Innovative Disruption in the World of Neuromuscular Blockade

What Is the "State of the Art?"

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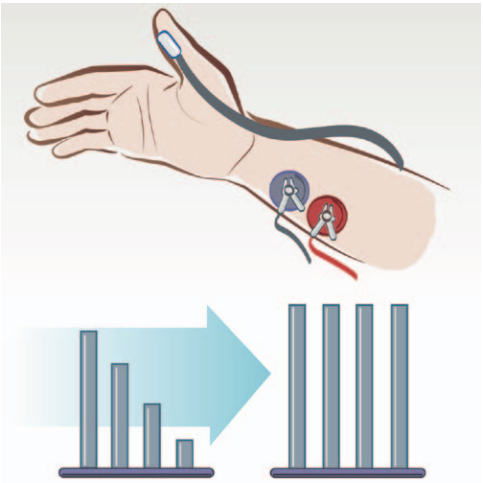
SUGAMMADEX represents an innovative disruption in drug technology. The recent approval of sugammadex by the Food and Drug Administration provides us with an opportunity to revisit the "state of the art" and emphasize important nuances in the administration, monitoring, and reversal of neuromuscular blockade. To that end, in this issue of ANESTHESIOLOGY, Brull and Kopman[1] review the status of monitoring and reversal of neuromuscular blockade, highlight persistent concerns with residual neuromuscular block, and address approaches on how to minimize them. This editorial highlights a few of the more important clinical implications of this review to include practice considerations of sugammadex *versus* neostigmine, the importance of monitoring neuromuscular blockade, clinically relevant drug interactions, adverse effects, and the pharmacoeconomics of sugammadex.



"… we encourage the American Society of Anesthesiologists committee on standards and practice parameters to consider adding a monitoring device … anytime a neuromuscular blocking drug is administered."

Why Use Sugammadex When I Can Get by with Neostigmine?

Sugammadex, a modified γ-cyclodextrin, is highly water soluble with a hydrophobic cavity large enough to encapsulate steroidal neuromuscular blocking drugs. The reversal activity of sugammadex is selective for steroidal neuromuscular blocking drugs (rocuronium > vecuronium >> pancuronium). Sugammadex has a little to no affinity for binding to benzylisoquinolinium neuromuscular blockers. The affinity of sugammadex for rocuronium is approximately 4,700 times that of atracurium.[2]

There are many potential applications of sugammadex of interest to anesthesiologists. The main advantages of sugammadex over neostigmine are its predictability and its ability to extend the range of neuromuscular blockade reversal. Reversal of residual competitive neuromuscular blockade by cholinesterase inhibitors has its limitations, as outlined by Drs. Brull and Kopman.[1] Neostigmine provides reversal for minimal, light (shallow), and moderate blockade. Sugammadex extends reversal capability, and in recommended doses of 2 to 16 mg/kg, it is capable of reversing any depth of neuromuscular block induced by rocuronium (from moderate to profound block) to a train-of-four ratio of more than or equal to 0.9 within 3 min. This has been and will continue to be a "game changer" for many patients who suffer from prolonged neuromuscular blockade. Sugammadex is also advantageous in that it does not have any cholinergic side effects that require the coadministration of an anticholinergic agent. However, the administration of sugammadex has been associated with life-threatening bradycardia that may require administration of anticholinergic agents.[3] Hypotension, ST-segment elevation unresponsive to vasopressors and anticholinergic drugs, and

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even cardiac arrest have been reported after administration of sugammadex.[4] Notably, administration of sugammadex may result in hypersensitivity and anaphylactic reactions, commonly seen within 5 min after administration. Although the incidence of allergic reactions after administration of 2 mg/kg sugammadex appears to be low, in a dedicated hypersensitivity trial (Trial P101), repeated administration of 4 and 16 mg/kg sugammadex was associated with an increased incidence (6.6% and 9.5%, respectively) of hypersensitivity as compared to placebo (1.3%).[4] Nearly 90% of these hypersensitivity reactions were judged to be mild by an adjudication committee.

Neuromuscular Blockade Monitoring: Why Go Blind When You Can See?

With all the enthusiasm regarding innovation in reversal of neuromuscular blockade, there may be a temptation to minimize or dismiss the use of neuromuscular monitoring. Indeed, if blockade is immediately reversible, why bother with monitoring? We advocate just the opposite. As our understanding of neuromuscular blockade matures, so does our ability to monitor it with higher resolution and make more informed management decisions. Perhaps the most important clinical implication is that of unrecognized residual neuromuscular block. The introduction of sugammadex has produced a hope that residual neuromuscular blockade after rocuronium would be virtually eliminated. Unfortunately, the data[5,6] indicate otherwise! The use of sugammadex is not an excuse to avoid monitoring the depth of blockade for every case when rocuronium or vecuronium is used. A conventional peripheral nerve stimulator (PNS, which requires the clinician to evaluate the evoked response visually or tactilely) would be sufficient to determine which dose is appropriate for a given depth of block. Other clinical implications include reversal agent choice and sugammadex dose. For reversal agent choice, an accurate assessment of neuromuscular blockade is required before selection of neostigmine *versus* sugammadex can be made. When selecting a sugammadex dose, the depth of blockade matters. Deep and profound blocks require larger doses of the drug and have associated cost implications. Accordingly, without formal evaluation of the degree of neuromuscular blockade, residual neuromuscular block is here to stay.

A typical dose of rocuronium (0.6 mg/kg) during opioid–nitrous oxide–oxygen anesthesia has a median onset of 1.8 min and duration of effect of 31 min, although there is substantial variability among patients with the onset of maximum blockade and duration times ranging from 0.6 to 13.0 and 15 to 85 min, respectively.[7] With this range of variability in duration of effect, the rationale for monitoring the depth of blockade is self-evident.

Why is it that anesthesia providers fail to use PNS to guide administration of neuromuscular blockers? Brull and Kopman[1] pointed out that the standard guidelines for neuromuscular monitoring are nonexistent in the United States and that the American Society of Anesthesiologists standards for basic anesthetic monitoring do not include neuromuscular blockade monitoring. We know that the clinical signs of recovery from neuromuscular blockade are insensitive and unreliable,[8] and we encourage the American Society of Anesthesiologists committee on standards and practice parameters to consider adding a monitoring device (whether a PNS or a quantitative monitor that measures and displays the train-of-four ratio in real time) anytime a neuromuscular blocking drug is administered. Why go blind when you can "see"?

What are the obstacles? To put it simply, many anesthesiologists are not convinced that it is beneficial to monitor the degree of neuromuscular blockade to guide clinical management of neuromuscular block. Clinicians may feel confident about their knowledge and experience and believe that they can safely manage neuromuscular blockade without monitoring.[9] Therefore, deviations from these "norms" are unwarranted because the majority of anesthesiologists believe that they have never experienced clinically significant adverse outcomes related to residual neuromuscular block.[10] Evidence, however, contradicts these beliefs.[9]

We recognize that even with a change in standards that recommend neuromuscular blockade monitoring, its impact on the incidence of residual neuromuscular block will be minimal without a change in motivation and attitude enforced by education and implementation strategies.[11] Only by adopting a strategy that could influence the practice of anesthesia providers would one expect to see a turn in the tide. Availability of a monitoring device (conventional or quantitative) *per se* will not result in a reduction in the incidence of residual neuromuscular block without training on the use of these monitors to avoid overzealous administration of neuromuscular blocking agents. What is evident is that effective implementation of educational programs (with feedback) combined with availability and the use of objective neuromuscular monitors can appreciably decrease the incidence of residual neuromuscular block.[12,13] There will always be many practical hurdles to overcome in implementing quantitative monitors given that the currently commercially available quantitative monitors are far from ideal.[13] Although quantitative monitors are superior to PNS, as outlined by Drs. Brull and Kopman,[1] the issue is not which type of device (conventional or quantitative) should be used but how knowledgeable the clinician is who is using the device. A quantitative monitor is no substitute for education and skill.

Drug Interactions That Matter: A Look at Sugammadex

The affinity of sugammadex to bind to corticosteroids is substantially less than that of rocuronium but may have clinical implications.[2] For instance, progestogens and estrogens show some affinity (2 to 22% of that of rocuronium).[14] The administration of a bolus dose of sugammadex is considered to be equivalent to one missed daily dose of oral

contraceptive steroids (either combined or progestogen only). The sugammadex package insert states that "Patients using hormonal contraceptives must use an additional, nonhormonal method of contraception for the next 7 days following [sugammadex] administration," and anesthesiologists should take on the responsibility of ensuring that patients are aware of this fact.

The Pharmacoeconomics of Sugammadex

The introduction of sugammadex may present cost challenges. The acquisition cost of sugammadex varies among different healthcare facilities in the United States. The average cost is $90 for a 200-mg vial (personal communication; Mohamed Naguib, M.D., Department of General Anesthesia, Anesthesiology Institute, Cleveland Clinic, Cleveland, Ohio, USA), a price that is comparable to the acquisition cost for neostigmine combined with glycopyrrolate to reverse a moderate block. The cost of sugammadex is greater when higher doses of sugammadex are required for antagonism of a deep or profound neuromuscular blockade.

The economic benefits of using sugammadex (*vs.* neostigmine) are unknown. One necessary step would be to investigate whether the use of sugammadex reduces the time to extubation when compared to neostigmine. This is not oversimplified because prolonged times to extubation limit operating room throughput.[15] No previous work has yet performed this randomized study. The principal confounders to be controlled are known (such as duration of surgical procedure and prone positioning). With consistent neuromuscular monitoring, the incidence of aggressive resuscitative measures such as tracheal intubation becomes small (albeit nonzero),[16] and residual weakness is confounded by opioid effects. Using cost savings per minute when comparing sugammadex to neostigmine reversal time to tracheal extubation *in lieu* of a proper pharmacoeconomic analysis, including accurate modeling of operating rooms time costs, is misleading and inappropriate.[17] An additional factor that might affect the cost of sugammadex is its patent life. U.S. and worldwide sugammadex patents will expire in early 2021.* This may lead to a lower price for generic sugammadex. On the other hand, neostigmine has been generic for decades, and yet its cost in the United States (but not in Europe) has recently skyrocketed as a consequence of the Food and Drug Administration's approach to grandfathered drugs.

Edrophonium: Does It Have a Role?

