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Effects of Combined Rocuronium and Cisatracurium in Laparoscopic Cholecystectomy

Woo Young Park[1,2], Kwang Ho Lee[3], Young Bok Lee[3], Myeong Hoon Kim[3], Hyun Kyo Lim[3,*], Jong Bum Choi[4,*]

[1]Department of Anesthesia, Sheikh Khalifa Specialty Hospital, Ras Al Khaimah, United Arab Emirates, [2]Department of Anesthesiology and Pain Medicine, College of Medicine, Seoul National University, Seoul, [3]Department of Anesthesiology and Pain Medicine, Yonsei University Wonju College of Medicine, Wonju, [4]Department of Anesthesiology and Pain Medicine, College of Medicine, Ajou University, Suwon, Korea

Background: Laparoscopic upper abdominal surgery can cause spontaneous respiration due to diaphragmatic stimulation and intra-abdominal CO_2 inflation. Therefore, sufficient muscle relaxation is necessary for a safe surgical environment.

Methods: We investigated if the combination of rocuronium and cisatracurium can counteract the delayed onset of cisatracurium's action and delayed recovery of muscle relaxation and whether the dosage of rocuronium, which is metabolized hepatically, can be reduced. A total of 75 patients scheduled for laparoscopic cholecystectomy with an American Society of Anesthesiology physical status I-II, in the age range of 20-60 years, and with a 20-30 kg/m^2 body mass index were included in the study.

Results: The patients were divided into the following groups: combination group (Group RC, rocuronium 0.3 mg/kg and cisatracurium 0.05 mg/kg), rocuronium group (Group R, rocuronium 0.6 mg/kg), and cisatracurium group (Group C, cisatracurium 0.1 mg/kg), and the onset, 25% duration, recovery index, and addition/time ratio were measured. Patients in Group RC exhibited a significantly different addition/time ratio compared with patients in the other two groups ($p = 0.003$).

Conclusion: During laparoscopic cholecystectomy, the 95% effective dose of rocuronium in combination with cisatracurium is expected to provide a sufficient muscle relaxant effect.

Key Words: Cholecystectomy, Cisatracurium, Laparoscopy, Rocuronium

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*Corresponding author: Jong Bum Choi
Department of Anesthesiology and Pain Medicine, College of Medicine, Ajou University, 164 WorldCup-ro, Yeongtong-gu, Suwon 16499, Republic of Korea
Tel: 82-31-219-5571, Fax: 82-31-219-5579
E-mail: romeojb@naver.com
*Corresponding author: Hyun Kyo Lim
Department of Anesthesiology and Pain Medicine, Yonsei University Wonju College of Medicine, 20 Ilsan-ro, Wonju, Gangwon-do 26426, Republic of Korea
Tel: 82-33-741-1536
Fax: 82-33-742-8198
E-mail: hyunkyolim@yonsei.ac.kr

INTRODUCTION

Since laparoscopic upper abdominal surgery can cause spontaneous respiration due to diaphragmatic stimulation and intra-abdominal CO_2 inflation, neuromuscular monitoring and the administration of a non-depolarizing muscle relaxant during surgery are required [1-6]. Cisatracurium, in comparison with rocuronium, has a delayed onset and a longer duration of action, which can lengthen post-operative recovery. However, rocuronium can cause an overdose of its muscle relaxant effect due to repetitive additional injections [7-10]. Based on the findings of previous studies, rocuronium has a faster onset time and faster spontaneous T1 and train-of-four recovery (TOF) time compared with cisatracurium, and the combination of the half equipotent dose of rocuronium and cisatracurium causes synergistic interaction [11-13]. In this study, we investigated if the combination of rocuronium and cisatracurium can complement the delayed onset of cisatracurium's action and the delayed recovery of muscle relaxation and whether the dosage of rocuronium can be reduced.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of our institute (ref. CR313029). A total of 75 patients scheduled for laparoscopic cholecystectomy were included in this study, and informed consent was obtained from all patients. Patients participating in the study were aged between 20 and 60 years, with a body mass index (BMI) of 20-30 kg/m^2, and an American Society of Anesthesiology (ASA) physical status of I-II [14,15]. Patients allergic to medication used in the research, patients with renal disease or radiculopathy, patients who were pregnant or breast-feeding, patients using antipsychotic medication or neuroleptics, and patients using medication that affects succinylcholine chloride were all excluded [16]. Computerized randomization was used for double blinding; a resident who did not participate in the anesthesia transferred the previously set dosage of a neuromuscular blocker to a scale-covered syringe according to a random number table and included this numbering in the case report form. A nurse who did not participate in the study transferred the test agents and the case report form to a researcher.

