THE INCIDENCE OF POSTOPERATIVE RESIDUAL CURARIZATION FOLLOWING THE USE OF INTERMEDIATE-ACTING MUSCLE RELAXANTS AND RELATED FACTORS

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Abstract

Purpose: To evaluate the incidence of residual curarization (RC) and related risk factors in the early and late postoperative periods in patients receiving general anesthesia with intermediate-acting muscle relaxants.

Methods: Two-hundred and eight American Society of Anesthesiologists class I and II patients, aged 18-70 years, who underwent general anesthesia with intermediate-acting muscle relaxants, were included. Heart rate, blood pressure, oxygen saturation, tympanic temperature were recorded for each patient who was transported to the recovery room, every 10 minutes by a trained nurse. To define the efficacy of residual muscle relaxants, neuromuscular monitoring was performed, and Train of Four (TOF) ratios <90% were regarded as RC whereas ratios ≥90% were considered as adequate neuromuscular recovery in early and late recovery periods. Age, duration of anesthesia, repeated doses, reversal and types of intermediate-acting neuromuscular blockers were evaluated as risk factors for RC. Logistic Regression Analysis was performed to define the risk factors for RC in early and late periods.

Results: The RC rate was 10.6% in the early recovery period, and short duration of anesthesia, repeated doses and lack of reversal use were the risk factors for RC. However, RC rate was 2.9% in the late recovery period, and the only risk factor was repeated doses.

Conclusion: Reversal use was shown to reduce residual effects of intermediate-acting muscle relaxants in early recovery period, whereas risk of RC in 30 min in PACU was shown to increase with repeated doses of muscle relaxants.

Keywords: Residual curarization, train-of-four, intermediate-acting muscle relaxants, post-anesthesia care unit.

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Introduction

Postoperative residual curarization (RC) in the recovery unit is a very important clinical problem and is described as the relationship of the train-of-four (TOF) fade ratio to signs and symptoms of muscle weakness[1-3]. Even when the effects of a muscle relaxant clinically disappear, some receptors in the nerve muscle junction are still blocked by the muscle relaxant agents[4,5].

Residual curarization was a problem due to the use of long-acting muscle relaxants in the past; however, it is also seen frequently with the use of intermediate-acting muscle relaxants[6-11]. High RC rates were reported by the use of both intermediate and long-acting muscle relaxants[12-16].

Generally, a single TOF measurement in the recovery room is used to determine the incidence of RC. In some studies, TOF was measured immediately after extubation, while in others[10,16-20] the measurement was made upon arrival of the patient to the recovery room. However, there are few studies on the early and late residual effects of intermediate-acting muscle relaxants[12].

The purpose of this study was to detect the incidence of RC and to investigate the related factors, by neuromuscular monitoring in early and late periods of recovery in patients in the recovery room after general anesthesia with either vecuronium, rocuronium or atracurium.

Materials and Methods

The study was a prospective, observational investigation performed in the Department of Anesthesiology and Reanimation. After local ethic committee approval, written informed consents were obtained from all patients. Patients between 18 and 70 years of age in American Society of Anesthesiologists (ASA) physical status I or II were randomly assigned to receive an intermediate-acting neuromuscular blocking (NMB) agent (vecuronium, atracurium or rocuronium) during general anesthesia.

The exclusion criteria were: 1) the presence of a renal, hepatic or a neuromuscular disease; 2) body mass index >30%; 3) use of drugs known to interfere with neuromuscular transmission; 4) pregnancy; 5) refusal to participate the study; 6) craniotomies, cardiothoracic and vascular surgeries, emergency operations, surgeries requiring longer than 6 hours of anesthesia and operations requiring blood and fluid replacement.

A dose of 0.05 mg/kg midazolam was given intramuscularly as a premedication 30 min before surgery. The selection of anesthetic induction (intravenous propofol 2-3 mg/kg, fentanyl 1-2µg/kg, lidocaine 1 mg/kg) and maintenance drugs (1-1.5% isoflurane and 1.5-2% sevoflurane), muscle relaxants (vecuronium, rocuronium, atracurium), intraoperative additional muscle relaxant use, the decision of extubation, reversal use and transfer to the recovery room was at the discretion of the anesthesiologist.