Given the current issues about the availability and cost of neostigmine, as outlined by Drs. Brull and Kopman,[1] there has been renewed interest in edrophonium to antagonize nondepolarizing neuromuscular blockade. Edrophonium has a fast onset of action, and in doses of 0.5 to 1.0 mg/kg, it can achieve a recovery profile comparable to that of neostigmine. Because of its pharmacokinetic profile, atropine appears to be the anticholinergic of choice to counteract the muscarinic side effects of edrophonium. Currently, the acquisition cost of edrophonium is about one third that of neostigmine at an equipotent dose (personal communication, Mohamed Naguib, M.D., Department of General Anesthesia, Anesthesiology Institute, Cleveland Clinic, Cleveland, Ohio, USA). This may favor edrophonium over neostigmine or sugammadex when considering the cost-effectiveness of each reversal. Although less expensive, edrophonium has a similar side-effect profile and dosing limitations to neostigmine; it cannot be used to reverse deep or profound neuromuscular blockade.

In summary, sugammadex represents a novel pharmacologic approach for reversing the neuromuscular blocking effects of rocuronium and vecuronium. It has an attractive pharmacologic profile but can be expensive, especially when reversing deep to profound blocks. It is important to emphasize that the increased versatility of sugammadex does not obviate the need for utilizing at least a PNS, as it is essential for identifying the appropriate dose of sugammadex. Without it, residual neuromuscular blockade will continue to affect patients recovering from anesthesia. As patient advocates, we encourage clinician educators and professional societies to implement educational programs to emphasize the proper use of neuromuscular monitoring devices any time a neuromuscular blocker is used regardless of the reversal agent used.

Competing Interests

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* Based on congruence of information from two Pharma intelligence subscription databases (MedTrack and Evaluate).

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Current Status of Neuromuscular Reversal and Monitoring

Challenges and Opportunities

Sorin J. Brull, M.D., F.C.A.R.C.S.I. (Hon), Aaron F. Kopman, M.D.

ABSTRACT

Postoperative residual neuromuscular block has been recognized as a potential problem for decades, and it remains so today. Traditional pharmacologic antagonists (anticholinesterases) are ineffective in reversing profound and deep levels of neuromuscular block; at the opposite end of the recovery curve close to full recovery, anticholinesterases may induce paradoxical muscle weakness. The new selective relaxant-binding agent sugammadex can reverse any depth of block from aminosteroid (but not benzylisoquinolinium) relaxants; however, the effective dose to be administered should be chosen based on objective monitoring of the depth of neuromuscular block.

To guide appropriate perioperative management, neuromuscular function assessment with a peripheral nerve stimulator is mandatory. Although in many settings, subjective (visual and tactile) evaluation of muscle responses is used, such evaluation has had limited success in preventing the occurrence of residual paralysis. Clinical evaluations of return of muscle strength (head lift and grip strength) or respiratory parameters (tidal volume and vital capacity) are equally insensitive at detecting neuromuscular weakness. Objective measurement (a train-of-four ratio greater than 0.90) is the only method to determine appropriate timing of tracheal extubation and ensure normal muscle function and patient safety. (ANESTHESIOLOGY 2017; 126:00-00)

> "We cannot solve our problems with the same thinking we used when we created them."
>
> Albert Einstein

IT is widely recognized that the introduction of neuromuscular blocking agents into clinical care has revolutionized surgery and facilitated significant medical advances in the last century. In their 2015 article, Game changers: the 20 most important anesthesia articles ever published, Barash *et al.*[1] list the seminal article by Griffith and Johnson[2] on the use of curare in general anesthesia as number 13. Appropriately, the other "top-20 contender" article is the study by Beecher and Todd[3] of surgical deaths during anesthesia that, although rebutted at the time, features a "special discussion of muscle relaxants (curare)." In the article, the authors cite a mortality rate of 1:2,100 anesthetics that did not include the use of curare and a mortality rate of 1:370 when curare was used.[3] Significant solutions to complex problems in medicine often introduce new and unintended clinical problems, and the introduction of neuromuscular blocking agents (NMBAs) is no exception.

Side Effects of Muscle Relaxant Drugs—Residual Block

Incomplete recovery from NMBAs (residual block) after anesthesia and surgery continues to be a common problem in the postanesthesia care unit (PACU). Despite the routine use of anticholinesterase reversal agents, between 20% and 40% of patients continue to arrive in the PACU with objective evidence of residual NMBAs.[4–8] In the past year alone, multiple investigations have demonstrated that residual NMBAs is an important patient safety issue,[7–10] and multiple letters,[11] surveys,[8] and editorials[12,13] have called for a solution to this recurring (and preventable) potential adverse event. Numerous clinical studies have documented that incomplete neuromuscular recovery is associated with a variety of adverse events in the early postoperative period, including airway obstruction, hypoxemic episodes, postoperative respiratory complications, intraoperative awareness,[10,14] and unpleasant symptoms of muscle weakness.[15–18] Despite the plethora of data documenting the importance of perioperative

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neuromuscular monitoring in preventing residual block,[17] recent surveys continue to document that subjective assessment using nerve stimulators is performed in less than 40% of patients,[9] while objective monitoring is even rarer (17% of patients).[19] In published studies, the use of neuromuscular monitoring is similarly widely variable; for instance, peripheral nerve stimulators (PNSs) are rarely, if ever, used in Japan,[20] while with a strong departmental champion and mentor, the use of objective neuromuscular monitoring using electromyography may approach 100%.[21] While clinicians have hypothesized (and hoped) that the introduction of sugammadex into clinical practice might eliminate residual neuromuscular block associated with aminosteroid-based relaxants, several studies have shown this not to be the case: when neuromuscular monitoring was not used intraoperatively, the incidence of residual block after sugammadex antagonism decreased, but was not always eliminated.[20,22,23]

Failure to monitor occurs not only in adult surgical patients, but also in the pediatric population that is even more vulnerable to the sequelae of incomplete reversal: 28% of pediatric patients were found to have residual block (defined as a train-of-four [TOF] ratio less than 0.90), while 6.5% of them had severe block (defined as a TOF ratio less than 0.70).[24] During periods of continuous administration of NMBAs, the most recent consensus guidelines for the use of muscle relaxants in critically ill children[25] call for the assessment of the depth of block "at least once every 24 h with TOF monitoring." These consensus guidelines recognize the lack of "quality of evidence available in the literature" and call for prospective, randomized, and controlled trials in this vulnerable patient population.

In the adult and pediatric intensive care unit (ICU), NMBAs are used routinely to enable emergency tracheal intubation, facilitate mechanical ventilation for acute respiratory distress syndrome, prevent patient-ventilator dyssynchrony during mechanical ventilation, manage status asthmaticus and elevated intracranial as well as intraabdominal pressure, and maintain induced hypothermia after cardiac arrest.[26,27] We must remember that NMBAs have no sedative or amnestic properties; that patients can have recall and "feel almost all of the procedures" they undergo in the ICU.[28] In fact, patients' recollection of therapeutic paralysis in the ICU includes themes of feeling "between life and death," loss of control, fighting or being tied down, and being terrified.[29] The literature suggests that in the adult ICU setting, the incidence of unintended patient awareness during periods of NMBAs exceeds 30%.[29,30]

The attempts to educate (and convince) clinicians that residual block is a real entity that needs solutions, not only recognition, have extended beyond the operating room (OR) and ICU settings. PACU nurses report that three of the most critical events that they may face requiring emergency intervention are residual NMBAs, acute postoperative hypertension, and acute hypotension.[31]

Residual Block: The Magnitude of the Problem

Clinical practice is extremely difficult to change, particularly when one's entire career decisions regarding neuromuscular management have been guided by subjective assessment of clinical signs of neuromuscular recovery. In fact, almost 20% of European and 10% of U.S., Australian, and New Zealand anesthesiologists never use nerve stimulators to guide management of NMBAs.[19,32]

The literature is replete with studies documenting the inadequacy of subjective assessment and clinical criteria ("bedside tests") to determine the adequacy of neuromuscular recovery, whether spontaneous or pharmacologic.[33] The current review is intended to underscore the gaps in current clinical practice regarding perioperative management of neuromuscular block and offer evidence of the importance of perioperative objective measurement of neuromuscular function whenever NMBAs are used. We continue to be optimistic and believe that with sufficient education and access to appropriate technology, the clinician will choose to do what is best and safest for the patient. To that end, we need to place current clinical practice in some global perspective. In the United States, the National Hospital Discharge Survey: 2010 from the Centers for Disease Control and Prevention estimated the total number of inpatient surgical procedures at 51.4 million.[34] If we reasonably assume that of these surgical cases, 60% receive general anesthesia requiring some form of muscle relaxation, then approximately 30.8 million patients are treated with NMBAs; we know that conservatively, one third of patients receiving NMBAs and anticholinesterase reversal will exhibit some degree of postoperative residual neuromuscular block (amounting to 10.1 million patients); of these patients, 0.8% will experience a critical respiratory event (CRE),[16] or more than 81,000 patients—every year. Worldwide, the number of major surgeries has been estimated to be 234.4 million per year[35]; this means that more than 0.5 million worldwide patients experience CREs every year!

Is this a significant patient safety issue? It seems that an increasing number of national specialty organizations now think so. The Czech Society of Anaesthesiology standards (2010) require that the method of monitoring be documented and define a TOF ratio greater than 0.90 as an adequate sign of recovery.[36] The French Society of Anaesthesiology and Intensive Care guidelines published in 2000[37] state, "instrumental [objective] monitoring is the main means for assessment" and "the presence of four responses to TOF stimulation is not a sufficient criterion of full reversal." Most recently in 2016, the Association of Anaesthetists of Great Britain and Ireland, London, United Kingdom, published their recommendations for standards of monitoring, which include, "A peripheral nerve stimulator must be used whenever neuromuscular blocking drugs are given. A quantitative peripheral nerve stimulator is recommended."[38] Many other European countries, as well as Australia and New Zealand, have addressed

the need for perioperative neuromuscular monitoring. Sadly, no such guidelines have been issued by the American Society of Anesthesiologists (ASA).

