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Efficacy of Tactile-guided Reversal from Cisatracurium-induced Neuromuscular Block

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Background: **Because tactile evaluation is the most common form of clinical neuromuscular monitoring, this study examines the relative efficacy of antagonizing residual block at different levels of recovery of the tactile train-of-four (TOF) response.**

Methods: **Anesthesia was induced in 64 adults with 2–5 μg/kg fentanyl and 1–3 mg/kg propofol and maintained with fentanyl, propofol, and nitrous oxide. The tactile response of the adductor pollicis to TOF stimulation was evaluated at one arm, and the mechanomyographic response was recorded at the other. Patients received 0.15 mg/kg cisatracurium and were randomized to receive 0.07 mg/kg neostigmine on reappearance of the first (group I), second (group II), third (group III), or fourth (group IV) tactile TOF response (16 patients per group). Times from administration of neostigmine until the TOF ratio recovered to 0.7 ($R_{0.7}$), 0.8 ($R_{0.8}$), and 0.9 ($R_{0.9}$) were measured.**

Results: **Data are presented as median with range in parentheses. $R_{0.7}$ was 10.3 (5.9–23.4), 7.6 (3.2–14.1), 5.0 (2.0–18.4), and 4.1 (2.4–11.0) min in groups I, II, III, and IV, respectively ($P < 0.05$, group I > II, III, and IV, group II > IV). $R_{0.8}$ was 16.6 (8.9–30.7), 9.8 (5.3–25.0), 8.3 (3.8–27.1), and 7.5 (3.0–74.5) min in groups I, II, III, and IV, respectively ($P < 0.05$, group I > II, III, and IV, group II > IV). $R_{0.9}$ was 22.2 (13.9–44.0), 20.2 (6.5–70.5), 17.1 (8.3–46.2), and 16.5 (6.5–143.3) min in groups I, II, III, and IV, respectively (no intergroup differences). Ten minutes after neostigmine, a TOF ratio of 0.7 or greater was achieved in 50, 75, 88, and 93% of patients in groups I, II, III, and IV, respectively ($P < 0.05$ group I > II, III, and IV). At 30 min, a TOF ratio of 0.9 or less was observed in 21, 13, 13, and 7% of patients in groups I, II, III, and IV respectively (no intergroup differences).**

Conclusions: **To achieve rapid (within 10 min) reversal to a TOF ratio of 0.7 in more than 87% of patients, three or four tactile responses should be present at the time of neostigmine administration. It was not possible within 30 min to achieve a TOF ratio of 0.9 in all patients, regardless of the number of tactile responses present at neostigmine administration.**

IN clinical practice, tactile evaluation of the adductor pollicis response to train-of-four (TOF) stimulation of the ulnar nerve is the most common method used to evaluate neuromuscular block. Although other modalities exist, such as posttetanic count and assessment of double burst response, they have limited application. The TOF count is often used in the guidelines for neostigmine-induced reversal of neuromuscular block.[1–3] It is not advised to attempt pharmacologic reversal before a TOF response has returned.[4] However, the efficacy of antagonizing residual block at different TOF counts has not been studied. Most studies of reversal use mechanomyography or electromyography to quantify twitch amplitude objectively and to guide administration of the anticholinesterase. Still, these measurement techniques are not normally available to the clinician who usually monitors TOF count. It has been assumed that results obtained from quantitative mechanomyography and electromyography studies could be translated to TOF counts to make recommendations for clinical practice, but this assumption may be flawed. Neuromuscular function measured with mechanomyography does not correlate well with the TOF count. At reappearance of the second TOF count, for example, the magnitude of the first TOF response (T1) varies from 0 to 15%.[5] Therefore, it is important to examine efficacy of reversal of residual neuromuscular block when neostigmine administration is guided by the clinically accessible measurement, namely, TOF count.

In addition, although a TOF ratio of 0.7 is the accepted norm for adequacy of reversal of neuromuscular block,[6] there is increasing evidence that significant residual effects, such as visual disturbances, decreased grip strength, and depressed swallowing reflexes, persist until the TOF ratio has reached 0.9.[7,8] Consequently, we examined the efficacy of neostigmine administered at different levels of TOF count and followed subsequent recovery until the TOF ratio at the adductor pollicis reached 0.9. We chose cisatracurium for this study because it is a neuromuscular blocking drug in common use and has a predictable recovery profile.

