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Single Acceleromyographic Train-of-Four, 100-Hertz Tetanus or Double-Burst Stimulation: Which Test Performs Better to Detect Residual Paralysis?

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Background: **Acceleromyography is regularly used as an isolated test to detect residual paralysis. The performance of acceleromyography, however, has not been investigated for the setting where calibration is impossible. This study first evaluated the reliability of a single acceleromyographic train-of-four (TOF) ratio (T4/T1) to detect residual paralysis and compared it with tactile estimation of fade after double-burst stimulation and 100-Hz, 5-s tetanus. The second part of the study investigated whether uncalibrated acceleromyographic TOF ratio can predict time to complete recovery.**

Methods: **Anesthesia was induced and maintained with propofol and sufentanil. In the first part of the study (n = 40) neuromuscular blockade was assessed by mechanomyography. After signal stabilization 0.15 mg/kg cisatracurium was given. At the end of surgery a first physician evaluated manual fade after double-burst stimulation, then, in the same patient, a single acceleromyographic TOF ratio was recorded; thereafter a second physician, unaware of the results, assessed fade after a 100-Hz, 5-s tetanus. Sensitivity, specificity, and negative and positive predictive value of the three tests to detect a mechanomyographic TOF ≥0.9 were calculated. In the second part of the study (n = 25) neuromuscular recovery was assessed simultaneously with mechanomyography and uncalibrated acceleromyography (current set manually at 60 mA); the time intervals from acceleromyographic TOF ratios of 0.6, 0.7, 0.8, and 0.9 until complete recovery, *i.e.*, adductor pollicis mechanomyography 0.9 TOF ratios, were determined.**

Results: **The sensitivity of double burst stimulation was 29% (95% confidence interval [CI], 13–45%), its specificity was 100%, the negative predictive value was 29% (95% CI, 13–45%), and the positive predictive value was 100%. For a single acceleromyographic TOF ratio the respective values were 70% (95% CI, 54–86%), 88% (95% CI, 67–100%), 47% (95% CI, 23–71%) and 95% (95% CI, 86–100%). The respective values for 100-Hz, 5-s tetanus were 74% (95% CI, 59–89%), 55% (95% CI, 23–88%), 38% (95% CI, 12–64%), and 85% (95% CI, 72 -99%). At an uncalibrated acceleromyographic TOF ratio was 0.6, complete recovery occurred within 16 min (95% CI, 13.5–17.8 min). At acceleromyographic TOF ratios of 0.7, 0.8, and 0.9 this time interval was 12.5 min (95% CI, 10.2–14.8 min), 8 min (95% CI, 6.1–9.9 min), and 4 min (95% CI, 2.7–5.8 min), respectively.**

Conclusions: **Acceleromyographic TOF performed better than double-burst stimulation or 100 Hz tetanus, but it did not reliably detect low degrees of residual paralysis when used as an isolated test at the end of surgery. The uncalibrated acceleromyographic TOF ratio, however, did predict the time to complete recovery.**

RESIDUAL paralysis (RP), defined as an adductor pollicis mechanomyographic train-of-four (TOF) ratio <0.9, is potentially harmful for patients and remains frequent even with myorelaxants of intermediate duration of action.[1–4] Several studies found that quantitative neuromuscular monitoring using acceleromyography can reliably detect RP.[5–10] However, in these studies acceleromyography was calibrated before the myorelaxant was given. In clinical practice subjective and objective neuromuscular monitoring are often used for the first time after relaxants have been given, when initial calibration of the acceleromyography is impossible.[3,4,11–13] It has been suggested that single, uncalibrated acceleromyographic TOF cannot detect TOF reliably,[13,14] but this has not been investigated systematically.

The aims of this study were 1) to asses the performance of acceleromyography as an isolated test for RP at the end of surgery and to compare it with commonly used subjective tests, *i.e.*, double-burst stimulation (DBS) and 100-Hz, 5-s tetanus and 2) to evaluate whether uncalibrated acceleromyography can be used as a tool to predict the time interval needed to achieve complete neuromuscular recovery.

