Residual Paralysis in the PACU after a Single Intubating Dose of Nondepolarizing Muscle Relaxant with an Intermediate Duration of Action

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Background: Residual neuromuscular blockade remains a problem even after short surgical procedures. The train-of-four (TOF) ratio at the adductor pollicis required to avoid residual paralysis is now considered to be at least 0.9. The incidence of residual paralysis using this new threshold is not known, especially after a single intubating dose of intermediate-duration nondepolarizing relaxant. Therefore, the aim of the study was to determine the incidence of residual paralysis in the postanesthesia care unit after a single intubating dose of twice the ED$_{95}$ of a nondepolarizing muscle relaxant with an intermediate duration of action.

Methods: Five hundred twenty-six patients were enrolled. They received a single dose of vecuronium, rocuronium, or atracurium to facilitate tracheal intubation and received no more relaxant thereafter. Neuromuscular blockade was not reversed at the end of the procedure. On arrival in the postanesthesia care unit, the TOF ratio was measured at the adductor pollicis, using acceleromyography. Head lift, tongue depressor test, and manual assessment of TOF and DBS fade were also performed. The time delay between the injection of muscle relaxant and quantitative measurement of neuromuscular blockade was calculated from computerized anesthetic records.

Results: The TOF ratios less than 0.7 and 0.9 were observed in 16% and 45% of the patients, respectively. Two hundred thirty-nine patients were tested 2 h or more after the administration of the muscle relaxant. Ten percent of these patients had a TOF ratio less than 0.7, and 37% had a TOF ratio less than 0.9. Clinical tests (head lift and tongue depressor) and manual assessment of fade showed a poor sensitivity (11–14%) to detect residual blockade (TOF < 0.9).

Conclusion: After a single dose of intermediate-duration muscle relaxant and no reversal, residual paralysis is common, even more than 2 h after the administration of muscle relaxant.

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Quantitative measurement of neuromuscular transmission is the only recommended method to diagnose residual block.

THE clinical importance of the residual neuromuscular blockade in the postanesthesia care unit (PACU) has been pointed out since 1979.[1] During the past 15 yr, numerous publications have confirmed that the incidence of partial paralysis correlated with the duration of action of the relaxant agents. The longer the duration of action, the higher the rate of residual paralysis.[2,3]

In all these studies, residual neuromuscular blockade was defined as a train-of-four (TOF) ratio at the adductor pollicis of less than 0.7 or 0.75. This level of recovery was considered acceptable because it was found to be the threshold above which volunteers given *d*-tubocurarine were found to have normal vital capacity and inspiratory force.[4] In 1996, a TOF ratio of 0.8 was proposed as the cutoff between residual paralysis and normal neuromuscular function[5] and was used in two recent studies.[6,7] This threshold was increased to 0.9 according to recent observations.[8] For example, pharyngeal function did not return to normal after vecuronium administration until an adductor pollicis TOF ratio greater than 0.9 was reached.[9] When using this new TOF ratio value as threshold of residual paralysis, the incidence of residual paralysis in the PACU would certainly be greater than that observed in the studies mentioned previously.[1–3] However, the rate of residual paralysis defined as a TOF ratio less than 0.9 instead of 0.7 has never been compared. It is important to notice that, in all these publications, patients received muscle relaxant to facilitate tracheal intubation and also to maintain an adequate level of paralysis according to surgical need. When the surgical procedure does not require muscle paralysis, relaxants are given only to facilitate tracheal intubation at a dose usually equal to twice the 95% effective dose at the adductor pollicis (ED$_{95}$).[10] If the duration of surgery is long enough, reversal might be omitted. Such a practice does not avoid the presence of partial paralysis even if the surgical procedure is longer than 90 min,[11] which corresponds to the accepted duration of intermediate-acting muscle relaxant.

Thus, the aims of this study were (1) to determine the incidence of residual paralysis following the administration of a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action, and correlate it with duration of surgery in the range of 1 to

more than 2 h; and (2) to compare this incidence when the residual paralysis was defined as a TOF ratio less than 0.7 or less than 0.9.