The ASA lists five requirements in the Standards for Basic Anesthesia Monitoring document (last affirmed October 28, 2015): the presence of qualified anesthesia personnel, oxygenation, ventilation, circulation, and body temperature monitoring. The Standards for Basic Anesthesia Monitoring document is silent on the need for neuromuscular monitoring.[39] An updated report by the ASA on Practice Guidelines for Postanesthetic Care[40] now states in the section on neuromuscular function guidelines, "assessment of neuromuscular function primarily includes physical examination and, on occasion, may include NMBAs monitoring." These recommendations are based on the committee's assessment of the evidence of the effectiveness of neuromuscular monitoring as Category B2-B. However, because of the continuing patient safety implications of postoperative residual weakness,[41] many have urged all anesthesia societies (national and international) to urgently create practice guidelines/standards governing the clinical management and monitoring of NMBAs.[32,42,43] We wholeheartedly agree and encourage clinicians to embrace the Association of Anaesthetists of Great Britain and Ireland standards for neuromuscular monitoring.[38]

Limitations of Anticholinesterase Pharmacologic Antagonism

General Principles

The key to understanding the limitations of acetylcholinesterase antagonists (or acetylcholinesterase inhibitors, also named anticholinesterases) is to remember that nondepolarizing block is competitive in nature. Molecules of acetylcholine compete with NMBA molecules for access to the postsynaptic receptor at the neuromuscular junction. When an acetylcholinesterase inhibitor is administered, acetylcholine breakdown is slowed, the acetylcholine concentration at the synaptic cleft increases, and the balance between the transmitter and blocking agent concentrations shifts in favor of acetylcholine-mediated normal function (resulting in reversal of block). However, once acetylcholinesterase activity is fully inhibited, the administration of any additional acetylcholinesterase inhibitor can have no further effect. Thus, there is a limit to the maximal concentration of acetylcholine that can exist at the receptor. However, there is no such limit to the concentration of NMBA molecules that can be present at the neuromuscular junction if the clinician administers very large doses of NMBA. A now classic study[44] nicely demonstrated this principle. The authors administered 0.10 mg/kg vecuronium (2× ED_{95}) to 40 patients. Fifteen minutes later, when there was no evoked response to ulnar nerve stimulation, either 0.07 mg/kg neostigmine or a saline placebo was administered. The authors then repeated this sequence at 10% twitch recovery. This resulted in four patient groups: (1) placebo/placebo, (2) placebo/neostigmine, (3) neostigmine/placebo, and (4) neostigmine/neostigmine. There were no differences in the recovery times of the first twitch of TOF (T1) to 90% of control nor in the recovery times of TOF ratio to 75% of control among the three groups who received neostigmine. The authors concluded that the total time from NMBA administration to 90% recovery of T1 was the same whether neostigmine is administered 15 min after vecuronium (when the neuromuscular function is 0%) or whether neostigmine is given when T1 has recovered to 10% of control. Furthermore, a second dose of neostigmine neither hastened nor prolonged recovery. Thus, repeated administration of neostigmine (even in the reported dose of 0.140 mg/kg) did not appear to alter the course of recovery and suggests that a single dose of 0.07 mg/kg neostigmine achieves essentially complete acetylcholinesterase inhibition. These data are not meant to imply that large overdoses of neostigmine (0.140 mg/kg) should ever be administered. While the second neostigmine dose of 0.07 mg/kg in this report[44] neither "hastened nor prolonged recovery," there is also evidence that neostigmine doses in excess of 0.06 mg/kg may lead to transient muscle weakness.[45–49]

Acetylcholinesterase Reversal of Profound and Deep Nondepolarizing Block

There is no current agreement on how to define profound (intense) *versus* deep *versus* moderate *versus* light (shallow) neuromuscular block. We propose the following definitions (table 1), which are modified slightly from a 2007 international consensus conference.[50]

During a nondepolarizing block, the high frequency of tetanic stimulation will induce a transient increase in the amount of acetylcholine released from the presynaptic nerve

Table 1. Suggested Definitions of Depth of Neuromuscular Block Based on Subjective and Measured (Objective) Criteria

Depth of Block	Posttetanic Count	Train-of-Four Count	Subjective Train-of-Four Ratio	Measured Train-of-Four Ratio
Intense (profound) block	0	0	0	0
Deep block	≥ 1	0	0	0
Moderate block	NA	1–3	0	0
Light (shallow) block	NA	4	Fade present	0.1–0.4
Minimal block (near recovery)	NA	4	No fade	> 0.4 but < 0.90
Full recovery (normal function)	NA	4	No fade	≥ 0.90–1.0

NA = not applicable

ending, such that the intensity of subsequent muscle contractions will be increased (potentiated) briefly (period of posttetanic potentiation, which may last 2 to 5 min; fig. 1). The neuromuscular response to stimulation during posttetanic potentiation can be used to gauge the depth of block when TOF stimulation otherwise evokes no responses (*i.e.*, when the TOF count [TOFC] = 0). The number of posttetanic responses is inversely proportional to the depth of block: fewer posttetanic contractions denote a deeper block. When the posttetanic count (PTC) is 6 to 8, recovery to TOFC = 1 is likely imminent from an intermediate-duration blocking agent; when the PTC is 0, the depth of block is profound, and no additional NMBA should be administered.

When antagonism of profound (PTC = 0) or deep (PTC more than or equal to 1 and TOFC = 0) block is (unadvisedly) attempted with an acetylcholinesterase inhibitor, there is convincing evidence that recovery is usually a very slow process.[51,52] When reversal of rocuronium at a PTC of 1 to 2 (see below for PTC) during sevoflurane anesthesia was attempted with 0.07 mg/kg neostigmine, the median recovery time to a TOF ratio of 0.90 was 49 min with a range of 13 to 146 min.[52] Similarly, during deep block (PTC of 1 to 2), reversal of vecuronium with 0.07 mg/kg neostigmine required a median of 50 min with an even wider range of 46 to 313 min.[51] If pharmacologic reversal is attempted 5 min after complete T1 ablation after vecuronium or atracurium administration, the spontaneous recovery time to a TOF ratio of 0.70 required a mean value of 66.7 ± 3.3 min. This duration was shortened to 43.5 ± 5.1 min by administration of 0.07 mg/kg neostigmine.[53] Thus, while neostigmine

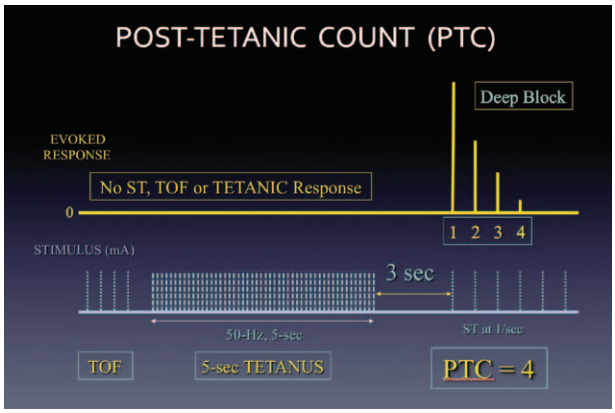

Fig. 1. Posttetanic count (PTC). During a nondepolarizing block, the high-frequency tetanic stimulation (50 Hz or 100 Hz) will induce a transient increase in the amount of acetylcholine released from the presynaptic nerve ending, such that the intensity of subsequent muscle contractions will be increased (or facilitated). This facilitated neuromuscular response to stimulation after tetanus can be used to gauge the depth of block when train-of-four (TOF) stimulation otherwise evokes no responses (*i.e.*, when the TOF count = 0). The number of posttetanic responses is inversely proportional to the depth of block: the fewer posttetanic contractions are elicited, the deeper the depth of block. In the illustration above, PTC = 4.

clearly accelerated recovery by 20 to 25 min, return of satisfactory neuromuscular function was hardly prompt or complete (table 2). Based on these data, we recommend that reversal of profound or deep neuromuscular block not be attempted using acetylcholinesterase inhibitors.

Acetylcholinesterase Reversal of Moderate Nondepolarizing Block

The literature on recovery times from moderate block can be confusing. For example, Kim *et al.*[6] administered 0.07 mg/kg neostigmine at a TOFC of 1 (TOFC = 1) after administration of a rocuronium dose of 0.60 mg/kg. The recovery time to a TOF ratio of 0.90 was 8.6 min (range, 5 to 19 min) under propofol anesthesia, but it was 28.6 min (range, 9 to 76 min) under sevoflurane anesthesia. This prolongation is not unexpected since most inhalational anesthetic agents potentiate neuromuscular block by varying degrees (desflurane > sevoflurane > isoflurane> halothane > nitrous oxide).[6,54–56]

Recovery times are also dependent on the class of nondepolarizing agent being antagonized (short-, intermediate-, or long-acting) and on the cumulative dose of the drug that has been administered before attempted pharmacologic reversal. The peak effects of edrophonium, neostigmine, and pyridostigmine occur in 1 to 2, 7 to 11, and 12 to 16 min, respectively.[57] Thus, any observed recovery after these intervals is a result of elimination or redistribution of the NMBA from the plasma. A now-classic study demonstrates this nicely.[58] The authors attempted to antagonize atracurium or alcuronium (a long-acting NMBA) once the first response of TOF (T1) values was 10% of control or less. Atracurium recovery times to a TOF ratio of 0.70 were 20.5 ± 13 and 9 ± 4.9 min after administration of 0.04 and 0.08 mg/kg neostigmine, respectively, suggesting that acetylcholinesterase inhibition occurred sooner in the high-dose neostigmine group. For alcuronium, these values were 31.4 ± 15.5 and 25 ± 17.6 min, respectively. As the authors[58] suggest, anticholinesterases have a *ceiling* to the depth of block that they can antagonize completely, even at these relatively advanced levels of neuromuscular recovery (moderate block; table 1).

Achieving prompt and reliable recovery of neuromuscular function by acetylcholinesterase inhibitor administration when T1 is less than or equal to 10% of control (corresponding to TOFC less than or equal to 1) is simply not a realistic goal. Attempted reversal at a TOFC = 1 is also an especially poor idea when objective (quantitative) monitoring of neuromuscular function is not employed. This was demonstrated in a study in which steady-state infusions of rocuronium or cisatracurium achieved approximately 94% T1 depression (deep block), confirmed with electromyography.[59] Two minutes after the infusion was stopped, all patients received 0.05 mg/kg neostigmine. The average TOF ratios 10 and 20 min later were 0.53 ± 0.15 and 0.83 ± 12, respectively, after cisatracurium administration and 0.57 ± 0.11 and 0.79 ± 0.12, respectively, after rocuronium administration.

