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Clinical UPDATE

# Improving Recognition and Prevention of Residual Paralysis After Surgery: Case Examples of Monitoring and Reversal

**TARGET AUDIENCE:** This activity has been designed to meet the educational needs of anesthesiologists and anesthesia providers.

## PROGRAM OVERVIEW

Neuromuscular blocking agents (NMBAs) cause generalized paralysis of skeletal muscles and prevent involuntary movement during surgical procedures. Often, residual paralysis remains postoperatively—a phenomenon known as residual neuromuscular blockade (RNMB)—and is associated with both short- and long-term morbidity. Despite the risks associated with RNMB, methods to reduce its occurrence through monitoring and reversal are not applied universally in clinical practice.

## EDUCATIONAL OBJECTIVES

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

1. Recognize the prevalence and degree of morbidity and adverse events associated with RNMB in patients who have undergone general anesthesia for a surgical procedure.
2. Advocate for the consistent use of quantitative monitoring for RNMB.
3. Describe the appropriate use of NMBA reversal agents based on their mechanisms of action.

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**ESTIMATED TIME TO COMPLETE ACTIVITY:** 1 hour

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## Introduction

Residual neuromuscular blockade (RNMB)—defined as postoperative muscle weakness after administration of neuromuscular blocking agents (NMBAs) as measured by a train-of-four (TOF) threshold value of less than 0.9—is a common postoperative complication that is substantially and perilously underrecognized. In a 2008 survey of nearly 1,800 US anesthesiologists, more than 50% of respondents believed the incidence of clinically significant postoperative RNMB to be less than 1%, and nearly 90% of clinicians claimed they had never observed a patient exhibiting postoperative residual paralysis.[1] More recently, a much smaller survey by Aytac et al found that 71% of anesthesiologists believe that the incidence of RNMB in their practices is 10% or less.[2] This is contrary to published data suggesting that 4% to 88% of patients receiving NMBAs experience some degree of residual paralysis. Table 1 summarizes the most recent studies examining the incidence of RNMB.[2-21] The wide range in frequencies reflects many variables in assessment, including the method of assessment, time of measurement (eg, before or after tracheal extubation or arrival to the post-anesthesia care unit [PACU]), type and dose of NMBA, degree of neuromuscular blockade (NMB), type of pharmacologic reversal, and patient factors, among others.[22]

In a meta-analysis of 24 studies that included 3,375 patients, Naguib et al found that 41% of patients receiving intermediate-acting NMBAs had TOF ratios (TOFRs) less than 0.9.[23] There are several predictors of RNMB, including monitoring site, time interval after last dose of an NMBA, total dose of NMBA, body mass index (BMI), female gender, shorter procedure time, and advanced age.[2,19,24] Many of these are illustrated in the case examples that follow. Interestingly, one study found significantly higher RNMB in patients receiving neostigmine than in those who did not (31% vs 17%; $P$=0.01),[14] and others found no difference in incidence of RNMB in patients who received neostigmine versus those who did not.[2,13] Although reversal of NMB is important and has been found to decrease postoperative morbidity and mortality, it must be achieved appropriately; common oversights in the administration of NMB reversal drugs also are highlighted in the case examples.

RNMB is a serious postoperative complication that is associated with significant morbidity, particularly adverse respiratory events. Volunteer studies have found that RNMB is associated with impaired pharyngeal and upper airway function, swallowing dysfunction, aspiration, and decreased hypoxic ventilatory drive.[22] In a review of 9 studies on the relationship between RNMB and critical respiratory events in surgical patients, Kiekkas et al found a significant association between hypoxemia and RNMB.[25] Moreover, hypoxic ventilatory response is impaired until patients achieve a TOFR greater than 0.9 and can result in atelectasis and postoperative pneumonia.[26] Murphy et al performed several studies demonstrating a number of complications in patients with residual paralysis, including delayed tracheal extubation and critical respiratory events.[27,28] Similarly, Norton et al concluded that patients with RNMB were significantly more likely to experience critical respiratory events than those without RNMB (51% vs 16%; $P$<0.001),[16] and Aytac et al found that 84% of patients with a TOFR less than 0.9 had a critical respiratory event ($P$<0.001).[2] These complications can be more pronounced in obese patients, as highlighted in the case examples that follow. In addition to adverse respiratory events, RNMB leads to longer duration of hospital stay, muscle weakness, and poorer quality of recovery.[22] For example, patients whose TOFR is less than 0.9 experience more general weakness, difficulty with eye opening and 5-second head lift, diminished ability to speak and cough, blurry and double vision, and facial numbness in the first 60 minutes after PACU arrival; these patients also report significantly lower quality of recovery.[29] Of note, most patients who achieve a TOFR greater than 0.9 have recovered sufficiently from NMB; however, impairment of respiratory function and muscle weakness may remain even after achieving a TOFR of 0.9, which is particularly relevant in patients undergoing ambulatory surgery.[26,30]

