ANESTHESIOLOGY

Ipsilateral and Simultaneous Comparison of Responses from Acceleromyography- and Electromyography-based Neuromuscular Monitors

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ANESTHESIOLOGY 2021; 135:597–611

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Quantitative intraoperative neuromuscular function monitoring decreases the incidence of residual neuromuscular blockade
- The reference method for quantitative neuromuscular monitoring is mechanomyography, but mechanomyography-based monitors are not commercially available
- Acceleromyography- and electromyography-based neuromuscular monitors are available, the latter of which address several practical limitations of the former

What This Article Tells Us That Is New

- Contractions and muscle action potentials from the same adductor pollicis muscle were measured simultaneously by acceleromyography- and electromyography-based neuromuscular monitors, respectively, in 48 patients undergoing surgery requiring muscle relaxation
- The electromyography-based device is a better indicator of adequate recovery from neuromuscular blockade and readiness for safe tracheal extubation because normalized train-of-four ratios of 80% or more were observed earlier and more frequently with acceleromyography

ABSTRACT

Background: The paucity of easy-to-use, reliable objective neuromuscular monitors is an obstacle to universal adoption of routine neuromuscular monitoring. Electromyography (EMG) has been proposed as the optimal neuromuscular monitoring technology since it addresses several acceleromyography limitations. This clinical study compared simultaneous neuromuscular responses recorded from induction of neuromuscular block until recovery using the acceleromyography-based TOF-Watch SX and EMG-based TetraGraph.

Methods: Fifty consenting patients participated. The acceleromyography and EMG devices analyzed simultaneous contractions (acceleromyography) and muscle action potentials (EMG) from the adductor pollicis muscle by synchronization *via* fiber optic cable link. Bland–Altman analysis described the agreement between devices during distinct phases of neuromuscular block. The primary endpoint was agreement of acceleromyography- and EMG-derived normalized train-of-four ratios greater than or equal to 80%. Secondary endpoints were agreement in the recovery train-of-four ratio range less than 80% and agreement of baseline train-of-four ratios between the devices.

Results: Acceleromyography showed normalized train-of-four ratio greater than or equal to 80% earlier than EMG. When acceleromyography showed train-of-four ratio greater than or equal to 80% (n = 2,929), the bias was 1.3 toward acceleromyography (limits of agreement, –14.0 to 16.6). When EMG showed train-of-four ratio greater than or equal to 80% (n = 2,284), the bias was –0.5 toward EMG (–14.7 to 13.6). In the acceleromyography range train-of-four ratio less than 80% (n = 2,802), the bias was 2.1 (–16.1 to 20.2), and in the EMG range train-of-four ratio less than 80% (n = 3,447), it was 2.6 (–14.4 to 19.6). Baseline train-of-four ratios were higher and more variable with acceleromyography than with EMG.

Conclusions: Bias was lower than in previous studies. Limits of agreement were wider than expected because acceleromyography readings varied more than EMG both at baseline and during recovery. The EMG-based monitor had higher precision and greater repeatability than acceleromyography. This difference between monitors was even greater when EMG data were compared to raw (nonnormalized) acceleromyography measurements. The EMG monitor is a better indicator of adequate recovery from neuromuscular block and readiness for safe tracheal extubation than the acceleromyography monitor.

(ANESTHESIOLOGY 2021; 135:597–611)

Residual neuromuscular blockade persists as a significant problem in everyday anesthesia practice. Objective (quantitative) monitoring has been shown to decrease the incidence of residual neuromuscular block.[1–3] Nevertheless,

This article is featured in "This Month in Anesthesiology," page A1. This article is accompanied by an editorial on p. 558. This article has a related Infographic on p. A23. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has a video abstract. This article has an audio podcast. This article has a visual abstract available in the online version. Parts of the results presented in this article have been submitted for abstract presentation at the 17th World Congress of Anesthesiology, Prague, Czech Republic, September 4 to 8, 2021.

Submitted for publication November 7, 2020. Accepted for publication June 23, 2021. Published online first on July 30, 2021. From the Department of Anesthesiology and Intensive Care, University of Debrecen, Debrecen, Hungary (R.N., G.N., E.T., B.F.); the Department of Tisza Research, Danube Research Institute, Centre for Ecological Research, Hungarian Academy of Sciences, Debrecen, Hungary (S.L.); the Institute of Biotechnology, University of Cambridge, Cambridge, United Kingdom (D.R.H.); Anaesthesia Technology Limited, Walshford, United Kingdom (M.G.); and the Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Jacksonville, Florida (J.R.R., S.J.B.).

 Anesthesiology 2021; 135:597–611. DOI: 10.1097/ALN.0000000000003896

<zdoi;. DOI: 10.1097/ALN.0000000000003896>

national and international surveys demonstrate continued unwillingness to adopt devices for monitoring intraoperative neuromuscular function and reveal clinicians' significant knowledge gaps in appropriate neuromuscular block management,[4–6] despite high levels of confidence in their own knowledge.[7] Experts have listed several factors to explain this lack of adoption of quantitative monitoring,[8] including the paucity of easy-to-use and reliable neuromuscular monitors, and the excessive time required for their setup.[9]

In recent years, several medical device manufacturers have introduced new neuromuscular monitoring devices of various technical solutions (electromyography [EMG], three-dimensional acceleromyography, cuff pressure-modality) to the market. Their common feature is their user-friendly interface, but validation studies are needed to compare their performance and usability to existing monitors and to prove their consistency and reliability in the clinical setting.[10–16]

Until recently, the most frequently used neuromuscular monitors were acceleromyography-based devices. To obtain precise train-of-four ratio measurements with these devices, clinicians need to take several precautions (such as fixation of the arm in supine position, use of preload on the thumb, calibration of the device, and normalization of results).[17] Although these measures improve the reliability of acceleromyography-derived train-of-four ratio measurements,[18,19] they make the use of the devices more complicated and might prevent clinicians from using them. In addition, acceleromyography is known to show faster recovery of neuromuscular function than mechanomyography,[17,20] and the overestimation of recovery can lead to early tracheal extubation and airway obstruction in the immediate postoperative period.[21]

EMG has been used successfully to monitor intraoperative neuromuscular function since the 1970s,[22–24] and experts in neuromuscular monitoring considered it the best alternative to mechanomyography; the two techniques show excellent agreement, while EMG is free of many disadvantages of acceleromyography.[25] However, the lack of portable EMG-based devices hindered the widespread adoption of the technique until recently. The TetraGraph (Senzime AB, Sweden) is a portable EMG-based neuromuscular monitor that received U.S. Food and Drug Administration (Silver Spring, Maryland) clearance in 2019. It records and analyzes the compound muscle action potentials in response to nerve stimulation.

The aim of this clinical study was to compare the neuromuscular responses obtained with the EMG-based monitor and acceleromyography-based TOF-Watch SX (Organon Teknika B.V., The Netherlands) recorded in a simultaneous, ipsilateral, same nerve/muscle configuration. While we attempted to correlate the EMG- and acceleromyography-derived responses over the entire range of monitoring (from induction of neuromuscular block to tracheal extubation), we believe the greatest significance (primary aim) is in the establishment of the relationship between the two monitoring technologies during offset of block, and in particular, around the threshold of neuromuscular recovery. Based on previous comparative examinations of acceleromyography- and EMG-based devices, we hypothesized that the EMG monitor would indicate slower recovery from neuromuscular block than its acceleromyography counterpart.

