Eliminating residual neuromuscular blockade: a literature review

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

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

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

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

Keywords: Neuromuscular blockade (NMB); quantitative monitoring; sugammadex; postoperative residual neuromuscular blockade; reversal of residual neuromuscular blockade

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Introduction

Approximately 21 million people receive a general anesthetic each year. As part of that anesthetic, many of these individuals receive succinylcholine and/or a nondepolarizing neuromuscular blocking agent (NMBA). NMBAs are used most commonly to facilitate endotracheal intubation and optimize surgical conditions. Although they are frequently incorporated into a general anesthetic, their use is associated with increased surgical morbidity and mortality—at least some of which is due to the physiologic effects of residual neuromuscular blockade (NMB). Depth of neuromuscular blockade is defined by the muscular response to stimulation of a motor nerve, commonly the ulnar nerve. Contraction of the adductor pollicis when four responses occur after train-of-four (TOF) stimulation, is quantified by the train-of-four ratio (TOFR), the strength of the fourth response relative to the first response. When there are fewer than four responses to stimulation, the response is described as the train-of-four count (TOFC), or the number of responses to TOF stimulation. The post-tetanic count (PTC) defines the level of profound

Table 1 The search strategy summary

Items	Specification
Date of search	Search originally initiated 2023/3/22 and was expanded with the article revision 2023/8/23
Databases and other sources searched	PubMed
Search terms used	Nondepolarizing neuromuscular blocking agents, cisatracurium, rocuronium, vecuronium, pharmacodynamics of neuromuscular blocking agents, reversal agents, anticholinesterases, neostigmine, selective relaxant binding agents, sugammadex, residual neuromuscular blockade, incidence of residual neuromuscular blockade, complications of residual neuromuscular blockade, monitoring depth of paralysis, quantitative monitoring, qualitative monitoring, clinical monitoring for weakness, and adequacy of recovery of neuromuscular function
Timeframe	1976–2023
Inclusion and exclusion criteria	Articles were published in English and includes clinical trials, retrospective analysis, clinical series. Case reports were excluded from the study
Selection process	The search was conducted by Drs. C.A.L. and M.F.

NMB (before a response to TOF stimulation occurs). The response to TOF stimulation is used to guide the dosing of maintenance doses of NMBAs and reversal when NMB is no longer needed. The TOFR is obtained by stimulating a superficial nerve, such as the ulnar nerve, with four supramaximal stimuli at a frequency of 0.5 Hz (over the course of 2 s) and measuring the number and strength of the responses to the stimuli. A TOFR =0.5 would have four responses to stimulation and the 4th response would be 50% the strength of the first response. Adequate recovery of neuromuscular function, defined as a TOFR ≥0.9, is the degree of recovery necessary for safe extubation of the trachea. Residual paralysis, a TOFR <0.9, is associated with postoperative pulmonary complications due to a decreased ability to protect the airway associated with an increased incidence of micro-aspirations and hypoxia, death, decreased patient satisfaction, and longer stays in the post-anesthesia care unit. It is both iatrogenic and avoidable.

The incidence of inadequate recovery of neuromuscular function occurs frequently and has been described in as many as 65% of patients receiving NMBAs (1). Some of the reasons that residual NMB occurs with any frequency include:

- Profound depths of NMB are maintained intraoperatively.
- Recovery from NMB varies from one individual to the next and is, in many cases impacted by the presence of co-morbidities.
- Reversal agents are not dosed as recommended and their administration is not based on the TOFR.
- While optimal dosing of NMBAs and reversal agents is based on the results of monitoring, monitoring depth of NMB is not routine.
- Complete recovery from NMB, even after administration of a reversal agent, is not guaranteed.

Adequate recovery of neuromuscular function depends on appropriate dosing of NMBAs and reversal agents as well as intraoperative quantitative monitoring of depth of NMB. As will be described in this review, use of these guiding principles can minimize the risk of residual NMB in patients receiving NMBAs and decrease its associated risks. We present this article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-23-1743/rc).

Methods

Research for this review was accomplished through a literature search of PubMed, a free resource that supports the identification of scientific literature based on topic area and other identifying features (*Table 1*). The PubMed database has more than 36 million citations and abstracts of biomedical literature. It does not consistently provide links to the selected references. PubMed has been available to the public as an online resource since 1996. It was developed and is maintained by the National Center for Biotechnology Information, at the US National Library of Medicine. Key words used in the search included: nondepolarizing NMBAs, cisatracurium, rocuronium, vecuronium, pharmacodynamics of NMBAs, reversal agents, anticholinesterases, neostigmine, selective relaxant binding agents, sugammadex, residual NMB, incidence of residual NMB, complications of residual NMB, monitoring

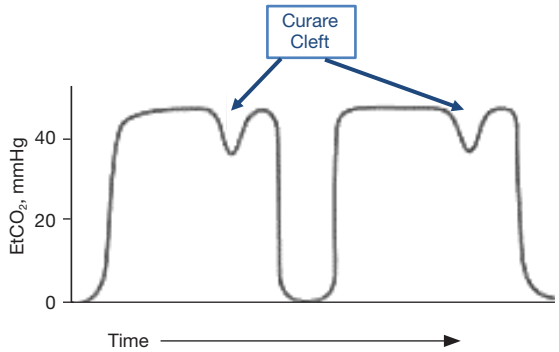


Figure 1 An image of the $EtCO_2$ during mechanical ventilation. The curare cleft, indicated by the arrow in the figure may be an indication that the patient is attempting to breath with the downward slope of the cleft indicating a decrease in exhaled CO_2 with diaphragmatic contraction. Adapted from the internet: https://www.emdocs.net/interpreting-waveform-capnography-pearls-and-pitfalls/ (accessed 8/27/2023). $EtCO_2$, end-tidal carbon dioxide.

depth of paralysis, quantitative monitoring, qualitative monitoring, clinical monitoring for weakness, and adequacy of recovery of neuromuscular function. While the focus of the search was to provide more recent literature to support recommended changes, older articles were included when necessary to provide context for the more recent work.

