

Neuromuscular Monitoring

More than Meets the Eye

PERSISTING neuromuscular blockade after anesthesia, commonly referred to as residual paralysis, is a well-recognized entity, but anesthesiologists do not always apply sound principles into clinical practice. This issue of ANESTHESIOLOGY contains yet another report describing an unacceptably high incidence of measured train-of-four (TOF) ratio less than 0.9 (42%) in the postanesthesia recovery unit (PACU), in spite of widespread use of neuromuscular monitoring.¹ This situation occurred because the well-known differences in the responses of muscles at different monitoring sites were ignored or misinterpreted.

A smooth and rapid recovery depends on full return of neuromuscular function in muscles that ensure adequate breathing. The diaphragm recovers earlier than the adductor pollicis after a neuromuscular blocking agent,² but return of diaphragmatic strength does not imply that the respiratory system as a whole functions normally. Upper airway muscles contract in synchrony with the diaphragm to ensure airway patency.³ They also play a role after anesthesia to clear secretions and regurgitated stomach content. These upper airway muscles are particularly sensitive to neuromuscular blocking agents. Mean geniohyoid and adductor pollicis recovery times are similar, and in some patients, the geniohyoid muscle takes longer to recover.⁴ The masseter is at least as sensitive as the adductor pollicis to neuromuscular blocking agents.⁵ Upper esophageal tone decreases and incidence of aspiration increases when the TOF ratio at the adductor pollicis is less than 0.9.⁶ Upper airway obstruction is a common finding in patients with residual neuromuscular blockade.⁷ The risk of significant neuromuscular weakness in upper airway muscles is greater when the TOF ratio at the adductor pollicis muscle



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is less than 0.9, so the adductor pollicis muscle response following ulnar nerve stimulation can be used as a guide for recovery. However, this association has been validated for the adductor pollicis only, not for other popular monitoring sites such as the muscles around the eye, which contract in response to facial nerve stimulation. The study by Thilen *et al.*¹ illustrates this point very well.

There has been some confusion in the literature regarding the name of the muscle that moves the eyebrow in response to facial nerve stimulation. Earlier studies erroneously attributed the response to the orbicularis oculi.² But movement of the eyebrow is because of the corrugator supercilii, which is solicited when frowning.⁸ Irrespective of the name of the muscle that contracts in response to facial nerve stimulation, the results of eyebrow twitching studies are clear: muscles around the eye recover early, much like the diaphragm, and earlier than upper airway muscles or the adductor pollicis.^{2,8} It follows that facial nerve stimulation should not be used to guide reversal and recovery.

Dose and timing recommendations for reversal are based on recovery at the adductor pollicis. When the recognized target for neuromuscular recovery was a TOF ratio of 0.7, it was suggested to administer neostigmine when at least two twitches were visible. With the new TOF threshold of 0.9, it is advisable to wait until four twitches are present, whether there is detectable fade or not.⁹ However, these recommendations apply only to the adductor pollicis. It is expected that when four twitches are seen at the corrugator supercilii, the adductor pollicis twitch count might be less, and there could be no twitch at all. Thus, if the timing of neostigmine administration is based on facial nerve monitoring, and even if four eyebrow responses are detected, the risk of residual paralysis is expected to be high. This is exactly what Thilen

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◆ This Editorial View accompanies the following article: Thilen SR, Hansen BE, Ramaiah R, Kent CD, Treggiari MM, Bhananker SM: Intraoperative neuromuscular monitoring site and residual paralysis. ANESTHESIOLOGY 2012; 117:964-72.

*et al.*¹ found in this issue of ANESTHESIOLOGY. They measured adductor pollicis TOF ratio by acceleromyography in the PACU in patients who had their intraoperative neuromuscular monitoring performed at the thumb or the eye, according to the preference of the anesthesiologist. A TOF ratio less than 0.9 in the PACU was more frequent in patients monitored at the eye in the operating room (52%) than in patients monitored at the thumb (22%), in spite of a comparable number of twitches seen in both groups: four twitches were seen in most patients, whether monitoring site was the eye (86%) or the thumb (88%). Interestingly, the eye was chosen as the monitoring site in two thirds of cases, suggesting that the known differences between monitoring sites were not appreciated by most anesthesiologists. The message here is clear: monitoring to guide reversal and recovery should be performed at the adductor pollicis muscle.

Still, the study by Thilen *et al.* raises a few questions. Why, for example, did as many as 22% of patients monitored at the wrist have a TOF ratio less than 0.9 when reasonable doses of neostigmine were usually given, four twitches were seen in most patients, and assessment in the PACU was carried out after neostigmine had time to be effective (20 min)? The patients who had inadequate recovery may have received neostigmine when fewer than four twitches were visible, or were evaluated a short time after neostigmine, or did not receive any neostigmine. But another factor might play a role: there are subtle sensitivity differences between the different intrinsic muscles of the hand. The muscles of the hypothenar eminence, which move the little finger, recover earlier than the adductor pollicis.¹⁰ In practice, it is not uncommon to observe four twitches at the little finger when there is only one or none at all at the thumb. Thus, it is possible that in some instances, recovery at the little finger was interpreted as “four twitches present,” although fewer were in fact present at the adductor pollicis. It is suggested to either feel the movement of the thumb to assess readiness for reversal or stimulate over the adductor pollicis muscle.¹¹

