

Current Status of Neuromuscular Reversal and Monitoring

Challenges and Opportunities

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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 benzyloquinolinium) 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; 126:173-90**)

“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 Johnson² on the use of curare in general anesthesia as number 13. Appropriately, the other “top-20 contender” article is the study by Beecher and Todd³ 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

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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 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 children²⁵ 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 amnesic 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 year³⁵; 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 2000³⁷ 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 Care⁴⁰ now states in the section on neuromuscular function guidelines, "assessment of neuromuscular function primarily includes physical examination and, on occasion, may include NMBA 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 NMBA.^{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 study⁴⁴ nicely demonstrated this principle. The authors administered 0.10 mg/kg vecuronium ($2 \times ED_{95}$) 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 report⁴⁴ 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)

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

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 ending, such that the intensity of subsequent muscle contractions will be increased (potentiated) briefly (period of post-tetanic 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 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 authors⁵⁸ 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

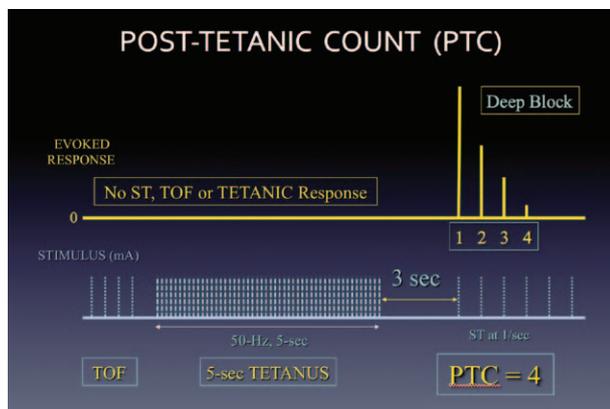


Fig. 1. Posttetanic count (PTC). During a nondepolarizing block, the high-frequency tetanic stimulation (50 Hz or 100 Hz) will induce a transient increase in the amount of acetylcholine released from the presynaptic nerve ending, such that the intensity of subsequent muscle contractions will be increased (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.

Table 2. Limitation of Acetylcholinesterases as Antagonists of Nondepolarizing Block

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

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

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 ± 0.12, respectively, after cisatracurium administration and 0.57 ± 0.11 and 0.79 ± 0.12, respectively, after rocuronium administration. 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 study⁶³ (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).

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 deviate from package insert recommendations. †When reversing vecuronium, use higher end of dosing range. ‡TOF ratio confirmed by quantitative monitoring.

TOF = train-of-four.

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 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 acetylcholinesterases are ionic and much weaker than the covalent bonds of neostigmine and acetylcholinesterases. 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 benzyliisoquinolinium 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 described¹⁰² 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

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 0.3ms may induce repetitive nerve stimulation and/or direct muscle stimulation
Stimulus charge	4–21 μ C	Charge (C) is the product of current (A) \times 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.

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 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

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 μ C	Charge (C) is the product of current (A) \times 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 0.2ms = 10 μ C. †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.

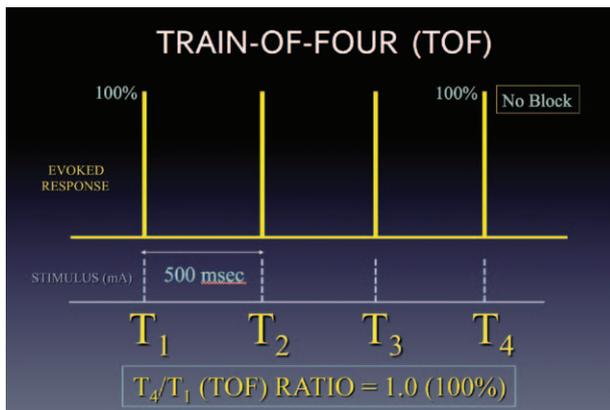


Fig. 2. A train-of-four (TOF) consists of four equal stimuli delivered at 0.5-s intervals. The TOF ratio is calculated by comparing the magnitude of the fourth evoked response or twitch (T_4) to that of the first response (T_1). In the unblocked state, the TOF ratio (T_4/T_1) should approximate 1.0 (100%).