Decreasing the incidence of residual NMB

Monitoring

Avoiding residual NMB is difficult. It requires monitoring of depth of NMB so that unnecessary overdosing of NMBAs can be avoided, maintenance doses of NMBAs are administered at the appropriate time, the correct dose of reversal agent, whether it's an anticholinesterase (neostigmine) with an antimuscarinic agent (glycopyrrolate) to minimize the incidence of indiscriminate systemic actions of acetylcholine (bradycardia) or a selective relaxant binding agent (sugammadex) can be administered, and patients are extubated only once they have fully recovered muscle strength. Accurate assessment of depth of paralysis is paramount to administering either additional doses of NMBAs or reversal agents. Historically three types of assessments have been used, the clinical exam, qualitative assessment, and quantitative monitoring of depth of paralysis. Each of these modalities has its challenges and only quantitative assessment can provide an accurate determination of the depth of NMB.

Clinical assessment of depth of NMB

Clinical assessment may include the presence of a curare cleft in the measured concentration of exhaled end-tidal carbon dioxide ($EtCO_2$), the ability of a patient to lift their head or legs up from a stretcher and maintain that position for 5 s, and a sustained strong hand grip. These assessments cannot indicate with any certainty that a patient either requires an additional dose of NMBA or has fully recovered from NMB.

Capnography in the mechanically ventilated patient is used to determine the adequacy of ventilation and the presence of physiologic conditions that may impact $EtCO_2$. The presence of a cleft in an $EtCO_2$ tracing (*Figure 1*) indicates movement of the diaphragm. For movement of the diaphragm to be suppressed, a patient needs to be deeply paralyzed (have a PTC of 3–5) or be anesthetized deeply enough to suppress respiratory drive. For reference, a PTC is elicited by providing a tetanic stimulus (50 Hz) to a superficial motor nerve for 5 s, waiting 3 s and then stimulating the same nerve with single twitch stimuli at a frequency of 1 Hz. The PTC is the number of muscle contractions (adduction of the thumb) that occurs in response to the 1 Hz stimuli. PTC can be used to assess depth of NMB when the block is too profound to allow a response to TOF stimulation.

The diaphragm is relatively resistant to NMBAs and recovers more quickly from NMB than the adductor pollicis (2). The varied responses of different muscle groups to NMBAs has been attributed to muscle type, with fast twitch muscles being relatively resistant to NMBAs (3-5), muscle fiber size, with sensitivity increasing with fiber size (6), and blood flow, with faster onset and relative resistance in muscles with greater blood flow (7,8). All dosing recommendations for NMBA and reversal agents are based on the response of the adductor pollicis to ulnar nerve stimulation.

Similarly, work from the 1970s suggested that vital capacity and inspiratory force could be surrogates for adequacy of recovery as both were significantly reduced at a TOFR <0.6 (9,10). However, the muscles of respiration recover from NMB earlier than the adductor pollicis and an adequate tidal volume cannot, by itself, be considered a reliable gauge of recovery from NMB (11). Subsequent work by Donati *et al.* (2) confirmed that the diaphragm recovers more quickly from NMB than the adductor pollicis. The orbicularis oculi and the laryngeal musculature also recover more quickly than the adductor pollicis. Since adequate recovery of neuromuscular function is now considered a TOFR ≥0.9, rather than a TOFR ≥0.7 as it

Table 2 Characteristics for qualitative assessment of depth of neuromuscular blockade

The monitor must have specific characteristics including
Ability to generate a supramaximal stimulus (at least 30–60 mA)
Ability to generate a stimulus of the proper duration (0.2–0.3 ms)
Adequate output in the presence of 2,000 Ω impedance
Ability to provide a train-of-four stimulus
Presence of a digital ammeter
Electrodes must be placed properly
The different responses of monitoring sites (sensitivity, onset, and recovery) to NMBAs must be understood
The digit being assessed needs to be able to move freely or clearly visible

NMBA, neuromuscular blocking agent.

was at the time of these studies, respiratory function in the intubated patient will certainly recover before there is adequate recovery of strength in the adductor pollicis. Recommendations to not use recovery of ventilatory parameters, including end-tidal CO_2, tidal volume, minute ventilation and peak inspiratory flow, as an indicator of adequacy of recovery of neuromuscular function have been recognized in veterinary medicine (12).

Although, the muscles of respiration recover earlier than the more peripherally located neuromuscular units, respiratory failure and pneumonia occur more commonly in patients who are inadequately recovered from NMB. In addition to decreased lower esophageal tone and discoordination of breathing relative to swallowing leading to increased likelihood of aspiration, residual neuromuscular block impairs the hypoxic ventilatory response through depression of carotid body chemoreceptor function (13,14). This impairment of the hypoxic ventilatory response has been documented in unanesthetized volunteers receiving either vecuronium or atracurium (15,16).

A "correct" head lift is done when a patient can lift their head off a surface from a supine position and maintain that position for 5 s. Historically, the ability to accomplish this task was assumed to indicate that the patient has regained enough muscle strength to breath spontaneously and protect their airway once the endotracheal tube was removed. A 5-s leg lift was presumed to provide the same information and in children, who may not follow a request to lift their heads, could be used as a surrogate clinical measure. However, a study published in 1997 found that young, healthy volunteers could perform either of these tasks when their TOFR was <0.6 (17), the TOFR at which vital capacity, inspiratory force, and peak expiratory flow rate were at clinically acceptable values (9).

