Residual Neuromuscular Block: Lessons Unlearned. Part I: Definitions, Incidence, and Adverse Physiologic Effects of Residual Neuromuscular Block

Glenn S. Murphy, MD,* and Sorin J. Brull, MD†

In this review, we summarize the clinical implications of residual neuromuscular block. Data suggest that residual neuromuscular block is a common complication in the postanesthesia care unit, with approximately 40% of patients exhibiting a train-of-four ratio <0.9. Volunteer studies have demonstrated that small degrees of residual paralysis (train-of-four ratios 0.7–0.9) are associated with impaired pharyngeal function and increased risk of aspiration, weakness of upper airway muscles and airway obstruction, attenuation of the hypoxic ventilatory response (approximately 30%), and unpleasant symptoms of muscle weakness. Clinical studies have also identified adverse postoperative events associated with intraoperative neuromuscular management. Large databased investigations have identified intraoperative use of muscle relaxants and residual neuromuscular block as important risk factors in anesthetic-related morbidity and mortality. Furthermore, observational and randomized clinical trials have demonstrated that incomplete neuromuscular recovery during the early postoperative period may result in acute respiratory events (hypoxemia and airway obstruction), unpleasant symptoms of muscle weakness, longer postanesthesia care unit stays, delays in tracheal extubation, and an increased risk of postoperative pulmonary complications. These recent data suggest that residual neuromuscular block is an important patient safety issue and that neuromuscular management affects postoperative outcomes. (Anesth Analg 2010;111:120–8)

In a landmark investigation examining mortality rates in 599,548 surgical patients undergoing procedures between the years 1948 and 1952, Beecher and Todd[1] observed that the use of neuromuscular blocking drugs (NMBDs) was associated with a 6-fold increased risk of death in the perioperative period. Important developments in neuromuscular management have occurred over the last 50 years, which improved the safety of general anesthesia when NMBDs are used. Second- and third-generation NMBDs with improved hemodynamic properties, more rapid onset and offset of effects, and more predictable recovery patterns have been introduced into clinical practice. Quantitative (objective) and qualitative (subjective) neuromuscular monitoring devices, which allow more accurate dosing and titration of NMBDs in the operating room, are now available to most clinicians. In addition, the publication of numerous investigations during the past 2 decades describing risk factors for residual neuromuscular block and methods to reduce the incidence of incomplete neuromuscular recovery have greatly enhanced clinicians' understanding and recognition of this anesthetic complication.

Despite these important advances, residual neuromuscular blockade remains a common but usually undetected occurrence in the early postoperative period.[2–4] Furthermore, recent data suggest that residual paralysis in the postanesthesia care unit (PACU) may contribute to morbidity in patients recovering from general anesthesia.[5–7] The aim of this 2-part review is to provide the clinician with a guide for neuromuscular management in the perioperative period. The number of randomized, controlled clinical trials directly related to this topic is limited; therefore, a formal meta-analysis of the studies was not attempted. Instead, we provide a narrative review of the relevant literature. In part I, the definitions, incidence, and adverse physiologic effects of residual neuromuscular block are discussed. In part II, methods that may be used by clinicians to reduce the incidence of this potentially life-threatening complication are reviewed. In addition, several novel pharmacologic approaches that promise to increase the safety of perioperative neuromuscular management are discussed.

DEFINITIONS OF RESIDUAL NEUROMUSCULAR BLOCK

Train-of-Four Ratio <0.7

Train-of-four (TOF) nerve stimulation was introduced in the early 1970s by Ali et al.[8] Four supramaximal stimuli are delivered every 0.5 second (2 Hz), and the muscle response to the fourth stimulus is compared with that of the first stimulus. Fade of force of muscle contraction in response to repetitive nerve stimulation provides the basis for evaluation; the degree of fade is proportional to the intensity of the neuromuscular block. Unlike the single-twitch mode of stimulation, TOF monitoring does not require a control, prerelaxant twitch height. Advantages of TOF stimulation over tetanic stimulation include less pain on stimulation and lack of posttetanic facilitation. It is difficult to exclude residual block using a subjective evaluation of the tactile or

From the *Department of Anesthesiology, NorthShore University HealthSystem, University of Chicago, Evanston, Illinois; †Department of Anesthesiology, Mayo Clinic College of Medicine, Jacksonville, Florida.

Accepted for publication February 4, 2010.

Supported by institutional and/or departmental sources (Department of Anesthesiology, NorthShore University HealthSystem and Mayo Clinic College of Medicine).

Address correspondence and reprint requests to Glenn S. Murphy, MD, Department of Anesthesiology, NorthShore University HealthSystem, 2650 Ridge Ave., Evanston, IL 60201. Address e-mail to dgmurphy2@yahoo.com.

DOI: 10.1213/ANE.0b013e3181da832d

visual TOF ratio (qualitative monitoring); objective (quantitative) neuromuscular monitoring devices, such as the TOF-Watch® (distributed by Bluestar Enterprises, Omaha, NE), must be used to reliably detect TOF ratios >0.4 to 0.6 (see part II for a detailed discussion).

Most clinicians and researchers define residual block using a preestablished TOF ratio "threshold" value. Traditionally, a TOF ratio of <0.7 measured using either compound electromyography (EMG) or mechanomyography (MMG) has been considered to represent inadequate neuromuscular recovery. This value was derived from several studies published in the 1970s.[9–11] In 1973, Ali and Kitz[9] demonstrated that a mean TOF ratio of 0.74 represented "acceptable recovery" from d-tubocurarine blockade. Patients with this level of recovery were able to open eyes widely, cough, protrude the tongue, sustain head lift for 5 seconds, develop a forced vital capacity of at least 15 to 20 mL/kg, and sustain tetanic stimulation without fade for 5 seconds. In another investigation by this same group, changes in measured respiratory variables, including tidal volume, vital capacity, inspiratory force, and peak expiratory flow rate, were "negligible" until TOF ratios decreased to <0.6.[10] Similar findings were observed by Brand et al.[11] At a TOF ratio of 0.7, all patients were able to sustain eye opening, hand grasp, and tongue protrusion, whereas 9 of 10 were able to maintain a 5-second head lift.

Train-of-Four Ratio <0.9

More recent data suggest that TOF ratios measured with EMG, MMG, or acceleromyography (AMG) must recover to values >0.9 to ensure optimal patient safety. Data derived from volunteer studies have demonstrated that pharyngeal dysfunction and an increased risk for aspiration occur at TOF ratios <0.9.[12,13] Impaired inspiratory flow and partial upper airway obstruction have been observed frequently at TOF ratios of 0.8.[14] Furthermore, subtle levels of neuromuscular blockade may produce distressing symptoms in awake patients, which may persist even at TOF ratios >0.9.[15] These recent data suggest that the new "gold standard" for the minimal acceptable level of neuromuscular recovery is an EMG or MMG TOF ratio of 0.9 (or perhaps 1.0 when AMG is used—see Discussion section in part II).

Residual neuromuscular block is perhaps most accurately defined as the presence of signs or symptoms of muscle weakness in the postoperative period after the intraoperative administration of an NMBD. Patients with adequate neuromuscular recovery should have the ability to breathe normally, maintain a patent upper airway, preserve protective airway reflexes, swallow, cough, smile, and talk. These physiologic end points are achieved in most patients (and volunteers) at a TOF ratio of 0.9. However, some patients may exhibit obvious weakness despite achieving TOF ratios >0.9, whereas complete recovery of muscle strength may be observed in patients with TOF ratios <0.9. Therefore, a precise definition of residual block requires not only the measurement of TOF ratios using objective neuromuscular monitoring devices (TOF ratio >0.9–1.0) but also a careful clinical assessment of each patient for adverse effects potentially attributable to the use of NMBDs.

INCIDENCE OF RESIDUAL NEUROMUSCULAR BLOCK

In 1979, Viby-Mogensen et al.[16] reported that 42% of patients administered long-acting NMBDs and standard doses of neostigmine (2.5 mg) in the operating room had a TOF ratio <0.7 (MMG) on arrival to the PACU. During the next 3 decades, many studies were published that examined the incidence of residual weakness/paralysis in the early postoperative period. Studies from the 1980s demonstrated that between 21% and 36% of patients who received long-acting NMBDs intraoperatively had TOF ratios <0.7 in the PACU.[17,18] Early data suggested that the incidence of residual block could be reduced when intermediate-acting NMBDs were used.[18,19] However, such expectations have not materialized; a review of studies published since 2000 has demonstrated that many patients continue to arrive in the PACU with TOF ratios <0.9 (Table 1).[2–4,6,20–29] The common practice of administering large doses (2–4 times the dose required for 95% depression of neuromuscular response [ED_{95}]) of intermediate-acting drugs to shorten onset times may account for the high incidence of residual block observed in many clinical settings.

Four recent large-scale studies have examined the incidence of residual neuromuscular block in contemporary anesthesia practice. In a study enrolling 526 patients undergoing gynecologic and plastic surgery, Debaene et al.[3] determined the percentage of patients in the PACU with TOF ratios <0.7 and <0.9 (AMG) after receiving a single intubating dose (twice the ED_{95}) of vecuronium, rocuronium, or atracurium. Neuromuscular block was not reversed intraoperatively. TOF ratios <0.7 and <0.9 were observed postoperatively in 16% and 45% of patients, respectively. In a subgroup of 239 patients in whom testing was performed >2 hours after NMBD administration, TOF ratios <0.9 were noted in 37% of subjects, and 10% of patients had TOF ratios <0.7 at this time. Baillard et al.[27] examined the incidence of residual paralysis in 568 consecutive surgical patients who received vecuronium but no anticholinesterase. On arrival to the recovery room, TOF ratios <0.7 measured with AMG were observed in 42% of subjects. Cammu et al.[4] assessed the occurrence of residual paralysis in patients undergoing outpatient (n = 320) and inpatient (n = 320) surgical procedures. Qualitative neuromuscular monitoring and reversal was used in only 12% and 25% of patients, respectively. TOF ratios <0.9 (AMG) were more frequent in the inpatient group (47%) compared with the outpatient group (38%, P = 0.001). In another investigation, residual block in the PACU, defined as a TOF ratio <0.8 (AMG), was assessed in patients receiving vecuronium (n = 50), atracurium (n = 50), or rocuronium (n = 50).[22] Neuromuscular block was monitored (qualitatively) in 41% of patients, and the block was reversed in 68% of patients. TOF ratios <0.8 were measured in 64%, 52%, and 39% of patients after the use of vecuronium, atracurium, and rocuronium, respectively.

The incidence of residual neuromuscular block varies widely among studies, with reported frequencies ranging from 2% to 64% (Table 1). Several perioperative management variables may have affected the measured incidence of residual block; these factors are listed in Table 2. Additional data about the incidence of postoperative residual

Table 1. Incidence of Residual Neuromuscular Blockade (2000–2008)

Author	Year	Number of patients	NMBD used	NM monitoring used (%)	Reversal used (%)	Site/time RNMB measured	Definition RNMB	Incidence RNMB	Type of anesthesia
Baillard et al.[27]	2000	568	Vecuronium	2	0	PACU	<0.7	42% (AMG)	Inhalational
Bissinger et al.[20]	2000	83	Pancuronium	NS	100	PACU	<0.7	20% (AMG)	Inhalational and TIVA
			Vecuronium	NS	100	PACU	<0.7	7%	
Hayes et al.[22]	2001	148	Vecuronium	41	68	PACU	<0.8	64% (AMG)	Primarily inhalational
			Atracurium	41	68	PACU	<0.8	52%	
			Rocuronium	41	68	PACU	<0.8	39%	
McCaul et al.[28]	2002	40	Atracurium	50	100	Extubation	<0.7	65% (MMG)	NS
Kim et al.[2]	2002	602	Vecuronium	0	100	PACU	<0.7	24.7% (AMG)	Inhalational
			Rocuronium	0	100	PACU	<0.7	14.7%	
Gatke et al.[23]	2002	60	Rocuronium	0	100	Extubation	<0.8	16.7% (MMG)	TIVA
Baillard et al.[21]	2005	101	Rocuronium	45	43	PACU	<0.9	9% (AMG)	Inhalational
			Vecuronium	45	43	PACU	<0.9	9%	Inhalational
Debaene et al.[3]	2003	526	Vecuronium	NS	0	PACU	<0.7	16% (AMG)	Inhalational
			Rocuronium	NS	0	PACU	<0.9	45%	Inhalational
			Atracurium	NS	0	PACU			
Baillard et al.[21]	2005	218	Vecuronium	60	42	PACU	<0.9	3.5% (AMG)	Inhalational
			Atracurium	60	42	PACU	<0.9	3.5%	Inhalational
Kopman et al.[24]	2004	60	Cisatracurium	100	100	Transfer to	<0.9	36.7% (MMG)	Inhalational
			Rocuronium	100	100	PACU	<0.9	50.0%	Inhalational
Murphy et al.[26]	2004	70	Pancuronium	100	100	PACU	<0.9	83% (AMG)	Inhalational
			Rocuronium	100	100	PACU	<0.9	29%	Inhalational
Murphy et al.[25]	2005	120	Rocuronium	100	100	Extubation	<0.9	88% (AMG)	Inhalational
Cammu et al.[4]	2006	640	Atracurium	11–12	25–26	PACU	<0.9	38–47% (AMG)	NS
			Mivacurium	11–12	25–26	PACU	<0.9	38–47%	NS
			Rocuronium	11–12	25–26	PACU	<0.9	38–47%	NS
Maybauer et al.[29]	2007	338	Cisatracurium	100	0	Extubation	<0.9	57% (AMG)	TIVA
			Rocuronium	100	0	Extubation	<0.9	44%	TIVA
Murphy et al.[6]	2008	90	Rocuronium	100	100	PACU	<0.9	30% (AMG) (TOF group)	Inhalational

NMBD = neuromuscular blocking drugs; NM monitoring= neuromuscular monitoring; RNMB = residual neuromuscular blockade; TIVA = total intravenous anesthesia; NS = not stated.

weakness ("curarization") can be derived from a recent meta-analysis by Naguib et al.[30] Twenty-four studies including 3375 patients (between 1979 and 2005) were analyzed. Antagonism of NMBDs was used in 62.1% of patients, and neuromuscular function was monitored (qualitatively and quantitatively) in 24.4% of subjects. When studies using intermediate-acting NMBDs were analyzed, the incidence of TOF <0.7 was 12% and TOF <0.9 was 41%. The authors concluded that there was a "continued high incidence of postoperative residual curarization reported from multiple academic centers" and that the incidence of this complication did not seem to be decreasing over time.

ADVERSE PHYSIOLOGIC EFFECTS OF RESIDUAL NEUROMUSCULAR BLOCK: VOLUNTEER STUDIES

Small degrees of residual muscle weakness may potentially impair recovery after surgery and produce postoperative complications (Table 3). In clinical studies, however, it may be difficult to differentiate the adverse physiologic effects resulting from incomplete neuromuscular recovery from the residual effects of opioids, benzodiazepines, volatile anesthetics, or anesthesia induction drugs. Upper airway obstruction and ventilatory depression may result from residual block or may be secondary to a number of other anesthetic drugs. Important safety information about NMBDs has been derived from volunteer studies (Table 3). In these investigations, intermediate-acting relaxants were titrated to various TOF values in awake subjects, and the physiologic effects of small degrees of neuromuscular block were determined in the absence of other anesthetic drugs. To differentiate between the direct physiologic effects of NMBDs from the physiologic effects of other anesthetics in combination with NMBDs, studies performed on volunteers excluded all other frequently used anesthetics.