Induction and maintenance doses of muscle relaxants are: vecuronium 0.1 mg/kg and 2 mg, rocuronium 0.5 mg/kg and 10 mg, atracurium 0.5 mg/kg and 10 mg, respectively. In the event of inadequate spontaneous respiration after surgery or if the last dose of muscle relaxant was in the last 40 minutes of the surgery or if weak motor responses to verbal stimuli were present after extubation, neostigmine at a dose of 0.05 mg/kg and atropine were given to the patients. After extubation, the patients breathed 100% oxygen by mask, and kept in the operating room. Patients, who had verbal and motor responses to verbal stimuli (take their tongue out, open their eyes, hold their hands up above their heads), and had adequate spontaneous respiration were transferred to the recovery room as per the decision of the anesthesiologist.

Neuromuscular monitoring was performed at the arrival and 30 minutes later in the recovery room.

TOF fade ratios were measured by using acceleromyography (TOF-Watch©-SX; Organon Teknika, Dublin, Ireland). The arm where the measurements were taken was immobilized with a splint and was positioned to assure free movement of the thumb during nerve stimulation. An acceleration transducer was taped to the distal interphalangeal joint of the thumb. Supramaximal TOF stimulation was delivered to the ulnar nerve via surface electrodes. Two consecutive responses to TOF stimulation (separated by 15 s) were obtained, and the average of the two values was recorded. If the measurements differed by

more than 10%, additional TOF ratios were obtained (up to four TOF values), and the closest two ratios were averaged.

The first measurement, taken as the patient arrives to the recovery room and the measurement taken 30 minutes after arrival were defined as "early recovery period" and "late recovery period", respectively. TOF ratios <90% were considered as "the presence of RC" while TOF ratios ≥90% were considered as "the absence of RC".

In the recovery room, routine hemodynamic monitoring of heart rate (HR), peripheral oxygen saturation (SpO_2), noninvasive blood pressure, and tympanic temperature was maintained. Patients' age, gender, body weight, type of surgery, drugs used for anesthesia induction and maintenance, type of muscle relaxants and time of administration of additional doses during the intraoperative period, reversal usage, duration of surgery and anesthesia were recorded from the anesthesia sheet. Patients were monitored for at least 30 minutes in the recovery room by trained nurses. Age, type of muscle relaxant used, number of additional doses of muscle relaxants during the operation, use of reversals after surgery, duration of anesthesia and tympanic temperature changes were analyzed as the risk factors that may affect RC in the logistic regression model. The variables were grouped according to age (18–39 years, 40–59 years and 60–70 years), the type of muscle relaxants (vecuronium, rocuronium, atracurium), number of additional doses of muscle relaxant used during the operation (only for induction, 1 time, 2 times, 3 times and 4 times), reversal use after operation (yes/no), duration of anesthesia (0-90 min, 91-180 min, 181-270 min and 271-360 min) and tympanic temperature (34.4-35.4°C, 35.5-36.4°C and 36.5-37.6°C).

Statistical analysis

Statistical Program for Social Sciences (SPSS, Inc., Chicago, IL, USA) version 10.0 was used for statistical analysis. Logistic regression analysis was performed to define the risk factors for RC in early (0 min) and late (30 min) recovery periods. The Chi-square test was used for comparison of the frequency. The Kolmogorov-Smirnov test was used to test the normal distribution of data. Descriptive statistics were presented as mean±standard deviation and median (25%-75% percentile). The Wilcoxon T-test was used for changing values of HR, mean arterial blood pressures (MAP) and SpO_2 in recovery room over the time (mean ± SD). A $p < 0.05$ was considered to be statistically significant.

Results

Two hundred and eighteen patients were enrolled in the study. Ten patients were excluded because of lack of data. Statistical analysis was performed on 208 patients. Patient characteristics, the duration of anesthesia, the duration of surgery and types of surgery are presented in Table 1.

Table 1
Patients characteristics, clinical parameters and surgical procedures

Patient Characteristics	
Gender (Female/Male)	110/98
Age (year)	43.2±14.2
Weight (kg)	73.1±12.9
ASA	
I	158
II	50
Duration of anesthesia (min)	123.6±58.9
Duration of operation (min)	92.9±52.7
Surgery	
Head and neck surgery	94
Laparoscopic abdominal surgery	34
Non-laparoscopic abdominal surgery	53
Extremity surgery	6
Others (breast, plastic, perineal surgery)	21

Data are presented as mean±standard deviation or number, where appropriate.