Qualitative assessment of depth of NMB

Qualitative assessment of the depth of neuromuscular block offers some advantage over clinical assessment in that it requires neither patient effort nor cooperation. That being said, there are several requirements for this type of assessment to even begin to deliver usable information (*Table 2*). The "twitch monitors" as they are commonly referred to must be able to deliver an adequate supramaximal current, they must be able to provide a TOF stimulus (4 stimuli given every 0.5 s) and they must have the ability to deliver a stimulus of 0.2–0.3 ms pulse duration, an output of more than 60 mA in the presence of 2,000 Ohm impedance, and a digital ammeter to display the delivered current. Even if a monitor were to have all of these features, visual or tactile interpretation of the response to stimulation would not be accurate. To interpret the response to stimulation, one looks for, or feels, the contractions resulting from stimulation, counts the responses and, if there are 4 responses, determines the strength of the 4th response relative to the 1st. While counting the number of responses to stimulation may seem simple—a study in a critical care unit demonstrated the difficulty associated with establishing consistency in the interpretation of the number of responses to a stimulus. It is even more difficult to assess fade in the TOFR and, unless the 4th response is less than 40% of the 1st response, fade cannot be reliably detected (18). This means that a patient may have a TOFR =40% and be assessed as having 4 equal responses to TOF stimulation, and therefore, erroneously erroneously determined to be adequately recovered from NMB. Qualitative assessment of the TOF count or ratio requires that a stimulus is applied

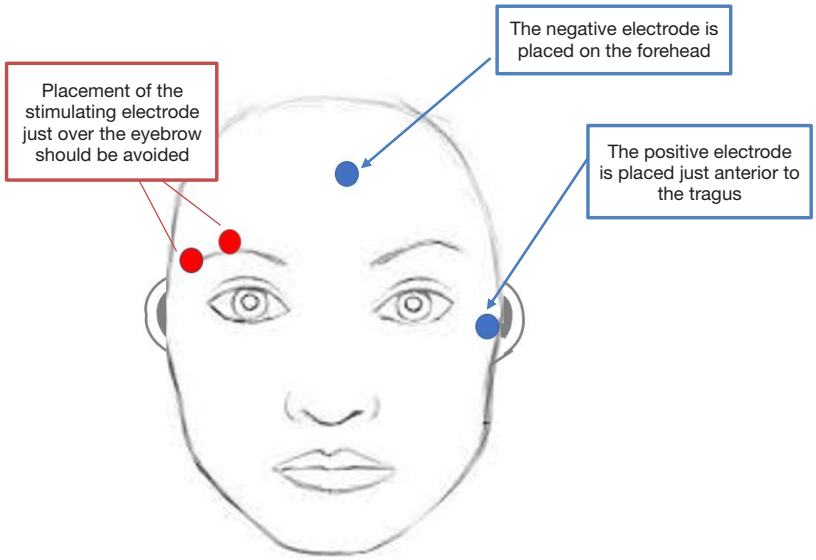


Figure 2 Typical placement of electrodes on the face when monitoring the eye for depth of neuromuscular block. The electrodes should be placed far apart in order to minimize the likelihood of direct muscle stimulation. Placement of the electrodes just over the eyebrow should be avoided. Image of the face accessed on the internet: www.pinterest.com/pin/336362665890513583/ (accessed 8/27/2023).

through a peripheral nerve stimulator to a superficially located motor nerve and the muscular response to this stimulation is assessed or "measured". While any superficially located motor nerve can be stimulated to elicit a muscle contraction, NMBA and reversal dosing recommendations are based on the response of the adductor pollicis to stimulation of the ulnar nerve. Because the patient's arms are frequently tucked by their side for surgery, or simply because it is more easily accessed, the facial nerve, which innervates the orbicularis oculi muscle is commonly used intraoperatively to assess depth of NMB. Although more convenient and accessible, the orbicularis oculi more closely reflects the onset of NMB and will, under the best of circumstances, overestimate the degree of recovery of neuromuscular function. Optimal monitoring at the orbicularis oculi requires that the stimulating electrodes be placed as far apart as is possible (not adjacent to each other over the patient's eyebrow) as is shown in *Figure 2* and that the maximal stimulating current used is 40 mA, or less, in order to minimize the likelihood of direct muscle stimulation. Even when monitored correctly, the response of the orbicularis oculi does not reflect recovery at the adductor pollicis. When NMB is monitored at the orbicularis, patients are more likely to have an inadequate recovery of neuromuscular function on admission to the post-anesthesia care unit (19).

Ideally, more peripherally located neuromuscular units are used for monitoring. All dosing recommendations for neuromuscular blocking and reversal agents have been based on the response of the adductor pollicis to ulnar nerve stimulation. Onset of neuromuscular block at the adductor pollicis is slower than it is at the orbicularis, larynx and diaphragm. Similarly, recovery occurs more slowly in the adductor pollicis than is does in these other muscle groups. As shown in *Figure 3*, when the arms are not available, strength can be monitored in the lower extremities by either stimulating the common peroneal nerve and assessing dorsiflexion of the foot or the posterior tibial nerve and assessing plantar flexion of the great toe. The utility of using the lower extremity for monitoring the depth of NMB has not been studied extensively. One study demonstrated slower recovery than at the adductor pollicis (20) and another found that the flexor hallucis brevis recovered more quickly (21).