Effects on Pharyngeal Function

Studies performed in the 1970s demonstrated that most respiratory variables, including tidal volume, vital capacity, and inspiratory and expiratory force, are minimally affected when TOF ratios ≥0.7 are achieved.[9–11] More recent investigations have demonstrated that muscles involved in upper airway function and protection may be more sensitive to the effects of small degrees of residual block. Several volunteer studies have assessed the effects of partial paralysis on pharyngeal function. In 1991, Isono et al.[31] administered a small subparalyzing dose of pancuronium (0.02 mg/kg) to 8 subjects. At a peripheral TOF ratio of 0.81, swallowing function (as measured by EMG of the suprahyoid muscles) and mesopharyngeal pressure were significantly impaired. Two later studies from Karolinska Hospital in Sweden performed functional assessment of the pharynx and upper esophagus during partial paralysis.[12,13] In the first, videoradiography and computerized pharyngeal manometry during contrast bolus swallowing were used to evaluate pharyngeal function at TOF ratios of 0.6, 0.7, 0.8, and >0.9 (MMG) achieved with a vecuronium infusion.[13] Six of 14 volunteers aspirated the contrast material to the level of the true cords at a TOF ratio <0.9, and upper esophageal sphincter resting tone was reduced

Table 2. Factors Influencing the Incidence of Postoperative Residual Neuromuscular Blockade

1. Definition of residual neuromuscular blockade
   - Objective TOF measurements (TOF ratio <0.7, 0.8, or 0.9)
   - Clinical signs or symptoms of muscle weakness
2. Method of objective measurement of residual neuromuscular blockade
   - Mechanomyography (MMG) "Gold Standard"
   - Electromyography (EMG)
   - Acceleromyography (AMG)
   - Kinemyography (KMG)
   - Phonomyography (PMG
3. Time of measurement of residual neuromuscular blockade
   - Immediately before tracheal extubation
   - Immediately after tracheal extubation
   - On arrival to PACU
4. Type and dose of NMBD administered intraoperatively
   - Intermediate-acting NMBD
   - Long-acting NMBD
5. Use of neuromuscular monitoring intraoperatively
   - Qualitative monitoring (TOF and DBS studied)
   - Quantitative monitoring (acceleromyography studied)
   - No neuromuscular monitoring (clinical signs)
6. Degree of neuromuscular blockade maintained intraoperatively
   - TOF count of 1–2
   - TOF count of 2–3
7. Type of anesthesia used intraoperatively
   - Inhalational drugs
   - TIVA
8. Type and dose of anticholinesterase reversal drug
   - Neostigmine
   - Pyridostigmine
   - Edrophonium
9. Duration of anesthesia
10. Time interval between anticholinesterase administration and objective TOF measurements.
11. Patient factors: metabolic derangements in the PACU (acidosis, hypercarbia, hypoxia, and hypothermia)
12. Drug therapy in PACU: opioids, antibiotics

TOF = train-of-four; PACU = postanesthesia care unit; NMBD = neuromuscular blocking drug; DBS = double-burst stimulation; TIVA = total intravenous anesthesia.

Table 3. Adverse Effects of Residual Neuromuscular Block

- Volunteer studies
  - Impairment of pharyngeal coordination and force of contraction (MMG TOF ratio 0.8)[12,13]
  - Swallowing dysfunction/delayed initiation of the swallowing reflex (MMG TOF ratio 0.8)[12]
  - Reductions in upper esophageal sphincter tone (MMG TOF ratio 0.9)[12]
  - Increased risk of aspiration (MMG TOF ratio 0.8)[13]
  - Reductions in upper airway volumes (AMG TOF ratio 0.8)[32]
  - Impairment of upper airway dilator muscle function (AMG TOF ratio 0.8)[32]
  - Decreased inspiratory air flow (AMG TOF ratio 0.8)[14]
  - Upper airway obstruction (AMG TOF ratio 0.8)[14]
  - Impaired hypoxic ventilatory drive (MMG TOF ratio 0.7)[34–36]
  - Profound symptoms of muscle weakness (visual disturbances, severe facial weakness, difficulty speaking and drinking, generalized weakness (AMG TOF ratios 0.7–0.75)[15]
- Clinical studies in surgical patients
  - Increased risk of postoperative hypoxemia (AMG TOF ratio <0.9)[7,26]
  - Increased incidence of upper airway obstruction during transport to the PACU (AMG TOF ratio <0.9)[6]
  - Higher risk of critical respiratory events in the PACU (AMG TOF ratio <0.9)[6,7]
  - Symptoms and signs of profound muscle weakness (pancuronium versus rocuronium)[26,53]
  - Delays in meeting PACU discharge criteria and achieving actual discharge (AMG TOF ratio <0.9)[26]
  - Prolonged postoperative ventilatory weaning and increased intubation times (cardiac surgical patients) (AMG TOF ratio <0.9)[53]
  - Increased risk of postoperative pulmonary complications (atelectasis or pneumonia) (MMG TOF ratio <0.7)[5]

MMG = mechanomyography; AMG = acceleromyography; TOF = train-of-four; PACU = postanesthesia care unit.

at all TOF ratios <0.9. In a similar investigation, the incidence and mechanisms of pharyngeal dysfunction during partial paralysis with atracurium were assessed.[12] Twenty awake patients were evaluated during liquid-contrast bolus swallowing at TOF ratios of 0.6, 0.7, 0.8, and >0.9. At a TOF ratio of 0.8, the incidence of pharyngeal dysfunction was 28%, and the majority of the episodes (80%) were associated with misdirected swallowing and penetration of the liquid-contrast bolus to the larynx. Delayed initiation of the swallowing reflex, impairment of pharyngeal coordination, and reduced contraction force of the pharyngeal constrictor muscles were observed at TOF ratios <0.8.

Effects on Airway Muscle Function

Several investigations have examined the effect of partial neuromuscular blockade on upper airway muscle function and inspiratory or expiratory airway obstruction. Eikermann et al.[14] related tests of pulmonary function to AMG of the adductor pollicis muscle during a rocuronium infusion titrated to TOF ratios of 0.5 to 1.0. At a mean TOF ratio of 0.83 ± 0.06, forced vital capacity had recovered to "acceptable" levels (within 10% of baseline values) in 10 of 12 volunteers. However, forced inspiratory volume in 1 second was impaired in half of the subjects, and signs of partial upper airway obstruction (defined using established spirometric guidelines) were observed in one-third of volunteers. The mechanisms of upper airway obstruction were further assessed in another volunteer study by Eikermann et al.[32] Supraglottic airway area was measured using magnetic resonance imaging, and upper airway dilator muscle function was assessed with genioglossus force monitoring and EMG. At a TOF ratio of 0.8, end-inspiratory upper airway volumes (retropalatal and retroglossal areas) were significantly decreased from baseline values, whereas end-expiratory volumes did not change. In addition, genioglossus EMG during swallowing and tongue protrusion was significantly impaired at a TOF ratio of 0.8 and remained impaired in 2 of 12 volunteers at a TOF ratio of 1.0. The authors concluded that signs of partial upper airway obstruction during partial paralysis were primarily attributable to weakness of the upper airway dilator muscles. However, it is important to note that arterial oxygen saturation was well maintained in most volunteer studies at TOF ratios of ≥0.8.

Effects on Hypoxic Ventilatory Drive

Partial neuromuscular blockade minimally affects tidal volumes, respiratory frequency, and the hypercapnic ventilatory response.[33] The hypoxic ventilatory response (HVR), however, can be significantly impaired by small degrees of residual paralysis. This was first demonstrated in 1992 by

Eriksson et al.[34] In 11 unanesthetized male patients, the ventilatory response to hypoxemia was reduced during a vecuronium infusion titrated to a TOF ratio of 0.7 (MMG). These findings were confirmed the following year using a poikilocapnic ventilatory test procedure to control for the effects of hypocapnia on the ventilatory drive.[35] In another investigation, Eriksson[36] measured the HVR at a TOF ratio of 0.7 (MMG) during steady-state infusions of atracurium, pancuronium, or vecuronium. The HVR was reduced by approximately 30% by all 3 drugs and did not recover to control values until TOF ratios >0.9 were achieved. The mechanism of HVR depression is likely attributable to impairment of carotid body chemoreceptor function by NMBDs. In animal models, neurotransmission of the carotid body is significantly reduced by low concentrations of NMBDs during hypoxia; this effect seems to be secondary to inhibition of neuronal nicotinic receptors in the carotid body.[37,38]

Effects on Subjective Symptoms of Weakness

Residual neuromuscular blockade may produce unpleasant symptoms of muscle weakness in the awake patient. The subjective experience of residual paralysis was examined in a study enrolling 10 ASA physical status I volunteers.[15] A mivacurium infusion was administered to maintain TOF ratios between 0.65 and 0.75 (EMG). TOF ratios in the range of 0.70 to 0.75 were associated with diplopia and visual disturbances, decreased grip strength, inability to maintain incisor teeth apposition, inability to sit without assistance, severe facial weakness, difficulty speaking and drinking, and generalized weakness. At TOF ratios between 0.85 and 1.0, generalized fatigue and visual problems remained, and in 7 of the 10 subjects, diplopia persisted for 45 to 90 minutes beyond the time when TOF ratios had recovered to 1.0.[15]

ADVERSE PHYSIOLOGIC EFFECTS OF RESIDUAL NEUROMUSCULAR BLOCK: CLINICAL STUDIES

Volunteer studies have provided important data on the mechanisms by which incomplete neuromuscular recovery can potentially produce adverse outcomes during the postoperative recovery period. Impaired pharyngeal function, weakness of upper airway muscles, and an attenuated HVR resulting from residual paralysis may potentially increase the risk of aspiration, hypoxemia, airway obstruction, need for reintubation, and pulmonary complications. It is likely that the incidence of these complications may be even greater in perioperative patients who receive, in addition to NMBDs, other anesthetic drugs such as opioids, benzodiazepines, volatile anesthetics, and induction drugs, all of which have been shown to affect physiologic functions. However, data demonstrating an association between intraoperative neuromuscular management and impaired clinical recovery and adverse postoperative outcomes are limited and are derived primarily from large databased investigations and observational trials.

Databased Investigations: Anesthetic Techniques and Outcomes

Major adverse outcomes are relatively rare events after anesthesia and surgery. To determine the incidence and etiology of infrequently occurring adverse events attributable to anesthetic care, investigators have conducted large prospective and retrospective databased studies. These investigations have identified NMBDs and residual neuromuscular block as important risk factors in anesthetic-related morbidity and mortality.

Several large databased studies examining the effect of anesthetic techniques on perioperative complications were published between 1965 and 1990. In a series of 240,483 anesthetics administered over a 10-year period (1967–1977) at a single institution in South Africa, the frequency of deaths to which anesthesia was considered to have contributed was 0.22 per 1000 anesthetics.[39] The second most common etiology of anesthetic-related mortality (after hypovolemia) was "respiratory inadequacy after myoneural blockade." In a prospective study from Great Britain, data (1979–1983) were collected on all admissions to the intensive care unit (ICU) with an admission diagnosis of "anesthetic complication."[40] Fifty-three of 2651 admissions (2%) were directly related to anesthetic complications, and the majority of these admissions were attributable to "ventilatory inadequacy after reversal of muscle relaxants." In a report from the Association of Anesthetists of Great Britain and Ireland in 1981, 32 deaths were identified as being "totally" due to anesthesia.[41] The primary cause of mortality in this series was postoperative respiratory failure due to neuromuscular weakness. An important limitation of these 3 studies is that, unlike later databased investigations, the criteria and methods used to define and detect respiratory inadequacy were not explicitly stated. Pedersen et al.[42] prospectively examined risk factors associated with postoperative pulmonary complications in 7306 patients (1986–1987). Two hundred ninety patients (4.1%) met predefined criteria for a postoperative pulmonary complication. Multiple logistic regression analyses showed that patients undergoing longer surgical procedures (≥180 minutes) and receiving pancuronium had a significantly increased risk of pulmonary complications compared with other patients (odds ratio, 2.64).

Databased studies performed since 1990 have continued to demonstrate an association between residual neuromuscular blockade and adverse outcomes. The incidence and predictors of survival after perioperative cardiac arrest were analyzed at the Mayo Clinic over an 11-year study period (1990–2000).[43] Cardiac arrest occurred in 223 of 518,294 noncardiac anesthetics (0.04%). Of the 24 cardiac arrests determined to be attributable to anesthesia, 9 (37.5%) were related to the use of NMBDs (the single largest etiologic category). In a case-control study from the Netherlands, data were collected (1995–1997) on all patients who died or remained comatose after surgery to determine the effect of anesthetic management on outcome measures.[44] The cohort comprised 869,483 patients; 807 "cases" and 883 matched "controls" were analyzed. The most significant risk factor identified in the analysis was related to neuromuscular management. Reversal of the effects of muscle relaxants was associated with a marked reduction (odds ratio, 0.10; 95% confidence interval, 0.03–0.31) in mortality and coma. Rose et al.[45] prospectively examined patient, surgical, and anesthetic factors associated with critical respiratory events in the PACU. Of the numerous

anesthetic factors analyzed, the rate of critical respiratory events was highest in patients who received high doses of atracurium. The relative risk of serious respiratory events was 2- to 3-fold higher in patients receiving high-dose NMBDs (atracurium >0.25 mg/kg/h) compared with lower doses of these drugs.

In conclusion, databased investigations assessing risk factors for anesthetic-related morbidity and mortality have demonstrated an association between NMBD use/residual paralysis and adverse postoperative outcomes. However, these studies have only demonstrated an association between neuromuscular management and major morbidity and mortality. In retrospective and prospective observational trials, associations may be identified but causality cannot be established definitively. In particular, the presence of residual neuromuscular block was not objectively demonstrated using quantitative neuromuscular monitoring in these investigations. Therefore, it is difficult to determine with certainty that the residual effects of NMBDs directly contributed to the adverse outcomes analyzed.

Clinical Investigations: Residual Neuromuscular Block and Outcomes

Although available evidence from volunteer studies and large database investigations has suggested a potential relationship between incomplete neuromuscular recovery and postoperative morbidity, clinical studies supporting this hypothesis have been limited. However, several recent clinical trials have demonstrated that residual neuromuscular block can impair clinical recovery after general anesthesia and increase the risk of adverse respiratory events in the postoperative period.

