Optimal dose of combined rocuronium and cisatracurium during minor surgery
A randomized trial
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Abstract
Background: Combined rocuronium and cisatracurium have synergistic effects. We investigated whether reduced doses are effective during coadministration, by monitoring neuromuscular relaxation during surgery.

Methods: This randomized, controlled clinical trial was registered at http://clinicaltrials.gov (registration number NCT02495038). The participants were 81 patients scheduled for elective mastoidectomy and tympanoplasty. Participants were assigned to groups, including the intubating dose group (Group I, \(n = 27\); combined \(ED_{95}\) rocuronium and \(ED_{95}\) cisatracurium), the small reduction group (Group S, \(n = 27\); dose reduced by 10\% of each \(ED_{95}\)), or the large reduction group (Group L, \(n = 27\); dose reduced by 20\% of each \(ED_{95}\)). Drugs were administered to patients and a timer was started using TOF-Watch monitoring. TOF (train-of-four) was monitored at the ulnar nerve, at a setting of 2 Hz/12 s. We recorded the time to TOF ratio of 0 (onset), time to first TOF ratio > 25\% (duration 25\%), and TOF 25–75\% (recovery index) under total intravenous anesthesia. One-way analysis of variance was used for statistical analyses (\(\alpha = 0.05, \beta = 0.2\)).

Results: There were no significant demographic differences between groups. Group L had a longer duration to onset (mean ± standard deviation, 399.3 ± 147.8 seconds) and shorter duration 25\% (39.4 ± 6.8 minutes) compared to Group I (212.8 ± 56.0 s and 51.3 ± 8.47 minutes, respectively) and Group S (230.7 ± 60.6 s and 47.9 ± 10.7 minutes, respectively). There were no other significant differences between groups.

Conclusion: Our findings contribute to determining clinically effective combinations of rocuronium and cisatracurium, as well as to predicting the pharmacokinetic characteristics of the synergistic effects. We suggest that reducing doses of both drugs by approximately 10\% of their respective \(ED_{95}\) values is sufficient to maintain neuromuscular relaxation during minor surgery.

Abbreviations: BIS = bispectral index, BMI = body mass index, DBP = diastolic blood pressure, \(ED_{95}\) = effective dose for 50\% of people receiving the drug, \(ED_{50}\) = effective dose for 95\% of people receiving the drug, IBW = ideal body weight, LBW = lean body weight, NIBP = noninvasive blood pressure, NMBAs = neuromuscular blocking agents, SBP = systolic blood pressure, TOF = train-of-four.

Keywords: cisatracurium, combination, drug synergism, neuromuscular monitoring, rocuronium

1. Introduction
Rocuronium is a widely used and representative neuromuscular blocking agent (N MBA), due to possessing a relatively fast onset of peak effects and short duration of muscle relaxation.\cite{1} Another NMBA, cisatracurium, has a comparatively longer duration of relaxation and slower degradation by Hofmann elimination and ester hydrolysis than rocuronium.\cite{2} Combinations of rocuronium and cisatracurium have synergic effects, and may also be used as primers for rapid sequence intubation.\cite{3,4} Clinical use of these drugs would be facilitated by determining effective combination doses and the pharmacodynamic characteristics that determine the extent of synergistic effects. The present study investigated whether clinical efficacy, as assessed by monitoring muscle relaxation during surgery, is achieved with reduced combination doses of rocuronium and cisatracurium.

2. Materials and methods
2.1. Study design
This randomized controlled trial received institutional review board approval (ref. CR313029) and was registered at http://clinicaltrials.gov (registration number NCT02495038). The participants were 81 patients scheduled for elective mastoidectomy and tympanoplasty, and all patients provided written informed consent. All patients met the criteria for American Society of Anesthesiologists physical status I to II, were 20 to 60 years of age, and had a body mass index (BMI) of 20 to 30 kg/m\(^2\). The exclusion criteria were as follows: a history of allergy to the
study drugs; neuromuscular disease; smoking; pregnancy or breastfeeding; preoperative medication such as antipsychotics, aminoglycosides, steroid or neuroleptics (which interact with non-depolarizing NMBAs); serum creatinine level > 1.2 mg/dL; or liver transaminase level > 40 U/L. Anthropometric variables, such as height and weight, were measured in the hospital ward before surgery. BMI was calculated as total body weight divided by height squared. Ideal body weight (IBW) was calculated using Devine formula \( \text{IBW} = \frac{\text{weight} \times 2}{\text{height} - 60} \) for men and \( \frac{\text{height} \times 2}{\text{weight}} \times 10 \) for women. IBW was used to determine the initial doses of NMBAs. Lean body weight (LBW) was calculated using James’ formula \( \text{LBW men} = (1.10 \times \text{weight (kg)}) - 128 \times (\text{height} \times 100) \) and \( \text{LBW women} = (1.07 \times \text{weight (kg)}) - 148 \times (\text{height} \times 100) \). Additive doses of NMBAs were determined using LBW values.