Table 2. Limitation of Acetylcholinesterases as Antagonists of Nondepolarizing Block

Depth of Block	Edrophonium Dose (mg/kg)	Neostigmine Dose (mg/kg)	Time (Range) to TOF	Comments	References
Deep (PTC < 5)		0.07	32 (9–123) min to TOF = 0.70 40 (11–144) min to TOF = 0.80 49 (13–146) min to TOF = 0.90	Rocuronium was investigated.	Jones *et al.*[52]
Deep (PTC < 5)		0.07	49 (28–192) min to TOF = 0.70 59 (35–251) min to TOF = 0.80 66 (46–313) min to TOF = 0.90	Vecuronium was investigated.	Lemmens *et al.*[51]
Deep (PTC < 5)	Spontaneous recovery		66 ± 2.2 min	Recovery to TOF = 0.70	Caldwell *et al.*[53]
Deep (PTC <5)	— 0.80	0.07 —	44 ± 5.1 min 60 ± 5.6 min	Vecuronium group. Antagonism 5 min after loss of T1 to TOF = 0.70	
Deep (PTC < 5)	— 0.80	0.07 —	44 ± 2.9 min 49 ± 3.8 min	Atracurium group. Antagonism 5 min after loss of T1 to TOF = 0.70	
T1 = 0–10% of baseline	0.50 1.00		18 ± 9.1 min 11 ± 6.7 min	Recovery times to a TOF = 0.70	Beemer *et al.*[58]
		0.04 0.08	20.5 ± 13.1 min 11.2 ± 6.7 min		
TOFC = 1		0.05	TOF @ 10 min = 0.70 ± 0.13 TOF @ 20 min = 0.81 ± 0.12	At 10 min after reversal, 73% of subjects had TOF ratios > 0.39 but < 0.70	Kopman *et al.*[59]
TOFC = 1 TOFC = 2 TOFC = 4		0.07	22.2 (14–44) min 20.2 (7–71) min 16.5 (7–143) min	Cisatracurium reversal. Recovery to TOF = 0.90	Kirkegaard *et al.*[61]
TOFC = 1 TOFC = 2 TOFC = 4		0.07	29 (9–76) min 23 (8–57) min 10 (5–26) min	Sevoflurane anesthesia. Recovery to TOF = 0.90	Kim *et al.*[6]
TOF = 0.20		Placebo 0.01 0.025 0.04 0.07	33 (11–68) min 15 (9.5–56) min 6 (3.0–11) min 4.5 (2.0–21) min 3.3 (1.7–19) min	Rocuronium block. Recovery to TOF = 0.90. Two of 26 subjects given > 0.025 mg/kg failed to reach a TOF of 0.90 within 10 min	Kaufhold *et al.*[67]
TOF = 0.40		Placebo 0.01 0.02 0.03	13 (7–27) min 6 (3–12) min 6 (4–9) min 4 (3–6) min	Recovery to TOF = 0.90	Fuchs-Buder *et al.*[63]
TOF = 0.60		Placebo 0.01 0.02 0.03	10 (5–16) min 4 (2–9) min 3 (2–7) min 4 (2–6) min	Recovery to TOF = 0.90	Fuchs-Buder *et al.*[63]
TOF = 0.50		Placebo 0.005 0.008 0.015 0.025 0.040	19 (12–33) min 9.3 (6–15) min 5.3 (4–9) min 4 (3–6) min 3.2 (2–6) min 2 (2–4) min	Recovery to TOF = 0.90	Schaller *et al.*[65]

PTC = posttetanic count; TOF = train-of-four; TOFC = train-of-four count.

Ten minutes after reversal, 29 of 40 subjects had TOF ratio greater than 0.39 but less than 0.70! However, once the TOF ratio exceeds 0.40, most clinicians cannot detect either tactile or visual (subjective) fade.[60] It must be emphasized that TOF ratios less than 0.70 represent an unacceptable degree of clinical recovery. Therefore, 10 min after antagonism, recovery will be grossly incomplete in more than 70% of patients, yet clinicians would be completely unaware of this, unless quantitative neuromuscular monitoring was utilized. Fifteen minutes after reversal, 43% of patients had a TOF 0.40 to 0.70, and this degree of residual block was still present in 13% of individuals 20 min after reversal with neostigmine.[59]

At the shallower end of moderate block (TOFC = 3; table 1), the median recovery time to a TOF ratio of 0.90 after 0.07 mg/kg neostigmine administration was reported as 17 (range, 8 to 46) min during nitrous oxide/propofol anesthesia.[61] The authors concluded that to achieve rapid (within 10 min) reversal to a TOF ratio of 0.7 in more than 87% of patients, three or four tactile responses should be present at the time of neostigmine administration. It was not possible within 30 min to achieve a TOF ratio of 0.9 in all patients, regardless of the number of tactile responses present at neostigmine administration. These data clearly indicate that subjective (visual and tactile) means of assessment are inadequate to ensure adequate recovery of neuromuscular function even after pharmacologic antagonism of moderate block with anticholinesterases. We again encourage clinicians to use objective monitoring whenever nondepolarizing NMBAs are administered to patients.

Acetylcholinesterase Reversal of Light and Minimal Nondepolarizing Block

Once the TOFC reaches 4 with minimal or absent TOF fade, the reliability (and speed of reversal) of acetylcholinesterase inhibitors increases markedly. In 1994, Harper *et al.*[62] attempted reversal of atracurium under nitrous oxide/enflurane anesthesia at T1 values of 40 to 50% of control (a TOFC = 4 with TOF fade). They observed recovery times to a TOF more than or equal to 0.70 of 4.5 (range, 3 to 8) min, 3.0 (2.3 to 5.2) min, and 2.3 (1.3 to 3.7) min after administration of 0.02, 0.04, and 0.08 mg/kg neostigmine, respectively.

Fuchs-Buder *et al.*[63] studied reversal times from a TOF ratio of 0.40 under total intravenous anesthesia. It should be remembered that once the TOF ratio exceeds a (measured) value of 0.40, most clinicians can no longer detect tactile or visual fade.[60] After 0.02 mg/kg neostigmine administration, the interval to recovery of TOF values of 0.90 and 1.00 was 6 (range, 4 to 9) and 9 (range, 6 to 13) min, respectively. If the dose of neostigmine was increased to 0.03 mg/kg, these times decreased to 4 (range, 3 to 6) and 5 (range, 3 to 7) min, respectively. These TOF ratios had not been referenced to the control TOF and thus were nonnormalized acceleromyographic results.[50,64] Therefore, the recovery times to a nonnormalized TOF ratio of 1.00 are most likely equivalent to the recovery times measured mechanomyographically or electromyographically to a TOF ratio of 0.90.

Other investigators have reported similar results.[65] Under total intravenous anesthesia with electromyography monitoring, reversal of rocuronium-induced block from a TOF ratio of 0.50 was attempted with various doses of neostigmine. The recovery time to a TOF ratio of 0.90 was 3.2 (range, 1.7 to 6.2) min after administration of 0.025 mg/kg neostigmine and 2.0 (1.7 to 4.2) min after administration of 0.04 mg/kg neostigmine. The authors estimated that a 0.034 mg/kg dose of neostigmine would reverse a TOF ratio of 0.50 to more than 0.90 within 5 min (table 2). Finally, Fuchs-Buder *et al.*[66] repeated their own 2010 study[63] (during nitrous oxide/desflurane anesthesia) and concluded that "neostigmine doses as low as 0.01 mg/kg may be sufficient to antagonize shallow atracurium neuromuscular block corresponding to a TOF ratio of 0.6, even under inhalational anesthesia." Such optimistic conclusions, however, are not supported by data from other investigators. A very recent study by Kaufhold *et al.*[67] supports the findings of Kirkegaard *et al.*[61] that even at a threshold TOFC of 4, neostigmine is not always a reliable antagonist of nondepolarizing block (table 2). The authors administered varying doses of neostigmine when recovery from rocuronium had spontaneously returned to a TOF ratio of 0.20. While 0.04 and 0.07 mg/kg doses of neostigmine usually achieved a TOF ratio greater than or equal to 0.90 in less than 10 min in both patient groups, there was one patient in each group in whom this value was not reached for 20 min. It is important, therefore, to ensure that there are no outlier patients who require unexpectedly long times for adequate recovery. In view of the lack of compelling data that doses of neostigmine as small as 0.01 mg/kg are effective, doses less than 0.02 mg/kg for reversal of light or minimal block cannot be recommended. Additionally, it should be reiterated that minimal neuromuscular block can only be determined by objective means of monitoring and that subjective assessment using a PNS will be inadequate to ensure sufficient recovery in all patients.