Materials and Methods

The research protocol was approved by the Institutional Review Committee (Centre Hospitalier Universitaire, Nancy/Brabois, France). Sixty-five adult American Society of Anesthesiologists physical status I–III patients were studied after giving written informed consent. All the patients were scheduled for elective surgical procedures under general anesthesia with tracheal intubation. Exclusion criteria included neuromuscular, hepatic, or renal disease, abnormal airway anatomy (Mallampati score 3 and 4), deviation from ideal body mass ≥25%, pregnancy, medication that influences neuromuscular blockade, or a history of allergic reaction to drugs used in the study. One hour before arrival on the operating room all patients were premedicated with 1 mg/kg hydroxyzine orally.

Forty patients were included in the first part of the

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study assessing the performance of an individual accelerometric TOF, DBS, and 100-Hz, 5-s tetanus to detect residual paralysis. Monitoring established on arrival in the operating room included electrocardiography, noninvasive arterial pressure monitoring, pulse oximetry and capnography. Anesthesia was induced in all patients with 2.5–3.5 mg/kg propofol and 0.2–0.3 μg/kg sufentanil and then maintained with propofol (8–12 $mg \cdot kg^{-1} \cdot h^{-1}$), intermittent bolus doses of sufentanil (0.1–0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and oxygen-nitrous oxide (50%/50%). The central temperature was maintained greater than 35°C using a warming blanket covering the upper body and both arms; end-tidal partial pressure of carbon dioxide was maintained between 32 and 36 mmHg. The force displacement transducer of the mechanomyography (Adductor Pollicis Monitoring®, Gould Instruments, Valley View, Ohio) was fixed to the thumb, and a 300 g preload was applied. The force displacement transducer was allocated randomly to the patient's dominant and nondominant hands. Surface electrodes were placed on the cleaned skin over the ulnar nerve of the corresponding wrist. A TOF Watch SX® nerve stimulator (Organon®, Oss, The Netherlands) was used for supramaximal TOF stimulation (four pulses of 0.2 ms in duration at a frequency of 2 Hz every 15 s). Mechanomyography was calibrated as recommended by the Good Clinical Research Practice Guidelines:[15] After a stable baseline response was obtained, *i.e.*, variation of no more than ±2% of the first response on TOF (T1) for at least 3 min, the supplied current was recalibrated and adjusted to produce supramaximal stimulation. Thereafter, cisatracurium 0.15 mg/kg was given as a bolus and tracheal intubation was performed. During surgery 0.03–0.05 mg/kg cisatracurium was reinjected as needed. Mechanomyography monitoring was continued until complete recovery of the TOF ratio (baseline values ±5%). At the end of surgery neuromuscular recovery was assessed at the opposite arm as follows. Surface electrodes were placed on the cleaned skin over the ulnar nerve of the corresponding wrist and the acceleration transducer of a second TOF Watch SX (Organon®) was fixed to the volar side of the distal phalanx of the respective thumb on a small elastic hand adapter (TOF Watch Handadapter®, Organon®). Then the TOF Watch SX was activated and the current was manually set at 60 mA. Thereafter a first physician tactilely evaluated the fade after a single DBS. Then the acceleromyography TOF ratio was obtained quantitatively after a single TOF stimulation (four pulses 0.2 ms in duration at a frequency of 2 Hz 2 s in duration). Thereafter a second physician, unaware of the results, replaced the TOF Watch SX by a DigiStim (Organon®) and visually evaluated the fade after a 100-Hz, 5-s tetanus stimulation. All three stimulation patterns were applied within 60 s and at the time of evaluation both physicians were unaware of the mechanomyography TOF ratio measured concomitantly at the opposite arm. In all cases neuromuscular recovery was assessed by the same two physicians not in charge of the patient.