Materials and Methods

Study Population and Perioperative Management

The study was conducted at the Department of Anesthesiology and Intensive Care of the University of Debrecen Medical Center (Debrecen, Hungary) from June 26, 2019, to December 18, 2019 (ClinicalTrials.gov Identifier: NCT03987607). The study had been previously approved by the Ethical Board of the National Institute of Pharmacy and Nutrition (Budapest, Hungary; approval No. OGYÉI2690/2018).

After gaining written informed consent, the study enrolled 50 patients undergoing elective surgery requiring muscle relaxation. The inclusion criteria were age less than 18 yr, American Society of Anesthesiologists (Schaumburg, Illinois) Physical Status I to III, and elective surgery requiring muscle relaxation. Exclusion criteria included patient history of neuromuscular disorder (*e.g.*, stroke, myasthenia gravis, myopathy, neuropathy, and carpal tunnel syndrome), use of medications that might interfere with neuromuscular transmission, any previous injury to the examined arm that might influence nerve conduction parameters, open wound at the site of electrode placement, pregnancy, breast feeding, pacemaker, or participation in a clinical study in the previous 30 days.

After arrival to the operating theater, IV access was established in one of the forearm veins, and standard monitors (electrocardiography, noninvasive blood pressure monitoring, pulse oximetry, and body temperature) were applied to the patient. Anesthesia was induced with 2 μg/kg of fentanyl, and the effect site concentration of propofol target controlled infusion was set to 6 μg/ml, targeting a Bispectral Index (Infinity BISx SmartPod, Drägerwerk AG & Co. KGaA, Germany) of 40. An Alaris PK (Cardinal Health, Switzerland) target-controlled infusion IV pump with Schnider pharmacokinetic model was used for propofol administration. Active forced-air warming (Bair-Hugger, Arizant Healthcare Inc., USA) was used to ensure that peripheral temperature was kept above 32°C and core temperature above 36°C. Intraoperative hypotension was treated with ephedrine, norepinephrine, or a fluid bolus as clinically indicated. Ondansetron 4 mg IV was administered routinely to prevent postoperative nausea and vomiting.

Management of Neuromuscular Blockade Monitoring

After proper cleansing of the skin along the ulnar nerve at the wrist, the thenar eminence, and the thumb, two

single-use electrocardiography electrodes 3 cm apart were applied to the volar forearm along the ulnar nerve 2 cm proximal to the wrist crease to provide stimulation to the ulnar nerve.[26] The two sensing (distal) electrodes of the TetraGraph (TetraSens electrodes) were applied according to the manufacturer's instructions on the thenar eminence and the interphalangeal joint of the thumb. The stimulating electrode pair of TetraSens was not used for neurostimulation and was electrically isolated by leaving in place the packaging plastic cover. After affixing the TetraSens electrodes, a Hand Adapter (Organon Teknika B.V.) was applied to the thumb, and the fingers were strapped to the arm board. The piezoelectric probe of acceleromyography monitor was secured to the thumb *via* the Hand Adapter. Then the stimulating leads of the acceleromyography monitor cable were connected to the electrocardiography stimulating electrodes, with the negative electrode placed distally (fig. 1A). Approximately 5 min were allowed from electrode application to commencement of the procedure to allow curing of the electrode silver–silver chloride gel.

In order to synchronize nerve stimulation and neuromuscular monitoring, a fiber optic link was constructed to link the two neuromuscular monitors (fig. 1B). In this configuration, the ulnar nerve was stimulated exclusively by the acceleromyography-based device, while the two connected monitors recorded simultaneous acceleromyographic (TOF-Watch SX) and electromyographic (TetraGraph) responses. This setup avoided cross-interference of stimulating currents between the two devices. The EMG processing was the same as the commercially available device, and the synchronization system's timing was checked with an oscilloscope. The stimulus provided by the TOF-Watch was of the same form, shape, and duration as that produced by the TetraGraph. Further information on the technical modifications of the devices is provided in the Supplemental Digital Content (http://links.lww.com/ALN/C662). The EMG study device, fiber optic cable link, modified patient cable of the acceleromyography device, and TetraViewer software (SW 4.0 DLL Test Version 1B) were provided by Senzime AB (Sweden) for the duration of the study.

After turning on both devices, the EMG monitor was set to manual mode, and the single twitch stimulation option was chosen for calibration and to measure baseline compound muscle action potential amplitudes. The predetermined current intensity for each patient was 60 mA with 0.2-ms pulse duration, and the predetermined calibration mode of the acceleromyography monitor was set to calibration mode 1 to determine the gain. After induction of anesthesia but before establishing neuromuscular block, neuromuscular monitoring was commenced, and calibration of the acceleromyography monitor was performed. This consisted of calibration of the acceleration transducer at 60 mA/200 μs by delivery of 10 single twitch stimulations (the first 7 set the gain of the accelerometer, and the last 3 ensured the stability of the signal).

After calibration, the EMG monitor was set to train-of-four mode, and the train-of-four sequence of the acceleromyography monitor was allowed to run automatically and facilitate stabilization of signals. If the baseline train-of-four ratios and first twitch of the train-of-four sequence amplitudes showed instability (defined as variation by more than 10% over a 30-s period), calibration was repeated until amplitudes of the first twitches were stable. If stabilization could not be achieved after two trials, the electrodes were repositioned, and the calibration was reattempted. After stabilization of the signals, between two and five baseline train-of-four ratios were recorded. Then the intermediate-duration neuromuscular blocking agent was administered IV. The type and dose of neuromuscular blocking agent were determined by the anesthesiologist responsible for the patient and tailored to the estimated length of surgery and individual patient characteristics. The anesthesiologist also decided the time of intubation and extubation of the trachea as per usual clinical practice based on the measurements obtained with the acceleromyography monitor. Additional neuromuscular blocking agent boluses during surgery were also at the discretion of the attending anesthesiologist, but all effort was made to achieve spontaneous recovery from neuromuscular block at the end of surgery.

Intraoperatively, train-of-four measurements were performed every 15 s according to the cycle time of the acceleromyography monitor. When there was no response to train-of-four stimulation (train-of-four count 0) by acceleromyography, posttetanic count stimulations were performed every 3 to 5 min to measure the exact level of deep (train-of-four count, 0; posttetanic count greater than or equal to 1) or complete (posttetanic count, 0)[8] neuromuscular block until the train-of-four count returned to 1. The posttetanic count consisted of a 5-s, 50-Hz tetanic stimulus (delivered only when train-of-four count was 0), followed 3 s later by a series of 15 single twitch stimuli at a frequency of 1 Hz. During posttetanic count stimulations, the EMG-based monitor was set to single twitch mode so that the number of potentiated responses, if any, could be determined.

We aimed to provide spontaneous recovery curves recorded by the two monitors (fig. 2); however, when surgery ended earlier than anticipated, neostigmine was used for reversal of neuromuscular block. Data collection was continued until tracheal extubation or return of both acceleromyography- and EMG-derived train-of-four ratios to baseline values. Demographic data and type of surgical procedure were recorded from the electronic medical record. Data were saved and stored electronically on a secure laptop computer using the TOF-Watch-SX software version 2.5 (Organon Ireland Ltd., Ireland).