The ultimate objective is to avoid the complications of residual paralysis, and evidence suggests that the risk of adverse events,⁷ subjective feeling of weakness,¹² and length of stay in the PACU¹³ increase markedly when TOF ratio at the adductor pollicis is less than 0.9. This does not mean that there is a cliff at an adductor pollicis TOF ratio of 0.9. Some patients do well in spite of a TOF ratio less than 0.9, whereas others might have difficulties in spite of a TOF ratio greater than 0.9. In Thilen *et al.*'s¹ study, two patients with a TOF ratio of zero felt weak, but did not need active treatment. However, in terms of risk management, the incidence and severity of residual paralysis increase as the TOF ratio decreases. For example, Murphy *et al.*⁷ studied patients in whom respiratory difficulties were detected in the PACU, and compared them with a control group without such events. Mean TOF ratio was 0.62 in the subjects with respiratory complications, and only 9.5% had a TOF ratio of more than 0.9. In contrast, mean TOF ratio was 0.98 in the control

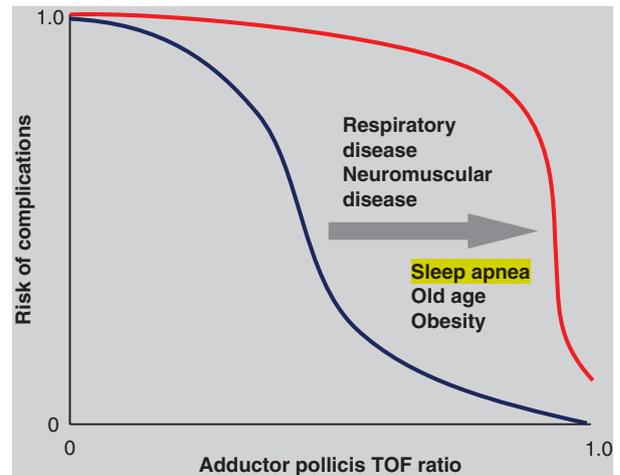


Fig. 1. Likely relationship between risk of respiratory complications and train-of-four (TOF) ratio at the adductor pollicis. The exact shape and position of the curve for normal patients (blue) depend on the definition of “complication,” and are not known for certain. Some conditions are likely to shift (arrow) the curve to the right (red), as might occur with the examples given. There are no hard data on the specific conditions and the extent of the shift.

group, and 90.5% of patients had a TOF ratio of more than 0.9. From these and other data, a mental model for the risk of complications from residual paralysis can be derived (fig. 1). The actual shape of the curve certainly depends on the definition of complications and type of patient. Because the weak link in neuromuscular recovery is the upper airway, it is likely that the curve is pushed to the right, meaning increased risk, in patients with conditions where either respiratory function as a whole and/or airway patency are compromised. Although in most patients most of the upper airway muscles have a similar recovery profile as the adductor pollicis, recovery of some muscles in some individuals might be delayed, with subsequent risk for impaired airway integrity even after recovery to an adductor pollicis TOF of close to 1.0. There is no direct evidence to help identify which individuals may be susceptible to delayed upper airway recovery, but it would appear prudent to pay special attention to patients at risk.

The clinical study performed by Thilen *et al.*¹ confirms what other studies indicated: ulnar nerve-adductor pollicis rather than facial nerve-corrugator supercillii monitoring should be used as a guide to timing of reversal or adequacy of recovery. The presence of four twitches at the adductor pollicis or the thumb following ulnar nerve stimulation should be ascertained before administration of neostigmine. Movement of the thumb should be seen or felt, disregarding movement of other fingers. The same principles apply when using sugammadex, because the proper dose depends on recovery at the thumb, not at the eye. When considering neuromuscular recovery, the corrugator supercillii behaves like the diaphragm, but it takes more than the diaphragm to breathe adequately; upper airway muscles, which follow

approximately the same recovery profile as the adductor pollicis, are important respiratory muscles. In practice, reversal and recovery should be guided by adductor pollicis response, and if needed, a switch from facial to ulnar nerve stimulation should be accomplished at the end of the surgical procedure. There is more than meets the eye; a hand is needed.

François Donati Ph.D., M.D., Department of Anesthesiology, Hôpital Maisonneuve-Rosemont and Université de Montréal, Montréal, Québec, Canada. francois.donati@umontreal.ca

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Intraoperative Neuromuscular Monitoring Site and Residual Paralysis

Stephan R. Thilen, M.D., M.S.,* Bradley E. Hansen, B.S.,† Ramesh Ramaiah, M.D.,‡
Christopher D. Kent, M.D.,‡ Miriam M. Treggiari, M.D., M.P.H., Ph.D.,§
Sanjay M. Bhananker, M.D.¶

ABSTRACT

Background: Residual paralysis is common after general anesthesia involving administration of neuromuscular blocking drugs (NMBDs). Management of NMBDs and reversal is frequently guided by train-of-four (TOF) monitoring. We hypothesized that monitoring of eye muscles is associated with more frequent residual paralysis than monitoring at the adductor pollicis.

Methods: This prospective cohort study enrolled 180 patients scheduled for elective surgery with anticipated use of NMBDs. Collected variables included monitoring site, age, gender, weight, body mass index, American Society of Anesthesiologists physical status class, type and duration of surgery, type of NMBDs, last and total dose administered, TOF count at time of reversal, dose of neostigmine, and time interval between last dose of NMBDs to quantitative measurement. Upon postanesthesia care unit admission, we measured TOF ratios by acceleromyography at the adductor pollicis. Residual paralysis was defined as a TOF ratio less than 90%. Multivariable logistic regression was used

* Acting Assistant Professor, ‡ Associate Professor, § Professor, ¶ Associate Professor, Department of Anesthesiology & Pain Medicine, University of Washington, Seattle, Washington; † Student, University of Washington School of [Medicine, Seattle](#), Washington.

