Earn CE/CME
Release Date: October 1, 2020 Expiration Date: October 1, 2021
Clinical UPDATE

Evaluating the Correlation Between Neuromuscular Blockade Reversal and Pulmonary Outcomes After Surgery: Implications for Clinical Practice

ESTIMATED TIME TO COMPLETE ACTIVITY
1 hour

TARGET AUDIENCE
This activity is intended for anesthesiologists, certified registered nurse anesthetists, and anesthesia providers.

PROGRAM OVERVIEW
This program briefly discusses the incidence and consequences of postoperative pulmonary complications (PPCs) and focuses on residual neuromuscular blockade (rNMB) as a modifiable risk factor for PPCs. Strategies to reduce the risk for rNMB are outlined, and evidence on the efficacy and safety of neostigmine or sugammadex for reversal of neuromuscular blockade (NMB) is summarized. Finally, recent data from both randomized controlled trials and database studies on the incidence of PPCs after the administration of neostigmine or sugammadex are reviewed.

EDUCATIONAL OBJECTIVES
After completing this activity, the participant should be better able to:

1. Cite the incidence of rNMB and PPCs after surgical procedures.
2. Describe strategies to manage NMB that reduce the risk for rNMB.
3. Summarize the data on PPCs after administration of neostigmine or sugammadex for reversal of NMB.

FACULTY
Timur Dubovoy, MD (Program Chair)
Assistant Professor
Department of Anesthesiology
University of Michigan Medical School
Ann Arbor, Michigan

Glenn S. Murphy, MD
Clinical Professor
The University of Chicago Pritzker School of Medicine
Chicago, Illinois
Director, Clinical Research
NorthShore University HealthSystem
Evanston, Illinois

Brad J. Phillips, DNP, RN, CRNA, NE-BC
Adjunct Clinical Instructor
University of Michigan School of Nursing
Assistant Chief Nurse Anesthetist
Michigan Medicine
Ann Arbor, Michigan

The authors thank Stephanie Breslan, MS, for writing support in preparing this manuscript.

JOINT ACCREDITATION STATEMENT
In support of improving patient care, this activity has been planned and implemented by the Postgraduate Institute for Medicine and Miller Medical Communications, LLC. Postgraduate Institute for Medicine is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the health care team.

PHYSICIAN CONTINUING MEDICAL EDUCATION
The Postgraduate Institute for Medicine designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

MOCA 2.0® CREDIT
This activity contributes to the patient safety CME requirement for the CME component of the American Board of Anesthesiology's (ABA) redesigned Maintenance of Certification in Anesthesiology™ (MOCA®) program, known as MOCA 2.0®. Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1 MOCA 2.0® credit and 1 patient safety MOCA credit in the ABA MOCA program. Participants will earn MOCA 2.0® credits equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to the ACCME for the purpose of granting ABA MOCA 2.0® credit. Please consult the ABA website, www.theABA.org, for a list of all MOCA 2.0® requirements. Maintenance of Certification in Anesthesiology™ program and MOCA® are registered trademarks of the American Board of Anesthesiology®. MOCA 2.0 is a registered trademark of the American Board of Anesthesiology®.

DISCLOSURE OF CONFLICTS OF INTEREST
Postgraduate Institute for Medicine (PIM) requires instructors, planners, managers, and other individuals who are in a position to control the content of this activity to disclose any real or apparent conflict of interest (COI) they may have as related to the content of this activity. All identified COI are thoroughly vetted and resolved according to PIM policy. PIM is committed to providing its learners with high quality activities and related materials that promote improvements or quality in health care and not a specific proprietary business interest of a commercial interest.

Faculty Disclosures

- Timur Dubovoy, MD: contracted research from Merck & Co., Inc
- Glenn S. Murphy, MD: fees for non-CME/CE services received directly from a commercial interest or their agents (eg, speakers' bureaus) from Merck & Co., Inc
- Brad J. Phillips, DNP, RN, CRNA, NE-BC: Dr. Phillips has nothing to disclose.

Planners and Managers

- The PIM planners and managers have nothing to disclose.
- The Miller Medical Communications, LLC, planners and managers have nothing to disclose.

METHOD OF PARTICIPATION AND REQUEST FOR CREDIT
There are no fees for participating and receiving CME/CE credit for this activity. During the period October 1, 2020 through October 1, 2021 participants must read the learning objectives and faculty disclosures and study the educational activity. To receive acknowledgment for completing this activity, participants should complete the post-test and evaluation on **www.CMEZone.com/CU207p**. Upon registering and successfully completing the post-test with a score of 75% or better and the activity evaluation, your certificate will be made available immediately.

MEDIA
Print (internet version also available)

COMPUTER SYSTEM REQUIREMENTS
- Operating system: Windows or Macintosh
- Media viewing requirements: Flash Player or Adobe Reader
- Supported browsers: Microsoft Internet Explorer, Firefox, Google Chrome, Safari, and Opera
- A good Internet connection

DISCLOSURE OF UNLABELED USE
This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. The planners of this activity do not recommend the use of any agent outside of the labeled indications. The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of the planners. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

DISCLAIMER
Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications and/or dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

ACCREDITOR CONTACT INFORMATION
For questions regarding accreditation, please contact the accredited provider at www.pimed.com.

PIM Postgraduate Institute for Medicine
Professional Excellence in Medical Education
MMC Miller Medical Communications, LLC.

Jointly provided by Postgraduate Institute for Medicine and Miller Medical Communications, LLC

This activity is supported by an independent educational grant from Merck & Co., Inc.

CMEZONE®

This activity is distributed by CMEZone.com.

Introduction

Postoperative pulmonary complications (PPCs) are heterogeneously defined but generally include any complication of the respiratory system after the administration of anesthesia during a surgical procedure.[1] Abbott and colleagues recently performed a systematic review using a 3-stage Delphi consensus process to define PPCs as a composite of respiratory diagnoses that share common pathophysiological mechanisms of pulmonary collapse and airway contamination, including[2]:

- Atelectasis (computed tomography or chest radiograph)
- Pneumonia (Centers for Disease Control and Prevention criteria)
- Acute respiratory distress syndrome (Berlin consensus definition)
- Pulmonary aspiration (clinical history and radiological evidence)

Reports of the incidence of PPCs vary widely because of differing definitions, but it is estimated that PPCs may occur after up to 40% of surgeries.[3] A recent multicenter observational study found that 14% of patients experienced 2 or more PPCs.[4] Respiratory failure, the most common PPC, has been identified as the fourth most common patient safety event by the Agency for Healthcare Research and Quality.[5] It is vital for anesthesia providers to recognize that more than 10% of PPCs occur days later,[3] long after the patient is delivered to the postanesthesia care unit (PACU), suggesting that awareness of the frequency of PPCs may be low.

