2023 American Society of Anesthesiologists Practice Guidelines for Monitoring and Antagonism of Neuromuscular Blockade: A Report by the American Society of Anesthesiologists Task Force on Neuromuscular Blockade

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ABSTRACT

These practice guidelines provide evidence-based recommendations on the management of neuromuscular monitoring and antagonism of neuromuscular blocking agents during and after general anesthesia. The guidance focuses primarily on the type and site of monitoring and the process of antagonizing neuromuscular blockade to reduce residual neuromuscular blockade.

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HIGHLIGHTS BOX

- This practice guideline provides evidence-based recommendations on the management of neuromuscular monitoring and antagonism of neuromuscular blocking agents. The objective is to guide practice that will enhance patient safety by reducing residual neuromuscular blockade. It is recommended to use quantitative neuromuscular monitoring at the adductor pollicis and to confirm a recovery of train-of-four ratio greater than or equal to 0.9 before extubation. Sugammadex is recommended from deep, moderate, and shallow levels of neuromuscular blockade that is induced by rocuronium or vecuronium. Neostigmine is a reasonable alternative from minimal blockade (train-of-four ratio in the range of 0.4 to less than 0.9). Patients with adequate spontaneous recovery to train-of-four ratio greater than or equal to 0.9 can be identified with quantitative monitoring, and these patients do not require pharmacological antagonism.

Practice guidelines are systematically developed recommendations that assist the practitioner and patient in making decisions about health care. These recommendations may be adopted, modified, or rejected according to clinical needs and constraints and are not intended to replace local institutional policies. In addition, practice guidelines developed by the American Society of Anesthesiologists (ASA) are not intended as standards or absolute requirements, and their use cannot guarantee any specific outcome. Practice guidelines are subject to revision as warranted by the evolution of medical knowledge, technology, and practice. They provide basic recommendations for anesthesia care that are supported by synthesis and analysis of the current literature, expert and practitioner opinion, public comment, and clinical feasibility data. Practice guidelines aim to improve patient care and patient outcomes by providing up–to–date information for patient care.

Purpose

This practice guideline provides evidence-based recommendations regarding the appropriate management of neuromuscular monitoring and antagonism of neuromuscular blocking drugs during and after general anesthesia. The guidance focuses primarily on the process of antagonizing neuromuscular blockade to reduce residual neuromuscular blockade (train–of–four ratio less than 0.9), addressing the appropriate type and site of monitoring and the use and dosing of different antagonist drugs depending on the depth

of the neuromuscular blockade. Suggestions for implementation of quantitative monitoring are included.

The appropriate use of neuromuscular blocking drugs in the context of difficult airway management is not addressed. Additionally, management of intraoperative neuromuscular blockade to optimize intubating conditions, surgical operating conditions, and patient outcomes is not addressed.

Background

Neuromuscular blocking drugs, both depolarizing (*e.g.*, succinylcholine) and nondepolarizing (*e.g.*, rocuronium, vecuronium, pancuronium, cisatracurium, atracurium), are among the most commonly used medications in anesthesia. They are used to facilitate airway management, to improve surgical conditions, and, in some cases, to insure immobility during critical points in an operation. However, their use can be associated with sometimes-serious complications, most importantly when their paralytic effects have not disappeared or been adequately antagonized at the end of surgery. Inadequate recovery from the effects of neuromuscular blocking drugs is associated with adverse outcomes including upper airway obstruction, reintubation, atelectasis, pneumonia, prolonged stay in the postanesthesia care unit (PACU), and decreased patient satisfaction.[1,2] While residual neuromuscular blockade is commonly unrecognized, there is convincing evidence that preventing its occurrence leads to improved patient outcomes.[3,4]

Although peripheral nerve stimulators (which could deliver a single stimulus and sometimes a tetanic stimulus) were introduced in the 1950s, the modern era of neuromuscular blockade assessment began with the introduction of the train-of-four by Ali *et al.* in 1970.[5] The train-of-four involves the delivery of four brief electrical pulses to a peripheral nerve at the rate of 2 Hz and assessing the "twitches" that result. With increasing paralysis, sequential twitches in the train decrease in amplitude with the progressive disappearance of the fourth, then the third, then the second, and finally the first twitch. The amplitude of the twitches can be measured quantitatively to permit the calculation of the *train-of-four ratio*: the amplitude of the fourth twitch divided by that of the first. A decreasing train-of-four ratio indicates greater degrees of paralysis.

Such quantitative measurements allowed an objective means of determining the presence of residual neuromuscular blockade after surgery. A seminal report by Viby-Mogensen *et al.*[6] published in ANESTHESIOLOGY in 1979 reported a 42% incidence on arrival to the PACU in a cohort of 72 patients. These authors defined residual neuromuscular blockade as a train-of-four ratio of less than 0.7, based on earlier work showing that vital capacity and inspiratory force had recovered to near normal at this value. However, over the subsequent years, this definition has been revised upwards, as others showed that a measured train-of-four ratio of less than 0.9 was associated with clinical symptoms of weakness,[7,8] impaired hypoxic ventilatory response,[9] increased risk of upper airway obstruction,[10] impaired airway protective reflexes,[11] increased risk of aspiration,[11] an experience of unpleasant symptoms of muscle weakness,[12] and a prolonged PACU stay.[13] There is now a broad consensus that adequate recovery of neuromuscular function is defined as a train-of-four ratio greater than or equal to 0.9, typically measured at the adductor pollicis muscle after ulnar nerve stimulation. Since the work of Viby-Mogensen *et al.*,[6] multiple published reports—using the current definition—have confirmed that residual neuromuscular blockade at the end of surgery and/ or in the PACU remains a frequent occurrence after the use

Recommendations

Recommendation	Strength of Recommendation	Strength of Evidence
1. When neuromuscular blocking drugs are administered, we recommend against clinical assessment alone to avoid residual neuromuscular blockade, due to the insensitivity of the assessment.	Strong	Moderate
2. We recommend quantitative monitoring over qualitative assessment to avoid residual neuromuscular blockade.	Strong	Moderate
3. When using quantitative monitoring, we recommend confirming a train-of-four ratio greater than or equal to 0.9 before extubation.	Strong	Moderate
4. We recommend using the adductor pollicis muscle for neuromuscular monitoring.	Strong	Moderate
5. We recommend against using eye muscles for neuromuscular monitoring.	Strong	Moderate
6. We recommend sugammadex over neostigmine at deep, moderate, and shallow depths of neuromuscular blockade induced by rocuronium or vecuronium, to avoid residual neuromuscular blockade.*	Strong	Moderate
7. We suggest neostigmine as a reasonable alternative to sugammadex at minimal depth of neuromuscular blockade.	Conditional	Low
8. To avoid residual neuromuscular blockade when atracurium or cisatracurium are administered and qualitative assessment is used, we suggest antagonism with neostigmine at minimal neuromuscular blockade depth. In the absence of quantitative monitoring, at least 10 min should elapse from antagonism to extubation. When quantitative monitoring is utilized, extubation can be done as soon as a train-of-four ratio greater than or equal to 0.9 is confirmed before extubation.	Conditional	Very low

*Deep: posttetanic count greater than or equal to 1 and train-of-four count 0; moderate: train-of-four count 1 to 3; shallow: train-of-four count 4 and train-of-four ratio less than 0.4; minimal: train-of-four ratio 0.4 to less than 0.9.

of nondepolarizing neuromuscular blocking agents, with an incidence as high as 64% of patients.[14,15]

Numerous factors contribute to this high incidence of residual neuromuscular blockade. Most importantly, there is the general lack of recognition of the extraordinary variability in the duration of action of neuromuscular blocking agents. This variability means that no specific amount of time (for example, "2 h have elapsed after the last dose of a nondepolarizing neuromuscular blocking drug") will guarantee adequate spontaneous recovery.[16,17] Similarly, there is no period of time that will ensure that administration of any antagonist drug will result in complete recovery of neuromuscular function.[16]

A second factor is the continued use of "clinical" assessments of paralysis. Generations of anesthesiologists and other anesthesia providers have used sustained head lift or grip strength or respiratory measurements (*e.g.*, tidal volume, inspiratory force) as markers of adequate recovery. Nevertheless, a substantial body of work has shown that these measures are insensitive to substantial degrees of paralysis. For example, Debaene *et al.*[17] found that the sensitivity of a 5-s head lift to detect residual neuromuscular blockade was only 11% in patients with a train-of-four ratio less than 0.9 and 19% in patients with a train-of-four ratio less than 0.7. Kopman *et al.*[7] found that healthy volunteers could sustain a head lift with a train-of-four ratio as low as 0.45.

