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Please review the following for details about an important change to the AANA Journal Courses:

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- As always, each issue of AANA Journal will contain a Journal Course article. Each course will be worth one CE credit with successful completion of the corresponding examination and evaluation.

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**AANA Journal Course—Residual Neuromuscular Blockade: Evidence-Based Recommendations to Improve Patient Outcomes**

**Ryan Wiatrowski, BSN, RN, CCRN**  
**Laura Martini, BSN, RN, CCRN, CSC**  
**Brandy Flanagan, BSN, RN, CRN, CCRN**  
**Kathryn Freeman, BSN, RN, CCRN**  
**Naomi Sloan, BSN, RN, CCRN**

Neuromuscular blocking drugs are administered to facilitate endotracheal intubation and induce paralysis to allow surgeons access to their anatomical target. Traditionally, qualitative measures; such as tactile observation of fade by a peripheral nerve stimulator, are used to assess the extent of the patient’s recovery after receiving the neuromuscular blocking agent. Use of these qualitative measures; however, can contribute to high rates of residual neuromuscular blockade (RNMB), placing patients at risk of serious postoperative adverse events. Such adverse events include the need for tracheal reintubation, impaired oxygen and ventilation, increased risk of aspiration and pneumonia, pharyngeal dysfunction, and delayed discharge from the postanesthesia care unit. This problem of RNMB is exacerbated by the use of traditional drugs to reverse the neuromuscular blockade, such as the acetylcholinesterase inhibitor neostigmine. This course will examine the current limitations of qualitative neuromuscular monitoring, introduce the reader to acceleromyography, and outline the advantages of monitoring neuromuscular blockade during the perioperative period. In addition, this course will review the contemporary neuromuscular antagonists, including the newer neuromuscular antagonist sugammadex.

**Keywords:** Acceleromyography, neostigmine, neuromuscular blockade monitoring, residual neuromuscular blockade, sugammadex.

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**Objectives:**  
At the completion of this course, the reader should be able to:  
1. Define residual neuromuscular blockade and list its major complications.  
2. Describe current practice and limitations of neuromuscular blockade monitoring and reversal.  
3. Describe objective monitoring of neuromuscular blockade.  
4. Discuss the pharmacology of sugammadex and its advantages over traditional neuromuscular blockade reversal agents.  
5. List considerations for reducing rates of residual neuromuscular blockade in the absence of objective monitoring measures, based on current evidence.

**Introduction**  
Neuromuscular blocking agents (NMBAs) are essential pharmacologic adjuncts that facilitate endotracheal intubation and produce skeletal relaxation, allowing surgical access for intra-abdominal and intrathoracic procedures. These medications require vigilant perioperative monitoring to minimize possible complications associated with their use. Ensuring complete recovery may prove challenging, as evidenced by the high rate of partial recovery, better known as residual neuromuscular blockade (RNMB), which occurs postoperatively in 20% to 60% of patients who receive nondepolarizers as part of their anesthetic care. Complications of RNMB include skeletal and upper airway muscular weakness, which may result in partial or complete airway obstruction, concurrent hypoxemia, and respiratory failure requiring reintubation. Failure to recognize RNMB may ultimately lead to patient death. A large survey of anesthesia providers in the United States and Europe found that 77% of respondents believed RNMB to be a “significant public health problem” (Figure 1A), yet 85% of respondents indicated never having observed a patient exhibiting “clinically significant residual neuromuscular paralysis” such as respiratory distress. The same survey found that respondents could not agree on the method of monitoring (qualitative vs quantitative) or on whether monitoring should be performed at all. Among respondents who indicated having access to qualitative and/or quantitative monitors, 41% admitted to not routinely using either monitoring device (Figure 1B). Furthermore, the survey found that 34% of providers indicated that they generally omit the use of a reversal agent in at least 25% of their cases.

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Despite a growing body of literature suggesting that RNMB may carry adverse consequences, the American Society of Anesthesiologists does not include neuromuscular monitoring in its Standards for Basic Anesthetic Monitoring, relegating its use as “occasional” in their Practice Guidelines for Postanesthetic Care.3,6,7 Although the American Association of Nurse Anesthetists (AANA) Standards for Nurse Anesthesia Practice state “when neuromuscular blocking agents are administered, monitor neuromuscular response to assess depth of blockade and degree of recovery,” the AANA does not specify a preferred monitoring technique.8

**Neuromuscular Blockade Monitoring**

The more traditional methods of monitoring neuromuscular blockade are qualitative/subjective measures, for example, 5-second head lift, leg lift, grip strength, tongue depressor test, forced vital capacity, and visual or tactile observation of fade by a peripheral nerve stimulator (PNS; see summary in Table 1).9-16 Subjective measures involving observation or palpation of the elicited muscle twitches are the most common methods for evaluating neuromuscular blockade.3

Traditionally, neuromuscular blockade has been assessed using a PNS, a small instrument (Figure 2) that sends electrical impulses to a peripheral nerve to stimulate the corresponding muscle to contract. The anesthesia provider then subjectively assesses the muscle contraction to determine recovery from or current status of neuromuscular blockade and thus assess for safety in tracheal intubation.