Neostigmine-induced Neuromuscular Weakness

When reversing minimal neuromuscular block with neostigmine, one caveat remains. In 1980, it was reported that when 2.5 mg neostigmine was given to subjects who previously had not been given a nondepolarizing relaxant, there was a substantial reduction in the peak tetanic contraction; severe tetanic fade, which persisted for about 20 min, was observed.[45] Others reported similar results. After atracurium-induced NMBAs corresponding to a TOF ratio of either 0.50 or 0.90, two doses of 2.5 mg neostigmine were given 5 min apart. Neuromuscular recovery was assessed with TOF and tetanic stimuli. The first dose of neostigmine antagonized the NMBAs. The second dose diminished tetanic height and increased tetanic fade.[68] More recent investigations have reported that neostigmine significantly impairs genioglossus muscle activity (upper airway dilator ability) when administered after full recovery from neuromuscular block[69,70]; others concluded that high doses of the acetylcholinesterase inhibitor neostigmine (more than 60 μg/kg), intended to reverse the effects of NMBAs, increased the risk of respiratory complications independent of NMBA effects.[46] These data are consistent with other reports that full doses of neostigmine administered to rats that had fully recovered from neuromuscular block decreased the upper airway dilator volume and impaired genioglossus muscle function, diaphragmatic function, and breathing.[47] Similar data were also reported in children: pharmacologic reversal with neostigmine resulted in an incidence of residual block in patients who had received anticholinesterases that was twice as high as in the group of pediatric patients in whom neostigmine had not been administered (37.5% *vs.* 19.4%, respectively).[24] The question whether smaller doses of neostigmine (*e.g.*, 0.01 to 0.03 mg/kg) have any effects of airway musculature weakness or residual paralysis if administered to fully (or near fully) recovered adult or pediatric patients remains unanswered. These data suggest that empiric, routine full-dose (neostigmine 0.07 mg/kg) reversal of light or minimal neuromuscular block is not advised, and they underscore the need for objective neuromuscular monitoring (table 3). At this shallow end of the reversal spectrum, however, there does not appear to be any evidence to suggest that doses of neostigmine of 0.03 mg/kg or less are associated with adverse clinical outcomes when administered empirically (*i.e.*, in the absence of neuromuscular monitoring). However, there is evidence that in the absence of routine reversal, the incidence of postoperative residual

Table 3. Recommendations for Pharmacologic Antagonism of Nondepolarizing Blockade According to the Depth of Block

Depth of Block	Neostigmine Dose (mg/kg)	Sugammadex Dose* (mg/kg)
Posttetanic count < 2	Delay reversal	4–16†
Posttetanic count ≥ 2	Delay reversal	2–4†
TOF count 0–1		
TOF count 2–4	0.05–0.07	1.0–2.0†
TOF with fade by tactile or visual means		
TOF < 0.40‡		
TOF count 4, no tactile or visual fade	0.02–0.03	0.25–0.5†
TOF = 0.40–0.90‡		
TOF ratio ≥ 0.90‡	Reversal unnecessary	Reversal unnecessary

*Dose ranges reported in the literature; cited doses may be deviate from package insert recommendations. †When reversing vecuronium, use higher end of dosing range. ‡TOF ratio confirmed by quantitative monitoring.
TOF = train-of-four.

neuromuscular block and associated complications is markedly increased.[71–73]

Neostigmine Shortage, the Food and Drug Administration, and Clinical Impact

Anesthesiologists have been experiencing nationwide drug shortages for decades, but the duration of drug unavailability and the number of drugs on the shortage list have increased dramatically in the last few years.[74] The reasons for drug shortages include scarcity of raw materials, inconsistent or inadequate quality control in manufacture, and industry consolidation that may result in the disappearance of some manufacturers. In 2011, the U.S. Food and Drug Administration (FDA) issued revised guidance on marketing of unapproved drugs and established an orderly approach for removing unapproved drugs from the market.[75] Eclat Pharmaceuticals (USA), a subsidiary of Flamel Technologies, was the only manufacturer to obtain FDA approval of their neostigmine preparation, Bloxiverz. Subsequent to this FDA approval, the makers of Bloxiverz sent a request letter to the FDA calling for removal from the U.S. market of all other unapproved formulations of neostigmine manufactured generically by five other competing manufacturers. Bloxiverz at the time cost more than six times as much as its FDA-unapproved predecessors partly attributed by Eclat on the FDA filing fee of more than $2 million.[76] Upon contacting Eclat Pharmaceuticals, the manufacturer confirmed that Bloxiverz is the only FDA-approved product on the market for neostigmine, while AmerisourceBergen (USA), Cardinal (USA) , H.D. Smith (USA), McKesson (USA), and Morris & Dickson (USA) are authorized distributors of Bloxiverz (Sorin J. Brull, M.D., Department of Anesthesiology, Mayo Clinic, Jacksonville, Florida; January 2016; written communication). The reliance on a single manufacturer of neostigmine can have ominous implications on U.S. drug availability in the future, as history clearly demonstrates.[74]

Edrophonium Reversal of Neuromuscular Block

Edrophonium is another anticholinesterase agent used clinically for reversal of neuromuscular block. It is less effective as a reversal agent, as the bonds it forms with NMBA molecules are ionic and much weaker than the covalent bonds of neostigmine and NMBA. Because of this lower potency, the degree of spontaneous recovery from neuromuscular block at the time of edrophonium administration should be at least a TOFC of 4. The usual dose of edrophonium in the clinical setting is 0.50 mg/kg; doses of 0.75 mg/kg provide minimal increases in efficacy.[77] Because of its propensity to induce bradycardia and its more rapid onset of action than neostigmine, edrophonium is usually administered in conjunction with atropine. The administration in divided doses over several minutes, as opposed to rapid single-bolus administration, will result in a lower peak plasma concentration of both agents and will minimize the potential for bradycardia (from edrophonium) or tachycardia (from atropine). Because of recent shortages of neostigmine, clinicians have had to resort to the use of this drug combination for reversal of neuromuscular block.

Lessons Learned

While neostigmine usually acts as an antagonist of nondepolarizing neuromuscular block, if administered incorrectly, it may either be ineffective or have undesirable paradoxical effects (table 3). During "profound and deep block," neostigmine (in any dose) will be ineffective and should not be administered; during "minimal block," only small doses are needed, and a full-reversal dose may in fact result in transient neuromuscular weakness.[45,68]

The limitations of anticholinesterases as antagonists of residual nondepolarizing block are greater than most clinicians appreciate. At TOFCs less than 3 or 4, prompt and satisfactory reversal of nondepolarizing block by neostigmine should not be anticipated, and attempts at reversal should be delayed until these values are attained. During moderate block, the dose of neostigmine necessary to achieve maximal effect is a subject of some debate but probably is not less than 0.04 mg/kg.[78] There is also no evidence that increasing dosage beyond 0.06 mg/kg will increase the drug's efficacy.[79] Unless quantitative monitoring provides evidence of full recovery, even TOFCs of 4 without fade (determined

subjectively) should be reversed. However, in these circumstances, doses of neostigmine of 0.02 to 0.03 mg/kg are sufficient to reliably assure satisfactory return of neuromuscular function within approximately 10 min, without inducing paradoxical neuromuscular weakness. Data suggest that routine administration of full doses of neostigmine (more than 0.06 mg/kg, for instance) to fully reversed patients to ensure full recovery or for medicolegal reasons (*i.e.*, chart documentation) may be counterproductive and should be avoided.[45–48,70]

Selective Relaxant-binding Agents

Sugammadex

A decade ago, because of the limitations inherent in the use of acetylcholinesterase inhibitors as antagonists of neuromuscular block, it seemed clear that the issue of postoperative residual block was unlikely to disappear unless an alternative method of pharmacologic reversal of deep and even moderate block became available. In 2006, articles by de Boer *et al.*[80,81] and others[82,83] described a new and promising agent.[84] Sugammadex (a modified γ-cyclodextrin) forms 1:1 complexes with aminosteroid neuromuscular blocking drug molecules but has no effect on benzylisoquinolinium compounds or on succinylcholine. A dose of 3.57 mg sugammadex is needed to encapsulate 1.0 mg rocuronium. The resulting complex has a very low dissociation rate. Encapsulated molecules of the NMBA that circulate in the plasma are no longer able to bind with muscle acetylcholine receptors, allowing blocking agents to diffuse away from the synaptic cleft and back into the plasma as the concentration of free drug in plasma decreases precipitously. Thus, clinicians now have for the first time the ability to rapidly and completely reverse profound nondepolarizing neuromuscular block, and do so directly by inactivating the activity of the NMBA, rather than indirectly, by inhibiting acetylcholinesterases.

Since sugammadex first became commercially available in 2008 (outside the United States), voluminous literature has emerged detailing the drug's pharmacology, safety, and clinical uses. Several excellent reviews are available.[85–91] An attempt to summarize this information is beyond the scope of the current review. Rather, our current focus is two-fold: first, we describe the safety issues that have prevented the U.S. FDA from approving sugammadex for clinical use until late 2015, and second, we focus on the potential for sugammadex to decrease the frequency of undetected residual block in the postoperative period.

Sugammadex does not appear to have affinity for any receptors, so it has no hemodynamic effects. It has been shown to bind to toremifene, fusidic acid, and flucloxacillin.[92] Additionally, sugammadex binds oral contraceptives, and women of childbearing age should be counseled about using alternative contraceptive methods for 1 week after exposure to sugammadex. In many institutions, this potential side effect is disclosed as part of the preoperative anesthesia consent. Hypersensitivity reactions to all anesthetics during the perioperative period have an incidence between 1:3,500 and 1:20,000 exposures, and the associated mortality approaches 9%.[93] Hypersensitivity to sugammadex appears to be relatively low, with only 15 cases being reported in a 2014 review.[94] In the majority of the reported cases, the anaphylactic reactions were evident within the first 4 min after administration of sugammadex, and cardiovascular collapse was treated successfully with fluid resuscitation and high-dose epinephrine therapy.[95] The other major factor that delayed the approval by the FDA has been the potential effect of sugammadex on coagulation. In patients receiving sugammadex, the activated partial thromboplastin time and the prothrombin time were increased by 5.5% and 3.0%, respectively; however, these increases returned to normal values within 60 min.[96] Likely as a consequence of these being relatively minor and short-lived effects on coagulation parameters, the incidence of bleeding events in patients receiving sugammadex (2.9%) and those not exposed to sugammadex (4.1%) was comparable. Additionally, effects on the various coagulation assays are likely an *in vitro* artifact.[96,97]

Regrettably, the number of studies that document the incidence of postoperative residual neuromuscular block after sugammadex reversal is rather limited. Nevertheless, existing data are encouraging. Della Rocca *et al.*[98] compared neostigmine- to sugammadex-aided recovery times after reversal of rocuronium at a TOFC of 2 in a large prospective multisite study. One hundred forty-two patients received neostigmine, and 163 received sugammadex. Because the study was observational, sugammadex and neostigmine were administered according to each anesthesiologist's clinical judgment. In the neostigmine group, 72%, 41%, and, 18% of patients had TOF ratios less than 0.90 at 5, 10, and 20 min, respectively, after reversal. In the sugammadex group, these values were 12%, 2%, and 0%, respectively.[98] An even more promising study was reported by Brueckmann *et al.*[99] They randomized 150 patients receiving rocuronium and having abdominal surgery to either sugammadex (n = 74) or neostigmine (n = 76) reversal groups. All drug doses and timing of reversal administration were per individual clinician preference. TOF-Watch (Organon Ireland Ltd., Ireland) monitors were available intraoperatively, and usage was left to the discretion of the anesthesiologist. Upon arrival in the PACU, 43% of patients in the neostigmine group had TOF ratios less than 0.90. In contrast, the incidence of residual block in the sugammadex group was zero!