PPCs have significant economic effects, including increased health care utilization costs. Patients with PPCs have a 91% higher rate of unplanned admissions to intensive care units (ICUs),[5] and even mild PPCs are associated with significantly increased length of hospital stay and number of emergency department visits and 30-day readmissions.[3,4] One study found that additional expenditures attributable to PPCs exceeded $25,000 per admission.[1] PPCs also increase both short- and long-term mortality. Approximately 20% of patients with a PPC will die within 30 days vs 3% of those without a PPC, and 90-day mortality rates are approximately 25% and 1%, respectively.[1] A long-term observational study found that mortality risk remains high at 5 years; more than 70% of patients with a PPC will die in this time frame vs 41% without a PPC.[1]

Preoperative risk stratification is essential to optimize perioperative management. Several nonmodifiable and modifiable patient- and procedure-related risk factors contribute to the risk for developing a PPC (**Table 1**).[1,5]

This article focuses on the role of neuromuscular blocking drugs (NMBDs) and residual neuromuscular blockade (rNMB) in the development of PPCs and recent evidence on the efficacy of reversal agents in reducing the incidence of PPCs.

rNMB Definition and Incidence

rNMB is defined as inadequate neuromuscular recovery after the administration of NMBDs, as measured using a quantitative train-of-four ratio (TOFr) <0.9.[6] The incidence of rNMB has been studied widely, and reported values vary based on the method of assessment, time of measurement, type and dose of NMBD, degree of neuromuscular blockade (NMB), type of pharmacologic reversal, and patient factors.[6] The Residual Curarization and its Incidence at Tracheal Extubation (RECITE) studies were prospective, multicenter, anesthetist-blind observational studies of 1,571 patients in China, 302 in Canada, and 255 in the United States who were undergoing elective abdominal surgery and received general anesthesia.[7-9] The studies were designed to assess the incidence and severity of rNMB defined as a TOFr <0.9 according to acceleromyographic quantitative monitoring. In China, 58% of patients had rNMB at tracheal extubation despite 78% of patients receiving neostigmine for reversal of NMB.[7] Nearly 1 in 4 had a TOFr <0.6. Approximately 64% of patients in Canada had a TOFr <0.9 at tracheal extubation with similar use of neostigmine as China for reversal of NMB.[8] Finally, the incidence of rNMB in the

Table 1. Risk Factors for Developing a PPC[1,5]

	Patient	Procedure
Nonmodifiable	• Age • Male sex • ASA ≥2 • Frailty • CVA	• Surgical site, such as upper abdominal, AAA, thoracic, neurosurgery, head and neck, and vascular • Emergency surgery • Duration of procedure (longer procedures associated with higher risk) • Re-operation • Multiple general anesthetics during admission
Modifiable	• Chronic health conditions, including COPD, asthma, CHF, OSA, hypertension, diabetes, obesity, and GERD • Smoking	• Mechanical ventilation strategy • General anesthesia • Long-acting NMBDs and TOFr <0.7 in PACU • rNMB • Intermediate-acting NMBDs with surgical time <2 hours • Open abdominal surgery • Perioperative nasogastric tube • Intraoperative blood transfusion

AAA, abdominal aortic aneurysm; **ASA,** American Society of Anesthesiologists; **CHF,** congestive heart failure; **COPD,** chronic obstructive pulmonary disease; **CVA,** cerebrovascular accident; **GERD,** gastroesophageal reflux disease; **NMBD,** neuromuscular blocking drug; **OSA,** obstructive sleep apnea; **PACU,** postanesthesia care unit; **rNMB,** residual neuromuscular block; **TOFr,** train-of-four ratio.

United States was 65%, with nearly 1 in 3 patients demonstrating a TOFr <0.6 at tracheal extubation despite nearly all receiving neostigmine for reversal of NMB.[9] Similar incidences of rNMB were reported more than 40 years ago,[10] and yet more than 50% of anesthesiologists reported in a survey that the incidence of clinically significant postoperative rNMB was less than 1%. Nearly 90% claimed they had never observed a patient exhibiting postoperative residual paralysis.[11]

There is a disconnect between how often rNMB occurs and how often clinicians think it occurs. The reason clinicians do not see rNMB in their practice is that they are not monitoring for it.

Physiologic Effects of rNMB and Associated PPCs

The introduction of NMBDs more than 50 years ago was a groundbreaking advance in general surgery, facilitating endotracheal intubation and improving surgical conditions; however, specific risks quickly become apparent. A study by Beecher et al in the 1950s found a 6-fold increase in deaths during the perioperative period after NMBD administration.[12]

Respiratory physiology is altered immediately on the induction of general anesthesia, as the central respiratory drive is suppressed, muscle function is altered, and lung volume is reduced.[1,5] In the postoperative period, respiratory function may be altered further by even small degrees of rNMB,[5] leading to impaired pharyngeal and upper airway function, swallowing dysfunction, aspiration, decreased hypoxic ventilatory drive,[6] and postoperative complications, including reintubation, delayed emergence, unplanned ICU admission, prolonged PACU and hospital stays, atelectasis and/or pneumonia, and increased mortality.[6,13,14]

A study of 202 adult patients receiving NMBDs found that critical respiratory events (CREs) were 3 times more likely in patients with a TOFr <0.9 (51% vs 16%; $P<0.001$),[15] and another study of 415 patients receiving intermediate-acting NMBDs found that among patients with a CRE, 84% had a TOFr ≤0.9 ($P<0.001$).[16] Overall, undetected rNMB is associated with increased risk for CREs in an estimated 112,000 US patients annually.[17] Although most patients who achieve a TOFr >0.9 have recovered sufficiently from NMB, impairment of respiratory function and muscle weakness may remain even after achieving a TOFr >0.9.[18,19] In an exploratory analysis of the POPULAR study, a multicenter, prospective, observational study of nearly 23,000 patients, tracheal extubation at a TOFr >0.95 vs >0.9 reduced the risk for PPCs to 3.5% from 11%.[20] Broens and colleagues found that even after full reversal of NMB, hypoxic chemoreflex is not fully restored.[21]