Third, there is the widespread use of peripheral nerve stimulators to assess blockade with the mistaken belief that "four visibly equal twitches" to train-of-four stimulation or "sustained tetanus" indicate full recovery. Several studies have established that clinically significant weakness cannot be identified with subjective assessment of the response to a peripheral nerve stimulator.[18] Using subjective assessment of the train-of-four, fade cannot be reliably appreciated until the train-of-four ratio is less than 0.4. Consequently, the lack of subjective fade in the train-of-four response represents the broad range of train-of-four ratios from 0.4 to 1.0.[19,20]

While the quantitative assessment of blockade and the recognized value of the train-of-four ratio has existed for over 50 years, it has not gained widespread clinical use, largely because of the limitations of the measurement technology. Some monitors were complex to use, had poor user interfaces, or required startup/calibration times that are inconsistent with a busy clinical schedule. Some were limited in when they can be used (*e.g.*, if the thumb cannot move, methods dependent on measuring the acceleration or strength of such movement are inaccurate). Fortunately, this situation is gradually changing with the recent introduction of substantially improved quantitative technology.

Finally, like the problems associated with relaxant variability, the relationship between the depth of blockade and pharmacologic antagonism is not well understood by many clinicians. The appropriate use of an antagonist agent (both the drug chosen and the dose given) is dependent on an accurate assessment of the depth of neuromuscular blockade. The result is frequent "fixed dose and blind" antagonism regimens (*e.g.*, 5 mg of neostigmine or 200 mg of sugammadex, given without previous block assessments), which may not result in full recovery, or antagonism may take far longer than expected. While the introduction of sugammadex has clearly reduced the incidence of residual neuromuscular blockade compared with neostigmine,[21] the problem has not been eliminated, and residual neuromuscular blockade remains an important clinical problem.

Methodology

The guideline task force included anesthesiologists, epidemiology-trained methodologists, and a patient representative, who was chosen from the contacts of the task force and who had experience as a patient. Members disclosed all relationships (industry and other entities) that might pose a conflict of interest. Members with conflicts of interest related to particular recommendations did not participate in the formulation, discussion, or approval of the relevant recommendations. The task force was responsible for developing key questions; the relevant patient populations, interventions, comparators, and outcomes; and the study inclusion/exclusion criteria to guide the systematic review. The study protocol is available as supplemental digital content (http://links.lww.com/ALN/C924).

- Population: all patients receiving neuromuscular blocking drugs in whom antagonism and extubation is intended. Patients receiving neuromuscular blocking drugs in the intensive care unit were excluded.
- Interventions: quantitative/objective monitoring; sugammadex or neostigmine.
- Comparators: qualitative/subjective assessment using a peripheral nerve stimulator assessment and clinical assessment without peripheral nerve stimulator; placebo and spontaneous recovery (no intervention).
- Outcomes relevant for both monitoring and antagonism questions were residual neuromuscular blockade (as assessed by train-of-four ratio and reported as such unless noted), time to recovery from neuromuscular blockade (*i.e.*, according to depth of block at antagonism, the time to train-of-four ratio greater than or equal to 0.9), reintubation, reparalysis, pulmonary complications, hypoxia, postoperative nausea and vomiting, anaphylaxis, and cardiac events. In addition to these primary outcomes, measures of agreement for train-of-four ratio were examined across different muscle sites and monitoring devices.

Task force members rated the importance of each outcome for decision-making on a scale of 1 to 9 (1 to 3, limited importance; 4 to 6, important; and 7 to 9, critical).[22] The evidence synthesis focused on the outcomes rated as important and critical.

Literature Search

Comprehensive database searches were conducted by a medical librarian using PubMed, EMBASE, and SCOPUS for literature published from 1990 through June 2022. The search start date was chosen to preserve applicability of results (the restriction is unlikely to meaningfully reduce search sensitivity[23]). In addition, the Cochrane Central Register of Controlled Trials was queried; task force members provided potentially relevant studies; references from systematic reviews and meta-analyses were hand-searched; and trial registries were searched. The literature search strategy (http://links.lww.com/ALN/C926) and PRISMA flow diagram (http://links.lww.com/ALN/C925) are available as supplemental digital content.

Study Screening and Selection

Screening of titles with abstract and full text was performed using systematic review software (DistillerSR,[24] Evidence Partners, Ottawa, Canada) by two reviewers, with disagreements resolved by consensus. All discrepancies were resolved. Potential inclusion–exclusion discrepancies were also examined with an artificial intelligence tool, a component of the systematic review software. Eligible studies included randomized and nonrandomized trials: diagnostic (*e.g.*, fully paired[25]), before–after/time series, cohort, and case-control designs. Case reports and case series, conference abstracts, letters not considered brief research reports, non-English publications, and animal studies were excluded. The list of excluded studies is available in the supplemental digital content (http://links.lww.com/ALN/C927).

Data Extraction and Management

Study results were extracted into DistillerSR. Data extraction was performed by a single methodologist, with a second methodologist reviewing the data for quality control. Conflicts were resolved by consensus between the two methodologists after reviewing discrepancies. When the relevant data were not reported in the published work, attempts were made to contact authors. The figures were digitized as necessary to obtain quantitative results for synthesis.

Evidence Synthesis

The body of evidence was first described according to study characteristics and treatment arms. The results were then summarized in tabular form by outcome. When relevant, decision-informative, and practicable, pairwise and network random-effects meta-analyses were performed. (Note that the number of studies cited in the text may not correspond to the meta-analyses owing to no events in some studies.) Analyses were conducted in R (R Foundation for Statistical Computing, Vienna, Austria).[26–29] Small-study effects and the potential for publication bias were evaluated using funnel plots and regression-based tests.[30] (See the methods supplement for further details, http://links.lww.com/ALN/C956.) The subject and study characteristics are described in Appendix 1.

Risk of Bias Assessment

Risk of bias for individual studies was evaluated using tools relevant for the study design (supplemental tables S1 to S5, http://links.lww.com/ALN/C928; figs. S1 to S5, http://links.lww.com/ALN/C929): for randomized controlled trials, the Cochrane risk of bias tool was used;[31] for nonrandomized studies, the Risk Of Bias In Non-randomized Studies of Interventions tool was used;[32] for diagnostic studies, Quality Assessment of Diagnostic Accuracy Studies tool 2 was used;[33] and for the observational results (including single arms of randomized controlled trials), train-of-four confirmation was examined before extubation, a Clinical Advances through Research and Information Technology tool.[34]

Strength of Evidence

The overall strength of evidence was rated by outcome, using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system (table 1). In this system, randomized controlled trials start as high strength of evidence, and nonrandomized studies start as low. The strength may be downgraded based on summary study-level risk of bias, inconsistency, indirectness, imprecision, and publication bias. Strength may be upgraded if the effect is large, if a dose-response is present, or if unaccounted residual confounding would likely have increased the effect.[35] For results obtained from network meta-analyses, the strength of evidence was assessed with the Confidence in Network Meta-Analysis tool using categories corresponding to Grading of Recommendations, Assessment, Development, and Evaluation.[36]

Strength of Recommendations

For each key question, the results of the detailed evidence synthesis for important benefits and harms were summarized. After reviewing the evidence summary and relevant detail from the synthesis, the task force then drafted recommendations and corresponding strength consistent with the body of evidence.

The categories of recommendations in the Grading of Recommendations, Assessment, Development, and Evaluation approach include strong in favor, conditional in favor, conditional against, and strong against an intervention. Strong recommendations reflect the task force believing that all or almost all clinicians would choose the specific action or approach. Conditional recommendations are those where most, but not all, would choose the action or approach.[37,38]

Table 1. GRADE Strength of Evidence Definitions

GRADE	Interpretation
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

GRADE, Grading of Recommendations, Assessment, Development, and Evaluation.

Neuromuscular Monitoring: Patient Outcomes

Key Question

What are the comparative effects of clinical assessment (*e.g.*, head lift), qualitative assessment (*e.g.*, peripheral nerve stimulator), and quantitative monitoring (measuring train-of-four ratios) on residual neuromuscular blockade, pulmonary complications, and other adverse events?

Recommendations

When neuromuscular blocking drugs are administered, we recommend against clinical assessment alone to avoid residual neuromuscular blockade, due to the insensitivity of the assessment.

- Strength of recommendation: Strong
- Strength of evidence: Moderate

We recommend quantitative monitoring over qualitative assessment to avoid residual neuromuscular blockade.

- Strength of recommendation: Strong
- Strength of evidence: Moderate

Summary of Evidence

Patients monitored quantitatively had less residual neuromuscular blockade compared with patients assessed qualitatively or clinically (table 2). Supplemental tables S6 and S7 (http://links.lww.com/ALN/C928) detail the strength–of–evidence ratings.