Materials and Methods

With approval from The Committee on Human Research, University of California San Francisco (San Francisco, CA), and written informed consent, we studied 64 adults (American Society of Anesthesiologists physical status I, II, or III) admitted for elective surgical procedures of the periphery. Exclusion criteria were age greater than 60 or less than 18 yr, history of neuromuscular disease, treatment with drugs known to interfere

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with neuromuscular function, or body weight exceeding 30% of ideal.

Anesthesia

Patients were premedicated with 2 mg intravenous midazolam within 15 min of the induction of anesthesia. In the operating room, routine blood pressure monitoring, electrocardiography, and pulse oximetry were initiated, and preoxygenation with 100% oxygen was performed for 3 min. Fentanyl, 2–5 μg/kg, was administered at the start of the preoxygenation procedure, and 1–3 mg/kg propofol was administered at the end to induce anesthesia. Anesthesia was maintained with 70% nitrous oxide in oxygen, propofol infusion of 100–150 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and 50 μg fentanyl as required. Initially, the patients' lungs were ventilated using a bag and mask; tracheal intubation was performed approximately 10 min later after neuromuscular monitoring was established and cisatracurium was administered (see the Neuromuscular Monitoring and Neuromuscular Block and Reversal). After tracheal intubation, mechanical ventilation was adjusted to maintain end-tidal carbon dioxide between 30 and 35 mmHg (Capnomac Ultima®; Datex Instrumentarium, Helsinki, Finland). Temperature was monitored continuously in the mid esophagus, and upper body forced-air warming units (Bair Hugger®; Augustine Medical, Minneapolis, MN) were used to maintain central temperature above 35.5 °C.

Neuromuscular Monitoring

In both arms, supramaximal stimuli (200 ms duration) were applied through cutaneous electrodes to the ulnar nerve at the wrist (Digistim II; Neuro Technology Inc., Houston, TX). In one arm, tetanic stimulation at 50 Hz was applied for 5 s; then, the stimulation mode was changed to a TOF sequence repeated every 12 s.[9] The resulting evoked mechanical responses of the adductor pollicis (preload 200–300 g) were measured with a calibrated force transducer (Myotrace; Life-Tech Inc., Houston, TX) and amplified (DC Signal Conditioner; Gold Electronics, Valley View, OH). The twitch tension of the first TOF response (T1) and the ratio of the fourth to the first response (TOF ratio) were digitized, displayed, and recorded on a Macintosh IIci computer (LabView; National Instruments, Austin, TX). After 2 min of TOF stimulation, the magnitude of the T1 response was used as the control to which all subsequent T1 responses were compared.

At the other arm, a 50-Hz tetanic stimulation was likewise applied for 5 s, followed by TOF stimulation sequences every 12 s. The patient's hand was kept supinated on an arm board, a moderate preload was applied to the thumb by the assessors second and third finger, and the number of felt responses after TOF stimulation was counted. A twitch response was defined to be present if any response, regardless of strength, was felt during three consecutive TOF stimulations. The number of tactile responses was counted every 2 min. In all patients, evaluation of tactile responses was performed by the same anesthesiologist, who was blinded to the mechanomyographic measurements on the contralateral arm but not to the treatment group.

Neuromuscular Block and Reversal

Neuromuscular block was induced with 0.15 mg/kg cisatracurium. After this single dose of cisatracurium, the patients received 0.07 mg/kg neostigmine and 0.014 mg/kg glycopyrrolate at different levels of TOF recovery. Patients were randomly assigned to one of four groups; 16 patients in each group received the reversal drugs at the reappearance of the first (group I), second (group II), third (group III), or fourth (group IV) tactile TOF response. The tactile duration of action was defined as time from administration of cisatracurium to reappearance of the first tactile TOF response. The mechanomyographic duration of action was defined as time from administration of cisatracurium to reappearance of T1. The recovery to T1 = 10% (duration10) was measured in those patients in whom this occurred before neostigmine was administered.

Neuromuscular monitoring continued until the TOF ratio exceeded 0.9. Reversal times were defined as time from administration of neostigmine until the TOF ratio recovered to 0.7 ($R_{0.7}$), 0.8 ($R_{0.8}$), and 0.9 ($R_{0.9}$).

Statistical Analysis

We studied a total of 64 patients, with 16 patients in each group. In a power analyses, α was set to 0.05, β was set to 0.20, and the likely proportion of patients with full recovery after 5 min was estimated from the results of other studies. This power analysis required a total of 64 patients in the study. One-way analysis of variance and the Bonferroni *post hoc* test were used to test for differences between unpaired groups. The Wilcoxon signed rank test was used to compare tactile and mechanomyographically measured duration of action. A chi-square test was used to test for differences between groups in proportions of patients reversed to TOF ratios of 0.70, 0.80, and 0.90, respectively, at 10, 20, and 30 min after neostigmine administration. $P < 0.05$ was considered statistically significant.