Quantitative assessment of depth of NMB

Quantitative assessment of the depth of NMB is the only monitoring methodology that allows determination, with certainty, of depth of NMB (22-24). As with qualitative monitoring, a stimulus (TOF, or PTC) is applied to a superficially located motor neuron. In contrast to a qualitative monitor, though, the response to stimulation is measured by the device. While the early studies of muscle

strength during onset and recovery from neuromuscular block used mechanomyography to measure the strength of contraction of the adductor pollicis in response to stimulation of the ulnar nerve, this monitoring modality is complex in its set-up, and not available for routine clinical use. Available quantitative monitors, monitor one of two responses to neural stimulation of a motor nerve. Acceleromyography determines the acceleration of movement of the thumb in response to stimulation of the ulnar nerve and electromyography measure electrical activity in response to neural stimulation. While each of these modalities has its advantages and disadvantages as outlined in *Table 3*, the use of either has been shown in many clinical trials to decrease the likelihood of unacceptable levels of NMB after an anesthetic. As with qualitative monitoring, neither modality requires patient cooperation. Guidelines recommending quantitative monitoring of NMB whenever a patient receives a NMBA have now been instituted through the American Society of Anesthesiologists, the European Society of Anaesthesiology and Critical Care (25), and the Spanish Society of Anaesthesiology and Resuscitation (26).

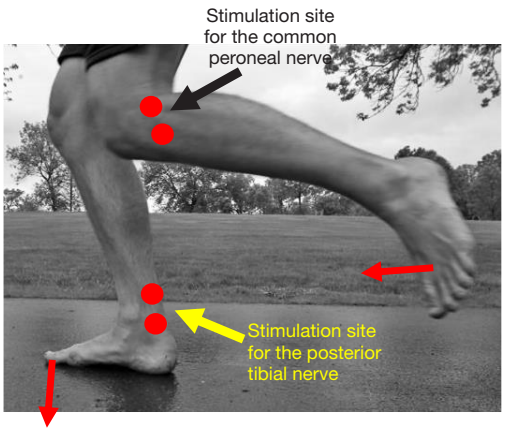


Figure 3 Common sites for monitoring muscle strength at the lower extremity. Either the common peroneal or posterior tibial nerve can be stimulated and responses of dorsiflexion of the foot or plantar flexion of the great toe, respectively, measured. Red arrows: the downward arrow represents plantar flexion and the arrow pointing to the left the movement associated with dorsiflexion. Image of the legs accessed on the internet: https://www.erswf.buzz/products.aspx?cname=feet+of+barefoot+runners&cid=60 (accessed 8/27/2023).

Nondepolarizing NMBAs

Duration of action

There have been many reviews of NMBAs (27-31) and repeating that information is beyond the scope of this chapter. NMBAs were developed to facilitate endotracheal

Table 3 Advantages and disadvantages of two different types of quantitative monitors of depth of neuromuscular blockade

Monitoring modality	Advantages	Disadvantages
Acceleromyography	Relatively easy to set up	Thumb has to be able to move in response to neural stimulation
	Provides the measured depth of neuromuscular blockade in an easy-to-see format	Degree of recovery may be overestimated unless the response to stimulation is normalized
	If the hand is not available to monitor, the monitor can be used on a lower extremity	Integration with the electronic medical record may be complex
		Subject to electrical interference
Electromyography	Relatively easy to set up	Integration with the electronic medical record may be complex
	The thumb does not have to move for detection of muscle strength	
	Provides the measured depth of neuromuscular blockade in an easy-to-see format	Subject to electrical interference
	If the hand is not available to monitor, the monitor can be used on a lower extremity	
	Measured responses are the same as those obtained with mechanomyography; the degree of recovery is not over estimated	

Table 4 Potency, dosing and elimination of commonly used neuromuscular blocking agents

NMBA	Chemical structure	Elimination/metabolism	ED_{95} (mg/kg)	Intubating dose (mg/kg)	Multiples of ED_{95}	Time to max block (min) after 2× ED_{95}	Clinical duration (min)
Rocuronium	Steroidal	Renal and biliary elimination	0.3	0.6–1.0	2–3.3	1.7	36
Vecuronium		Hepatic metabolism, renal and hepatic elimination	0.05	0.1–0.2	2–4	2.4	41
Cisatracurium	Benzylisoquinolinium	Hofmann degradation and renal elimination	0.05	0.15–0.2	3–4	7.7	46

NMBA, neuromuscular blocking agent; ED_{95}, the dose of a NMBA that will, on average, cause 95% suppression of the muscle response to stimulation.

Table 5 Pharmacodynamics of select neuromuscular blocking agents

NMBA	ED_{95} (mg/kg)	Onset time (min) of 2× ED_{95}	Minutes to 25% recovery
Short-acting neuromuscular blocking agents			
Mivacurium	0.08	3–4	15–20
Intermediate-acting neuromuscular blocking agents			
Atracurium	0.25	3–4	35–45
Cisatracurium	0.05	5–7	35–45
Rocuronium	0.3	1.5–2	30–40
Vecuronium	0.05	2–3	35–45
Long-acting neuromuscular blocking agents			
Pancuronium	0.07	2–4	60–120

NMBA, neuromuscular blocking agents; ED_{95}, the dose of a NMBA that will, on average, cause 95% suppression of the muscle response to stimulation.

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

In the current practice of anesthesiology, the most commonly used NMBA is rocuronium followed by much less frequent use of vecuronium and cisatracurium (32). Each of these compounds is an intermediate-acting NMBA, which means that following administration of an intubating dose, the time to recovery to T1 (the first response in the TOFR) to 25% of its baseline value is between 20 and 50 min (33). The differences in the NMBAs are outlined in *Table 4*.

Dosing

The ED_{95} of a NMBA is the dose that, on average, will cause 95% suppression of the single twitch response to stimulation of the ulnar nerve. Onsets of NMBA vary with the neuromuscular unit being monitored (2) and the potency of the NMBA. *Table 5* lists the ED_{95} of several NMBAs and the onset of action of an ED_{95} dose. When comparing the onset of effect of equipotent of cisatracurium, vecuronium, rocuronium, and succinylcholine, the least potent compounds, rocuronium and succinylcholine, have the most rapid onset of effect (34). To decrease the time required for onset of block and to better guarantee that complete NMB will occur following a single dose, the recommended

intubating dose of a NMBA is typically 2–4 times the ED_{95} (*Table 4*). The increase in dose in order to achieve a more rapid onset results in an increased clinical duration of action. It is this increase in clinical duration of action as well as an increased likelihood of adverse reactions with larger doses that limit the size of an intubation dose when speed of onset is important.