Management of Neuromuscular Block

The goal of both surgeons and anesthesia providers is to get a patient through a surgical procedure safely; however, distinct and disparate clinical focuses and poor communication and collaboration can lead to inadvertent but avoidable patient harm.[22] One clinical scenario in which disagreement and poor collaboration occurs is related to the administration of NMBDs. According to a survey of more than 500 surgeons and anesthesiologists, surgeons request additional NMBDs in approximately 25% of surgeries, most often during the final hour of the procedure, but anesthesia providers often disagree with the request due to concern for postoperative ventilatory function.[22] A mutual plan and decision only occurs in one-third of surgical cases.[22] Answine and Lamberg stated in response to a case report of such a scenario, "*All have to be on board with the benefits and potential complications when re-administration of NMBDs occurs, especially near the end of the surgical case. It should be obvious to all providers that these patients may have a prolonged recovery prior to extubation and more time may be needed in the operating room or the PACU before appropriate spontaneous respirations are returned.*"[23]

Anesthetized surgical patients paralyzed with NMBDs have been described as the most vulnerable patients in health care[24]; thus, it is imperative that surgeons and anesthesiologists work collaboratively to optimize surgical conditions while minimizing the risk for rNMB in order to improve outcomes for these patients.

The systems-based care team model often used by anesthesia providers can also lead to poor communication and collaboration that result in inadequate handoff of information between intraoperative providers. This handoff is frequently rushed and poorly structured, resulting in adverse patient outcomes.[25]

Most literature highlights the importance of structured PACU handoff, but intraoperative structured handoffs are arguably as important for maintaining the integrity of the anesthesia care plan.

The appropriate use of NMBDs involves careful consideration of the agent used, the timing of administration, and the total amount given. In general, short-acting agents such as rocuronium, vecuronium, cisatracurium, and atracurium are preferable over long-acting NMBDs such as pancuronium.[26] It is important to recognize, however, that the use of shorter-acting NMBDs has not reduced the incidence of rNMB substantially.[27,28] Appropriate dosing and timing of NMBDs is also essential. For example, the duration between administration of the last dose of rocuronium to recovery is longer and more variable than that for cisatracurium.[29] Furthermore, repeated administration increases the duration and variability of recovery associated with rocuronium.

NMBDs may not be necessary for all surgical procedures, and the decision to use them should be individualized.[26] Deep neuromuscular block (post-tetanic count [PTC] of 1-2) should be avoided when clinically appropriate[26] and may only be needed in certain ophthalmic, laryngeal, neurosurgical, thoracic, cardiac, microsurgical, robotic, and laparoscopic surgeries, according to current research.[30–32]

The use of neuromuscular monitoring is critical to patient safety and avoidance of rNMB. Furthermore, appropriate quantitative neuromuscular monitoring may reduce the risk for PPCs.[20,33] The 2017 *Consensus Statement on Perioperative Use of Neuromuscular Monitoring* strongly recommended quantitative monitoring.[17] However, fewer than 20% of US clinicians use quantitative monitors routinely,[11] mainly because an

easy-to-use, accurate, and reliable quantitative monitor has not been available for routine clinical use.[34] However, the FDA recently approved several new quantitative monitors that require minimal setup times and are easier to use than earlier acceleromyography and electromyography devices. For example, small, portable, electromyography-based devices that require minimal setup time include TetraGraph[35] and TwitchView.[36] The StimPod[37] and TOFscan[38] devices use 3-dimensional acceleromyography technology and provide TOF data without requiring calibration. Modules and pods for anesthesia machines, such as the Infinity Trident NMT SmartPod,[39] are also available.

The consensus statement authors acknowledge that access and education need to improve for quantitative monitoring to become standard of care; in the interim, at a minimum, the use of a peripheral nerve stimulator (PNS) should be mandatory in any patient receiving an NMBD.[17] It is important to recognize that although PNSs are widely available in the United States, they have limitations. For example, they cannot confirm the absence of residual paralysis and instead rely on subjective assessment of the strength of twitches.[40] The TOFr can be as low as 0.4 when no fade is detected with TOF nerve stimulation[41]; this has been referred to as the zone of blind paralysis.[40] Consequently, the consensus statement authors suggest that visual and tactile evaluation of TOFr is inadequate and could increase the risk for undetected rNMB and subsequent CREs. Strategies to optimize the use of PNS include: 1) initiating monitoring before NMBDs are administered to confirm appropriate electrode placement, 2) monitoring at the adductor pollicis muscle by stimulating the ulnar nerve, and 3) using the PNS at the time of reversal to determine the timing and dose of the reversal agent.[40]

Providers should verify that the operating room is equipped with a functional neuromuscular monitor that is routinely used for monitoring NMB as a standard of care. Providers should also be trained on appropriate electrode placement.

Reversal of NMB

Spontaneous Recovery

Spontaneous recovery after administration of an NMBD occurs as the drug is metabolized and excreted, allowing neuromuscular function to return. As many as 65% of US anesthesiologists routinely allow spontaneous recovery to occur,[11] presumably making the decision based on the dose of and time since the last administration of an NMBD. However, one study found that after a single 2×ED_{95} dose of an intermediate-acting NMBD, nearly 40% of patients had not achieved a TOFr >0.9 2 hours later.[42] Even a small rocuronium dose of 1×ED_{95} or 25 mg results in rNMB in 21% of patients approximately 3 hours later.[43]

Because of the different durations of action of NMBDs and the significant variability in the rate at which patients metabolize NMBDs, Brull and Naguib urged clinicians in their editorial, *How to catch unicorns (and other fairytales)*, that the decision to use pharmacologic antagonism and determine readiness for tracheal extubation should never be made based on the time since last administration of an NMBD.[44]

A reversal agent should always be administered unless quantitative monitoring is used to verify full neuromuscular recovery.

