Optimal dose of combined rocuronium and cisatracurium during minor surgery

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Optimal dose of combined rocuronium and cisatracurium during minor surgery

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Abstract

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Background: Combined rocuronium and cisatracurium have synergistic effects. We investigated whether reduced doses are effective during co-administration, 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 = 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 (α = 0.05, β = 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 s) and shorter duration 25% (39.4 ± 6.8 min) compared to Group I (212.8 ± 56.0 s and 51.3 ± 8.47 min, respectively) and Group S (230.7 ± 60.6 s and 47.9 ± 10.7 min, respectively). There were no other significant differences between groups.

Conclusions: 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.

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

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I. INTRODUCTION

Rocuronium is a widely used and representative neuromuscular blocking agent (NMBA), due to possessing a relatively fast onset of peak effects and short duration of muscle relaxation.[1] Another NMBA, cisatracurium, has a comparatively longer duration of relaxation and slower degradation by Hofmann elimination and ester hydrolysis than rocuronium.[2] Combinations of rocuronium and cisatracurium have synergic effects, and may also be used as primers for rapid sequence intubation.[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.

II. MATERIALS AND METHODS

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–II, were 20–60 years of age, and had a body mass index (BMI) of 20–30 kg/m2. 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 prior to surgery. BMI was calculated as total body weight divided by height squared. Ideal body weight (IBW) was calculated using Devine's formula {50 kg + 2.3 × (height [inch] - 60) for men and 45.5 kg + 2.3 × (height [inch] - 60) for women}. IBW was used to determine the initial doses of NMBAs. Lean body weight (LBW) was calculated using James' formula {LBW men = (1.10 × weight [kg]) – 128 × (weight^2/ (100 × height [m])^2); LBW women = (1.07 × weight [kg]) – 148 × (weight^2/ (100 × height [m])^2)}.[5] Additive doses of NMBAs were determined using LBW values. The groups included an intubating dose group (Group I, n = 27; combined ED95 rocuronium, 0.3 mg/kg, and ED95 cisatracurium, 0.05 mg/kg), a small reduction group (Group S, n = 27; dose reduced by 10% of each

ED95), and a large reduction group (Group L, n = 27; dose reduced by 20% of each ED95).

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, USA). The T1/T4 ratio was measured using TOF-Watch® monitors (Organon, Teknica B.V., Boxtel, Netherlands). Measurements were performed at 5 min 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 h prior to surgery. Anesthesia was induced with propofol 1.5–2.5 mg/kg and remifentanil 0.4–0.6 mcg/kg, followed by maintenance with target controlled infusion of propofol 5–10 mg/kg/h and remifentanil 0.05–2 mcg/kg/min. The infusion pump (Orchestra Module DPS, Fresenius-Vial, Brezins, France) was operated based on Minto and Marshall's 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 25–75% (recovery index), and 90% recovery time (TOF 25–90%) 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℃, using a warm air blanket. The arterial pressure cuff was placed on the contralateral arm to TOF monitoring.

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.

4. Adverse events and management

Anesthesia levels were assessed based on BIS scores of 40–60 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 mmHg or >200 mmHg) 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%.

5. Statistical analyses

All data are expressed as means ± standard deviations, numerical values, and percentages, as appropriate. Between-group comparisons were conducted using χ 2 tests, Fisher's exact tests, or one-way analysis of variance, as appropriate. Statistically significant differences were further analyzed by Turkey's 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, USA). P values < .05 were considered to be statistically significant.

III. RESULTS

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 two patients were aged over 60 years and the four 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 = .511). The baseline dynamic variables such as blood pressure, heart rate, and temperature did not differ between groups (Table 1). Preoperative post-induction 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 35–55 during surgery (Table 2).

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).