Endpoints of the Study

The primary endpoint of the study was the agreement of acceleromyography- and EMG-derived train-of-four ratios in the recovery range of greater than or equal to 80%

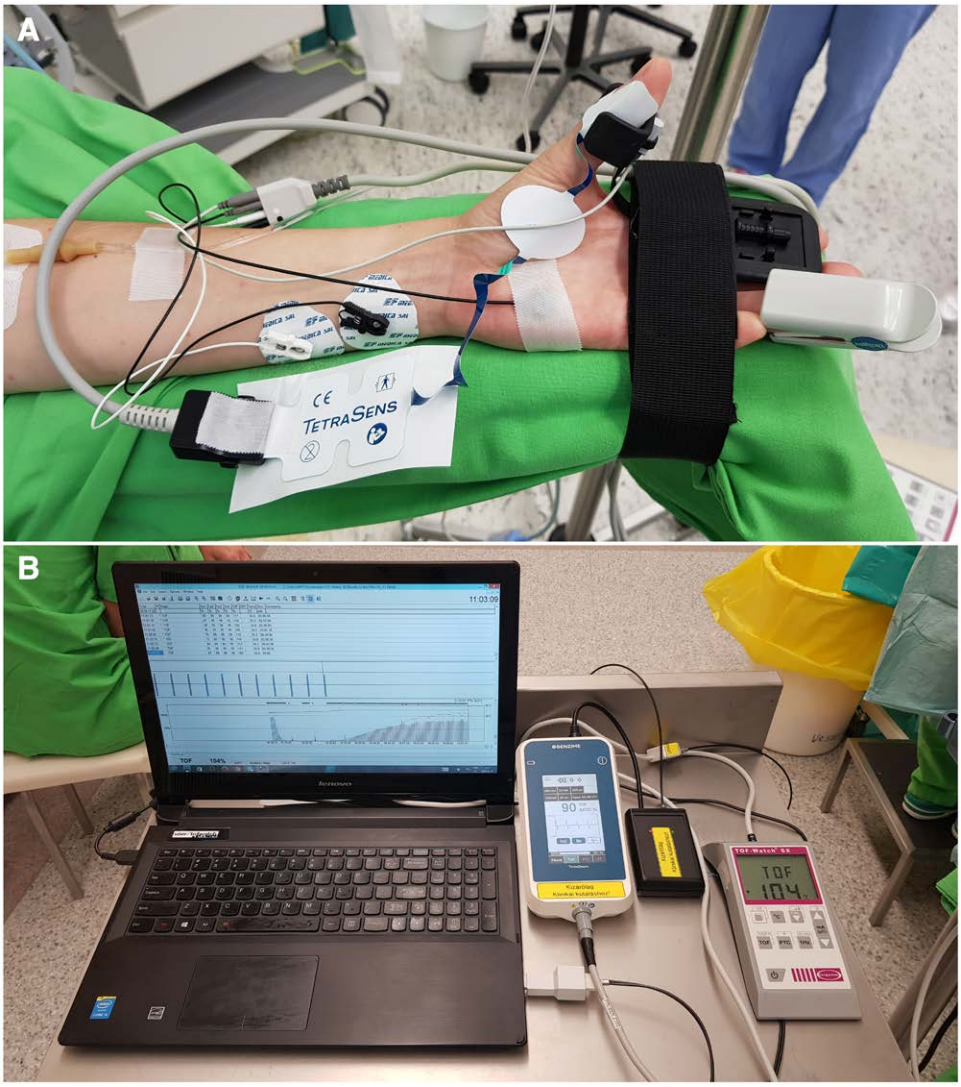

Fig. 1. Setup of the two interfaced monitors. (*A*) Electrode placement on the hand; (*B*) synchronization of the two monitors and connection to computer.

(near-recovery). Secondary endpoints of the study were (1) the agreement of acceleromyography- and EMG-derived train-of-four ratios in the less than 80% range, and (2) the agreement of measurements of the baseline train-of-four ratio between the two devices. Because the 80% boundary can be judged based on either the acceleromyography or the EMG measurement, we performed analyses of the primary and secondary endpoints using data obtained with both devices to assess the sensitivity of the acceleromyography and EMG monitors. Additional endpoints of the study were the agreement of acceleromyography and EMG devices in measurements of (1) posttetanic counts during deep block, (2) train-of-four counts during deep and moderate block, and (3) the first recovery of the train-of-four ratio (reappearance of the fourth twitch of the train-of-four).

Sample Size Calculation

To estimate sample size, we used data from a pilot study conducted with a preproduction prototype of TetraGraph at the Mayo Clinic (Jacksonville, Florida) in 2018.[27] The dataset consisted of 574 measurements obtained in 50 patients. A preliminary Bland–Altman analysis of these data showed a generally low repeatability ($r \approx 0.2$), with increasing repeatability at higher train-of-four ranges, low bias (–8.41 ± standard error 1.4), and well-separated limits of agreement (–38.96 to 22.14). Because repeatability was low and could change during recovery, we aimed for a higher number of measurements per patient.

To estimate the necessary sample size, we considered that a 10% difference in estimates of repeatability, bias, and

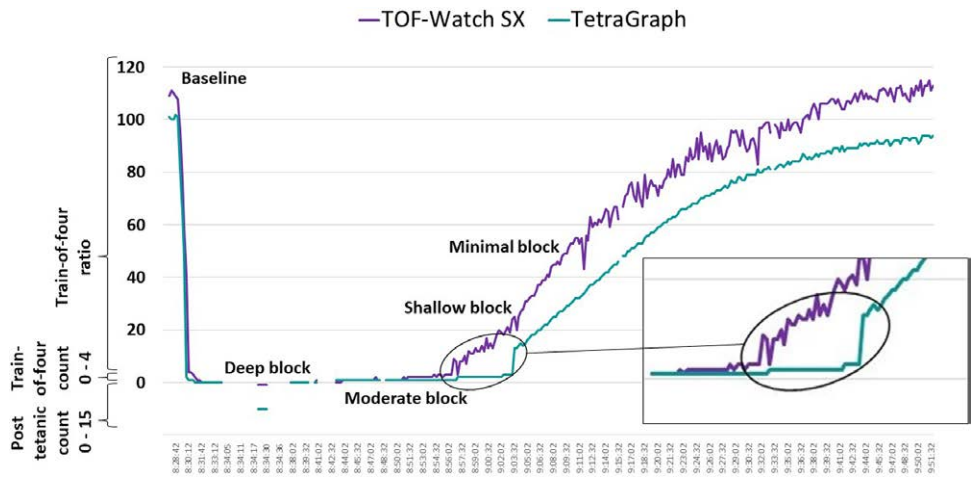

Fig. 2. A representative case that illustrates the examined phases of neuromuscular blockade (baseline, deep, moderate, shallow, and minimal neuromuscular blockade) recorded with the two neuromuscular monitors. The *purple line* indicates measurements with TOF-Watch SX (Organon Teknika B.V., The Netherlands), and the *turquoise line* indicates measurements with TetraGraph (Senzime AB, Sweden). The *y-axis* shows phases of neuromuscular blockade; the *x-axis* represents actual time. The *circled area* shows the transition period from moderate to shallow neuromuscular block; this segment is enlarged in the *right bottom corner* of the figure for better visualization.

limits of agreement was clinically acceptable and used estimates from the pilot study and formulas from Liang *et al.*[28] Calculations based on repeatability resulted in a required sample size of 213 and 253 comparisons for EMG and acceleromyography, respectively; calculations based on bias resulted in 98 comparisons; and calculations based on limits of agreement resulted in 293 comparisons.

With consideration to the primary endpoint, we required at least 100 comparisons each from at least 30 patients so that at least 20 comparisons would be available from the train-of-four range of primary interest for each patient. Expecting dropouts due to technical difficulties with the setup caused by electrical disturbances of operating room equipment, motion artefacts caused by patient positioning, and pharmacologic protocol violations (*e.g.*, sugammadex administration), we decided to enroll 50 patients and monitor the entire neuromuscular block period. Further details on sample size calculation are presented in the Supplemental Digital Content (http://links.lww.com/ALN/C662).