Residual Block and Adverse Respiratory Events

Postoperative respiratory events are the most common adverse outcomes associated with residual paralysis reported in both observational and randomized clinical studies. In 1997, Berg et al.[5] observed that more patients randomized to a pancuronium group (10%) needed postoperative oxygen supply in excess of 3 L/min to maintain arterial saturation >90% compared with those in an atracurium group (4.8%, $P = 0.047$). Bissinger et al.[20] assessed the incidence of postoperative hypoxemia after the use of pancuronium and vecuronium. Hypoxemia was defined as a peripheral hemoglobin oxygen saturation (Spo_2) ≥5% below baseline values with an arterial hemoglobin oxygen saturation (Sao_2) <93% while patients were breathing room air. In the pancuronium group, the incidence of hypoxemic episodes was significantly higher in subjects with AMG-measured TOF ratios <0.7 (60%) compared with those with TOF ratios >0.7 (10%, $P < 0.05$). In a study of orthopedic patients randomized to receive either pancuronium or rocuronium, the number of patients developing postoperative hypoxemia was higher in the pancuronium group (21 of 35, 60%) compared with the rocuronium group (10 of 34, 29%; $P = 0.015$).[26] In both groups, patients with TOF ratios <0.9 (AMG) on arrival to the PACU were more likely to develop hypoxemia. Murphy et al.[7] performed a case-control prospective study examining the association between residual neuromuscular blockade and critical respiratory events (CREs) in the PACU. Quantitative (AMG) TOF data were collected on all patients with signs or symptoms of CREs over a 1-year period. These patients were compared with a control group studied during the same time period (matched for age, gender, and surgical procedure). Sixty-one of 7459 patients (0.82%) developed CREs, of which 42 were matched with a control. Significant residual paralysis was observed in the patients with CREs in the PACU (mean TOF ratios of 0.62 ± 0.20, with 74.8% of patients exhibiting TOF ratios <0.7) compared with matched control patients without CREs (mean TOF ratios 0.98 ± 0.07). In another clinical trial, the same investigators randomized 185 surgical patients to intraoperative AMG monitoring or standard qualitative peripheral nerve monitoring.[6] On arrival to the PACU, TOF ratios ≤0.9 were observed less frequently in the AMG group (4.5% vs 30%, $P < 0.0001$). Furthermore, the incidence of adverse respiratory events (hypoxemia and airway obstruction) was significantly reduced during transport and during PACU admission in the AMG group.

In the largest outcome study to date, 691 patients were randomized to receive pancuronium, atracurium, or vecuronium to determine the effect of residual neuromuscular blockade on the incidence of postoperative pulmonary complications (pneumonic infiltrations or atelectasis).[5] TOF ratios were quantified with MMG shortly after tracheal extubation, and residual neuromuscular blockade was defined as a TOF ratio <0.7. Incomplete neuromuscular recovery was most frequent in the pancuronium group (26%) compared with the vecuronium (6%) and atracurium (5%) groups ($P < 0.0001$). In the pancuronium group, significantly more patients with residual block developed pulmonary complications (16.9%) than subjects with TOF ratios >0.7 (4.8%, $P < 0.02$). However, in the atracurium and vecuronium groups, the incidence of pulmonary complications was not significantly different in patients with or without residual block. The authors hypothesized that the longer duration of residual paralysis observed with pancuronium predisposed surgical patients to more serious postoperative complications.

Residual Block and Postoperative Recovery Times

Postoperative recovery times may be prolonged in patients with clinical signs and symptoms of muscle weakness caused by NMBDs. In the 1990s, arguments were made to replace intermediate-acting NMBDs with inexpensive long-acting drugs to reduce total anesthesia costs. This issue was addressed in a prospective, before and after comparison study from Duke University Medical Center.[46] Practice guidelines were introduced that promoted the use of less costly anesthetic drugs (induction drugs, NMBDs, inhaled drugs, opioids, benzodiazepines, and IV fluids). In the protocol, pancuronium and succinylcholine were the default NMBDs. After institution of the guidelines, pancuronium use in cases lasting >90 minutes increased from 20% to 70%. However, PACU admission times did not increase, and requirements for postoperative mechanical ventilation remained unchanged. Ballantyne and Chang[47] specifically examined the effect of choice of NMBDs (long- versus intermediate-acting drugs) on postoperative recovery times. Data on 270 surgical patients were analyzed retrospectively. Mean PACU recovery times associated with

each NMBD were calculated, and regression analysis was used to account for confounding variables. Adjusted mean recovery time was 33 minutes (95% confidence interval, 1–66 minutes) less in patients receiving vecuronium compared with those receiving pancuronium. Although the authors hypothesized that residual blockade contributed to prolonged recovery in the pancuronium subjects, postoperative neuromuscular function was not quantified.

Investigators performing a randomized trial in orthopedic surgical patients assessed the effect of choice of NMBD (pancuronium or rocuronium) on PACU recovery times as the primary outcome variable.[26] TOF ratios were quantified on arrival to the PACU, and the time required to meet and achieve discharge criteria was determined. Significant delays in meeting PACU discharge criteria (50 minutes vs 30 minutes) and achieving actual discharge (70 minutes vs 57.5 minutes) were observed in the pancuronium group compared with the rocuronium group ($P < 0.001$). Patients with TOF ratios <0.9 (AMG) in the PACU were more likely to have PACU admission times >60 minutes than patients with TOF values >0.9 ($P = 0.004$). Delayed recovery times were likely caused by an increase in the frequency of hypoxemic events and unpleasant symptoms of muscle weakness observed in the pancuronium group.

Residual Block in Cardiac Surgical Patients

Incomplete recovery of neuromuscular function may be associated with delayed clinical recovery even when patients remain tracheally intubated after the surgical procedure. In the United States, pancuronium is the primary NMBD administered during cardiac surgery, and neuromuscular function is rarely monitored (or reversed) perioperatively.[48] Recent data suggest that this practice of neuromuscular management may compromise patient safety after tracheal extubation in the ICU. A large retrospective study by Butterworth et al.[49] concluded that choice of NMBD (pancuronium or rocuronium) did not influence the duration of intubation or ICU length of stay after cardiac surgery. In contrast, several prospective investigations have demonstrated that delays in clinical and neuromuscular recovery do occur when long-acting NMBDs are used.[50–53] An initial investigation randomized 20 coronary artery bypass grafting patients to receive pancuronium or rocuronium.[50] TOF ratios (EMG) recorded in the ICU were significantly less in the pancuronium group (0.03 ± 0.05) compared with the rocuronium group (0.68 ± 0.34), and tracheal extubation was delayed by 4 hours in patients receiving pancuronium. Thomas et al.[51] examined the time required to achieve TOF ratios >0.9 (AMG) in the ICU in cardiac surgical patients randomized to receive pancuronium or rocuronium. Median times to recover to a TOF >0.9 were 218 minutes in the rocuronium group versus 472 minutes in the pancuronium group. Tracheal extubation was delayed because of residual paralysis in 7 of 10 pancuronium patients, compared with none in the rocuronium group.

A larger investigation randomized 110 coronary artery bypass graft patients to receive pancuronium or rocuronium intraoperatively.[52] Despite careful dosing and monitoring of NMBDs, significant increases in the duration of weaning of ventilatory support (70 minutes) and delays in tracheal extubation (150 minutes) were observed in patients administered pancuronium as compared with rocuronium. A follow-up study by the same investigators measured TOF ratios (AMG) each hour in the cardiac ICU until weaning of ventilatory support was initiated.[53] At the time of ventilatory weaning, significant residual neuromuscular block (median TOF ratio, 0.14; range, 0.00–1.11) was present in patients randomized to receive pancuronium; residual paralysis was absent in the rocuronium group (median TOF ratio, 0.99; range, 0.87–1.21). Significantly more patients in the pancuronium group had symptoms of muscle weakness after tracheal extubation (visual difficulties, difficulty speaking, and generalized weakness) and were unable to perform a 5-second leg lift or strongly appose their incisor teeth.

CONCLUSIONS

Data published during the past 2 decades have demonstrated that residual neuromuscular block (now defined as a TOF ratio <0.9 measured using MMG) continues to be a common clinical occurrence in the PACU and ICU. Data-based investigations have established an association between NMBD use/residual neuromuscular block and increased perioperative morbidity and mortality. Recent clinical trials have demonstrated that incomplete neuromuscular recovery during the early postoperative period may result in acute respiratory events (hypoxemia and airway obstruction), unpleasant symptoms of muscle weakness in the awake patient, longer PACU stays, and delays in tracheal extubation. Furthermore, prolonged neuromuscular block in the PACU has been associated with an increased risk of significant postoperative pulmonary complications. These data provide important clinical evidence that residual neuromuscular block is a primary and frequent anesthetic risk factor for postoperative complications.

Despite accumulating laboratory and clinical evidence that residual block can adversely affect postoperative outcomes, it seems that most patients with TOF ratios <0.9 in the PACU do not experience complications. If approximately 40% of postoperative patients have TOF ratios <0.9,[30] only a small minority (<1%–3%) actually develop clinically evident events that can be attributed to inadequate neuromuscular recovery. As recently noted, "most patients seem to tolerate residual block of modest extent without untoward results."[54] Furthermore, in the early recovery period, it is difficult to differentiate the adverse effects of NMBDs from the lingering effects of opioids, benzodiazepines, and inhaled drugs. These observations may explain why so few clinicians perceive residual block as an important patient safety issue. However, some patients will develop short- and long-term complications directly related to neuromuscular management in the operating room. It is also possible that small degrees of residual paralysis may result in more subtle adverse effects in postoperative surgical patients that have not been detected in previous clinical trials. We believe that increased awareness of the hazards of unrecognized residual paralysis may lead to improved neuromuscular management and enhanced patient outcomes. Methods that can be used to

reduce the risk of residual block are discussed in part II of this review.

RECUSE NOTE

Sorin J. Brull is Section Editor of Patient Safety for the Journal. The manuscript was handled by Tony Gin, Section Editor of Anesthetic Clinical Pharmacology, and Dr. Brull was not involved in any way with the editorial process or decision.

REFERENCES

1. Beecher HK, Todd DP. A study of the deaths associated with anesthesia and surgery: based on a study of 599, 548 anesthesias in ten institutions 1948–1952, inclusive. Ann Surg 1954;140:2–35
2. Kim KS, Lew SH, Cho HY, Cheong MA. Residual paralysis induced by either vecuronium or rocuronium after reversal with pyridostigmine. Anesth Analg 2002;95:1656–60
3. Debaene B, Plaud B, Dilly MP, Donati F. Residual paralysis in the PACU after a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action. Anesthesiology 2003;98:1042–8
4. Cammu G, De Witte J, De Veylder J, Byttebier G, Vandeput D, Foubert L, Vandenbroucke G, Deloof T. Postoperative residual paralysis in outpatients versus inpatients. Anesth Analg 2006;102:426–9
5. Berg H, Roed J, Viby-Mogensen J, Mortensen CR, Engbaek J, Skovgaard LT, Krintel JJ. Residual neuromuscular block is a risk factor for postoperative pulmonary complications. A prospective, randomized, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium. Acta Anaesthesiol Scand 1997;41:1095–103
6. Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS, Nisman M. Intraoperative acceleromyographic monitoring reduces the risk of residual neuromuscular blockade and adverse respiratory events in the postanesthesia care unit. Anesthesiology 2008;109:389–98
7. Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS. Residual neuromuscular blockade and critical respiratory events in the postanesthesia care unit. Anesth Analg 2008;107:130–7
8. Ali HH, Utting JE, Gray C. Stimulus frequency in the detection of neuromuscular block in humans. Br J Anaesth 1970;42:967–78
9. Ali HH, Kitz RJ. Evaluation of recovery from nondepolarizing neuromuscular block, using a digital neuromuscular transmission analyzer: preliminary report. Anesth Analg 1973;52:740–5
10. Ali HH, Wilson RS, Savarese JJ, Kitz RJ. The effect of tubocurarine on indirectly elicited train-of-four muscle response and respiratory measurements in humans. Br J Anaesth 1975;47:570–4
11. Brand JB, Cullen DJ, Wilson NE, Ali HH. Spontaneous recovery from nondepolarizing neuromuscular blockade: correlation between clinical and evoked responses. Anesth Analg 1977;56:55–8
12. Sundman E, Witt H, Olsson R, Ekberg O, Kuylenstierna R, Eriksson LI. The incidence and mechanisms of pharyngeal and upper esophageal dysfunction in partially paralyzed humans. Pharyngeal videoradiography and simultaneous manometry after atracurium. Anesthesiology 2000;92:977–84
13. Eriksson LI, Sundman E, Olsson R, Nilsson L, Witt H, Ekberg O, Kuylenstierna R. Functional assessment of the pharynx at rest and during swallowing in partially paralyzed humans: simultaneous videomanometry and mechanomyography of awake human volunteers. Anesthesiology 1997;87:1035–43
14. Eikermann M, Groeben H, Husing J, Peters J. Accelerometry of adductor pollicis muscle predicts recovery of respiratory function from neuromuscular blockade. Anesthesiology 2003;98:1333–7
15. Kopman AF, Yee PS, Neuman GG. Relationship of the train-of-four fade ratio to clinical signs and symptoms of residual paralysis in awake volunteers. Anesthesiology 1997;86:765–71
16. Viby-Mogensen J, Jørgensen BC, Ording H. Residual curarization in the recovery room. Anesthesiology 1979;50:539–41
17. Beemer GH, Rozental P. Postoperative neuromuscular function. Anaesth Intensive Care 1986;14:41–5
18. Bevan DR, Smith CE, Donati F. Postoperative neuromuscular blockade: a comparison between atracurium, vecuronium, and pancuronium. Anesthesiology 1988;69:272–6
19. Andersen BN, Madsen JV, Schurizek BA, Juhl B. Residual curarisation: a comparative study of atracurium and pancuronium. Acta Anaesthesiol Scand 1988;32:79–81
20. Bissinger U, Schimek F, Lenz G. Postoperative residual paralysis and respiratory status: a comparative study of pancuronium and vecuronium. Physiol Res 2000;49:455–62
21. Baillard C, Clec'h C, Catineau J, Salhi F, Gehan G, Cupa M, Samama CM. Postoperative residual neuromuscular block: a survey of management. Br J Anaesth 2005;95:622–6
22. Hayes AH, Mirakhur RK, Breslin DS, Reid JE, McCourt KC. Postoperative residual block after intermediate-acting neuromuscular blocking drugs. Anaesthesia 2001;56:312–8
23. Gätke MR, Viby-Mogensen J, Rosenstock C, Jensen FS, Skovgaard LT. Postoperative muscle paralysis after rocuronium: less residual block when acceleromyography is used. Acta Anaesthesiol Scand 2002;46:207–13
24. Kopman AF, Zank LM, Ng J, Neuman GG. Antagonism of cisatracurium and rocuronium block at a tactile train-of-four count of 2: should quantitative assessment of neuromuscular function be mandatory? Anesth Analg 2004;98:102–6
25. Murphy GS, Szokol JW, Marymont JH, Franklin M, Avram MJ, Vender JS. Residual paralysis at the time of tracheal extubation. Anesth Analg 2005;100:1840–5
26. Murphy GS, Szokol JW, Franklin M, Marymont JH, Avram MJ, Vender JS. Postanesthesia care unit recovery times and neuromuscular blocking drugs: a prospective study of orthopedic surgical patients randomized to receive pancuronium or rocuronium. Anesth Analg 2004;98:193–200
27. Baillard C, Gehan G, Reboul-Marty J, Larmignat P, Samama CM, Cupa M. Residual curarization in the recovery room after vecuronium. Br J Anaesth 2000;84:394–5
28. McCaul C, Tobin E, Boylan JF, McShane AJ. Atracurium is associated with postoperative residual curarization. Br J Anaesth 2002;89:766–9
29. Maybauer DM, Geldner G, Blobner M, Pühringer F, Hofmockel R, Rex C, Wulf HF, Eberhart L, Arndt C, Eikermann M. Incidence and duration of residual paralysis at the end of surgery after multiple administrations of cisatracurium and rocuronium. Anaesthesia 2007;62:12–7
30. Naguib M, Kopman AF, Ensor JE. Neuromuscular monitoring and postoperative residual curarisation: a meta-analysis. Br J Anaesth 2007;98:302–16
31. Isono S, Ide T, Kochi T, Mizuguchi T, Nishino T. Effects of partial paralysis on the swallowing reflex in conscious humans. Anesthesiology 1991;75:980–4
32. Eikermann M, Vogt FM, Herbstreit F, Vahid-Dastgerdi M, Zenge MO, Ochterbeck C, de Greiff A, Peters J. The predisposition to inspiratory upper airway collapse during partial neuromuscular blockade. Am J Respir Crit Care Med 2007;175:9–15
33. Eriksson LI. The effects of residual neuromuscular blockade and volatile anesthetics on the control of ventilation. Anesth Analg 1999;89:243–51
34. Eriksson LI, Lennmarken C, Wyon N, Johnson A. Attenuated ventilatory response to hypoxaemia at vecuronium-induced partial neuromuscular block. Acta Anaesthesiol Scand 1992;36:710–5
35. Eriksson LI, Sato M, Severinghaus JW. Effect of a vecuronium-induced partial neuromuscular block on hypoxic ventilatory response. Anesthesiology 1993;78:693–9
36. Eriksson LI. Reduced hypoxic chemosensitivity in partially paralysed man. A new property of muscle relaxants? Acta Anaesthesiol Scand 1996;40:520–3
37. Wyon N, Joensen H, Yamamoto Y, Lindahl SG, Eriksson LI. Carotid body chemoreceptor function is impaired by vecuronium during hypoxia. Anesthesiology 1998;89:1471–9
38. Igarashi A, Amagasa S, Horikawa H, Shirahata M. Vecuronium directly inhibits hypoxic neurotransmission of the rat carotid body. Anesth Analg 2002;94:117–22
39. Harrison GG. Death attributable to anaesthesia. A 10-year survey (1967–1976). Br J Anaesth 1978;50:1041–6