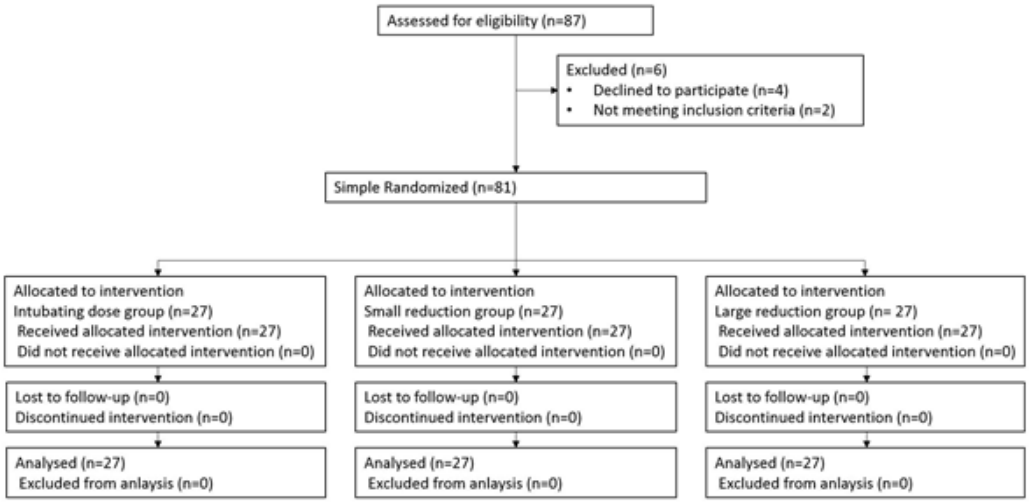

Figure 1. Flow diagram of the study design.

Table 1. Demographic and clinical characteristics of the study participants

Characteristic	Group I (n=27)	Group S (n=27)	Group L (n=27)	*P* value
Age, years	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/m^2	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, ℃	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, mmHg	128.3±17.7	128.3±20.7	128.4±19.1	.996
DBP, mmHg	75.6±9.7	76.7±9.2	74.8±9.0	.749

Data presented as mean ± standard deviation, unless otherwise indicated. ASA = American Society of Anesthesiologists, DBP = diastolic blood pressure, SBP = systolic blood pressure.

Table 2. Preoperative post-induction dynamic variable data

Parameter	Group I (n=27)	Group S (n=27)	Group L (n=27)	*P* value
SBP, mmHg	102.0±9.4	105.4±10.2	103.4±11.1	.460
DBP, mmHg	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±0.2	100±0.0	.373
Body temperature, ℃	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.

Table 3. Pharmacodynamic data

Parameter	Group I (n=27)	Group S (n=27)	Group L (n=27)	*P* value
Onset, s	212.8±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.

*Statistically significant difference between groups according to Turkey post-hoc tests.

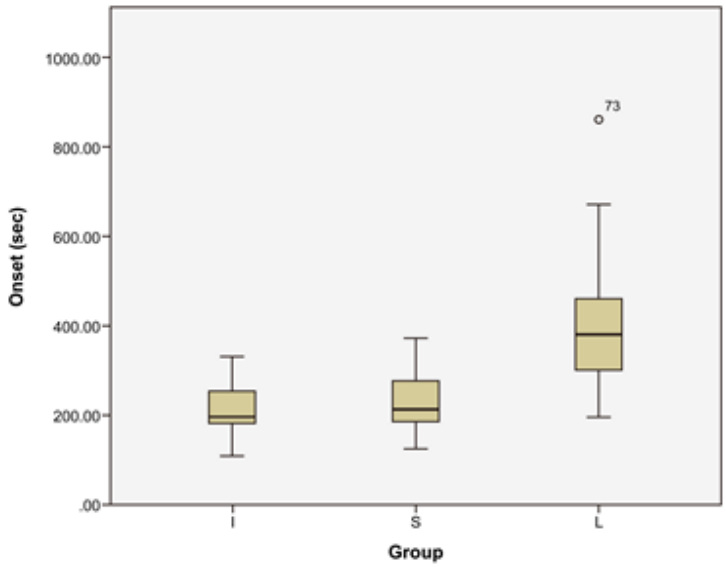

Figure 2. Time to TOF ratio=0 (onset). TOF=train-of-four. I=intubating dose group. S=small reduction group. L=large reduction group.