The groups included an intubating dose group (Group I, \( n = 27 \)); combined \( ED_{95} \) rocuronium, 0.3 mg/kg, and \( ED_{95} \) cisatracurium, 0.05 mg/kg), a small reduction group (Group S, \( n = 27 \); dose reduced by 10% of each \( ED_{95} \)), and a large reduction group (Group L, \( n = 27 \); dose reduced by 20% of each \( ED_{95} \)).

### 2.2. Monitoring and medication

Monitoring in the operating room consisted of noninvasive blood pressure (NIBP) measurement, pulse oximetry, electrocardiography, and body temperature, using a Bispectral Index (BIS) (BIS VISTA Monitoring System; Aspect Medical Systems Inc., Norwood, MA). The T1/T4 ratio was measured using TOF-Watch monitors (Organon; Teknika B.V., Boxtel, the Netherlands). Measurements were performed at 5-minute intervals and NIBP was monitored on the arm opposite to the arm used for the intravenous fluid line without disturbing flow.

Midazolam (2 mg) and glycopyrrolate (0.2 mg) were intramuscularly administered to patients 1 hour before surgery. Anesthesia was induced with propofol 1.5 to 2.5 mg/kg and remifentanil 0.4 to 0.6 mcg/kg, followed by maintenance with target-controlled infusion of propofol 5 to 10 mg/kg/h and remifentanil 0.05 to 2 mcg/kg/min. The infusion pump (Orchestra Module DPS; Fresenius-Vial, Brezins, France) was operated based on Minto and Marshall pharmacokinetic model for effect site target-controlled infusion. Subsequently, the patient was administered 100% oxygen mask ventilation.

The arm contralateral to the operation side was used for neuromuscular monitoring and was attached to the arm board of the TOF-Watch monitor. Study drugs connected with 3-way stop cocks were administered to the patients simultaneously with flushing 5 mL normal saline; a timer was started for T1/T4 ratio monitoring. Surface electrodes for the ulnar nerve were placed at the wrist and train-of-four (TOF) stimulation was conducted with supramaximal square wave impulses of 200 μs duration, at 2 Hz/12 s. We assessed time to TOF ratio = 0 (onset), first TOF ratio > 25% (duration 25%), TOF 25% to 75% (recovery index), and 90% recovery time (TOF 75–90%) under total intravenous anesthesia. We also recorded the rate of additional rescue doses administered with 10% of the initial NMBA doses, operation duration from incision to surgical wound dressing, and anesthesia duration from entry to exit of the operation room. Body temperature was maintained above 35°C, using a warm air blanket. The arterial pressure cuff was placed on the contralateral arm to TOF monitoring.

### 2.3. Randomization and masking

Eligible patient was designated as their own sequence number and simple randomization was used. Patients were randomly assigned to groups by opening a sealed allocation envelope by an assistant unrelated to study. After data collection, the allocation number was matched to each group and both investigator and participant did not know matching group until analyses. Before patients arrived in the operating room, rocuronium and cisatracurium were prepared by an assistant who was not involved in the study. Each drug dosage was determined by an allocation number. The syringe containing each study drug was given to the researcher with the contents concealed. Separate syringes were used for each drug, although the researcher could not identify the contents because the scale of the syringe was concealed.