Pharmacologic Reversal With Neostigmine

Neostigmine has been available in the United States since the 1930s but was only formally approved by the FDA to reverse the effects of NMBDs in 2013.[45,46] Neostigmine is an anticholinesterase that indirectly increases the concentration of acetylcholine (ACh) in the neuromuscular junction by blocking acetylcholinesterase, the enzyme that breaks down ACh. As the ACh concentration increases, the competition between the NMBD and ACh favors ACh, allowing the NMB to be overcome.[47] The limitation of neostigmine is that it demonstrates a ceiling effect: Once acetylcholinesterase has been fully inhibited, the maximum concentration of ACh has been achieved.[47] Thus, in the presence of deeper block, involving higher plasma concentrations of NMBD, the concentration of ACh is not high enough to favor binding to nicotinic ACh receptors.

Consequently, total twitch suppression at the time of reversal should be avoided, as this depth of block cannot be reversed promptly by neostigmine.[48,49] From a TOF count of 1, neostigmine reversal to a TOFr >0.9 takes 29 minutes on average, with a range of 9 to 76 minutes. From a TOF count of 2, reversal with neostigmine takes an average of 23 minutes but ranges from 8 to 57 minutes. Similarly, from TOF counts of 3 and 4, neostigmine reversal takes an average of 16 and 10 minutes with ranges of 7 to 44 minutes and 5 to 26 minutes, respectively.[50] These data highlight the risk for rNMB when clinicians do not allow sufficient time for neostigmine to exert its effects before tracheal extubation. In a study of 120 patients, clinicians were ready to extubate the trachea within 8 minutes of neostigmine administration. The study found the mean TOFr was 0.67 but only 12% of patients had reached full neuromuscular recovery.[51] Indeed, nearly 90% of anesthesiologists report that they extubate the trachea within 5 to 10 minutes after neostigmine administration.[16]

Despite its limitations, neostigmine can be effective when used appropriately. Neostigmine 0.02 to 0.07 mg/kg should be administered only after neuromuscular function has returned to a TOF count of 4, and at least 15 minutes should be allowed before tracheal extubation is performed.[34] Higher or repeat doses do not decrease the time to neuromuscular recovery and are not recommended. Full doses (0.05-0.07 mg/kg) administered in the presence of full neuromuscular recovery may cause transient, clinically insignificant weakness that does not affect postoperative symptoms.[43]

Unmitigated cholinergic activation from neostigmine can lead to bronchospasm and bradycardia, necessitating coadministration of muscarinic receptor antagonists, such as atropine or glycopyrrolate.[47] These agents in turn, can be associated with side effects of dry mouth, urinary retention, and blurred vision.[52]

Pharmacologic Reversal With Sugammadex

Sugammadex is a synthetic, γ-cyclodextrin selective relaxant binding agent that forms high-affinity complexes in a 1:1 ratio with rocuronium and to a lesser degree vecuronium, but has no affinity for

benzylisoquinolinium compounds or succinylcholine.[34,53] Sugammadex was approved by the FDA in 2015.[53]

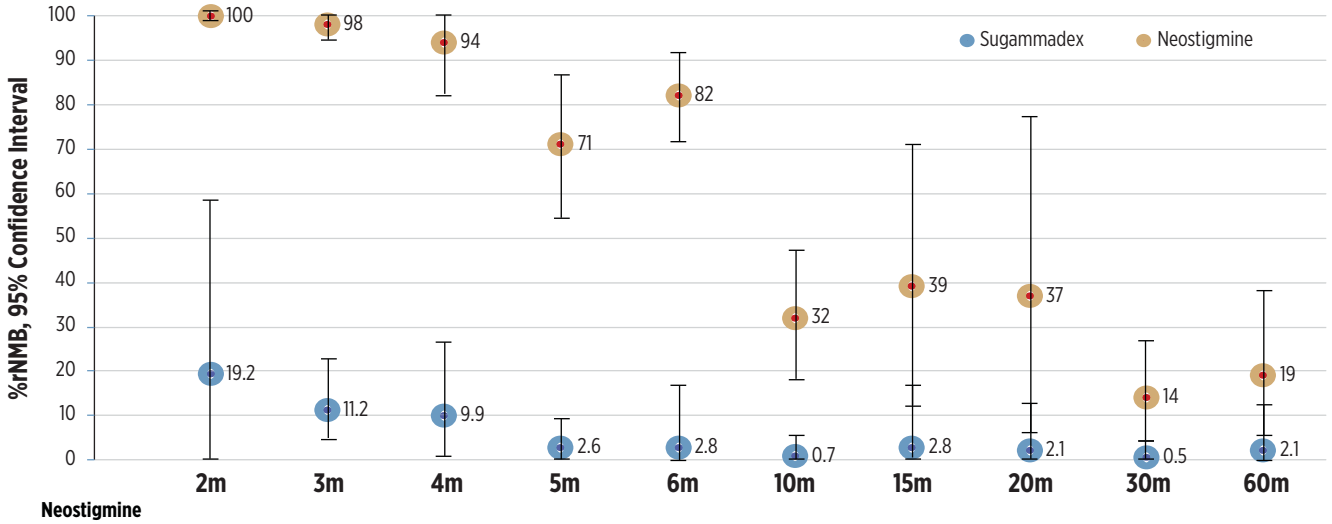
The recommended sugammadex dose depends on the depth of block; therefore, monitoring for twitch responses is necessary.[53] Without proper monitoring, the incidence of rNMB after sugammadex administration may be increased.[34] For routine reversal if recovery has reached a TOF count of 2, the dose is 2 mg/kg, and the average time to reach a TOFr >0.9 is 2 minutes. For routine reversal if recovery has reached a PTC ≥2, the recommended dose is 4 mg/kg, and the average time to reach a TOFr >0.9 is 3 minutes.[53] For emergent reversal from rocuronium, such as in failed rapid sequence intubation, a dose of 16 mg/kg can be used 3 minutes after a single 1.2-mg/kg dose of rocuronium. Dose recommendations for elderly patients are the same as for younger individuals, but expected recovery time is slightly slower.[53] Recommended dosing for children aged 2 to 17 years is 2 mg/kg at the reappearance of the second twitch response to TOF stimulation.[54] The dose necessary to reverse vecuronium-induced neuromuscular block is the same as for routine reversal, but the speed of recovery to TOF >0.9 is slower.

