

Retrospective analysis of spontaneous recovery from neuromuscular blockade produced by empirical use of rocuronium

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Abstract

Purpose A train-of-four ratio (TOF ratio) of >0.9 should be the clinical cut-off to avoid residual paralysis. However, it is not rare to extubate patients without measurement of the TOF ratio, although the safe interval from the last administration of rocuronium assuring a TOF ratio of >0.9 has not been established in the daily clinical setting. In this study, to estimate the safe interval to avoid residual paralysis, we retrospectively selected patients in whom the TOF ratio was measured during remifentanil administration before extubation, and we studied the characteristics of recovery from the neuromuscular blockade produced by the empirical use of rocuronium.

Methods Patients undergoing surgery under general anesthesia with sevoflurane and remifentanil were studied ($n = 134$). Rocuronium was administered at 0.7–1.0 mg/kg for tracheal intubation, and repeated bolus administration (10 mg) or continuous infusion (15–25 mg/h) was performed by the anesthesiologists in charge of the patient to maintain intraoperative paralysis. At the end of the surgery, the TOF ratio was measured, during remifentanil infusion and the contribution of clinical parameters to spontaneous recovery from the rocuronium-induced paralysis was studied by multivariate logistic regression analyses.

Results Spontaneous recovery from rocuronium-induced paralysis within 2 h after the last administration of rocuronium varied among the patients. Multivariate logistic

regression analyses showed that age ($P = 0.002$) and time elapsed from the last administration of rocuronium ($P < 0.0001$) significantly contributed to TOF recovery, and elderly patients demonstrated significantly slower recovery.

Conclusion Because of the large variation in the recovery from rocuronium-induced paralysis, TOF-based evaluation of residual paralysis is essential to determine the appropriate indication for reversal, especially for elderly patients.

Keywords Rocuronium · Residual paralysis · Train-of-four test · Sugammadex

Introduction

Residual paralysis is an important factor in postoperative complications. Although it is difficult to detect by clinical observation, residual paralysis can result in respiratory muscle weakness and problems in pharyngeal function [1]. Recent reports have suggested that the train-of-four (TOF) test is sensitive to detect residual paralysis, and a TOF ratio of >0.9 should be the clinical cut-off to avoid residual paralysis [1–4]. Although cumulative results suggest the importance of perioperative TOF monitoring, many recent surveys suggest that neuromuscular blockers are often administered without proper monitoring [5, 6]. In such cases, clinical diagnosis of sufficient recovery from neuromuscular blocking drugs is still judged empirically from the timing of the last dose of the nondepolarizing relaxant and the clinical presentation. However, the time needed for sufficient recovery that would assure a TOF ratio of >0.9 has not been established in the daily clinical setting. In this study, to estimate the safe interval to avoid residual

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paralysis, we retrospectively studied the relationship between the time interval from the last administration of rocuronium and the TOF ratio at the end of the surgery when the dose and the timing was empirically decided by the anesthesiologist in charge of the patient. We also studied factors that contributed to the prolongation of recovery from rocuronium-induced paralysis in our clinical practice.

Methods

This study was designed as a single-center, open-label, nonrandomized retrospective observational study. All drugs in this study were used in accordance with their labeling and all the procedures were performed as clinical treatment procedures. All the data were retrospectively abstracted from patients' medical records. The study protocol was approved by the local institutional ethics committee, which waived the need for informed consent in the retrospective data analyses.

Patients undergoing surgery under general anesthesia with sevoflurane and remifentanyl were retrospectively included in this study. Exclusion criteria were: (1) patients extubated without TOF monitoring, (2) patients with malfunction of TOF monitoring devices, defined as cases without improvement of the TOF ratio after sugammadex administration, and (3) patients requiring postoperative mechanical ventilation.

Anesthetic management

Anesthetic management and reversal of rocuronium-induced paralysis were based on the following standard institutional protocol. General anesthesia was induced with propofol (1.5–2 mg/kg) and with continuous infusion of remifentanyl, and was maintained with sevoflurane (1.5–2.5%) and remifentanyl. Rocuronium was administered at 0.7–1.0 mg/kg for the facilitation of tracheal intubation, and 10-mg bolus administration was repeated to maintain the paralyzed condition intraoperatively. Alternatively, rocuronium was administered continuously at 15–25 mg/h for the maintenance of intraoperative paralysis. The timing and dose of additional bolus administration or the stopping of continuous infusion of rocuronium was determined by the anesthesiologists in charge of the patient. At the end of the surgery, the administration of sevoflurane was stopped, and the TOF test was performed during remifentanyl infusion and mechanical ventilation: the unilateral ulnar nerve was stimulated at the wrist with 50 mA and square-wave stimuli of 0.2-ms duration, which was delivered in a TOF mode at 2 Hz every 12 s. Contraction of the ipsilateral adductor pollicis was measured