**Figure 1A.** Survey Respondents’ Beliefs Regarding Public Health Impact of Postoperative Residual Paralysis

**Figure 1B.** Respondents’ Use of Monitoring Devices (Adapted from Naguib et al.5)

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**Editor’s Note**

The current AANA Journal Course is especially timely given the recently released International Anesthesia Research Society (IARS) “Consensus Statement on Neuromuscular Monitoring.” Before you read and benefit from this course, please review the IARS statement.9 A brief summary of the statement appears here. The IARS consensus statement was developed to improve the use and safety of neuromuscular blockade monitoring in the perioperative setting. The statement includes recommendations from physician experts about the proper use of neuromuscular monitoring, with the goal of increasing awareness of the potential for residual neuromuscular blockade with its associated risk of death.

Recommendations for anesthesia providers are as follows:9,10:

- **Objective (quantitative) monitoring**—a real-time measurement of the train-of-four ratio equal to or greater than 0.90—should be used during administration of nondepolarizing neuromuscular blockade drugs. Subjective measurements using peripheral nerve stimulator devices should not be used because they “are prone to error.”
- **Clinical (subjective) tests** for neuromuscular blockade (eg, 5-second head lift) are not adequate and should be abandoned.
- Professional societies must develop practice guidelines and standards for perioperative use of neuromuscular blockade drugs.
- Terms for neuromuscular blockade levels should be standardized.

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exubation. The 2 most common nerves used in PNS assessment are the ulnar nerve associated with the adductor pollicis muscle and facial nerve associated with the orbicularis oculi. When using a PNS, the anesthesia provider can choose from various modes to assess neuromuscular function: single-twitch (or single-stimulus), train-of-four (TOF), tetanus (or tetanic stimulation), and double-burst stimulation (DBS).

Single twitch delivers a supramaximal stimulus, to ensure all nerve fibers are stimulated and achieve maximal contraction, to the chosen nerve/muscle system for 0.1 to 0.3 milliseconds. Twitch height after administration of an NMBA is compared with the control twitch height, providing an estimation of overall blockade of the nicotinic acetylcholine receptors by the NMBA. It is important to note that twitch height is an estimation based on visual or tactile observation by the anesthesia provider and that a baseline twitch height must be obtained from the patient before the use of any NMBA when using the single-twitch mode.

Train-of-four is a means of neuromuscular monitoring performed by delivering 4 separate stimuli 0.5 seconds apart at a frequency of 2 Hz for 2 seconds, where the 4 observed twitches are referred to as T1 to T4. Of particular importance is the comparison of T4 (the last twitch) with T1 (the first twitch), as this comparison aids the provider in determining the degree of neuromuscular blockade. The degree of progressive depression of twitch height in TOF mode is known as the concept of fade; as blockade is deepened, the twitches will progressively fade in height and ultimately disappear, with the fourth twitch disappearing first. A train-of-four ratio (TOFR) of 0.9 or above indicates that the strength of T4 is 90% or greater of the strength of T1 (Figure 3B). Tetanus is commonly used at a frequency of 50 Hz and results in a sustained contraction of the muscle rather than a single twitch. Again, the concept of fade, or a decreased response to tetanic stimulation, is used to determine the degree of neuromuscular blockade. When fade is present, 70% to 75% of the acetylcholine receptors are estimated to be blocked by the NMBA, and when the blockade is deep, no contraction will be felt at all. Tetanus should be used sparingly to assess the degree of blockade because it is very painful and can cause muscle fatigue. In addition, there is the possibility of posttetanic facilitation, which is an exaggerated response to tetanus due to an increase in acetylcholine caused by enhanced synthesis of acetylcholine after tetanic stimulation. Ultimately, posttetanic facilitation will lead to underestimation of neuromuscular blockade; it has been associated with nondepolarizing agents.

Double-burst stimulation, which was developed primarily to detect RNMB and has been shown to be less painful than tetanus, delivers 2 bursts of tetanic stimuli separated by 750 milliseconds. Two commonly used burst sequences are DBS3,3 (2 bursts of three 0.2-millisecond impulses separated by 750 milliseconds) and DBS0,2 (1 burst of three 0.2-millisecond impulses and 1 burst of two 0.2-millisecond impulses separated by 750 milliseconds). Regardless of the mode used, evidence supports that vigilant monitoring of NMBA is necessary in the perioperative period.