Statistical Analysis

General Statistical Methods. As a general approach, we used the Bland–Altman analysis to assess the agreement of simultaneous measurements by the two devices.[29] The Bland–Altman analysis assesses the agreement of two measurement methods by quantifying the bias, limits of agreement, within-subject and between-subject variance, and repeatability of the methods.[30] Because multiple measurements were made on the same patient during the recovery process, we performed calculations appropriate for such data,[31] using the online calculator of the Leiden University Medical Center (The Netherlands) available at https://sec.lumc.nl/method_agreement_analysis/ba.html (accessed April 12, 2020).

We applied the Bland–Altman method in the analysis of the primary, secondary, and additional endpoints. In all analyses, we considered a difference less than 10% as acceptable agreement (bias, less than 10; limits of agreement, –5 to 5). For these calculations, original acceleromyography measurements were normalized to the mean of baseline train-of-four ratio, as recommended by Murphy.[32] Because normalization is unfortunately often neglected in clinical practice, raw data are probably more meaningful to clinicians; therefore, we also present results of the primary and secondary endpoints based on nonnormalized, raw data in the Supplemental Digital Content (http://links.lww.com/ALN/C662).

We used the R statistical environment (version 3.6.3., R Core Team 2020; Austria)[33] to prepare Bland–Altman plots using the "BlandAltmanLeh" package of R and to calculate statistics other than Bland–Altman analyses. We checked the normality of variables and residuals by the Shapiro–Wilk test, and the homogeneity of variances by the Bartlett test. Linear regression was calculated by the "lm" function of the "nlme" package. We used a paired *t* test to compare means of paired, normally distributed samples and the Wilcoxon signed-rank test to compare medians of paired, nonnormally distributed samples. In the text, we present means and either SDs or standard errors, as specified.

In 11 of 48 surgeries, 1 mg of neostigmine was administered to achieve complete recovery of shallow neuromuscular block before tracheal extubation, which likely

accelerated the train-of-four ratio recovery process compared with spontaneous recovery. To assess whether and how neostigmine affected our results, we performed all analyses excluding the measurements after neostigmine administration (n = 542 or 5.9% of 5,731 measurements). These results were qualitatively identical to those obtained with the full dataset; therefore, we present results obtained using the full dataset.

Specific Analyses. To analyze differences in the baseline measurements of train-of-four ratios recorded by the two devices, we calculated mean baseline train-of-four ratio values, SDs, and coefficients of variation for each patient and then used a paired *t* test to analyze the differences in means and F-test to analyze the difference in variance between acceleromyography and EMG readings. We also performed a random-effects one-way ANOVA to calculate the repeatability of nonmatched baseline train-of-four ratio measurements.

We analyzed the number of posttetanic counts (detected by the two devices during deep block (train-of-four count, 0; posttetanic count greater than or equal to 1) by Bland–Altman analysis to study bias, limits of agreement, and repeatability. We also used a linear mixed-effects model with device (acceleromyography or EMG) as fixed effect and patient identity as a random effect to calculate adjusted means to compare the number of posttetanic counts by the two devices and to control for the repeated measurements.

We also used the Bland–Altman analysis to compare train-of-four counts during deep and moderate block. During the transition period from moderate to shallow neuromuscular block (train-of-four count, 4; train-of-four ratio less than 40%), often one device indicated moderate block (train-of-four count 1 to 4) while the other device indicated shallow block (train-of-four ratio; Supplemental Digital Content fig. S1, http://links.lww.com/ALN/C662). These data pairs were not included in the analysis to avoid comparing train-of-four counts to train-of-four ratios.

Results

Demographic Parameters

A total of 50 patients were enrolled in this study. Two patients were excluded due to drug administration protocol violations, resulting in data from 48 patients being available for analysis (table 1). The reasons for excluding patients were succinylcholine administration due to difficult mask ventilation (patient 6) and intraoperative administration of magnesium sulfate after sugammadex reversal due to intraoperative supraventricular arrhythmia (patient 24). No technical difficulties were experienced with synchronization of the devices that would warrant patient exclusion. The number of patients available for data analysis was considerably larger than that required for meaningful estimates of bias, limits of agreement, and repeatability anticipated in the power analysis.

Primary Endpoint

We recorded 5,731 pairs of simultaneous measurements of train-of-four ratios with acceleromyography and EMG during recovery in the 48 patients (mean ± SD, 119.4 ± 50.6 data pairs per patient; range, 39 to 221), of which at least one measurement showed train-of-four ratio greater than or equal to 80% in 2,977 data pairs. Of these 2,977 data pairs, both acceleromyography and EMG recordings showed a train-of-four ratio greater than or equal to 80% in 2,236 (75.1%) pairs. In 693 (23.3%) of the data pairs, the acceleromyography-measured train-of-four ratio was greater than or equal to 80%, while the EMG train-of-four ratio was less than 80%; in the remaining 48 (1.6%) data pairs, the EMG-measured train-of-four ratio was greater than or equal to 80%, while acceleromyography train-of-four ratio was less than 80%. Acceleromyography more frequently indicated recovery earlier than EMG, resulting in more acceleromyography measurements of train-of-four ratio greater than or equal to 80% than with the EMG monitor (fig. 2).

The Bland–Altman analysis of normalized data showed that the bias when the acceleromyography train-of-four ratio reading was greater than or equal to 80% (n = 2,929 data pairs) was 1.3 ± standard error 1.0 with limits of agreement −14.0 to 16.6 (table 2, fig. 3A; for nonnormalized data, see Supplemental Digital Content table S1 and Supplemental Digital Content fig. S2 (http://links.lww.com/ALN/C662). The bias was less (−0.5 ± standard error 0.9), and the limits of agreement were similar (−14.7 to 13.6) when the EMG reading was greater than or equal to 80% (n = 2,284 data pairs; table 2, fig. 3B). The positive bias confirmed that the acceleromyography monitor showed recovery earlier than the EMG monitor (fig. 2).

The between-subject variance was greater than the within-subject variance, and smaller repeatability coefficients indicated that repeatability and precision were higher for acceleromyography (6.3) than for EMG (8.4)

Table 1. Patient Characteristics (n = 48)

Variable	Parameter	Value
Age (yr)	Median (range)	49 (43–60)
Weight (kg)	Mean ± SD	75.7 ± 14.1
Height (cm)	Median (range)	165.6 (159–171)
Body mass index (kg/m^2)	Median (range)	27.8 (23.8–30.9)
Male: female	No. of individuals	10: 38
Examined side	Dominant: nondominant	3: 45
Neuromuscular blocking agent	Rocuronium: atracurium: mivacurium: cisatracurium	31: 11: 5: 1
Intraoperative repeat of neuromuscular blocking agent	Yes: no	7: 41
Neostigmine reversal	Yes: no	11: 37

Table 2. Results of Bland–Altman Analysis of the Primary Endpoint (Normalized Train-of-four Ratio Greater than or Equal to 80%)