ASA: American Society of Anesthesiologists.

Table 2
Distribution of patients according to risk factors affecting residual curarization during early recovery period

Risk factors		Residual curarization		
		Yes (n=22)	No (n=186)	p value
Age (years)	18-39	10	73	0.42
	40-59	10	83	
	60-70	2	30	
Type of muscle relaxants	Vecuronium	13	81	0.20
	Atracurium	5	58	
	Rocuronium	4	47	
Number of additional doses of muscle relaxant	Induction	11	97	0.40
	1 time	5	66	
	2 times	4	20	
	3 times	0	3	
	4 times	2	0	
Reversal use after operation	yes	6	86	0.09
	no	16	100	
Duration of anesthesia (min)	0-90	8	54	0.46
	91-180	12	109	
	181-270	1	18	
	271-360	1	5	
Tympanic temperature (˚C)	34.4-35.4	2	32	0.32
	35.5-36.4	11	92	
	36.5-37.6	9	62	

The induction of anesthesia was similar in all patients. Anesthesia was maintained with isoflurane in 147 patients, and sevoflurane in 61 patients. Rocuronium, atracurium and vecuronium was given to 51, 63 and 94 patients, respectively.

Residual curarization (TOF<90%) occurred in 22 patients (10.6%) in the early period and continued in six patients (2.9%) in the late recovery period.

The distribution of patients with RC according to risk factors during the early recovery period is presented in Table 2. No significant difference was observed in the number of patients with and without RC in terms of risk factor subgroups.

Lack of reversal use (Odd's ratio 0.311, 95% confidence interval (CI) 0.104-0.932), short duration of anesthesia (Odd's ratio 0.363, 95% CI 0.146 to 0.898) and increased number of additional doses of muscle relaxants (Odd's ratio 2.762, 95% CI 1.420 to 5.373) were shown to increase the incidence of RC in the early postoperative recovery period (Table 3).

The distribution of patients with RC according to risk factors in the late recovery period is shown in Table 4. A significant difference was observed between the patients with and without RC regarding the number of additional doses of muscle relaxants ($p < 0.05$) (Table 4).

The increase in the number of additional doses of muscle relaxants was the only factor that increased the risk of RC (Odd's ratio 4.241, 95% CI 1.378 to 13.054) in the late recovery period. The effects of other risk factors were not significant (Table 5).

Table 3
Effects of risk factors to residual curarization for the early recovery period (0 min)

Residual curarization (0 min)	Beta	Wald	p	Odds Ratio	95% CI
Age	-0.259	0.499	0.480	0.772	0.376-1.583
Type of muscle relaxants	0.561	3.403	0.065	1.752	0.966-3.180
Number of additional doses of muscle relaxant	1.016	8.956	0.003	2.762	1.420-5.373
Reversal use after operation	-1.169	4.352	0.037	0.311	0.104-0.932
Duration of anesthesia	-1.015	4.807	0.028	0.363	0.146-0.898
Tympanic temperature	0.116	0.084	0.772	1.123	0.514-2.455

CI: Confidence interval

Table 4
Distribution of patients according to risk factors affecting residual curarization during the late recovery period

Risk factors		Residual curarization		
		Yes (n=6)	No (n=202)	p value
Age (years)	18-39	2	81	0.76
	40-59	3	90	
	60-70	1	31	
Type of muscle relaxants	Vecuronium	5	89	0.11
	Atracurium	1	62	
	Rocuronium	0	51	
Number of additional doses of muscle relaxant	Induction	1	107	0.02
	1 time	2	69	
	2 times	2	22	
	3 times	0	3	
	4 times	1	1	
Reversal use after operation	Yes	4	112	0.58
	No	2	90	
Duration of anesthesia (min)	0-90	1	61	0.42
	91-180	4	117	
	181-270	0	19	
	271-360	1	5	
Tympanic temperature (°C)	34.4-35.4	1	24	0.48
	35.5-36.4	4	91	
	36.5-37.6	1	87	

The average central body temperatures of the patients were 36.1±0.6 °C (with a range of 34.4°C-37.4°C) and 36.2±0.5 °C (with a range of 34.6°C-37.4°C) in early and late recovery period, respectively.

SpO_2 of 21 patients fell below 94% in the early recovery period. In these patients, oxygen was delivered at a rate of 4 L/min via facemasks and additional reversals were given in three of them. Respiratory distress was not observed in any patient in the late recovery period.