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Address correspondence to Dr. Thilen: Department of Anesthesiology & Pain Medicine, University of Washington, 325 Ninth Avenue, Box 359724, Seattle, Washington 98104. sthilen@uw.edu or sthilen@yahoo.com. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

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What We Already Know about This Topic

- Assessing the degree of spontaneous recovery at the time of reversal from neuromuscular blockade is important, but has only been performed at the adductor pollicis

What This Article Tells Us That Is New

- In 150 patients receiving neuromuscular blockers during surgery, qualitative assessment of train-of-four monitoring of eye muscles led to a 5-fold increased risk of postoperative residual paralysis compared with the adductor pollicis

to account for unbalances between the two groups and to adjust for covariates.

Results: 150 patients received NMBDs and were included in the analysis. Patients with intraoperative TOF monitoring of eye muscles had significantly greater incidence of residual paralysis than patients monitored at the adductor pollicis ($P < 0.01$). Residual paralysis was observed in 51/99 (52%) and 11/51 (22%) of patients, respectively. The crude odds ratio was 3.9 (95% CI: 1.8–8.4), and the adjusted odds ratio was 5.5 (95% CI: 2.1–14.5).

Conclusions: Patients having qualitative TOF monitoring of eye muscles had a greater than 5-fold higher risk of postoperative residual paralysis than those monitored at the adductor pollicis.

RESIDUAL paralysis is frequently present after general anesthesia involving the administration of neuromuscular blocking drugs (NMBDs), and is associated with potential morbidity.^{1,2} Residual paralysis is commonly defined as a train-of-four (TOF) ratio less than 90% at the

◇ This article is featured in “This Month in Anesthesiology.” Please see this issue of ANESTHESIOLOGY, page 9A.

◆ This article is accompanied by an Editorial View. Please see: Donati F: Neuromuscular monitoring: More than meets the eye. ANESTHESIOLOGY 2012; 117:934–6.

adductor pollicis and has been reported to occur in 38–64% of cases in which conventional qualitative or subjective evaluation of the TOF monitoring was employed.^{3–6} This type of assessment is the predominant mode of intraoperative monitoring in the United States.⁷ The nerve stimulator may be applied at various anatomical sites, such as at the wrist with stimulation of the ulnar nerve and evaluation of the response of the adductor pollicis, or on the face with stimulation of the facial nerve and evaluation of the twitch response of the orbicularis oculi or corrugator supercilii muscles (henceforth referred to as eye muscles). Although residual paralysis is defined as TOF ratio less than 90% at the adductor pollicis, intraoperative monitoring of the eye muscles may be chosen when the thumb is not easily accessible because of surgical positioning. However, several previous studies have documented that the twitch response recovers more promptly at the level of the orbicularis oculi muscle compared with the adductor pollicis.^{8–16} Published reports that provide information applicable to the guidance of reversal of NMBDs with anticholinesterase inhibitors have documented the importance of assessing the degree of spontaneous recovery at time of reversal and have reported the twitch response of the adductor pollicis only.^{17–23} Similar studies using the twitch response of muscles surrounding the eye to guide reversal are lacking. Moreover, guidelines on good clinical research practice in neuromuscular research emphasize that alternative muscles cannot be used interchangeably with adductor pollicis responses.²⁴ We designed the present study to test the hypothesis that intraoperative monitoring at the eye muscles is associated with an increased risk of residual paralysis compared with monitoring at the adductor pollicis.

Materials and Methods

The study was approved by the University of Washington Institutional Review Board (Seattle, Washington), and written informed consent was obtained from all patients. This prospective, observational cohort study was conducted at two teaching hospitals, the University of Washington Medical Center and Harborview Medical Center. Between June 16, 2011, and Aug 20, 2011, we enrolled 180 patients with American Society of Anesthesiologists (ASA) physical status I–IV who were free from underlying neuromuscular disorders and scheduled to undergo elective surgery with anticipated use of nondepolarizing muscle relaxants, and who gave written informed consent. Exclusion criteria included age less than 18 yr or greater than 80 yr.

The primary providers of anesthesia were certified registered nurse anesthetists and residents with attending staff supervision. Because the study was not blinded, to minimize awareness of the study, anesthesia providers were not informed about the details and purpose of the study and whether a particular patient was actually enrolled in the study. Patients received usual anesthesia care including standard monitoring, such as electrocardiography, pulse oximetry, end-tidal carbon dioxide concentration, and

noninvasive blood pressure monitoring. Each operating room is equipped with a conventional, qualitative, peripheral nerve stimulator for TOF monitoring (Digistim II Nerve Stimulator; Neuro Technology, CCR Medical, Inc., St. Petersburg, FL). These monitors are also capable of delivering 50 Hz and 100 Hz tetanic stimulation. Although no written policy exists, the use of this conventional nerve stimulator is part of routine practice at our hospitals. At the time of the study, quantitative monitors were not available for clinical practice in our hospitals.