Other studies, however, suggest that sugammadex is not totally fool proof. Ledowski *et al.*[22] reported on 126 patients in an observational study. The choice of anesthetic technique, NMBA, reversal agent (neostigmine, sugammadex, or no reversal), dosages, and so forth, was left to the individual anesthesiologist. Conventional PNSs (qualitative devices) were available in the operative room, but their use was not mandated. When the clinician deemed that the patient was ready

for tracheal extubation, an independent investigator measured the TOF ratio at the adductor pollicis with a kinemyographic monitor. Thirty-three patients received pharmacologic reversal with neostigmine. In this group, 19 (58%) had TOF ratios less than 0.90, and 8 (24%) had TOF ratios less than 0.70. Of the 57 patients who received sugammadex, only four individuals (7%) had TOF ratios less than 0.90, and none had a TOF ratio less than 0.70.[22] Kotake *et al.*[20] studied 117 patients who had received rocuronium (0.60 to 0.90 mg/kg) followed by pharmacologic reversal with sugammadex. In this multisite study, intraoperative monitoring of neuromuscular function was not employed. The average dose of sugammadex administered was 2.7 ± 1.0 mg. TOF ratios were measured after tracheal extubation (8 ± 4 min after reversal). The incidence of TOF ratios less than 0.90 was 4.3% (95% CI, 1.7 to 9.4). The authors concluded that the risk of TOF ratio less than 0.9 in the PACU remained at least 1.7% and may be as high as 9.4% even with sugammadex in a clinical setting when no neuromuscular monitoring is used routinely.[20] Finally, a prospective study comparing residual neuromuscular block and postoperative pulmonary complications in patients receiving either neostigmine or sugammadex found that the residual paralysis incidence was 28.6% in the patients who received neostigmine reversal, while in the sugammadex group, the incidence was 1.2%. Of note, intraoperative neuromuscular monitoring (which did not specify subjective or objective assessment) was performed in only 30% of patients.[100]

These studies suggesting that residual neuromuscular block may still occur after sugammadex reversal need special mention. Because of the 1:1 molar ratio between sugammadex and the aminosteroid NMBA, there have to be sufficient sugammadex molecules administered to encapsulate all of the free molecules of the NMBA. For this reason, sugammadex reversal dose is calculated based on the depth of neuromuscular block at the time of reversal. For reversal of moderate block (TOFC, 1 to 3), a dose of 2 mg/kg is recommended; for reversal of deep block (PTC more than or equal to 1), a dose of 4 mg/kg is recommended, and for rescue from a failed rapid-sequence induction in the cannot-intubate-cannot-ventilate scenario (profound block, PTC = 0), a dose of 16 mg/kg is recommended (table 3). Therefore, if clinicians use subjective or clinical means of assessment of neuromuscular block rather than objective monitoring, it is possible that the dose of sugammadex may be insufficient, resulting in incomplete reversal. This is likely a limitation of inappropriate monitoring rather than a failure of the drug.[20]

It also appears that sugammadex should be administered based on actual body weight, particularly in the obese patient. Failure to administer a sufficient dose may result in reappearance of postoperative neuromuscular weakness (recurarization).[101]

Residual Paralysis and Potential Solutions—Monitoring

Before discussing neuromuscular monitoring as a potential solution to postoperative residual weakness, a brief review of nomenclature is warranted: there is a critical difference between a nerve stimulator and a monitor, yet these terms are often used interchangeably (and incorrectly). A PNS is a simple medical device that delivers current impulses to a peripheral nerve. The assessment of evoked responses from the innervated muscle is detected *subjectively* by the clinician, by watching or feeling the strength of muscle contraction. Such PNSs are not monitors since the assessment is made subjectively. Neuromuscular monitors are objective medical devices that measure and display the evoked TOF ratio in real time.

Any discussion of appropriate neuromuscular monitoring should include a description of the ideal monitor. All neuromuscular monitors fulfill two distinct but separate functions: the first is to deliver an electrical stimulus to a peripheral nerve, an action that can be provided by any PNS; the second function is to detect, measure, and analyze the evoked muscle contraction or the muscle action potential (MAP) that results from this peripheral nerve stimulation. This latter function is the actual monitoring and can only be performed by a limited number of medical devices. Existing neuromuscular monitors can be either stand-alone, portable devices or modular units that are integral parts of anesthesia workstations and that use acceleromyography, kinemyography, or electromyography (table 4).

The characteristics of the ideal PNS have been described[102] and include those listed in table 5. The characteristics of the ideal monitor are more difficult to define, because every technology currently in clinical use has not only certain advantages, but also limitations (table 6).

Careful management of NMBAs in the OR reduces the risk of residual NMBAs in the PACU. Several strategies that can be utilized by anesthesiologists in the OR will decrease the incidence of residual muscle weakness after tracheal extubation. The use of shorter acting NMBAs[103,104] and routine administration of drugs that antagonize the effects of NMBAs (for instance, neostigmine) result in fewer although still unacceptably high incidence of postoperative patients with clinically evident muscle weakness.[6,105] The routine use of perioperative neuromuscular monitoring has been advocated as another important method of reducing the incidence of residual weakness (residual paresis, residual neuromuscular block, or residual curarization).[11,18,21,106,107] Three general categories of perioperative neuromuscular monitoring exist: clinical or bedside testing, subjective or qualitative evaluation, and objective or quantitative measurement.

Clinical (bedside) testing has been used since the introduction of NMBAs into clinical practice: measurement of respiratory parameters (tidal volume, vital capacity, minute ventilation, negative inspiratory force, and so forth) has been correlated with neuromuscular recovery (TOF ratio), but just like other clinical tests of muscle function (5-s head-lift, grip strength, and leg-lift tests), these tests are unreliable and nonspecific.[108] These tests generally require that the patient being evaluated be awake and cooperative, but

Table 4. List of Stand-alone and Modular, Integrated Neuromuscular Monitors Available in 2016

NMT Monitor*	Operation	Technology	Manufacturer	Comments
TOF-Watch	Stand alone	AMG	Organon Ireland Ltd., Ireland	No availability of new neuromuscular monitors. The TOF-Watch SX is the only unit that displays raw TOF ratios
STIMPOD NMS450	Stand alone	AMG	Xavant Technology Ltd., South Africa	Triaxial accelerometer calculates vector of contraction in three dimensions
TofScan†	Stand alone	AMG	IDMed, France	Three-dimensional accelerometer
TOF-Cuff‡	Stand alone	CMG	RGB Medical Devices, Spain	Senses pressure peaks in the blood pressure cuff induced by stimulation of the brachial plexus
M-NMT	OEM—modular, integrated	KMG	GE Healthcare, USA	The piezoelectric sensor converts physical motion to electric current
E-NMT	OEM—modular, integrated	EMG	GE Healthcare, USA	The E-NMT-01 module was recalled by the FDA in 2014
IntelliVue NMT Module	OEM—modular, integrated	AMG	Philips NV, The Netherlands	Acceleromyography-based monitor available on workstations

*To date, there are no studies comparing the STIMPOD, TofScan, TOF-Cuff, IntelliVue NMT Module, or the GE Healthcare modules with any accepted standard devices. †TofScan is not available in the United States. ‡TOF-Cuff is not available in the United States. It measures TOF responses by changes in pressure peaks in the blood pressure cuff induced by muscle contraction. This appears to be a form of compressomyography technique although the actual technology is described by the manufacturer as modified blood pressure cuff with integrated stimulation electrodes.

AMG = acceleromyography; CMG = compressomyography; EMG = electromyography; KMG = kinemyography; OEM = original equipment manufacturer (modular, integrated into anesthesia workstations); TOF = train-of-four.

Table 5. Characteristics of the Ideal Peripheral Nerve Stimulator

Feature	Characteristic	Comments
Portability	Light weight, hand-held, battery operated	Can be interfaced with anesthesia workstations and electronic medical records
Impulse characteristics	Square wave	The impulse should be monophasic and rectangular
Current characteristics	Constant current	A constant current (not constant voltage)
Delivered current	0–70 mA	Current needed for supramaximal stimulation
Stimulus duration (pulse width)	0.2–0.3 ms	Pulse widths longer than 0.3 ms may induce repetitive nerve stimulation and/or direct muscle stimulation
Stimulus charge	4–21 μC	Charge (C) is the product of current (A) × stimulus duration (s)
Stimulus patterns	ST (1–0.1 Hz) TOF every 15 s TET at 50 Hz PTC	Various patterns of stimulation to detect onset time, depth of block, and adequacy of recovery
Display	Visual	Should display the delivered current intensity (mA)
Electrode connection	Circuit integrity	Should be able to indicate proper electrode placement and skin resistance
Audio	Stimulus indicator	Should indicate when the stimulus is delivered; provide auditory/visual alarm when circuit is not intact

PTC = posttetanic count; ST = single twitch; TET = 5-s tetanic stimulation; TOF = train-of-four; TOFC = train-of-four count.

these characteristics are not shared by patients recovering from general anesthesia whose tracheas are still intubated. The vastly overused (and overrated) 5-s head-lift test, for instance, was unable to identify TOF ratios as low as 0.5 in more than 70% of patients.[109,110] In fact, none of the clinical tests has a sensitivity greater than 0.35 or a positive predictive value greater than 0.52.[5] The clinical test with the greatest positive predictive value (0.52) is the tongue depressor test, which cannot be used in intubated patients.

Qualitative neuromuscular devices (or more accurately named, PNSs) are utilized in most clinical practices. These battery-powered devices provide an electrical stimulus to a peripheral nerve (most commonly the ulnar nerve), and the response of the stimulated muscle (usually the thumb) is evaluated subjectively by visual or tactile means. The presence or absence of muscle weakness is determined by evaluating fade (decreasing muscle contractions) with repetitive nerve stimulation. Clinicians use several different patterns of nerve stimulation in order to evaluate fade. The most common pattern of nerve stimulation is TOF (fig. 2). TOF stimulation consists of four stimuli at 2-Hz frequency. The force of contraction of the fourth muscle twitch is subjectively compared to the contraction of the first twitch, and fade is considered absent when both muscle contractions (twitches) appear equal (no block; fig. 2). When the fourth twitch in the TOF sequence starts decreasing in amplitude, the TOF ratio becomes less than 1.0 and TOF fade ensues (partial block; fig. 3).