Sugammadex is not recommended for use in patients with creatinine clearance <30 mL/min because of the long elimination time of the sugammadex–NMBD complex.[53] Sugammadex should be used with caution in patients taking toremifene, an estrogen receptor modulator used in the treatment of metastatic breast cancer, due to a potential displacement reaction. Patients taking oral contraceptives should be advised to follow label instructions for a missed dose of contraceptive after sugammadex administration because of likely binding to steroidal oral contraceptives; patients taking oral and non-oral hormonal contraceptives should use an additional, non-hormonal contraceptive or back-up method for 7 days.[53] It is important to provide patient education and communicate with the PACU staff (via direct communication or order set) if concerns related to the need for patient education arise.

Sugammadex has been demonstrated to be safe and well tolerated. A retrospective analysis of nearly 15,500 patients in Japan found that 0.22% of patients had a hypersensitivity reaction over a 3-year period.[55] A retrospective analysis of sugammadex clinical trials found no cases of anaphylaxis among more than 3,500 patients,[56] and postmarketing safety surveillance of 11.5 million patients who have received sugammadex has shown a rate of anaphylaxis of 0.01%.[56] The 3-year retrospective analysis in Japan found only 6 cases, at a rate of 0.039%.[55]

rNMB and PPCs After Neostigmine vs Sugammadex Administration

Neostigmine and sugammadex have been studied comparatively in more than 50 randomized controlled trials (RCTs) and numerous systematic reviews and meta-analyses. The most recent meta-analysis, by Raval and colleagues, included 20 RCTs and found that, for moderate block, 81% of patients who received sugammadex had a TOFr >0.9 at 2 minutes, which increased to 99.3% at 10 minutes. Conversely, no patients who received neostigmine had reached a TOFr >0.9 at 2 minutes and only 68% did so at 10 minutes (**Figure 1**).[57] The percentage to reach a TOFr >0.9



Neostigmine	2m	3m	4m	5m	6m	10m	15m	20m	30m	60m
Studies, n	4	4	3	6	3	7	4	3	5	2
Patients, n	182	263	152	340	152	449	173	152	353	87

Sugammadex	2m	3m	4m	5m	6m	10m	15m	20m	30m	60m
Studies, n	3	3	2	4	2	3	2	2	3	2
Patients, n	122	212	93	241	93	241	93	93	241	93

Figure 1. Proportion of patients with rNMB after antagonism of moderate block.[57]

Reprinted from *Journal of Clinical Anesthesia*, 64, Raval AD, Uyei J, Karabis A, Bash LD, Brull SJ, Incidence of residual neuromuscular blockade and use of neuromuscular blocking agents with or without antagonists: a systematic review and meta-analysis of randomized controlled trials, 109818, Copyright 2020 [Epub ahead of print], with permission from Elsevier.

from deep block was 89% in the sugammadex group at 10 minutes and zero in the neostigmine group. The authors concluded that sugammadex is faster and more effective at reversing NMB than neostigmine.

The results from Raval and colleagues support a previous Cochrane systematic review and meta-analysis of 41 studies including more than 4,200 patients.[58] This study found that the time to achieve a TOFr >0.9 from 2 twitches was 2 minutes after administration of sugammadex 2 mg/kg and approximately 13 minutes after neostigmine 0.05 mg/kg. The reversal of deep block (post-tetanic count of 1-5) to TOFr >0.9 was approximately 3 minutes after administration of sugammadex 4 mg/kg and 49 minutes after neostigmine 0.07 mg/kg. This meta-analysis also examined adverse events (AEs) and found significantly fewer composite AEs in the sugammadex group than the neostigmine group (risk ratio: 0.6; 95% confidence interval [CI], 0.49-0.74). Neostigmine was associated with greater risk for bradycardia and postoperative nausea and vomiting. No significant difference in risk for serious AEs was observed.

To a provider, the speed and completeness of reversal is a significant consideration related to operating room efficiency and patient safety.

Given that rNMB is a risk factor for PPCs, several RCT and database studies have examined the effect of sugammadex vs neostigmine on incidence of PPCs. An open-label, assessor-blinded, RCT included 98 individuals who received sugammadex 2 mg/kg and 99 who received neostigmine 0.07 mg/kg for rocuronium reversal at surgical closure.[59] All patients were aged 70 years or older and undergoing planned procedures with general anesthesia expected to last more than 3 hours. The primary end point was PPCs defined as postoperative pneumonia, aspiration pneumonitis, atelectasis, pneumothorax, desaturation or hypoxemia, upper airway obstruction, or acute respiratory insufficiency. A significantly lower incidence of rNMB was observed with sugammadex vs neostigmine (10% vs 49%; odds ratio [OR], 0.11; 95% CI, 0.04-0.25; *P*<0.001). There was no significant difference in the primary end point of postoperative pulmonary complications (33% vs 40%; OR, 0.74; 95% CI, 0.40-1.37; *P*=0.30), although a trend toward reduced incidence was observed in the sugammadex group. An exploratory analysis found fewer 30-day hospital readmissions with sugammadex group vs neostigmine (5% vs 15%; OR, 0.30; 95% CI, 0.08-0.91; *P*=0.03).

In a study of 126 patients who had major abdominal surgery, 64 received neostigmine 0.04 mg/kg or sugammadex 4 mg/kg to reverse NMB.[60] The primary outcome was forced vital capacity (FVC) loss 1 hour after surgery. Secondary outcomes examined the rate and size of atelectasis 1 and 24 hours after surgery. There were no differences in FVC between the groups, and 39% of patients in the neostigmine group and 29% in the sugammadex group had visible atelectasis. The median atelectasis area was 9.7 and 6.8 cm^2 in the neostigmine and sugammadex groups, respectively.