Clinical Assessment or Qualitative Assessment *versus* Quantitative Monitoring

Residual Neuromuscular Blockade. A total of five randomized controlled trials[3,12,39–41] and three observational studies[42–44] reported lower incidences of residual neuromuscular blockade with quantitative monitoring compared with qualitative assessment or clinical assessment (supplemental tables S8 and S9, http://links.lww.com/ALN/C928). Although both train-of-four ratio thresholds and place (operating room or PACU) where residual neuromuscular blockade were assessed differently across the studies, there is general consistency in the estimated risk ratios. A prospective study[42] and a retrospective cohort study[43] included comparisons of quantitative monitoring with clinical assessment alone; a before–after design[44] compared quantitative monitoring with peripheral nerve stimulator or clinical assessment—all defined *residual neuromuscular blockade* as a train-of-four ratio less than 0.9 assessed in the PACU. Recognizing the clinical and methodological diversity across studies, given the consistent effects reported, the results were pooled both for randomized controlled trials alone (pairwise) and in a network meta-analysis. This approach yielded similar results (moderate strength of evidence for less residual neuromuscular blockade); only in the retrospective cohort study[43] were some patients given sugammadex (supplemental table S10, http://links.lww.com/ALN/C928; fig. S6, http://links.lww.com/ALN/C929).

Pulmonary Complications. A large multinational prospective cohort study[45] did not detect a difference in a composite pulmonary complication outcome (respiratory failure, hypoxia, pulmonary infection or infiltrates, atelectasis, aspiration pneumonia, bronchospasm, or pulmonary edema) in patients with quantitative *versus* qualitative assessment (very low strength of evidence for pulmonary complications). A single-institution before–after quality improvement study reported fewer pulmonary complications using quantitative monitoring compared with qualitative assessment.[46] Three randomized controlled trials[3,41,47] reported the incidence of hypoxia (two of the three reported a lower incidence with quantitative monitoring, one no events; low strength of evidence). A single trial[41] reported episodes of bronchospasm (1 event, 72 participants), and a prospective cohort study[48] reported pneumonia (2 events, 155 participants; both very low strength of evidence). Events were uncommon, and a quantitative evidence synthesis was not performed. It should be noted that there is not one universally accepted definition of postoperative pulmonary complications.

Comment. There is convincing evidence that quantitative neuromuscular monitoring reduces the risk of residual neuromuscular blockade. The relative reductions appear consistent and substantial compared with qualitative assessment or clinical assessment. Limitations in the body of evidence include clinical and methodological aspects of study conduct (*e.g.*, train-of-four ratio threshold used to define residual neuromuscular blockade, lack of sugammadex use, device type, manner of qualitative assessment, and clinical assessment), which are reflected in the moderate strength–of–evidence rating.

An important issue with acceleromyography is that baseline (also referred to as *control*) train-of-four ratio measurements (*i.e.*, before muscle relaxation) often exceed 1.0. It is common with baseline values in the range of 1.1 to 1.15, but significantly

Table 2. Strength of Evidence for Quantitative Monitoring Compared with Qualitative or Clinical Assessment

Outcome*	Studies		Patients	Strength of Evidence	Effect (95% CI)
	Nonrandomized	Randomized Controlled Trial			
Residual neuromuscular blockade					Risk ratio
Train-of-four ratio < 0.7, < 0.8, or < 0.9					
Quantitative *versus* clinical		3	232		0.18 (0.06 to 0.50)
Train-of-four ratio < 0.9					
Quantitative *versus* qualitative		2	329		0.24 (0.13 to 0.43)
Train-of-four ratio < 0.7, < 0.8, or < 0.9 (network meta-analysis)*				Moderate	
Quantitative *versus* clinical	3	8	1,211		0.15 (0.10 to 0.22)
Quantitative *versus* qualitative					0.36 (0.26 to 0.51)
Hypoxia					Risk ratio
Quantitative *versus* qualitative or clinical		2	347	Low	0.22 (0.05 to 0.88)
Pulmonary complications (composite)†					Odds ratio
Quantitative *versus* qualitative	2		8,678	Very low	Inconsistent results‡
Any monitoring *versus* none	1		17,150	Very low	1.31 (1.15 to 1.49)§

*The network meta-analysis results (naïve pooling) are included to support pairwise results (no separate strength-of-evidence rating).

†Reintubation and upper airway obstruction lack reported events in studies; one prospective cohort study (n = 155) reported two cases of pneumonia (very low strength of evidence); one randomized controlled trial (n = 76) reported one case of bronchospasm (very low strength of evidence); and one before–after study (n = 1,810) reported fewer cases of pulmonary complications after introduction of quantitative monitors.

‡A prospective cohort (n = 6,868) did not detect a difference—adjusted odds ratio, 1.07 (95% CI, 0.90 to 1.29). A before–after study (n = 1,810) reported fewer pulmonary complications with quantitative monitoring (-0.5% [95% CI, -0.8 to -0.1%]).

§Adjusted for potential confounders. Pulmonary complications included hypoxia, suspected pulmonary infection or infiltrates, atelectasis, aspiration pneumonia, bronchospasm, or pulmonary edema.

higher baseline values have been reported. Therefore, the clinical definition of adequate recovery of neuromuscular function may vary when the results of monitoring with acceleromyography are not normalized, and the train-of-four ratio may recover to values greater than 1.0. Normalization of train-of-four ratios to the baseline (control) value obtained before neuromuscular block is accomplished by dividing the postoperative measurements by the baseline value. As an example, if the baseline train-of-four ratio is 1.15 and the raw postoperative train-of-four ratio is 0.95, then the normalized train-of-four ratio is $0.95/1.15 = 0.83$. Normalization usually yields lower train-of-four ratios, and therefore normalized observations are more likely than nonnormalized observations to be classified as positive for residual neuromuscular blockade. When neuromuscular blockade is measured with either electromyography or normalized acceleromyography, adequate recovery of neuromuscular function is a train-of-four ratio greater than or equal to 0.9.

Depolarizing Blockade. Succinylcholine is the only depolarizing neuromuscular blocking agent in clinical use. It is rapidly metabolized in the blood stream by pseudocholinesterase. Given the absence of an antagonist drug, succinylcholine blockade must resolve spontaneously. The functional half-life is typically short (less than 10 min) but may be prolonged in patients with genetic or disease-related variations in pseudocholinesterase activity. Blockade monitoring after succinylcholine reveals a different pattern of recovery than after a nondepolarizing agent, with gradual but equal return of twitch height as blockade resolves in patients with normal pseudocholinesterase activity. However, with genetic variants such as homozygous atypical pseudocholinesterase, it is common that fade appears upon the return of muscle activity mimicking a phase 2 depolarizing block. The only way to effectively monitor both normal and abnormal succinylcholine-induced neuromuscular blockade is by measuring a single twitch baseline height and using the percentage of that single twitch to gauge return of strength. When the rate of block regression is not within the normal range, this will alert the clinician to the presence of abnormal pseudocholinesterase activity. As this is often impractical for clinicians who administer only a single dose of succinylcholine without subsequent use of nondepolarizing neuromuscular blockers, the task force suggests using neuromuscular monitoring to guide extubation when there are clinical signs of delayed recovery from succinylcholine.

Neuromuscular Monitoring: Confirmation of Train-of-four Ratio Greater than or Equal to 0.9 before Extubation

Key Question

When using quantitative monitoring, does confirming a train-of-four ratio greater than or equal to 0.9 decrease the risk of residual neuromuscular blockade?

Recommendations

When using quantitative monitoring, we recommend confirming a train-of-four ratio greater than or equal to 0.9 before extubation.

- Strength of recommendation: Strong
- Strength of evidence: Moderate

Summary of Evidence

Patients whose train-of-four ratio was confirmed before extubation experienced less residual neuromuscular blockade compared to when the train-of-four ratio was not confirmed after neostigmine or sugammadex (table 3). Supplemental tables S11 and S12 (http://links.lww.com/ALN/C928) detail the strength-of-evidence ratings, and supplemental tables S13 and S14 (http://links.lww.com/ALN/C928) describe the studies included in the analysis.

Train-of-four Ratio Confirmed *versus* Not Confirmed

Residual Neuromuscular Blockade. When sugammadex was used and a train-of-four ratio greater than or equal to 0.9 was confirmed before extubation, the pooled incidence proportion of residual neuromuscular blockade (train-of-four ratio less than 0.9) was 0.5% (95% CI, 0.0 to 6.0%). If a train-of-four ratio greater than or equal to 0.9 was not confirmed before extubation, although quantitative monitoring was used, the incidence proportion was 2.2% (95% CI, 0.5 to 9.0%). With neostigmine, the pooled incidence proportions were 5.3% (95% CI, 2.5 to 10.7%) and 44.9% (95% CI, 29.9 to 60.8%), respectively, with and without confirmation. Supplemental fig. S7 (http://links.lww.com/

ALN/C929) displays the entirety of the results (moderate strength of evidence for train-of-four ratio greater than or equal to 0.9 confirmation before extubation).