Results

The four study groups did not differ with respect to age, weight, or sex distribution (table 1).

Duration of action measured mechanomyographically (41.2 [24.6–63.2] min, median [range]) was significantly shorter compared with that measured tactically (44.8 [27.5–69.1], $P < 0.0001$). Duration10 (47.8 [34.1–69.7] min) was

Table 1. Demographic Data

Group	Weight (kg)	Age (yr)	Gender (M/F)
I	77 (54–119)	38 (18–57)	11/5
II	71 (53–86)	40 (21–58)	7/9
III	75 (53–105)	42 (18–56)	3/13
IV	73 (48–109)	37 (19–58)	6/10

Numbers are median (range).

similar to the time to reappearance of the second tactile TOF response (49.2 [35.5–73.3] min).

There was a significant difference between groups with respect to $R_{0.7}$ ($P < 0.0001$) and $R_{0.8}$ ($P < 0.002$). *Post hoc* testing showed a significant difference between group I and the other three groups and between groups II and IV (fig. 1, table 2). There was no difference between groups in $R_{0.9}$. In group IV, there was one patient with prolonged recovery ($R_{0.8}$ and $R_{0.9}$, 74.5 and 143.3 min, respectively; table 2). These data were not included in the statistical tests. There was no obvious explanation for this prolonged recovery.

Figure 2 shows that for patients who had only one or two tactile TOF responses present at the time of neostigmine administration, 10 min later, 50% (n = 8) and 25% (n = 4), respectively, had a TOF ratio less than 0.7. Even when three or four tactile TOF responses were present at the time of reversal, 12% (n = 2) and 7% (n = 1) of patients had a TOF ratio less than 0.7 ($P < 0.05$, group I > II, III, and IV). At 20 min after reversal, one patient in group I but none in the other groups had a TOF ratio less than 0.7 (fig. 3). Figure 3 also shows that 20 min after reversal, 64% (n = 9), 56% (n = 9), 37% (n = 6), and 27% (n = 4) of patients in groups I, II, III, and IV,

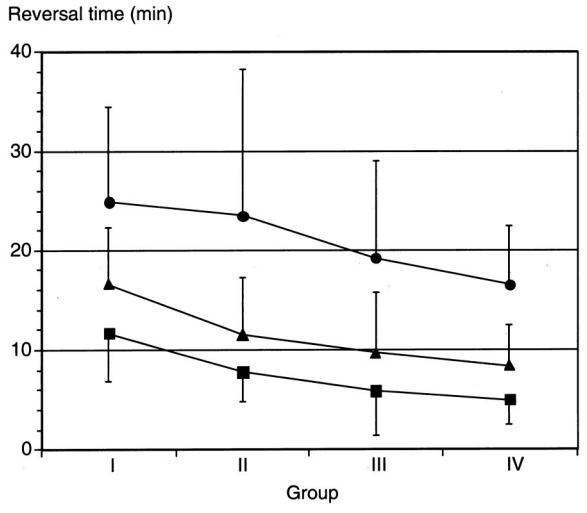

Fig. 1. Reversal time: The mean time from reappearance of the first (group I), second (group II), third (group III), and fourth (group IV) tactile train-of-four response to train-of-four ratios of 0.7 (squares), 0.8 (triangles), and 0.9 (circles). Error bars indicate one SD. Data from one group IV patient with a prolonged recovery ($R_{0.8}$, 74.5 min; $R_{0.9}$, 143.3 min) were excluded from the figure.

Table 2. Time (min) from Neostigmine Administration to TOF Ratio 0.7 ($R_{0.7}$), 0.8 ($R_{0.8}$), and 0.9 ($R_{0.9}$)

	Group			
TOF Ratio	I	II	III	IV
0.7				
Median	10.3*	7.6†	5.0	4.1
Range	5.9–23.4	3.2–14.1	2.0–18.4	2.4–11.0
0.8				
Median	16.6*	9.8†	8.3	7.5
Range	8.9–30.7	5.3–25.0	3.8–27.1	3.0–74.5
0.9				
Median	22.2	20.2	17.1	16.5
Range	13.9–44.0	6.5–70.5	8.3–46.2	6.5–143.3

* $P < 0.05$, group I > group II, III, and IV. † $P < 0.05$, group II > group IV.