**Table 1. Incidence of RNMB (TOFR <0.9)[2-21]**

| Author/ Year | N | NM Assessment, % | Reversal, % | Time Measured | Incidence of RNMB, % |
|---|---|---|---|---|---|
| Debaene et al, 2003[3] | 526 | NS | 0 | PACU | 45 |
| Kopman et al, 2004[4] | 60 | 100 (S) | 100 | Transfer to PACU | 37-50 |
| Murphy et al, 2004[5] | 70 | 100 (S) | 100 | PACU | 29-83 |
| Murphy et al, 2005[6] | 120 | 100 (S) | 100 | Extubation | 88 |
| Baillard et al, 2005[7] | 101 | 45 (O) | 43 | PACU | 9 |
| | 218 | 60 (O) | 42 | PACU | 3.5 |
| Cammu et al, 2006[8] | 640 | 11-12 (O) | 25-26 | PACU | 38-47 |
| Maybauer et al, 2007[9] | 338 | 100 (O) | 0 | Extubation | 44-57 |
| Murphy et al, 2008[10] | 179 | 50 (O)<br>50 (S) | 100 | PACU | 4.5<br>30 |
| Thilen et al, 2012[11] | 150 | 100 (S) | 89 | PACU | 22-52 |
| Cammu et al, 2012[12] | 624 | 47 (S) | 29 | PACU | 2-15 |
| Ledowski et al, 2013[13] | 146 | 88 (S) | 62 | Extubation | 8-59 |
| Esteves et al, 2013[14] | 350 | NS | 67 | PACU | 26-30 |
| Kotake et al, 2013[15] | 249 | 0 | 90 | Extubation | 4-24 |
| Norton et al, 2013[16] | 202 | NS | 86 | PACU | 30 |
| Brueckmann et al, 2015[17] | 150 | 87 (O) | 100 | PACU | 0-43 |
| Fortier et al, 2015[18] | 241 | 67 (S) | 74 | Extubation | 64 |
| | 207 | 66 (S) | 72 | PACU | 57 |
| Murphy et al, 2015[19] | 150 | 100 (S) | 100 | PACU | 30 |
| | 150 elderly | | 100 | PACU | 58 |
| Pietraszewski et al, 2015[20] | 415 | 0 | 0 | PACU | 18 |
| Yu et al, 2016[21] | 1,571 | NS | 78 | Extubation | 58 |
| | | | | PACU | 45 |
| Aytac et al, 2016[2] | 415 | NS | 66 | PACU | 43-46 |

**N,** subject number; **NM,** neuromuscular; **NS,** not specified; **O,** objective; **PACU,** post-anesthesia care unit; **RNMB,** residual neuromuscular blockade; **S,** subjective; **TOFR,** train-of-four ratio

The consequences of residual paralysis are costly in terms of reduced PACU throughput and costs associated with respiratory complications.[26] Recent changes in the landscape of NMB reversal drugs, however, have expanded the pharmacoeconomic considerations of RNMB. Although difficult to quantify because of the many variables that affect cost, some authors have speculated that sugammadex (Bridion, Merck) will reduce the incidence of prolonged intubation and improve PACU throughput.[31] Recently, Carron et al provided such evidence, finding that the use of sugammadex resulted in more rapid turnover and no unplanned intensive care unit admissions in their institution.[32] Because sugammadex has consistently been associated with improved efficacy in reversing NMB compared with neostigmine,[33] it may become the preferred agent for reversal, especially because in many markets, the difference between the cost of sugammadex and that of neostigmine plus glycopyrrolate is minimal. The increase in the price of neostigmine in the United States likely reflects the FDA requirement for approval of neostigmine and the withdrawal from the market of all other unapproved formulations. A review of the comparative efficacy of sugammadex versus neostigmine can be found at www.cmezone.comIP153/.