Train-of-four Ratio ≥ 80% by	Metric	Value
Acceleromyography (No. = 2,929)	Bias ± standard error	1.3 ± 1.0
	95% CI of the bias	–0.6 to 3.3
	Limits of agreement	–14.0 to 16.6
	95% CI lower limits of agreement	–17.3 to –11.5
	95% CI upper limits of agreement	14.1 to 20.0
	Within-subject variance ± standard error	21.7 ± 0.6
	Between-subjects variance ± standard error	39.2 ± 8.6
	Spearman ρ ± standard error	–0.2 ± 0.1
	Ratio of between-subjects variance and total variance ± standard error	0.6 ± 0.1
	Repeatability acceleromyography	6.3 (95% CI, 6.2 to 6.5)
	Repeatability EMG	8.4 (95% CI, 8.2 to 8.6)
	Repeatability acceleromyography/EMG	0.8 (95% CI, 0.7 to 0.8)
EMG (No. = 2,284)	Bias ± standard error	–0.5 ± 0.9
	95% CI of the bias	–2.4 to 1.3
	Limits of agreement	–14.7 to 13.6
	95% CI lower limits of agreement	–18.0 to –12.2
	95% CI upper limits of agreement	11.1 to 17.0
	Within-subject variance ± standard error	15.7 ± 0.5
	Between-subjects variance ± standard error	36.4 ± 8.1
	Spearman ρ ± standard error	0.3 ± 0.1
	Ratio of between-subjects variance and total variance ± standard error	0.7 ± 0.1
	Repeatability acceleromyography	5.1 (95% CI, 5.0 to 5.3)
	Repeatability EMG	4.8 (95% CI, 4.7 to 4.9)
	Repeatability acceleromyography/EMG	1.1 (95% CI, 1.0 to 1.1)

EMG, electromyography.

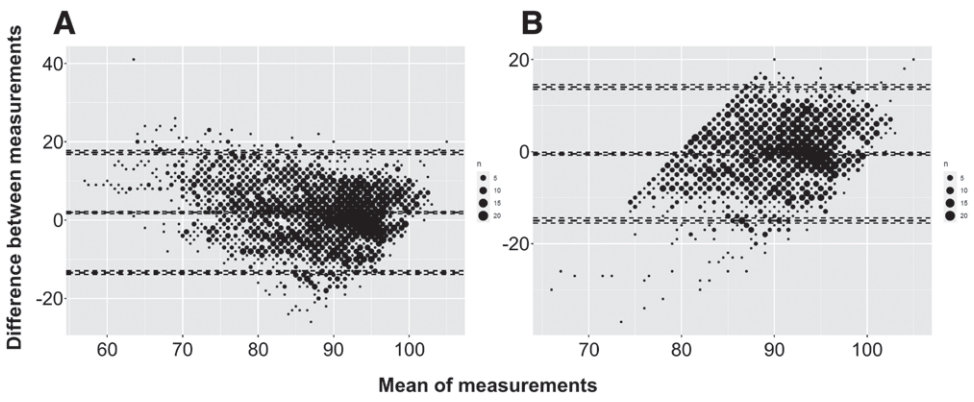

Fig. 3. Bland–Altman plots of the pairwise differences between train-of-four ratios measured by acceleromyography and electromyography (EMG; *y-axis*) against the mean of the two measurements (*x-axis*) in the recovery range of train-of-four ratio greater than or equal to 80% based on the acceleromyography measurement (*A*) and based on the EMG measurement (*B*). The *center line* represents the bias with 95% CI, and *bottom* and *top lines* represent the lower and upper limits of agreement with 95% CI, respectively. The size of data points is proportional to the number of measurements.

when the acceleromyography reading was above 80% (table 2), likely as a result of more measurements and larger sample size from the acceleromyography monitor than from the EMG monitor in this range (noted earlier in this section). When the EMG reading was above 80%, repeatability was slightly higher for EMG than for acceleromyography (4.8 *vs.* 5.1, respectively; table 2).

Secondary Endpoints

In the train-of-four ratio less than 80% range based on acceleromyography measurement (n = 2,802 data pairs), the Bland–Altman analysis of normalized data showed that the bias was 2.1 ± standard error 1.1 with limits of agreement –16.1 to 20.2 (table 3, fig. 4). In the train-of-four

Table 3. Results of Bland–Altman Analysis of the Secondary Endpoint (Normalized Train-of-four Ratios Less than 80%)

Train-of-four Ratio < 80% by	Metric	Value
Acceleromyography (No. = 2,802)	Bias ± standard error	2.1 ± 1.1
	95% CI of the bias	–0.2 to 4.4
	Limits of agreement	–16.1 to 20.2
	95% CI lower limits of agreement	–20.1 to –13.0
	95% CI upper limits of agreement	17.2 to 24.3
	Within-subject variance ± standard error	24.7 ± 0.7
	Between-subjects variance ± standard error	61.0 ± 12.7
	Spearman ρ ± standard error	0.3 ± 0.1
	Ratio of between-subjects variance and total variance ± standard error	0.7 ± 0.0
	Repeatability acceleromyography	16.7 (95% CI, 16.3 to 17.1)
	Repeatability EMG	16.1 (95% CI, 15.7 to 16.6)
	Repeatability acceleromyography/EMG	1.0 (95% CI, 1.0 to 1.0)
EMG (No. = 3,447)	Bias ± standard error	2.6 ± 1.0
	95% CI of the bias	0.5 to 4.7
	Limits of agreement	–14.4 to 19.6
	95% CI lower limits of agreement	–18.1 to –11.6
	95% CI upper limits of agreement	16.8 to 23.3
	Within-subject variance ± standard error	24.0 ± 0.6
	Between-subjects variance ± standard error	51.2 ± 10.6
	Spearman ρ ± standard error	0.4 ± 0.1
	Ratio of between-subjects variance and total variance ± standard error	0.7 ± 0.1
	Repeatability acceleromyography	19.0 (95% CI, 18.5 to 19.4)
	Repeatability EMG	17.7 (95% CI, 17.3 to 18.1)
	Repeatability acceleromyography/EMG	1.1 (95% CI, 1.1 to 1.1)

EMG, electromyography.

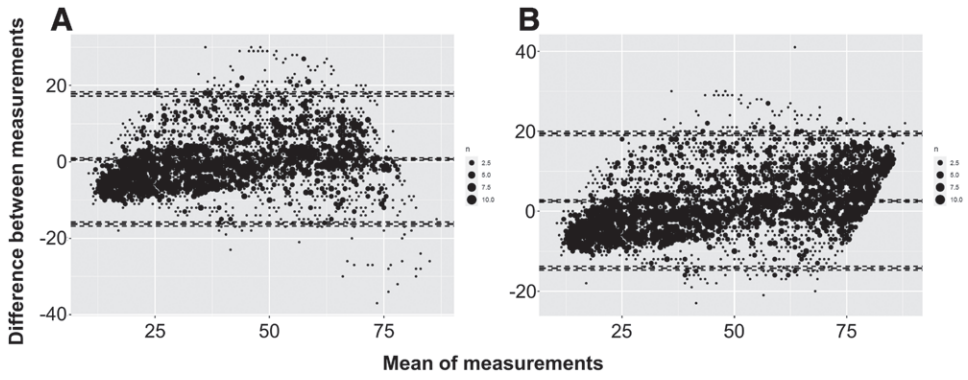

Fig. 4. Bland–Altman plots of the pairwise differences between train-of-four ratios measured by acceleromyography and electromyography (EMG; *y-axis*) against the mean of the two measurements (*x-axis*) in the range train-of-four ratio less than 80% based on the acceleromyography measurement (*A*) and based on the EMG measurement (*B*). The *center line* represents the bias with 95% CI, and *bottom* and *top lines* represent the lower and upper limits of agreement with 95% CI, respectively. The size of data points is proportional to the number of measurements.

ratio less than 80% range based on EMG measurement (n = 3,447 data pairs; table 3, fig. 4), the bias and limits of agreement were similar (2.6 ± standard error 1.0 and –14.4 to 19.6, respectively). Results of Bland–Altman analyses in successive train-of-four ratio ranges of 20% (as previously reported)[28] are given in Supplemental Digital Content (tables S3 and S4, figs. S3 and S4, http://links.lww.com/ALN/C662).