The second aim was addressed in a study of 25 patients. Both arms were placed in the abducted position on padded arm boards and each patient was monitored on one arm with the mechanomyography (Adductor Pollicis Monitoring®, Gould Instruments) and on the other arm with the acceleromyography (TOF Watch SX®, Organon). The anesthetic protocol was the same as in the first part of the study. The force-displacement transducer of the mechanomyography was fixed to the thumb, and a 300 g preload was applied. The acceleration transducer of the acceleromyography was fixed to the volar side of the distal phalanx of the contralateral thumb, and the other fingertips were tightly fixed with tape. The transducers of mechanomyography and acceleromyography were allocated randomly to the patient's dominant and nondominant hands. Surface electrodes were placed on the cleaned skin over the ulnar nerves of both wrists and two TOF Watch SX® nerve stimulators were used for supramaximal TOF stimulation (four pulses of 0.2 ms in duration at a frequency of 2 Hz every 15 s). The mechanomyography was calibrated according to the Copenhagen Consensus Conference recommandations:[15] After obtaining a stable baseline of the mechanomyography response, *i.e.*, variation of no more than ±2% of the first response in TOF for at least 3 min, the supplied current was recalibrated and adjusted to produce supramaximal stimulation. Thereafter, cisatracurium 0.15 mg/kg was given as a bolus and orotracheal intubation was performed. During surgery bolus doses of 0.03–0.05 mg/kg cisatracurium were reinjected as clinically needed. At the end of surgery the acceleromyography was set manually at 60 mA without any period of calibration or signal stabilization. Stimulation of the acceleromyography and mechanomyography devices were synchronized, permitting simultaneous measurement of the force of contraction of the adductor pollicis on one hand and the acceleration of the thumb on the contralateral hand. Simultaneous mechanomyography and acceleromyography monitoring were continued until complete recovery of the mechanomyography (baseline TOF ratio ±5%). For each patient we calculated the time interval from an uncalibrated acceleromyography TOF ratio of 0.6, 0.7, 0.8, and 0.9 until a mechanomyography TOF ratio of 0.9.

Data were expressed as mean ± SD or mean and 95% confidence interval (CI). Sensitivity, specificity, and negative and positive predictive values of double-burst stimulation, punctual acceleromyographic train-of-four, and 100-Hz 5-s tetanus were calculated according to standard formulae[16] and presented as percentage and 95% confidence interval.

Table 1. Demographic Data

	Part I (n = 40)	Part II (n = 25)
Age (yr)	53 ± 16	55 ± 15
Weight (kg)	73 ± 14	72 ± 14
Sex (male/female)	24/16	14/11
ASA (I/II/III)	8/22/10	6/14/5

Values are mean ± SD.

ASA = American Society of Anesthesiologists (physical status); Part I = Comparison between a single acceleromyographic Train-Of-Four, Double-Burst Stimulation and 100-Hertz Tetanus to detect residual paralysis; Part II: Acceleromyography-based prediction of the time needed to complete neuromuscular recovery, i.e. an adductor pollicis mechanomyographic 0.9 Train-of-Four ratio.

Results

Data from all 65 patients could be analyzed without any dropouts. Demographic data of both parts of the study are shown in table 1.

Of the 40 patients included in the first part of the study only nine had no residual paralysis when neuromuscular recovery was assessed (*i.e.*, a mechanomyographic adductor pollicis TOF ratio ≥0.9), but simultaneous evaluation by DBS, a single acceleromyographic TOF, and 100 Hz, 5-s tetanus suggested complete neuromuscular recovery in 31, 17, and 13 patients, respectively. Moreover, DBS, single acceleromyographic TOF, and 100 Hz, 5-s tetanus revealed false negative tests in 22, nine, and eight patients, respectively. These results are summarized in table 2. The sensitivity of DBS, single acceleromyographic TOF ratio and 100-Hz, 5-s tetanus to detect an adductor pollicis mechanomyographic TOF ratio ≥0.9 were 29% (95% CI, 13–45%), 70% (95% CI, 54–86%), and 74% (95% CI, 59–89%), respectively. The specificity of these three tests were 100% (95% CI, 100–100%), 88% (95% CI, 67–100%), and 55% (95% CI, 23–88%), respectively. The negative predictive values were 29% (95% CI, 13–45%), 47% (95% CI, 23–71%), and 38% (95% CI, 12–64%); the positive predictive values of the three tests were 100% (95% CI, 100–100%), 95% (95% CI, 86–100%), and 85% (95% CI, 72–99%), respectively. These results are summarized in table 3.

When the uncalibrated acceleromyographic TOF ratio was 0.6, an adductor pollicis mechanomyographic TOF ratio ≥0.9 occurred within 16 min (95% CI, 13.5–17.8 min). At acceleromyographic ratios of 0.7, 0.8, and 0.9 this time interval was 12.5 min (95% CI, 10.2–14.8 min), 8 min (95% CI, 6.1–9.9 min), and 4 min (95% CI, 2.7–5.8 min), respectively. These results are displayed in figure 1.