Comment. These results are consistent with less residual neuromuscular blockade when a train-of-four ratio greater than or equal to 0.9 is confirmed before extubation, but limitations in these analyses are important to note. Direct evidence from randomized trials that compare confirming or not confirming train-of-four ratios before extubation are lacking. The analysis is an indirect comparison that does not include potential confounding between studies such as depth of block at antagonism. However, the effects are substantive and clinically meaningful for either drug—unlikely explained by residual confounding.

Neuromuscular Monitoring: Technical Performance

Key Question

What factors affect the performance of quantitative monitoring?

Recommendations

We recommend using the adductor pollicis muscle for neuromuscular monitoring.

- Strength of recommendation: Strong
- Strength of evidence: Moderate

We recommend against using eye muscles for neuromuscular monitoring.

- Strength of recommendation: Strong
- Strength of evidence: Moderate

Table 3. Residual Neuromuscular Blockade in Randomized and Nonrandomized Studies with Sugammdex or Neostigmine According to Train-of-Four Ratio Greater than or Equal to 0.9 Confirmed Before Extubation

Outcome	Studies*	Patients	Strength of Evidence	Incidence Proportion (95% CI)
Less residual neuromuscular blockade				
Incidence by agent				
Sugammadex				
Train-of-four ratio confirmed	10	552	Low	0.5 (0.0 to 6.0)
Train-of-four ratio not confirmed	11	1,004	(Confirmed *vs.* not confirmed)	2.2 (0.5 to 9.0)
Train-of-four ratio not stated	7	735	Not rated	1.5 (0.0 to 11.9)
Qualitative assessment	1	29	Not rated	13.8 (5.3 to 31.5)
Clinical assessment/not stated	4	450	Not rated	8.9 (2.6 to 25.9)
Neostigmine				
Train-of-four ratio confirmed	10	486	Moderate	5.3 (2.5 to 10.7)
Train-of-four ratio not confirmed	15	1,446	(Confirmed *vs.* not confirmed)	44.9 (29.9 to 60.8)
Train-of-four ratio not stated	10	700	Not rated	6.5 (0.9 to 34.5)
Qualitative assessment	9	988	Not rated	35.7 (29.6 to 42.3)
Clinical assessment/not stated	10	947	Not rated	24.9 (13.2 to 42.0)

Residual neuromuscular blockade (train-of-four ratio less than 0.9) in arms of randomized and nonrandomized studies using quantitative monitoring and sugammadex or neostigmine.
*Randomized and nonrandomized individual study arms.

Summary of Evidence

Time to reach train–of–four ratio greater than or equal to 0.9 at the adductor pollicis muscle was longer compared with eye muscles and flexor hallucis brevis. There was less residual neuromuscular blockade when patients were monitored at the adductor pollicis muscle compared to the corrugator supercilii (table 4). Supplemental tables S15 and S16 (http://links.lww.com/ALN/C928) describe studies comparing different muscles to adductor pollicis for monitoring and time to train–of–four ratio from different muscle groups. Supplemental tables S17 and S18 (http://links.lww.com/ALN/C928) detail the strength–of–evidence ratings.

Adductor Pollicis *versus* Other Muscles

Time to Train-of-four Ratio Greater than or Equal to 0.8, 0.9, or 1.0. Times to train–of–four ratio greater than or equal to 0.8, 0.9, or 1.0 were longer in patients monitored with the adductor pollicis muscles compared with the corrugator supercilii (moderate strength of evidence), orbicularis oculi (low strength of evidence), and flexor hallucis brevis muscles (very low strength of evidence).[49–55] No difference was detected in the time to train–of–four ratio greater than or equal to 0.9 when monitoring the adductor pollicis muscle compared with the masseter (very low strength of evidence).[56]

Residual Neuromuscular Blockade. One prospective cohort study reported less residual neuromuscular blockade when monitoring the adductor pollicis muscle compared with the corrugator supercilii (very low strength of evidence).[57]

No Normalization versus Normalization with Acceleromyography Monitors

Residual Neuromuscular Blockade. One fully paired study detected less residual neuromuscular blockade (train–of–four ratio less than 1.0) when using nonnormalized acceleromyography measures compared with normalized measures (very low strength of evidence).[58] The same study did not detect a difference in severe residual neuromuscular blockade (train–of–four ratio less than 0.7) between nonnormalized and normalized measures.

Additional Technical Performance Comparisons. Several studies compared no calibration to calibration, various arm stabilization techniques, and no preload *versus* preload. Evidence synthesis was not performed due to the diversity of outcomes reported across the studies.

Comment

Complete recovery of all muscles from neuromuscular blockade optimizes patient safety; therefore, measurements should be obtained at sites with longer times to recovery. When monitoring a muscle with relative resistance such as the eye muscles to neuromuscular blocking drugs, there is a potential for neuromuscular blocking drug overdose and for concluding that a patient is adequately antagonized when, in fact, they are not (see Appendix 2).

Table 4. Summary and Strength of Evidence for Technical Performance of Neuromuscular Monitors by Muscle and Normalization

| Comparisons | Studies | | Patients | Strength of Evidence | Summary |
	Nonrandomized	Paired/Randomized Controlled Trial			
Train-of-four ratios					
Adductor pollicis *versus*					
Corrugator supercilii		4	140	Moderate	Three of four studies reported longer times to train-of-four ratio greater than or equal to 0.9 or greater than or equal to 1.0 at adductor pollicis *versus* corrugator supercilii
Orbicularis oculi		2	46	Low	Longer times to train-of-four ratio greater than or equal to 0.8 or greater than or equal to 0.9 at adductor pollicis *versus* orbicularis oculi
Masseter		1	10	Very low	Difference not detected
Flexor hallucis brevis		1	52	Very low	Longer time to train-of-four ratio greater than or equal to 0.9 at adductor pollicis *versus* flexor hallucis brevis
First dorsal interosseous *versus* flexor hallucis brevis		1	28	Very low	Longer time to train-of-four ratio greater than or equal to 0.9 at first dorsal interosseous *versus* flexor hallucis brevis
Residual neuromuscular blockade					
No normalization *versus* normalization		1	122	Very low	Less residual neuromuscular blockade (train-of-four ratio less than 1.0) detected when using nonnormalized measurements
Adductor pollicis *versus* corrugator supercilii	1		150	Very low	Less residual neuromuscular blockade (train-of-four ratio less than 0.9) detected when monitoring at the adductor pollicis *versus* corrugator supercilii

Antagonism of Neuromuscular Blockade

Key Question

What are the comparative efficacy and safety of antagonist drugs among patients receiving nondepolarizing neuromuscular blocking drugs?

Recommendations

We recommend sugammadex over neostigmine at deep, moderate, and shallow depths of neuromuscular blockade induced by rocuronium or vecuronium, to avoid residual neuromuscular blockade.

- Strength of recommendation: Strong
- Strength of evidence: Moderate

We suggest neostigmine as a reasonable alternative to sugammadex at minimal depth of neuromuscular blockade.

- Strength of recommendation: Conditional
- Strength of evidence: Low

Summary of Evidence

Table 5 defines the depths of neuromuscular blockade referred to in the recommendations. The incidence of residual neuromuscular blockade was lower and time to recovery was shorter with sugammadex compared to neostigmine (table 6). However, there were no differences in reparalysis and reintubation rates (table 7). Supplemental tables S19 and S20 (http://links.lww.com/ALN/C928) detail the strength-of-evidence ratings.

Sugammadex versus *Neostigmine*
Residual Neuromuscular Blockade. Ten randomized controlled trials reported a lower incidence of residual neuromuscular blockade in patients antagonized with sugammadex compared with neostigmine (moderate strength of evidence; supplemental fig. S8, http://links.lww.com/ALN/C929).[59–68]
Time to Train-of-four Ratio Greater than or Equal to 0.9. Times to train-of-four ratio greater than or equal to 0.9 were shorter in patients antagonized with sugammadex compared with neostigmine from deep[65,69–71] to moderate[62,72–85] depths of blockade (moderate strength of evidence) and from shallow[86–90] (moderate strength of evidence) to minimal[69] depths of blockade (very low strength of evidence; supplemental figs. S9 to S12, http://links.lww.com/ALN/C929).
Adverse Events. Anaphylaxis was reported with neostigmine in one study[91] of five (supplemental table S21; http://links.lww.com/ALN/C928).[91–95] Among patients receiving sugammadex, the pooled incidence rate of anaphylaxis was 1.6 per 10,000 (low strength of evidence).[92,93,96,97] Differences in rates of bradycardia or tachycardia were not apparent among patients who received sugammadex