using an acceleromyograph (TOF watch[®]; Schering-Plough, Kenilworth, NJ, USA). Results of the TOF test were recorded as the TOF ratio or TOF count. When TOF watch[®] indicated only the value of the TOF count, the TOF ratio was recorded as 0. When the TOF ratio was <0.9, 2 mg/kg of sugammadex was administered after confirmation of a TOF count of ≥ 2 , and we continued observation under TOF stimulation every 12 s. When the TOF ratio had recovered to >0.9 with or without administration of sugammadex, the administration of all the anesthetic drugs was stopped and patients were extubated after confirmation of their awareness.

Clinical data records

Clinical data records were abstracted from the medical records. The time of last administration of rocuronium, the time of finishing continuous administration of rocuronium, the time of measurement of the TOF, and the TOF counts and TOF ratios at the end of surgery were recorded from computer-based anesthesia records.

Statistical analyses

All statistical analyses were performed using STATA IC software version 11 (StataCorp, College Station, TX, USA). Multivariate logistic regression analyses were performed to study the contribution of clinical parameters to recovery with a TOF ratio of >0.9. As clinical parameters, patients' characteristics (age, gender, body weight, serum albumin level, serum creatinine level, aspartate aminotransferase level, alanine aminotransferase level, total bilirubin level) and time elapsed from the last administration of rocuronium were studied. In this multivariate test, backward elimination was performed at $P > 0.20$. Because age was found to be a significant factor for TOF recovery in this study, we trichotomized the whole study cohort by age, and comparisons among trichotomized groups were performed to study the difference in TOF recovery over time. For these analyses, we performed two-way analysis of variance (ANOVA) tests. The Dunnett test was performed as a post-hoc multiple comparison test. Statistical significance was defined as $P < 0.05$.

Results

Between 26 September 2010 and 12 November 2010, based on the inclusion criteria described in “Methods”, one hundred and thirty-four patients were included in the study population. Their perioperative characteristics are summarized in Table 1.

Table 1 Patients' characteristics

	Median	Range
Age (years)	59	24–85
Body weight (kg)	59	34–108
Albumin (g/dL)	4.3	2.6–5.3
Creatinine (mg/dL)	0.74	0.43–8.4
Aspartate aminotransferase (IU/L)	20	12–121
Alanine aminotransferase (IU/L)	16	5–139
Total bilirubin (mg/dL)	0.7	0.3–1.6
Duration of surgery (min)	153	25–690
Duration of anesthesia (min)	226	75–783
Total dose of rocuronium (mg)	60	25–268

Number of patients = 134 (male/female = 70/64)

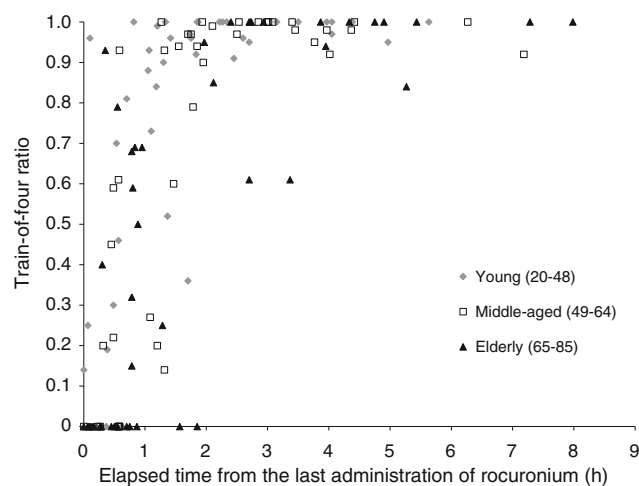


Fig. 1 Scattergram for recovery of train-of-four ratio (TOF ratio) over time. The TOF ratio was measured at the end of each operation before the administration of sugammadex. The whole study cohort was trichotomized by age; young (*gray dots*) aged from 20 to 48 years, middle-aged (*open squares*) aged from 49 to 64 years, and elderly (*black triangles*) aged from 65 to 85 years. For patients whose TOF ratios were unavailable on TOF watch[®] because of insufficient recovery, values are indicated as TOF ratio = 0