POPULAR was a multicenter, prospective, observational study of 22,803 adult patients undergoing general anesthesia for non-cardiac surgeries at 211 hospitals in 28 countries.[61] The primary outcome was incidence of PPCs occurring up to 28 days post-procedure. PPCs were

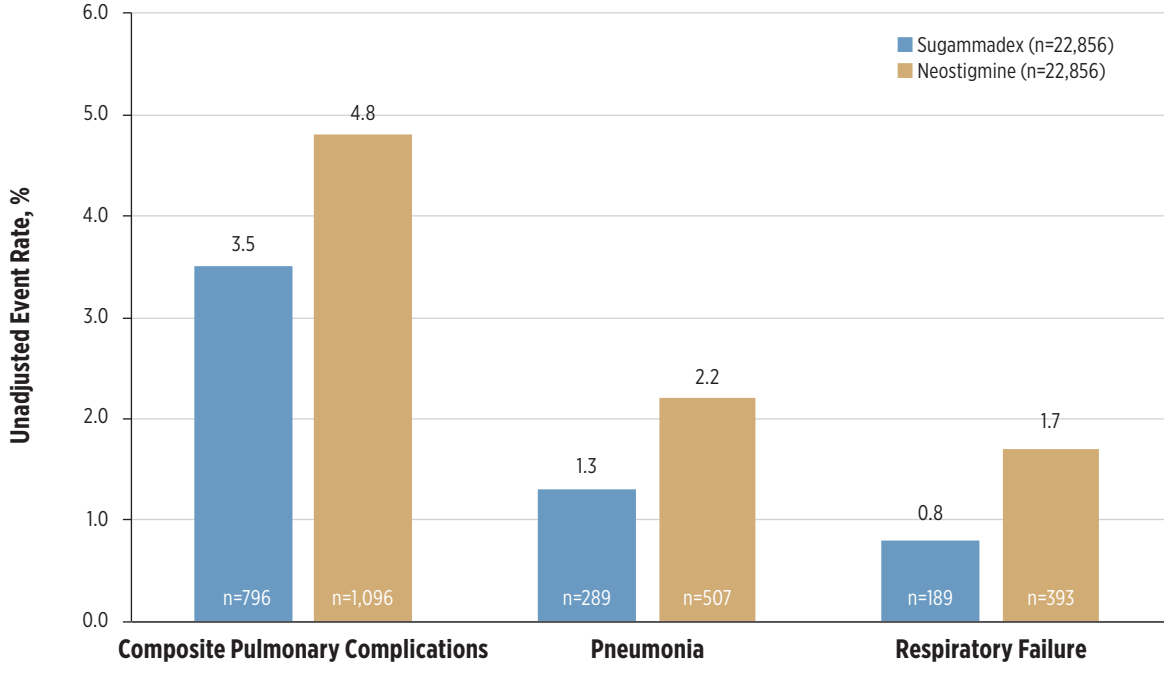


Figure 2. Major PPC event rates in patients receiving sugammadex or neostigmine.[65]

Reprinted with permission. Kheterpal S, Vaughn MT, Dubovoy TZ, et al, Sugammadex versus neostigmine for reversal of neuromuscular blockade and postoperative pulmonary complications (STRONGER): a multicenter matched cohort analysis, *Anesthesiology*, 132, 6, 1371-1381, https://doi.org/10.1097/ALN.0000000000003256.

defined as respiratory failure, suspected pulmonary infection or infiltrates, atelectasis, aspiration pneumonitis, bronchospasm, and pulmonary edema. Although NMBDs were associated with an increased incidence of PPCs (1,658 [7.6%]; adjusted OR, 1.86; 95% CI, 1.53-2.26; adjusted absolute risk reduction [ARR], −4.4%; 95% CI, −5.5 to −3.2), neither neuromuscular monitoring nor the administration of a reversal agent were associated with fewer PPCs. Furthermore, there was no difference between sugammadex and neostigmine in pulmonary outcomes, and tracheal extubation at a TOFr >0.9 did not influence outcomes. The study was met with a number comments describing limitations that made interpretation of the results challenging: lack of standardization of anesthetic techniques,[62] lack of comparable groups to assess effects of neuromuscular monitoring and reversal,[63] substandard care in neuromuscular management,[63] lack of information on quantitative monitor calibration,[64] and inability to oversee protocol violations,[64] among others.

Finally, STRONGER was an observational matched cohort study of more than 45,000 adults undergoing elective inpatient noncardiac surgical procedures involving general anesthesia, an NMBD, and pharmacologic reversal at 12 US hospitals.[65] The primary outcome measure was incidence of PPCs defined as pneumonia, respiratory failure, or other pulmonary complications, such as pneumonitis pulmonary congestion, iatrogenic pulmonary embolism, infarction, or pneumothorax. Components of pneumonia and respiratory failure were assessed as secondary outcomes. The study matched 22,856 patients receiving sugammadex to 22,856 patients receiving neostigmine. The average age in the matched cohort was 59 years, and 45% were men. The majority (95.6%) were American Society of Anesthesiologists physical status II or III. PPCs occurred in 1,892 patients, or 4% of the population (3.5% vs 4.8% with sugammadex vs neostigmine, respectively; **Figure 2**). A total of 796 patients (1.7%) had pneumonia (1.3% vs 2.2%), and 582 patients (1.3%) had respiratory failure (0.8% vs 1.7%). A multivariable logistic regression analysis found that sugammadex resulted in a 30% lower risk for PPCs, attributable to a 47% reduced risk for pneumonia and a 55% reduced risk for respiratory failure.

Conclusions

Although substantially underrecognized, rNMB is a common and clinically significant postoperative complication. Until universal adoption of quantitative neuromuscular monitoring is a reality, the appropriate use of peripheral nerve stimulators can reduce the incidence of rNMB. Both neostigmine and sugammadex, when used appropriately, can also reduce rNMB, but sugammadex shows clear advantages, as described in this article. The most recent evidence suggests that sugammadex is associated with a lower incidence of PPCs. Clinical collaboration and effective communication between surgeons and anesthesia providers, along with best practices in neuromuscular monitoring and the use of reversal agents, can maximize patient safety and improve overall outcomes.

