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Original Contribution

Cisatracurium- and rocuronium-associated residual neuromuscular dysfunction under intraoperative neuromuscular monitoring and postoperative neostigmine reversal: a single-blind randomized trial☆,☆☆

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Abstract

Background: Postoperative residual neuromuscular blockade (RNMB) is a common complication in the postanesthesia care unit (PACU), but also one of the most controversial issues. Many studies and trials demonstrated that some methods and techniques can reduce the incidence and the extent of the phenomenon.

Study Objective: To determine the incidence of RNMB in the PACU at standardized times after extubation with the implementation of a protocol of careful neuromuscular blockade management.

Design: Randomized, single-blinded controlled clinical trial.

Setting: Operating room and PACU.

Patients: A total of 120 patients of either sex with American Society of Anesthesiologists grades 1, 2, and 3, aged 18 to 80 years were scheduled to undergo elective abdominal surgical procedures lasting for at least 60 minutes.

Interventions: Patients were randomized to receive either cisatracurium (n = 60) or rocuronium (n = 60) at the time of intubation and during surgery. Every patient received quantitative neuromuscular monitoring during general anesthesia. On completion of surgery, patients were given neostigmine 0.05 mg kg^{-1}. Patients were extubated at a train-of-four (TOF) ratio ≥0.9.

Measurements: TOF measurements were performed 15, 30, and 60 minutes after extubation. Tolerability of neuromuscular monitoring was evaluated with a scale from 1 to 10 (with 1 meaning no discomfort at all and 10 meaning maximal discomfort or pain).

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Results: Six, 11, and 14 patients (5.0%, 9.2%, and 11.7%) exhibited a TOF ratio <0.9 at 15, 30, and 60 minutes after extubation, respectively. No statistically significant difference in the postoperative RNMB between cisatracurium and rocuronium was found. The median tolerability score for neuromuscular monitoring was 3.

Conclusion: Careful conduction, monitoring, and subsequent reversal of neuromuscular block may allow for obtaining considerably low incidence of residual neuromuscular block. However, our trial shows that some mid- and long-term cases of TOF ratios <0.9 can still occur, possibly jeopardizing the patients' postoperative recovery.

1. Introduction

Postoperative residual neuromuscular blockade (RNMB) is a relatively common and unrecognized complication of early postoperative recovery. Although the increasing use of intraoperative monitoring of neuromuscular transmission has been proven to be useful in titrating the dose of neuromuscular blocking agents and facilitating the recovery of patients' optimal muscle strength, the presence of significant muscle weakness has been invariably documented in the postanesthesia care unit (PACU) [1-4]. Various recent studies have, in fact, demonstrated that many patients continue to arrive in the PACU with a T4:T1 ratio (TR) on accelerographic monitoring of <0.9, a value universally considered unsafe for a valid neuromuscular recovery [5,6].

Currently, a return of the TR at the adductor pollicis muscle to a value of at least 0.90 or greater is considered a reasonable index of satisfactory muscle recovery from nondepolarizing neuromuscular block [7,8].

Some surveys showed that anesthesiologists underestimate the incidence of RNMB and inconstantly use the approaches, which proved to be effective at preventing it [9,10]. Moreover, there are only a limited number of studies investigating the recurrence and evolution of RNMB later than the arrival of the patient in the PACU [11].

This single-center, single-blind, randomized study aimed at determining the incidence of RNMB at standardized times after tracheal extubation, after either cisatracurium or rocuronium intraoperative administration and regular neostigmine reversal. A protocol of attentive management of intraoperative neuromuscular blockade was adopted.

We also explored the individual's subjective pain and tolerability on repeated train-of-four (TOF) stimulations after complete awakening from anesthesia.

2. Materials and methods

This study was approved by the local ethics committee (Ref.: 2633P/bis) and registered with EudraCT (Ref.: 2012-002398-68). Written informed consent was obtained from all patients.

One hundred twenty patients of either sex with American Society of Anesthesiologists (ASA) grades 1, 2, and 3, aged 18 to 80 years, coming for elective abdominal surgical procedures lasting for at least 60 minutes, and requiring intraoperative neuromuscular, blockade were recruited for a single-center single-blind randomized trial. Data were collected at the University Hospital of Padua, Italy.