Study Procedures

The primary endpoint was a quantitative assessment of neuromuscular block performed by acceleromyography (TOF-Watch SX[®], Bluestar Enterprises, Omaha, NE) within 5 min of arrival to the postanesthesia care unit (PACU). Two standard electrocardiogram electrodes, placed 3 cm apart, were applied on alcohol-cleansed skin over the ulnar nerve at the wrist. The TOF-Watch Hand Adapter[®] was used to apply the acceleration transducer to the distal phalanx of the thumb and to apply the temperature probe to the palm. We used 50-mA TOF stimulation without calibration, *i.e.*, four pulses of 0.2-ms duration at a frequency of 2 Hz, and averaged two measurements that were separated by 20 s. If the initial two measurements were not within 10% agreement, then we performed additional measurements separated by 20-s intervals (up to four total measurements) and averaged the two closest TOF ratios. We defined residual paralysis as a TOF ratio less than 90%. We noted the time of the last valid measurement. We measured hand temperature at the thenar aspect of the palm.

Data Collection

For each patient, we collected information on multiple other variables with potential relevance to recovery from neuromuscular block. Demographic variables included age, gender, height, weight, and ASA physical status. Clinical variables obtained by way of electronic medical record review included type of surgery, duration of surgery, type of muscle relaxant and whether provided by bolus or continuous infusion, total amount of muscle relaxant, time and amount of last dose of muscle relaxant, time and amount of neostigmine, type of preoperative antibiotic, agent used for maintenance of general anesthesia, and core temperature. We converted all doses of NMBDs to multiples of ED₉₅ with the following conversion factors: 0.3 mg/kg rocuronium, 0.05 mg/kg vecuronium, and 0.05 mg/kg cisatracurium. Obesity needs to be considered when dosing NMBDs because rocuronium, vecuronium, and cisatracurium have been reported to have prolonged duration of action if dosing is based on total body weight.^{25–27} We calculated body mass index (BMI = kg/m²) and three different weights for each patient. We categorized patients to three categories based on BMI, normal weight (BMI less than 25 kg/m²), overweight (BMI of 25 kg/m² or more but less than 30 kg/m²), and

obese (BMI of 30 kg/m² or more). The calculated weights were: ideal body weight (IBW) was defined as 50.0 + 2.3 kg per inch over 5 feet for males and 45.5 + 2.3 kg per inch over 5 feet for females, adjusted body weight (ABW) 20 was defined as IBW + 20% of excess weight, and ABW40 was defined as IBW + 40% of excess weight. We calculated adjusted doses of NMBDs by using these calculated weights. When a patient received more than one type of muscle relaxant, we categorized this patient based on the last dose.

Additional clinical variables were obtained by way of interviewing the anesthesia provider in the PACU: site of intraoperative qualitative neuromuscular blockade monitoring, response of qualitative monitoring at time of reversal (TOF count and presence of fade when four twitches were present), and duration from reversal with neostigmine to extubation.

Statistical Analysis

Normally distributed data are reported as a mean with SD and were compared using two-sample Student *t* test. Categorical data are reported as counts and frequency distributions and were compared using the chi-square test. The main study endpoint, residual paralysis, was compared between patients monitored at the eye muscles and those monitored at the adductor pollicis as the difference in proportions, using the chi-square statistic. We used multivariable logistic regression to account for potential unbalances between the two groups and adjust the association of monitoring site with residual paralysis for other explanatory variables. The covariates used include monitoring site (eye muscles or adductor pollicis), gender (male or female), hospital (University of Washington Medical Center or Harborview Medical Center), ASA class (I to II or III to IV, *i.e.*, two categories), BMI (less than 25, BMI of 25 or more but less than 30, and BMI 30 kg/m² or more), and type of surgical procedure (two categories, thoracic and abdominal or other procedure) as categorical variables. The remaining variables were used as continuous variables: age, last dose of NMBD (expressed as ED₉₅) and neostigmine (mcg/kg), duration of surgery, and the time interval from last dose of NMBD to assessment in the PACU. For the primary analysis, last dose of NMBD was adjusted using ABW20, and a sensitivity analysis was performed using total body weight, IBW, and ABW40.

Covariate balance was investigated by performing bivariate analyses between the two levels of monitoring site and potential confounding variables. Absolute standardized differences were also calculated. We conducted a propensity score analysis (for monitoring site) as a sensitivity analysis to confirm the multivariable logistic regression model provided adequate adjustment for potential confounding.

Regarding sample size considerations, we assumed a frequency of 30% residual paralysis in the group conventionally monitored at adductor pollicis, based on a recent report by Murphy *et al.*²⁸ We hypothesized that monitoring of eye muscles was associated with a

higher frequency of residual paralysis and considered that a frequency of 50% in this group would be a clinically relevant difference. Assuming equal size groups, a two-sided α level of 0.05, and 80% power, the required sample would be 206 (103 per group). By the end of the projected study period, the study had enrolled 180 patients. Because of unavailability of supplemental funds, recruitment could not be continued, and an analysis was conducted. After accounting for exclusions, 150 patients were available for the analysis. Because the null hypothesis was rejected with a two-sided α level less than 0.01, the study was not reopened to enrolment.

All analyses were conducted using Stata 12 (Stata Corporation, College Station, TX).

All hypothesis tests and their associated *P* values are two-sided.