Materials and Methods

The study was conducted over an 8-month period, in one center (Institut Gustave Roussy, Villejuif, France). It was a prospective, open-labeled, nonrandomized, and observational study. Adult patients with American Society of Anesthesiologists physical status I–III who were scheduled for gynecologic and plastic surgery and required tracheal intubation were included in this study. All these patients received a single intubating dose of atracurium, rocuronium, or vecuronium equal to twice the ED_{95} to facilitate tracheal intubation. Patients were excluded from the study if they received a dose of muscle relaxant less than or greater than twice the ED_{95}, or when additional doses of relaxant were given during the surgical procedure. They were also excluded when neuromuscular blockade was reversed at the end of anesthesia. Other exclusion criteria were neuromuscular diseases, preoperative medication that may interfere with neuromuscular transmission, and kidney or liver disease.

The choice of the anesthetic protocol and the use of neuromuscular transmission monitoring were left to the discretion of the anesthesiologist in charge of the patient, who was unaware that the patient was to be included in this evaluation.

On arrival in the PACU, a senior anesthesiologist and a trained nurse who were not involved in the anesthetic procedure checked all the inclusion and exclusion criteria. If the patients met the inclusion criteria, neuromuscular transmission monitoring was immediately performed. In all the patients, 40-mA TOF stimulation (four pulses of 0.2 ms in duration, at a frequency of 2 Hz, 2 s in duration) was performed at the ulnar nerve every 15 s *via* two surface electrodes. First, the nurse assessed the presence or the absence of fade at the thumb in response to TOF stimulation, using visual and tactile means. No quantitative measurements were performed at that time. Then, the muscular response of the adductor pollicis after TOF stimulation was measured using an acceleromyographic method allowing quantitative measurement of the TOF ratio. The evoked responses at the thumb were measured by TOF Watch acceleromyograph (Organon Teknika, Boxtel, The Netherlands). The probe was positioned on the distal part of the thumb. The other fingertips were tightly fixed with tape. Another probe was positioned over the hand to measure peripheral temperature. When the TOF ratio was constant for three consecutive measurements, the TOF stimulation was stopped. Thereafter, the senior anesthetist, blinded to the true depth of neuromuscular blockade, assessed

Table 1. Demographic Data

	Mean ± SD	Range
Age, yr	54 ± 14	15–92
Sex ratio, male/female	125/401	—
Weight, kg	66 ± 13	38–124
Height, cm	165 ± 8	145–196
Body mass index	24 ± 4	17–44
ASA status (I/II/III)	361/151/14	—
Temperature, °C*	35.9 ± 0.6	33.6–37.7
Duration, min†	127 ± 56	22–397

n = 526.

* Peripheral temperature was measured at the arrival in the postanesthesia care unit. †Time interval between the injection of the neuromuscular blocking agent and the train-of-four ratio measurement in the PACU.

ASA = American Society of Anesthesiologists.

visually the presence or the absence of fade at the thumb in response to $DBS_{3.3}$. A 5-s head lift test and tongue depressor test proposed by Kopman *et al.*[12] were then performed by the nurse. Total duration of this complete evaluation was never longer than 2 min.

Time delay from the injection of muscle relaxant to the objective measurement of the neuromuscular blockade was precisely calculated using a computerized anesthetic record.

Two thresholds of TOF ratio were used to assess the presence of a residual neuromuscular blockade: less than 0.7 and less than 0.9.

The primary outcome measure of our study was to determine the incidence of residual paralysis on arrival in the PACU following a single intubating dose of muscle relaxant, taking into account the time from the administration of the relaxant to the quantitative TOF measurement. This time delay was divided into 30-min intervals. As the surgical duration showed a large variability in our institution, it has been estimated that at least 500 patients need to be enrolled to obtain a sufficient number of patients in each 30-min interval.

Patient characteristics are expressed as mean ± SD and range. Sensitivity, specificity, and predictive values of the qualitative tests (head lift test, tongue depressor test, and clinical fade after TOF and DBS stimulation) were calculated according to standard formulae[13] and presented with the 95% confidence interval. After testing normal distribution, residual paralysis rate was compared using a chi-square test. A P value less than 0.05 was considered statistically significant.