40. Cooper AL, Leigh JM, Tring IC. Admissions to the intensive care unit after complications of anaesthetic techniques over 10 years. 1. The first 5 years. Anaesthesia 1989;44:953–8
41. Lunn JN, Hunter AR, Scott DB. Anaesthesia-related surgical mortality. Anaesthesia 1983;38:1090–6
42. Pedersen T, Viby-Mogensen J, Ringsted C. Anaesthetic practice and postoperative pulmonary complications. Acta Anaesthesiol Scand 1992;36:812–8
43. Sprung J, Warner ME, Contreras MG, Schroeder DR, Beighley CM, Wilson GA, Warner DO. Predictors of survival following cardiac arrest in patients undergoing noncardiac surgery: a study of 518,294 patients at a tertiary referral center. Anesthesiology 2003;99:259–69
44. Arbous MS, Meursing AE, van Kleef JW, de Lange JJ, Spoormans HH, Touw P, Werner FM, Grobbee DE. Impact of anesthesia management characteristics on severe morbidity and mortality. Anesthesiology 2005;102:257–68
45. Rose DK, Cohen MM, Wigglesworth DF, DeBoer DP. Critical respiratory events in the postanesthesia care unit. Patient, surgical, and anesthetic factors. Anesthesiology 1994;81:410–8
46. Lubarsky DA, Glass PS, Ginsberg B, Dear GL, Dentz ME, Gan TJ, Sanderson IC, Mythen MG, Dufore S, Pressley CC, Gilbert WC, White WD, Alexander ML, Coleman RL, Rogers M, Reves JG. The successful implementation of pharmaceutical practice guidelines. Analysis of associated outcomes and cost savings. Anesthesiology 1997;86:1145–60
47. Ballantyne JC, Chang Y. The impact of choice of muscle relaxant on postoperative recovery time: a retrospective study. Anesth Analg 1997;85:476–82
48. Murphy GS, Szokol JW, Marymont JH, Vender JS, Avram MJ. The use of neuromuscular blocking agents in adult cardiac surgery: results of a national postal survey. Anesth Analg 2002;95:1534–9
49. Butterworth J, James R, Prielipp RC, Cerese J, Livingston J, Burnett DA. Do shorter-acting neuromuscular blocking drugs or opioids associate with reduced intensive care unit or hospital lengths of stay after coronary artery bypass grafting? CABG Clinical Benchmarking Data Base Participants. Anesthesiology 1998;88:1437–46
50. McEwin L, Merrick PM, Bevan DR. Residual neuromuscular blockade after cardiac surgery: pancuronium vs rocuronium. Can J Anaesth 1997;44:891–5
51. Thomas R, Smith D, Strike P. Prospective randomised double-blind comparative study of rocuronium and pancuronium in adult patients scheduled for elective 'fast-track' cardiac surgery involving hypothermic cardiopulmonary bypass. Anaesthesia 2003;58:265–71
52. Murphy GS, Szokol JW, Marymont JH, Avram MJ, Vender JS, Rosengart TK. The impact of shorter-acting neuromuscular blocking agents on fast-track recovery of the cardiac surgical patient. Anesthesiology 2002;96:600–6
53. Murphy GS, Szokol JW, Marymont JH, Vender JS, Avram MJ, Rosengart TK, Alwawi EA. Recovery of neuromuscular function after cardiac surgery: pancuronium versus rocuronium. Anesth Analg 2003;96:1301–7
54. Kopman AF. Residual neuromuscular block and adverse respiratory events. Anesth Analg 2008;107:1756

CME

Residual Neuromuscular Block: Lessons Unlearned. Part II: Methods to Reduce the Risk of Residual Weakness

Sorin J. Brull, MD,* and Glenn S. Murphy, MD†

The aim of the second part of this review is to examine optimal neuromuscular management strategies that can be used by clinicians to reduce the risk of residual paralysis in the early postoperative period. Current evidence has demonstrated that frequently used clinical tests of neuromuscular function (such as head lift or hand grip) cannot reliably exclude the presence of residual paralysis. When qualitative (visual or tactile) neuromuscular monitoring is used (train-of-four [TOF], double-burst, or tetanic stimulation patterns), clinicians often are unable to detect fade when TOF ratios are between 0.6 and 1.0. Furthermore, the effect of qualitative monitoring on postoperative residual paralysis remains controversial. In contrast, there is strong evidence that acceleromyography (quantitative) monitoring improves detection of small degrees (TOF ratios >0.6) of residual blockade. The use of intermediate-acting neuromuscular blocking drugs (NMBDs) can reduce, but do not eliminate, the risk of residual paralysis when compared with long-acting NMBDs. In addition, complete recovery of neuromuscular function is more likely when anticholinesterases are administered early (>15–20 minutes before tracheal extubation) and at a shallower depth of block (TOF count of 4). Finally, the recent development of rapid-onset, short-acting NMBDs and selective neuromuscular reversal drugs that can effectively antagonize deep levels of blockade may provide clinicians with novel pharmacologic approaches for the prevention of postoperative residual weakness and its associated complications. (Anesth Analg 2010;111:129–40)

Careful management of the depth of neuromuscular blockade in the operating room may reduce the incidence of residual paralysis in the postanesthesia care unit (PACU) or intensive care unit (ICU). Several principles related to neuromuscular blocking drug (NMBD) dosing, monitoring, and reversal have been shown to reduce the risk of incomplete neuromuscular recovery in postoperative patients. Although use of these techniques has been recommended in editorials and reviews,[1–4] at this time, there are no published standards or guidelines defining optimal neuromuscular management strategies. Part II of the review provides a narrative review of the methods that can be used by clinicians to reduce the risk of complications due to residual neuromuscular blockade. The number of randomized, controlled clinical trials directly related to this topic is limited; therefore, a formal meta-analysis of the studies was not attempted. Instead, the authors provide a narrative review of the relevant literature. The recent development of several novel NMBDs that promise increased flexibility with regard to block onset time, duration of effect, and ease of reversal will also be reviewed.

From the *Department of Anesthesiology, Mayo Clinic College of Medicine, Jacksonville, Florida; and †Department of Anesthesiology, NorthShore University HealthSystem, University of Chicago, Evanston, Illinois.

Accepted for publication February 4, 2010.

Supported by institutional and/or departmental sources (Department of Anesthesiology, NorthShore University HealthSystem and Mayo Clinic College of Medicine).

Address correspondence and reprint requests to Sorin J. Brull, MD, Department of Anesthesiology, Mayo Clinic College of Medicine, 4500 San Pablo Rd., Jacksonville, FL 32224. Address e-mail to SJBrull@me.com.

DOI: 10.1213/ANE.0b013e3181da8312

METHODS TO REDUCE THE RISK OF RESIDUAL NEUROMUSCULAR BLOCKADE

Use of Shorter-Acting NMBDs

The administration of intermediate-acting NMBDs is associated with a lower incidence of residual neuromuscular blockade in the PACU and ICU compared with long-acting NMBDs. Observational and randomized clinical trials comparing the frequency of residual paralysis in patients receiving either long- or intermediate-acting NMBDs are summarized in Table 1.[5–14] All of the published clinical studies have demonstrated that the risk of residual blockade is increased when patients receive long-acting NMBDs. A recent meta-analysis estimated the pooled incidence of residual neuromuscular block in patients receiving long- or intermediate-acting NMBDs.[15] The use of long-acting NMBDs was associated with a 3-fold higher risk of a train-of-four (TOF) ratio <0.7 in the postoperative period (35% vs 11%, $P < 0.001$). Furthermore, clinical trials have demonstrated that patients receiving pancuronium have an increased incidence of hypoxemic episodes in the PACU,[10,12,14] prolonged PACU admissions,[14,16] longer postoperative intubation times,[11,13,17,18] and an increased risk of pulmonary complications.[10] These data provide compelling evidence that the use of long-acting NMBDs places the surgical patient at increased risk of complications related to residual paralysis. The role of pancuronium in contemporary anesthesia practice is limited, and many correctly argue that its clinical use should cease; in fact, its clinical benefits (long duration) can be achieved with repeated administration of intermediate-duration drugs (rocuronium, cisatracurium), but with lower risk of drug accumulation or residual paralysis.

Table 1. Studies Comparing the Incidence of Residual Neuromuscular Blockade in Patients Receiving Long- or Intermediate-Acting NMBDs

Author	Year	No. of patients	NMBD used	Definition RNMB	Incidence RNMB (%)
Bevan et al.[6]	1988	150	Pancuronium	<0.7	36.2*
			Atracurium	<0.7	4.3
			Vecuronium	<0.7	8.8
Howardy-Hansen et al.[7]	1989	19	Gallamine	<0.7	50*
			Atracurium	<0.7	0
Pedersen et al.[5]	1990	80	Pancuronium	<0.7	60*
			Vecuronium	<0.7	27.5
Brull et al.[8]	1991	64	Pancuronium	<0.7	45*
			Vecuronium	<0.7	8
Kopman et al.[9]	1996	91	Pancuronium	<0.9	66.1*
			Mivacurium	<0.9	5.7
Berg et al.[10]	1997	691	Pancuronium	<0.7	26*
			Atracurium	<0.7	5
			Vecuronium	<0.7	6
McEwin et al.[11] (cardiac)	1997	20	Pancuronium	<0.7	100*
			Rocuronium	<0.7	40
Bissinger et al.[12]	2000	83	Pancuronium	<0.7	20*
			Vecuronium	<0.7	7
Murphy et al.[13] (cardiac)	2003	82	Pancuronium	<0.8	82.1*
			Rocuronium	<0.8	0
Murphy et al.[14]	2004	70	Pancuronium	<0.7	40*
			Rocuronium	<0.7	5.9

NMBD = neuromuscular blocking drug; RNMB = residual neuromuscular blockade.
* Statistically significant differences.

However, the promise that NMBDs of intermediate duration might markedly reduce the incidence of residual paralysis has not been realized.[6] The reason for this failure is multifactorial. First, when administered in large doses (such as 3–4 times the dose needed for 95% block, or ED_{95}), the duration of all intermediate-acting neuromuscular blockers is prolonged (by 50%–300%) compared with the duration of action attained after administration of a 1 to 2 times ED_{95} dose. Second, there is a great variability among patients in response to intermediate-duration NMBDs. Third, there is great variability in the duration of neostigmine-induced reversal, even with intermediate-duration NMBDs. During cisatracurium- or rocuronium-induced block, pharmacologic reversal administration at a TOF count of 2 required at least 15 minutes, whereas some patients still had significant residual paralysis (TOF <0.90) >30 minutes after reversal.[19] Thus, current clinical practice of tracheal extubation 5 to 10 minutes after administration of anticholinesterases may not allow sufficient time for adequate return of neuromuscular function, especially in patients at risk. This potentially unsafe practice (e.g., early tracheal extubation before complete neuromuscular recovery) may be a direct result of the increasingly common production pressure for "quick turnover" of surgical cases, especially in ambulatory surgery settings. The desire to expedite surgical case volume may shorten the time between administration of anticholinesterases and tracheal extubation, increasing the potential for residual block.

Last, monitoring of evoked responses intraoperatively, regardless of the NMBD used, is only a tool and may not actually decrease the incidence of residual paralysis.[15] To decrease the incidence of residual paralysis, return of neuromuscular function to baseline must be documented objectively (i.e., measured) before tracheal extubation. Documentation of residual paralysis is not sufficient to solve the problem of residual neuromuscular block; acting on the available evidence is ultimately the most important step.