### 2.4. Adverse events and management

Anesthesia levels were assessed based on BIS scores of 40 to 60 for all patients. Moderate hypertension (>120% of baseline) or hypotension (<80% of baseline) were treated by increasing or decreasing the rate of propofol infusion using fluid supplementation. Severe hemodynamic changes (systolic pressure < 90 or > 200 mm Hg) were controlled by intravenous administration of phenylephrine (50 μg) or nicardipine (250 μg), which were repeated until hemodynamically stable status was achieved. When hiccups or self-contained respiration occurred, additional rescue doses of NMBAs were administered to the patient even if the T1/T4 ratio was < 25%.

### 2.5. Statistical analyses

All data are expressed as means ± standard deviations, numerical values, and percentages, as appropriate. Between-group comparisons were conducted using \( \chi^2 \) tests, Fisher exact tests, or 1-way analysis of variance, as appropriate. Statistically significant differences were further analyzed by Turkey post-hoc analyses. A preliminary study determined that 24 patients would be required in each group to achieve power of 0.9 and a type I error rate of 0.05. By estimating an attrition rate of 10%, we calculated that 27 patients would be required for each group. All statistical analyses were performed using SPSS version 18.0 (IBM Corporation, Chicago, IL). \( P \) values < 0.05 were considered to be statistically significant.

### 3. Results

#### 3.1. Participant characteristics

This study included 81 patients who underwent mastoidectomy. The screened cohort of patients were 87 patients and enrolled patients were 81 patients aged 20 to 60 years. The 2 patients were aged over 60 years and the 4 patients declined to participate (Fig. 1). Baseline characteristics were similar between the groups, and there were no significant differences in age, BMI, or gender. There were 14 patients classified as American Society of Anesthesiologists level I in Group I, which was lower than in Group S (17) or Group L (18); however, these differences were not statistically significant (\( P = 0.511 \)). The baseline dynamic variables such as blood pressure, heart rate, and temperature did not differ between groups (Table 1). Preoperative postinduction dynamic variables such as blood pressure, temperature, saturation, and heart rate also did not differ between groups. Furthermore, BIS scores did not differ between groups and were maintained at 35 to 55 during surgery (Table 2).
3.2. Primary outcomes

There were no significant differences between groups for the durations of operation or anesthesia. However, onset differed significantly between groups (Fig. 2), as well as duration 25% (Fig. 3). Post-hoc analyses indicated that Group L was significantly different from both Group I and Group S, for both onset and duration 25% (Tables 3 and 4). However, the recovery index did not differ between groups (Fig. 4).

3.3. Secondary outcomes

The duration of intubation did not differ between groups. Group I and S were categorized as grade 0 (excellent) intubation. However, Group L included 1 patient with ratings of grade 1 (good) and 2 patients with grade 2 (poor) intubation. The patients with Grade 2 intubation coughed during intubation and

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**Table 1**

| Characteristic                        | Group I (n=27) | Group S (n=27) | Group L (n=27) | P     |
|---------------------------------------|----------------|----------------|----------------|-------|
| Age, y                                | 47.9±10.7      | 50.3±8.0       | 49.3±9.4       | .652  |
| Sex, n                                |                |                |                | .793  |
| Female                                | 18             | 18             | 20             |       |
| Male                                  | 9              | 9              | 7              |       |
| Body mass index, kg/m²                | 24.1±2.7       | 24.4±2.8       | 24.2±2.3       | .906  |
| ASA, n                                |                |                |                | .511  |
| I                                     | 14             | 17             | 18             |       |
| II                                    | 13             | 10             | 9              |       |
| Baseline dynamic variables            |                |                |                |       |
| Body temperature, °C                  | 36.4±0.2       | 36.4±0.2       | 36.5±0.2       | .114  |
| Heart rate, beats/min                | 69.4±8.6       | 72.1±10.7      | 68.4±12.6      | .430  |
| SBP, mm Hg                            | 128.3±17.7     | 128.3±20.7     | 128.4±19.1     | .906  |
| DBP, mm Hg                            | 75.6±9.7       | 76.7±9.2       | 74.8±9.0       | .740  |

Data presented as mean±standard deviation, unless otherwise indicated.

ASA=American Society of Anesthesiologists, DBP=diastolic blood pressure, SBP=systolic blood pressure.