Exclusion criteria were as follows: patients with cardiorespiratory abnormalities (New York Heart Association heart failure grades 3 and 4, bronchial asthma, chronic obstructive pulmonary disease, and restrictive lung disease), renal insufficiency (serum creatinine >1.6 mg/dL), liver dysfunction (liver enzymes—serum glutamic oxaloacetic transaminase/serum glutamic pyruvic transaminase values elevated by more than 50% of normal), underlying neuromuscular disease, the use of drugs known to interfere with neuromuscular transmission, intraoperative hypothermia (core temperature <35°C), history of heavy smoking, and severe obesity (body mass index >35 kg/m^2).

Patients were informed about the TOF measurements they were listed to undergo postoperatively, and the possible discomfort or pain associated with it.

A computer-generated 1:1 randomization list was used to allocate the muscle relaxant to be used intraoperatively (cisatracurium or rocuronium). This was revealed to the anesthesiologist upon entering the operating room (OR); the patient was unaware of it.

Standard intraoperative monitoring included electrocardiography, capnography, noninvasive or invasive blood pressure, pulse oxymetry, and body temperature measurement.

Anesthesia was induced with 1.5 to 2.5 mg kg^{-1} propofol and 2 μg kg^{-1} fentanyl. Before anesthesia induction, 2 standard electrocardiogram electrodes were applied over the ulnar nerve at the wrist; the acceleration transducer was taped to the distal phalanx of the thumb and the temperature probe was applied to the palm. Right after propofol induction dose and before administering the muscle relaxant, calibration of the TOF-Watch SX (Organon Ltd, Dublin, Ireland) was obtained in every patient. After that, patients received for muscle relaxation and intubation either cisatracurium (0.2 mg kg^{-1}) or rocuronium (0.6 mg kg^{-1}).

The administration of the neuromuscular blocking drug (NMBD) was repeated in the course of surgery, as necessary, to maintain a TOF count ≤2. No additional muscle relaxant was administered if surgery was expected to end within 30 minutes after the last administration.

General anesthesia was maintained with a continuous infusion of propofol (targeting a bispectral index in the range of 30-40) plus boluses of fentanyl, and/or remifentanil in continuous infusion. Physical methods and warm fluids were constantly adopted to maintain body temperature.

On completion of surgery, all patients received neostigmine 0.05 mg kg^{-1} (and atropine 0.03 mg kg^{-1}), only after they had reached spontaneously a TOF count of 4. Tracheal extubation was performed at a TOF ratio ≥0.9.

All TOF measurements were performed 15, 30, and 60 minutes after tracheal extubation. Postoperative TR values were detected and recorded by an anesthesiologist unaware of the intraoperatively administered NMBD. Similar to the procedure reported by Murphy and colleagues [12,13], to ensure precision, we averaged 2 measurements that were separated by 20 seconds; if the initial 2 measurements were not within 10% agreement, 2 additional measurements were then performed (again at 20-second interval), and averaged the 2 closest TOF ratios. Careful attention was paid to not disconnect the TOF sensors and electrodes while moving the patients from the OR to the PACU.

Patients were made aware before and after surgery that if they would have been unable to tolerate the TOF stimulations, they would have been let free to withdraw from the clinical trial.

At the same scheduled postoperative time points (15, 30, and 60 minutes after extubation), soon after the TOF ratio measurements, all patients were asked to perform the "head-lift test" (ie, the ability to lift the head for 5 seconds).

After the third and last TOF determinations, the individual's subjective discomfort/pain caused by neuromuscular stimulation was assessed with a visual analog scale (VAS) from 1 to 10 (VAS score, with 1 meaning no discomfort at all and 10 maximal discomfort or pain).

Patient demographic data including age, sex, weight, height, body mass index, ASA physical status, and preexisting medical conditions were recorded from the preoperative anesthesia evaluation form. Intraoperative variables such as type of surgery, duration of general anesthesia, duration of surgery, type and dose of administered analgesics, time from first to last NMBD administration, time from last dose of NMBD to neostigmine reversal, and time from reversal to extubation, were recorded from the anesthesia record.

2.1. Statistical methods

Patients' characteristics are presented as count and percentage of patients in each category and compared between the 2 groups with χ^2 or Fisher exact test in case of categorical variables. In case of quantitative variables, mean and standard deviation (SD), median, minimum, and maximum are displayed, and the 2 groups were compared with Wilcoxon rank sum test because the distribution of the variables was not normal. Normality was evaluated with Shapiro-Wilk test.