Results

At the end of the study period, we had enrolled 180 patients who gave written, informed consent. Of those, 150 patients received intraoperative NMBDs, had intraoperative TOF monitoring of either eye muscles or adductor pollicis, and had postoperative quantitative measurements made. Reasons for exclusion included: measurements not obtained because of unavailability of research personnel (13), no use of NMBDs (six), no monitoring at one of the two sites (seven), and case cancellation (four). With the exception of hospital and type of surgical procedure, there were no significant differences between groups in gender, age, BMI, and ASA physical status (table 1). Likewise, the two groups did not differ significantly in perioperative variables, including surgery duration, TOF response at time of reversal (TOF count and fade), total dose of NMBD and last dose of NMBD (doses compared as multiples of ED₉₅), dose of neostigmine (mcg/kg), core and hand temperatures, and type of muscle relaxants. There were also no significant differences between the two groups in the following measured time intervals: last dose of NMBD to TOF ratio measurement in the PACU, neostigmine to extubation, and extubation to PACU arrival. Rocuronium, vecuronium, and cisatracurium were administered to 81%, 11%, and 6% of patients, respectively (table 2). No patient received NMBD by continuous infusion. Maintenance of anesthesia was achieved with inhalational agents (sevoflurane, isoflurane, or desflurane) in 149 patients. Use of perioperative antibiotics was as follows: cefazolin (127), clindamycin (seven), vancomycin (three), fluoroquinolones (three), gentamicin (one), none (three) and unknown (six).

Patients who had intraoperative TOF monitoring of eye muscles had significantly greater incidence of residual paralysis than patients monitored at the adductor pollicis, 51/99 (52%) at the eye muscles and 11/51 (22%) at the adductor pollicis, *P* < 0.01. The distribution of TOF ratios in each study group is shown in figure 1. The mean \pm SD TOF ratios were 0.86 \pm 0.22 (median 0.90) for the patients monitored at eye muscles and 0.93 \pm 0.18 (median 1.01)

Table 1. Patient Characteristics

	Total Cohort, No. = 150	Monitoring Site		P Value	Absolute Standardized Difference, %
		Eye Muscles, No. = 99	Adductor Pollicis, No. = 51		
Age (year)	48.8 (16)	49.2 (15)	49.2 (17)	0.65	0.0
Female, n (%)	84 (56)	58 (59)	26 (51)	0.37	15.3
ASA, n (%)	—	—	—	0.05	—
I to II	99 (66)	60 (61)	39 (77)	—	35.2
III to IV	51 (34)	39 (39)	12 (24)	—	34.8
BMI, kg/m ²	30 (8)	30 (8)	29 (7)	0.75	4.2
BMI categories, n (%)	—	—	—	0.90	—
Less than 25 kg/m ²	46 (31)	31 (31)	15 (29)	—	4.1
25 kg/m ² or more, but less than 30 kg/m ²	46 (31)	31 (31)	15 (29)	—	4.1
30 kg/m ² or more	58 (39)	37 (37)	21 (41)	—	7.8
Surgical procedures, n (%)	—	—	—	<0.01	—
Abdominal or thoracic	105 (70)	84 (85)	21 (41)	—	101.2
Other	45 (30)	15 (15)	30 (59)	—	101.2
Hospital, n (%)	—	—	—	<0.01	—
A	50 (33)	19 (19)	31 (61)	—	93.7
B	100 (68)	80 (81)	20 (39)	—	93.7

Data are mean \pm SD or number of patients (%). Percentages may not add to 100 because of rounding. Data for all variables were available for all 150 patients.

A and B = the two hospitals that participated in the study; ASA = American Society of Anesthesiologists physical status class; BMI = body mass index; other surgery = ear, nose, and throat surgery, orthopedic surgery, neurosurgery, urological surgery, gynecological surgery, and vascular surgery.

for patients monitored at the adductor pollicis. The ranges of values of TOF ratios were 0 to 1.15 and 0.40 to 1.16 for the two groups, respectively. TOF ratios more than 1.0 were present in 27% and 51% of patients monitored at the eye muscles and adductor pollicis, respectively. 17.2% of patients monitored at the eye muscles had TOF ratios less than 0.7, and 34.3% had TOF ratios in the range 0.7 to less than 0.9. Comparative results for patients monitored at the adductor pollicis were 11.8% and 9.8%, respectively. The time interval from neostigmine administration to TOF ratio measurement was not significantly different between the two groups (table 2).

The crude odds ratio (OR) for the association of site of monitoring and residual paralysis was 3.9 (95% CI: 1.8–8.4) comparing monitoring at the eye muscles with monitoring at the adductor pollicis. Multivariable logistic regression adjusting for age, gender, hospital, ASA class, time interval from last dose of NMBD to measurement in the PACU, last dose of NMBD (expressed as ED₉₅), amount of neostigmine, duration of surgery, type of surgery, and BMI yielded an adjusted OR of 5.5 (95% CI: 2.1–14.5, table 3). The variables that were significantly associated with residual paralysis were monitoring site, time interval from last dose of NMBD to time of measurement in the PACU, and BMI. For each 10 additional minutes between last dose of NMBD and measurement, there was 10% lower odds of postoperative residual paralysis (OR: 0.90; 95% CI: 0.83 to 0.99, $P = 0.03$), irrespective of monitoring site. We performed a sensitivity analysis by using total body

weight, IBW, and ABW40 for calculations of the dose of NMBD and found that this did not change the results compared with our primary analysis, which used dose calculations according to ABW20.

The results of the propensity score model were substantially unchanged from the final multivariable logistic regression (OR: 4.7, 95% CI: 1.8–12.4).