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**Table 2**

| Parameter                  | Group I (n=27) | Group S (n=27) | Group L (n=27) | P     |
|----------------------------|----------------|----------------|----------------|-------|
| SBP, mm Hg                 | 102.0±9.4      | 105.4±10.2     | 103.4±11.1     | .460  |
| DBP, mm Hg                 | 63.8±9.0       | 66.6±8.0       | 63.2±6.7       | .246  |
| Heart rate, beats/min      | 68.4±12.0      | 67.7±11.7      | 64.6±10.6      | .419  |
| Oxygen saturation, %       | 100±0.0        | 99.9±0.7       | 100±0.0        | .373  |
| Body temperature, °C       | 36.3±0.3       | 36.3±0.2       | 36.3±0.2       | .971  |
| Bispectral index           | 46.0±8.2       | 46.1±7.5       | 44.3±9.4       | .685  |

Data presented as mean±standard deviation, unless otherwise indicated.

DBP=diastolic blood pressure, SBP=systolic blood pressure.

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**Figure 1.** Flow diagram of the study design.

**Figure 2.** Time to TOF ratio=0 (onset). TOF=train-of-four. I=intubating dose group. S=small reduction group. L=large reduction group.
1 of these patients produced small arm movements during coughing (Table 5).

4. Discussion

The purpose of the present study was to determine whether reduced doses of rocuronium and cisatracurium maintain clinical efficacy via synergistic effects during intubation.[6–12] We found that potency, duration, and recovery were maintained when the ED95 doses of rocuronium and cisatracurium were reduced by 10%. Therefore, reduced doses of these NMBAs are appropriate during intubation and operative immobility for minor surgeries, such as mastoidectomy, which involve minimal stimulation during surgery. We did not find differences between groups for the recovery index because the additional rescue dose was 10% of the initial dose in all groups.

NMBAs are administered on the basis of both intubation and operative requirements. However, the purpose of the initial intubation dose is to maintain neuromuscular blockade during surgery, within the allowable time.[13,14] Longer duration surgeries may result in additional rescue doses or continuous infusion of NMBAs. In contrast, short duration surgeries can result in unnecessary prolongation of anesthetic duration if 300% to 400% of the cisatracurium ED95 is administered.[2,15] In addition, if the patient has severely decreased liver function or renal creatinine clearance, continuous infusion of rocuronium may produce residual blockade.[12] Sugammadex is typically used for immediate reversal by entrapment of rocuronium.[16] However, anticholinesterase has been universally used for recovery from neuromuscular blockade, due to cost-effectiveness; it is also associated with recurarization, which is minimized by the predictable pharmacodynamics of NMBAs. In minor surgery, although lower surgical stimulation does not mean smaller dosage of NMBAs, the appropriate neuromuscular blockade is able to improve the surgical environment.[17,18] However, unnecessary, excessive use of NMBAs increases the risk for residual muscle relaxation. The use of combined NMBAs of rocuronium and cisatracurium in minor surgery is beneficial for similar effectiveness with 10% smaller doses, even though

| Parameter                  | Group I (n = 27) | Group S (n = 27) | Group L (n = 27) | P    |
|----------------------------|-----------------|-----------------|-----------------|------|
| Onset, s                  | 212.9 ± 56.0    | 230.1 ± 60.6    | 399.3 ± 147.8   | .001 |
| Duration 25%, min         | 51.3 ± 8.4      | 47.9 ± 10.7     | 39.4 ± 6.8      | <.001|
| Recovery index, min       | 15.9 ± 3.8      | 16.2 ± 4.8      | 14.1 ± 3.4      | .123 |
| Operation duration, min   | 151.8 ± 27.2    | 147.0 ± 31.4    | 145.9 ± 27.6    | .654 |
| Anesthetic duration, min  | 163.0 ± 26.8    | 159.9 ± 30.6    | 161.4 ± 25.9    | .917 |

Data presented as mean ± standard deviation, unless otherwise indicated.

| Parameter                  | Mean difference | Standard error | P    |
|----------------------------|-----------------|----------------|------|
| Intubation time, s         | 50.8 ± 24.1     | 40.8 ± 12.3    | 44.6 ± 14.3 | .117 |
| Intubation grade           | 0 (0)           | 0 (0)          | 0 (0)    | 1 (3.7) |
| Coughing                   | 0 (0)           | 0 (0)          | 0 (0)    | 2 (7.4) |
| Desaturation               | 0 (0)           | 0 (0)          | 0 (0)    | 0 (0)  |

Multiple comparisons using Turkey honest significant difference test.