Subjective evaluation is performed either by looking at the evoked responses and assessing fade to TOF stimulation

Table 6. Characteristics of the Ideal Neuromuscular Monitor

Feature	Characteristic	Comments
Connectivity	Easily integrated into electronic medical record	Should record all measured parameters to patient record Should output raw data to an interfaced computer
Impulse characteristics	Square wave	The impulse should be monophasic and rectangular
Calibration	Determine threshold and supramaximal stimulation levels	Calibration of single twitch by determining threshold and supramaximal current requirements Document baseline train-of-four ratio
Current	Constant current	A constant current (not constant voltage) will assure delivery of consistent charge despite fluctuations in skin resistance
Delivered current	0–70 mA	Current needed for supramaximal stimulation
Stimulus duration (pulse width)	0.2 and 0.3 ms*	Pulse widths longer than 0.3 ms may induce repetitive nerve stimulation and/or direct muscle stimulation
Stimulus charge	4–21 μC	Charge (C) is the product of current (A) × stimulus duration (s)*
Stimulus patterns	ST (1–0.1 Hz) TOF every 15 s TET at 50 Hz PTC	Various patterns of stimulation to detect onset time, depth of block, and adequacy of recovery Stimulation patterns should change automatically according to the depth of block†
Display	Visual	Real-time display of the following parameters: Delivered current intensity (in mA) Evoked muscle responses in graphical and/or numerical format (*e.g.*, TOF ratio, TOFC, and PTC)
Electrode connection	Circuit integrity	Indicate proper electrode placement and skin resistance
Audio	Stimulus indicator	Indicate when the stimulus is delivered; provide auditory/visual alarm when circuit is not intact
Memory	Nonvolatile memory	Record, recall, and display parameter data history

e.g., 50 mA for 0.2 ms = 10 μC. †During onset of neuromuscular block, the train-of-four (TOF) ratio pattern should switch to TOF count when the ratio = 0, and then to post-tetanic count when the TOF count = 0. This sequence should proceed in reverse order during recovery of neuromuscular block. PTC = post-tetanic count; ST = single twitch; TET = 5-sec tetanic stimulation; TOF = train-of-four; TOFC = train-of-four count.

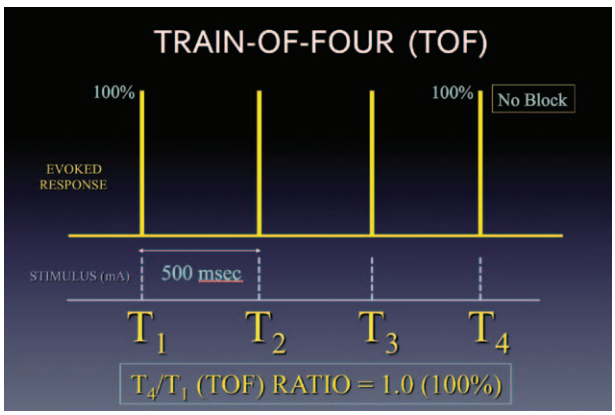

Fig. 2. A train-of-four (TOF) consists of four equal stimuli delivered at 0.5-s intervals. The TOF ratio is calculated by comparing the magnitude of the fourth evoked response or twitch (T_4) to that of the first response (T_1). In the unblocked state, the TOF ratio (T_4/T_1) should approximate 1.0 (100%).

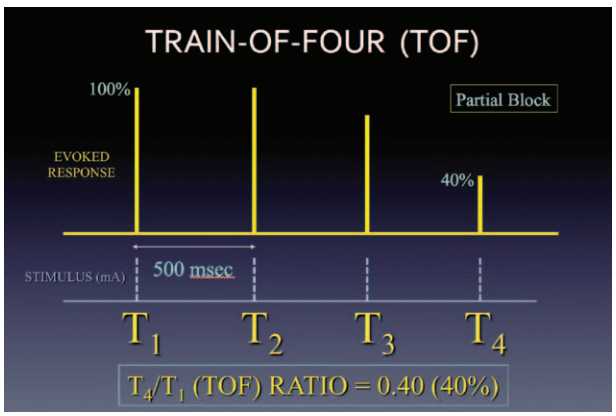

Fig. 3. A train-of-four (TOF) consists of four equal stimuli delivered at 0.5-s intervals. The TOF ratio is calculated by comparing the magnitude of the fourth evoked response or twitch (T_4) to that of the first response (T_1). During partial nondepolarizing block, T_4 decreases preferentially, such that there is fade (*i.e.*, TOF ratio less than 1.0). In the illustration above, the TOF ratio = 0.40 (40%).

(visual means) or by feeling the strength of contraction of muscles and assessing TOF fade (tactile means). Such subjective evaluation is the most commonly used method of evaluating the depth of neuromuscular block and adequacy of reversal. However, clinical decisions guided by subjective evaluation of neuromuscular function have not decreased the postoperative risk of desaturation or need for tracheal reintubation.[48] Although some studies have shown tactile evaluation to be slightly more sensitive than visual means, others have shown that the ability to detect fade was not significantly different between visual and tactile means.[111] The effectiveness of qualitative neuromuscular monitoring in decreasing the incidence of residual blockade remains controversial since this type of monitoring is ineffective in detecting residual blockade when TOF ratios are more than 0.40.[60,111]

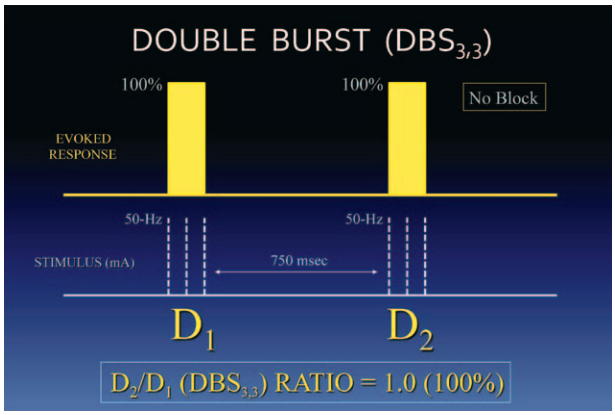

Fig. 4. A double burst stimulus (DBS) consists of two brief, 50-Hz tetanic bursts delivered 0.75 s apart. Each burst consists of three stimuli ($DBS_{3,3}$) that result in two sustained muscle contractions. The DBS ratio (D_2/D_1) approximates the train-of-four (TOF) ratio. When quantitative monitoring is not available, the advantage of DBS over TOF is that subjectively determined fade is more easily perceived than the fade induced by TOF stimulation. However, once the TOF ratio exceeds 0.60, fade to DBS generally cannot be detected subjectively.

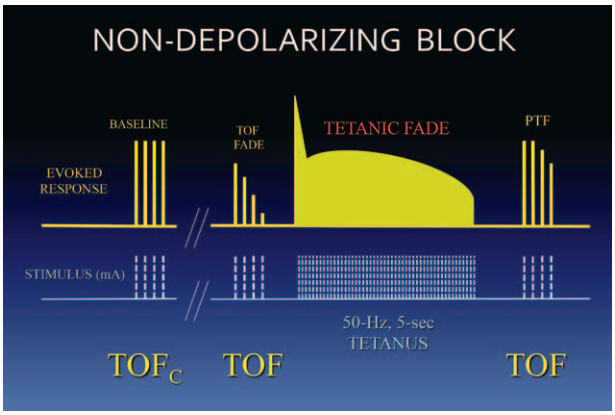

Fig. 5. In the unblocked state, the peak height of an evoked mechanical response to 5-s tetanic stimulation (TET) stimulation is generally 7 to 10 times that of a single stimulus, and the muscle contraction in response to a 5-s, 50-Hz tetanus can be well sustained. During a partial nondepolarizing neuromuscular block, tetanic tension exhibits fade (decreases in strength over time). The tetanic stimulation is followed by a 2- to 5-min period of posttetanic facilitation.

Despite the widespread availability of PNSs in the ORs (76% of European departments and 97% of U.S. departments), 19% of European and 9% of U.S. clinicians never use them, and their use does not seem to always help clinicians identify residual neuromuscular weakness: more than half of clinicians incorrectly estimated the incidence of clinically significant residual block to be less than 1%.[32] A survey, as well as numerous previous clinical investigations, has reported on the limitations of subjective evaluation.[112] The ability to detect TOF fade by subjective (tactile) means appears to be influenced by clinical experience only marginally; anesthesiologists inexperienced in assessing tactile fade were able to identify it only when the TOF ratio was less than 0.30, while only one in five experienced anesthesiologists was able to correctly identify it when the TOF ratio was between 0.51 and 0.70.[60] While other stimulation patterns such as double-burst stimulation (DBS; fig. 4) were introduced into clinical care to facilitate the subjective assessment of fade, such attempts have been minimally successful: the threshold (lowest TOF ratio) for detection of fade using subjective evaluation of TOF is approximately 0.40, while the TOF threshold for detecting DBS fade is 0.60.[113] Thus, even when there is no tactile detection of fade to either TOF or DBS stimulation, there is almost a 50% risk that the actual measured ratio is below 0.70. Clearly, the proportion of clinicians who will miss the presence of residual block will be even higher at the recovery TOF threshold of 0.9. Some clinicians rely on a 5-s tetanic (50 Hz) stimulation (fig. 5) and subjective assessment of the fade of muscle contraction. However, the 50-Hz tetanic stimulation pattern is the least sensitive subjective method: tetanic fade can only be detected reliably when the TOF ratio is less than or equal to 0.3.[114]

Other limitations of subjective evaluation relate to the site (muscle) that is monitored. There are well-known differences in the timecourse of responses to NMBAs at different muscle groups. Central muscles (diaphragm) recover earlier than peripheral muscles (adductor pollicis), but that does not imply that the rest of the respiratory muscles are functioning normally. Upper airway muscles critical to maintaining airway patency and protection from pulmonary aspiration of secretions or gastric contents are very sensitive to NMBAs and do not recover fully until the TOF ratio is near baseline. Monitoring of adductor pollicis muscle, which lags the recovery of the diaphragm, will ensure that if recovery is sufficient at the thumb, the diaphragm and upper airway muscles will function normally. Monitoring TOF recovery in response to facial nerve stimulation can lead to erroneous decisions: the eyebrow muscle, the corrugator supercilii, recovers faster than the upper airway or the adductor pollicis muscles. Clinical decision about spontaneous ventilation and airway protection that are made based on recovery of facial muscles (corrugator supercilii or orbicularis oculi) will, therefore, overestimate the degree of recovery and may place the patient at risk of CREs.[115,116] In fact, TOF monitoring at this anatomic site (face) should be the location of last resort, and the clinician should remember that airway protection might be impaired even when the eyebrow muscle shows no TOF fade. Assessment of function should be sought from the adductor pollicis muscle as soon as practical.