Table 1. Subjective Measures of Monitoring Neuromuscular Blockade

<table>
<thead>
<tr>
<th>Subjective measure</th>
<th>Corresponding train-of-four ratio (TOFR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visible or tactile fade</td>
<td>Fade is indistinguishable once TOFR exceeds 0.4</td>
</tr>
<tr>
<td>5-Second head lift</td>
<td>TOFR 0.45-0.75 with average approximately 0.6</td>
</tr>
<tr>
<td>Tongue depressor test</td>
<td>TOFR 0.68-0.95; test cannot be used in intubated patients but has highest predictive value of the subjective measures</td>
</tr>
<tr>
<td>Grip strength</td>
<td>Grip strength averaged 57% of the control, with a range of 43%-77% at TOFR 0.7. This strength increased to 83% of the control (range, 70%-105%) at TOFR of 0.90 in one study</td>
</tr>
<tr>
<td>Forced vital capacity</td>
<td>Shown to be impaired at TOFR 0.5</td>
</tr>
<tr>
<td>50-Hz tetanic stimulation</td>
<td>Demonstrates no fade between TOFR 0.16 and 0.46</td>
</tr>
<tr>
<td>100-Hz tetanic stimulation</td>
<td>Demonstrates no fade at TOFR as low as 0.7</td>
</tr>
<tr>
<td>Double-burst stimulation</td>
<td>Undetectable fade at TOFR 0.6-0.8</td>
</tr>
<tr>
<td>Acceleromyography</td>
<td>Found to correlate best with TOFR obtained via mechanomyography; however, acceleromyography was found to exceed TOFR 1.0 at mechanomyography TOFR 0.83-0.95, indicating that acceleromyography is not 100% accurate</td>
</tr>
</tbody>
</table>

Figure 2. Peripheral Nerve Stimulator
is vital in decreasing the risk of RNMB.\textsuperscript{3,4,17,18} In terms of qualitative monitoring, the measured values that are considered safe for neuromuscular blockade recovery have changed over the years.\textsuperscript{17} In the 1970s to 1990s, a TOFR of 0.7 or greater was considered the “gold standard” value representing safe levels of recovery from neuromuscular blockade.\textsuperscript{17} However, the current gold standard has risen to a TOFR of 0.9 or greater, as evidence became available suggesting that a TOFR below 0.9 is associated with compromised airway patency, impaired pharyngeal musculature, symptoms of muscle weakness, and even decreased hypoxic ventilatory response, which can lead to respiratory distress.\textsuperscript{3,4,17}

Regrettably, TOFRs determined by qualitative measures are subject to a high degree of potential interrater variance as well as patient variability, which may translate into a lower degree of patient safety. For example, various studies have found that the 5-second head lift, a commonly used qualitative measure to determine adequate recovery from blockade, has been correlated with TOFRs as low as 0.25 and as high as 0.8, indicating a lack of sensitivity in the test.\textsuperscript{17} Furthermore, absence of observed or tactile fade in response to TOF stimulation does not indicate adequate recovery of the block as TOF fade is indistinguishable once the TOFR exceeds 0.4 and when it exceeds 0.6 to 0.7 for DBS.\textsuperscript{10,11} Some qualitative tests for RNMB such as head lift or grip strength are not only imprecise but require that the patient be awake and cooperative.\textsuperscript{3} In addition, a study on the pharyngeal and facial muscle function and spirometry values of 12 volunteers who were given rocuronium to maintain a TOFR of 0.5 to 0.8 (measured via accelerometry) found that respiratory and pharyngeal functions were affected even at a TOFR of 0.8.\textsuperscript{13}

With these results in mind, and considering the research showing qualitative measurements to be imperfect assessments of the TOFR, Cammu et al\textsuperscript{15} suggest that “assessment via accelerometry of the TOFR of adductor pollicis muscle is more useful to predict the effects of residual paralysis on respiratory function than visual assessment of fade of thumb abduction or testing the ability to sustain a head lift for longer than five seconds.” Furthermore, a study of 640 surgical patients, in which rates of RNMB were assessed on arrival to the postanesthesia care unit (PACU) using an accelerometer as well as qualitative methods, such as 5-second head lift and ability to speak and swallow, found that each patient who experienced RNMB had been monitored via qualitative methods (a TOFR of 0.9 was used as the cutoff value for RNMB).\textsuperscript{15} None of the traditional, qualitative clinical tests used had a sensitivity greater than 0.35, and accelerometry was able to more accurately detect RNMB, prompting the authors to suggest the use of accelerometry in the operating room (OR).\textsuperscript{3,15} These findings, the degree of variability of NMBAs and reversal agents, and the fact that a patient may present a unique response to NMBAs and reversal agents suggest the importance of adopting some form of systematic neuromuscular blockade monitoring as a “standard” of perioperative anesthesia care. Moreover, knowledge of the pharmacology of various NMBAs and reversal agents, in addition to awareness of the importance and prevalence of RNMB, may lead to improved safety and optimized outcomes.