compared with neostigmine when glycopyrrolate (low strength of evidence; supplemental fig. S13, http://links.lww.com/ALN/C929).[61,68,69,74,95,98] Differences were also not detected for arrhythmias irrespective of antimuscarinic used[89,95,99–101] (low strength of evidence; supplemental fig. S14, http://links.lww.com/ALN/C929; table S22, http://links.lww.com/ALN/C928).
Pulmonary Complications. A pooled result from six randomized trials did not detect a difference in pulmonary complications (a composite of respiratory failure, hypoxia, pulmonary infection or infiltrates, atelectasis, aspiration pneumonia, bronchospasm, or pulmonary edema) in patients given neostigmine or sugammadex (low strength of evidence; supplemental fig. S15, http://links.lww.com/ALN/C929).[66,82,99,102–104] A pooled estimate from seven nonrandomized studies also did not detect a difference in pulmonary complications (very low strength of evidence).[45,93,105–109] Five randomized controlled trials[59,61,66,104,110] and four cohort studies[93,106,108,109] reported fewer episodes of pneumonia with sugammadex than neostigmine (low to very low strength of evidence; supplemental fig. S16, http://links.lww.com/ALN/C929). A difference in hypoxia was not detected between sugammadex and neostigmine in six randomized controlled trials (Sao$_2$ less than or equal to 90%, low strength of evidence; supplemental fig. S17, http://links.lww.com/ALN/C929).[64,68,110–113] Postoperative reintubation was unreported in five randomized trials for sugammadex and neostigmine (low strength of evidence).[81,104,110,112,114] A single trial reported postoperative reintubation with neostigmine only.[104] Four studies reported lower rates of reintubation with sugammadex (very low strength of evidence; supplemental fig. S18, http://links.lww.com/ALN/C929).[106,115–117] As noted previously, there is not one universally accepted definition of postoperative pulmonary complications.

Table 5. Depths of Neuromuscular Blockade by Quantitative and Qualitative Measurement

Depth of Blockade	Peripheral Nerve Stimulator and Qualitative Assessment	Quantitative Monitor
Complete	Posttetanic count = 0	Posttetanic count = 0
Deep	Posttetanic count ≥ 1; train-of-four count = 0	Posttetanic count ≥ 1; train-of-four count = 0
Moderate	Train-of-four count = 1–3	Train-of-four count = 1–3
Shallow*	Train-of-four count = 4; train-of-four fade present	Train-of-four ratio < 0.4
Minimal*	Train-of-four count = 4; train-of-four fade absent	Train-of-four ratio = 0.4–0.9
Acceptable recovery	Cannot be determined	Train-of-four ratio ≥ 0.9

*The quantitative threshold of train-of-four ratio of 0.4 cannot reliably be subjectively determined by the presence or absence of fade in the train-of-four ratio response. The absence of subjectively appreciated fade has been reported with a train-of-four ratio of less than 0.3, and the presence of fade has been reported with train-of-four ratio of greater than 0.7.[149]

Table 6. Benefits and Strength of Evidence Comparing Sugammadex with Neostigmine for Incidence of Residual Neuromuscular Blockade and Time to Recovery to Train-of-four Ratio Greater than or Equal to 0.9

Outcome	Randomized Controlled Trials	Patients	Strength of Evidence	Effect (95% CI)
Less residual neuromuscular blockade				Risk ratio
Train-of-four ratio < 0.9	8	1,451	Moderate	0.18 (0.07 to 0.42)
				Risk difference
Train-of-four ratio < 0.9	8	1,451	Moderate	-21.6% (-33.8 to -9.4%)
Shorter time to train-of-four ratio ≥ 0.9 from				Mean difference, min
Deep block	4	308	Moderate	-33.6 (-59.3 to -7.9)
Moderate block	17	1,114	Moderate	-10.0 (-12.7 to -7.2)
Shallow block	5	153	Moderate	-3.9 (-6.1 to -1.6)
Minimal block	1	17	Very low	-1.4 (-2.0 to -0.8)

Reparalysis. The incidence of reparalysis was variable across trials not occurring with either neostigmine or sugammadex in 10 of 13 randomized trials (supplemental fig. S19, http://links.lww.com/ALN/C929, risk difference for sugammadex *versus* neostigmine of -2.9% [95% CI, -8.5 to 2.7]; low strength of evidence).[65,68,70,72,73,81,86–88,90,99,118,119]

Postoperative Nausea and Vomiting. The incidence of postoperative nausea and vomiting was reported in 16 randomized controlled trials,[66,68,89,102,103,110,114,119–127] 1 non-randomized trial,[128] and 4 cohort studies.[107,129–131] In a network meta-analysis (including placebo and spontaneous arms), the incidence appeared lower with sugammadex but with low confidence in the estimate (low strength of evidence; supplemental fig. S20, http://links.lww.com/ALN/C929).

Postoperative nausea was reported in 31 studies (26 randomized controlled trials,[61,62,65,67,69–71,73,74,77,79–81,84,100,102,132–141] 1 nonrandomized study,[142] and 3 cohort studies[48,143,144]). No difference was apparent between sugammadex and neostigmine (very low strength of evidence; supplemental fig. S21, http://links.lww.com/ALN/C929).

Postoperative vomiting was reported in 24 studies (21 randomized controlled trials,[61,62,65,67,69–71,74,75,77,79,81,102,132,133,136,139–141] 1 nonrandomized study,[142] and 2 cohort studies[143,144]). No difference was detected between sugammadex and neostigmine (low strength of evidence; supplemental fig. S22, http://links.lww.com/ALN/C929).

Comment

The antagonist drugs currently available include anticholinesterases and sugammadex, a selective relaxant binding drug. Neostigmine is the most commonly used anticholinesterase and the only drug in this class of drugs that was evaluated for this guideline.

Selective use of neostigmine or sugammadex is based on identifying patients highly likely to achieve an effective antagonism with neostigmine. The degree of spontaneous recovery at the time of antagonism has been shown to be the major determinant of successful and timely antagonism with neostigmine. Several studies have demonstrated that administering neostigmine at a train-of-four count of 4 is much more likely to yield a satisfactory and timely antagonism than neostigmine administered at a lower train-of-four count.[145,146] However, it is also clear from several studies that an effective antagonism is not guaranteed even when spontaneous recovery has progressed to a train-of-four count of 4 if the fourth twitch is still very weak.[145] In one study, a cohort of patients were antagonized when the train-of-four ratio was 0.4, and all patients had a timely successful antagonism as defined by a train-of-four ratio greater than or equal to 0.9 within 10 min of neostigmine administration.[147] Another study compared sugammadex with neostigmine at a train-of-four ratio of 0.5 and found that both were equally effective at this depth of blockade.[68] Additional studies have confirmed that the likelihood of an effective antagonism with neostigmine is much improved when the neuromuscular blockade is minimal (*minimal block* is the proposed consensus term for a quantitatively measured block with a train-of-four ratio of 0.4 to 0.9, or a qualitatively assessed block with no subjective fade to train-of-four stimulation).[68,148,149] The quantitative determination of train-of-four ratio greater than or equal to 0.4 is more reliable than subjective determination of no fade with train-of-four stimulation and is associated with improved predictability of neostigmine.

The evidence synthesis did not address the dosages of antagonist drugs. However, neostigmine and sugammadex both have Food and Drug Administration (FDA)–approved dose recommendations. The FDA-approved dose recommendations for antagonizing rocuronium or vecuronium with sugammadex are 2 mg/kg for train-of-four count 2 to train-of-four ratio less than 0.9, 4 mg/kg for posttetanic count 1 to train-of-four count 1, and 16 mg/kg immediate antagonism after administration of a single dose of rocuronium 1.2 mg/kg. A neostigmine dose of 30 μg/kg

Table 7. Harms and Strength of Evidence Comparing Sugammadex with Neostigmine

Outcome	Studies		Patients	Strength of Evidence	Effect (95% CI)*
	Nonrandomized	Randomized Controlled Trials			
Anaphylaxis					Incidence proportion
Sugammadex	5	2	204,152	Low	1.4/10,000 (0.7 to 3.1)
Neostigmine	3	2	168,852	Low	0.3/10,000 (0.1 to 0.9)
Cardiac complications					Risk difference
Bradycardia					
Neostigmine/glycopyrrolate		6	663	Low	−5.0% (−11.7 to 1.7%)
Neostigmine/atropine		8	689	Moderate	−12.7% (−12.7 to −5.1%)
Tachycardia					
Neostigmine/glycopyrrolate		3	314	Low	−6.7% (−14.5 to 1.0%)
Neostigmine/atropine		1	74	Very low	−10.8% (−23.0 to −5.1%)
Arrhythmias		5	178	Low	−1.0% (−3.8 to 1.9%)
Pulmonary complications					Odds ratio
Composite	5	6	67,323	Low/very low†	0.71 (0.56 to 0.90)
Pneumonia	4	5	57,745	Low/very low†	0.59 (0.38 to 0.93)
					Risk difference
Hypoxia (SaO$_2$ ≤ 90%)		6	670	Low	−6.0% (−18.2 to 6.2%)
Hypoxia (SaO$_2$ > 90 to 95%)		7	792	Low	1.6% (−3.6 to 6.8%)
					Risk difference
Reintubation		5	425	Low	−0.2% (−2.1 to 1.6%)
	4		18,736	Very low	−1.7% (−4.1 to 0.6%)
					Risk difference
Reparalysis		13	705	Low	−2.9% (−8.5 to 2.7%)
					Risk ratio
Postoperative nausea and vomiting		16‡	1,536	Low	0.77 (0.61 to 0.97)
Postoperative nausea		26‡	2,781	Very low	0.94 (0.78 to 1.12)
Postoperative vomiting		21‡	2,178	Low	0.84 (0.60 to 1.18)

*Sugammadex *versus* neostigmine. †Strength of evidence for randomized and observational results considered separately. Pooled result shown for combined randomized and observational studies (consistent across designs). ‡Number of trials included in network meta-analysis.

at minimal neuromuscular blockade is consistent with the FDA–approved dosage recommendations.