TOF = train-of-four.

respectively, had a TOF ratio less than 0.9 (no intergroup differences). At 30 min after neostigmine administration, all patients had a TOF ratio greater than 0.70. However, 21% (n = 3), 13% (n = 2), 13% (n = 2), and 7% (n = 1) of patients in groups I, II, III, and IV, respectively, had a TOF ratio less than 0.90 (no intergroup differences). Because of a short surgical procedure, neuromuscular monitoring and anesthesia was stopped in three patients (two in group I and one in group II) at 15, 16, and 25 min after neostigmine administration, respectively. At this time, TOF ratios were 0.81, 0.70, and 0.77, respectively. One patient in group IV was excluded because of nonadherence to the protocol.

The variation in the mechanomyographic T1 response at reappearance of the first, second, third, and fourth tactile TOF responses are shown in table 3.

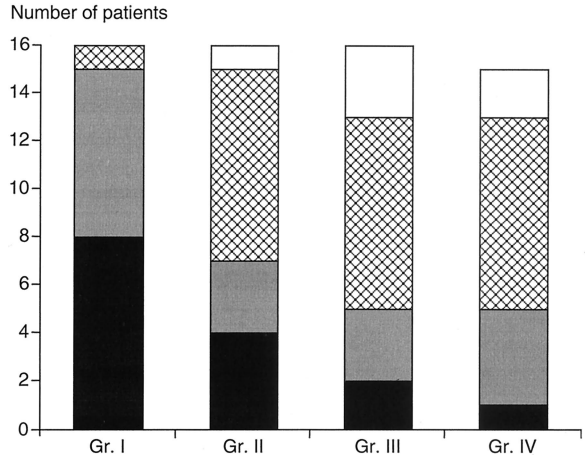

Fig. 2. Degree of antagonism at 10 min after neostigmine administration. Group I patients reversed at reappearance of the first tactile train-of-four (TOF) response, group II patients reversed at reappearance of the second tactile TOF response, group III patients reversed at reappearance of the third tactile TOF response, and group IV patients reversed at reappearance of the fourth tactile TOF response. TOF ratio < 0.7 (black columns), TOF ratio ≥ 0.7 and < 0.8 (grey columns), TOF ratio ≥ 0.8 and < 0.9, (hatched columns), and TOF ratio ≥ 0.9 (white columns).

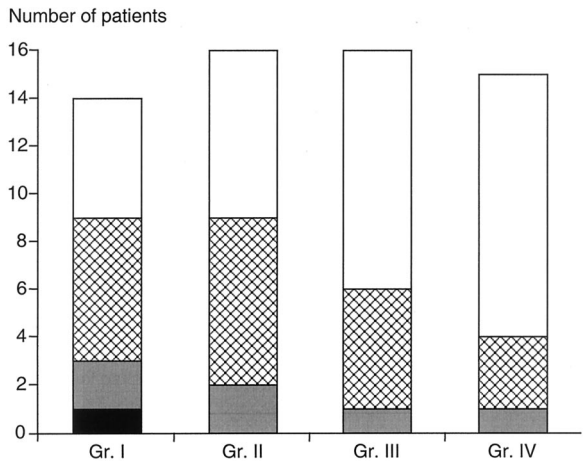

Fig. 3. Degree of antagonism at 20 min after neostigmine administration. Group I patients reversed at reappearance of the first tactile train-of-four (TOF) response, group II patients reversed at reappearance of the second tactile TOF response, group III patients reversed at reappearance of the third tactile TOF response, and group IV patients reversed at reappearance of the fourth tactile TOF response. TOF ratio < 0.7 (black columns), TOF ratio ≥ 0.7 and < 0.8 (grey columns), TOF ratio ≥ 0.8 and < 0.9 (hatched columns), and TOF ratio ≥ 0.9 (white columns).

Discussion

This study showed that the presence of a tactile response to TOF stimulation (the TOF count) at the time of neostigmine administration does not guarantee even a minimum standard (TOF ratio = 0.7) of adequate recovery of neuromuscular function within 10 min. With only one tactile response at the time of reversal, just 50% of patients (eight patients) had achieved a TOF ratio of 0.7 within 10 min. Even with four tactile responses present, one patient (7%) failed to achieve a TOF ratio of 0.7 by 10 min. If a more stringent criterion for adequate reversal is used (TOF ratio = 0.9), even at 20 min after reversal, 64% (nine patients) and 27% (four patients) with one or two tactile response at neostigmine administration fail to achieve this standard.