Results

Five hundred twenty-six patients met the inclusion criteria and were then studied. Demographic data are shown in table 1. Anesthesia was maintained using isoflurane (end-tidal concentration ranged between 0.9 and 1.2%) and nitrous oxide (50%). Rocuronium, atracurium, and vecuronium were administered in 76, 15, and 9% of cases, respectively. The doses of the relaxant

A: all patients (n = 526)

B: rocuronium (n = 402)

C: atracurium (n = 77)
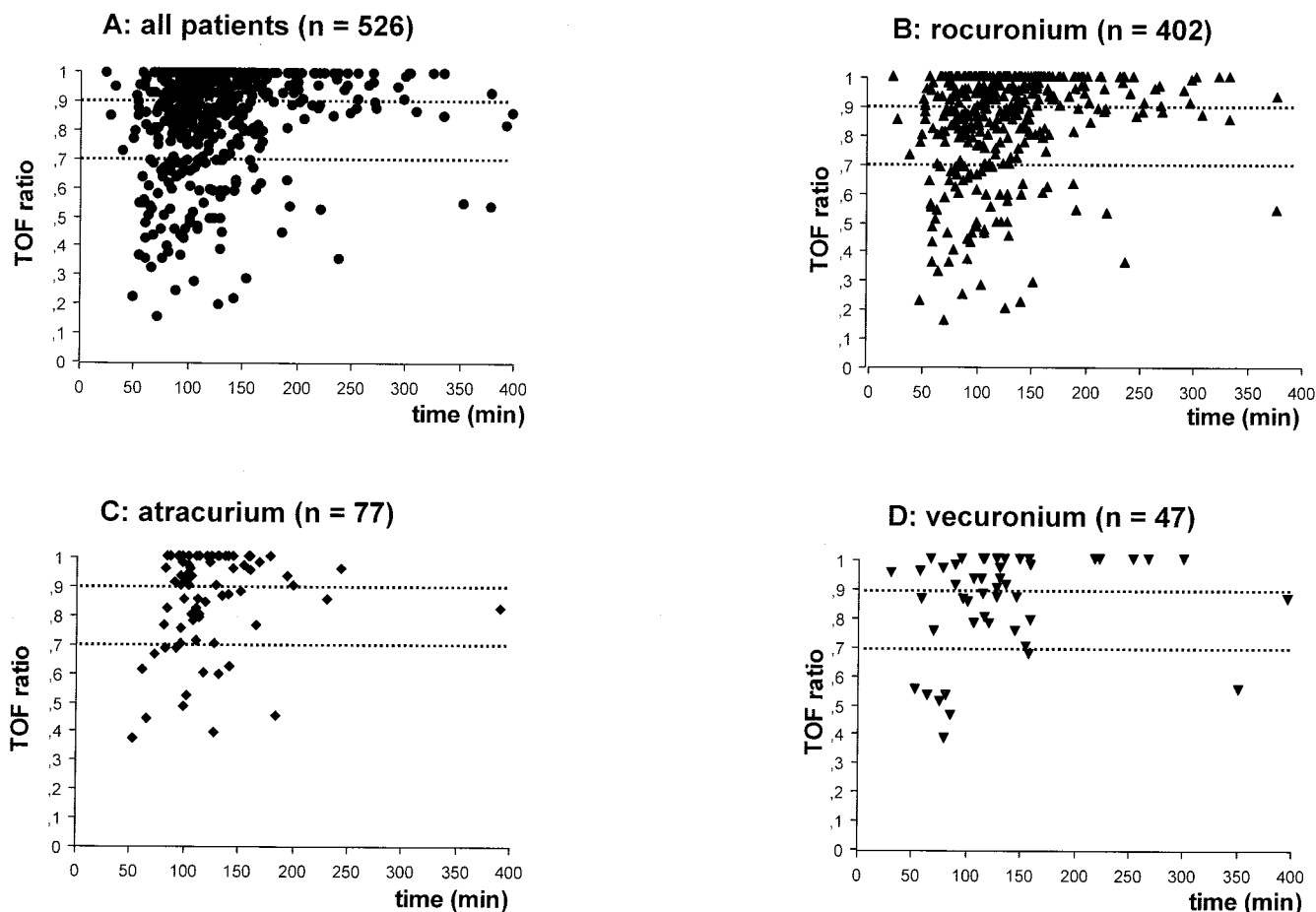
D: vecuronium (n = 47)