Repeated baseline train-of-four ratio measurements could be obtained in 47 of the 48 patients. In these patients, between two and five baseline train-of-four stimulations were recorded after induction of anesthesia but before neuromuscular blocking agent administration. The mean baseline train-of-four ratio measurements was higher with acceleromyography (mean ± SD, 108.8 ± 7.2%; median, 108%; range, 93 to 141%) than with EMG (100.7 ± 1.5%;

101%; 96 to 108%; paired $t = 7.95$; $df = 46$; $P < 0.0001$). The variance of baseline train-of-four ratio measurements with the acceleromyography device was higher than the variance of measurements with the EMG device (51.85 *vs*. 2.22, respectively; F = 23.35; $P < 0.0001$). As a result, the mean coefficient of variation was more than four times higher in baseline train-of-four ratio measurements by acceleromyography (6.6) than by EMG (1.4). The calculation of repeatability by a random-effects one-way ANOVA showed higher repeatability for EMG (repeatability coefficient: 0.48 ± standard error 0.09; 95% CI, 0.29 to 0.64) than for acceleromyography (0.73 ± 0.06; 95% CI, 0.61 to 0.82).

The mean ± SD of baseline compound muscle action potential amplitudes recorded by the EMG device was 11.47 ± 4.36 mV (range, 3.2 to 20.9 mV).

Additional Endpoints (Based on Acceleromyography Measurements)

Posttetanic Count Measurements in Deep Block. During deep block, 87 posttetanic count measurements were recorded in 34 patients. The mean ± SD number of measurements per patient was 2.6 ± 1.6 (range, 1 to 9). The acceleromyography monitor recorded twice as many signals (mean adjusted for repeated measurements: 8.6 ± standard error 0.7; 95% CI, 7.3 to 9.9) as the EMG monitor (4.3 ± standard error 0.7; 95% CI, 3.0 to 5.6; F(1,139) = 29.32; $P < 0.0001$). The Bland–Altman analysis showed a bias of 4.3 and suggested wide limits of agreement, heteroscedasticity of variances, and higher between-subject than within-subject variance (table 4, fig. 5A).

Train-of-four Count Measurement in Deep and Moderate Block. During deep and moderate neuromuscular block, 4,186 data pairs were analyzed. In the Bland–Altman analysis, the train-of-four count measurements were biased toward acceleromyography by 0.7 ± standard error 0.1 responses (95% CI, 0.4 to 0.9 responses), with limits of agreement of −1.5 to 2.8 responses (table 4, fig. 5B). Clinically, this suggests that in general, the acceleromyography monitor indicated a higher number of train-of-four counts than the EMG monitor by one response.

Transition from Moderate to Shallow Block. At the time of recovery from moderate to shallow block, the median of the first train-of-four ratios displayed by the acceleromyography monitor was 12% (interquartile range, 9.5 to 14%). This was significantly lower than the median of the first displayed train-of-four ratios by the EMG monitor (19%; 17 to 24%; Wilcoxon signed-rank test, $P < 0.001$). The first recovery train-of-four ratios displayed by EMG were influenced by the baseline compound muscle action potential amplitudes, so that higher baseline compound muscle action potential amplitudes yielded earlier detection of recovery train-of-four ratios (fig. 6, linear regression, $R^2 = 0.55$; b = −1.30 ± standard error 0.17; F(1,46) = 56.92; $P < 0.0001$).

Discussion

In this simultaneous, ipsilateral, same nerve/muscle comparison of the acceleromyography-based and EMG-based neuromuscular monitors, the EMG-derived train-of-four ratios showed good agreement with acceleromyography-derived measurements in shallow and minimal neuromuscular block. The bias in the primary endpoint was 1.3 or 0.5, depending on whether acceleromyography greater than or equal to 80% or EMG greater than or equal to 80% was used to determine the range boundary, and this bias was less than the acceptable difference set *a priori* (10%). However, the bias based on the nonnormalized (raw) data was considerably larger (9.3 or 7.8, respectively; Supplemental Digital Content table S1, http://links.lww.com/ALN/C662), and this bias was close to the acceptable limit (10%). In contrast, the limits of agreement (−14.0 to 13.6 at the minimum) were wider than the acceptable difference (−5 to 5).

Nevertheless, our results of raw train-of-four ratios showed a lower bias between acceleromyography- and electromyography-derived train-of-four ratios than previous reports did[14,18,28]; the overall bias of raw train-of-four ratios was 7.0 ± standard error 1.1 with limits of agreement of −12.0 to 25.9 (Supplemental Digital Content table S3, http://links.lww.com/ALN/C662). Some investigators reported a bias of 14.9,[14] while others reported an overall bias of 17.6, with similarly wide limits of agreement (−4.5 to 39.6).[28] These differences might be explained by the different study designs and statistical approaches, and by the recording of evoked responses from different devices and muscles. A likely explanation for the lower bias between EMG and acceleromyography devices reported in our study is its design. Previous comparisons of acceleromyography and EMG technologies have been hampered by the inability to simultaneously record acceleromyography and EMG responses from the same muscle, introducing another potential source of variability. The synchronization of the two neuromuscular monitors in this investigation *via* fiber optic link provided an opportunity to exclude the arm-to-arm variability factors, such as hand dominance, electrode positioning, blood perfusion, temperature, drug administration site, and lack of stimulation synchronization.[34] Because of simultaneous stimulation and recording in the same muscle afforded by the two monitors, any differences observed in the study can only be attributable to the two monitoring technologies (and the fact that they are recording different physiologic phenomena), and not to external factors or differences in individual muscle response.

In line with previous investigations,[18,19] this study has also shown that the normalization of acceleromyography-derived train-of-four ratios is crucial to correctly identify the threshold of recovery. First, if a baseline (before administration of a neuromuscular blocking agent) train-of-four ratio of 140% was obtained by acceleromyography, a return to 90% of baseline would not occur until train-of-four ratio was 126% (0.9 × 140%). In this study, the normalization

Table 4. Bland–Altman Analysis Results for Posttetanic Count Measurements and Train-of-four Count Measurements by the Acceleromyography and Electromyography Monitors

Variable	Metric	Value ± Standard Error	95% CI (Lower, Upper)
Posttetanic count	Bias	4.3 ± 1.1	2.1 to 6.5
	Limit of agreement, lower	–8.7	–13.0 to –5.7
	Limit of agreement, upper	17.3	14.2 to 21.6
	Within-subject variance	10.4 ± 2.0	
	Between-subjects variance	33.6 ± 9.7	
Train-of-four count	Bias	0.7 ± 0.1	0.4 to 0.9
	Limit of agreement, lower	–1.5	–1.9 to –1.2
	Limit of agreement, upper	2.8	2.5 to 3.2
	Within-subject variance	0.6 ± 0.0	
	Between-subjects variance	0.7 ± 0.1	