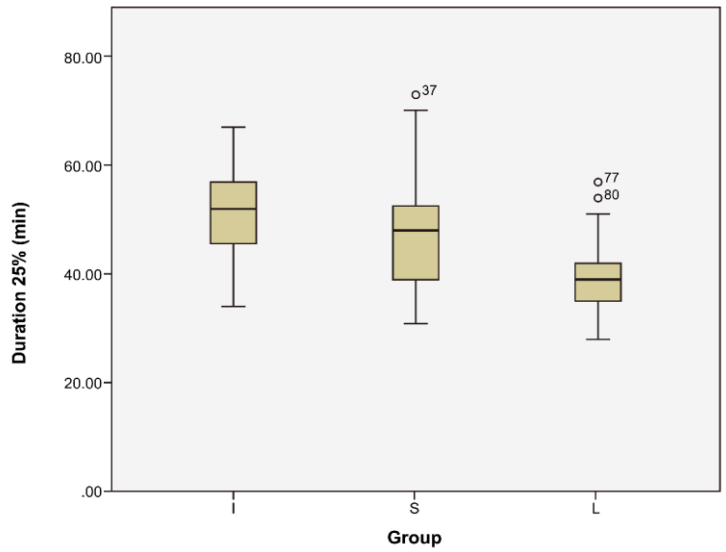

Figure 3. Time to first TOF ratio >25% (duration 25%). TOF=train-of-four.

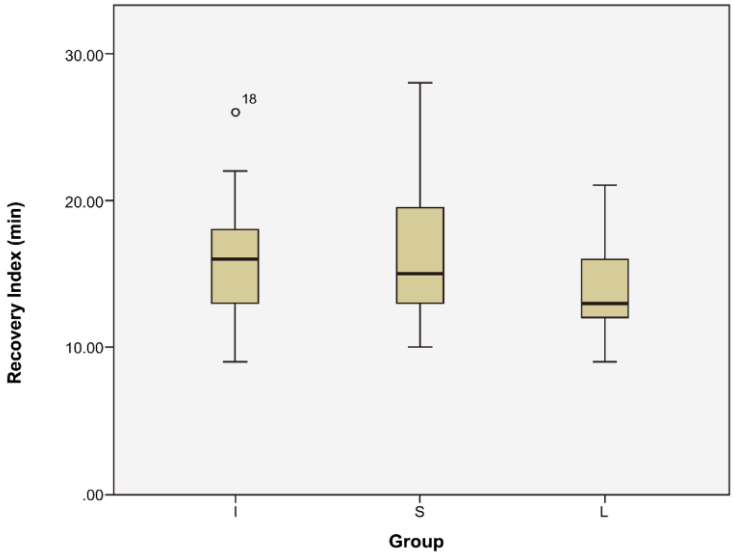

Figure 4. Time to TOF 25–75% (recovery index). TOF=train-of-four.

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

Parameter	**Mean difference**	**Standard error**	***P* value**
Onset			
Group I vs Group S	-17.9	26.6	.781
Group I vs Group L	-186.4	26.6	<.001*
Group S vs Group L	-168.6	26.6	<.001*
Duration 25%			
Group I vs Group S	3.4	2.4	.324
Group I vs Group L	12.0	2.4	<.001*
Group S vs Group L	8.5	2.4	.002*

Multiple comparisons using Turkey honest significant difference test.

*Statistically significant difference between groups.