Fig. 1. Train-of-four (TOF) ratio *versus* time interval between injection of drug and assessment. Each symbol represents one patient. Upper dotted line shows the 0.9 TOF ratio threshold; lower dotted line shows the 0.7 TOF ratio threshold. All the patients were presented on *A*, and patients receiving rocuronium, atracurium, and vecuronium were shown on *B*, *C*, and *D*, respectively.

were 0.58 ± 0.08, 0.55 ± 0.08, and 0.09 ± 0.02 mg/kg, respectively. Peripheral temperature was $35.9 \pm 0.6°C$ (mean $\pm$ SD) with a range from 33.6 to 37.7°C.

Among the 526 patients, 85 (16%) had a TOF ratio less than 0.7 and 237 (45%) had a TOF ratio less than 0.9 on arrival in the PACU. The incidence of partial paralysis, defined as a TOF ratio less than 0.7, was 15.9, 16.9, and 17.0% following rocuronium, atracurium, and vecuronium, respectively (NS), and 45.0, 41.6, and 46.8% when a TOF ratio less than 0.9 was used (NS). Individual TOF ratios *versus* time are shown in figure 1A. Moreover, data obtained for each relaxant (rocuronium, atracurium, and vecuronium) are given in figures 1B, C, and D, respectively.

The incidence of residual paralysis according to the time delay between the injection of the muscle relaxant and the arrival at the PACU is displayed in figure 2. Two hundred thirty-eight patients were evaluated more than 2 h after administration of relaxant. The partial paralysis rates were 10% and 37% when the residual blockade was defined as a TOF less than 0.7 and 0.9, respectively. Whatever the delay, the incidence of partial paralysis, defined as a TOF less than 0.9, was significantly higher

compared to a TOF less than 0.7 ($P < 0.01$). When a TOF ratio less than 0.7 was used to defined the residual neuromuscular blockade, the rate of residual paralysis began to decrease 90 min after the relaxant administra-
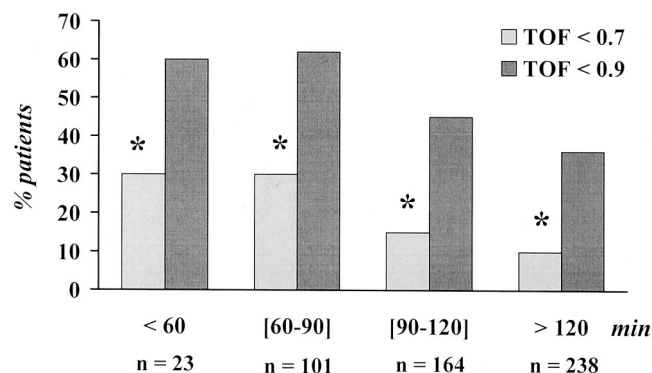

Fig. 2. Residual paralysis rate. Partial paralysis rate (percent) according to the delay between the administration of muscle relaxant and the arrival in the postanesthesia care unit (PACU). Partial paralysis was defined as a train-of-four (TOF) ratio less than 0.7 or less than 0.9. n = number of patients. *Significantly different from TOF < 0.9.

Table 2. Relationship Between Measured Train-of-Four Ratio Threshold (0.7 or 0.9) and Clinical Weakness

		Measured TOF Ratio		Measured TOF Ratio	
		<0.7 (n = 85)	>0.7 (n = 441)	<0.9 (n = 237)	>0.9 (n = 289)
TOF fade detected	Yes	23 (27)	6 (1)	27 (12)	2 (<1)
(n = 526)	No	62 (73)	435 (99)	210 (88)	287 (99)
DBS fade detected	Yes	30 (35)	6 (1)	35 (15)	1 (<1)
(n = 526)	No	55 (65)	435 (99)	202 (85)	288 (99)
		Measured TOF Ratio		Measured TOF Ratio	
		<0.7 (n = 51)	>0.7 (n = 280)	<0.9 (n = 146)	>0.9 (n = 185)
Head lift test	Failure	10 (20)	41 (15)	27 (18)	24 (13)
(n = 331)	Success	41 (80)	239 (85)	119 (82)	161 (87)
		Measured TOF Ratio		Measured TOF Ratio	
		<0.7 (n = 46)	>0.7 (n = 262)	<0.9 (n = 139)	>0.9 (n = 169)
Tongue depressor test	Failure	10 (22)	25 (10)	19 (14)	16 (10)
(n = 308)	Success	36 (78)	237 (90)	120 (86)	153 (90)