The antagonist effect of neostigmine is maximal within approximately 10 min,[150] and therefore, there is no benefit in administering neostigmine much more than 10 min before emergence and extubation. If recovery time exceeds 10 min (*i.e.*, a train–of–four ratio greater than or equal to 0.9 has not been reached within 10 min after neostigmine administration), it is unlikely to be the result of delayed activity of neostigmine. Rather, the explanation is more likely to be that sufficient spontaneous recovery was not achieved before administration of neostigmine. When neostigmine has peaked but the train–of–four ratio is less than 0.9, three options remain to accomplish adequate antagonism: (i) allow for continued spontaneous recovery; (ii) administer sugammadex if appropriate to the relaxant given; or (iii) if a low dose of neostigmine was initially used, administer additional neostigmine (but not exceeding a total of 50 µg/kg because higher doses have not been reported as more effective).

The following factors should be considered when choosing the neuromuscular antagonist drug: the type of neuromuscular blocking drug used (*e.g.*, steroidal, benzylisoquinolinium), depth of neuromuscular blockade, efficacy of

the antagonist drug for the class of neuromuscular blocking drug, any ceiling effect of the antagonist drug, and time required to attain full antagonism. The occurrence of residual neuromuscular blockade is affected in large part by the appropriate use of antagonist drug and monitoring equipment. Finally, for women using hormonal contraceptives (oral or non–oral) receiving sugammadex, FDA labeling states a backup contraception method must be used for 7 days.

Depth of Neuromuscular Blockade and Choice of Antagonist Drug. When neostigmine is used at minimal blockade (train–of–four ratio greater than or equal to 0.4 and less than 0.9), the dose should not exceed 40 µg/kg. The shallower the blockade, the lower the neostigmine dose required—when the train–of–four ratio exceeds 0.6, 15 to 30 µg/kg is usually adequate. Higher doses may have the paradoxical effect of causing weakness with neostigmine when a dose exceeding 30 µg/kg is administered after spontaneous recovery to train–of–four ratio greater than or equal to 0.9. This can be avoided if quantitative monitoring is used.[16] When quantitative monitoring is not available and spontaneous recovery has progressed to a train–of–four count of 4 without fade, it is advisable to routinely administer a small dose of 15 to 30 µg/kg neostigmine. The reason

is that, as has been discussed above, it is not possible to rule out residual neuromuscular blockade with the use of a peripheral nerve stimulator. When quantitative monitoring is not available, and to be relatively sure that the block is adequately recovered, a minimum of 10 min should pass after neostigmine-induced antagonism before extubation is performed. With quantitative monitoring, extubation can be performed as soon as the train-of-four ratio is greater than or equal to 0.9. Depending on clinical judgment and in the context of quantitative monitoring, neostigmine may be considered for a depth of block deeper than minimal (train-of-four ratio of 0.4 to 0.9), with the understanding that deeper blocks will require more time to attain a train-of-four ratio greater than or equal to 0.9.

Adverse Effects of Antagonism. The adverse effects of sugammadex and neostigmine (coadministered with glycopyrrolate) do not favor either drug. The strength-of-evidence ratings do not support differences in rates of anaphylaxis, bradycardia, or tachycardia when glycopyrrolate is used with neostigmine, postoperative nausea and vomiting, postoperative nausea alone, and postoperative vomiting (table 7).

Economic Considerations. Although outside the scope of this guideline, many raise concerns regarding the cost of sugammadex. It is important to note that regardless of the perspective, the decision calculus for an economic evaluation of sugammadex is complex.[151,152] Factors beyond drug costs require consideration—*e.g.*, time to recovery and operating room costs, residual neuromuscular blockade and reparalysis, as well as the costs associated with adverse events caused by residual neuromuscular blockade. Finally, in discussions regarding costs during guideline development, the patient representative noted to the panel the rather small proportion added by sugammadex to overall operative charges.

Pancuronium. The systematic review did not identify published clinical trials of antagonism of pancuronium by sugammadex. It also did not identify published studies comparing the antagonism of pancuronium-induced neuromuscular blockade by sugammadex *versus* neostigmine. Therefore, no recommendations were developed. Sugammadex has a lower affinity for pancuronium, and higher doses may be required.[153,154]

Key Question

What are the antagonism strategies for benzylisoquinolinium (*e.g.*, cisatracurium) neuromuscular blockade?

Recommendations

To avoid residual neuromuscular blockade when atracurium or cisatracurium are administered and qualitative assessment is used, we suggest antagonism with neostigmine at minimal neuromuscular blockade depth. In the absence of quantitative monitoring, at least 10 min should

elapse from antagonism to extubation. When quantitative monitoring is utilized, extubation can be done as soon as a train-of-four ratio greater than or equal to 0.9 is confirmed before extubation.

- Strength of recommendation: Conditional
- Strength of evidence: Very low

Benzylisoquinolinium Neuromuscular Blockade Antagonism
Time to Train-of-four Ratio Greater than or Equal to 0.9. Times to train-of-four ratio greater than or equal to 0.9 after neostigmine administration ranged from 1 to 143 min reported in six studies as shown in supplemental fig. S23 (http://links.lww.com/ALN/C929; very low strength of evidence).[77,145,147,155–157] Time to train-of-four ratio greater than or equal to 0.9 for neostigmine antagonism of cisatracurium and atracurium is shown in table 8. Supplemental tables S19 and S20 (http://links.lww.com/ALN/C928) detail the strength-of-evidence ratings.

Comment. Benzylisoquinolinium neuromuscular blocking drugs (cisatracurium and atracurium) can be antagonized only with an acetylcholinesterase inhibitor such as neostigmine—sugammadex is ineffective. However, neostigmine can be accompanied by a longer time to recovery than may be recognized. Assuming that (i) neostigmine is given once a muscle relaxant is no longer required for surgery, (ii) there is some spontaneous recovery from neuromuscular blockade, and (iii) emergence from anesthesia is expected in approximately 10 min, antagonism success depends primarily on the depth of block at the time of administration. Full antagonism within 10 min is most likely when neostigmine is given with four twitches and no visible or tactile fade. Success is unlikely when given with fewer than four twitches. Under these circumstances limited evidence is consistent with a median time to antagonism less than 10 min, but with a wide range in time to recovery from a train-of-four ratio of less than 0.4 to a train-of-four count 2 to 3 blockade (table 8). Therefore, verifying adequate recovery necessitates measuring train-of-four ratio with a quantitative monitor.

Research Gaps and Major Uncertainties

- Train-of-four ratio cutoff for acceleromyography *versus* electromyography in the context of patient outcomes. Are there additional improved patient outcomes if an acceleromyography train-of-four ratio greater than or equal to 1.0 is used instead of 0.9? Studies are needed to directly confirm that an electromyography train-of-four ratio greater than or equal to 0.9 is associated with improved patient outcomes.
- This guideline did not examine sugammadex dosing. Lower-than-recommended doses are potentially

associated with reparalysis. Sugammadex has a greater affinity for rocuronium than vecuronium. Therefore, a lower dose of sugammadex is required for rocuronium when compared with vecuronium at the same depths of blockade. The appropriate mg/kg dose and use of ideal *versus* total body weight at various depths of blockade should be determined for rocuronium and vecuronium separately to ensure full antagonism without reparalysis.

- There is a need for additional studies comparing sugammadex and neostigmine at minimal blockade, including effectiveness, safety, and pharmacoeconomic analysis.
- There is a need to evaluate the routine avoidance of pharmacological antagonism for patients with spontaneous recovery to a train-of-four ratio greater than or equal to 0.9, including clinical outcomes, safety, adverse outcomes, and economic implications.
- The relationship between residual neuromuscular blockade and postoperative pulmonary complications requires further investigation. Patient comorbidities (*e.g.*, morbid obesity, chronic pulmonary diseases) and site of surgery (abdominal/thoracic *versus* other sites) strongly influence postoperative pulmonary complications. Intraoperative ventilation strategies using lung protective ventilation, extubation strategies using pressure support ventilation with positive end-expiratory pressure, and emergency procedures all are strong predictors of postoperative pulmonary complications. The effects of residual neuromuscular blockade need to be further studied, focusing upon higher-risk surgical patients.