Discussion

In this study, we showed that 10.6% of the patients who underwent general anesthesia with intermediate-acting muscle relaxants (vecuronium, rocuronium, atracurium) had RC upon arrival to the recovery room. It was found that shorter duration of anesthesia, lack of reversals use and repeated doses of muscle relaxants increased the risk of RC during early recovery period. In 2.9% of patients, TOF ratio was below 90% and RC continued up to 30 minutes after arrival to the recovery room. The intraoperative use of repeated doses of intermediate acting muscle relaxants was found to be a factor increasing the risk of RC in the late recovery period.

Baillard et al.[1] investigated the frequency and risk factors of RC upon arrival to the recovery room. Short duration of surgery, lack of reversal use, no intraoperative monitoring and excess doses of muscle relaxants were found to increase the risk of RC. In

Table 5
Effects of risk factors to residual curarization for the late recovery period (30 min)

Residual curarization (30 min)	Beta	Wald	p	Odds Ratio	95% CI
Age	-0.173	0.062	0.804	0.841	0.215-3.289
Type of muscle relaxants	1.189	2.517	0.113	3.283	0.756-14.264
Number of additional doses of muscle relaxant	1.445	6.344	0.012	4.241	1.378-13.054
Reversal use after operation	-1.827	2.182	0.140	0.161	0.014-1.817
Duration of anesthesia	-0.847	1.199	0.274	0.429	0.094-1.953
Tympanic temperature	-0.960	1.318	0.251	0.383	0.074-1.971

CI: Confidence interval

this study, the reduction in the incidence of RC over time was related to the physicians' clinical practice. Residual curarization usually regarded as a concern with the use of long-acting muscle relaxants[5], can be frequently encountered with the use of intermediate-acting muscle relaxants[2-7]. Naguib et al.[11] in a meta-analysis, reported that the incidence of postoperative RC was significantly decreased by using intermediate-acting muscle relaxants. The decrease in the incidence was attributed to better clinical evaluation, widespread performance of intraoperative neuromuscular monitoring and increased use of intermediate-acting muscle relaxants in recent years[1,11].

Residual curarization (TOF<90%) rates with rocuronium in healthy adult patients undergoing elective orthopedic surgery were reported as 29% and 2.9% upon arrival to the recovery room and after 30 minutes, respectively[9]. Debane et al.[6] reported that TOF in 45% of the patients (who were given vecuronium, rocuronium or atracurium) were below 90% in the early recovery period. In our study, the RC incidence after the use of intermediate-acting muscle relaxants was 10.6% and 2.9%, in the early and late recovery periods, respectively. The lower RC incidence in our study was attributed to the monitoring of patients in the operating room until the patients showed verbal or motor responses to verbal stimuli and had adequate tidal volumes. In addition, considering the duration of surgeries, the number of additional doses used for maintenance of muscle relaxation was very low. This may also explain the low incidence of postoperative RC.

In Baillard et al.[3] study, 42% of the patients who received vecuronium with no reversals were found to have RC. The cumulative doses of vecuronium were 7.7±3.6 mg and 6.2±2.7 mg in patients with and without RC, respectively. RC was shown to increase significantly with the increase in the cumulative dose. Similarly, we found that the increase in the number of additional doses of muscle relaxants was an important factor affecting RC both in early and late recovery periods. In addition, "number of additional doses of muscle relaxants" was the only factor affecting RC in the late recovery period. We thought that the cumulative effect of additional doses might be the most probable cause of this finding. Although, some studies[1,2] confirmed the role of reversals and intraoperative neuromuscular monitoring in reducing the risk of RC, others[16-18] claimed that these two factors had no effect on RC. Furthermore, it was emphasized[18] that even high doses of reversals could not eliminate RC. In our study, reversals were administered according to the clinical findings of patients after the surgery. Reversals were given to 44% of patients. No significant difference was found in the incidence of RC between patients using reversals or not in the late recovery period. However, in the regression analysis, the use of reversals was found to be a factor for reducing RC in the early recovery period. The effect of neostigmine starts in 2-5 min and lasts until 30 to 45 min[19]. Therefore the use of reversal not being an effective factor for reducing RC in the late recovery period may be attributed to a reduction in its effect over time. It is almost impossible to eliminate RC completely with routine clinical evaluation, neuromuscular monitoring or use of a reversal agent. However, it has been reported that objective neuromuscular monitoring may be useful when the reversals are not used[20].