## Clinical Case Examples

### *Case 1: 47-Year-Old Woman With Ulcerative Colitis and Undergoing Colectomy*

**Patient Characteristics**

- Height: 5 feet 4 inches
- Weight: 180 pounds (82 kg); BMI: 31 kg/m$^2$ (obese)
- American Society of Anesthesiologists (ASA) physical status (PS): 3

**Outcomes**

The patient received general endotracheal anesthesia with sevoflurane 2%, fentanyl, and rocuronium. Her TOF count was 1 of 4 at the time of pharmacologic reversal. During subcuticular closure of the abdominal incision, the patient received a total of 5 mg of neostigmine. ***At the conclusion of surgery, the peripheral nerve stimulator (PNS) twitch count was 4 of 4, with sustained tetanus and spontaneous ventilations*** at 14 per minute. Tidal volume (TV) with pressure support was 300 cc, and end-tidal carbon dioxide ($CO_2$) was 50 mm Hg. The volatile anesthetic agent sevoflurane was discontinued. The patient awoke shortly thereafter and ***displayed head lift on command, TV 600 cc, and firm hand grasp. Approximately 15 minutes after arrival in the PACU, the patient experienced respiratory arrest with bradycardia.*** Her arterial blood gas test revealed the following: pH, 7.25; partial pressure of $CO_2$, 90 mm Hg; partial pressure of oxygen ($O_2$), 57 mm Hg; bicarbonate, 27 mmol/L; and $O_2$ saturation, 89%. ***TOF accelerometry was performed at this time and displayed a TOFR of 0.7.*** Sugammadex 164 mg (2 mg/kg) was administered, and the TOFR reached 0.95 within 4 minutes. Tracheal reintubation was avoided.

**Key Learning Points**

Obesity is associated with many comorbidities. A large body habitus has long been known to increase the work of breathing and decrease lung volume.[34] Generally, low-level NMB, in addition to muscle weakness, decreases hypoxic drive and predisposes patients to airway collapse.[35] ***Obesity also is associated with hypoventilation syndrome, which in conjunction with residual paralysis, predisposes the obese patient to respiratory depression*** and, as in this case example, leads to respiratory failure.[36] If possible, it may be wise to avoid NMB in this patient demographic and consider whether muscle relaxation, which can be achieved by volatile anesthetics, is adequate for surgery.

In this case, NMB was deemed necessary, and neostigmine was administered when the patient's TOF count was 1 of 4. The indirect action of neostigmine, a cholinesterase inhibitor–type reversal drug, and its well-known ceiling effect necessitate a greater degree of spontaneous recovery before administration. ***An understanding of the limitations of neostigmine has led to recommendations that include waiting until 2 to 4 twitches are present (TOFC 2-4) before initiating neostigmine reversal.***[37,38] Even with a degree of spontaneous recovery before neostigmine reversal, achievement of a TOFR of 0.9 or greater can be delayed. Joshi et al found that overweight and obese patients receiving neostigmine reversal of vecuronium-induced block experienced longer times to achieve a TOFR of 0.9 (9.18 minutes for a BMI of 22.11 kg/m$^2$, 12.18 minutes for a BMI of 27.51 kg/m$^2$, 13.78 minutes for a BMI of 32.27 kg/m$^2$; $P<0.05$).[39] Rocuronium reversal with sugammadex occurs within 3 minutes, and the reversal time has not been found to be delayed significantly in obese patients.[40] In this case, the patient received sugammadex 164 mg (2 mg/kg based on total or actual body weight). The dosing of sugammadex based on twitch responses is discussed further in the next case example, but it is important to note that the prescribing information for sugammadex is based on dose-finding studies that used total or actual body weight[41] versus ideal body weight or lean body weight, which may result in underdosing and RNMB.[42]

In this case example, accelerometry was available, but reversal of the NMBA was assessed qualitatively (subjectively) using a PNS before tracheal extubation. This practice may, in fact, be common. A recent study found that despite the availability of quantitative monitors in each operating room and a trained staff, the monitors were used in less than 50% of surgeries in which NMBAs were given, resulting in nearly one-third of patients arriving in the PACU with a TOFR less than 0.9.[43] ***Acceleromyography monitors are significantly more effective in identifying RNMB than clinical tests of muscle weakness[10] or qualitative assessment,[44] and their use is the only reliable way to assess recovery from NMB.***[38] Had accelerometry been used in this patient before tracheal extubation, a TOFR less than 0.9, indicating inadequate reversal, could have been identified and appropriate steps taken to ensure adequate ventilation before PACU transport.