Variability of duration of action

Interpatient variability in response to an intubating dose and speed of recovery is often overlooked and is an important factor to consider when administering NMBAs. When the ED_{95} of a NMBA is described, it is often described as a single value in a study. Similarly, when recovery is described, it is most commonly the mean value that is reported along with the standard deviation. There is a significant amount of interpatient variability in recovery amongst young, healthy patients of ideal body weight (35). In elderly patients, this difference becomes greater with the steroidal NMBAs. The increase in duration of action and interpatient variability observed in geriatric patients are not observed following the administration of benzylisoquinolinium NMBAs. This is likely due to the metabolism of the benzylisoquinoliniums rather than dependence on hepatic and renal systems for inactivation and elimination.

Reversal agents

Neostigmine and sugammadex

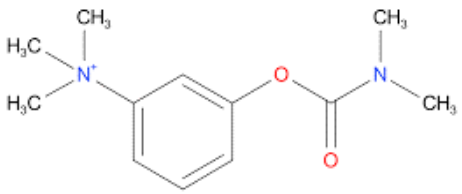
There are two different classes of reversal agents: anticholinesterases (neostigmine, edrophonium, pyridostigmine) of which neostigmine is the one that is currently available for clinical use (36), and selective relaxant binding agents, of which sugammadex is used clinically (*Figure 4*). Administration of these reversal agents will increase muscle strength after administration of an NMBA. Neostigmine works as an indirect antagonist, inhibiting acetylcholinesterase—which is responsible for the breakdown of acetylcholine. The result is that the acetylcholine released from the presynaptic terminal is not metabolized and the levels of acetylcholine at the neuromuscular junction are increased allowing the competitive NMB of acetylcholine receptors to be at least partially overcome and neuromuscular transmission increased. Once acetylcholinesterase is completely inhibited, administration of additional anticholinesterase will not have any effect and, if it administered when there are significant concentrations of NMBAs present, the competitive neuromuscular block cannot be overcome. Sugammadex encapsulates free rocuronium in the plasma so that it cannot enter the neuromuscular junction and bind to acetylcholine receptors (37,38) and it increases the movement of rocuronium from the neuromuscular junction to the plasma by decreasing the concentration of free rocuronium there (37,39,40). One molecule of sugammadex binds noncovalently to 1 molecule or rocuronium, incorporating its steroidal rings into its hydrophobic central core. The affinity constant value of rocuronium for sugammadex is 25,000,000 M, which is about 2.5 times greater than the affinity of vecuronium (38) for sugammadex and, once bound, there is no evidence that the complex dissociates appreciably.

Dosing of reversal agents

Neostigmine cannot reverse deep NMB and in the recently published guidelines (*Table 6*) is not recommended for reversal of anything other than shallow depths of neuromuscular block, 0.4≤ TOFR <0.9 (41). Stated differently, neostigmine should not be used to antagonize residual neuromuscular block when the TOFC <4, and when fade is appreciable in the TOF response. If used to reverse these deeper levels of NMB, there will be some increase in muscle strength. However, recovery will likely not be complete. Since there will be some increase in muscle strength, though, residual NMB may not be appreciated unless a quantitative monitor of NMB is being used. Larger doses of neostigmine will cause greater inhibition of acetylcholinesterase and perhaps facilitate greater recovery. Once the enzyme is maximally inhibited, though, administration of additional neostigmine will have no further impact on the concentration of acetylcholine and residual neuromuscular block will persist if significant levels of NMBA are present at the neuromuscular junction. This limited degree of efficacy was demonstrated many years ago with the attempted neostigmine reversal of 60% and 95% pancuronium-induced block (42). The authors found that, contrary to what would have been expected, excessive doses of neostigmine caused increased fade in the TOFR with repeated stimulation (43,44). Similarly, unwarranted administration of neostigmine will cause decreased grip strength (45) and, in animals, impairs normal function of the musculature of the airway (46,47).

Of note, NMBAs also bind to presynaptic acetylcholine receptors causing decreased release of acetylcholine in response to neural stimulation and inhibition of neuromuscular transmission (48,49) as demonstrated by