**Neuromuscular Blockade Antagonism: Current Practice and Limitations**

The blockade of acetylcholine receptors on the motor end plate to produce skeletal muscle paralysis through the use of NMBAs and their subsequent reversal, while complex, is central to the practice of anesthesia. When a motor nerve is depolarized, voltage-gated calcium channels open up, resulting in an influx of calcium into the motor nerve, causing the vesicles that store acetylcholine to be exocytosed into the synaptic cleft.\textsuperscript{10,19} Acetylcholine then diffuses across the synaptic cleft, eventually binding to nicotinic acetylcholine receptors on the motor end plate, leading to an influx of sodium into and efflux of potassium out of the muscle cell, and resulting in depolarization of the muscle cell.\textsuperscript{10,19} If the depolarization reaches threshold, a muscle contraction ensues.\textsuperscript{10,19}

There are 2 classes of NMBAs: depolarizers, such as succinylcholine, and nondepolarizers, such as ro-
curonium and atracurium. This course will concentrate on the latter, specifically steroidal compounds such as rocuronium. When administered, nondepolarizing NMBAs produce muscle paralysis by competing with acetylcholine and binding to the nicotinic receptor sites at the motor end plate, thus blocking those receptors and inhibiting muscle contraction.1,3,10,19 Characteristically, nondepolarizing NMBAs will result in the presence of fade with TOF and tetanic stimulation, posttetanic facilitation, and a decreased response to single-twitch stimuli, all of which the anesthesia provider can use to judge adequate neuromuscular blockade and recovery.10,19

Acetylcholinesterase is an enzyme present in the neuromuscular junction that breaks down acetylcholine; in the absence of an NMBA in a normal muscle, acetylcholinesterase is responsible for muscle relaxation.10,19 Traditionally, reversal of NMBAs is achieved via acetylcholinesterase inhibitors, such as neostigmine, which prevent the enzyme acetylcholinesterase from breaking down acetylcholine (Figure 4A).10,19 The blocking of acetylcholinesterase results in accumulation of acetylcholine in the synaptic cleft, ultimately “outcompeting” the NMBA at the nicotinic acetylcholine receptor and reversing muscle paralysis.10,19 However, acetylcholinesterase inhibitors are not selective at the neuromuscular junction; thus, acetylcholine levels increase throughout the body, which can result in undesirable muscarinic effects such as nausea, vomiting, and bradycardia.10,19 For this reason, antimuscarinic medications such as glycopyrrolate are given along with acetylcholinesterase inhibitors to temper these undesirable effects.10,19 Finally, various factors affect the antagonism of NMBAs. These factors include the acetylcholinesterase inhibitor itself, metabolism and elimination of the NMBA from the body independent of the acetylcholinesterase inhibitor; volatile agents that are known to potentiate NMBAs; and various metabolic factors and electrolyte disturbances such as hypermagnesemia, hypocalcemia, and hypokalemia (all of which can potentiate the effects of NMBAs).10,19 Other factors affecting antagonism of NMBAs that are most important to this course are the dose of the acetylcholinesterase inhibitor administered and the depth of blockade that is being attempted to be reversed.10,19

Despite its usefulness in reversing drug-induced paralysis, neostigmine may actually contribute to rates of RNMB if used improperly.3 In addition, neostigmine may either be ineffective or have undesired, contradictory effects depending on the dosage given, the level of neuromuscular block the patient is experiencing, and the NMBA used.3 Depending on dose, neostigmine can block 100% of acetylcholinesterase at the neuromuscular junction, resulting in a persistent, depolarizing-like block from the excess acetylcholine; this ceiling effect is a primary factor in establishing essentially a maximum dose for neostigmine administration.1 A recent study20 of 10 patients found that administration of 30 µg/kg of neostigmine increased airway collapsibility in healthy volunteers to a degree comparable with neuromuscular blockade with a TOFR of 0.5. These results are concerning. The typical dose range of neostigmine for the reversal of NMBAs is 25 to 75 µg/kg; therefore, these results suggest that even “normal” doses can lead to RNMB and airway compromise.10,20 Furthermore, research has shown that when reversal is attempted with TOF counts of 1 or less, clinical recovery is not only slow but may play a role in the development of RNMB.21 Kopman et al21 examined reversals of nondepolarizing NMBAs with TOF counts of 1 or less and found that safe reversals were excessively delayed, in that 29 of 40 subjects had not reached a TOFR of 0.7 or more within 10 minutes of reversal with neostigmine and 5 of 40 subjects “failed to reach a TOF ratio of 0.70 within 20 minutes.” These findings are worrisome because delayed recovery to safe levels of neuromuscular function may result in RNMB, placing the patient’s safety at risk.21 Kopman et al21 also point out that reversal of deep blocks, which results in low TOFRs, further compounds the issue because visual and tactile observation of low TOFRs has been shown to be difficult and inaccurate for practitioners.