Also in this case example, clinical signs of muscle function were used to assess RNMB after neostigmine reversal. Nearly 70% of US anesthesiologists believe these are dependable indicators of neuromuscular function[1]; however, the data clearly and consistently demonstrate that clinical tests to assess muscle weakness are unreliable.[8,37] ***Most patients can maintain head lift for 5 seconds at a TOFR of 0.5 or less,[45] and TV may be near normal at a TOFR of 0.4.[46] Negative inspiratory force also is commonly used, despite often returning to normal at a TOFR of 0.8.***[46] A recent study suggested that a combination of clinical tests only predicted patients with a TOFR less than 0.9 in 46% of cases.[8]

## *Case 2: 63-Year-Old Man Undergoing 3-Level Spinal Fusion*

### Patient Characteristics

- Chronic obstructive pulmonary disease
- Height: 5 feet 7 inches
- Weight: 140 pounds (64 kg); BMI: 22 kg/m$^2$
- ASA PS: 4

### Outcomes

The procedure was performed with the patient in the prone position, with his arms tucked in at his sides and his head in Mayfield pins. Standard anesthesia induction with fentanyl, propofol, and rocuronium was used for tracheal intubation. Because the patient's arms were unavailable during surgery, ***neuromuscular monitoring was performed using a PNS with the electrodes placed on the face and subjective evaluation of the orbicularis oculi muscle.*** At surgical closure, the anesthesia practitioner felt "4 strong twitches" at the orbicularis oculi and administered 1 mg of rocuronium to ensure that the patient did not move while in the head pins. At the time of reversal, the patient's TOF count was 2 of 4 at the orbicularis oculi, and sugammadex 2 mg/kg was administered. Because the patient could not maintain $O_2$ saturation, tracheal extubation was delayed.

### Key Learning Points

Recent research efforts have focused on the level of NMB necessary during various surgical procedures; these data will be important to guide clinical practice and optimize surgical conditions while minimizing the incidence of RNMB. In a survey, surgeons reported requesting additional neuromuscular relaxation in nearly 25% of surgeries, most often during the last hour of the procedure.[47] Of note, for every 10 minutes between the last dose of an NMBA and subjective assessment of NMB, the risk for RNMB is lowered by 10%.[11]

**Table 2. Recommendations for Use of Different Stimulation Patterns To Monitor NMB[58]**

| Stimulation Pattern | Onset of Block | Deep Block (TOF=0) | Moderate Block (TOF >0) | Recovery |
|---|---|---|---|---|
| TOF | Adequate | Not adequate | Adequate | Adequate (quantitative) |
| | | | | Intermediate (tactile) |
| Double-burst stimulation | Intermediate | Not adequate | Not adequate | Intermediate |
| Tetanus (50/100 Hz) | Not adequate | Not adequate | Not adequate | Intermediate |
| Post-tetanic count | Not adequate | Adequate | Not adequate | Not adequate |

**NMB,** neuromuscular blockade; **TOF,** train-of-four

**Table 3. Sugammadex Dose and Mean Time to TOF >0.9 in Rocuronium-Induced NMB[41,59]**

| Dose, mg/kg | Indication | Mean Time, minutes to TOF >0.9 (Range) |
|---|---|---|
| 2 | Routine reversal if recovery has reached reappearance of second twitch in response to TOF stimulation | 2 (1.2-1.7) |
| 4 | Routine reversal if recovery has reached 1-2 post-tetanic counts and no twitch response to TOF stimulation is observed | 3 (2.7-4.3) |
| 16 | Immediate reversal 3 minutes after 1.2 mg/kg of rocuronium | 1.5 (0.48-14.3)[61] |

**NMB,** neuromuscular blockade; **TOF,** train-of-four

***Current research suggests that deep NMB is beneficial in robotic,[48] laparoscopic,[49] intracranial,[50]*** *and* ***laryngeal procedures,[51]*** but in general, the risks and benefits associated with a bolus dose of an NMBA near the end of a procedure must be discussed thoroughly among members of the surgical team, and the use of volatile anesthetics or opioids to produce sufficient muscle relaxation without additional NMBAs or completion of the procedure with some degree of neuromuscular function should be considered.