Based on the results of the 2 recent randomized studies published by Murphy and coworkers [11,14], where the incidence of RNMB (TOF ratio ≤0.9) with intraoperative acceleromyographic monitoring and neostigmine reversal is reported to be 4.5% and 14.5%, respectively, a sample size of 60 patients per group has been estimated to allow for a precision of ±8.5% for the 95% confidence interval (95% CI) considering an incidence equal to 10.5%.

The incidence and 95% CI for TR < 0.9 at 15, 30, and 60 minutes, and of positive head-lift test at 15, 30, and 60 minutes were estimated with the binomial method.

The time course of incidence of TR < 0.9 and of positive head-lift test were compared between the 2 groups with a binary logistic regression model for repeated measures, and the results were expressed as odds ratio and 95% CI.

The statistical significance was set at the 5% level. The data were entered in an Excel spreadsheet. The randomization list and the statistical analysis were performed by a statistician with SAS 9.2 (SAS Institute Inc, Cary, NC) for Windows.

3. Results

Of 231 patients screened, 120 were randomized, and all of them completed the study (Fig. 1). Patients' characteristics are presented in Table 1. There were no differences between groups in demographic, clinical characteristics, preexisting medical conditions (data not shown), or ASA physical status. The 2 groups did not differ in duration of anesthesia, duration of surgery, type of administered analgesia, time interval from first to last administration of NMBD, and time interval from reversal to extubation. However, the 2 treatment groups did show a statistically significant difference in the time interval from the last administration of NMBD to the administration of reversal (ie, the time needed to achieve spontaneous recovery of 4 twitches). In fact, the mean (SD) time interval in the cisatracurium group was 55.3 (25.8) minutes, compared with 70.3 (26.4) minutes in the rocuronium group ($P = .0008$).

In Table 2, the number of patients with TOF ratio <0.9 at the considered time points, and the repeated-measures logistic regression results are reported. In particular, in the cisatracurium group, at 15, 30, and 60 minutes after extubation, 2, 7, and 5 patients respectively displayed a TR < 0,9; 5 out of 7 patients with TR < 0,9 at 30 minutes, and 3 out of 5 patients with TR < 0,9 at 60 minutes were "de novo" patients. In the rocuronium group, all the 4 patients with TR < 0.9 at 15 minutes displayed also similar values at 30 minutes, whereas at the 60-minute time measurement, all 9 patients but 2 with a TR < 0.9 were de novo patients.

No statistically significant difference between the 2 groups was found in TOF ratio <0.9 incidence, at the scheduled time course ($P = .5772$).

Table 3 shows the incidence of positive head-lift test and the repeated-measures logistic regression results. No statistically significant difference between the 2 groups was found

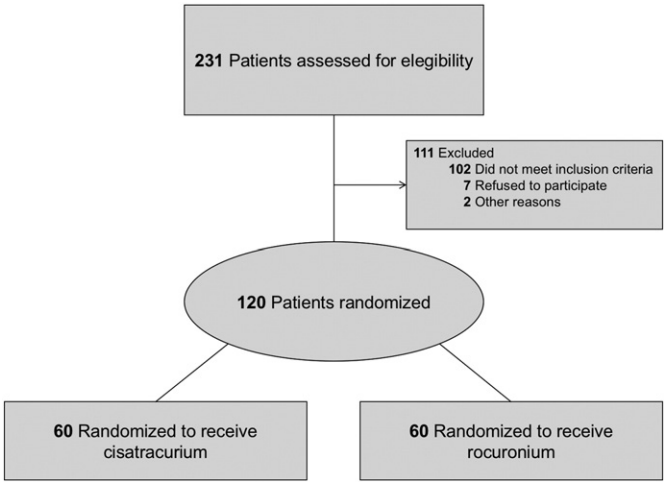

Fig. 1 Flow diagram of the study.

in the head-lift test incidence (P = .1462) at the considered time course.

When we considered the discomfort/pain suffered at postoperative NMT stimulations, the mean (SD) VAS score was 2.9 (1.6) and the median was 3 (first quartile = 2, third quartile = 4; Fig. 2).

TOF discomfort/pain was not different between the 2 treatment groups (Wilcoxon rank sum test, P = .3842).

4. Discussion

In this trial, the incidence of RNMB 15 minutes after extubation was considerably low: 5.0% overall, and precisely 3.3% with cisatracurium and 6.7% with rocuronium. Cisatracurium- and rocuronium-associated incidences of RNMB at 15 minutes should be considered similar because the 95% CIs were overlapping in the 2 groups.