Neostigmine, an anticholinesterase



Sugammadex, a selective relaxant binding agent

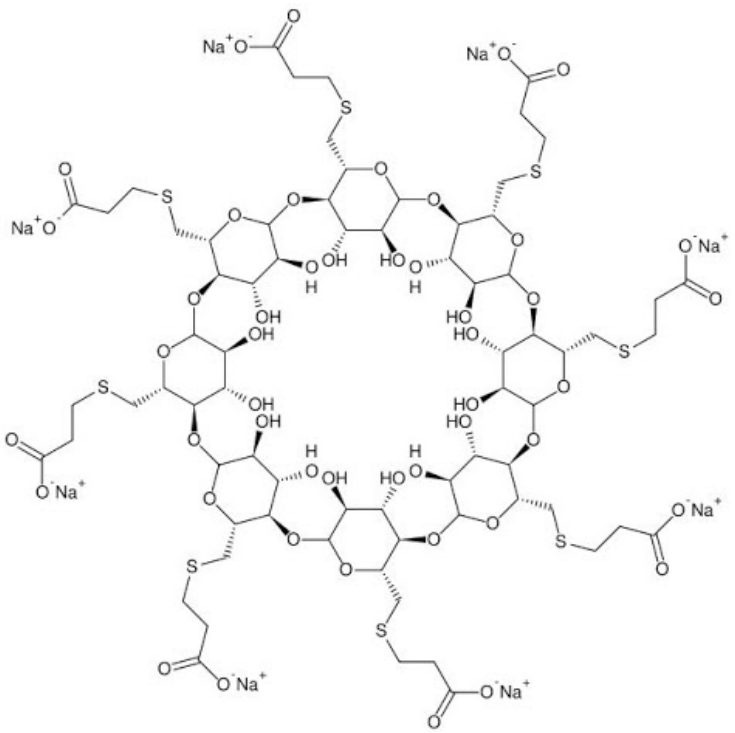


Figure 4 Chemical structures of the commonly used reversal agents. Neostigmine, an anticholinesterase, inhibits breakdown of acetylcholine into choline and acetate, increasing its availability at the neuromuscular junction to bind with the acetylcholine receptor. Sugammadex is a cyclodextrin, specifically designed to encapsulate steroidal neuromuscular blocking agents. By encapsulating rocuronium or vecuronium, essentially irreversibly, it renders the neuromuscular blocking agent unable to enter the neuromuscular junction and bind to the acetylcholine receptor. The encapsulation of rocuronium changes the concentration gradient of the NMBA in the neuromuscular junction and the plasma so that it will move from the neuromuscular junction to the plasma, where it is subsequently encapsulated and eliminated. Images of the structures obtained from: Neostigmine | $C_{12}H_{19}N_2O_2$+ | CID 4456 - PubChem (nih.gov) (accessed 10/3/2023) and Sugammadex sodium (Org25969) | Neuromuscular Block Reversal | MedChemExpress (accessed 10/3/2023).

Table 6 Dosing of reversal agents (41)

Response to stimulation	Sugammadex dose (mg/kg)	Neostigmine dose (mcg/kg)
PTC =0	16	
PTC =2 to TOFC =1	4	
TOFC =2, 3, or 4 (if TOFR <0.9)	2	
TOFC =4 and 0.4≤ TOFR <0.9		30

PTC, post-tetanic count; TOFC, train-of-four count; TOFR, train-of-four ratio.

increased fade in the TOF. Conversely, in the presence of large concentrations of acetylcholine, the neuromuscular blockade becomes noncompetitive (49), further complicating attempts to reverse deep levels of NMB with anticholinesterase.

Smaller doses of neostigmine 30 µg/kg or less, are effective in reversing shallow degrees of residual NMB (44,50-52). Since full reversal doses of neostigmine (50–70 mcg/kg) can cause neuromuscular block when administered unnecessarily recommendations are to administer smaller doses of neostigmine to reverse shallow depths of NMB (41).

The mechanism of action of sugammadex is completely different than that of neostigmine. While neostigmine is an indirect antagonist, inhibiting acetylcholinesterase and increasing the amount of acetylcholine at the neuromuscular junction, sugammadex is a direct antagonist, encapsulating the steroidal NMBAs so that they cannot enter the neuromuscular junction and bind to acetylcholine receptors (37,38). Sugammadex was designed to specifically interact with the steroidal NMBAs (rocuronium > vecuronium > pancuronium) and will not reverse NMB induced with benzylisoquinoliniums (atracurium, cisatracurium).

Sugammadex has a much more rapid onset of effect than neostigmine, 1 to 2 minutes versus 9–10 (53), and, in contrast to neostigmine, administration of a large dose, 16 mg/kg, will rapidly antagonize profound levels of neuromuscular block.

The definition of an appropriate dose is still being examined and smaller doses of sugammadex have been found to effectively antagonize shallow depths of NMB (a TOFR =0.5) (50). When considering that the same dose of sugammadex is currently recommended for depths of NMB ranging from a PTC of 2 to a TOF count of 1, and a TOF count of 2 to a TOFR <0.9, either of which is a very wide range of depth of NMB, there is room for greater delineation of an "optimal" dose of sugammadex for different levels of block. A recent dose-finding study identified a range of doses necessary to reverse NMB at the conclusion of cardiac surgery (54). The study results indicated that there was significant inter-patient variability in the response to sugammadex, that 87% of patients required less sugammadex than would have been administered based on current recommendations, and 13% of patients required more sugammadex.

Significantly decreasing the dose of sugammadex beyond those currently recommended may increase the likelihood of inadequate recovery of neuromuscular function (55,56). If quantitative monitoring is not being used, the inadequate recovery of neuromuscular function may not be detected. As with all neuromuscular blocking and reversal agents, there is interpatient variability in the response to a dose of sugammadex. Even administration of a correct dose of sugammadex, while it is more likely to result in complete reversal of neuromuscular function, does not guarantee adequate reversal of residual NMB (57). Recurarization can occur even after complete recovery of neuromuscular function following sugammadex administration (54) and the likelihood of residual NMB, even after administration of an appropriate dose of sugammadex, is increased especially if considering a TOFR =1, rather than 0.9, as the endpoint of recovery (58).

Neostigmine and sugammadex in patients with renal failure

Of the currently used NMBAs all have some component of renal elimination (59-61), Vecuronium and its metabolites have the greatest renal elimination and vecuronium has a prolonged duration of action in patients with decreased renal function, as well as the decreases in renal blood flow associated with advanced age (62). Neostigmine is also eliminated through the kidneys and has a decreased clearance in patients with renal disease (63). Therefore, its dosing does not have to be adjusted in patients with renal failure even when reversing NMB induced by vecuronium—which has a longer duration of action in patients with end-stage renal disease (60).