The subjective evaluation of muscle function at the orbicularis oculi in this case also may have contributed to RNMB. ***The muscle groups used commonly during NMB assessment have varying sensitivity to and recovery from NMBAs.[46]*** Central muscles, such as the diaphragm, and facial muscles, such as the corrugator supercilii and orbicularis oculi, are resistant to NMBAs and recover from the effects of these agents more quickly than peripheral muscles, such as the adductor pollicis.[11,46,52] For example, when the TOF count is 4 at the facial muscles, it may be 1 or 2 at the adductor pollicis.[52] Even among facial muscles, data suggest variability in response to NMBAs; the corrugator supercilii demonstrates resistance to blockade and a shorter duration of effect, whereas the orbicularis oculi exhibits more sensitivity and a longer duration of effect.[53] Thus, although use of facial muscles may be appropriate in assessing conditions for intubation or paralysis of the diaphragm, ***the adductor pollicis is the recommended site to monitor recovery from NMB.[52]*** Compared with assessment at the eye muscles, TOF monitoring at the adductor pollicis was associated with a 5-fold decrease in residual paralysis in a recent study ($P<0.01$).[11] When a patient's arms are unavailable, as in this case example, ***the flexor hallucis is an alternative that provides a TOF response similar to that of the adductor pollicis.[46]***

Finally, many studies have found that ***visual and tactile TOFR evaluation is highly unreliable.[54]*** In fact, Viby-Mogensen et al concluded more than 20 years ago that ***"it is very difficult, if not impossible, to estimate a TOFR with sufficient certainty to exclude residual curarization,"*** even among those with a special interest and much experience in neuromuscular monitoring.[55] More recently, a study by Bhananker et al found that subjective assessment of TOF count overestimates the number of twitches when compared with acceleromyography measurement in 96% of cases.[56] Dosing and timing of pharmacologic reversal based on these inaccurate assessments may thus be another reason for the high incidence of RNMB. Just as visual and tactile assessment of TOF fade is unreliable, so is the subjective evaluation of TOF count. Certainly, other modes of neurostimulation, such as double-burst stimulation, may improve visual and tactile recognition of fade up to a TOF of 0.7, but they do not reliably improve fade identification.[57] Table 2 summarizes recommendations for the use of different stimulation patterns to monitor NMB.[58]

Sugammadex has been shown to be effective for the reversal of NMB; however, its efficacy depends on appropriate dosing.[41] Some clinicians believe that with the availability of sugammadex, NMBAs can be administered with impunity; however, data suggest that RNMB can occur after the administration of sugammadex, particularly in the absence of objective neuromuscular monitoring.[15,59] Thus, ***it is recommended that sugammadex administration be based on monitoring for twitch responses[41];*** in order to dose sugammadex optimally, objective neuromuscular monitoring should be used.[56] In this case example, evaluation of the TOF count at the orbicularis oculi led to administration of an insufficient dose of sugammadex. Table 3 highlights the approved dosing for sugammadex.[41,59]

## *Case 3: 34-Year-Old Woman Undergoing Laparoscopic Gastric Banding*

### Patient Characteristics

- Height: 5 feet 5 inches
- Weight: 240 pounds (109 kg); BMI: 40 kg/m$^2$ (obese)
- ASA PS: 4

### Outcomes

Standard general anesthesia induction with fentanyl, propofol, and vecuronium for tracheal intubation was used. Neuromuscular assessment was performed with PNS and subjective (visual) evaluation. At the end of the 2-hour procedure (total vecuronium dose, 22 mg), the practitioner visually assessed the presence of 1 twitch to TOF stimulation at the adductor pollicis and administered 6 mg of neostigmine (0.06 mg/kg) plus 0.6 mg of glycopyrrolate. ***Approximately 8 minutes later, the patient had spontaneous ventilation (TV 350 cc), and her trachea was extubated.*** In the PACU, she reported discomfort and symptoms of muscle weakness, including difficulty swallowing and speaking, blurry vision, and fatigue.

### Key Learning Points

Because obesity can affect the pharmacokinetics and pharmacodynamics of NMBAs, dosing NMBAs by ideal body weight versus total body weight has been well characterized in the literature and should be carefully considered against the risk for underdosing and incomplete reversal.[42,61] Data suggest that the pharmacokinetics of vecuronium are not altered in obese patients, and that the duration of action of this drug is prolonged when dosed according to total body weight; consequently, it is recommended that vecuronium be administered according to ideal body weight.[62] In this case example, the vecuronium dose was based on total body weight, thus contributing to the observed RNMB. (For this patient, ideal body weight is calculated as approximately 130 pounds.)