A total of 113 patients had multiple doses of NMBDs, and 37 patients had a single dose of NMBDs. We conducted a secondary subgroup analysis on these two subgroups. The crude OR for the association of site of monitoring and residual paralysis in the group that received multiple doses was 4.38 (95% CI: 1.82–10.50), whereas in the group having received a single dose the association was not statistically significant (OR: 2.81, 95% CI: 0.5–15.77).

All patients had a hand temperature of at least 32.3°C.

The SD for neostigmine dose was large; in table 2, the dose is listed according to total body weight. We also calculated the weight-based neostigmine doses according to the other weights (IBW, ABW20, and ABW40) and the standard deviations remained high with the different weight adjustments. In the final multivariable logistic regression model (table 3), neostigmine dose was calculated according to total body weight. Sixteen patients did not receive neostigmine; there was not a statistically significant association between not receiving neostigmine and residual paralysis.

Eighteen patients were not extubated before TOF ratio measurement in the PACU. All were ventilating spontaneously

Table 2. Perioperative Data

	Monitoring Site			Subjects with Data, No.	P Value	Absolute Standardized Difference, %
	Total Cohort, No. = 150	Eye Muscles, No. = 99	Adductor Pollicis, No. = 51			
TOF count, N (%)	—	—	—	147	0.94	—
1–3	20 (14)	14 (14)	6 (12)	—	—	7.1
4	23 (16)	15 (16)	8 (16)	—	—	1.4
4 without fade	104 (71)	68 (70)	36 (72)	—	—	4.2
NMBD	—	—	—	147*	0.29	—
Rocuronium	122 (81)	77 (78)	45 (88)	—	—	28.0
Vecuronium	16 (11)	14 (14)	2 (4)	—	—	36.2
Cisatracurium	9 (6)	6 (6)	3 (6)	—	—	0.8
Unknown (data missing)	3 (2)	2 (2)	1 (2)	—	—	0.0
Total dose NMBD (ED ₉₅)	3.9 (2)	3.1 (2)	4.0 (2)	147*	0.54	46.0
Last dose (ED ₉₅)	1.1 (1)	1.2 (1)	1.1 (1)	147*	0.79	11.6
Neostigmine (mcg/kg)	35 (19)	35 (21)	34 (16)	150	0.89	2.2
Surgery duration (min)	167 (79)	162 (75)	176 (86)	150	0.31	17.0
Last NMBD to TOFR measurement (min)	115 (61)	114 (63)	118 (56)	147*	0.75	5.5
Neostigmine to TOFR measurement (min)	31.6 (20.4)	31.8 (23.3)	31.3 (13.2)	134†	0.89	2.6
Neostigmine to extubation (min)	16 (14)	16 (15)	17 (10)	123†,‡	0.68	8.7
Extubation to PACU (min)	6.5 (5)	6.7 (5)	6.0 (4)	132‡	0.46	15.9
Temperature (core, °C)	36.5 (0.5)	36.5 (0.5)	36.5 (0.5)	149	0.65	0.0
Temperature (hand, °C)	33.2 (0.64)	33.2 (0.5)	33.3 (0.8)	150	0.54	15.0

Data are mean ± SD or n = number of patients (%). Percentages for categories may not add to 100 because of rounding.

* 147 patients had data, the three patients with missing data for NMBD are listed by group under the category NMBD. † 16 patients had neostigmine dose = 0, and these patients consequently did not have data for the time intervals for which the definition includes administration of neostigmine. ‡ 18 patients were not extubated prior to PACU arrival.

ABW = adjusted body weight; ED₉₅ = effective dose to produce 95% twitch depression, calculated with the following conversion factors: 0.3 mg/kg rocuronium, 0.05 mg/kg vecuronium, and 0.05 mg/kg cisatracurium, and using the ABW20 weight, defined as ideal body weight plus 20% of excess weight; NMBD = neuromuscular blocking drug; PACU = postanesthesia care unit; TOF = train-of-four; TOFR = train-of-four ratio.

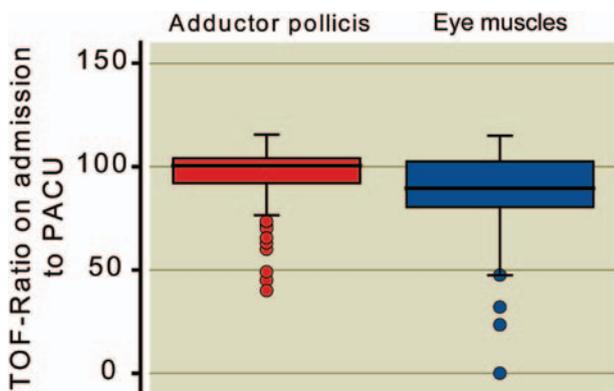


Fig. 1. Box-and-whisker plots showing the distribution of train-of-four ratios on admission to the postanesthesia care unit, by study group. The two groups had intraoperative neuromuscular monitoring of adductor pollicis and eye muscles, respectively. The box contains the second and third quartile of values, and the whiskers extend up to 1.5 times the height of the box. Outliers are shown as dots. Low values were more common in the group that was monitored at the eye muscles and there was a greater variation in train-of-four ratios in this group. Two patients had a train-of-four ratio of 0. Both of these patients showed signs of weakness, but they did not require intervention beyond close monitoring. TOF-ratio = train-of-four ratio; PACU = postanesthesia care unit.

and were planned for extubation in the PACU. The majority (13/18 patients) had undergone orthopedic procedures and were kept anesthetized with a propofol infusion until a peripheral nerve block for postoperative analgesia had been performed. All were extubated in the PACU. For patients who were extubated in the operating room, the average time interval between extubation and arrival to the PACU was 6.5 min (SD: 4.7).