The low rates of RNMB we observed are comparable with those of Baillard and colleagues [15], who described a 3.5% incidence in one cohort of patients (mostly treated with atracurium) and 9% in another cohort treated with rocuronium or vecuronium. Our data are also similar to those reported in the previously cited studies by Murphy and coworkers [11,14]: 4.5% RNMB incidence in their 2008 report and 14.5% in the cohort of 2011study.

The rate of RNMB observed in our patients at 15 minutes after extubation greatly differs from that described in the studies by Xie and colleagues [17] (30.6%) and in the meta-analysis by Naguib et al [16] (TR < 0.9 upon arrival in the PACU detected in >40% of patients). However, in the Xie study, despite acceleromyographic neuromuscular intraoperative monitoring, the combination of 2 different nondepolarizing NMBDs during surgery, lack of treatment of hypothermia, and NMBD dose adjusting according to the "arbitrary" order of the attending anesthesiologists, could have contributed to a >30% rate of TR < 0.9. The 40% incidence of residual muscle dysfunction reported by Naguib et al [16] could instead be ascribed to the old studies included, often very different in design and with different surgical procedures, where long- and intermediate-acting NMBDs were used,

Table 1 Patients' demographic and clinical characteristics

		Cisatracurium (n = 60)	Rocuronium (n = 60)	P
Sex, female/male, n (%)		24/36 (40.0/60.0)	27/33 (45.0/55.0)	.5796
Age (y)	Mean (SD)	56.9 (13.9)	56.9 (12.3)	.8955
	Median (min-max)	59 (21-79)	61 (24-79)	
Weight (kg)	Mean (SD)	71.3 (14.9)	70.7 (12.1)	.5476
	Median (min-max)	66.5 (52-110)	72 (46-94)	
Height (cm)	Mean (SD)	167.9 (9.2)	168.3 (8.5)	.7584
	Median (min-max)	169.5 (145-193)	168 (150-189)	
BMI (kg/m^2)	Mean (SD)	25.3 (4.6)	25.0 (3.6)	.9916
	Median (min-max)	25.0 (18.5-38.1)	24.4 (18.3-34.3)	
ASA status I/II/III, n (%)		8/30/22 (13.3/50.0/36.7)	12/31/17 (20.0/51.7/28.3)	.4825

BMI = body mass index; ASA = American Society of Anesthesiologists.

Table 2 Incidence of TOF ratio <0.9 and repeated-measures logistic regression results

	Cisatracurium (n = 60)		Rocuronium (n = 60)		Group effect from logistic regression	
	n (%)	95% CI	n (%)	95% CI	OR (95% CI)	*P*
15 min	2 (3.33)	0.41-11.53	4 (6.67)	1.85-16.20		
30 min	7 (11.67)	4.82-22.57	4 (6.67)	1.85-16.20	0.81 (0.38-1.71)	.5772
60 min	5 (8.33)	2.76-18.39	9 (15.00)	7.10-26.57		

TOF = train-of-four; CI = confidence interval; OR, odds ratio.

intraoperative TOF monitoring rarely applied, and with a significant heterogeneity both in the time and the dose of anticholinesterase antagonism.

It is to underline that 15 minutes after extubation, no patient showed a TR < 0.7 and just one (0.8%) had a TR between 0.7 and 0.8; in the patient population who displayed a TOF ratio < 0.9, the mean (SD) TR was still high, 0.85 (0.04), hence close to a value considered "quite safe."

Our anesthetic approach approximately resembles the protocol by Murphy and coworkers with a 14.5% incidence of TR < 0.9 at PACU arrival in the acceleromyography group [11]. Minimal differences between the 2 studies are the reversal, which started also at 3 TOF counts in the study by Murphy et al (instead of 4 in our series), and the timing of tracheal extubation, performed in 10 patients of their series before a TR of 0.8.

The results we observed at the other 2 scheduled time measurements showed a 9.2% overall incidence of TR < 0.9 at 30 minutes after extubation (11.7% with cisatracurium and 6.7% with rocuronium), and 11.7% at 60 minutes (8.3% with cisatracurium and 15.0% with rocuronium).

These data, which do not a mark difference between the 2 NMBDs (95% CIs still overlapping), are consistent with an increase in the incidence of residual muscle dysfunction when compared with the observations at 15 minutes, and are more closely related to the RNMB rates described at various times after PACU arrival in previous series [18]. No significant differences in the recovery patterns of cisatracurium vs rocuronium at 20 minutes postreversal were also reported by Kopman and colleagues [19].