Clinical weakness was detected by visual and tactile assessment of TOF and DBS fade, head lift and tongue depressor tests. Clinical assessment of TOF and DBS fade was performed in all patients (n = 526). Head lift and tongue depressor tests were correctly evaluated in only 331 and 308 patients respectively. Data are presented as actual number and percentage (in parentheses). By example, among the 85 patients having a TOF ratio less than 0.7, a tactile TOF fade was detected in 23 (27%) of them and was absent in 62 (73%).

DBS = double-burst stimulation; TOF = train-of-four.

tion, while it took more than 120 min when the residual blockade was defined as a TOF less than 0.9.

Table 2 shows the relation between measured TOF ratio threshold (0.7 or 0.9) and the clinical weakness detected by qualitative assessment of TOF and DBS fade, head lift test, and tongue depressor test. It was not possible to correctly evaluate the head lift test and the tongue depressor test in 37% and 41% of the patients, respectively, mainly because of the residual effects of anesthetic agents. However, the clinical evaluation of TOF and the DBS fade was performed easily in all patients. The head lift tests and tongue depressor tests were failed in 51 (15%) and 35 (11%), respectively. TOF fade and DBS fade were detected by tactile means in only 29 (5.5%) and 36 (6.8%), respectively. Specificity was good for all the tests, especially for the tactile TOF and DBS assessments. However, sensitivity was poor for all tests performed, especially for the 0.9 TOF ratio threshold. Tables 3 and 4 show the sensitivity, specificity, and positive and negative predictive values of these four tests

(*i.e.*, the head lift test, the tongue depressor test, and the clinical determination of fade following a TOF and a DBS stimulation) when residual paralysis was defined as a TOF ratio less than 0.7 or 0.9.

Discussion

Our results showed that following a single intubating dose of intermediate-acting nondepolarizing muscle relaxant, residual paralysis occurred in the PACU more than 2 h after administration. Whatever the thresholds used to define residual paralysis, the sensitivity of the clinical (head lift and tongue depressor) and qualitative instrumental (visual and tactile detection of fade after TOF or DBS stimulation) tests to detect neuromuscular blockade was too low to recommend these tests in the clinical setting. Furthermore, a time interval greater than 120 min between the administration of muscle relaxant and the arrival in the PACU did not guarantee the lack of

Table 3. Sensitivity and Specificity of the Different Tests

		Sensitivity % (CI)		Specificity %(CI)	
	n	TOF < 0.7	TOF < 0.9	TOF < 0.7	TOF < 0.9
Head lift	331	19 (15–23)	11 (9–14)	85 (81–89)	87 (83–90)
Tongue depressor	308	21 (17–26)	13 (10–17)	90 (87–93)	90 (87–93)
TOF	526	27 (23–31)	11 (9–13)	98 (97–99)	99 (98–99)
DBS	526	35 (33–38)	14 (11–16)	98 (97–99)	99 (99–100)

Sensitivity and specificity [13] of the clinical tests (head lift and tongue depressor) and the clinical detection of fade following train of four and double burst stimulation. Residual paralysis was defined as a TOF ratio less than 0.7 (left part of the table) and less than 0.9 (right part of the table). Data are presented with their 95% CI.

DBS = double-burst stimulation; TOF = train-of-four.

Table 4. Positive and Negative Predictive Values of the Different Tests

	n	Positive Predictive Value % (95% CI)		Negative Predictive Value % (95% CI)	
		TOF < 0.7	TOF < 0.9	TOF < 0.7	TOF < 0.9
Head lift	331	19 (15–23)	53 (47–58)	85 (81–89)	58 (52–63)
Tongue depressor	308	28 (23–33)	54 (48–59)	86 (83–90)	56 (51–62)
TOF	526	79 (75–82)	93 (91–94)	87 (84–90)	57 (53–61)
DBS	526	83 (78–86)	97 (95–98)	88 (85–90)	58 (54–62)

Positive predictive value and negative predictive value [13] of the clinical tests (head lift test and tongue depressor test) and the clinical detection of fade after TOF and DBS. The residual paralysis was defined as a TOF ratio less than 0.7 (left part of the table) and less than 0.9 (right part of the table).