Prior to surgery, patient height and body weight were measured, and BMI was calculated. Patients were injected with midazolam 2 mg and glycopyrrolate 0.2 mg as premedication 1 hour before surgery. Once a patient arrived in the operating room, a non-invasive blood pressure measurement, pulse oximetry, electrocardiogram, and bispectral index measurement (BIS) were performed. The patient's tympanic temperature was measured, and a TOF-Watch® (Organon, Teknica B.V., Boxtel, the Netherlands) was applied to the ulnar nerve on the opposite side as the surgical site. Total intravenous anesthesia (TIVA) was performed using an infusion pump (Orchestra Module DPS, Fresenius-Vial, Brezins, France), and propofol 1.5-2.5 mg/kg and remifentanil 0.4-0.6 mcg/kg were administered for the induction of anesthesia. According to Minto's or Marshall's pharmacokinetic model, target controlled infusion was then performed using propofol 5-10 mg/kg/hr and remifentanil 0.05-2 mcg/kg/min. For neuromuscular blockers usually injected at priming dose, the intubating dose, which was twice the 95% effective dose (ED_{95}), was administered based on the ideal body weight.

The study groups (N = 25) were as follows: rocuronium group (Group R, 0.6 mg/kg rocuronium), cisatracurium group (Group C, 0.1 mg/kg cisatracurium), and combination group (Group RC, rocuronium 0.3 mg/kg and cisatracurium 0.05 mg/kg). For TOF stimulation, supramaximal square wave impulses of 200 μs duration and 2 Hz per 12 sec were utilized. The primary outcome was the number of injections per hour of additional rescue dose, and 10% of the initial neuromuscular blocking agent dosage, and the TOF ratio = 0 (onset), 1st TOF ratio >25% (duration 25%), and TOF 25-75% (recovery index) were measured. In addition, the patient's blood pressure and pulse rate before and after anesthesia, body temperature and O_2 saturation, and operation and anesthetic durations were measured. The occurrence of spontaneous respiration and movements during surgery and the absence or presence of post-operative respiratory distress complication were also monitored. In hypotensive cases, with systolic blood pressure <90 mmHg, phenylephrine 50 mcg IV was injected, while in hypertensive cases, with systolic blood pressure >200 mmHg, nicardipine 250 mcg was administered [17]. Even if the T1/T4 ratio was less than 25%, an additional rescue dose was intravenously injected in cases of unanticipated movement of respiratory muscles.

The three groups were statistically compared using the Chi-square test, Fisher's exact test, and one-way ANOVA. For post-hoc tests after one-way ANOVA, the Tukey method was used. Based on a preliminary study, the number of patients required for each group to achieve a power of 0.9 and type I error of 0.05 was 22; therefore, 25 patients in total were required for each group accounting for a withdrawal rate of 10%. All data were expressed as mean ± standard deviation or number, and statistical significance was accepted at $p < 0.05$.

Table 1. Demographic characteristics

Study group	Group RS (*n* = 25)	Group R (*n* = 25)	Group C (*n* = 25)	p-value
Age, yrs	44.4 ± 9.3	44.3 ± 6.7	43.8 ± 8.4	0.961
Gender, *n*				0.671
Female	11	9	8	
Male	14	16	17	
Body mass index, kg/m^2	25.5 ± 2.7	23.3 ± 2.9	24.2 ± 2.7	0.036*
ASA, *n*				0.022*
I	20	24	25	
II	5	1	0	
HTN, *n*	4	1	0	
DM, *n*	1	0	0	

Characteristics of the patients of each study group. Values are mean ± SD; *n* is the number of patients.
SD: standard deviation, ASA: American Society of Anesthesiologists, SBP: systolic blood pressure, DBP: diastolic blood pressure.
*p-value < 0.05.