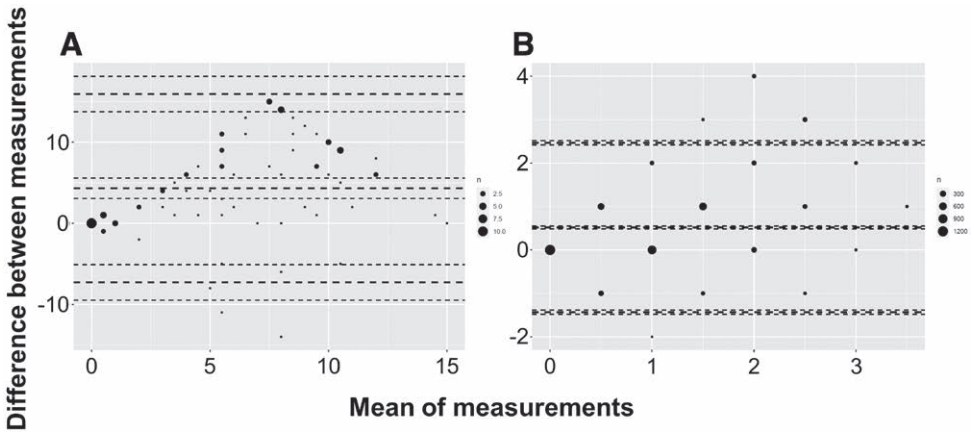

Fig. 5. Bland–Altman plots of the pairwise differences in deep-block posttetanic count (*A*) and train-of-four count (*B*) measurements by acceleromyography and electromyography monitors (*y-axis*) as a function of the mean of the two measurements (*x-axis*). The *center line* represents the bias with 95% CI, and *bottom* and *top lines* represent the lower and upper limits of agreement with 95% CI, respectively. The size of data points is proportional to the number of measurements.

of acceleromyography train-of-four ratios not only significantly decreased the bias between the two techniques but also improved the precision of acceleromyography measurements (tables 2 and 3 and Supplemental Digital Content tables S1 and S2, http://links.lww.com/ALN/C662). In the clinical setting, however, normalization of acceleromyography-derived train-of-four ratios before tracheal extubation is rarely, if ever, performed. It is therefore likely that the patients' degree of recovery immediately before extubation is overestimated; this may explain the persistently high incidence of residual neuromuscular block when tested in the postanesthesia care unit.[35] Second, in light of existing data that the patients' hypoxic ventilatory response may well be blunted at a train-of-four ratio of 90%,[36] while the vital capacity is depressed by 16% at this level of recovery,[37] a difference of 10% between nonnormalized and normalized train-of-four ratios may well be clinically significant for patient safety. This difference also lends support to the contention[20] that the minimum threshold of neuromuscular recovery with acceleromyography should be a train-of-four ratio greater than or equal to 100%, rather than the current threshold of train-of-four ratio greater than or equal to 90%.

Similar to previous observations,[28] EMG had slightly higher repeatability (lower coefficients) in the primary endpoint (except in the acceleromyography greater than or equal to 80% range due to larger sample size), and lower variance and higher repeatability in the secondary endpoint in our investigation (tables 2 and 3). The difference was even more evident when EMG data were compared to raw acceleromyography measurements (Supplemental Digital Content tables S1 and S2, http://links.lww.com/ALN/C662). Based on all these observations, our results suggest that the EMG-based device is a better indicator of adequate recovery from neuromuscular block and readiness for safe tracheal extubation than the acceleromyography monitor.

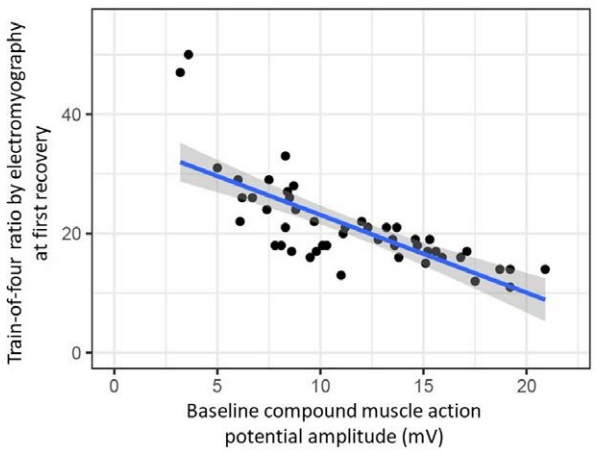

Fig. 6. Relationship between baseline compound muscle action potential amplitude (in millivolts) and first recovery train-of-four ratio measured by the electromyography monitor.

As previously reported,[18,38] baseline train-of-four ratios obtained with EMG were more consistent and showed less deviation from the baseline train-of-four ratio of 100% than with acceleromyography. As recommended for acceleromyography-based investigations,[26] we performed our measurements using the TOF-Watch Hand Adapter to improve the stability of baseline responses. This application of preload to the thumb and fixation of the monitored extremity also improves the precision of the EMG-derived baseline train-of-four ratios.[39] Nevertheless, the low variation coefficient of the baseline measurements with EMG suggests that the use of preload and normalization of responses to baseline value is unnecessary with this device (as opposed to acceleromyography-based monitors), improving its clinical acceptance and routine use.

The primary aim of our study was to describe the EMG-based monitor's ability to accurately indicate recovery from neuromuscular block. Precise measurement of neuromuscular block is essential throughout surgery to maintain adequate muscle relaxation, and to facilitate making correct decisions about additional dosing of neuromuscular blocking agents, as well as the timing, type, and dose of antagonist. Therefore, we aimed to also examine the performance and reliability of the EMG monitor during deep, moderate, shallow, and minimal phases of neuromuscular block.

The agreement between acceleromyography and EMG responses during deep and moderate block was not as narrow as during shallower degrees of block. The EMG showed a delay (*i.e.*, indicated slower recovery from neuromuscular block) in posttetanic counts and train-of-four counts compared to the acceleromyography monitor; this difference was not attributable exclusively to the differences between the two techniques, but rather to a relatively high sensing threshold (noise filter) of the EMG-based monitor. A technology-specific limitation of EMG is that it can be disturbed by electromagnetic emissions in the operating room environment.[25] To avoid false train-of-four readings induced by electrical interference, the EMG monitor employs a noise filter set to 1 mV, which disregards any electrical signals below this amplitude threshold. The last decaying responses (less than 1 mV) to posttetanic count and train-of-four stimulation may thus be disregarded as "subthreshold," indicating lower degrees of recovery (deeper block). This may explain the discrepancy between the number of posttetanic count and train-of-four counts detected by the EMG- *versus* acceleromyography-based monitor.

During recovery from neuromuscular block, the difference in the time to first reappearance of the fourth twitch of train-of-four between the EMG and acceleromyography monitors was variable (Supplemental Digital content fig. S1, http://links.lww.com/ALN/C662). While some patients showed good synchrony between the start of train-of-four recovery (first return of fourth twitch of train-of-four) with both monitors, others exhibited significant delay in the return of fourth twitch of train-of-four by EMG (fig. 2). We investigated the factors that might explain this difference and found a correlation between the baseline compound muscle action potential amplitude and the recovery of fourth twitch of train-of-four: The greater the baseline compound muscle action potential signal (the better the signal quality), the earlier the EMG monitor displayed train-of-four ratios, and the closer it correlated with the acceleromyography-obtained train-of-four ratio values (fig. 6). This should be predictable, since a fixed 1-mV threshold represents a greater percent of a smaller amplitude baseline response than of a larger baseline EMG amplitude. Based on previous work, which has shown that the first twitch of the train-of-four ratio becomes discernible by palpation when its mechanomyographic height recovers to between 5 to 10% of control,[40] we might conclude this filter would affect the sensitivity of the measurements when the baseline compound muscle action potential amplitudes are low (less than 10 mV). When the train-of-four count is 2, the compound muscle action potential amplitude of the first twitch is 16 to 20% of baseline amplitude.[41,42] Thus, if the baseline value of the first twitch is 7.5 mV, the EMG monitor will at best display a train-of-four count of 1 (20% of 7.5 mV = 1.5 mV). At a baseline compound muscle action potential height of 5 mV, the EMG monitor is likely to display a train-of-four count of 0 or 1 when the acceleromyography-derived train-of-four count is 2. Baseline EMG responses of this magnitude (less than 7 mV) may be anticipated in 5 to 10% of individuals (fig. 6). A moderate block (a train-of-four count of 1 to 2) may thus be assessed as deep block (train-of-four count, 0) at baseline compound muscle action potential height values less than 7.0 mV.

