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

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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

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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.

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