Clinical Tests to Exclude Residual Muscle Weakness

Ideally, clinical tests of neuromuscular recovery should not require an awake and cooperative patient. Such tests should be applicable and reliable before emergence from anesthesia and tracheal extubation. Unfortunately, most clinical tests fail to meet either of these 2 criteria. In addition, many clinical tests (leg lift, hand grip, and head lift) are not specific for the respiratory function, so they cannot be used clinically to infer adequacy of respiratory muscle function. In practice, however, most clinicians rely primarily on clinical signs or tests of muscle weakness to determine the presence or absence of residual blockade before tracheal extubation.[20] Surveys have also demonstrated that most clinicians believe that it is always possible to exclude residual neuromuscular blockade using clinical tests.[21,22] Available evidence does not support this belief. A 5-second head lift is the most frequently applied clinical test of residual paralysis used by clinicians.[20] However, in a volunteer study, 11 of 12 subjects were able to maintain a head lift for more than 5 seconds at a TOF ratio of 0.5.[23] Pedersen et al.[5] observed that 16 of 19 postoperative patients were able to maintain a 5-second head lift despite having TOF ratios <0.5. Clearly, this degree of recovery (TOF of 0.5) is clinically unacceptable. Clinical studies also have demonstrated that other frequently used clinical tests of muscle weakness (sustained hand grip, leg lift, or eye opening) can be performed when significant degrees of residual neuromuscular blockade are present.[24–26]

The ability to maintain masseter muscle strength (clench teeth on a tongue blade or bite block) may be a more sensitive test of residual paralysis than head lift, but it is not infallible. In awake volunteers, the ability to retain a tongue

Table 2. Diagnostic Attributes of the Clinical Tests: Sensitivity, Specificity, Positive and Negative Predictive Values of an Individual Clinical Test for a Train-of-Four <90%

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Inability to smile	0.29	0.80	0.47	0.64
Inability to swallow	0.21	0.85	0.47	0.63
Inability to speak	0.29	0.80	0.47	0.64
General weakness	0.35	0.78	0.51	0.66
Inability to lift head for 5 s	0.19	0.88	0.51	0.64
Inability to lift leg for 5 s	0.25	0.84	0.50	0.64
Inability to sustained hand grip for 5 s	0.18	0.89	0.51	0.63
Inability to perform sustained tongue depressor test	0.22	0.88	0.52	0.64

The sensitivity of a test is the number of true positives divided by the sum of true positives + false negatives; the specificity is the number of true negatives divided by the sum of true negatives + false positives. True positives are patients scoring positives for a test and having a train-of-four (TOF) <90%. False negatives are patients with a negative test result but a TOF <90%. True negatives have a negative test score and a TOF not <90%; false positives score positively but have a TOF not <90%. A positive test result means inability to smile, swallow and speak, general muscular weakness, etc.
Reprinted with permission from Cammu et al.[24]

depressor between the clenched incisor teeth "despite vigorous attempts to dislodge it" did not return until TOF ratios exceeded 0.86.[27] However, the sensitivity of this test in predicting residual paralysis (TOF ratio <0.9) in postoperative patients was low (13%–22%).[24,28] More important from a patient safety standpoint, however, is the fact that the tongue depressor test seems to be more specific; few patients with a TOF >0.9 are likely to fail this test. The sensitivity, specificity, positive predictive value, and negative predictive value of frequently used clinical tests for residual paralysis were recently examined in a cohort of 640 surgical patients.[24] As noted in Table 2, the sensitivity and positive predictive values of all the tests were low for predicting TOF ratios <0.9. None of the 8 individual tests (or a sum of these tests) was able to reliably predict the occurrence of residual neuromuscular block. Another large clinical trial (n = 526 patients) noted similarly low sensitivity values (11%–14%) for clinical tests in detecting patients with TOF values <0.9.[28] In summary, current evidence demonstrates that frequently used clinical tests of neuromuscular function cannot reliably exclude the presence of residual paralysis unless TOF ratios are <0.5.

Use of Neuromuscular Monitoring: Qualitative Means

A subjective (qualitative) visual or tactile assessment of a response to peripheral nerve stimulation is the most common method of neuromuscular monitoring used in the operating room, PACU, and ICU. Available data suggest that tactile evaluations may be slightly (but not significantly) more sensitive in detecting residual neuromuscular block than visual assessments. At a TOF ratio of 0.41 to 0.50, only 37% of inexperienced anesthesiologists were able to detect fade visually, compared with 57% who detected fade manually (P = not significant).[29] Similarly, the ability to detect fade was comparable for visual or tactile assessments regardless of the method of neurostimulation (TOF, double-burst stimulation [$DBS_{3,3}$; $DBS_{3,2}$]) at both high and low currents.[30] In contrast, Tammisto et al.[31] observed that the tactile method (movement of the patient's thumb against the observer's fingers) was more accurate in detecting fade than visual assessment.

The most frequently used patterns of neurostimulation are TOF, DBS, and tetanic stimulation. The ability of each mode of neurostimulation to diagnose residual neuromuscular blockade (determined using mechanomyography [MMG] on the contralateral arm) has been studied extensively. In 1985, Viby-Mogensen et al.[29] measured the ability of anesthesiologists to detect fade using TOF stimulation at varying levels of neuromuscular blockade. Anesthesiologists inexperienced in tactile fade detection were able to feel fade only when TOF ratios were <0.30. Although outcomes were better in observers with extensive experience in neuromuscular monitoring, these observers were unable to detect fade 80% of the time when TOF ratios were between 0.51 and 0.70. Other investigators have confirmed that the majority of evaluators are unable to detect fade when TOF ratios exceed 0.40.[30,32,33] Despite this readily available information, it is likely that most clinicians are unaware of the limitations of the subjective evaluation of TOF fade.

The use of DBS seems to improve detection of residual paralysis using subjective means compared with qualitative (subjective) TOF monitoring. When using DBS monitoring, the threshold for subjective detection of fade is a TOF ratio of 0.60 to 0.70, whereas the threshold for detection of fade with TOF monitoring is 0.40.[33] One of the mechanisms proposed for the apparent improvement in the ability to detect fade with DBS compared with TOF is that DBS relies on the direct comparison of 2 rapidly sequential, evoked stimuli (the muscle contraction in response to the 2 individual minitetanic bursts) rather than the indirect comparison of the fourth twitch with the first twitch in the series of 4 evoked responses of TOF. In this latter setting, the comparison of the fourth to the first twitches is likely muddled by the intervening second and third twitches that provide no useful information. Other investigators have shown that it is not the amplitude of individual responses in TOF or DBS that facilitates detection of fade (the amplitude of the individual DBS responses is greater than that of TOF responses) but the pattern of stimulation (2 responses in DBS vs 4 responses in TOF).[34]

In a preliminary investigation using $DBS_{3,3}$, manual evaluation of the DBS response allowed detection of TOF ratios up to 0.6.[33] However, probability analysis showed that when no fade was detected with either TOF or DBS, there was still a 47% risk that the "true" TOF ratio (i.e., determined by MMG) was <0.7. Other investigators have

demonstrated that the ability of clinicians to detect fade in the TOF range of 0.3 to 0.7 is greater with DBS than TOF monitoring.[30,32–34] The 50-Hz tetanic stimulation pattern is the least sensitive qualitative method of monitoring; fade can only be reliably detected when TOF ratios are ≤0.3.[32,35] However, the threshold for detecting fade is increased using a 5-second, 100-Hz stimulating current. Although fade could be reliably detected up to TOF ratios of 0.85 to 0.88 using 100-Hz tetanus,[32,36] other investigators reported no fade at MMG TOF values as low as 0.47.[37] In addition, tetanic stimulation rates >70 Hz may induce neuromuscular fade (detected by MMG) even in the absence of any neuromuscular block because even normal neuromuscular transmission may fatigue at these high stimulation rates.[38,39]

The effect of qualitative neuromuscular monitoring on postoperative residual paralysis has been evaluated in observational and randomized trials. Three randomized clinical studies have specifically examined the usefulness of conventional peripheral nerve stimulators in reducing the occurrence of residual neuromuscular blockade in the PACU. Pedersen et al.[5] randomized 80 subjects to receive either TOF monitoring (tactile evaluation of TOF stimulation) or no neuromuscular monitoring (in which clinical criteria such as spontaneous muscle activity determined the administered NMBD dose). No differences were observed between the 2 groups in TOF ratios measured in the PACU or in clinical signs of postoperative muscle weakness. The maintenance of a deep level of neuromuscular blockade in the monitored group (TOF count of 1–2 during surgery and at reversal) likely contributed to the high incidence of residual paralysis in these subjects (20 of 40 patients with TOF ratio <0.7), complicating the interpretation of findings. Shorten et al.[40] randomized 39 patients to TOF monitoring (tactile assessment at the adductor pollicis) or no monitoring (clinical criteria) during anesthesia with pancuronium and enflurane. In contrast to the previous investigators, Shorten et al. determined that the proportion of patients with TOF ratios <0.7 was significantly less in a monitored group (15%) compared with unmonitored patients (47%, $P < 0.05$). Another randomized trial demonstrated that tactile evaluation of the response to DBS reduced, but did not eliminate, the occurrence of residual paralysis.[26] In the DBS-monitored group, the trachea was extubated when no fade was detectable in both the TOF- and DBS-evoked response. Immediately after extubation, significantly fewer patients in the monitored group had TOF ratios <0.7 (24%) compared with the unmonitored group (57%). In a recent meta-analysis, investigators examined the effect of neuromuscular monitoring (qualitative and quantitative) on the incidence of postoperative residual paralysis.[15] Data were analyzed on 11 observational and 13 randomized trials (total of 3375 patients) published between 1979 and 2005. The authors were unable to demonstrate that the use of monitoring decreased the incidence of residual paralysis. However, conclusions from the meta-analysis were limited by the quality of the individual studies reviewed, which were "often poorly designed to detect any advantages conferred by monitoring." Further large-scale, well-designed randomized clinical trials are needed to assess the effect of qualitative monitoring on postoperative outcomes.

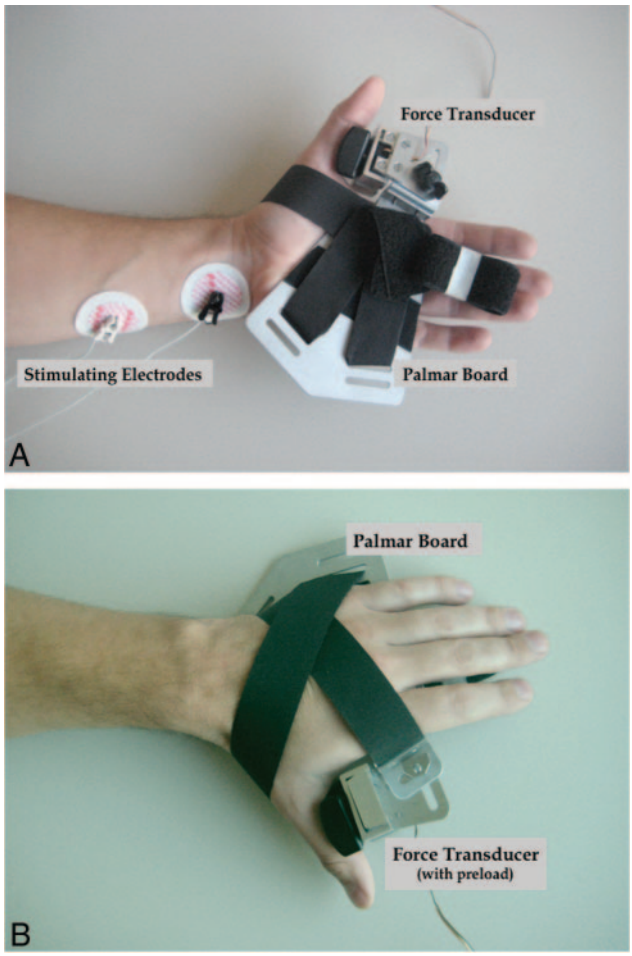

Figure 1. Example of mechanomyograph (MMG). A, Palmar view. The adductor pollicis monitor consists of a rigid palmar board on which the hand is fixed with straps. The thumb is placed against the force transducer under slight tension (200–300 g, also called "preload") and the force transducer records thumb contraction in response to nerve stimulation. B, Dorsal view of the MMG. Although still used in research settings, the MMG monitor is not available commercially.

Use of Neuromuscular Monitoring: Quantitative Means

Clinicians are unable to reliably exclude residual neuromuscular blockade when using conventional peripheral nerve stimulators because fade is difficult to detect subjectively when TOF ratios are between 0.4 and 0.9.[32] However, TOF ratios >0.4 can be measured accurately and displayed numerically using quantitative neuromuscular monitoring. Several methods of quantitative monitoring have been used in clinical studies: MMG, electromyography (EMG), kinemyography (KMG), phonomyography (PMG), and acceleromyography (AMG).[41–43]

- MMG quantitatively measures isometric contraction of a peripheral muscle (usually the adductor pollicis) in response to ulnar nerve stimulation (Fig. 1, A and B). The thumb is placed on the force transducer under mild tension (preload, usually 200–300 g) to produce an isometric contraction and improve consistency of

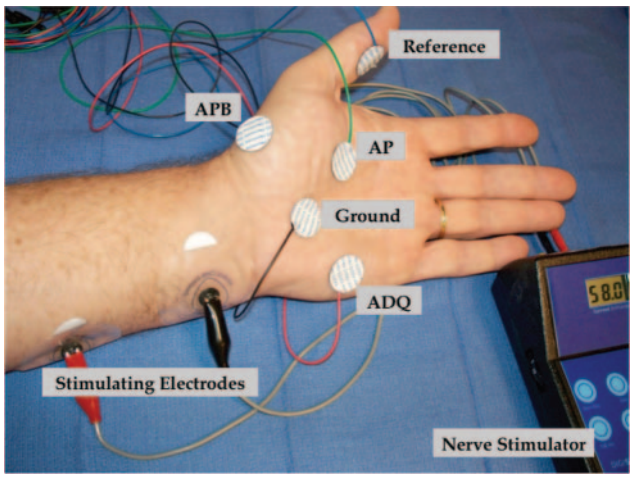

Figure 2. Example of electromyograph (EMG). The various electrodes can monitor different hand muscles—the abductor pollicis brevis (APB), the abductor digiti quinti (ADQ), or the most frequently monitored hand muscle, the adductor pollicis (AP), can be used to record the EMG signal in response to ulnar nerve stimulation. In addition to the muscle electrodes, 2 additional electrodes are needed: the reference and ground electrodes.

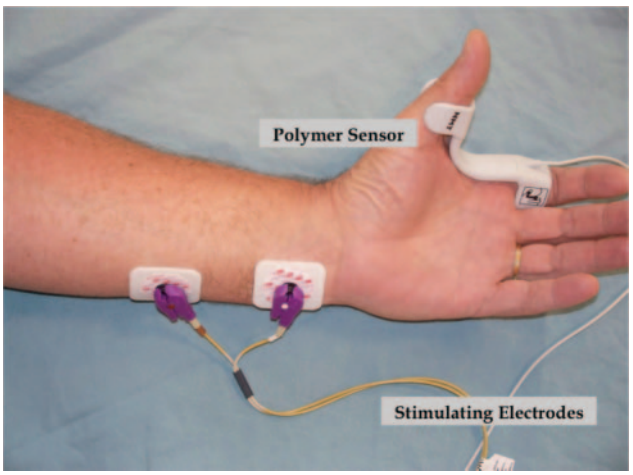

Figure 3. Example of kinetomyograph (KMG). The polymer sensor that detects the bending movement of the thumb is placed in the groove between the index finger and thumb, and the thumb adduction in response to ulnar nerve stimulation is recorded on the interfaced monitor.

evoked responses. The force of contraction is converted to an electrical signal and the amplitude of the signal is recorded on an interfaced pressure monitor; because the amplitude of the electrical signal is proportional to the strength of the muscle contraction, measurement of the TOF ratio will yield results that are precise and reproducible. Until the mid-1990s, MMG was used in the majority of clinical studies involving NMBDs and has been considered the "gold standard" method of assessing evoked responses. Because of the relatively elaborate set up and bulk of the equipment, today MMG is used less frequently in the clinical research setting and almost never clinically.