**Value of Objective Monitoring**

Objective monitoring devices that provide numeric output regarding TOF levels are available to monitor neuromuscular blockade and minimize the occurrence of RNMB.1,3,22 Mechanomyography (MMG) measures the force of isometric contraction of a muscle after nerve stimulation (typically the adductor pollicis muscle and the ulnar nerve in the case of NMBA monitoring); it is considered the gold standard in quantitative measure-
In fact, the gold standard of a TOFR of 0.9 or greater to ensure adequate neuromuscular blockade recovery is based on data from MMG devices. However, as MMG devices are cumbersome and time-consuming to set up, these devices are typically used only for research purposes. Conversely, acceleromyography (AMG) devices have been used since 1988; newer devices such as the TOF-Watch are the most commonly used of these devices, because they are compact and designed for intraoperative applications. Unfortunately, AMG devices can be prohibitively expensive, with costs ranging from $800 to $2,400 per unit. Although MMG is based on isometric measurements, AMG measures isotonic contraction of muscle tissue (most commonly the thumb) in response to nerve stimulation (most commonly the ulnar nerve); with both devices, a transducer is fixed to the muscle of interest and senses the movement, generating an electrical signal that ultimately is converted into numeric output representing the TOF. A criticism of AMG devices is that the thumb must be free of manipulation from surgical drapes and from contact with the palm, because these scenarios may lead to erroneous readings. To ameliorate this situation, many newer AMG devices such as the TOF-Watch include a “preload” device that aims to prevent the thumb from coming into contact with the palm during nerve stimulation and ensure that the thumb returns to its original position after stimulation. Whereas little research has been conducted regarding the effectiveness of using a preload, one study involving 60 patients randomized into 2 groups, 1 with the use of a preload mechanism and 1 group without, found that the use of a preload improved the accuracy of AMG by 21% with use of the TOF-Watch SX. An extensive literature review compared AMG and MMG, the results of which suggest that the 2 methods of quantitative measuring devices, as incorrect measurements can lead to higher rates of RNMB. Research suggests that control readings for AMG are higher than those for MMG; however, use of a preload improved the accuracy of the AMG devices, which in turn improved agreement between AMG and MMG readings (patients in both groups had AMG devices on one hand and MMG devices on the other). In addition, the differences between AMG (with preload use) and MMG were significantly decreased when the TOFR was used in reference to the original control TOF reading (ie, the data was normalized), allowing data from AMG and MMG to be compared. Furthermore, the use of a preload increased the mean control TOFR from 1.07 to 1.13. As previously mentioned, the gold standard that the TOFR be 0.9 or greater to avoid RNMB was determined based on data provided by MMG devices. The literature consistently finds that TOF readings obtained from AMG devices are typically higher than readings obtained from MMG devices. Therefore, it is suggested that baseline TOF values should be referred to when one is determining the TOFR and that the standard TOF value used to ensure complete recovery should be at least 1.00 during use of AMG devices.

A seminal review by Brull and Kopman emphasized objective quantitative measurement as the only method to determine appropriate timing of tracheal extubation and ensure normal muscle function, a recommendation urged by other authorities as well. Fewer patients enter the PACU with a TOFR below 0.9 when AMG is used than when qualitative nerve stimulators are used. A randomized controlled trial (RCT) comparing the use of AMG with the use of PNS revealed that the recovery time to reach a TOFR of 0.9 or greater was 0.9 minutes for the AMG group and 0.8 minutes for the PNS group. Although the authors urge the use of an accelerometer when available, their results revealed that a PNS was as efficacious as an accelerometer in their sample.

An observational study of 27 anesthesia providers compared their ability to judge the TOF using visual and tactile means with TOF values obtained by AMG and MMG devices. Results revealed not only that AMG measurements closely correlated with MMG measurements but also that AMG ratios were safer for reducing rates of RNMB, as visual and tactile fade was imperceptible above a mean MMG ratio of 0.31. Likewise, a study comparing the use of the TOF-Watch SX with traditional subjective measures such as visual and tactile detection in 75 patients cared for by 38 anesthesia providers found that providers frequently assessed higher TOF counts by subjective measurements than the TOF counts obtained by the TOF-Watch SX. Falsely assessing higher TOF counts by subjective measurements underscores the importance of quantitative measuring devices, as incorrect measurements can lead to higher rates of RNMB. A large multicenter observational study of 326 patients aimed to determine the rates of RNMB in patients whose providers used only subjective monitoring (PNS monitor or visual and tactile observation) to quantify TOF. Observers were blinded to quantitative TOF results recorded by the TOF-Watch SX at 10 time points, including 10 minutes after administration of the reversal agent, immediately before extubation, and at PACU arrival. The study revealed that RNMB, evidenced by a TOFR of 0.9 or below as recorded by a TOF-Watch SX, occurred in 63.5% and 56.5% of patients at tracheal extubation and arrival to the PACU, respectively.