No serious complications, such as airway obstruction or need for assisted ventilation, were identified in either monitoring site group. Two patients had a TOF ratio of 0. Both of these patients showed signs of weakness, but they did not require intervention beyond close monitoring.

Discussion

In this cohort of 150 patients who were administered NMBDs as part of anesthesia care for a variety of surgical procedures, patients who were monitored by facial nerve stimulation and evaluation of muscles surrounding the eye had a significantly higher incidence of residual paralysis than patients monitored by ulnar nerve stimulation and evaluation of the response of the adductor pollicis.

Table 3. Results from the Multivariable Logistic Regression Model

	Odds Ratio	P Value	95% CI
Monitoring site*	5.48	<0.01	2.08–14.46
Age (year)	0.99	0.68	0.97 to 1.02
Gender (male)	1.17	0.70	0.53–2.59
Hospital†	0.80	0.73	0.22 to 2.87
ASA‡	0.92	0.73	0.58 to 1.47
Last NMBD to TOFR measurement (10 min)	0.90	0.03	0.83 to 0.99
Last NMBD dose (ED ₉₅)§	1.17	0.53	0.72 to 1.90
Neostigmine (mcg/kg)	0.99	0.29	0.97 to 1.01
Surgery duration (min)	1.00	0.22	1.00 to 1.01
Surgical procedure	0.84	0.79	0.22–3.14
BMI#	—	—	—
Overweight, BMI of 25 or more but less than 30 kg/m ²	3.73	0.01	1.33–10.40
Obesity, BMI of 30 kg/m ² or more	3.89	0.01	1.39–10.89

The response variable is residual paralysis in the PACU, defined as TOF ratio less than 0.90 (n = 147).

* Eye muscles vs. adductor pollicis (referent). † There were two hospitals included in the study. ‡ ASA physical classes I and II (referent) versus III and IV. § The dose is adjusted using ABW20 = ideal body weight plus 20% of excess weight and was calculated with the following conversion factors: 0.3 mg/kg rocuronium, 0.05 mg/kg vecuronium, and 0.05 mg/kg cisatracurium. || Thoracic and abdominal procedures (referent) versus all other procedures. # Normal weight (BMI less than 25 kg/m²) is referent.

ABW = adjusted body weight; ASA = American Society of Anesthesiologists; BMI = body mass index; ED₉₅ = effective dose to produce 95% twitch depression; NMBD = neuromuscular blocking drug; PACU = postanesthesia care unit; TOF = train-of-four.

This finding is consistent with previous reports documenting that muscles surrounding the eye are relatively resistant to NMBDs. Multiple previous studies have consistently documented an earlier recovery of twitches with facial nerve stimulation and evaluation of the orbicularis oculi compared with when the ulnar nerve is stimulated and the response of the adductor pollicis is evaluated.^{8–16} A more recent report by Plaud *et al.* evaluated the difference between various muscles surrounding the eye, and observed that the corrugator supercillii, and not the orbicularis oculi, appears to be the muscle responsible for the documented relative resistance to NMBDs.²⁹ Other studies have also attempted to distinguish between the orbicularis oculi and the corrugator supercillii,^{30,31} although such distinction may be difficult. Gätke, in her detailed report on technical aspects of acceleromyographic monitoring of the orbicularis oculi, concluded: “when monitoring in the face, with its many small nerves and muscles, it is difficult to ensure that only one single nerve is being stimulated and accordingly that only one muscle is contracting.” It may be quite difficult for anesthesia providers to distinguish between twitches of different muscles surrounding the eye. This in turn may lead to twitches of the relatively resistant corrugator supercillii muscle to be counted, even in the absence of a twitch by the orbicularis oculi muscle. Therefore, in this report we refer to monitoring of the eye muscles.

According to our multivariable logistic model, the time interval from last dose of NMBD to acceleromyographic measurement was a significant predictor of residual paralysis. We believe this is an important factor in clinical practice, although it may not always be easily controlled (*e.g.*, when a surgeon requests paralysis near the end of the surgical procedure).

The lack of a statistically significant association between monitoring site and residual paralysis in the subgroup

given a single dose of NMBD is not surprising, because intraoperative monitoring may not substantially impact on management in cases where a single dose of muscle relaxant is given for intubation.

We do not believe that the patients who arrived to the PACU intubated (all of whom were planned for extubation in the PACU) had their NMBDs managed differently, because this would have been contrary to our institutional routines.

More than 70% of patients in both groups had four twitches without fade, and more than 85% in both groups were reported to have had four twitches at time of reversal (table 2). Although omission of reversal medication based on clinical and qualitative monitoring is associated with residual paralysis,⁶ the requirement for neostigmine may be modest when the residual block is small.³² A TOF count of four without fade at the adductor pollicis has been reported to be consistent with a TOF ratio of approximately 0.4.³³ Fuchs-Buder reported that a neostigmine dose of 10 mcg/kg had a high probability of providing successful reversal from a TOF ratio of 0.4. However, when monitoring is performed at the eye muscles, the provider may be challenged to confirm that the residual block is indeed small.

We found that neostigmine doses (measured in mcg/kg) were highly variable, as reflected by their SD. The most common doses were 3 mg and 4 mg, which were administered to 48 and 24 patients, respectively. It is possible that providers do not calculate the dose based on weight, TOF count, and presence or absence of fade. It is also possible that there is substantial variation between providers in how they dose neostigmine. We do not believe that our hospitals have unique practice patterns in this regard. In this study, neostigmine dose was not associated with residual paralysis.