Recovery of neuromuscular function after administration of sugammadex is due to the binding of rocuronium by sugammadex, rather than the elimination of the complex from the body (64). Because of this, even though the sugammadex and the sugammadex-rocuronium complex are eliminated in the urine (65), sugammadex is effective in patients with end-stage renal disease. Since the rocuronium—sugammadex complex will not dissociate, even though the complex remains in the plasma, the rocuronium remains associated with the sugammadex and is unable to enter the neuromuscular junction (66,67). In patients with end-stage renal disease the rocuronium-sugammadex is dialyzable (68).

Pharmacologic interactions of reversal medications

Both neostigmine and sugammadex interact with other medications. Neostigmine appears to potentiate anti-inflammatory medications, will inhibit plasma cholinesterase and prolong the duration of action of medications metabolized by this enzyme, such as succinylcholine and mivacurium (69,70). Additionally, neostigmine may reduce the effectiveness of tricyclic antidepressants, such as amitriptyline and has been used to treat tricyclic

Table 7 Residual neuromuscular blockade over the years with different neuromuscular blocking agents

Year (reference)	Neuromuscular blocking agent	TOFR in the PACU	% of patients
1979 (78)	Pancuronium, gallamine, D-tubocurarine	<70%	42
1988 (79)	Pancuronium	<70%	36
	Atracurium, vecuronium	<70%	5
2003 (80)	Atracurium, vecuronium, rocuronium	<90%	37
2008 (81)	Rocuronium	<90%	30
2019 (1)	Rocuronium	<90%	40**

**, at Academic Medical Centers. TOFR <0.9 at Academic and Community hospitals combined was 65%. TOFR, train-of-four ratio; PACU, postanesthesia care unit.

antidepressant overdoses (71). On the other hand, the main pharmaceutical interaction with sugammadex is concern that it may bind to, and reduce the levels of, progesterone within the body (72). This is of special in individuals taking hormonal, progesterone-based, contraceptives and the manufacturer recommends that individuals using hormonal birth control use an additional contraceptive for 7 days after exposure to sugammadex. While sugammadex may reduce progesterone levels within the body, there has been no evidence supporting the assumption that the levels will drop enough to cause early cessation of pregnancy. In fact, there is no evidence in humans and a trial in which rats were exposed to high doses of sugammadex in the first trimester did not increase the rates of stillbirth (73,74). Since national consensus guidelines recommend the use of rocuronium as an alternative to succinylcholine for rapid sequence induction in pregnant patients (75), one can expect that sugammadex will be used to reverse NMB in the "cannot intubate – cannot ventilate" scenario. There is no published data on the presence of sugammadex in human breast milk. Because of its large molecular size and polarization, though, there is likely to be little maternal-fetal transfer of sugammadex (72,76,77).

Residual NMB

Incidence

Residual NMB has been recognized since the 1970's when long-acting NMBAs were used (*Table 7*). Adequate recovery of neuromuscular function at that time was defined as a TOFR ≥0.7 and 42% of patients were identified as having a TOFR <0.7 on admission to the recovery room after having received pancuronium, gallamine, or d-tubocurarine (78). Almost 10 years later, after the introduction of atracurium and vecuronium into clinical practice, a similar observational study was done. In this study, 36% of patients were found to have a TOFR <0.7 if they had received pancuronium while only 5% of patients who had received either of the intermediate-acting NMBAs had a TOFR <0.7 (79). In addition to the availability of atracurium and vecuronium, the difference in the more recent study was that qualitative monitors for assessment of depth on NMB were available. Based on these results, one could have easily expected the incidence of residual NMB to decrease with the increased use of intermediate-acting NMBAs. However, as the effects of residual NMB were increasingly recognized, the definition of adequate recovery of neuromuscular function was changed from a TOFR ≥0.7 to ≥0.9. With this, as well as changing surgical practices, the incidence of residual NMB following administration vecuronium, rocuronium or atracurium (TOFR <0.9) was 37% (82). More recently, The RECITE-US study (1) found that the incidence of unacceptable levels of recovery in patients receiving NMBAs across community and academic medical centers was almost 65%. In this study, risk factors for residual NMB included male gender, increased body mass index, and surgery at a community hospital. Other independent risk factors for residual paralysis have been identified and include abdominal surgery, advanced age and surgery of longer duration (62,83,84).

Adverse effects of residual NMB

Residual NMB, defined as a TOFR <0.9, is a concern because of the adverse consequences with which it is associated (*Table 8*). These adverse effects range from relatively minor (such as generalized fatigue) (17) to significant (respiratory failure requiring reintubation) (85)—with some of these adverse effects persisting beyond recovery of neuromuscular function to a TOFR =1.0 (86).

Of the adverse effects of residual NMB, its interference with the hypoxic ventilatory response is one of the least

Table 8 Adverse effects of residual neuromuscular block in individuals with a TOFR <0.9

Prolonged postoperative ventilatory weaning times in cardiac surgery patients
Visual disturbances, including diplopia
General fatigue
Decreased patient satisfaction
Delayed discharge from the post-anesthesia care unit
Increased risk of critical respiratory events, upper airway obstruction, postoperative hypoxemia, postoperative pulmonary complication
Decreased upper esophageal motor tone
Decreased sensitivity to hypercapnea
Impaired ventilatory response to hypoxia
Reintubation
Death

TOFR, train-of-four ratio.

discussed. Since the diaphragm is relatively resistant to NMBAs and because it recovers from NMB more quickly than the adductor pollicis (2), it is possible for patients to breath when inadequately recovered from NMB (11). However, in addition to being more likely to develop a critical respiratory event (81), the hypoxic respiratory drive remains attenuated even with recovery to a TOFR ≥0.9 (86). As described previously in this chapter, NMB depresses carotid body chemoreceptor function resulting in an impaired hypoxic ventilatory response (13,14).