Recently, investigators assessed the effect of implementing universal use of AMG in an institution’s OR over the course of a year. The initial mean (SD) TOFR in 91 patients before implementation was 0.9 (0.18; median = 0.94); moreover, the initial proportion of patients with TOFRs at or below 0.5, 0.8, and 0.9 was 4%, 17%, and 31%, respectively. After implementation, the
mean TOFR in 101 patients had increased to 0.95 (SD = 0.08; median = 0.98), and the proportion of patients with TOFRs at or below 0.5, 0.8, and 0.9 had decreased to 0%, 5%, and 15%, respectively.27

An RCT involving 150 patients comparing the use of AMG with a control group that utilized qualitative monitoring methods found that the number of patients with a TOFR of 0.9 or less was significantly lower in the AMG group: 11 patients in the AMG group (14.5%) vs 37 patients in the qualitative monitoring group (50.0%; P < .0001).28 Furthermore, the AMG group reported lower perceived muscle weakness in the PACU and reported significantly higher recovery on a 100-mm visual analog scale than the qualitative monitoring group, indicating that patient satisfaction had a positive correlation to lower rates of RNMB.28

**New Horizons: Sugammadex**

Sugammadex, the first selective relaxant binding agent, is a molecule composed of cyclic dextrose units: a modified γ-cyclodextrin.29 Due to the cyclic structure of sugammadex, there is a large lipophilic internal cavity in the molecule, enabling an encapsulation mechanism of action to occur with the amino steroid class of NMBAs, with evidence showing a favoring of rocuronium > vecuronium >> pancuronium.29,30 Sugammadex selectively forms complexes in a 1:1 ratio with the amino steroid class of NMBAs such as rocuronium, reversing paralysis by preventing the drug from binding to the nicotinic acetylcholine receptor sites (Figure 4B).2-4 This encapsulation process makes rocuronium unavailable to the acetylcholine receptor at the neuromuscular junction, allowing acetylcholine to bind without competition and promoting the reemergence of muscle contraction.2 Furthermore, this encapsulation, due to intermolecular forces such as hydrogen bonds, creates an immensely tight complex with the nondepolarizing NMBA, such that only 1 in every 25 to 30 million sugammadex-rocuronium complexes dissociates.19,20 Compared with acetylcholinesterase inhibitors, this unique method of action has been shown to decrease rates of RNMB.2-4 Although not specifically related to RNMB, another advantage of sugammadex compared with traditional acetylcholinesterase inhibitors is that it avoids possible muscarinic side effects, such as bradycardia, bronchoconstriction, and nausea and vomiting, because its mechanism of action does not increase acetylcholine levels (which can lead to muscarinic side effects).1,19 Finally, it should be noted that sugammadex does not interact with any receptor system in the body and is excreted unchanged in the urine because of the external hydrophilic properties of the sugammadex-rocuronium complex.19,29 Despite its promising pharmacologic properties, caution must be exerted when one is using sugammadex, just as when using any other medication.

Tempering injudicious use are findings suggesting caution in the use of sugammadex. Intraoperative anaphylaxis and increased bleeding with prolonged activated partial thromboplastin time and prothrombin time (or international normalized ratio), although infrequent, have been associated with its use.3,29,31,32 In contrast, a recent observational study comparing 142 patients in 3 groups—without sugammadex, with administration of 2 mg/kg of sugammadex, and with 4 mg/kg of sugammadex—found no significant difference in measures of blood coagulation after sugammadex at either dose.31 In a randomized, double-blind, placebo-controlled, parallel-group, repeat-dose study of 299 healthy and 176 nonhealthy individuals, in which 151 subjects received 4 mg/kg of sugammadex, 148 subjects received 16 mg/kg, and 76 received a placebo, the frequency of anaphylaxis was 0.3%.33 Recent findings suggest that providers should be aware of the risk of anaphylaxis associated with the use of sugammadex, as its use continues to rise after its relatively recent (2015) approval in the United States.3,32 Of note, sugammadex is a cyclodextrin, which are used in the food industry as carriers and stabilizers of flavors, colors, fat-soluble vitamins, and polyunsaturated fatty acids.34 The authors suggest that patients may become sensitized to sugammadex because of contact with foods or other products, despite having no preoperative history of allergy to cyclodextrin-containing foods.34 Finally, it is important to note that sugammadex reduces the effects of progesterone, and female patients are thus urged to use an additional method of contraception for 1 week following sugammadex use and/or follow the directions for missing 1 dose of their currently used oral contraceptive.29

Despite these risks, initial outcomes of sugammadex use are appealing: a meta-analysis published by The Cochrane Library of 18 RCTs revealed many promising