Statistically significant difference between groups.

Table 3 Pharamacodynamic data.

Table 4 Post-hoc analyses of onset and duration at 25%.

Figure 3. Time to first TOF ratio > 25% (duration 25%). TOF=train-of-four.

Figure 4. Time to TOF 25–75% (recovery index). TOF=train-of-four.
sugammadex cannot be applied for reversal. In addition, liver and kidney are less affected by smaller doses of NMBAs.[12]

Continuous infusion of rocuronium can result in residual muscle relaxation, severe hepatic failure, reduced hepatic blood flow, or prolonged renal excretion.[12,13,19] Therefore, the combination of rocuronium and cisatracurium is a promising method to control the timing of muscle relaxation. Cisatracurium is administered additively during long duration surgeries without limitations, after an intubating dose of rocuronium to achieve rapid patient responses.[4,20] Neuromuscular blockade can be induced by a single administration, although continuous infusion of additional doses of cisatracurium is also sometime administered.[12,19,21] This procedure requires estimating the synergic effects of drug combinations, while also considering the duration of surgery. Prolonging the effective duration of muscle relaxation due to synergic effects of NMBAs enables reductions in additional drug administrations.[7–9,22] However, objective assessment is required to determine the parameters for prolonged synergistic paralysis.[23] When rocuronium is used as a priming agent to complement the slow onset of cisatracurium, onset is reduced; however, the duration of muscle relaxation may be prolonged due to synergic effects of the 2 NMBAs.[20] In addition, previous research has found that the duration of muscle relaxation is prolonged by 33% when cisatracurium is administered following an initial dose of rocuronium.[6] However, the extent of prolonged muscle relaxation after administration of identical doses of rocuronium and cisatracurium has not been investigated; this information would enable estimates of the effect duration of these NMBAs.

In the present study, we verified that a 10% reduction of the NMBAs, used in combination, produced comparable effects to ED₉₅ doses. However, 20% reductions produced statistically significant prolongation of onset, and additional drug administrations were required to compensate for reduced effect durations. Rapid sequence intubation can be challenging to perform; therefore, repetitive administration of additional NMBAs may be required and mask breathing before intubation may be prolonged. A previous study found that administration of 200% of the ED₉₅ values of rocuronium and cisatracurium produced onset durations of 1.7 and 5.2 minutes, respectively; the durations of time to T₁ recoveries of 25% were 36 and 43 minutes, respectively.[24,25] In the present study, the onset duration was 3.5 minutes for Group I and the T₁ recovery of 25% was 51 minutes, indicating prolonged effect durations. However, reduced early manifestation effects did not occur, likely due to cisatracurium inhibiting rapid early manifestation through competitive binding of rocuronium and cisatracurium to acetylcholine receptors. We set the peak effect time as TOF ratio = 0, and there were therefore no significant differences between intubating conditions. However, the coughing reflex occurred even if BIS was maintained below 60, and the postintubation TOF ratio was < 25% in 2 patients from Group L. Additional NMBAs was administered to these patients regardless of their TOF ratios, after which the coughing reflex disappeared and muscle relaxation resumed.