Implementation

Routine quantitative monitoring for patients receiving neuromuscular blocking agents represents a change in clinical practice. As demonstrated in recent surveys,[158,159] quantitative monitors are infrequently available, and peripheral nerve stimulators used in less than 50% of anesthetics when patients receive neuromuscular blockers.[159] Many clinicians continue to use clinical indicators such as sustained head lift to guide their decision on when to extubate patients.[20,159–161] There is no clinical test that is predictive of adequate neuromuscular recovery, and clinical tests are not sensitive to the presence of residual neuromuscular blockade. Clinical tests are also not applicable to the patient still under anesthesia. The clinician needs reliable information as to the patient's neuromuscular function before emergence from anesthesia. Therefore, opportunities to accelerate adoption of quantitative monitoring and improve patient outcomes need to be identified.

The benefits of complete recovery include increased patient satisfaction,[12,162] decreased length of PACU stay,[13,163] decreased postoperative pulmonary complications,[3] and decreased mortality.[164] Because of these benefits, there have been multiple calls to develop guidelines to monitor depth of neuromuscular block.[149,159,165–167]

Champions for adoption of routine quantitative monitoring must educate fellow anesthesia clinicians of the benefits of monitoring: increased understanding of the patient's physiologic condition, more effective antagonism of blockade, decreased need for PACU airway interventions, and decreased morbidity. Increasing local acceptance of monitors will require multiple approaches (table 9), as well as constant oversight and feedback.[44]

There have been quality improvement projects aimed at bringing the advantages of this technology to patients. Projects previously described strategies such as placing quantitative neuromuscular monitoring equipment in all anesthetizing locations, departmental education, and departmental feedback. One project reduced residual paralysis in the PACU over 9 years (1995 to 2004) from 62 to 3.5% of patients as a result of increasing quantitative neuromuscular monitoring in the operating room from 2 to 60% of patients.[168] Another project resulted in a reduction of residual paralysis in the PACU from 31 to 15%

Table 8. Time to Train-of-four Ratio Greater than or Equal to 0.9 for Neostigmine Antagonism of Benzylisoquinolinium Drugs Cisatracurium and Atracurium

				Time to Train-of-four ≥ 0.9	
Study	Drug	Depth at Neostigmine Administration	Neostigmine Dose, µg/kg	Mean, min (SD)	Median, min (range)
Goldhill *et al.*[155]	Atracurium	Train-of-four count 2	35	10.3 (1.3)	
Flockton *et al.*[77]	Cisatracurium	Train-of-four count 2	50		7.3 (4.2 to 28.2)
Kirkegaard *et al.*[145]	Cisatracurium	Train-of-four count 4	70		16.5 (6.5 to 143.3)
Song *et al.*[157]	Cisatracurium	Train-of-four count 4	70		11 (2 to 28)
Song *et al.*[157]	Cisatracurium	Train-of-four count 4 no fade	70		8 (1 to 25)
Fuchs-Buder *et al.*[147]	Atracurium	Train-of-four ratio 0.4	30		4 (3 to 6)
Preault *et al.*[156]	Cisatracurium	Train-of-four ratio 0.4	40		3.8 (2.3 to 7)

after introducing quantitative monitoring in all operating rooms.[44] This accompanied a 2-year period without any PACU reintubations associated with residual paralysis (two to four reintubations occurred per year before the project). A more recent project benefitted from a broader range of commercially available equipment choices and leveraged that by involving the department end users in the equipment purchasing decision. This decision was supplemented by communication regarding acquisition and ongoing disposable cost projections. Educational efforts included equipment instructional videos, and alerts were built into the electronic medical record for real-time reminders to record train-of-four ratios. Additionally, performance feedback was provided on an individual level. These efforts led to a cultural shift that saw 93% of patients with a documented train-of-four ratio greater than or equal to 0.9 in December 2020, which increased to 97% by March 2022.[46] Merely placing a quantitative monitor in each anesthetizing location will not by itself reduce the incidence of residual postoperative neuromuscular block. A substantial and sustained educational effort is also necessary.[44]

The exact strategies employed by any given practice will vary, but a systematic approach may include restructuring the clinical environment by placing monitors in all anesthetizing locations, educational efforts on the departmental and individual levels utilizing different mediums, and performance feedback on the departmental and individual levels.

Conclusions

This practice guideline makes clinical recommendations about monitoring and antagonism of neuromuscular blocking agents with the aim of preventing residual neuromuscular blockade. It is recommended to use quantitative neuromuscular monitoring at the adductor pollicis and to confirm recovery of a train-of-four ratio greater than or equal to 0.9 before extubation. Sugammadex is recommended for deep, moderate, and shallow depths of neuromuscular blockade induced by rocuronium or vecuronium. Neostigmine is a reasonable alternative for minimal blockade (train-of-four ratio ranging from 0.4 to less than 0.9). Patients with adequate spontaneous recovery to train-of-four ratio greater than or equal to 0.9 can be identified only with quantitative monitoring, and these patients do not require pharmacological antagonism.

Appendix 1. Study and Patient Characteristics

Neuromuscular Monitoring: Patient Outcomes

The body of evidence included 16 studies (10 randomized controlled trials,[3,12,39–41,47,169–172] 2 before–after design,[44,46] 3 prospective cohort studies,[42,45,48] and 1 retrospective cohort study[43]) comparing the effects of quantitative monitoring with qualitative assessment or clinical assessment on patient outcomes. Studies enrolled a median of 135 participants (range, 30 to 17,150). The mean age was 46.6 years, 56% were

Table 9. Strategies for Implementation and Acceptance of Routine Quantitative Monitoring

Educate clinicians on the prevalence and consequences of residual neuromuscular blockade in routine care; provide key references.

Provide in-service training on quantitative monitoring technology, emphasizing the increasing ease of use and interpretation.

Work with the operating room value-based-purchasing committee (or local equivalent) to define appropriate indications and contraindications for quantitative monitoring. Include all patients receiving neuromuscular blocking drugs, with particular focus on patients receiving nondepolarizing neuromuscular blocking drug.

Ensure that monitors are readily available.

Seek opportunities to document and promote results within your group and institution to enable:

- A decrease in incidence of postoperative respiratory complications.
- A decrease in ICU and hospital length of stay.
- An increase in patient satisfaction.
- Changes in the use of antagonist drugs.

Provide team and individual feedback on appropriate use of quantitative monitoring.

ICU, intensive care unit.

female, and the average body mass index was 26.2 kg/m². Six studies (40%) enrolled participants rated ASA Physical Status I to II, and seven (47%) included participants rated ASA Physical Status I to III (unreported in two studies [13%]).

Neuromuscular Monitoring: Confirmation of Train-of-four Ratio Greater than or Equal to 0.9 before Extubation

The body of evidence included 41 studies (26 randomized controlled trials,[41,59–63,65–68,71,73,86,118,139,145,147,173–181] 1 before–after design,[44] 4 nonrandomized trials,[142,182–184] 6 prospective cohort studies,[105,117,185–188] 3 retrospective cohort studies,[43,189,190] and 1 fully paired study[58]) using quantitative monitoring and sugammadex or neostigmine and reporting residual neuromuscular blockade (train-of-four ratio less than 0.9). For studies stratifying randomization, the arms were considered independent. In studies reporting results by subgroup, the subgroups were combined to remove dependence (subgroup differences were not of interest). Studies enrolled a median of 120 participants (range, 20 to 624). The average mean or median age was 53.6 years, 54% were female, and the average body mass index was 26.1 kg/m².

Sugammadex was administered for antagonism in 28 studies (supplemental table S13, http://links.lww.com/ALN/C928). Based on the available information (reported in the publication or obtained from authors), the train-of-four ratio was confirmed greater than or equal to 0.9 before extubation in 10 studies,[60,62,68,73,86,118,139,142,179,180] greater than or equal to 0.8 or not stated in 2 studies,[128,191] and unconfirmed in 11 studies[59,63–66,105,176,184,186,187,189]; in 6 studies (1 had two strata), whether train-of-four ratio was confirmed could not be determined.[43,61,67,117,182,190] Neostigmine was administered as the antagonist drug in 40 studies (supplemental

table S14, http://links.lww.com/ALN/C928). A train-of-four ratio greater than or equal to 0.9 was confirmed before extubation in 10 studies,[41,60,62,68,73,86,118,173–175] greater than or equal to 0.8 or not stated in 5 studies,[3,12,191–193] and unconfirmed in 15 studies[58,59,63,65,66,71,105,181,183–189]; in 9 studies, whether train-of-four ratio was confirmed could not be determined.[43,44,61,67,117,145,147,177,182]

Neuromuscular Monitoring: Technical Performance

The body of evidence included 22 studies (17 fully paired,[49–51,53–56,58,194–202] 4 randomized controlled trials,[52,203–205] and 1 prospective cohort study[57]) evaluating various factors that may affect the performance of neuromuscular monitors. Studies enrolled a median of 36 participants (range, 8 to 150). The mean age of participants was 47.8 years, 50% were female, and the average body mass index was $26.3\,kg/m^2$. Fifteen studies (68%) enrolled participants rated ASA Physical Status I to II, 4 studies (18%) enrolled participants rated ASA Physical Status I to III, and 1 study (4%) included participants rated ASA Physical Status I to IV (unreported in 2 studies). Eight of the studies focused on comparing time to recovery at the adductor pollicis with other muscles. Supplemental tables S15 and S16 (http://links.lww.com/ALN/C928) describes this subset of studies.