References

1. Miskovic A, Lumb AB. Postoperative pulmonary complications. *Br J Anaesth*. 2017;118(3):317-334.
2. Abbott TEF, Fowler AJ, Pelosi P, et al. A systematic review and consensus definitions for standardised end-points in perioperative medicine: pulmonary complications. *Br J Anaesth*. 2018;120(5):1066-1079.
3. Patel K, Hadian F, Ali A, et al. Postoperative pulmonary complications following major elective abdominal surgery: a cohort study. *Perioper Med*. 2016;5(1):10.
4. Fernandez-Bustamante A, Frendl G, Sprung J, et al. Postoperative pulmonary complications, early mortality, and hospital stay following noncardiothoracic surgery: a multicenter study by the Perioperative Research Network investigators. *JAMA Surg*. 2017;152(2):157-166.
5. Rao VK, Khanna AK. Postoperative respiratory impairment is a real risk for our patients: the intensivist's perspective. *Anesthesiol Res Pract*. 2018;2018:3215923.
6. Murphy GS, Brull SJ. Residual neuromuscular block: lessons unlearned. Part I: definitions, incidence, and adverse physiologic effects of residual neuromuscular block. *Anesth Analg*. 2010;111(1):120-128.
7. Yu B, Ouyang B, Ge S, et al. Incidence of postoperative residual neuromuscular blockade after general anesthesia: a prospective, multicenter, anesthetist-blind, observational study. *Curr Med Res Opin*. 2016;32(1):1-9.
8. Fortier L-P, McKeen D, Turner K, et al. The RECITE study: a Canadian prospective, multicenter study of the incidence and severity of residual neuromuscular blockade. *Anesth Analg*. 2015;121(2):366-372.
9. Saager L, Maiese EM, Bash LD, 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.
10. Viby-Mogensen J, Jørgensen BC, Ording H. Residual curarization in the recovery room. *Anesthesiology*. 1979;50(6):539-541.
11. Naguib M, Kopman AF, Lien CA, Hunter JM, Lopez A, Brull SJ. A survey of current management of neuromuscular block in the United States and Europe. *Anesth Analg*. 2009;111(1):1.
12. Beecher HK, Todd DP. A study of the deaths associated with anesthesia and surgery: based on a study of 599, 548 anesthesias in ten institutions 1948-1952, inclusive. *Ann Surg*. 1954;140(1):2-35.
13. Belcher AW, Leung S, Cohen B, et al. Incidence of complications in the post-anesthesia care unit and associated healthcare utilization in patients undergoing non-cardiac surgery requiring neuromuscular blockade 2005-2013: a single center study. *J Clin Anesth*. 2017;43:33-38.
14. Xará D, Silva A, Mendonça J, Abelha F. Inadequate emergence after anesthesia: emergence delirium and hypoactive emergence in the Postanesthesia Care Unit. *J Clin Anesth*. 2013;25(6):439-446.
15. Norton M, Xará D, Parente D, Barbosa M, Abelha FJ. Residual neuromuscular block as a risk factor for critical respiratory events in the post anesthesia care unit. *Rev Esp Anestesiol Reanim*. 2013;60(4):190-196.
16. Aytac I, Postaci A, Aytac B, et al. Survey of postoperative residual curarization, acute respiratory events and approach of anesthesiologists. *Brazilian J Anesthesiol*. 2016;66(1):55-62.
17. Naguib M, Brull SJ, Kopman AF, et al. Consensus statement on perioperative use of neuromuscular monitoring. *Anesth Analg*. November 2018;127(1):71-80.
18. Eikermann M, Blobner M, Groeben H, et al. Postoperative upper airway obstruction after recovery of the train of four ratio of the adductor pollicis muscle from neuromuscular blockade. *Anesth Analg*. 2006;102(3):937-942.
19. Farhan H, Moreno-Duarte I, McLean D, Eikermann M. Residual paralysis: does it influence outcome after ambulatory surgery? *Curr Anesthesiol Rep*. 2014;4(4):290-302.
20. Blobner M, Hunter JM, Meistelman C, et al. Use of a train-of-four ratio of 0.95 versus 0.9 for tracheal extubation: an exploratory analysis of POPULAR data. *Br J Anaesth*. 2020;124(1):63-72.
21. Broens SJL, Boon M, Martini CH, et al. Influence of reversal of a partial neuromuscular block on the ventilatory response to hypoxia: a randomized controlled trial in healthy volunteers. *Anesthesiology*. 2019;131(3):467-476.
22. Devine S, Babrowicz J, Hahn R. Intra-operative communication regarding neuromuscular blockade: a survey of anaesthesiologists and surgeons. *J Anesth Clin Res*. 2015;6(4):524.
23. Answine JF, Lamberg JJ. In response: interdisciplinary intraoperative communication and collaboration needed for optimal neuromuscular blockade management. *J Anaesthesiol Clin Pharmacol*. 2014;30(3):443-444.
24. Scarlet S, Doerr P. Bringing down the drapes. *AMA J Ethics*. 2020;22(4):E263-266.