To reaffirm the recognized discordance between the classical clinical signs of recovery of muscular strength and TR values, also in our population, of those patients with TR < 0.9 at 30 minutes, "only" 28.6% of cisatracurium and 50.0% of rocuronium group were not able to keep the head up for 5 seconds). At 60 minutes, in the rocuronium group, 5 of 9 patients (55.6%) with TR < 0.9 could not raise the head for 5 seconds, whereas none of those in the cisatracurium group with a TR < 0.9 at 60 minutes had a positive head-lift test result.

Unfortunately, our results cannot be comparable with data of similar clinical trials because no studies investigating the RNMB phenomenon with TOF quantitative monitoring at fixed postoperative times have been published yet.

Nevertheless, the presence of rates up to 15% of TR < 0.9 till 1 hour after the end of the procedures should be considered a relevant occurrence. It is recognized that the intermediate-acting NMDBs can show some clinical effect up to 2 hours after the last administration [6], long after the cessation of the effects of neostigmine. It is very likely that at least some of the mid- and long-term cases of TR < 0.9 we detected, were due to a resume of the effect of the NMBD, which revealed when the neostigmine effect was over (neostigmine is known to last 30-120 minutes). We can reasonably exclude that these cases were due to drug interference with muscle paralysis, because no patient received any known recurarization-triggering substances or treatments (such as benzodiazepines, magnesium sulfate, calcium-channel blockers, aminoglicoside antibiotics, or auto-transfusion procedures).

We presume that the low incidences of RNMB we detected at different times postoperatively can be attributed to the specific design of our trial, which was based on accurate intraoperative TOF monitoring, TOF-guided NMBD administration, regular antagonist administration at recovery from anesthesia, and correct clinical test evaluation before extubation.

It should be noted, however, that neither a careful conduction of an intraoperative neuromuscular blockade nor the routine administration of reversal drugs at appropriate time and dose can guarantee the avoidance of neuromuscular dysfunction in the early postoperative period. As mentioned above

Table 3 Incidence of positive head-tilt test and repeated-measures logistic regression results

	Cisatracurium (n = 60)		Rocuronium (n = 60)		Group effect from logistic regression	
	n (%)	95% CI	n (%)	95% CI	OR (95% CI)	*P*
15 min	3 (5.00)	1.04-13.92	5 (8.33)	2.76-18.39		
30 min	3 (5.00)	1.04-13.92	3 (5.00)	1.04-13.92	0.48 (0.18-1.29)	.1462
60 min	1 (1.67)	0.04-8.94	6 (10.00)	3.76-20.51		

CI = confidence interval; OR, odds ratio.

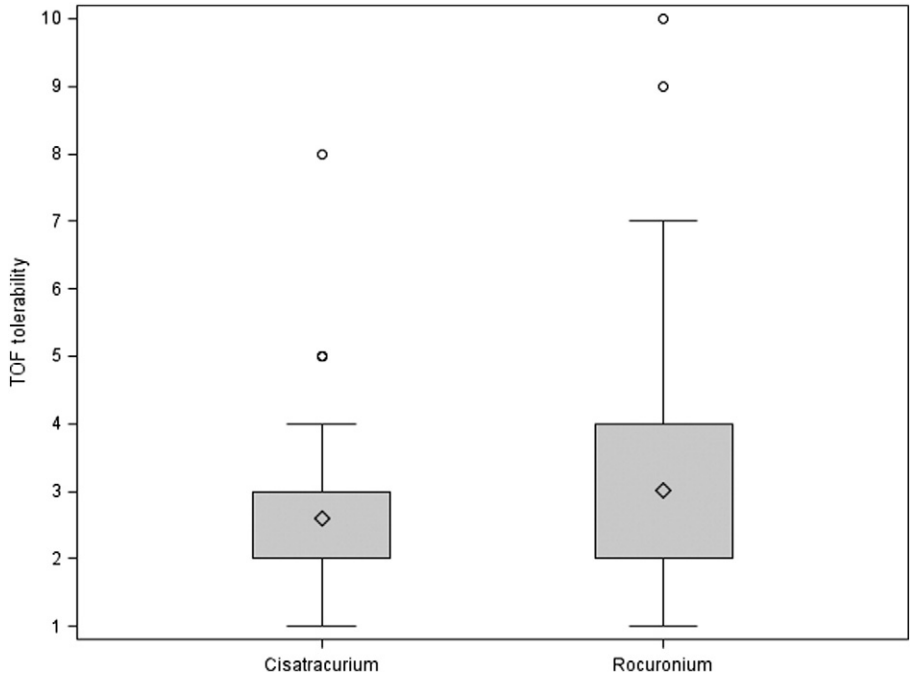

Fig. 2 Box plot for VAS scores at postoperative TOF stimulation. The boundaries of the boxes represent the 25th and 75th percentiles, respectively; whiskers extend 1.5-fold interquartile range distance from the box. The mean value is denoted by diamond. Circles represent the outlier values. VAS = visual analog scale; TOF = train-of-four.