For years, a TOF ratio of 0.70 has been considered to represent adequate recovery from a nondepolarizing neuromuscular block. This clinical guideline is mainly based on two studies evaluating respiratory function (vital capacity, tidal volume, inspiratory flow, and peak expiratory flow rate)[10] and clinical response (eye opening, head lift, hand grip, and tongue protrusion).[6] Our results show that this level of neuromuscular recovery is commonly not achieved within 10 min if only one TOF response is present at the time of neostigmine administration. Waiting until three or four TOF responses are present allows the TOF ratio to reach 0.7 within 10 min in more than 87% of patients (fig. 2). Furthermore, $R_{0.70}$ was significantly shorter in group IV compared with groups I and II. A similar result was found in a study by Kopman[2] in which edrophonium was administered at four TOF responses to antagonize atracurium and vecuronium. Consequently, we would recommend that three or four tactile TOF responses be present at the time of neostigmine administration if achieving a high probability of rapid reversal to a TOF ratio of 0.7 is the clinical goal.

Table 3. Mechanomyographic Magnitude of the First TOF Twitch (T1) Measured at Reappearance of Each of the Four Tactile TOF Responses

Tactile TOF Response	N	T1 (%)	
		Median	Range
1st	16	4	1–12
2nd	16	12	4–30
3rd	16	24	5–64
4th	15	26	12–70

TOF = train-of-four; N = number of patients.

However, several recent studies have suggested that a TOF ratio of 0.7 may not represent adequate neuromuscular recovery and that higher values, 0.8 or 0.9, must be achieved before neuromuscular function is adequate. Eriksson *et al.*[8] demonstrated that TOF ratios of less than 0.9 were associated with functional impairment of the muscles of the pharynx and upper esophagus and therefore a decreased ability to protect the airway against aspiration. Engbæk *et al.*[11] showed that the TOF ratio had to recover to 0.8 before all patients could sustain head lift for 5 s. Finally, Kopman *et al.*[7] showed that TOF ratios of 0.9 or less were accompanied by diplopia, difficulty in tracking moving objects, and generalized fatigue. The ability to clench the incisor teeth strongly did not return until the TOF ratio (on average) exceeded 0.85. Therefore, one could argue that a TOF ratio of at least 0.90 is needed to consider the neuromuscular block to be adequately reversed. This may be especially important in patients with increased risk of aspiration, those who have significant comorbidity, or patients for whom rapid recovery is important for early discharge, *e.g.*, in ambulatory surgery.

Our results suggest that achieving a TOF ratio of 0.9 within 10 min of neostigmine administration is not a realistic goal. Regardless of whether neostigmine administration occurs at the reappearance of the first or fourth tactile response, the overwhelming majority of patients fail to reach a TOF ratio of 0.9 within 10 min. Therefore, counting the number of tactile responses to TOF stimulation cannot be used as a guide for neostigmine administration if the end point for reversal is a TOF ratio of 0.90 or greater within 10 min.

In contrast to the situation at 10 min, at 20 min after neostigmine administration, there is a relation between the number of TOF responses at reversal and the proportion of patients who achieve a TOF ratio of 0.9 (fig. 3). However, this difference has little clinical significance. Even at 20 and 30 min, 27% (four patients) and 7%

(one patient) respectively, of patients with four TOF responses at reversal failed to reach a TOF ratio of 0.9, and to wait even this long cannot be considered clinically practical.

It is known that neostigmine has a "ceiling effect" with respect to the block, which can be antagonized. When a deep neuromuscular block is attempted antagonized, the peak effect of the antagonist is followed by a plateau phase in which the balance between diminishing anticholinesterase activity and spontaneous recovery of neuromuscular block determines the slope of the recovery curve.[12] This effect, in combination with the sigmoid-shaped spontaneous recovery curve, has a great impact on the results in the current study. It is responsible for the increasing variability in reversal time when the TOF ratio target is increasing from 0.70 to 0.90. For example, in group IV, the reversal time range at a TOF ratio of 0.70 was 2.4–11 min, and it increased to 6.5–143.3 min when the target TOF ratio was 0.90. It also makes it understandable why a time limit of 10 min for obtaining a TOF ratio of 0.90 in all patients is unrealistic.