Table 2. Pharmacodynamic data

Study group	Group RS (*n* = 25)	Group R (*n* = 25)	Group S (*n* = 25)	p-value
Onset, sec	209.9 ± 71.6	189.1 ± 55.9	377.0 ± 54.3*	<0.001
Duration 25%, min	51.6 ± 6.6*	41.6 ± 9.4	43.4 ± 8.5	<0.001
Recovery index, min	15.9 ± 3.8	16.2 ± 4.8	14.1 ± 3.4	0.123
Addition/time ratio	1.53 ± 0.56*	2.22 ± 0.77	2.17 ± 0.79	0.001
Operation time, min	75.0 ± 22.2	66.4 ± 13.2	70.0 ± 22.5	0.306
Anesthetic time, min	90.5 ± 20.7	82.2 ± 14.6	86.0 ± 23.8	0.346

*There are significant differences between the three groups in post-analysis using Turkey's method. Values are mean ± SD.

RESULTS

This study investigated 75 patients who underwent laparoscopic cholecystectomy between September 2014 and March 2015. There was no statistically significant difference in age or gender between the three study groups. However, there was a significant difference in ASA classification ($p = 0.022$) and BMI ($p = 0.036$) between the groups (Table 1).

There was no significant difference in blood pressure or pulse rate before and after anesthesia, body temperature, peripheral arterial O_2 saturation, operation and anesthetic durations, or recovery index between the three groups. However, the onset time in Group C, 25% duration in Group RC, and addition/time ratio in Group RC were statistically significantly different compared with the other groups ($p < 0.001$, $p < 0.001$, and $p = 0.003$, respectively). The post-hoc test (Tukey method) results for onset time, 25% duration, and addition/time ratio are presented in Table 2 and Fig. 1.

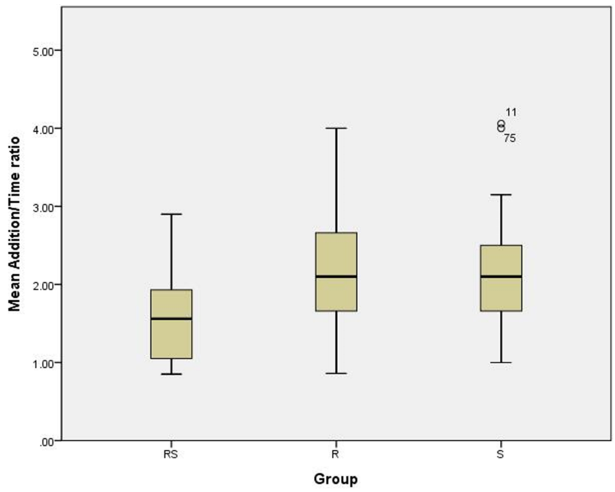

Fig. 1. Addition/time ratio is the number per hour of additional rescue doses administrated at 10% of the initial NMBA dose. The formula is ((Addition number + 1) / Anesthetic time (min)) × 60. Values are mean ± SD.

DISCUSSION

Upper abdominal surgery via laparoscopy requires additional administration of non-depolarizing neuromuscular blocking agents [1,2,4]. For surgical procedures with a short operation time (approximately 1 hour), the recovery time can be delayed due to residual blockade from the continuous infusion of muscle relaxants [9,18,19]. Therefore, during anesthesia for laparoscopic cholecystectomy, a reduction in additional injections and the administration of a muscle relaxant with a similar duration to the anesthetic duration are required. In this study, we found that injecting a combination of rocuronium and cisatracurium provided stable muscle relaxation during laparoscopic cholecystectomy and maintained the duration of muscle relaxation corresponding to the operation duration.