Realizing the limitations of subjective evaluation of TOF fade and readiness for tracheal extubation, some clinicians rely on the use of PNS to determine the depth of block and degree of recovery before administering pharmacologic reversal by counting the number of responses to TOF stimulation (TOFC; fig. 6). The TOFC assessed subjectively by anesthesia providers was compared with the TOFC obtained

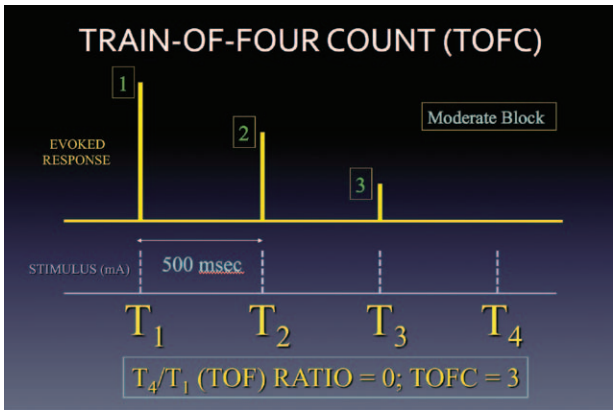

Fig. 6. During moderate block, once the train-of-four (TOF) ratio becomes 0 (*i.e.*, T_4 disappears), the depth of block may be assessed by counting the number of responses to TOF stimulation. The depth of neuromuscular block is proportional to the TOF count (TOFC): the lower the count, the deeper the block.

objectively with an acceleromyography (TOF-Watch) monitor.[117] An agreement between subjective and objective methods was present in only 56% of observations; moreover, at TOFCs of 1, 2, and 3, the agreement was 36%, and when there was no agreement between the two assessment methods, providers assessed a higher TOFC in 96% of the observations! This overestimation of the degree of recovery may obviously influence the timing and dosing of pharmacologic reversal agents and may partly explain the high incidence of residual block.

In short, despite adoption of PNSs and subjective evaluation into clinical practice, the literature continues to document this method's significant limitations.

Quantitative neuromuscular monitoring devices objectively measure residual blockade and display the results numerically in real time. The TOF stimulation pattern is most commonly used to assess NMBAs when quantitative devices are employed. The TOF ratio (or T4/T1 ratio) should exceed 0.9 (90%) in order to exclude clinically significant muscle weakness. Maintenance of the ability to swallow and protection against aspiration of pharyngeal fluids can only be assured above this minimum level of neuromuscular recovery.[118] Partial recovery of muscle function to TOF ratios less than 0.9 in volunteers[118,119] and surgical patients[120] is associated with a variety of postoperative adverse events. The use of quantitative monitoring was shown to be effective in identifying and reducing the risk of residual blockade.[4,17] Although evidence strongly suggests that quantitative monitors should be used intraoperatively whenever NMBAs are administered, these devices are not widely available.[19,32,121]

Electromyography devices measure electrical activity (compound MAPs) resulting from nerve stimulation (usually at the adductor pollicis muscle after ulnar nerve stimulation). Electromyography-based monitoring is perhaps the most physiologic and precise method of measuring the synaptic transmission (and thus, the degree of neuromuscular relaxation), is not susceptible to changes in contractility such as the staircase effect, and has advantages in facilitating the recording of compound MAPs from virtually any muscle, including the diaphragm and laryngeal muscles.[122]

Unfortunately, this technology is not yet commercially available in any stand-alone, portable device although one such monitor is currently under development (Sorin J. Brull, M.D., Department of Anesthesiology, Mayo Clinic, Jacksonville, Florida; September 2016; written communication). The only original equipment manufacturer monitor (the E-NMT-01 Datex-Ohmeda S/5 Neuromuscular Transmission Module [GE Healthcare, USA]) that was based on electromyography was subject to a Class 2 Recall by the U.S. FDA on May 21, 2014, because neuromuscular transmission values may indicate "a deeper level of muscle relaxation than the actual level of muscle relaxation."[123] Other limitations of electromyography for monitoring of neuromuscular block include its sensitivity to inherent noise in electronic equipment, motion artifact, electrocardiographic artifacts produced by the electrical activity of the heart, and interference by electromagnetic and radio frequency emissions.[124]

Despite these limitations, the implementation of routine, electromyography-based neuromuscular monitoring in a single department has recently underscored the significant improvements in clinical care and the elimination of CREs (such as emergent tracheal reintubations in the PACU) that the use of routine neuromuscular monitoring can effect. This report[11] and the year-later update[21] document the significant amount of time, education, and dedication needed to implement a department-wide neuromuscular monitoring program.[11,21]

Mechanomyography measures the force of contraction of the adductor pollicis (thumb) muscle after ulnar nerve stimulation. Mechanomyographic responses are precise and reproducible (as long as a 200- to 300-g muscle preload is maintained) and have been considered the accepted standard for neuromuscular monitoring. However, because of a relatively complex setup, mechanomyography is currently used only for research purposes. These devices are no longer commercially available.

Acceleromyography measures acceleration of muscle tissue (most commonly the thumb) in response to nerve stimulation (most commonly the ulnar nerve). This technique is based on Newton second law of motion ($F = m \times a$). A piezoelectric transducer is attached to a muscle, and when the innervating nerve is stimulated, the muscle movement is sensed by the transducer; a voltage is generated in the piezoelectric crystal, and this electrical signal is analyzed by the acceleromyography monitor. There are several manufacturers of acceleromyography-based monitors (table 4). The acceleromyography devices are small, portable, and designed for intraoperative applications. Their routine use in the clinical setting has been limited by initial acquisition costs ($800 to $2,400), the need for experience with acceleromyography

monitoring to obtain accurate results, the unavailability of appropriate electrode placement sites when the patient's arms are tucked under surgical drapes, and limitations of the technology in the OR (requirement for baseline measurements and normalization, the long 5- to 10- min setup required before use, and reduced precision in awake patients).[122,125,126] Many studies, however, have documented this technology's unquestionable efficacy in decreasing the incidence of residual neuromuscular block in both adult[17,127] and pediatric patients.[128]

Kinemyography devices are similar to acceleromyography-based devices, but they measure the degree of bending of a piezoelectric sensor.[129] This mechanosensor is placed along the space between the thumb and index fingers and quantifies the degree of bending as the thumb and index fingers appose in response to ulnar nerve stimulation. To date, several clinical validation studies of kinemyography have been performed.[130]

At the current time, it appears that one of the main barriers to routine adoption of quantitative monitoring is the lack of availability of an easy-to-use, accurate, and reliable monitor. Several recent publications have expressed the urgent need for such a quantitative neuromuscular device.[12,131]

Conclusions

Modern surgery would not be possible without the availability of NMBAs. To quote Foldes, "…curare had the same importance for anesthesiology as asepsis had for the progress of surgery."[132] However, the use of these agents also introduced significant patient safety concerns. For instance, residual neuromuscular block dates back to the days of curare when this complication was termed, "residual curarization." Since then, attempts have been made to eliminate it: introduction of PNSs into clinical practice and development of new shorter duration NMBAs and selective NMBA-specific reversal agents. These advances have decreased the incidence of residual block, pulmonary complications, and incidence of other sequelae, but they have not eliminated them.[133] The potential solution has been obvious for decades; if emergence from anesthesia and tracheal extubation are allowed to occur only after adequate neuromuscular function has been attained (as documented by a measured TOF ratio more than 0.90), these complications will (and must) become never events. Neuromuscular function assessment with a PNS is mandatory whenever neuromuscular blocking drugs (both depolarizing and nondepolarizing) are used; patients who received large doses of NMBAs, those undergoing prolonged surgical procedures, or patients at increased risk of postoperative complications from residual block ideally should be monitored using objective means.

Pharmacologic antagonism, whether using anticholinesterases or sugammadex, must be guided by, at a minimum, subjective (and preferably, objective) monitoring. Intense and deep levels of neuromuscular block cannot be antagonized by anticholinesterases, and reversal should not be attempted at this level of block. This depth of block induced by aminosteroidal NMBAs, however, can be reversed rapidly and reliably by administration of sugammadex: 16 mg/kg (when PTC = 0, intense block) or 4 mg/kg (when PTC more than or equal to 1, deep block).

Moderate block can be antagonized by anticholinesterase agents as long as sufficient recovery is documented by the presence of at least three responses to TOF stimulation (TOFC 3 or 4). At this level of block, a full dose of neostigmine (0.05 to 0.06 mg/kg) or sugammadex (2 mg/kg) should be administered.

A light level of neuromuscular block (evidenced by fade to TOF, whether determined subjectively or objectively) should be antagonized with lower doses of neostigmine (0.02 to 0.03 mg/kg) or sugammadex (1 mg/kg).

Finally, it must be emphasized that the timing of tracheal extubation must be determined based on the degree of recovery (whether spontaneous or pharmacologic), and a minimum TOF ratio of 0.90 must be the desired goal. This implies that objective (not subjective) monitoring techniques are necessary. If an objective monitor is not available, the anesthesia record should document, at a minimum, the TOFC at the time of reversal and the dose of antagonist administered. Other indicators of recovery, such as subjective assessment of lack of TOF fade, sufficient time since administration of reversal agents (or NMBA), adequate tidal volume, the presence of 5-s head lift, and so forth, cannot be used to exclude residual block and the potential for postoperative complications. In short, neuromuscular monitoring is not optional, and national societies must propose recommendations for the rational and safe management of perioperative neuromuscular blockers and their antagonists.

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Competing Interests

Dr. Brull has had investigator-initiated funded research from Merck, Inc., Kenilworth, New Jersey, and is a shareholder and member of the Board of Directors in Senzime AB, Uppsala, Sweden. Dr. Kopman declares no competing interests.

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