- EMG also has been used relatively rarely in the clinical setting because of the set up required (5 electrodes) and the expensive equipment that is necessary (Fig. 2). EMG measures the electrical activity (compound muscle action potential) of the stimulated muscle. The EMG response may be calculated by the peak amplitude of the signal (either peak-to-baseline or peak-to-peak amplitude) or by the total area under the EMG curve. The quality of the EMG signal can be affected adversely by a number of variables in the operating room (such as electrocautery), limiting the clinical utility of EMG monitoring, especially when a processed EMG monitor (such as the Datex Relaxograph, Datex Instrumentarium, Finland) was used. However, EMG responses are very consistent over time, and some experts think that the EMG should be considered the gold standard for neuromuscular monitoring because it is not subject to changes in the force of myofibril contractility (i.e., the "staircase effect").[44]
- KMG relies on 2 stimulating electrodes usually placed along the ulnar nerve at the wrist and a piezoelectric polymer sensor that is placed in the groove between the thumb and the index finger; the sensor detects the degree of movement (bending) that is produced by the thumb in response to electrical stimulation of the ulnar nerve (Neuromuscular Transmission Module, E-NMT; GE Healthcare, Helsinki, Finland) (Fig. 3). When the thumb contracts and bends the piezoelectric sensor, the degree of movement is sensed, and it is converted into electrical signals that are proportional to the force of thumb contraction. Much like MMG, KMG can yield signals that can be measured and that can give an indication of the degree of neuromuscular block.[45] Unlike MMG, however, KMG may be less reproducible because it may be affected by the variable positioning of the sensor on the hand, and some experts do not consider this method to be a reliable clinical monitor.[46]
- PMG relies on recording of the sounds that a muscle contraction evokes. A special high-fidelity and narrow-bandwidth microphone is placed alongside the monitored muscle, and the sounds from the isometric muscle contractions can be recorded; the sound intensity is proportional to the force of contraction. Studies have documented a high degree of agreement among PMG, MMG, and KMG for determination of recovery of neuromuscular function in the clinical setting.[41,47] However, this technology is not used clinically, and its future development is uncertain.
- AMG calculates muscle activity using a miniature piezoelectric transducer attached to the stimulated muscle (Fig. 4). Acceleration of the muscle generates a voltage in the piezoelectric crystal that is proportional to the force of contraction (based on Newton's second law, force = mass × acceleration, or $F = m \times A$). AMG monitors are small, portable, and relatively easy to use in the perioperative setting. In contrast, MMG and EMG were developed primarily for research purposes and are no longer commercially available. The most widely available AMG device is the TOF-Watch®

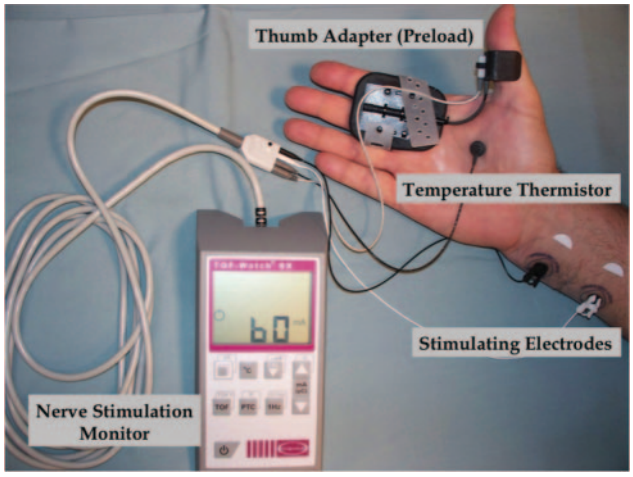

Figure 4. Example of acceleromyograph (AMG). The thumb movement in response to ulnar nerve stimulation is sensed by the piezoelectric sensor that is fixed to the thumb via the thumb adapter, and the acceleration (which is proportional to the force of muscle contraction) is sensed by the interfaced monitor. The current amplitude is displayed by the AMG monitor (60 mA on the screen). To improve the consistency of responses, the piezoelectric sensor is fixed to the thumb, which is placed under slight tension (200–300 g, "preload") by the thumb adapter.

(Schering-Plough Corp., Kenilworth, NJ). It is available in 3 models: (1) TOF-Watch, (2) TOF-Watch S, and (3) TOF-Watch SX (Fig. 4). Only the latter model, which is designed for research, will display a TOF ratio >1.00. The other 2 units (which are used clinically much more widely) use a modified algorithm designed for clinical use.[48] As with MMG, the application of an elastic preload to the thumb during AMG monitoring will increase its precision.[49,50]

Three randomized clinical trials have examined the effect of intraoperative AMG monitoring on the incidence of postoperative residual neuromuscular blockade. In the first investigation, 40 surgical patients received pancuronium and were randomized to receive AMG monitoring or no neuromuscular monitoring (clinical criteria were used to determine dosing and adequacy of reversal).[51] The incidence of residual neuromuscular blockade (defined as a TOF ratio <0.7 measured with MMG) was significantly lower in the AMG group (5.3%) than in the group without monitoring (50%), and the number of patients with clinical signs of muscle weakness after tracheal extubation was reduced by AMG monitoring.[51] Using a similar study design, Gätke et al.[52] examined the effect of AMG monitoring on the incidence of residual paralysis in 120 patients given an intermediate-acting NMBD. Postoperative MMG TOF ratios <0.8 were observed in only 3% of patients in the AMG group, compared with 16.7% of patients receiving no intraoperative monitoring. In the largest investigation, 185 patients were randomized to intraoperative AMG monitoring (AMG group) or qualitative TOF monitoring (TOF group).[53] A lower frequency of residual neuromuscular blockade in the PACU (TOF ratio ≤0.9) was observed in the AMG group (4.5%) compared with the conventional, qualitative (subjective) TOF group (30.0%, $P < 0.0001$). In addition, during transport to the PACU and during the first 30 minutes of PACU admission, fewer AMG-monitored patients developed adverse respiratory events (hypoxemic episodes and upper airway obstruction). Of interest, the total dosing of NMBDs was unaffected by AMG monitoring in any of the 3 studies. However, the time from end of surgery until tracheal extubation was prolonged by 2 to 5 minutes in all of the AMG group patients.

Available evidence suggests that use of AMG monitoring intraoperatively reduces residual neuromuscular blockade, signs of muscle weakness, and adverse respiratory events after tracheal extubation.[51–53] However, there are important limitations to the devices that are currently available commercially: TOF-Watch, TOF-Watch S, TOF-Watch SX, and Infinity Trident NMT SmartPod (Dräger Medical AG & Co., Lübeck, Germany). Control (baseline) TOF ratios obtained before administration of NMBDs usually exceed 1.0 (typically, TOF = 1.15 with a range of 0.95–1.30, compared with an MMG-derived TOF value of 0.98).[54,55] Therefore, results obtained by AMG may differ significantly from those obtained by MMG or EMG. Bias among these methods can be reduced by referring all AMG-derived TOF values to baseline measurements ("normalization").[49,50] If the control TOF ratio is, for instance, 1.20, a TOF ratio of 0.9 in the PACU corresponds to a normalized TOF value of 0.75 (90 divided by 120). If AMG-derived TOF values are approximately 10% higher than MMG values, an AMG TOF measurement of at least 1.0 therefore should be achieved to exclude significant muscle weakness.[56] However, because significant variability in baseline TOF measurements (0.95–1.47) has been reported with AMG,[57] a TOF ratio of 1.0 at the conclusion of an anesthetic does not reliably exclude the possibility of incomplete neuromuscular recovery. Results obtained by AMG (as well as PMG) may also be influenced by an increase in the amplitude (strength) of muscle contraction in response to repetitive stimulation. This phenomenon, known as the "staircase effect," may significantly affect the monitoring of neuromuscular transmission (single twitch but not TOF) at some peripheral muscle groups but may not be present at other muscle groups such as the corrugator supercilii.[44,58] The accuracy of AMG-derived TOF values in awake postoperative patients has also been questioned; paired measurements in the PACU were discordant in 24% of patients.[59] A recent systematic review examined the evidence supporting the use of AMG in clinical practice and research.[49] The authors concluded that AMG could not be used interchangeably with MMG or EMG for construction of dose-response relationships or for pharmacodynamic studies. However, there was strong evidence that AMG improved detection of residual neuromuscular blockade, and that it was more sensitive than clinical tests or subjective evaluation of evoked responses in detecting residual paralysis. Available evidence suggests that AMG can reliably detect a full range of TOF ratios.

Nomenclature of Monitoring Equipment

In addition to the multiple technologies available for monitoring of evoked neuromuscular responses (MMG, AMG, EMG, KMG, and PMG), there is additional inconsistency regarding the nomenclature of the neuromuscular monitoring devices that are used clinically. For instance, "nerve

stimulator," "twitch monitor," "qualitative monitor," and "train-of-four monitor" may be used interchangeably, although they may well describe differing monitoring end points. The "nerve stimulator" is just a device that delivers current to a nerve; such a device should not be termed "monitor," because it does not provide actual monitoring or physiologic data; similarly, the "twitch monitor" is certainly not a monitor, because it also delivers only an electrical current. However, the 2 (nerve stimulator and twitch monitor) are used interchangeably. At best, a nerve stimulator allows clinicians the ability to subjectively assess the presence of evoked responses, and for TOF stimulation, it allows clinicians to determine the degree of neuromuscular block by counting the number of TOF twitches present (TOF count). Such nerve stimulators are notoriously unreliable for discerning the degree of neuromuscular recovery necessary for spontaneous ventilation and tracheal extubation. To assess readiness for tracheal extubation, much more precise medical devices are needed: neuromuscular monitors that provide objective (i.e., measured or quantitative) responses to nerve stimulation. Such monitors use different methods to measure the evoked muscle responses to electrical nerve stimulation (EMG, MMG, AMG, KMG, and PMG—see above).

Routine Reversal of Neuromuscular Blockade

Surveys from Germany and France (and most recently, the United States—Brull SJ, personal communication) suggest that only a minority of clinicians routinely reverse neuromuscular blockade at the end of an anesthetic.[22,60] The reasons for a relaxed view toward the use of anticholinesterases are unclear. It is likely that most clinicians believe that spontaneous recovery of neuromuscular function occurs by the end of the surgery when no NMBDs have been administered within the previous 1 to 4 hours. Available data, however, do not support this belief. Caldwell[61] assessed the degree of neuromuscular blockade for up to 4 hours after a single dose of vecuronium (0.1 mg/kg). The TOF ratio was <0.75 in 4 of 20 patients at 2 hours, 3 of 10 patients at 3 hours, and 1 of 20 patients at 4 hours. A large clinical study (n = 526) examined the incidence of residual paralysis after a single intubating dose of an intermediate-acting NMBD and no reversal.[28] On arrival to the PACU, TOF ratios <0.7 and <0.9 were observed in 16% and 45% of patients, respectively. In the 239 patients tested >2 hours after the administration of the NMBD, TOF ratios <0.7 and <0.9 were noted in 10% and 37% of patients, respectively. Although a high incidence of residual neuromuscular block has been reported when anticholinesterases are omitted, routine administration of reversal drugs, however, does not guarantee complete recovery of neuromuscular function in the PACU. In a study of 150 surgical patients, 60% of patients in whom neuromuscular blockade had not been reversed had TOF ratios <0.8 in the PACU, compared with 49% of those patients who received anticholinesterases (P = not significant).[25] Careful management of anticholinesterase administration may further reduce the risk of incomplete neuromuscular recovery after tracheal extubation.

Based on the above, one could make the argument that routine administration of anticholinesterases should be recommended in all patients who received intraoperative nondepolarizing muscle relaxants, thus diminishing the possibility of residual paralysis. Such practice, if universal, might render the need for neuromuscular monitoring obsolete. In fact, such a practice would be far from ideal. There are several reports of neuromuscular weakness induced by the administration of neostigmine. Payne et al.[62] reported that "neostigmine 2.5 mg IV given 5 minutes after exposure to halothane antagonized nondepolarizing neuromuscular block, whereas a second dose given 2 to 5 minutes later depressed the peak tetanic contraction and reestablished tetanic fade." These investigators further reported that in patients who had received no NMBDs, administration of 2.5 mg neostigmine caused a significant reduction in peak tetanic contraction and the development of severe tetanic fade lasting for 20 minutes. Similar decreases in peak tetanic force and enhancement of tetanic fade were also reported by Goldhill et al.,[63] who administered 2 doses of neostigmine 5 minutes apart once the TOF ratio had recovered to 0.5 and 0.9. The authors concluded that neostigmine, when administered after spontaneous recovery from nondepolarizing block, may adversely affect neuromuscular function, although they also acknowledged that such neostigmine effects "are probably short lived." More recent work from Caldwell[61] and Eikermann et al.[64,65] confirms the effects of neostigmine on neuromuscular function during spontaneous recovery and offers specific mechanisms for the observed decrease in muscle function: impairment of genioglossus and diaphragm muscles, resulting in decreased upper airway volume.[64,65] Although the causal relationship between neostigmine use and postoperative nausea and vomiting is debatable, some investigators have noted that the risk of nausea and emesis is greater with larger doses (>2.5 mg) of neostigmine than with smaller doses (1.5 mg) or placebo.[66] However, omitting NMBD antagonism introduces a significant risk of residual paralysis even with short- and intermediate-acting NMBDs.[66]

The above data point to a single, best practical solution to the current clinical limitations: perioperative monitoring of evoked neuromuscular responses that guides the administration of anticholinesterases and documents return of neuromuscular function should be a standard of care. Only then will the clinician use quantitative criteria that indicate when it is safe to administer additional muscle relaxant; when the minimal degree of spontaneous recovery is present such that pharmacologic reversal with anticholinesterases is possible; when anticholinesterase-aided recovery is sufficient to allow safe tracheal extubation; and when the residual neuromuscular block is significant enough to warrant additional anticholinesterase therapy.