Discussion

Our results demonstrate that acceleromyographic TOF as an isolated test for the detection of RP performs better than tactile estimation of the fade after DBS or 100-Hz, 5-s tetanus but cannot distinguish accurately patients

Table 2. Individual Mechanomyographic TOF ratio and the corresponding response after a single Acceleromyographic TOF, 100 Hz Tetanus and DBS (n = 40)

No.	MMG TOF ratio	AMG TOF ratio ≥ 0.9	100 Hz Tetanus No fade	DBS No fade
1	0.06			
2	0.16			
3	0.18			
4	0.20			
5	0.24			
6	0.28			
7	0.39			+
8	0.44			+
9	0.47		+	
10	0.48			
11	0.50			
12	0.52		+	+
13	0.57	+		+
14	0.60		+	+
15	0.60			+
16	0.63			+
17	0.66			+
18	0.67			+
19	0.72			+
20	0.73		+	+
21	0.76	+	+	+
22	0.76	+		+
23	0.79	+		+
24	0.79			+
25	0.80			+
26	0.81	+	+	+
27	0.82	+		+
28	0.84	+		+
29	0.85	+	+	+
30	0.86	+		+
31	0.87		+	+
32	0.90	+		+
33	0.90	+		+
34	0.91	+	+	+
35	0.91	+	+	+
36	0.92	+		+
37	0.93		+	+
38	0.94	+	+	+
39	0.94	+	+	+
40	1.00	+		+

AMG = acceleromyography; DBS = double-burst stimulation; MMG = mechanomyography; TOF = train-of-four.

+ = AMG TOF ratio ≥0.9, no detectable fade after 100 Hz Tetanus or DBS, respectively.

Table 3. Double-Burst Stimulation, Single Acceleromyographic Train-Of-Four and 100-Hertz, 5-s Tetanus to detect Residual Paralysis

	DBS	Single AMG	100-Hertz tetanus
Sensitivity	29 (13–45)	70 (54–86)	74 (59–89)
Specificity	100 (100–100)	88 (67–100)	55 (23–88)
Negative predictive value	29 (13–45)	47 (23–71)	38 (12–64)
Positive predictive value	100 (100–100)	95 (86–100)	85 (72–99)

Data are presented as percentage and 95% confidence interval.

AMG = acceleromyography; DBS = Double-Burst stimulation.

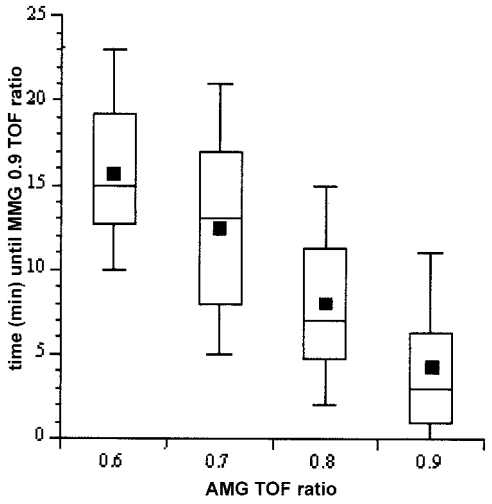

Fig. 1. ***Open boxes*** **represent the 25th to 75th percentiles and contain the median (*horizontal bars*) and mean (*full box*); vertical bars represent 10th and 90th percentiles. MMG = mechanomyography; AMG = acceleromyography; TOF = train-of-four.**

with low degrees of RP. However, uncalibrated acceleromyography may be a valuable tool to predict the time needed to attain a mechanomyographic (MMG) TOF ratio >0.9.