![Figure 4B. Neuromuscular junction with sugammadex mechanism of action. Note encapsulation of rocuronium by sugammadex.](image-url)
findings related to the use of sugammadex compared with more traditional agents such as neostigmine. Of note, 6 studies demonstrated that doses of 2 mg/kg and 4 mg/kg of sugammadex were able to reverse blockade with a mean time of less than 3 minutes, regardless of the dosage of rocuronium used for intubation and/or maintenance. Additionally, 3 studies compared sugammadex with neostigmine and found that reversal using sugammadex was 5 to 17 times faster than when using neostigmine. More importantly, 5 trials compared the safety of sugammadex with that of neostigmine and found no relationship between adverse events and sugammadex use, whereas neostigmine and glycopyrrolate were associated with more changes in blood pressure and heart rate. Another meta-analysis, consisting of 13 RCTs and a total of 1,384 patients, found sugammadex to be both safer and more effective at reversing neuromuscular blockade compared with neostigmine. This meta-analysis found that both respiratory complications (eg, hypoxemia, bronchospasm, and atelectasis) and cardiovascular events (eg, arrhythmias and atrial pressure variance) were more frequently associated with neostigmine than with sugammadex.

The safety of sugammadex use in the pediatric population is unknown. Although the literature regarding this topic is sparse, some studies are encouraging in this regard. Results of an RCT comparing the use of sugammadex and neostigmine in reversal of rocuronium in 60 patients aged 2 to 10 years undergoing abdominal surgery revealed that those given sugammadex experienced statistically significantly shorter (faster) muscle recovery times on average (1.4 [SD 1.2] minutes) compared with the neostigmine group (25.2 [6.5] minutes). No adverse events were reported by either group during the study. This RCT, as well as a recent case report reporting use of sugammadex in a “can’t ventilate/can’t intubate” scenario, further suggests the need for more research in pediatric patients.

Additionally, sugammadex may benefit patients with complex disease states. It has been associated with fewer adverse events such as respiratory and cardiovascular complications compared with neostigmine in a recent meta-analysis.

An RCT of 99 patients randomly assigned to 3 overall groups (saline placebo, sugammadex, and neostigmine) aimed to find doses of sugammadex and neostigmine that would reverse rocuronium-induced blockade (measured as TOFR ≥ 0.2) to a TOFR of 0.9 or greater in 50% of the patients within 2 minutes and 95% of the patients within 5 minutes. The results revealed that neostigmine is not able to reverse a TOFR from 0.2 or higher to 0.9 or more within 10 minutes in 95% of patients. On the other hand, sugammadex is able to reverse a TOFR from 0.2 or greater to 0.9 or more in 93% of patients within 5 minutes at a dose of approximately 0.50 mg/kg and within 10 minutes at a dose of approximately 0.26 mg/kg. Ultimately, one can conclude from these results that sugammadex may be faster, more reliable, and better at preventing RNMB than neostigmine. These conclusions are supported by the meta-analysis by Carron et al whose findings also suggest that sugammadex is a safer drug than neostigmine; they found that sugammadex use was associated with a significantly lower risk of respiratory and cardiovascular adverse events as well as postoperative weakness.

Unfortunately, sugammadex use is not infallible. Some studies (including the meta-analysis by Carron et al) reveal that, although rates tend to be lower, RNMB still occurs when sugammadex is used to reverse NMBAs. Thus, even with the use of sugammadex, the anesthesia provider cannot rely on drugs alone to prevent RNMB and should not overlook the importance of vigilant perioperative monitoring of neuromuscular blockade while using any NMB, especially during emergence and extubation. The fact that anesthesia providers must rely on both monitoring and careful administration of medications during the perioperative period might seem somewhat “self-evident.” However, with current research findings showing that our current, more traditional methods of subjective monitoring and the use of anticholinesterase agents may place patients’ safety at risk, a change in practice may lead to better patient outcomes.

### Recommendations for Clinical Practice to Reduce the Risk of RNMB

The following are evidence-based recommendations for reducing RNMB risk:

- Consider the PNS as part of routine monitoring practice, become familiar with its shortcomings, and place the PNS monitor on the patient before induction, to ensure proper placement and establish a baseline reading.

- If an accelerometer is available, consider its use over that of a PNS because evidence shows accelerometers aid in the prevention of RNMB.

- Use the adductor pollicis muscle when possible, because the facial nerve and orbicularis oculi muscles have been found to be unreliable and the abductor hallucis and orbicularis oculi have been associated with premature recovery readings. Furthermore, direct muscle stimulation of the orbicularis oculi has been shown to confound PNS readings despite the nerve being blocked, leading to overdosing of the NMBA and overappreciating the degree of recovery from the NMBA.

- Take care to not give patients unnecessary amounts of neostigmine, as this practice has been associated with paradoxical paralysis. The typical dose range is 25 to 75 μg/kg.