Pharmacodynamics of NMBAs are affected by several factors, including aminoglycosides, lincosamides, calcium channel blockers, inhalation agents, temperature, magnesium, local anesthetics, lithium, antiepileptic drugs, diuretics, steroid, dantrolene, and azathioprine.[4,20] We excluded these causes. As well as we selected ASA I–II patients and maintained body temperature of the patients within the normal range. However, the present study has some limitations. First, IBW was used to determine drug doses. Although this process is appropriate for initial rocuronium doses, repeated doses of cisatracurium should be determined on the basis of LBW, due to its low lipid solubility.[5,27] In the present study, early manifestation and effect durations were assessed according to initial doses. A second limitation was that patients with BMI > 25kg/m², which corresponds to overweight or obese, were included in the experimental group. Obesity results in an increased volume of distribution and the doses of NMBAs based on IBW may, therefore, be insufficient.[28] However, prolonged muscle relaxation has been reported with doses of rocuronium that were determined on the basis of real body weight in morbidly obese patients.[5] Third, we found that NMBAs could only be reduced by 10% while maintaining clinical effects. We found a marked reduction in the drug effects with 20% reductions compared with 10% reductions in a preliminary study with 7 participants. Furthermore, the peak dose–response effect was not diminished with 10% drug reductions. Thus, the reduction interval of doses was determined as 10%, and this finding was supported by the full study data. However, we cannot produce a dose–response curve. Ideally, a study of drug effects at ED₅₀ doses would be conducted to verify dose responses for combined NMBAs.[8,10] Finally, the present study did not find reduced oxygen saturation due to rapid heart rate changes, changes in hepatic function, or residual muscle relaxation after administration of the NMBAs. These outcomes likely occurred because the study was performed with selected patients. To minimize the influence on muscle relaxation, the doses of NMBAs were limited to ED₉₅ values and constant monitoring was performed to assess recovery of muscle relaxation. Therefore, caution is recommended in generalizing the results to other populations.

The present study verified that clinically unstable muscle relaxation for intubation occurred with a 20% reduction in the doses of combined rocuronium and cisatracurium, and that additional administration of NMBAs may, therefore, be required. There are hypotheses describing the existence of multiple binding sites at presynaptic and postsynaptic receptors, and different binding affinities of 2 α subunits of the acetylcholine receptor, although the pathophysiology of interaction between nondepolarizing NMBAs remains uncertain.[28,30] Through our clinical investigation of synergism of combined NMBAs, binding affinities of acetylcholine receptor of combined NMBAs are considered to potentiate with 10%; however, further evaluation is needed. In addition, we suggest that using a combination of rocuronium and cisatracurium at the 10% reduced initial dose of NMBAs, clinically sufficient muscle relaxation may be achieved for surgery durations ≤ 50 minutes.

5. Conclusion

We found that clinically effective neuromuscular blocking can be achieved with 10% reductions in combined doses of rocuronium and cisatracurium. These findings may facilitate decision-making in determining the appropriate dose of NMBAs to use during minor surgeries.

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References

[1] Lee H, Jeong S, Choi C, et al. Anesthesiologist’s satisfaction using between cisatracurium and rocuronium for the intubation in the anesthesia induced by remifentanil and propofol. Korean J Anesthesiol 2013;64:34–9.
[2] Lighthall GK, Jamieson MA, Kotlik J, Brock-Utne JG. A comparison of the onset and clinical duration of high doses of cisatracurium and rocuronium. J Clin Anesth 1999;11:220–5.

[3] Leykin Y, Pellis T, Lucca M, Gullo A. Intubation conditions following rocuronium: influence of induction agent and priming. Anesth Intensive Care 2005;33:462–8.

[4] Mak PH, Irwin MG. The effect of cisatracurium and rocuronium on cisatracurium precurarization and the priming principle. J Clin Anesth 2004;16:83–7.

[5] Leykin Y, Pellis T, Lucca M, et al. The pharmacodynamic effects of rocuronium when dosed according to real body weight or ideal body weight in morbidly obese patients. Anesth Analg 2004;99:1086–9.

[6] Breslin DS, Jiao K, Habib AS, et al. Pharmacodynamic interactions between cisatracurium and rocuronium. Anesth Analg 2004;98:107–10.

[7] Kim KS, Chun YS, Chon SU, Suh JK. Neuromuscular interaction between cisatracurium and mivacurium, atracurium, vecuronium or rocuronium administered in combination. Anaesthesia 1998;53:872–8.

[8] Liu M, Dilger JP. Synergy between pairs of competitive antagonists at adult human muscle acetylcholine receptors. Anesth Analg 2008;107:525–33.

[9] Zeidan A, Nahle N, Maaliki H, Baraka A. Cisatracurium or rocuronium versus rocuronium-cisatracurium combination. Middle East J Anaesthesiol 2006;18:879–86.

[10] Naguib M, Samarkandi AH, Ammar A, et al. Comparative clinical pharmacology of rocuronium, cisatracurium, and their combination. Anesthesiology 1998;89:1116–24.

[11] Donati F, Plaud B. Rocuronium-cisatracurium combinations. Anesthesiology 1999;91:587–8.