It has been previously demonstrated that tactile or visual evaluation of fade after DBS is more sensitive than TOF to detect residual neuromuscular block.[17] However, the limit of fade detection with DBS corresponds to a mechanomyographic 0.6 TOF ratio at best,[4,18] whereas an adductor pollicis mechanomyographic 0.9 TOF ratio is needed to exclude RP.[19–21] Detectable fade after DBS stimulation is a clear sign of inadequate neuromuscular recovery, but lack of fade does not exclude residual paralysis. Especially low degrees of residual paralysis are not detected by DBS (table 2). Moreover, the 100-Hz, 5-s tetanus has been evaluated for the detection of residual blockade.[22–24] In the current study the sensitivity of the 100-Hz, 5-s tetanus is 74% (59–89%) and thus in accordance with the findings from Baurain *et al.*[24] Nevertheless, one of four patients still had RP despite the absence of fade. The specificity of tetanus is poor. Only half of the patients without any degree of residual paralysis did not exhibit manually detectable fade (table 2). As a corollary, both stimulation patterns (*i.e.*, DBS and 100-Hz, 5-s tetanus) do not permit anticholinesterase to be reserved for those patients who actually need a reversal agent. These tests may only be part of a concept by which every patient previously exposed to a myorelaxant is also routinely antagonized at the end of surgery. Kopman *et al.*[25] recently affirmed this point of view, reporting that subjective monitoring with a simple nerve stimulator is sufficient to make critical episodes of postoperative weakness an infrequent occurrence, as long as every patient previously exposed to a myorelaxant is reversed at the end of surgery.

Justification of the routine use of objective acceleromyographic neuromuscular monitoring requires evidence that it further improves the management of residual paralysis, reliably allowing one to distinguish those patients who need reversal from those who do not.[26,27] Capron *et al.*[14] recently provided first evidence that set-up may influence the performance of acceleromyography. Only when there is an initial calibration of the acceleromyography a recovery of the TOF ratio to unity excludes residual paralysis with a high degree of certainty, *i.e.*, >95%. In clinical practice, however, acceleromyographic monitoring is often applied subsequent to the administration of muscle relaxants, without there having been an initial calibration.[3,4,11–13] As revealed by our study, in this clinical setting acceleromyographic TOF ratio ≥0.9 corresponds to the absence of residual paralysis in only half of the patients who have it (table 2). Several authors reported a certain interindividual variability in the response after acceleromyographic TOF stimulation.[5,13,28] Therefore one may speculate that a series of stimuli rather than one single TOF would further improve the performance of uncalibrated acceleromyographic TOF to detect RP. However, to eliminate any differences between both arms a one-arm technique was used in the current study, *i.e.*, all three tests were applied at the same arm, and to minimize the impact of the ongoing spontaneous neuromuscular recovery all three tests were applied within 60 s. Therefore we limited to one single acceleromyographic TOF rather than to a series of TOF stimuli. Moreover, the comparison of the negative predictive value of a single acceleromyographic TOF ratio assessed in the current study with the negative predictive value of uncalibrated but continuously applied acceleromyographic TOF recently determined by our group led us to suppose that both values are in the same range with no relevant difference between a single acceleromyographic TOF and a series of TOF stimuli (47%; 95% CI, 23–71% *versus* 40%; 95% CI, 23–59%, respectively). This may be explained by the high stimulus current chosen in the current study, *i.e.*, 60 mA, the highest stimulus current possible with the TOF Watch SX accelerometer. As a corollary, supramaximal stimulation may be expected in almost all patients.

Debaene *et al.*[4] examined the incidence of residual paralysis in more than 500 patients who received a single dose of intermediate-duration relaxant; of the 237 patients who had RP more than 60% of them had low degrees of RP with a TOF ratio between 0.7–0.9. Similar results have been reported by others.[9,13,29] As recently demonstrated by Eikermann *et al.*,[2] even slight degrees of RP (TOF ratio ~ 0.8) may have significant clinical consequences such as impaired inspiratory flow and upper airway obstruction. Therefore extubation at these slight degrees of RP may put the patient at risk. These findings have major consequences for the management of neuromuscular recovery: To avoid routine reversal