Timely Reversal of Neuromuscular Blockade/ Reversal at a Higher TOF Count

Prompt recovery of satisfactory neuromuscular function may be difficult or impossible to achieve with anticholinesterases when dealing with profound block. Clinicians often underestimate the time required for reversal drugs to fully antagonize the effects of NMBDs. In a study of 120 surgical patients, TOF ratios were assessed immediately before tracheal extubation when clinicians had determined that

full neuromuscular recovery had occurred using qualitative neuromuscular monitoring and clinical criteria.[67] On average, clinicians were ready to perform tracheal extubation 8 minutes after neostigmine was administered; mean TOF ratios at this time were 0.67 ± 0.2. Of significance, 88% of the patients whose tracheas were extubated actually did not fulfill the extubation criteria if we consider TOF ≥0.9 to be the standard. Even if we consider a TOF ≥0.70 as the minimal threshold for extubation, 58% of the patients had failed to achieve this degree of recovery.[67] Pharmacodynamic studies suggest that reversal of intermediate-acting NMBDs may require much longer time intervals. Kim et al.[68] administered neostigmine 0.07 mg/kg to surgical patients at a TOF count of 1, 2, 3, and 4 to determine the time required to achieve an MMG-derived TOF ratio of 0.7, 0.8, and 0.9. The median (range) times from neostigmine administration until a TOF ratio of 0.9 was reached in patients receiving sevoflurane anesthesia were 28.6 (8.8–75.8), 22.6 (8.3–57.4), 15.6 (7.3–43.9), and 9.7 (5.1–26.4) minutes in patients with TOF counts of 1, 2, 3, and 4, respectively. At a TOF count of 4, only 55% of patients achieved a TOF of 0.9 within 10 minutes. The authors recommended a TOF count of 4 for adequate reversal from rocuronium within 15 minutes, because significant variability in neuromuscular recovery was noted among patients.[68] There is 1 additional cogent reason for waiting until the TOF count is 4 before administering neostigmine. If given at a TOF count of 1, all 4 twitches may be palpable 10 minutes later with no detectable fade, even though the TOF ratio is as low as 0.40. This is followed by a prolonged period in which the clinician may erroneously think that reversal has been accomplished satisfactorily, when in fact the patient is still at risk.[69]

Similar findings have been observed in other investigations. Kopman et al.[19] antagonized cisatracurium and rocuronium neuromuscular block at a tactile TOF count of 2. In the rocuronium group, TOF ratios 10 minutes after reversal were 0.76 ± 0.11 (range, 0.47–0.95), and 5 of 30 patients did not reach a TOF ratio ≥0.9 30 minutes after neostigmine was administered. In the cisatracurium group, TOF ratios 10 minutes after reversal averaged 0.72 ± 0.10 (range, 0.38–0.94), and 2 of the 30 patients did not reach a TOF ratio ≥0.9 within 30 minutes of reversal.[19] The same investigators antagonized steady-state infusions of NMBDs at a single twitch depression of 10% of control.[70] Twenty minutes after reversal with neostigmine, EMG TOF ratios of 0.89 ± 0.06 were observed in patients randomized to receive vecuronium. These studies illustrate an important limitation of anticholinesterase drugs: regardless of the TOF count at the time of reversal, it is not always possible to achieve a TOF ratio >0.9 in all patients within 30 minutes of anticholinesterase administration.[19] However, it is generally true that complete recovery of neuromuscular function is more likely when neostigmine is administered early (>15–20 minutes before tracheal extubation) and at a shallower depth of block (TOF count of 4).

Avoidance of Total Twitch Suppression

Reversal of neuromuscular blockade should not be attempted until evidence of spontaneous recovery of neuromuscular function has occurred (i.e., there is at least 1 response to TOF stimulation). Anticholinesterases inhibit the enzyme that breaks down acetylcholine (ACh), allowing ACh to accumulate at the neuromuscular junction and compete with the NMBD from the nicotinic receptor recognition sites (the α subunits). The degree of ACh increase at the neuromuscular junction is, however, limited; once the cholinesterases are inhibited maximally, no further increase in ACh at the neuromuscular junction is possible. If the concentration of the NMBD at the neuromuscular junction is high, the increase in ACh levels as a result of cholinesterase inhibition will be insufficient, and thus anticholinesterases will be ineffective in competing with the NMBD for receptors. This mechanism explains why recovery times are prolonged when neostigmine is administered during intense neuromuscular blockade. At a posttetanic count of 1 to 2 during a rocuronium neuromuscular block, the geometric mean time between neostigmine administration and recovery to an AMG TOF ratio of 0.9 was >50 minutes.[71] The risk of intense neuromuscular block at the end of the surgical procedure is thus increased if a TOF count of 0 is maintained intraoperatively. Fortunately, assuming sufficient anesthetic depth, surgical relaxation adequate for abdominal surgery is usually present at a TOF count of 2 to 3.[72] New reversal drugs and rapidly degrading, short-acting NMBDs currently in clinical trials may in future allow clinicians to effectively antagonize deeper levels of neuromuscular blockade.

THE FUTURE: NEW DRUGS

Prevention of postoperative residual weakness and its associated complications need not involve only adequate perioperative quantitative monitoring, early reversal from shallow block, and avoidance of total twitch suppression and long-acting NMBDs. What is most likely needed is the introduction into clinical practice of NMBDs whose reversal of neuromuscular blocking activity is not dependent on acetylcholinesterase inhibition; some of these drugs (gantacurium, CW002) are currently in initial phase 1 and 2 testing,[73–77] whereas the clinical development and viability of other compounds (SZ1677, cucurbituril) is more uncertain.[78–81] The other potentially successful pharmacologic approach to eliminate residual neuromuscular block is the use of selective relaxant binding drugs such as sugammadex[82–84] or amino acids (e.g., cysteine) that facilitate the rapid conversion of chlorofumarate muscle relaxants (gantacurium) into inactive derivatives.[85–87] Unfortunately, none of these compounds are currently available clinically in the United States.

Sugammadex, a modified γ-cyclodextrin, is the first selective relaxant binding drug. Sugammadex forms very tight complexes in a 1:1 ratio with steroidal NMBDs (rocuronium > vecuronium ≫ pancuronium). This guest-host complex, which exists in equilibrium, is stable because of its very high association rate and very low dissociation rate. Sugammadex has no effect on acetylcholinesterases or on any receptor system in the body, eliminating the need for anticholinergic drugs. Phase 1 to 3 trials found that sugammadex can antagonize any level of neuromuscular blockade, including the profound blockade induced by rocuronium, adding flexibility to the use of nondepolarizing relaxants. Sugammadex, however, has no affinity for

isoquinolinium drugs (atracurium, cisatracurium) or for succinylcholine, so it will not antagonize the block induced by these drugs.[82] Although not yet available in the United States, sugammadex is available for clinical use in the European Union (marketed as Bridion®, Schering-Plough, Kenilworth, NJ). It is recommended for use in doses of 2, 4, and 16 mg/kg, depending on the clinical situation and the degree of spontaneous recovery at the time of administration. At doses of 2 mg/kg, sugammadex will reverse a shallow block (defined as spontaneous recovery to reappearance of the second TOF twitch); at 4 mg/kg dose, sugammadex will reverse a deep block (defined as spontaneous recovery to 1–2 posttetanic twitches); and at 16 mg/kg, sugammadex can be used for "rescue" in a failed rapid-sequence induction and intubation scenario in which very large doses of rocuronium ($4 \times ED_{95}$) were administered.[83] In all these clinical scenarios, initial publications report reversal of neuromuscular block to a TOF >0.90 in <3 to 5 minutes.[84] Sugammadex rapidly clears from most organs, except in renal failure; metabolism is at most very limited, and the drug is eliminated in the urine unchanged. Sugammadex has no effect on QT interval even in patients with severe heart disease. Although patients with pulmonary disease (asthma, bronchitis, and chronic obstructive disease) tolerated sugammadex administration without any side effects, the Food and Drug Administration did not approve its application in 2008, citing the need for more clinical information about its allergic potential.

CONCLUSIONS

Careful neuromuscular management may reduce the risk of postoperative residual weakness and its associated complications. Available data suggest that adherence to evidence-based practices related to NMBD dosing, monitoring, and reversal may improve patient outcomes during the early recovery period from anesthesia and surgery.

Based on the evidence presented, it seems reasonable to offer the following suggestions regarding the perioperative care of the surgical patient:

1. General Principles for Avoidance of Residual Paralysis
   - NMBDs should only be administered to patients who require this therapy. Dosing should be individualized based on surgical necessity, patient factors, and presence of coexisting disease.
   - Long-acting NMBDs (e.g., pancuronium) should be avoided. Intermediate-acting NMBDs should be used whenever feasible.
   - Clinical tests of muscle function (head lift, jaw clenching, grip strength, tidal volume, etc.) are unreliable predictors of recovery of neuromuscular function.
   - To exclude with certainty the possibility of residual paralysis in patients at risk, clinicians should use objective (quantitative) neuromuscular monitoring tests.
   - Ideally, neuromuscular function should be monitored objectively (quantitatively) in all patients receiving NMBDs.
2. Principles of Monitoring in Clinical Practice
   - Objective (quantitative) monitoring of neuromuscular function should be used.
   - Peripheral nerve stimulator units should display the delivered current output, which should be at least 30 mA.
   - Assessment of neuromuscular responses should take into consideration the musculature group that is monitored. The time course (onset, recovery) of muscle relaxants is different at peripheral muscles (adductor pollicis) than at central muscles (orbicularis oculi, corrugator supercilii).
   - Adequate spontaneous recovery (TOF count of 4) should be established before pharmacologic antagonism of NMBD block with anticholinesterases. This requirement does not apply to reversal with sugammadex.
   - Tactile evaluation of TOF and DBS fade reduces (but does not eliminate) the incidence and degree of postoperative residual paralysis compared with the use of clinical criteria to assess readiness for tracheal extubation.[26,88,89]
   - The timing of tracheal extubation should be guided by quantitative monitoring tests such as TOF >0.9 or $DBS_{3,3}$ >0.9.
3. Principles for Pharmacologic Reversal with Anticholinesterases
   - During anesthetic techniques that do not enhance the effects of muscle relaxants (such as total IV anesthesia), a minimal TOF count of 2 should be present before administration of anticholinesterases.[90]
   - During anesthetic techniques that enhance the effects of muscle relaxants (such as inhaled volatile anesthesia), a TOF count of 4 should be present before administration of anticholinesterases.[19,90]
   - If recovery to TOF >0.90 is documented by MMG (quantitatively), neostigmine administration should be withheld. Administration of neostigmine to fully recovered patients may decrease upper airway muscle activity and tidal volume.[64]
4. Reversal Considerations in Clinical Practice
   A. No neuromuscular monitor or peripheral nerve stimulator used.
      i. Clinical tests of adequacy of reversal are unreliable—pharmacologic reversal should be administered routinely and only when spontaneous muscle activity is present.
   B. Peripheral nerve stimulator—subjective (visual, tactile) assessment
      i. TOF count 1 or no TOF response—delay reversal.
      ii. TOF count 2 or 3—administer pharmacologic reversal.
      iii. TOF with fade (TOF <0.40)—administer pharmacologic reversal.
      iv. TOF with no perceived fade (TOF ≥0.40)—administer pharmacologic reversal, consider low dose (20 μg/kg) of neostigmine.[91]
   C. Quantitative evoked response monitor (e.g., AMG, KMG, and EMG)
      i. No TOF response or TOF count of 1—delay reversal.
      ii. TOF count 2 or 3—administer pharmacologic reversal.

iii. TOF <0.40—administer pharmacologic reversal.
iv. TOF = 0.40 to 0.90—administer pharmacologic reversal, consider low dose (20 μg/kg) of neostigmine.
v. TOF >0.90—no reversal recommended.

The development of several novel NMBDs and reversal drugs represents exciting new progress in the field of neuromuscular pharmacology, and use of these drugs may significantly alter intraoperative neuromuscular management and reduce the incidence of postoperative residual paralysis and its associated morbidity.

RECUSE NOTE

Sorin J. Brull is the Section Editor of Patient Safety for the Journal. The manuscript was handled by Tony Gin, Section Editor of Anesthetic Clinical Pharmacology, and Dr. Brull was not involved in any way with the editorial process or decision.

REFERENCES

1. Brull SJ. Indicators of recovery of neuromuscular function: time for change? Anesthesiology 1997;86:755–7
2. Murphy GS. Residual neuromuscular blockade: incidence, assessment, and relevance in the postoperative period. Minerva Anestesiol 2006;72:97–109
3. Eriksson LI. Evidence-based practice and neuromuscular monitoring: it's time for routine quantitative assessment. Anesthesiology 2003;98:1037–9
4. Viby-Mogensen J. Postoperative residual curarization and evidence-based anaesthesia. Br J Anaesth 2000;84:301–3
5. Pedersen T, Viby-Mogensen J, Bang U, Olsen NV, Jensen E, Engboek J. Does perioperative tactile evaluation of the train-of-four response influence the frequency of postoperative residual neuromuscular blockade? Anesthesiology 1990;73:835–9
6. Bevan DR, Smith CE, Donati F. Postoperative neuromuscular blockade: a comparison between atracurium, vecuronium, and pancuronium. Anesthesiology 1988;69:272–6
7. Howardy-Hansen P, Rasmussen JA, Jensen BN. Residual curarization in the recovery room: atracurium versus gallamine. Acta Anaesthesiol Scand 1989;33:167–9
8. Brull SJ, Ehrenwerth J, Connelly NR, Silverman DG. Assessment of residual curarization using low-current stimulation. Can J Anaesth 1991;38:164–8
9. Kopman AF, Ng J, Zank LM, Neuman GG, Yee PS. Residual postoperative paralysis. Pancuronium versus mivacurium, does it matter? Anesthesiology 1996;85:1253–9
10. Berg H, Roed J, Viby-Mogensen J, Mortensen CR, Engbaek J, Skovgaard LT, Krintel JJ. Residual neuromuscular block is a risk factor for postoperative pulmonary complications. A prospective, randomized, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium. Acta Anaesthesiol Scand 1997;41:1095–103
11. McEwin L, Merrick PM, Bevan DR. Residual neuromuscular blockade after cardiac surgery: pancuronium vs rocuronium. Can J Anaesth 1997;44:891–5
12. Bissinger U, Schimek F, Lenz G. Postoperative residual paralysis and respiratory status: a comparative study of pancuronium and vecuronium. Physiol Res 2000;49:455–62
13. Murphy GS, Szokol JW, Marymont JH, Vender JS, Avram MJ, Rosengart TK, Alwawi EA. Recovery of neuromuscular function after cardiac surgery: pancuronium versus rocuronium. Anesth Analg 2003;96:1301–7
14. Murphy GS, Szokol JW, Franklin M, Marymont JH, Avram MJ, Vender JS. Postanesthesia care unit recovery times and neuromuscular blocking drugs: a prospective study of orthopedic surgical patients randomized to receive pancuronium or rocuronium. Anesth Analg 2004;98:193–200
15. Naguib M, Kopman AF, Ensor JE. Neuromuscular monitoring and postoperative residual curarisation: a meta-analysis. Br J Anaesth 2007;98:302–16
16. Ballantyne JC, Chang Y. The impact of choice of muscle relaxant on postoperative recovery time: a retrospective study. Anesth Analg 1997;85:476–82
17. Thomas R, Smith D, Strike P. Prospective randomised double-blind comparative study of rocuronium and pancuronium in adult patients scheduled for elective 'fast-track' cardiac surgery involving hypothermic cardiopulmonary bypass. Anaesthesia 2003;58:265–71
18. Murphy GS, Szokol JW, Marymont JH, Avram MJ, Vender JS, Rosengart TK. The impact of shorter-acting neuromuscular blocking agents on fast-track recovery of the cardiac surgical patient. Anesthesiology 2002;96:600–6
19. Kopman AF, Zank LM, Ng J, Neuman GG. Antagonism of cisatracurium and rocuronium block at a tactile train-of-four count of 2: should quantitative assessment of neuromuscular function be mandatory? Anesth Analg 2004;98:102–6
20. Grayling M, Sweeney BP. Recovery from neuromuscular blockade: a survey of practice. Anaesthesia 2007;62:806–9
21. Sorgenfrei IF, Viby-Mogensen J, Swiatek FA. Does evidence lead to a change in clinical practice? Danish anaesthetists' and nurse anesthetists' clinical practice and knowledge of postoperative residual curarization. Ugeskr Laeger 2005;167:3878–82
22. Osmer C, Vogele C, Zickmann B, Hempelmann G. Comparative use of muscle relaxants and their reversal in three European countries: a survey in France, Germany and Great Britain. Eur J Anaesthesiol 1996;13:389–99
23. Eikermann M, Groeben H, Husing J, Peters J. Accelerometry of adductor pollicis muscle predicts recovery of respiratory function from neuromuscular blockade. Anesthesiology 2003;98:1333–7
24. Cammu G, De Witte J, De Veylder J, Byttebier G, Vandeput D, Foubert L, Vandenbroucke G, Deloof T. Postoperative residual paralysis in outpatients versus inpatients. Anesth Analg 2006;102:426–9
25. Hayes AH, Mirakhur RK, Breslin DS, Reid JE, McCourt KC. Postoperative residual block after intermediate-acting neuromuscular blocking drugs. Anaesthesia 2001;56:312–8
26. Fruergaard K, Viby-Mogensen J, Berg H, El-Mahdy AM. Tactile evaluation of the response to double burst stimulation decreases, but does not eliminate, the problem of postoperative residual paralysis. Acta Anaesthesiol Scand 1998;42:1168–74
27. Kopman AF, Yee PS, Neuman GG. Relationship of the train-of-four fade ratio to clinical signs and symptoms of residual paralysis in awake volunteers. Anesthesiology 1997;86:765–71
28. Debaene B, Plaud B, Dilly MP, Donati F. Residual paralysis in the PACU after a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action. Anesthesiology 2003;98:1042–8
29. Viby-Mogensen J, Jensen NH, Engbaek J, Ording H, Skovgaard LT, Chraemmer-Jorgensen B. Tactile and visual evaluation of the response to train-of-four nerve stimulation. Anesthesiology 1985;63:440–3
30. Brull SJ, Silverman DG. Visual and tactile assessment of neuromuscular fade. Anesth Analg 1993;77:352–5
31. Tammisto T, Wirtavuori K, Linko K. Assessment of neuromuscular block: comparison of three clinical methods and evoked electromyography. Eur J Anaesthesiol 1988;5:1–8
32. Capron F, Fortier LP, Racine S, Donati F. Tactile fade detection with hand or wrist stimulation using train-of-four, double-burst stimulation, 50-hertz tetanus, 100-hertz tetanus, and acceleromyography. Anesth Analg 2006;102:1578–84
33. Drenck NE, Ueda N, Olsen NV, Engbaek J, Jensen E, Skovgaard LT, Viby-Mogensen J. Manual evaluation of residual curarization using double burst stimulation: a comparison with train-of-four. Anesthesiology 1989;70:578–81
34. Brull SJ, Silverman DG. Visual assessment of train-of-four and double burst-induced fade at submaximal stimulating currents. Anesth Analg 1991;73:627–32
35. Dupuis JY, Martin R, Tessonnier JM, Tetrault JP. Clinical assessment of the muscular response to tetanic nerve stimulation. Can J Anaesth 1990;37:397–400