[12] Miller DR, Wherrett C, Hull K, et al. Cumulation characteristics of cisatracurium and rocuronium during continuous infusion. Can J Anaesth 2000;47:943–9.

[13] Cammu G, de Baerdemaeker L, den Blauwen N, et al. Postoperative residual curarization with cisatracurium and rocuronium infusions. Eur J Anaesthesiol 2002;19:129–34.

[14] Hans P, Welte P, Dewandre PY, et al. Recovery from neuromuscular block after an intubation dose of cisatracurium and rocuronium in lumbar disc surgery. Acta Anaesthesiol Belg 2004;55:129–33.

[15] de Morais BS, de Castro CH, Teixeira VC, Pinto AS. Residual neuromuscular block after rocuronium or cisatracurium. Rev Bras Anestesiol 2005;55:622–30.

[16] Flackton EA, Mastronardi P, Hunter JM, et al. Reversal of rocuronium-induced neuromuscular block with sugammadex is faster than reversal of cisatracurium-induced block with neostigmine. Br J Anaesth 2008;100:622–30.

[17] Barrio J, Errando CL, San Miguel G, et al. Effect of depth of neuromuscular blockade on the abdominal space during pneumoperitoneum establishment in laparoscopic surgery. J Clin Anesth 2016;34:197–203.

[18] Donati F, Brull SJ. More muscle relaxation does not necessarily mean better surgeons or “the problem of muscle relaxation in surgery”. Anesth Analg 2014;119:1019–21.

[19] Fassbender P, Geldner G, Blohmer M, et al. Clinical predictors of duration of action of cisatracurium and rocuronium administered long-term. Am J Crit Care 2009;18:439–45.

[20] Lin SP, Chang KY, Chen YJ, et al. Priming with rocuronium to accelerate the onset time of cisatracurium during intubation. J Clin Anesth 2009;21:15–9.

[21] Kopman AF, Zank LM, Ng J, Neuman GG. Antagonism of cisatracurium and rocuronium block at a tactile train-of-four count of 2: should quantitative assessment of neuromuscular function be mandatory? Anesth Analg 2004;98:102–6.

[22] Amin AM, Mohammad MY, Ibrahim MF. Comparative study of neuromuscular blocking and hemodynamic effects of rocuronium and cisatracurium under sevoflurane or total intravenous anesthesia. Middle East J Anaesthesiol 2009;20:39–51.

[23] Kopman AF, Kopman DJ, Ng J, Zank LM. Antagonism of profound cisatracurium and rocuronium block: the role of objective assessment of neuromuscular function. J Clin Anesth 2005;17:30–5.

[24] Belmont MR, Lien CA, Quessy S, et al. The clinical neuromuscular pharmacology of 51W89 in patients receiving nitrous oxide/opioid/barbiturate anesthesia. Anesthesiology 1995;82:1139–45.

[25] Naguib M. Neuromuscular effects of rocuronium bromide and atracurium during continuous infusion. Can J Anaesth 2000;47:943–9.

[26] Kopman AF, Zank LM, Ng J, Neuman GG. Antagonism of cisatracurium and rocuronium block: the role of objective assessment of neuromuscular function. J Clin Anesth 2005;17:30–5.

[27] Paul M, Kindler CH, Fokt RM, et al. Isobolographic analysis of non-depolarizing NMBAs interactions at their receptor site. Eur J Anaesthesiol 1999;16:31–7.

[28] van Kralingen S, van de Garde EM, Knibbe CA, et al. Comparative study of atracurium dosed on ideal body weight vs. total body weight in morbidly obese patients. Br J Clin Pharmacol 2011;71:34–40.

[29] Adams M, Gabrhelik T, Marek O. Influence of gender on the course of neuromuscular block following a single bolus dose of cisatracurium or rocuronium. Eur J Anaesthesiol 2008;25:589–95.

[30] Motamed C, Menad R, Farnoosi R, et al. Potentiation of mivacurium blockade by low dose of pancuronium. Anaesthesiology 2003;98:1057–62.

[31] Paul M, Kindler CH, Fokt RM, et al. Isobolographic analysis of non-depolarising NMBAs interactions at their receptor site. Eur J Pharmacol 2002;438:35–43.