DBS = double-burst stimulation; TOF = train of four.

residual blockade. This highlights the need for quantitative TOF ratio monitoring each time a muscle relaxant is used.

Many surgical procedures require muscle paralysis to improve the quality of intubation, while maintenance of blockade is not mandatory. In this setting, the overall incidence of residual paralysis, defined by a TOF ratio less than 0.7, reached 16% in our study. When using intermediate-acting muscle relaxants, some studies found different rates of residual paralysis compared with our results. These discrepancies can be explained by several differences among the study designs, such as the use of neuromuscular monitoring, the maintenance of a certain degree of paralysis throughout the procedure, the administration of reversal at the end of anesthesia, and the TOF ratio thresholds used to define the presence of residual paralysis (*i.e.*, TOF ratio less than 0.7, 0.8, or 0.9). When muscle relaxation was maintained during the procedure, intraoperative monitoring was used, and reversal was given, a TOF ratio less than 0.7 was observed in 2 and 5% of cases following atracurium and vecuronium, respectively.[2,14] However, following vecuronium administration, Baillard *et al.*[15] found that 239 of the 568 studied patients (42%) had a TOF ratio less than 0.7 in the PACU when neuromuscular monitoring and reversal were not used. The rates of residual paralysis were 41% and 52% when a TOF ratio less than 0.7 or 0.8 was used, respectively, indicating that the incidence of residual paralysis increases as the TOF threshold for its detection increases. Our results confirmed that overall incidence reached 45% of the patients instead of 16% when the thresholds were 0.9 and 0.7, respectively. A long interval between the last administration of muscle relaxant and the assessment of the measured TOF ratio in the PACU does not guarantee full recovery. Thus, from a clinical point of view, it is not possible to exclude the likelihood of residual paralysis taking into account the time elapsed from the last muscle relaxant administration. Only one study has investigated this particular issue but on a small cohort of patients.[11] In that study, 60 patients received a single intubating dose of vecuronium (0.1 mg/kg) only, and the TOF ratio was measured 1–4 h before reversal. Residual paralysis was defined as a TOF ratio less than 0.75. The incidences of residual paralysis were 90%, 20%, and 5% at

1, 2, and 4 h following vecuronium administration, respectively. These results clearly demonstrated that the duration of action of intermediate-acting muscle relaxant showed a wide interindividual variability and might be prolonged in some patients. The findings of our study, obtained in a large sample of patients, confirmed those from Caldwell *et al.*[11] A 30% and a 10% residual paralysis rate were observed 1 and 2 h after relaxant (without reversal) when a TOF ratio less than 0.7 was used to confirm the residual blockade. These incidences were increased to 60 and 36% with a 0.9 TOF ratio threshold.

Previous studies,[11,15] as our own study, have clearly showed a high incidence of residual paralysis when reversal was not administered. Administration of reversal agents at the end of anesthesia appears indicated to avoid the known deleterious consequences of partial paralysis. However, the administration of reversal does not guarantee the lack of partial paralysis in all patients when they arrive in the PACU. Hayes *et al.*[6] reported recently that there was no significant difference in the incidence of postoperative residual block between patients who did or did not have their block reversed. However, patients were not randomized to receive reversal, and it is likely that reversal was administered preferentially to patients who had a greater degree of paralysis. When there is clear evidence of adequate neuromuscular function assessed by quantitative monitoring, the administration of reversal appears unnecessary. In contrast, when neuromuscular monitoring detects residual block, routine administration of an anticholinesterase is required.