As described in the previous case examples, subjective evaluation of neuromuscular function and inadequate spontaneous recovery before administration of neostigmine allowed RNMB to go undetected. The maximum recommended dose of neostigmine is 5 mg,[63] and because of the ceiling effect mentioned previously, higher doses are unlikely to improve reversal.[64] Of note, many clinicians extubate the trachea too soon after administration of neostigmine; based on data demonstrating median times of 29, 23, 16, and 10 minutes to achieve a TOFR greater than 0.9 from TOF counts of 1, 2, 3, and 4, respectively, it is currently recommended that clinicians wait at least 15 minutes before extubation.[65] However, Aytac et al found that 86% of anesthesiologists extubate the trachea within 5 to 10 minutes of neostigmine administration.[2] In this case example, tracheal extubation occurred at 8 minutes; in a recent study, only 12% of patients had reached a TOFR greater than 0.9 at this time point, and their mean TOFR was 0.67.[6]

Because neostigmine stimulates muscarinic receptors leading to unwanted side effects such as bronchospasm, respiratory depression, nausea, vomiting, and bradycardia, it is coadministered with a muscarinic antagonist. In this case, the clinician selected glycopyrrolate, which can be associated with blurred vision, sedation, and other adverse events.

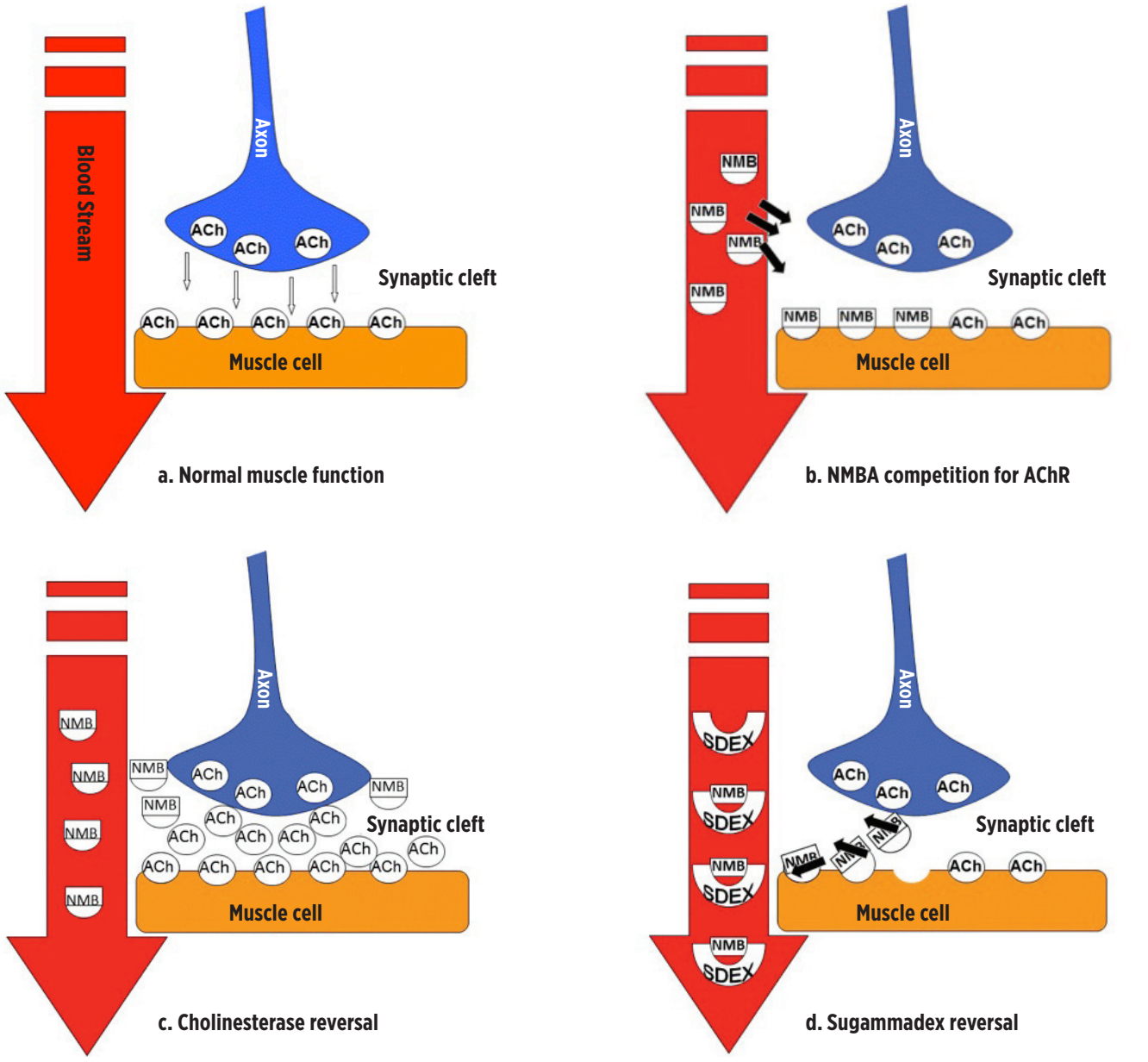


**Figure 1. Neuromuscular transmission, blockade, and reversal.[67]**

**ACh,** acetylcholine; **AChR,** ACh receptor; **NMB,** neuromuscular blockade; **NMBA,** neuromuscular blocking agent; **SDEX,** sugammadex

Reprinted with permission from Harris A, et al. Orthopaedic surgery implications of a novel encapsulation process that improves neuromuscular blockade and reversal. *Int J Orthop Surg*. 2006;7(2).