Table 5. Adverse events

Characteristic	Group I (n=27)	Group S (n=27)	Group L (n=27)	*P* value
Intubation time, s, mean ± SD	50.8±24.1	40.8±12.3	44.6±14.3	.117
Intubation grade				
0	27 (100)	27 (100)	24 (88.9)	
1	0 (0)	0 (0)	1 (3.7)	
2	0 (0)	0 (0)	2 (7.4)	
Adverse event				
Coughing	0 (0)	0 (0)	2 (7.4)	
Agitation	0 (0)	0 (0)	1 (3.7)	
Desaturation	0 (0)	0 (0)	0 (0)	

Data presented as n (%), unless otherwise indicated.

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 1 of these patients produced small arm movements during coughing (Table 5).

IV. 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 based on 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 300–400% of the cisatracurium ED95 is administered.[2,15] Additionally, 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 sugammadex cannot be applied for reversal. Additionally, 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.[12,13,15,19] 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 are 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 synergistic 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 prior to 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 min and 5.2 min, respectively; the durations of time to T1 recoveries of 25% were 36 min and 45 min, respectively.[24,25] In the present study, the onset duration was 3.5 min for Group I and the T1 recovery of 25% was 51 min, 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 post-intubation 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.[26] 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 based on 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 >25 kg/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 based on 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 to 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 two α subunits of the acetylcholine receptor, although the pathophysiology of interaction between non-depolarizing NMBAs remains uncertain.[29,30] 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. Additionally, 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 min.

V. CONCLUSION

We found that clinically effective muscle relaxation 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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ABSTRACT (IN KOREAN)

근이완제 로큐로늄과 시스아트라큐리움의 병용투여시 적정용량

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배경: 근이완제 로큐로늄과 시스아트라큐리움은 병용시 상승 효과를 나타낸다. 본 연구는 병용된 근이완제의 용량을 줄이더라도 상승 효과를 통하여 수술중 충분한 근이완 효과를 나타내는지에 대해 신경근 이완 상태를 감시하여 알아보았다.

방법: 본 연구는 무작위 대조군 연구로 유양돌기절제술 및 고실성형술이 예정된 81 명의 환자를 대상으로 시행되었다. 연구 참가자들은 각각 기도삽관용량군 27 명 (로큐로늄과 시스아트라큐리움 각각의 95%유효용량을 병용한 군), 저용량 감소군 27 명 (각각의

95%유효용량에서 10%를 감소하여 병용한 군), 고용량 감소군 27 명 (각각의 95%유효용량에서 20%를 감소하여 병용한 군) 에 할당되었다. 근이완제 투여와 함께 시간을 측정하였고 TOF-Watch®를 사용하여 자신경에서 사연속자극을 2Hz/12s 로 맞추어 근이완 감시를 시작하여 각 군의 근이완 효과를 평가하였다. 전정맥마취 상태에서 초기 근이완제 투여 후 사연속자극 비율이 0 이 되는 시간을 발현시간으로, 사연속자극 비율이 25%를 처음 초과한 시간을 25%지속시간으로, 사연속자극 비율이 25%를 처음 초과한 시간부터 75%를 처음 초과한 시간까지의 기간을 회복지수로 기록하였다.

결과: 고용량 감소군은 기도삽관용량군과 저용량 감소군에 비해 긴 발현시간 (평균 ± 표준편차, 399.3 ± 147.8 s) 과 짧은 25%지속시간 (39.4 ± 6.8 min)을 나타내었다.

결론: 본 연구의 결과는 로큐로늄과 시스아트라큐리움의 병용시 상승효과의 약동학적 특징을 예측할 수 있을 뿐 아니라 임상적으로 효과적인 용량을 결정하는데 공헌할 것으로 생각된다. 또한 경미한 수술시 두 약제의 95%유효용량에서 10%를 감량하여 사용하더라도 충분한 신경근 이완효과가 유지될 수 있을 것으로 사료된다.

핵심되는 말: 로큐로늄, 시스아트라큐리움, 병용, 신경근 감시, 약물 상승효과