- Allow for a sufficient degree of spontaneous recovery before administration of reversal agents. The timing of neostigmine administration is important to successful reversal of neuromuscular blockade: research has shown...
that reversal attempts with TOF counts of 1 or less are less likely to achieve safe levels of neuromuscular recovery in the same amount of time as patients reversed with all 4 twitches present.21,37

- Consider the use of sugammadex, as current evidence has shown that sugammadex aids in the prevention of RNMB and is safer than more traditional reversal agents such as neostigmine.2,35

Although the aforementioned suggestions will likely minimize rates of RNMB, they are not foolproof. The clinical evidence reveals that the use of qualitative measures and traditional reversal agents such as neostigmine are associated with higher rates of RNMB and that, if available, sugammadex is an attractive alternative to traditional reversal agents. Additionally, literature reveals that sugammadex is associated with decreased rates of RNMB and allows for more reliable blockade reversal compared with acetylcholinesterase inhibitors. Unfortunately, as sugammadex was only recently approved for use in the United States and 200-mg vials reportedly cost more than $90, the novelty and cost associated with sugammadex have hindered its widespread use.35,41 Additionally, the cost of reversing a moderate blockade at one major teaching institution with sugammadex at a dose of 2 mg/kg for an 80-kg patient ($80) is similar to that of neostigmine and glycopyrrolate administered together at 5 mg and 1 mg, respectively ($35 and $30). However, for reversing a deep blockade, the neostigmine/glycopyrrolate combination yields a savings of $100 compared with sugammadex at a dose of 4 mg/kg for an 80-kg patient ($160). Although evidence is sparse, initial findings suggest that, despite the outright high cost of sugammadex, the prevention of adverse events, lower rates of RNMB, and overall faster recovery time leading to faster OR turnover may translate into overall lower cost.42,43 Moreover, overwhelming evidence suggests that quantitative monitoring is superior to traditional qualitative monitoring in reducing postoperative RNMB. With the above evidence in mind (see summary in Table 2), current practice may need to be modified to reduce rates of RNMB and to increase patient safety outcomes.

### REFERENCES


### Table 2. Summary of Traditional and Evidence-Based Methods

<table>
<thead>
<tr>
<th>Traditional methods</th>
<th>Evidence-based methods</th>
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<tbody>
<tr>
<td>Reversal agents</td>
<td>Acetylcholinesterase inhibitors, eg, neostigmine</td>
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<tr>
<td>Monitoring techniques</td>
<td>Subjective measures</td>
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<tr>
<td></td>
<td>Tactile and/or visual observation of TOFR via PNS</td>
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<td></td>
<td>Five-second head lift</td>
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<td></td>
<td>Tongue depressor test</td>
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<tr>
<td>Benefits</td>
<td>Qualitative measures: PNS are much cheaper than AMG devices</td>
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<tr>
<td></td>
<td>Neostigmine: Increased rates of RNMB and associated adverse events, including death</td>
</tr>
<tr>
<td></td>
<td>Neostigmine: Increased rates of RNMB and associated adverse events, including death</td>
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<tr>
<td>Shortcomings</td>
<td>Qualitative measures: Imprecise and not reliable</td>
</tr>
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<td>Increased rates of RNMB</td>
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<tr>
<td>Bottom line</td>
<td>Traditional methods are associated with increased rates of RNMB and associated adverse events. Objective monitoring techniques and sugammadex have been shown to decrease rates of RNMB but are costly and have limited availability. When sugammadex and other objective measures are not available, anesthesia providers should, at the very least, know the limitations of subjective monitoring and use PNS for intraoperative monitoring.</td>
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</table>


Full Prescribing Information: Sugammadex. 2015.


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AUTHORS
Ryan Wiatrowski, BSN, RN, CCRN, is a student registered nurse anesthetist at Virginia Commonwealth University in Richmond, Virginia. He
earned his BSN at Georgetown University, Washington, DC, in 2013. Email: wiatrowskim@mymail.vcu.edu.

Laura Martini, BSN, RN, CCRN, CSC, is a student registered nurse anesthetist at Virginia Commonwealth University. She earned her BSN at Villanova University, Villanova, Pennsylvania, in 2013. Email: martinil@mymail.vcu.edu.

Brandy Flanagan, BSN, RN, CRN, CCRN, is a student registered nurse anesthetist at Virginia Commonwealth University. She earned her BSN at University of Nebraska Medical Center College of Nursing, Omaha, Nebraska, in 2009. Email: flanaganbl@mymail.vcu.edu.

Kathryn Freeman, BSN, RN, CCRN, is a student registered nurse anesthetist at Virginia Commonwealth University. She earned her BSN at George Mason University, Fairfax, Virginia, in 2010. Email: reberskm@mymail.vcu.edu.

Naomi Sloan, BSN, RN, CCRN, is a student registered nurse anesthetist at Virginia Commonwealth University. She earned her BSN at University of Kentucky, Lexington, Kentucky, in 2013. Email: sloann@mymail.vcu.edu.

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