## Neuromuscular Transmission, Blockade, and Reversal

### *Transmission and Blockade*

During normal muscle function, an action potential reaches the motor neuron, and stored acetylcholine (ACh) is released from the motor neuron into the synaptic cleft.[66] ACh diffuses across the synaptic cleft and binds the nicotinic ACh receptors (AChRs) on the muscle fiber endplate (Figure 1a).[66,67] An AChR is made of 5 subunits, including 2 $\alpha$ subunits that contain active binding sites for ACh and NMBAs.[66] If the concentration of ACh is such that both $\alpha$ subunits are bound, depolarization of the muscle fiber occurs, creating a chemical cascade that leads to muscle contraction.[66,68] Of note, substantially more ACh is released than needed, and only a portion of AChRs require binding in order to generate the necessary action potential for muscle contraction.[68] Cholinesterase in the synapse breaks down ACh in order to allow muscle relaxation.

Nondepolarizing NMBAs competitively inhibit ACh at the postsynaptic AChR (Figure 1b).[67] Although it is only necessary for the NMBA to bind one of the $\alpha$ subunits to prevent depolarization of the muscle fiber, more than 90% of the receptors need to be occupied by the NMBA to completely block neuromuscular transmission.[66-68] To simplify, the balance between the concentration of ACh and NMBA in the neuromuscular junction (NMJ) determines neuromuscular function or NMB.[68]

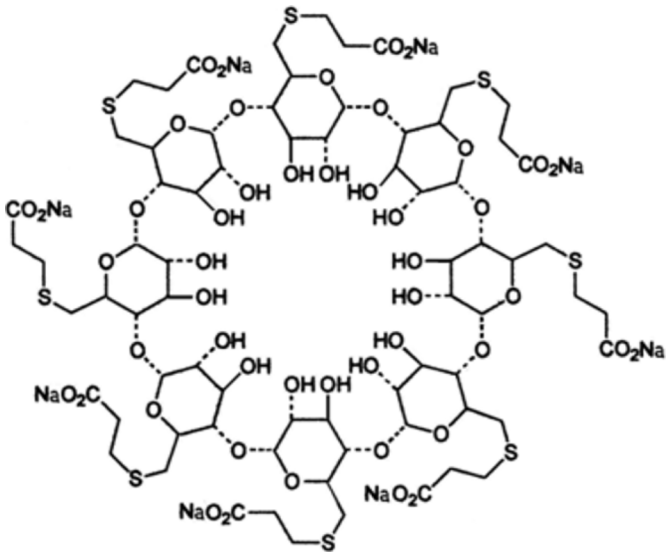

**Figure 2. Sugammadex.[67]**

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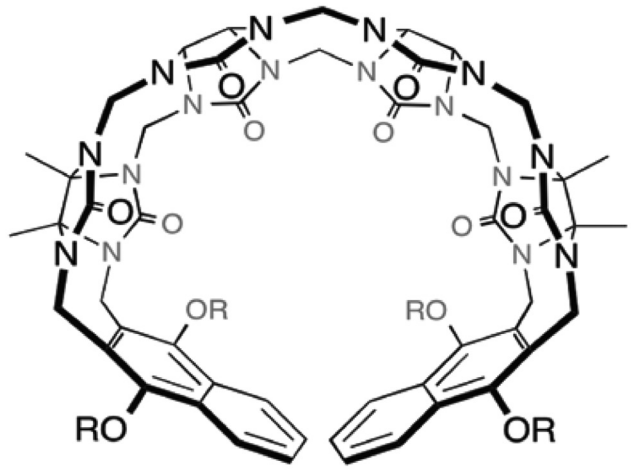