A finding of higher total doses of NMBDs provided to patients with monitoring of the eye muscles would have supported the presumed mechanism behind the association of monitoring site and residual paralysis, namely by an underestimation of the extent of neuromuscular block. However, this increased use of NMBDs was not apparent in this study. A recent report by Murphy *et al.*,³⁴ in which patients who were randomized to intraoperative acceleromyography monitoring, had reduced symptoms of muscle weakness, and improved quality of recovery, also did not find differences in total amount of NMBDs between study groups. It is possible that quite small differences in management, especially at the end of surgery, including small differences in amount and timing of NMBDs, made a significant difference in the risk of residual paralysis. Our study, and the one by Murphy *et al.*, may not have sufficient statistical power to document such small differences.

Limitations

This is an observational study that should be interpreted in the context of its design. We are not able to establish causality, only an association. Supporting a potentially causal relation is the biologic plausibility of these findings and the strength of the association. There were some imbalances between groups with regard to type of surgical procedures and hospital, and such imbalances could lead to confounding. We believe that we have been able to adjust for these measured differences by applying appropriate statistical methods and thus corrected for the presence of confounding in the data. However, there is still the possibility of residual confounding or bias by preferences of the individual practitioners. There may be variations in practices related to dosing, monitoring, and reversal between different institutions, and it is possible that our two participating hospitals have unique practice patterns. However, we believe our practice is representative of a large proportion of U.S. hospitals; the same anesthesia residents rotate at the two hospitals and the training they receive in management of NMBDs is consistent with current Accreditation Council for Graduate Medical Education requirements. We are not aware of any differences in training, procedures, or equipment between our two hospitals.

Our study was not designed to evaluate monitoring of specific muscles surrounding the eye (*e.g.*, the corrugator supercilii *vs.* the orbicularis oculi), and we do not know which muscle that anesthesia providers were evaluating; however, we believe that our providers use monitoring at the eye muscles in a manner that is typical for anesthesia providers in the United States and many other countries. We also do not know how many of the providers understood that the study was ongoing or the purpose of the study; 78 different providers were involved in the management of 157 patients recruited to the study (this includes seven patients who were excluded).

When acceleromyography is used without calibration, as was done in our study, there is a tendency to overestimate the

TOF ratio.³⁵ Therefore, our method may have underestimated the true incidence of residual paralysis. Although multiple previous studies have used the same method that we used to identify residual paralysis in the PACU,^{6,28,36,37} it should be noted that the accuracy of accelerography in awake patients has been questioned.³⁸

Recovery from paralysis is important at time of extubation, and measurements should ideally be made at that time. Although the average time from extubation to the PACU was limited to 6.5 min, measurements separated by this interval are not equivalent. A previous study confirmed that there is a significant decrease in residual paralysis when comparing time of extubation with time of arrival to the PACU.³⁹ The average difference between the two measurements was 11 min in that study. Any postextubation delay of measurement is undesirable in studies on residual paralysis.

Conclusion

Our findings are relevant to clinical practice, and we believe that recommendations on NMBDs should include site of monitoring when discussing reversal of muscle relaxation. In addition, providers should be vigilant to the time between last administration of NMBDs and administration of reversal. Considering that both the application of acceleromyography, as used in our study, and the postextubation delay in measurement contribute to a decreased estimate of residual paralysis, it is concerning that the incidence of residual paralysis was found to be 22% and 52% among patients with monitoring of the adductor pollicis or eye muscles, respectively.

There are a variety of possible approaches to mitigate the risk factor related to site of monitoring. An apparently excellent approach would be to substitute use of quantitative monitoring at “the gold standard site,” *i.e.*, the adductor pollicis, even when this is not readily accessible for tactile evaluation by the anesthesia provider. Several technologies that may be useful for this purpose have been described but are not yet widely adopted.^{40–42} Another approach, although likely more time-consuming, may be to defer reversal and extubation until the adductor pollicis becomes available to the anesthesia provider at the conclusion of a surgical procedure. Further research may be indicated to more precisely evaluate the usefulness of monitoring at sites other than the adductor pollicis.

Our study is a reminder of the limitations of monitoring with conventional nerve stimulators. These monitors do not allow us to diagnose residual paralysis, not even when used at the more reliable site, which is the adductor pollicis. When used for monitoring of eye muscles, they perform worse. Understandably, several authorities on clinical use of muscle relaxants have suggested that routine use of quantitative monitoring should be implemented.^{43–45}

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ANESTHESIOLOGY REFLECTIONS

Curved Spatulas for Harvesting Opium



Often mass-produced in China and distributed to Afghanistan and other parts of Asia and Latin America, curved spatulas have been used for centuries in harvesting opium from its poppy, *Papaver somniferum*. Either the point or the thinner, sharper convex part of the spatula blade is used to lightly "score" vertical incisions on the immature pods or fruits of the opium poppy, typically in the afternoon. The milky latex which oozes out air dries, and by morning, the thicker, duller concave portion of the spatula blade is used to skim off the exudate. Although labor-intensive, this ancient technique can recover scrapings of dried opium on multiple mornings in succession. Narcotic opiates extracted from this opium include morphine, codeine, and thebaine. (Copyright © the American Society of Anesthesiologists, Inc.)

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.