lines 342-368) and Adverse Effects of Residual Neuromuscular Blockade (Lines 369-382): Please provide some examples of the "minor to significant" effects mentioned for a better understanding of the range of potential outcomes.

Reply 10: Examples have been included.

Changes in the text: These adverse effects range from relatively minor (such as generalized fatigue) to significant (respiratory failure requiring reintubation) – with some persisting beyond recovery of neuromuscular function to a TOFR = 1.0 (52).

Comment 11: Adequate Recovery of Neuromuscular Function (Lines 398-438): Please emphasize the need for more accurate monitoring.

Reply 11: Thank you for this suggestion. The suggested addition to the text has been included.

Changes in the text: Quantitative monitoring of depth of neuromuscular blockade is essential not only to guide intraoperative dosing of NMBAs but, as discussed previously in this review, to also determine the dose of reversal agent that should be administered and to verify that adequate

recovery of neuromuscular function has occurred at the completion of surgery. While quantitative monitoring improves a clinician's ability to identify residual neuromuscular blockade, the monitors must work reliably even in an environment that is bound to provide both electrical interference and movement of the extremity where the monitoring is being done. Improved monitoring is essential since evidence, both old and new, indicates that a TOFR $\geq$ 0.9 may not reflect "full".