Further studies are needed to determine the optimal balance between threshold amplitude sensitivity and patient safety. However, it is difficult to define a "twitch" as the

sensation threshold during clinical examination, and such tactile evaluations of response (contractions) do not necessarily correlate with quantitative measurements. According to previous investigations, clinicians are likely to perceive the number of subjectively determined twitches higher than objective acceleromyography monitors.[43,44] In a recent study, the order of sensitivity in detecting twitch count was mechanomyography (most sensitive), EMG was most similar to palpation, and acceleromyography was least sensitive.[15]

Our study has several limitations. First, the type and dose of neuromuscular blocking agent were not standardized. This was a conscious decision during study design; it allowed us to obtain spontaneous recovery curves from several neuromuscular blocking agents, since there is no reason to suspect that acceleromyography and EMG recovery curves would be differentially influenced by the type of neuromuscular blocking agent.

Second, we used a predetermined stimulating current intensity (60 mA) instead of performing type 2 calibration of the acceleromyography monitor, which would have identified the supramaximal current intensity as well as set the gain. The reason for this was that the two devices could not be calibrated separately; the same acceleromyography device was used to provide nerve stimulation, while both monitors recorded the responses simultaneously. In a previous volunteer study using the TetraGraph and in which no neuromuscular blocking agent was administered, 20-, 30-, and 40-mA stimulating current intensities proved insufficient to evoke detectable muscle twitches in 18%, 9%, and 5% of the volunteers, respectively.[45] Therefore, using low stimulating current intensity in the clinical setting could have artificially decreased the performance of the EMG-based monitor when monitoring deep and moderate neuromuscular block by decreasing the baseline (and subsequent) compound muscle action potential amplitudes.

Third, tetanic stimulation was not included in the calibration protocol to prevent the staircase phenomenon typical of acceleromyography (amplification induced by repetitive stimulation).[46] As EMG is less subject to baseline drift,[47] we attempted to test the TetraGraph monitor in everyday clinical settings, and we omitted this step, which is not part of routine clinical practice.

Fourth, while we attempted to describe the entire spectrum of neuromuscular recovery, our analyses could not include cases when the simultaneous measurements recorded distinct types of data, *e.g.*, train-of-four ratio, a continuous variable on one device, and train-of-four count, a discrete variable on the other device (Supplemental Digital Content fig. S1, http://links.lww.com/ALN/C662). Because measurements could not be compared quantitatively in such cases, it is possible that our results may be biased in the direction of minimizing differences between the two devices, which needs to be considered in the interpretation of our results.

Finally, this study did not compare the EMG device to mechanomyography as recommended by the 2007 Good Clinical Research Practice Guidelines, which state that new monitoring devices should be validated against mechanomyography.[26] However, mechanomyography is no longer commercially available. Although several investigations showed that acceleromyography-derived train-of-four stimulation results are not interchangeable with mechanomyography-derived measurements,[20,48,49] the acceleromyography-based monitor has been used in multiple investigations as the reference device.[10–13,50] Our aim was to provide relevant and comparable information for clinicians regarding the usability of the EMG device.

Conclusions

In this study, the acceleromyography-based monitor was more sensitive in detecting the early return of neuromuscular recovery but was less sensitive at near-recovery or complete recovery of neuromuscular function than the EMG-based monitor. The normalization of acceleromyography-derived recovery measurements appears crucial to correctly identify the threshold for adequate recovery (train-of-four ratio greater than or equal to 90%). The EMG-based monitor had greater repeatability in the primary and secondary endpoints (recovery train-of-four ratios) than acceleromyography. This difference between monitors was even more evident when EMG data were compared to raw (nonnormalized) rather than normalized acceleromyography measurements. Our results suggest that the EMG-based device is a better indicator of adequate recovery from neuromuscular block and readiness for safe tracheal extubation than the acceleromyography monitor.

Acknowledgments

The authors would like to express their acknowledgments to medical students Nóra Mező and Maria-Regina Udochi Obodozie, Faculty of Medicine, University of Debrecen, Debrecen, Hungary, for their contribution to intraoperative data collection.

Research Support

The study was supported by the Hungarian Brain Research Program grant 510 No. KTIA 13 NAP A II/5 (Budapest, Hungary) and funded by the University of Debrecen Department of Anesthesiology and Intensive Care (Debrecen, Hungary). The study device (TetraGraph) and synchronization system were provided by Senzime AB (Sweden) for the duration of the study.

Competing Interests

Dr. Hampton is a shareholder in Senzime AB (Uppsala, Sweden). Mr. Gray is a consultant design engineer to

Senzime AB. Dr. Brull has intellectual property assigned to Mayo Clinic (Rochester, Minnesota); has received research funding form Merck & Co., Inc. (Kenilworth, New Jersey; funds to Mayo Clinic, Jacksonville, Florida); is a consultant for Merck & Co., Inc.; is chief medical officer and shareholder in Senzime AB; and is a member of the Scientific Advisory Boards for the Doctors Company (Napa, California), NMD Pharma (Aarhus, Denmark), Coala Life Inc. (Irvine, California), and Takeda Pharmaceuticals (Cambridge, Massachusetts). The other authors declare no competing interests.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

From Paralytic Poison to Medicinal Marvel: Curare Advances Anesthesia

After extracting curare from vines like *Chondrodendron tomentosum* (*left*), South American natives stored the tarry toxin in pots (*right*) and slathered it on arrow tips to slay enemies and prey. Scientists would call the active compound *d*-tubocurarine for the bamboo tubes (*right*) that held the arrows. In the 1730s, French mathematician Charles Marie de La Condamine became the first to study curare during an Andean expedition to prove Newton's view of Earth as an oblate spheroid—rounder at the Equator than the poles. At the time, he attributed the death of a curare-injected hen to respiratory muscle paralysis. In a famed 1814 experiment, English naturalist Charles Waterton and colleagues used artificial ventilation to keep a curarized donkey alive. But it was not until 1938, when North American explorer Richard Gill imported 12 kg of Ecuadorian curare to treat his own muscle spasms, that the arrow poison would enter anesthetic practice. After E. R. Squibb & Sons acquired Gill's supply and purified it to make Intocostrin (*right*), former anesthesiologist and Squibb advisor Lewis H. Wright supplied the drug to Canadian anesthesiologist Harold Griffith. The latter soon published in Anesthesiology his success with Intocostrin for rapid muscle relaxation in 25 lightly anesthetized patients (1942; 3:418–20). And so began a revolution, in which the drawbacks of deep anesthesia—cardiac depression, explosion risk, severe nausea, and prolonged emergence—could finally be mitigated. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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