While the use of NMBAs has been demonstrated to decrease mortality in critically ill, ventilated patients (87,88), several databased studies have found an association between intraoperative use of NMBAs and increased morbidity and mortality. Retrospective studies from the 1970–1980's found that there was a 2–3% increase in mortality when NMBAs were administered that was most commonly associated with compromised respiratory function (89,90). While this represented an improvement over the 6-fold increase in mortality described by Beecher and Todd in 1954 (91), it is a significant increase in risk especially when the reported risk of mortality associated with anesthesia is between 0.01% and 0.02% (92). More recently, high doses of intermediate-acting NMBAs were found to be associated with an increased rate of respiratory complications, readmission, prolonged length of stay, and increased hospital costs (93-95). Bronsert *et al.* (93) described a decrease in that risk when residual NMB was antagonized. Because these are retrospective databased trials, only the relationship between NMBAs and mortality, but not causality, can be described.

Adequate recovery of neuromuscular function

Definition of adequate recovery of neuromuscular function

The definition of adequate recovery of neuromuscular function after administration of a NMBA has evolved over time as indicated by endpoints for monitoring muscle strength (*Table 8*). Revision of the standard for adequate recovery occurred as the negative impact of residual NMB was increasingly appreciated, the duration of action of our NMBAs became shorter, our ability to monitor depth of NMB evolved, surgical practice advanced, and our ability to rapidly reverse residual NMB improved (*Figure 5*).

Quantitative monitoring of depth of NMB is essential not only to guide intraoperative dosing of NMBAs but, as discussed previously in this review, to also determine the dose of reversal agent that should be administered and to verify that adequate recovery of neuromuscular function has occurred at the completion of surgery. While quantitative monitoring improves a clinician's ability to identify residual NMB, the monitors must work reliably even in an environment that is bound to provide both electrical interference and movement of the extremity where the monitoring is being done. Improved monitoring is essential since evidence, both old and new, indicates that a TOFR ≥0.9 may not reflect "full" recovery of neuromuscular function. There is a significant amount of redundancy built into neuromuscular transmission allowing for appropriate functioning of the system even in times of stress. Decreases in functional acetylcholine receptors in patients with myasthenia correlate with the fatigue and

Figure 5 A timeline of some of the major developments in the clinical use of neuromuscular blocking and reversal agents.

weakness (96). In a related fashion, 80% of acetylcholine receptors may be blocked before depression in response to twitch response can be appreciated and recovery of muscle strength can begin even with 80% of receptors occupied (97). Residual occupancy by nondepolarizing NMBAs and significant plasma concentrations of NMBAs during recovery of neuromuscular function (98), may account at least in part for the greater sensitivity patients have for subsequent doses of NMBAs (99), and is the reason that doses of approximately 20–40% of an ED_{95} of a NMBA are recommended for maintenance of NMB after an intubating dose.

Duchenne muscular dystrophy (DMD) causes hypertrophy of muscle tissue due to fatty infiltration and a progressive decrease in muscle strength. Patients with DMD have a greater sensitivity to nondepolarizing NMBAs and a prolonged duration of action of these compounds (100,101). Anticholinesterases (neostigmine and pyridostigmine) can be used to reverse NMB in patients with DMD (64,100); as in otherwise healthy patients, there is marked interpatient variability in response to anticholinesterases. Sugammadex has been used successfully in these patients (102-105), and based on case reports allows complete recovery of neuromuscular transmission within 3 minutes of administration. As complications caused by residual NMB, such as respiratory failure and aspiration, also occur in patients with DMD, ensuring complete recovery of neuromuscular function to baseline after the conclusion of a surgical or diagnostic procedure is exceptionally important.

Is more recovery of neuromuscular function required?

The physiology of pharmacologically-induced NMB

is complex and involves, in addition to competitive blockade of the acetylcholine receptors at the subsynaptic or postsynaptic portion of the neuromuscular junction, blockade of prejunctional acetylcholine receptors (48,106). In a study of strength after complete recovery of neuromuscular function, Eikermann found that patients who had completely recovered muscle strength were unable to generate the same force as volunteers who had never received a NMBA (107). More recent work by Broens *et al.* (86) demonstrated that hypoxic ventilatory response was not restored even once a patient's TOFR had recovered to ≥0.9 after the administration of either neostigmine or sugammadex. Interestingly, the POPULAR study (108) found that the use of neuromuscular monitoring, and reversal with either sugammadex or neostigmine to a TOFR ≥0.9 did not decrease the incidence of postoperative pulmonary complications. A subsequent re-analysis of this data, though (109), did demonstrate that the risk of postoperative pulmonary complications was decreased when patients were extubated at a TOFR ≥0.95. While the standard for recovery of neuromuscular function remains recovery to a TOFR ≥0.9, the results indicate that there is still more to be learned regarding safety in the use of NMBAs. To do that, monitors of depth of NMB will have to be more accurate and deliver reliable results—and, they will have to be used.

Conclusions

With the increasing use of NMBAs in clinical practice and documented incidence of inadequate recovery of neuromuscular function on arrival to the post-anesthesia care unit, it is imperative that clinicians adapt their practices to decrease the postoperative complications that are secondary to the use of these agents. Eliminating residual NMB is entirely feasible within modern anesthetic practice. Technological research and advancement have made quantitative measurement of depth of NMB possible so that qualitative observation and assessment of recovery of neuromuscular function and all the error associated therewith is avoidable. With quantitative measurement every time a patient receives a NMBA, clinicians can dose NMBAs to provide the necessary depth of NMB intraoperatively, adjust the dose of the reversal agent based on the results of monitoring, ensure complete recovery of neuromuscular function before extubating the patient, and decrease the incidence of the complications associated with residual NMB. Just as using the pulse oximeter in modern practice reduces the frequency of peri anesthetic hypoxia, the use of quantitative neuromuscular monitors of depth of NMB will further enhance the safety of modern anesthesia practice.

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