36. Baurain MJ, Hennart DA, Godschalx A, Huybrechts I, Nasrallah G, d'Hollander AA, Cantraine F. Visual evaluation of residual curarization in anesthetized patients using one hundred-hertz, five-second tetanic stimulation at the adductor pollicis muscle. Anesth Analg 1998;87:185–9
37. Samet A, Capron F, Alla F, Meistelman C, Fuchs-Buder T. Single acceleromyographic train-of-four, 100-Hertz tetanus or double-burst stimulation: which test performs better to detect residual paralysis? Anesthesiology 2005;102:51–6
38. Stanec A, Heyduk J, Stanec G, Orkin LR. Tetanic fade and post-tetanic tension in the absence of neuromuscular blocking agents in anesthetized man. Anesth Analg 1978;57:102–7
39. Merton PA. Voluntary strength and fatigue. J Physiol 1954;123:553–64
40. Shorten GD, Merk H, Sieber T. Perioperative train-of-four monitoring and residual curarization. Can J Anaesth 1995;42:711–5
41. Trager G, Michaud G, Deschamps S, Hemmerling TM. Comparison of phonomyography, kinemyography and mechanomyography for neuromuscular monitoring. Can J Anaesth 2006;53:130–5
42. Petitjean M, Ripart J, Couture J, Bellemare F. Diaphragmatic fatigue investigated by phonomyography. Am J Respir Crit Care Med 1997;155:1162–6
43. Hemmerling TM, Donati F, Beaulieu P, Babin D. Phonomyography of the corrugator supercilii muscle: signal characteristics, best recording site and comparison with acceleromyography. Br J Anaesth 2002;88:389–93
44. Kopman AF, Kumar S, Klewicka MM, Neuman GG. The staircase phenomenon: implications for monitoring of neuromuscular transmission. Anesthesiology 2001;95:403–7
45. Motamed C, Kirov K, Combes X, Duvaldestin P. Comparison between the Datex-Ohmeda M-NMT module and a force-displacement transducer for monitoring neuromuscular blockade. Eur J Anaesthesiol 2003;20:467–9
46. Hemmerling TM, Donati F. The M-NMT mechanosensor cannot be considered as a reliable clinical neuromuscular monitor in daily anesthesia practice. Anesth Analg 2002;95:1826–7
47. Hemmerling TM, Michaud G, Trager G, Deschamps S, Babin D, Donati F. Phonomyography and mechanomyography can be used interchangeably to measure neuromuscular block at the adductor pollicis muscle. Anesth Analg 2004;98:377–81
48. Kopman AF, Kopman DJ. An analysis of the TOF-watch algorithm for modifying the displayed train-of-four ratio. Acta Anaesthesiol Scand 2006;50:1313–4
49. Claudius C, Viby-Mogensen J. Acceleromyography for use in scientific and clinical practice: a systematic review of the evidence. Anesthesiology 2008;108:1117–40
50. Claudius C, Skovgaard LT, Viby-Mogensen J. Is the performance of acceleromyography improved with preload and normalization? A comparison with mechanomyography. Anesthesiology 2009;110:1261–70
51. Mortensen CR, Berg H, el-Mahdy A, Viby-Mogensen J. Perioperative monitoring of neuromuscular transmission using acceleromyography prevents residual neuromuscular block following pancuronium. Acta Anaesthesiol Scand 1995;39:797–801
52. Gätke MR, Viby-Mogensen J, Rosenstock C, Jensen FS, Skovgaard LT. Postoperative muscle paralysis after rocuronium: less residual block when acceleromyography is used. Acta Anaesthesiol Scand 2002;46:207–13
53. Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS, Nisman M. Intraoperative acceleromyographic monitoring reduces the risk of residual neuromuscular blockade and adverse respiratory events in the postanesthesia care unit. Anesthesiology 2008;109:389–98
54. Kopman AF, Klewicka MM, Neuman GG. The relationship between acceleromyographic train-of-four fade and single twitch depression. Anesthesiology 2002;96:583–7
55. Viby-Mogensen J, Jensen E, Werner M, Nielsen HK. Measurement of acceleration: a new method of monitoring neuromuscular function. Acta Anaesthesiol Scand 1988;32:45–8
56. Capron F, Alla F, Hottier C, Meistelman C, Fuchs-Buder T. Can acceleromyography detect low levels of residual paralysis? A probability approach to detect a mechanomyographic train-of-four ratio of 0.9. Anesthesiology 2004;100:1119–24
57. Suzuki T, Fukano N, Kitajima O, Saeki S, Ogawa S. Normalization of acceleromyographic train-of-four ratio by baseline value for detecting residual neuromuscular block. Br J Anaesth 2006;96:44–7
58. Deschamps S, Trager G, Mathieu PA, Hemmerling TM. The staircase phenomenon at the corrugator supercilii muscle in comparison with the hand muscles. Br J Anaesth 2005;95:372–6
59. Baillard C, Bourdiau S, Le Toumelin P, Ait Kaci F, Riou B, Cupa M, Samama CM. Assessing residual neuromuscular blockade using acceleromyography can be deceptive in postoperative awake patients. Anesth Analg 2004;98:854–7
60. Fuchs-Buder T, Hofmockel R, Geldner G, Diefenbach C, Ulm K, Blobner M. The use of neuromuscular monitoring in Germany. Anaesthesist 2003;52:522–6
61. Caldwell JE. Reversal of residual neuromuscular block with neostigmine at one to four hours after a single intubating dose of vecuronium. Anesth Analg 1995;80:1168–74
62. Payne JP, Hughes R, Al Azawi S. Neuromuscular blockade by neostigmine in anaesthetized man. Br J Anaesth 1980;52:69–76
63. Goldhill DR, Wainwright AP, Stuart CS, Flynn PJ. Neostigmine after spontaneous recovery from neuromuscular blockade. Effect on depth of blockade monitored with train-of-four and tetanic stimuli. Anaesthesia 1989;44:293–9
64. Eikermann M, Zaremba S, Malhotra A, Jordan AS, Rosow C, Chamberlin NL. Neostigmine but not sugammadex impairs upper airway dilator muscle activity and breathing. Br J Anaesth 2008;101:344–9
65. Eikermann M, Fassbender P, Malhotra A, Takahashi M, Kubo S, Jordan AS, Gautam S, White DP, Chamberlin NL. Unwarranted administration of acetylcholinesterase inhibitors can impair genioglossus and diaphragm muscle function. Anesthesiology 2007;107:621–9
66. Tramer MR, Fuchs-Buder T. Omitting antagonism of neuromuscular block: effect on postoperative nausea and vomiting and risk of residual paralysis. A systematic review. Br J Anaesth 1999;82:379–86
67. Murphy GS, Szokol JW, Marymont JH, Franklin M, Avram MJ, Vender JS. Residual paralysis at the time of tracheal extubation. Anesth Analg 2005;100:1840–5
68. Kim KS, Cheong MA, Lee HJ, Lee JM. Tactile assessment for the reversibility of rocuronium-induced neuromuscular blockade during propofol or sevoflurane anesthesia. Anesth Analg 2004;99:1080–5
69. Kopman AF, Kopman DJ, Ng J, Zank LM. Antagonism of profound cisatracurium and rocuronium block: the role of objective assessment of neuromuscular function. J Clin Anesth 2005;17:30–5
70. Kopman AF. Recovery times following edrophonium and neostigmine reversal of pancuronium, atracurium, and vecuronium steady-state infusions. Anesthesiology 1986;65:572–8
71. Jones RK, Caldwell JE, Brull SJ, Soto RG. Reversal of profound rocuronium-induced blockade with sugammadex: a randomized comparison with neostigmine. Anesthesiology 2008;109:816–24
72. Ali HH, Savarese JJ. Monitoring of neuromuscular function. Anesthesiology 1976;45:216–49
73. Savarese JJ, Belmont MR, Hashim MA, Mook RA Jr, Boros EE, Samano V, Patel SS, Feldman PL, Schultz JA, McNulty M, Spitzer T, Cohn DL, Morgan P, Wastila WB. Preclinical pharmacology of GW280430A (AV430A) in the rhesus monkey and in the cat: a comparison with mivacurium. Anesthesiology 2004;100:835–45
74. Boros EE, Samano V, Ray JA, Thompson JB, Jung DK, Kaldor I, Koble CS, Martin MT, Styles VL, Mook RA Jr, Feldman PL, Savarese JJ, Belmont MR, Bigham EC, Boswell GE, Hashim MA, Patel SS, Wisowaty JC, Bowers GD, Moseley CL, Walsh JS, Reese MJ, Rutkowske RD, Sefler AM, Spitzer TD. Neuromuscular blocking activity and therapeutic potential of mixed-tetrahydroisoquinolinium halofumarates and halosuccinates in rhesus monkeys. J Med Chem 2003;46:2502–15

75. Lien CA, Savard P, Belmont M, Sunaga H, Savarese JJ. Fumarates: unique nondepolarizing neuromuscular blocking agents that are antagonized by cysteine. J Crit Care 2009;24:50–7
76. Savarese JJ, Belmont MR, Savard PR, Sunaga H, Van Ornum S. The dose-response for immediate reversal of AV002 by cysteine in the Rhesus monkey [abstract]. Anesthesiology 2008;109:A1403
77. Sunaga H, Malhotra JK, Savarese JJ, Heerdt PM. Dose response relationship for cysteine reversal of the novel muscle relaxant AV002 in dogs [abstract]. Anesthesiology 2007;107:A983
78. Blazewicz A, Fijalek Z, Warowna-Grzeskiewicz M, Banasiuk J. Application of high-performance liquid chromatography with amperometric and coulometric detection to the analysis of SZ1677, a new neuromuscular blocking agent, and its two derivatives. J Chromatogr 2008;1204:114–8
79. Michalek-Sauberer A, Nicolakis EM, Vizi ES, Gilly H. Effects of SZ1677, a new non-depolarizing steroidal neuromuscular blocking drug, and rocuronium on two laryngeal muscles and the anterior tibial muscle in guinea pigs. Acta Anaesthesiol Scand 2006;50:481–7
80. Kim K, Selvapalam N, Ko YH, Park KM, Kim D, Kim J. Functionalized cucurbiturils and their applications. Chem Soc Rev 2007;36:267–79
81. Lagona J, Mukhodpadhyay P, Chakrabarti S, Isaacs L. The cucurbit[n]uril family. Angew Chem Int Ed Engl 2005;44:4844–70
82. de Boer HD, van Egmond J, von de Pol F, Bom A, Booij LH. Sugammadex, a new reversal agent for neuromuscular block induced by rocuronium in the anaesthetized Rhesus monkey. Br J Anaesth 2006;96:473–9
83. Cammu G, De Kam PJ, Demeyer I, Decoopman M, Peeters PA, Smeets JM, Foubert L. Safety and tolerability of single intravenous doses of sugammadex administered simultaneously with rocuronium or vecuronium in healthy volunteers. Br J Anaesth 2008;100:373–9
84. Naguib M, Brull SJ. Sugammadex: a novel selective relaxant binding agent. Expert Rev Clin Pharmacol 2009;2:37–53
85. Savarese JJ, Belmont MR, Sched B, Vanrnum S. SAR of reversal of isoquinolinium fumarate and succinate diester NMBA's by cysteine/glutathione [abstract]. Anesthesiology 2007;107:A985
86. Olney JW, Ho OL. Brain damage in infant mice following oral intake of glutamate, aspartate or cysteine. Nature 1970;227:609–11
87. Janáky R, Varga V, Hermann A, Saransaari P, Oja SS. Mechanisms of L-cysteine neurotoxicity. Neurochem Res 2000;25:1397–405
88. Shorten GD, Merk H, Sieber T. Perioperative train-of-four monitoring and residual curarization. Can J Anaesth 1995;42:711–5
89. Ueda N, Muteki T, Tsuda H, Inoue S, Nishina H. Is the diagnosis of significant residual neuromuscular blockade improved by using double-burst nerve stimulation? Eur J Anaesth 1991;8:213–8
90. Kim KS, Cheong MA, Lee HJ, Lee JM. Tactile assessment for the reversibility of rocuronium-induced neuromuscular blockade during propofol or sevoflurane anesthesia. Anesth Analg 2004;99:1080–5
91. Fuchs-Buder T, Meistelman C, Junke E, Longrois D, Donati F. Dose requirements of neostigmine to antagonize low levels of atracurium-induced residual paralysis [abstract]. Anesthesiology 2008;109:A1402