In the PACU, residual paralysis can be assessed by clinical tests (head lift test and tongue depressor test) and qualitative instrumental tests (visual or tactile fade detection following TOF or DBS stimulation). While instrumental tests can be easily performed in all patients, the quality of the assessments of neuromuscular function provided by the clinical tests requires that patients are awake and cooperative and without the residual effects of other anesthetic drugs on arrival in the PACU. These conditions are not always possible to achieve, except in awake volunteers.[12] In our study, at least one third of our patients were unable to perform these clinical tests correctly. When these tests were performed, the sensitivity

reached approximately 10%, while the specificity was excellent with a TOF ratio less than 0.7 or 0.9 as the threshold of residual blockade. Clearly, these results mean that when patients were unable to sustain the head lift or to maintain a tongue depressor clenched between their incisor teeth, neuromuscular recovery was not complete. However, when these tests were successfully performed, the presence of a certain degree of residual paralysis could not be excluded. It is, however, noticeable that 24 patients were unable to sustain a head lift and 16 could not hold a tongue depressor, while quantitative measurements of TOF showed a ratio higher than 0.9 assessed by acceleromyography. Three reasons can be put forward to explain these surprising findings. First, these patients could be too sedated to perform these tests correctly. However, we examined patients carefully before performing this clinical evaluation, which finally was performed in only two thirds of them. Second, the relation between TOF ratio values and clinical tests is not constant in all individuals. For example, Kopman et al.[12] found that the range of TOF values at which the tongue depressor test was passed in height individuals ranged between 0.68 and 0.95. Thus, it is likely that some of our patients could not keep a tongue depressor between their teeth at TOF values of 0.9 or greater. Finally, acceleromyography overestimates the TOF ratio when compared with mechanomyography. A TOF ratio of 0.9 measured by acceleromyography corresponds to a TOF ratio of 0.85 obtained by mechanomyography.[16]

It has been previously demonstrated that DBS is more sensitive than TOF in the manual detection of residual neuromuscular blockade.[17] However, the limit of manual fade detection using DBS corresponds to a TOF ratio of 0.6.[18] Recent evidence showed that a TOF ratio greater than 0.9, not 0.7,[8] is required to avoid partial paralysis; it is not surprising that absence of fade following DBS nerve stimulation does not mean complete recovery. Our data confirmed this because the sensitivities of both manual TOF and DBS were unacceptably low (11–14%) and associated with a very high specificity (98–100%). Thus, neither the clinical tests nor the qualitative instrumental tests are accurate enough to detect residual paralysis. In contrast, when fade is detected by tactile means, a certain degree of residual paralysis can be expected with a high degree of certainty.

Residual blockade (TOF < 0.9) is present in 92–96% of subjects who demonstrate fade in response to TOF or DBS stimulation (positive predictive value). However, complete recovery is seen in only half the patients with no fade (negative predictive value, 53–62%). In other words, complete recovery cannot be confirmed using either qualitative instrumental tests or clinical tests but requires the use of measured TOF ratio.

There are several clinical implications from the current study. First, a long duration between the administration of a single dose of an intermediate-acting nondepolariz-

ing muscle relaxant and the arrival in the PACU does not guarantee the lack of a residual paralysis, even if this delay is longer than 2 h. Because of the wide variability of the speed of spontaneous recovery (impeded by hypothermia and interaction between halogenated agent and muscle paralysis), it is impossible to determine precisely the minimum delay after the administration of a relaxant that will be associated with complete recovery.

Second, as it is now accepted that the TOF ratio threshold allowing complete recovery is closer to 0.9 than 0.7, clinical tests (i.e., head lift, leg lift, or tongue depressor tests) and qualitative instrumental tests (i.e., manual detection of fade following TOF or DBS stimulation) are not sufficiently sensitive to assess full recovery.

Third, even after the administration of a single intubating dose of intermediate-acting muscle relaxant, quantitative assessment of TOF ratio is mandatory at the end of the surgical procedure to assess the presence or the absence of residual paralysis. At best, this measurement needs to be performed in the operating room rather than in the PACU to reverse the block before extubating the trachea. However, clinical tests such as head lift or tongue depressor tests need to be performed even if the TOF ratio is higher than 0.9.

Fourth, in the absence of a quantitative measurement of neuromuscular recovery, such as acceleromyography, it appears safer to use reversal agents, even more than 2 h after administration of the muscle relaxant. The main result of our study clearly demonstrates the high incidence of residual paralysis after a single intubating dose of relaxant and calls into question the not uncommon clinical practice of absence of reversal.

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