If a TOF ratio of 0.9 is the new standard for adequate recovery of neuromuscular function, what can be done to make this an achievable goal? As discussed, the number of tactile TOF responses present at the time of reversal cannot guarantee recovery from cisatracurium-induced block within a reasonable time period (20–30 min). Using neuromuscular blocking agents with a long duration of action does not solve the problem. In a study by Kopman *et al.*,[13] it was shown that when pancuronium was antagonized at a TOF count of two with 50 μg/kg neostigmine, the average TOF fade ratio at 10 min after reversal was 0.66, with a range from 0.32 to 0.90. When patients were transferred to the postanesthesia care unit 30 min later, the average TOF ratio was 0.85 (range, 0.63–0.97), and only one third of patients had achieved a ratio of 0.90 or greater. However, because success of reversal is influenced by the duration of action of the relaxant, the use of shorter acting relaxants might allow a TOF ratio of 0.9 to be achieved. Kopman *et al.*[3] antagonized mivacurium-induced block at four TOF responses. They found that using 0.75 mg/kg edrophonium, a TOF ratio of 0.90 could be obtained within 15 min in 100% of patients.

Another approach is to quantify the level of neuromuscular block objectively. Using mechanomyography is not likely to become clinically feasible, but acceleromyography is easy to handle and can be used with confidence in the clinical setting.[14] With quantification of the block, it is possible to identify subjects with prolonged reversal time and, if appropriate, to delay tracheal extubation until the desired level of recovery has been achieved.

An interesting aspect of our results was the large interindividual variability in reversal times (table 2). This suggests that in achieving adequate reversal, individual response to cisatracurium may play greater role than the number of TOF responses present at the time of neostigmine administration. For example, in group I, there are patients with $R_{0.70}$ of 5.9 min, whereas in group IV, there are patients with $R_{0.70}$ of 11 min. In a study with atracurium, the duration of action of the initial relaxant dose was related to the length of reversal time. Therefore, duration of action of the relaxant in a given individual is a predictor of reversal time, and computational tools may be developed to allow this to be used as guide for neostigmine administration.[15]

Atracurium is structurally related to cisatracurium, and neostigmine seems to be equally efficacious for reversal of both drugs.[16] However, because of differences in pharmacokinetics, results from the current study may not be extendable to other relaxants with an intermediate duration of action (vecuronium and rocuronium). Regardless of this difference between the drugs, we would predict that few patients would achieve a TOF ratio of 0.9 within 10 min of neostigmine reversal of rocuronium- or vecuronium-induced block.

We used the number of tactile responses to define the groups for neostigmine administration because this is the only widely available clinical measurement tool. There was a large variability in the level of mechanomyographic recovery at the different TOF counts (table 3), a variability that has also been shown in other studies using electromyography and mechanomyography.[2,17] We suggest two possible explanations for this large variability. First, we measured tactile and myographic responses on opposite hands. We did this to maintain the integrity and stability of the mechanomyographic measurements that would have been disrupted by the thumb movement necessary to perform simultaneous tactile evaluation. Second, tactile evaluation is a subjective measurement, and detection of a response depends on the strength relative to the control T1 and also on the absolute magnitude of the response. This second explanation is supported by two studies performed by Kopman,[2,3] who found wide variations in the relation between a TOF count of four and T1 using electromyography at the ipsilateral hand. To minimize observer variability, a single anesthesiologist, experienced in neuromuscular research, performed the tactile evaluation in every patient. The side of mechanomyographic measurement was not randomized; however, we consider the chance of thereby introducing a bias to be negligible.

The 70-μg/kg neostigmine dose was chosen because we intended to study the maximal antagonizing effect, and a dose of 70 μg/kg is recommended when a profound level of block is antagonized.[4] A previous study showed that adding a second dose of 70 μg/kg neostigmine to an earlier dose of 70 μg/kg produced no faster recovery of neuromuscular function, suggesting that the first dose produced maximum reversal effect.[18]

In conclusion, if the goal of antagonism is to have a high probability of rapidly achieving a TOF ratio of 0.7, the number of tactile TOF responses can be used as a

guide for neostigmine administration, and we recommend that three or four be present. If the goal of antagonism is to obtain a TOF ratio greater than 0.90, this may be difficult to achieve in a clinically practical period of time, and the TOF count cannot be used as a guide for administration of neostigmine. It is not possible to propose a realistic time delay from reversal to full recovery. Even at 20 and 30 min after neostigmine administration, there are patients with a TOF ratio less than 0.90, regardless of the number of tactile TOF responses present at the time of reversal.

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