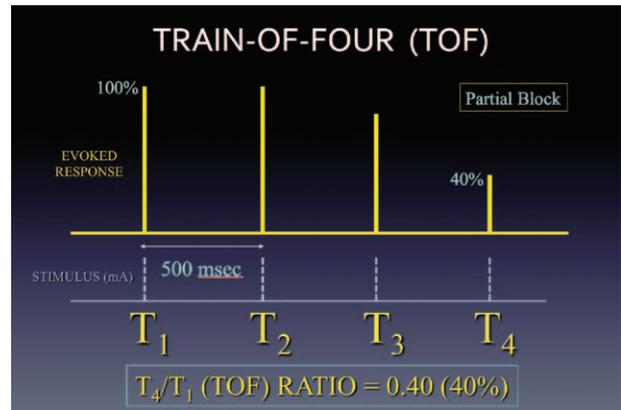


Fig. 3. A train-of-four (TOF) consists of four equal stimuli delivered at 0.5-s intervals. The TOF ratio is calculated by comparing the magnitude of the fourth evoked response or twitch (T_4) to that of the first response (T_1). During partial nondepolarizing block, T_4 decreases preferentially, such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

(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 (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

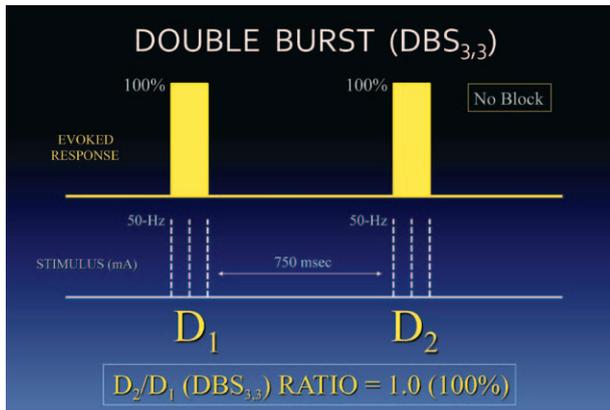


Fig. 4. A double burst stimulus (DBS) consists of two brief, 50-Hz tetanic bursts delivered 0.75 s apart. Each burst consists of three stimuli ($DBS_{3,3}$) that result in two sustained muscle contractions. The DBS ratio (D_2/D_1) approximates the train-of-four (TOF) ratio. When quantitative monitoring 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.

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}

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

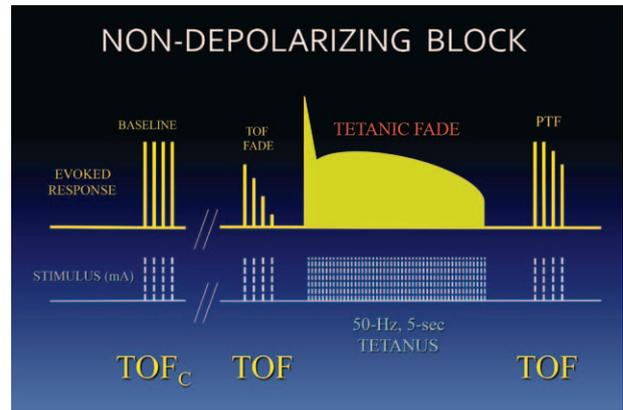


Fig. 5. In the unblocked state, the peak height of an evoked mechanical response to 5-s tetanic stimulation (TET) stimulation is generally 7 to 10 times that of a single stimulus, and the muscle contraction in response to a 5-s, 50-Hz tetanus can be well sustained. During a partial nondepolarizing neuromuscular 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.

(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.

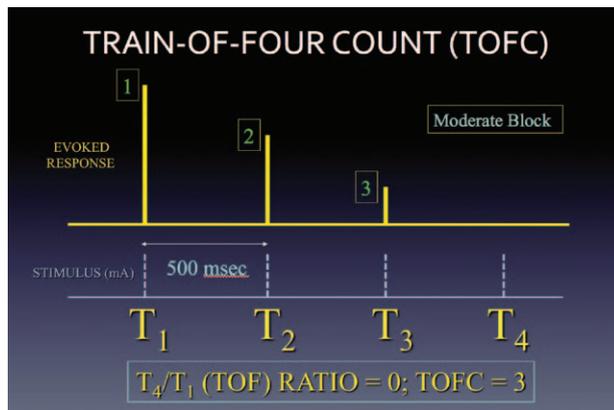


Fig. 6. During moderate block, once the train-of-four (TOF) ratio becomes 0 (i.e., T_4 disappears), the depth of block may be assessed by counting the number of responses to TOF stimulation. The depth of neuromuscular block is proportional to the TOF count (TOFC): the lower the count, the deeper the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

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 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 NMBA when quantitative devices are employed. The TOF ratio (or T_4/T_1 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 patients¹²⁰ 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 NMBA 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 report¹¹ and the year-later update²¹ 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 sepsis 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

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