Antagonism of Neuromuscular Blockade

The body of evidence enrolling adults included 191 studies (133 randomized controlled trials,[4,59–90,92,95,98–104,110–114,118–127,132–141,145–148,155–157,163,173–181,206–254] 11 nonrandomized trials,[17,128,142,182–184,191,255–258] 45 cohort studies,[15,42,86,91,93,94,96,97,105–109,116,117,129–131,143,144,186–190,227,259–277] and 2 before–after designs[115,168]) evaluating efficacy and safety of antagonist drugs for neuromuscular blockade. The randomized controlled trials enrolling only adults had a median of 88 participants (range, 16 to 350). The mean age was 47.6 years, 52% were female, and average body mass index was $28.7\,kg/m^2$. The remaining studies enrolled a median of 187 participants (range, 17 to 45,712). The mean age was 54.0 years, 56% were female, and average body mass index was $30.5\,kg/m^2$. Industry supported 21% of the randomized controlled trials, and 17% of the studies were limited to adults.

Appendix 2. Technical Performance of Quantitative Neuromuscular Monitors

Although not directly informing the strength of evidence for quantitative monitoring to reduce postoperative pulmonary complications, the evidence synthesis considered the clinical validity of quantitative monitoring to reduce residual paralysis (supplemental tables S23 to S26, http://links.lww.com/ALN/C928). This appraisal relates to both device–diagnostic performance and the reduction of residual

neuromuscular blockade. Mechanomyography, which measures twitch strength using a force transducer, is considered the most appropriate reference standard. As a tool to measure underlying residual neuromuscular blockade, measurement error is apparent with all quantitative monitors. The limits of agreement for train-of-four ratio between devices or even with measurements of the same device (including mechanomyography) often approach ±10% at the adductor pollicis muscle. Proper device use, including calibration and muscle selection, may help limit measurement error. Despite these limitations, quantitative monitoring has a large effect in reducing residual neuromuscular blockade so that measurement error is unlikely to have clinical consequences. The evidence concerning the comparative diagnostic performance of different device types suggests that the preferred device is the one that a clinician uses appropriately.

Regarding specific quantitative monitors, the reference standard has generally been mechanomyography, despite the aforementioned measurement bias of train-of-four ratio of approximately 0.1. Electromyography has some advantages; immobilization of the muscle to be monitored is not necessary, and therefore, it also works well when arms and hands are tucked for surgical positioning. No preload is needed, and because of good agreement with mechanomyography with baseline values close to train-of-four ratio 1.0, there is no need for normalization. The electromyography response is less influenced by temperature changes than mechanical techniques. The advantages with electromyography compared to acceleromyography comes at a cost; all FDA-approved stand-alone electromyography monitors require proprietary, single-use electrodes that often cost $15 to $20 each. Acceleromyography can be *normalized* (the train-of-four ratio as a fraction of the baseline train-of-four ratio, which is often greater than 1.0) or *nonnormalized* (no baseline measurement). Nonnormalized acceleromyography measures the train-of-four ratio approximately 0.1 higher than mechanomyography, but normalized acceleromyography is fairly similar to mechanomyography.[58] Acceleromyography units can measure acceleration of the thumb in one direction (uniaxial) or in three directions (triaxial), the latter of which is more common in newer devices. There are limited data comparing uniaxial and triaxial acceleromyography (see supplemental table S24, http://links.lww.com/ALN/C928). Some manufacturers of acceleromyographs have incorporated their own proprietary algorithms to the displayed train-of-four ratio values. This includes either suppressing any value higher than 1.0 (*i.e.*, displaying 1.0 when the value is actually higher) or calculating the ratio as T4/T2. It is important for the clinician to be aware of these modifications.

Preload is defined as the application of a set resistance to thumb movement that has been used with mechanomyography and acceleromyography. Preload may improve acceleromyography precision, but the data are limited.

In studies comparing devices, the time to a specified train-of-four ratio offers some indirect insight regarding the safety of the device (supplemental table S26, http://links.lww.com/ALN/C928). Technologies that show longer time to recovery to a specified train-of-four ratio are thought to offer greater safety. This is in the context of no known devices that provide erroneously low train-of-four ratios. The literature suggests that the time to train-of-four ratio of 0.9 is as follows, in order of longest to shortest (highest to lowest margin of safety): mechanomyography ≈ electromyography > acceleromyography.

Monitoring Sites

While different eye muscles have different characteristics, distinguishing the evoked responses from orbicularis oculi and corrugator supercilii muscles is often difficult.[39,51] We therefore make the same recommendations for all eye muscles. The adductor pollicis muscle recovers more slowly than the corrugator supercilii or orbicularis oculi muscle. There are higher simultaneous train-of-four ratios at the corrugator supercilii and orbicularis oculi muscles compared with the adductor pollicis. *Residual neuromuscular blockade* is defined as a train-of-four ratio less than 0.9 at the adductor pollicis muscle, and it is therefore optimal to confirm adequate recovery by obtaining a valid measurement at this site. A valid measurement of the depth of the neuromuscular blockade is also essential to guide selection of the pharmacological antagonist drug and dosage. Therefore, if intraoperative neuromuscular monitoring has been performed at the eye muscles because no other site was easily accessible intraoperatively, then we recommend changing the site to the adductor pollicis muscle before antagonism. Dosage recommendations for pharmacological antagonist drugs are based on the adductor pollicis muscle responses. When monitoring at the corrugator supercilii muscle, dosage recommendations approved by the FDA for sugammadex are not applicable.[54] For these reasons, the adductor pollicis muscle is a safer option than the orbicularis oculi or corrugator supercilii. The time to recovery is similar between the adductor pollicis and masseter muscles, although the data are very limited.

In the hand, there are three muscles most commonly monitored using electromyography. These muscles are the adductor pollicis (palmar portion of the thumb), the first dorsal interosseous (posterior aspect of hand between the thumb and index finger), and the abductor digiti minimi (medial aspect of palm proximal to the pinky finger). The reference site of measurement is the adductor pollicis muscle. Train-of-four ratios at the adductor pollicis and first dorsal interosseous muscles are similar when measured simultaneously, and therefore, it appears reasonable to use data interchangeably between these sites, especially if the adductor pollicis muscle is not available or signal quality is poor. Train-of-four ratios at the adductor pollicis muscle are lower than the abductor digiti minimi when measured simultaneously, indicating a relative resistance to neuromuscular blockade at the abductor digiti minimi. Therefore,

data from the abductor digiti minimi muscle should be used with caution to guide neuromuscular blockade management (understanding the patient is more deeply paralyzed than the monitor indicates). Direct comparisons of the two alternate muscles, the first dorsal interosseous and the abductor digiti minimi, reveal the same pattern of relative resistance at the abductor digiti minimi muscle, reinforcing that measurements at the adductor pollicis and the first dorsal interosseous offer a higher margin of patient safety.

The time to recovery is similar between the adductor pollicis and masseter muscles, although the data are very limited. The data on the flexor hallucis muscle are inconsistent; however, the time to recovery is more similar between the adductor pollicis and flexor hallucis than between adductor pollicis and the eye muscles.

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Address correspondence to American Society of Anesthesiologists: 1061 American Lane, Schaumburg, Illinois 60173. kdomino@uw.edu. This Practice Guideline, as well as all published ASA Practice Parameters, may be obtained at no cost through the Journal Web site, https://pubs.asahq.org/anesthesiology.

Supplemental Digital Content

Systematic Review Protocol, http://links.lww.com/ALN/C924
PRISMA Diagram, http://links.lww.com/ALN/C925

Search Strategy, http://links.lww.com/ALN/C926
Excluded Studies, http://links.lww.com/ALN/C927
Supplemental Tables, http://links.lww.com/ALN/C928
Supplemental Figures, http://links.lww.com/ALN/C929
Methods Supplement, http://links.lww.com/ALN/C956

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