Some studies reported that RC incidence was not related to the type of the intermediate-acting neuromuscular relaxant[11-14]. In Hayes et al. study, RC (TOF <80%) incidence in patients using vecuronium, atracurium and rocuronium were found to be 64%, 52% and 39%, respectively upon arrival to the recovery room. No statistical difference was observed in RC rates by using different intermediate-acting muscle relaxants[12]. However, in Khan et al study, the patients using rocuronium had higher RC incidence (37%) than in patients using vecuronium (17%)[15]. In our study, no significant difference was observed in RC incidences between patients using atracurium, vecuronium or rocuronium in early and late recovery periods. However, the RC incidences we observed were much lower compared to other studies.

Duration of anesthesia is a factor increasing the risk of RC in surgeries with short duration, in which a single-dose of intermediate-acting muscle relaxant is used[7]. On the other hand, duration of anesthesia does not affect the risk of RC in long duration surgeries[6]. It is postulated that the risk of RC may increase in surgeries with long duration with increased frequency of muscle relaxant use[7]. Similarly, risk of RC was

found to increase with shorter duration of anesthesia in early recovery period, whereas duration of anesthesia had no effects on RC in the late recovery period in our study.

Hypothermia is known to prolong the effect of muscle relaxants[19]. The elimination of muscle relaxants from the liver is related to body temperature, and hypothermia has been found to decrease the clearance of muscle relaxants[19]. Although exact hypothermia limit leading to prolongation of the effects of muscle relaxants is not known, there are some studies showing increased incidence of RC when the central temperature is below 34°C[18,21,22]. In the current study the central body temperatures of patients were within normal ranges and as such the "body temperature" could not be a risk factor for RC.

In conclusion, dose adjustment of intraoperative muscle relaxants in accordance with the duration of surgery and the use of reversals may reduce the risk of RC.

Conflict of interest

None.

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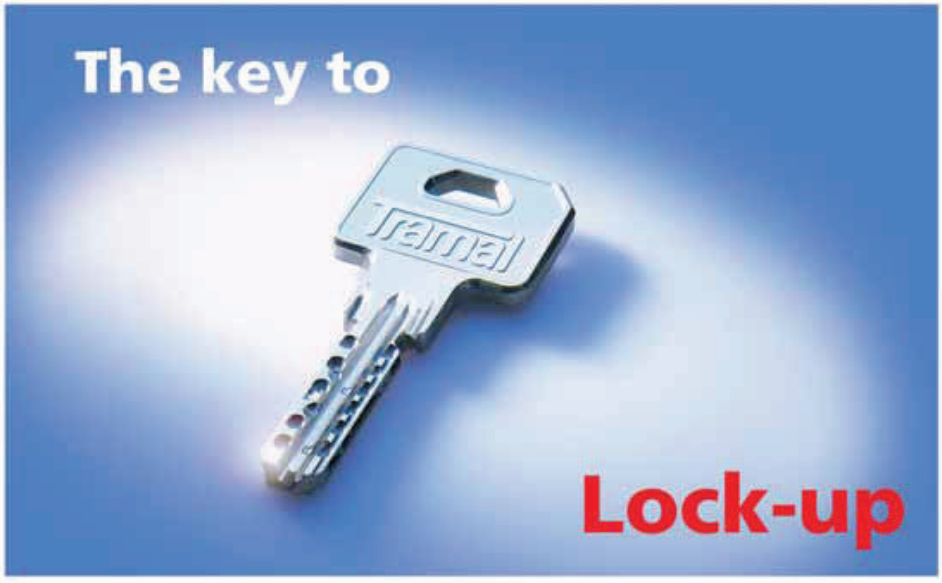