without impairing patient safety one must also be able to reliably detect those low degrees of RP. However, as revealed in the first part of this study a single, uncalibrated acceleromyographic TOF does not perform enough to detect low degrees of RP with certainty. Therefore we investigated in the second part whether uncalibrated but continuously applied acceleromyographic TOF may be used as a tool to predict the time interval needed to attain complete recovery from neuromuscular block (*i.e.*, a mechanomyographic TOF ratio of 0.9). Mechanomyography was applied as recommended in the Good Clinical Research Practice Guidelines,[15] whereas acceleromyography applied at the opposite arm was used as in most clinical cases *i.e.*, without calibration or period of signal stabilization and with current manually set. This particular set-up allows concluding from an acceleromyographic TOF ratio determined under conditions of current clinical practice to complete neuromuscular recovery assessed mechanomyographically as recommended for research purposes.[15] Our results demonstrate that an acceleromyographic TOF ratio can indicate the time interval needed to achieve complete recovery (fig. 1). These data apply to spontaneous recovery from cisatracurium neuromuscular block; they may differ when other neuromuscular blocking agents or anticholinesterases are used. Focusing on the time interval until complete neuromuscular recovery rather than on the raw TOF value can help the anesthesiologist to predict how long it will take for complete recovery to occur. Taking into account this information together with the time needed to finish surgery and the expected time to emergence from anesthesia, (derived from the anesthetic regimen and the depth of anesthesia), the anesthetist may decide whether in a given clinical situation reversal of neuromuscular blockade is indicated or not. Subjective monitoring, however, can provide only binary information (*i.e.*, presence or absence of fade) with no further insight in the degree of neuromuscular blockade. In addition, once the fade disappeared subjective monitoring can neither assess the effectiveness of reversal nor the speed of recovery from neuromuscular block.[11] Whether this new approach may contribute to decrease the still alarmingly high incidence of RP needs to be evaluated by further research.

In conclusion, even a single acceleromyographic TOF performs better than both subjective tests investigated, *i.e.*, DBS and 100 Hz, 5-s tetanus, but it does not reliably detect lesser degrees of RP. In the second part of the current study a new approach for the management of low degrees of RP is proposed, *i.e.*, acceleromyography-based prediction of the time interval until complete recovery from neuromuscular blockade. This concept may further improve the clinical value of the acceleromyographic TOF ratio.

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Appendix: Statistical Analysis

The adductor pollicis mechanomyographic TOF ratio was used as reference and residual paralysis was defined as a mechanomyographic TOF ratio <0.9.

The three evaluated tests were considered positive, *i.e.*, suggesting residual paralysis, with respectively fade detectable after 100 Hz tetanus or DBS or an acceleromyographic TOF ratio <0.9. These three tests were considered negative, *i.e.*, suggesting no residual paralysis, with no fade detectable after 100 Hz tetanus or DBS or an acceleromyographic TOF ratio ≥ 0.9, respectively.

Therefore, a true positive test is a positive test (*e.g.*, acceleromyographic TOF ratio <0.9) given that residual paralysis is present (mechanomyographic TOF ratio <0.9), and a true negative test is a negative test (*e.g.*, acceleromyographic TOF ratio ≥0.9) given that residual paralysis is absent (mechanomyographic TOF ratio ≥0.9) (table 1).

"Sensitivity" is defined as the probability that a test is positive given the person presents a residual paralysis. Sensitivity = A/A+C, *i.e.*, number of patients with a true positive test/number of patients with a residual paralysis.

"Specificity" is defined as the probability that a test is negative given the person does not present a residual paralysis. Specificity = D/B+D, *i.e.*, number of patients with a true negative test/number of patients without a residual paralysis.

"Positive predictive value" is defined as the probability that a person has a residual paralysis given a positive test. Positive predictive value = A/A+B, *i.e.*, number of patients with a true positive test/total number of patients with a positive test.

"Negative predictive value" is defined as the probability that a person does not have a residual paralysis given a negative test. Negative predictive value = C/C+D, *i.e.*, number of patients with a true negative test/total number of patients with a negative test.

Example

Diagnosis value of acceleromyography (table 2)

Sensitivity: 22 of 31 = 0.71, *e.g.*, 71% of patients with a residual paralysis had an acceleromyographic TOF ratio <0.9.

Specificity: 8 of 9 = 0.89, *e.g.*, 89% of patients without a residual paralysis had an acceleromyographic TOF ratio ≥0.9.

Positive Predictive Value: 22 of 23 = 0.96, *e.g.*, 96% of patients with an acceleromyographic TOF ratio <0.9 had effectively a residual paralysis.

Negative Predictive Value: 8 of 17 = 0.47, *e.g.*, 47% of patients with an acceleromyographic TOF ratio ≥0.9 do not have a residual paralysis.