The relationship between the TOF ratio and the elapsed time from the last administration of rocuronium is demonstrated in Fig. 1. At the end of surgery, there were no patients with a TOF count = 0, and all the patients who required reversal had recovered to a TOF ratio of >0.9 by the administration of sugammadex. Results of multivariate logistic regression analyses to study the contribution of clinical variables to the achievement of a TOF ratio of >0.9 are shown in Table 2. As clinical variables, age, gender, body weight, serum albumin level, serum creatinine level, aspartate aminotransferase level, alanine aminotransferase level, total bilirubin level, and time elapsed from the last administration of rocuronium were studied. In this model, age and time elapsed from the last administration of

Table 2 Logistic regression analysis for recovery from paralysis equivalent to train-of-four ratio of >0.9

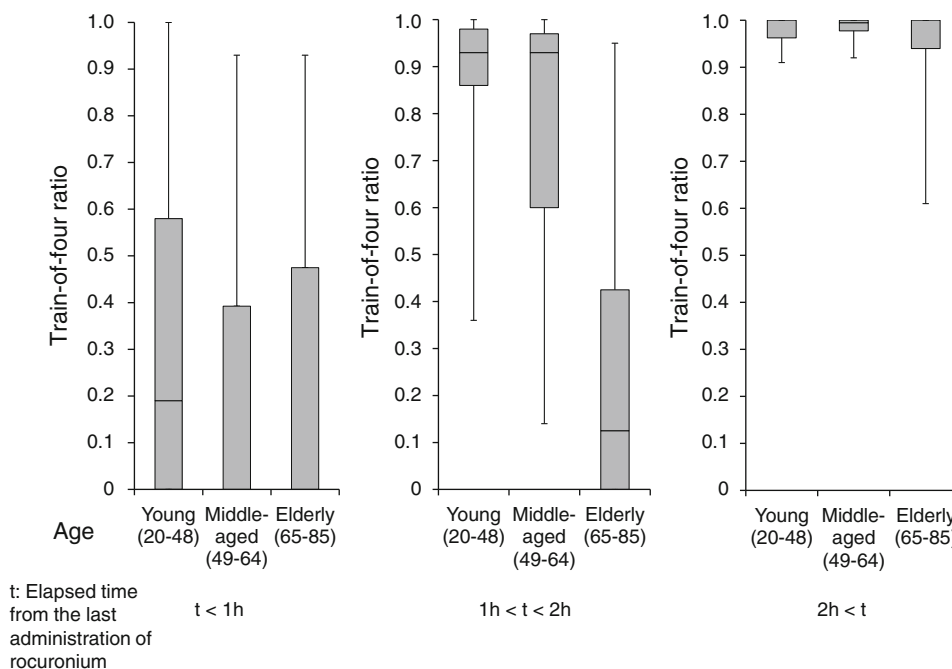
	Odds ratio	95% Confidence interval	P value
Age (per 1-year increment)	0.94	0.91–0.98	0.002
Aspartate aminotransferase (per 1-IU/L increment)	0.96	0.91–1.01	0.099
Elapsed time from the last administration of rocuronium (per 1-h increment)	7.1	3.5–14.2	<0.0001

rocuronium showed significant contributions to TOF recovery. Then, we trichotomized the whole study cohort by age [young (age 20–48 years, $n = 44$), middle-aged (age 49–64, $n = 43$), and elderly (age 65–85, $n = 47$)], and compared the TOF ratios in each age group. Figure 2 demonstrates the TOF ratio in each age group in three time frames, less than 1 h, less than 2 h, and more than 2 h elapsed from the last administration of rocuronium. Two-way ANOVA test showed significant contributions of time ($P < 0.0001$) and age ($P = 0.0014$) to the TOF ratio, and also a significant interaction ($P = 0.0387$) was observed between these two factors. Post-hoc multiple comparison analysis demonstrated that the TOF ratio in the elderly group was significantly lower than that in the young group ($P < 0.0001$). When rates of achievement of a TOF ratio of >0.9 over time were compared among the three age groups, the elderly group showed a significantly lower rate compared with the young group ($P = 0.0286$). In the young and middle-aged groups, when the elapsed time was less than 1 h, approximately 10% of patients had a TOF ratio of >0.9 (13% in the young group, and 7% in the middle-aged group), whereas when the elapsed time in these age groups was >2 h, all patients recovered to a TOF ratio of >0.9.