also in our series, the numerical TOF ratio showed a slight incremental rate of TR < 0.9 at 30 minutes, and moreover at 60 minutes after extubation.

The time interval from the last administration of NMBD to the administration of reversal (ie, the time needed to obtain spontaneous recovery of 4 twitches) was significantly higher in the rocuronium group (mean, 70.3 minutes) compared with cisatracurium (mean, 55.3 minutes); this is in accordance with some observations that report an intrinsic clinical variability of rocuronium and a rocuronium-induced neuromuscular block, to some extent deeper and longer lasting than cisatracurium-induced block [20,21].

At the end, in no cases we omitted the reversal, even when a long time interval lasted from the last NMBD administration. Neostigmine was given only upon reaching the 4 twitches at adductor pollicis, and extubation was performed when both the defined quantitative TR and clinical criteria were achieved.

The feasibility of a repeated postoperative TOF monitoring on an awake patient has not been evaluated in most of the clinical trials. The main cause refraining anesthesiologists from performing TOF quantitative monitoring early after surgery is the supposed discomfort/pain and reluctance of the patient to peripheral nerve stimulation. In our series, the mean VAS score (SD) evaluating the discomfort/pain at postoperative NMT stimulations was 2.9 (1.6), and the median was 3 (first quartile = 2, third quartile = 3.5). No patient refused to undergo repeated peripheral nerve stimulation at successive postoperative times. TOF discomfort/pain was not different between the 2 treatment groups.

Murphy and colleagues [22] performed a TOF-Watch monitoring in the OR and PACU using 50-mA stimulation currents; only 8% of patients recalled TOF stimulations.

Similarly to previous trials [14], to obtain more reliable results, we opted to maintain higher current intensities (range, 40-60 mA, as derived from the preoperative calibration).

Our results show that TOF monitoring on the postoperative awake patient is well tolerated, with 87.5% of the patients communicating a VAS score between 1 and 4. Prolonged effects of intraoperative opioids, along with other "transitional" analgesics, likely contributed to such a high tolerance to repeated TOF stimulations. Thirty-one percent of patients were administered analgesics soon after surgery; this could have possibly increased their tolerance to awake TOF stimulations. These data encourage and support the repeated use of neuromuscular monitoring at PACU arrival, as a mean to discover a delayed recovery from RNMB.

This study has limitations. There was a lack of anesthesiologist's blindness to muscle relaxant; however, the computer-generated randomization made her and/or him aware of the type of NMDB only during the intraoperative period; the physician in charge for detecting postoperative TR values was unaware of it. The TOF ratio of 0.9 we considered to exclude a potential RNMB may be judged a surrogate marker of satisfactory neuromuscular function recovery, and we could have missed low levels of residual paralysis and underestimated the real incidence of RNMB.

According to some authors, with the widespread use of acceleromyography, a TOF recovery to 1.0 has to be

considered a better target [23]. We have nevertheless opted for 0.9 after 2 TOF stimulations applied successively and recorded at a 20-second interval, because, also in various recent studies, this threshold is still reported to be harmless in preventing major adverse effects of RNMB [3,17,18].

We are aware that by measuring TR at intervals longer than that last scheduled, we could have possibly detected higher rates of RNMB; a great variability among individuals in the duration of neostigmine-induced reversal, despite the correct drug dosage, has, in fact, been described [24].

In conclusion, despite the improvement in their use, the administration of intermediate-acting NMBDs cisatracurium and rocuronium is still associated with a variable incidence of postoperative incomplete neuromuscular recovery.

Vigilant intraoperative quantitative neuromuscular monitoring, NMBD administration at the occurrence of TOF count = 2, constant reversal long before extubation, and cautious extubation with a TR $\geq$ 0.9 may contribute to a considerably low incidence of residual neuromuscular block.

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