25. Lorinc A, Henson C. All handoffs are not the same: What perioperative handoffs do we participate in and how are they different? Anesthesia Patient Safety Foundation. Published October 2017. Accessed July 5, 2020. www.apsf.org/article/all-handoffs-are-not-the-same-what-perioperative-handoffs-do-we-participate-in-and-how-are-they-different/
26. Renew JR, Joshi G, Crowley M. Clinical use of neuromuscular blocking agents in anesthesia. UpToDate. Last update April 9, 2020. Accessed June 10, 2020. www.uptodate.com/contents/clinical-use-of-neuromuscular-blocking-agents-in-anesthesia
27. Naguib M, Kopman AF, Ensor JE. Neuromuscular monitoring and postoperative residual curarisation: a meta-analysis. *Br J Anaesth*. 2007;98(3):302-316.
28. Grayling M, Sweeney BP. Recovery from neuromuscular blockade: a survey of practice. *Anaesthesia*. 2007;62(8):806-809.
29. Maybauer DM, Geldner G, Blobner M, et al. Incidence and duration of residual paralysis at the end of surgery after multiple administrations of cisatracurium and rocuronium. *Anaesthesia*. 2007;62(1):12-17.
30. Brull SJ, Kopman AF, Naguib M. Management principles to reduce the risk of residual neuromuscular blockade. *Curr Anesthesiol Rep*. 2013;3(2):130-138.
31. Kim HJ, Lee K, Park WK, et al. Deep neuromuscular block improves the surgical conditions for laryngeal microsurgery. *Br J Anaesth*. 2015;115(6):867-872.
32. Yoo Y-C, Kim NY, Shin S, et al. The Intraocular pressure under deep versus moderate neuromuscular blockade during low-pressure robot assisted laparoscopic radical prostatectomy in a randomized trial. *PLoS One*. 2015;10(8):e0135412.
33. Carron M, Linassi F, De Cassai A, Navalesi P. Exploratory analysis of POPULAR data: learning to improve. *Br J Anaesth*. 2020;0(0).
34. Brull SJ, Kopman AF. Current status of neuromuscular reversal and monitoring. *Anesthesiology*. 2017;126(1):173-190.
35. Senzime. TetraGraph. Accessed August 19, 2020. www.senzime.com/us/products/tetragraph/
36. Blink Device Company. TwitchView. Accessed August 19, 2020. www.blinkdc.com/twitchview
37. Xavant Technology. Stimpod NMS450X. Accessed August 19, 2020. www.xavant.com/products/stimpod-nms450x/
38. Drager. TOFscan. Accessed August 19, 2020. www.draeger.com/en-us_us/Hospital/Products/Patient-Monitoring/Patient-Monitoring-Pods/TOFscan
39. Drager. Infinity Trident NMT SmartPod. Accessed August 19, 2020. www.draeger.com/en_aunz/Hospital/Products/Patient-Monitoring/Patient-Monitoring-Pods/Infinity-Trident-NMT-SmartPod
40. Thilen SR, Bhananker SM. Qualitative neuromuscular monitoring: how to optimize the use of a peripheral nerve stimulator to reduce the risk of residual neuromuscular blockade. *Curr Anesthesiol Rep*. 2016;6(2):164-169.
41. Murphy GS, Kopman AF. "To reverse or not to reverse?" *Anesthesiology*. 2016;125(4):611-614.
42. Debaene B, Plaud B, Dilly M-P, Donati F. Residual paralysis in the PACU after a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action. *Anesthesiology*. 2003;98(5):1042-1048.
43. Murphy GS, Szokol JW, Avram MJ, et al. Neostigmine administration after spontaneous recovery to a train-of-four ratio of 0.9 to 1.0. *Anesthesiology*. 2018;128(1):27-37.
44. Brull SJ, Naguib M. How to catch unicorns (and other fairytales). *Anesthesiology*. 2018;128(1):1-3.
45. Bloxiverz (neostigmine methysulfate injection) [package insert]. Chesterfield, MO; Eclat Pharmaceuticals; 2017.
46. US Food and Drug Administration. *Center for Drug Evaluation and Research Application Number: 204078Orig1s000 Summary Review*; 2013.
47. Luo J, Chen S, Min S, Peng L. Reevaluation and update on efficacy and safety of neostigmine for reversal of neuromuscular blockade. *Ther Clin Risk Manag*. 2018;14:2397-2406.
48. Lien CA, Kopman AF. Current recommendations for monitoring depth of neuromuscular blockade. *Curr Opin Anaesthesiol*. 2014;27(6):616-622.
49. Brull SJ, Murphy GS. Residual neuromuscular block: lessons unlearned. Part II: methods to reduce the risk of residual weakness. *Anesth Analg*. 2010;111(1):1.
50. Kim KS, Cheong MA, Lee HJ, Lee JM. Tactile assessment for the reversibility of rocuronium-induced neuromuscular blockade during propofol or sevoflurane anesthesia. *Anesth Analg*. 2004;99(4):1080-1085, table of contents.
51. Murphy GS, Szokol JW, Marymont JH, Franklin M, Avram MJ, Vender JS. Residual paralysis at the time of tracheal extubation. *Anesth Analg*. 2005;100(6):1840-1845.
52. Kester M, Karpa KD, Vrana KE. Autonomic Nervous System. In: *Elsevier's Integrated Review Pharmacology*. Elsevier; 2012:91-109.
53. Bridion (sugammadex) [package insert]. Whitehouse Station, NJ: Merck & Co., Inc; 2018.
54. Schaller SJ, Fink H. Sugammadex as a reversal agent for neuromuscular block: an evidence-based review. *Core Evid*. 2013;8:57-67.
55. Miyazaki Y, Sunaga H, Kida K, et al. Incidence of anaphylaxis associated with sugammadex. *Anesth Analg*. 2018;126(5):1505-1508.
56. Min KC, Woo T, Assaid C, et al. Incidence of hypersensitivity and anaphylaxis with sugammadex. *J Clin Anesth*. 2018;47:67-73.
57. Raval AD, Uyei J, Karabis A, Bash LD, Brull SJ. Incidence of residual neuromuscular blockade and use of neuromuscular blocking agents with or without antagonists: a systematic review and meta-analysis of randomized controlled trials. *J Clin Anesth*. 2020;64.
58. Hristovska A-M, Duch P, Allingstrup M, Afshari A. The comparative efficacy and safety of sugammadex and neostigmine in reversing neuromuscular blockade in adults. A Cochrane systematic review with meta-analysis and trial sequential analysis. *Anaesthesia*. 2018;73(5):631-641.
59. Togioka BM, Yanez D, Aziz MF, Higgins JR, Tekkali P, Treggiari MM. Randomised controlled trial of sugammadex or neostigmine for reversal of neuromuscular block on the incidence of pulmonary complications in older adults undergoing prolonged surgery. *Br J Anaesth*. 2020;124(5):553-561.
60. Alday E, Muñoz M, Planas A, Mata E, Alvarez C. Effects of neuromuscular block reversal with sugammadex versus neostigmine on postoperative respiratory outcomes after major abdominal surgery: a randomized-controlled trial. *Can J Anesth Can d'anesthésie*. 2019;66(11):1328-1337.
61. Kirmeier E, Eriksson LI, Lewald H, et al. Post-anaesthesia pulmonary complications after use of muscle relaxants (POPULAR): a multicentre, prospective observational study. *Lancet Respir Med*. 2019;7(2):129-140.
62. Thakkar KD, Hrishi AP. Neuromuscular monitoring and reversal: responses to the POPULAR study. *Lancet Respir Med*. 2019;7(2):e6.
63. Plaud B, Gayat E, Nicolas P. Neuromuscular monitoring and reversal: responses to the POPULAR study. *Lancet Respir Med*. 2019;7(2):e5.
64. de Boer HD, Brull SJ, Naguib M, Murphy GS, Kopman AF. Neuromuscular monitoring and reversal: responses to the POPULAR study. *Lancet Respir Med*. 2019;7(2):e4.
65. Kheterpal S, Vaughn MT, Dubovoy TZ, et al. Sugammadex versus neostigmine for reversal of neuromuscular blockade and postoperative pulmonary complications (STRONGER). *Anesthesiology*. 2020;132(6):1371-1381.