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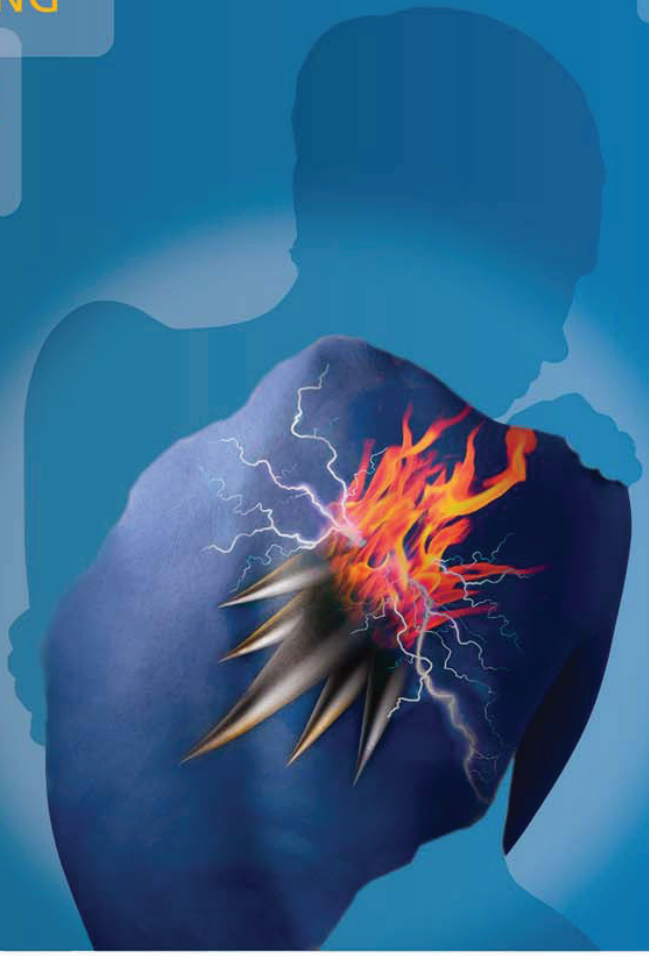

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BRIDION is not recommended in patients with severe renal impairment. Studies in patients with hepatic impairment have not been conducted and, therefore, patients with severe hepatic impairment should be treated with great caution. Caution should be exercised when administering BRIDION to pregnant women as no clinical data on exposed pregnancies are available.
BRIDION has not been investigated in patients receiving rocuronium or vecuronium in the Intensive Care Unit (ICU) setting.
If neuromuscular blockade is required within 24 hours of BRIDION administration, a nonsteroidal neuromuscular blocking agent should be used instead of rocuronium or vecuronium. The most commonly reported adverse reactions were dysgeusia (metal or bitter taste) and anesthetic complications (movement, coughing, grimacing, or suckling on the endotracheal tube). In patients treated with BRIDION, a few cases of awareness were reported. The relation to BRIDION was uncertain. In a few individuals, allergic-like reactions (ie, flushing, erythematous rash) following BRIDION were reported. Clinicians should be prepared for the possibility of allergic reactions and take the necessary precautions. In a trial of patients with a history of pulmonary complications, bronchospasm was reported in 2 patients and a causal relationship could not be fully excluded. Volunteer studies have demonstrated a slight (17%-22%) and transient (<30 minutes) prolongation of the prothrombin time/activated partial thromboplastin time (PT/aPTT) with BRIDION; however, clinical studies have demonstrated no clinically relevant effect on peri- or postoperative bleeding complications with BRIDION alone or in combination with anticoagulants. As BRIDION has demonstrated an in vitro pharmacodynamic interaction with anticoagulants, caution should be exercised in patients on anticoagulation for a pre existing or comorbid condition. This pharmacodynamic interaction is not clinically relevant for patients receiving routine postoperative prophylactic anticoagulation. Although formal interaction studies have not been conducted, no drug interactions were observed in clinical trials. Preclinical data suggest that clinically significant drug interactions are unlikely with the possible exceptions of toremifene, fusidic acid, and hormonal contraceptives.

* Train of four
† Post-tetanic counts
‡ Second twitch

REFERENCES: 1. BRIDION Summary of Product Characteristics (SPC). **2.** Blobner M, Eriksson LI, Scholz J, Motsch J, Della Rocca G, Prins ME. Reversal of rocuronium induced neuromuscular blockade with sugammadex compared with neostigmine during sevoflurane anaesthesia: results of a randomised, controlled trial. [published online ahead of print July 30, 2010]. Eur J Anaesthesiol. doi:10.1097/EJA.0b013e32833c56b7.
3. Jones RK, Caldwell JE, Brull SJ, Soto RG. Reversal of profound rocuronium-induced blockade with sugammadex: a randomized comparison with neostigmine. Anesthesiology. 2008;109(5):816-824.

Please see summary of product characteristics for full prescribing information.

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