**Figure 3. Calabadion 2.[73]**

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*Pharmacologic Reversal*

NMB can be reversed in 2 ways: 1) by increasing the concentration of ACh (inhibiting its breakdown), or 2) by lowering the concentration of NMBA at the NMJ. In the United States, neostigmine and sugammadex are the primary agents used for pharmacologic reversal of NMBAs.

Neostigmine is an anticholinesterase inhibitor that has been in use for decades, and the FDA approved a regulated neostigmine, Bloxiverz (Éclat), in 2013. It functions by blocking cholinesterase, an enzyme in the NMJ that breaks down ACh. By increasing the concentration of ACh at the NMJ, neostigmine improves the competition between the NMBA and ACh in favor of ACh and facilitates normal neuromuscular conduction (Figure 1c).[66,67] The ceiling effect associated with neostigmine is the result of its indirect action on the concentration of ACh; in other words, additional ACh is not being released from the motor neuron, so the maximum concentration of ACh available to compete with NMBA molecules for receptor binding is maximal once cholinesterase inhibition is maximal. Displacement of NMBAs by ACh is not possible, and in the presence of a high concentration of an NMBA, as in deep NMB, the concentration of ACh is not high enough to favor binding of ACh to receptors to affect normal motor function.[67] Conversely, when neostigmine is administered in the absence of NMB, it can impede normal neuromuscular transmission and affect upper airway function through 3 mechanisms[69]: 1) desensitization of the AChR, a reversible reduction in response to sustained ACh binding[70]; 2) depolarization block, a prolonged refractory period during which further depolarization cannot occur[71]; and 3) open channel block, whereby high concentrations of ACh block open AChRs and limit activation.[72]

Sugammadex is a synthetic, γ-cyclodextrin selective relaxant binding agent that forms high-affinity complexes with rocuronium and vecuronium and to a lesser degree, pancuronium. It has been used in Europe and other countries for many years and was FDA-approved for use in the United States in late 2015. Sugammadex is synthesized using a naturally occurring γ-cyclodextrin (nonmetabolized, 8-glucose ring) that is modified with 8 side chains that create a hydrophilic molecule with a large, lipophilic core that can encapsulate steroidal NMBAs (Figure 2).[41,59,66,67] Sugammadex noncovalently binds steroidal NMBAs in a 1:1 molar ratio in the plasma, creating a concentration gradient between the NMJ and the blood where all of the NMBA is bound; this decreasing NMBA concentration at the NMJ allows ACh to bind to the AChR and restore muscle function (Figure 1d).[66,67] The high affinity and low dissociation rate between sugammadex and NMBAs allows for reversal of all levels of NMB without recurrence at recommended doses.[66]

Calabadion 2 is a cucurbit[n]uril container made of glycoluril chains and linked by methylene bridges that increase the solubility of drugs by forming host–guest complexes (Figure 3).[73] By binding NMBA in the plasma, calabadion 2 creates a concentration gradient that pulls free NMBA out of the NMJ and into the plasma; it is associated with higher in vivo binding affinity than sugammadex and appears to be well tolerated in initial studies.[73] Calabadion 2 is being studied in rats currently and may proceed to human studies in the future.[73]

## Conclusions

Overwhelmingly, anesthesiologists believe that residual paralysis is a rare postoperative patient safety issue, but studies clearly demonstrate that a substantial number of patients experience postoperative complications and distress associated with RNMB. The causes of RNMB are multifactorial, as highlighted in the case examples. It is imperative that anesthesiologists recognize the prevalence and consequences of RNMB and improve their care of patients through appropriate quantitative neuromuscular monitoring and effective reversal of NMB. Appropriate timing and dosing of reversal agents requires proper assessment, making objective monitoring the single most effective tool to prevent residual paralysis in patients and improve postoperative outcomes.

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