Discussion

Residual neuromuscular block contributes to morbidity in patients recovering from general anesthesia [1]. Previous studies in volunteers have shown that pharyngeal function [2, 3], airway muscle function [7], and also hypoxic ventilatory drive could be impaired [8, 9], and residual paralysis could result in upper airway obstruction [7] and aspiration [3]. Clinical studies in surgical patients have also demonstrated a higher risk of critical postoperative respiratory events in patients with residual muscular blockade with a TOF ratio of <0.9 [10, 11]. However, without objective neuromuscular monitoring, the diagnosis of residual paralysis is difficult when a patient's recovery is equivalent to a TOF ratio rated as between 0.5 and 0.9

Fig. 2 Box-whisker plot of train-of-four ratio (TOF ratio) in the subgroups trichotomized by age; young (aged from 20 to 48 years), middle-aged (aged from 49 to 64 years), and elderly (aged from 65 to 85 years). Data are shown in three time frames as indicated. In each graph, the horizontal line, box, and whisker represent the median value, interquartile range, and range of distribution of the TOF ratio, respectively



[7, 12, 13]. Considering the situation that extubation without TOF monitoring is not rare in our daily clinical practice, we cannot eliminate the possibility of occult residual paralysis, especially in patients without administration of reversal agents. The results of the present study, in which the protocol of rocuronium administration was comparable with those suggested by the drug labeling (0.6–0.9 mg/kg for intubation and 0.1–0.2 mg/kg repeated bolus or 7 µg/kg/min continuous infusion for maintenance of paralysis), demonstrated that the majority of patients needed more than 1 h for spontaneous recovery from the rocuronium-induced paralysis to a level with a TOF ratio of >0.9, and more than one-third of the patients showed a TOF ratio of <0.9 even in the period when the elapsed time from the last administration of rocuronium was between 1 and 2 h (33% in the young group, 38% in the middle-aged group, and 75% in the elderly group). The results of our present study also demonstrated that ranges of the TOF ratio within 2 h from the last administration of rocuronium were relatively wide, and elderly patients showed slow recovery. These results suggest the importance of the TOF test for evaluating residual paralysis and for the determination of appropriate indications for drugs used to reverse rocuronium-induced paralysis.

Spontaneous recovery from a single intubation dose of rocuronium was studied by Debaene et al. [14], and they reported that 37% of patients had a TOF ratio of <0.9 at 2 h or more after the administration of rocuronium. Our results for the recovery of the TOF ratio showed a more rapid recovery than their results. Several factors might be able to explain this discrepancy in the results. First, our

study cohort included patients with multiple or continuous administration of rocuronium, which results in a lower plasma concentration at the last administration compared with the plasma concentration for the protocol using a single intubation dose. Second, ethnic differences should be considered, because our study cohort consisted exclusively of Asian patients. Nevertheless, these differences do not affect our conclusion that TOF monitoring is essential for the precise evaluation of spontaneous recovery from the paralysis induced by nondepolarizing muscle relaxants.

The results of our present study demonstrated slower recovery from rocuronium-induced paralysis in the elderly group. This result was consistent with the results demonstrated by Matteo et al. [15], which showed prolonged action of rocuronium in patients aged more than 70 years because of decreased elimination of the drug. However, the true cut-off value for the age of decreased rocuronium elimination could not be determined from the present results because of the insufficient size of the study cohort.

To eliminate residual neuromuscular blockade, monitoring using nerve-stimulating tests and reversal of neuromuscular-blocking drugs are key approaches. However, the routine use of objective neuromuscular monitoring is still not common for several reasons. First, the patient's spontaneous movements can interfere with monitoring procedures using acceleromyography, and supramaximal stimulation could be intolerable for some patients with emergence from anesthesia [16]. In this context, the TOF ratio might be a more precise evaluation of recovery in anesthetized subjects [17, 18]. Second, using sugammadex, a recently developed drug for the reversal of

non-depolarizing muscle relaxants, the TOF ratio can be recovered to more than 0.9 with high probability without TOF monitoring [19]. However, the routine use of this drug without TOF monitoring might include patients in whom reversal is unnecessary because of sufficient spontaneous recovery, which would result in over-treatment. Considering these factors and the large variation shown in spontaneous recovery from rocuronium-induced paralysis, TOF monitoring under remifentanyl administration before extubation might be an appropriate choice for the precise evaluation of spontaneous recovery from rocuronium-induced paralysis, and such monitoring might be helpful for deciding on the appropriate indications for drugs used for the reversal of neuromuscular-blocking agents.

In conclusion, from our evaluation of spontaneous recovery from rocuronium-induced paralysis, the recovery of TOF varied among patients within 2 h after the last administration of rocuronium. Elderly patients tended to show slow recovery, and some elderly patients had significant residual paralysis even 2 h after the last administration of rocuronium. Recovery from rocuronium-induced paralysis should be evaluated by TOF monitoring, and appropriate indications for drugs used for the reversal of neuromuscular-blocking agents should be determined, especially for elderly patients.

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