Laparoscopic cholecystectomy can delay the excretion of rocuronium in biliary obstruction. This can be caused by the predisposing condition, cholecystitis, and the interruption of the hepatic metabolism of rocuronium in cases where hepatic circulation is reduced by increased abdominal pressure [20-24]. The resulting prolonged muscle relaxation can complicate the prediction of post-operative recovery time from muscle relaxation and increase the risk of residual muscle relaxation by inducing the utilization of an inappropriate muscle relaxant. In cases where cisatracurium, which is unaffected by hepatic metabolism, is administered, the onset time of the muscle relaxant can be delayed and prolonged [19,25].

Repetitive injection of rocuronium can complicate the pharmacokinetic prediction of residual or prolonged post-operative muscle relaxation because its effect may be prolonged in diseases causing biliary tract obstruction [20,22]. Therefore, for patients with diseases causing biliary tract obstruction, objective neuromuscular monitoring and anti-cholinesterase drugs or sugammadex administration are required to reduce residual muscle relaxation and respiratory complications [16,26,27]. However, sugammadex is still utilized in this country, although limitedly due its high cost [28,29]. This study was performed in order to find a solution to these issues and to examine whether the prolonged effect of muscle relaxation is adequately applied to the operation duration when rocuronium is injected in combination with cisatracurium. The number of muscle relaxant injections required during 60 minutes of operation time (addition/time ratio) was calculated; the injected muscle relaxant was assumed to have a sufficient duration of 1 operative hour, since the number of muscle relaxant injections was close to 1. If the addition/time ratio is less than 1, unnecessary anesthetic time can be prolonged while waiting for recovery from residual muscle relaxation. If this ratio is greater than 1, additional injection of muscle relaxant is required to maintain muscle relaxation for surgery. Injection of rocuronium in combination with cisatracurium had an addition/time ratio of 1.53, indicating that it was more suitable for 1 hour of operation compared with rocuronium or cisatracurium alone (2.17 and 2.22, respectively). If the early dosage of rocuronium is increased for 1 hour of operation, there is possibility of residual muscle relaxation in laparoscopic cholecystectomy. If the early dosage of cisatracurium is increased, its duration may be prolonged by more than 1 hour.

In this study, there was no spontaneous respiration or movement recorded. There was also no reduction of O_2 saturation (<90%) in pulse oximetry after surgery. This is assumed to be due to the injection of additional muscle relaxants upon constant monitoring of muscle relaxation status. This study performed TIVA using propofol and remifentanil in order to exclude the potentiating effect of muscle relaxation caused by inhalation anesthetics [7,8,10,18]. In addition, after the initial measurement of body temperature prior to anesthesia, body temperature was maintained at 36.0 ± 0.5℃ using a forced-air warmer in order to prevent a change in the duration of muscle relaxation due to body temperature change [30]. It was also verified that there was no significant difference between groups by measuring blood pressure, as well as the pulse rate, before and after anesthesia induction [17]. Furthermore, the target concentration of propofol was adjusted to maintain the anesthetic depth with BIS 35-55, and the end-tidal CO_2 pressure was adjusted to 35-40 mmHg in order to reduce pH change due to hyperventilation or laparoscopic CO_2 inflation [5,16].

This study has a few limitations. First, pre- and post-operative comparative assessments of liver function, which can affect the metabolism of rocuronium, were not performed. This factor can affect the residual muscle relaxation effect of rocuronium. These assessments were not performed because the aim of this study was to investigate whether the intubation dose of rocuronium provided sufficient muscle relaxation during laparoscopic cholecystectomy. Second, there was statistically significant difference in ASA classification and BMI among the three groups. Although there were four hypertensive patients with ASA II in Group RS, there was no difference in baseline or post-intubation hemodynamics since patients were controlled with anti-hypertensive medications. However, there was a statistically significant difference in the BMI of Group R compared with Group RS; this may be related to the prolongation of 25% duration in Group R. Third, two syringes were utilized for double-blindness, additional injection of muscle relaxants included. A time discrepancy due to the order of injections could not be corrected because each syringe contained a muscle relaxant and the same amount of saline or two kinds of muscle relaxants without saline. Finally, the residual muscle relaxation was not measured in the recovery room. For TOF ratio ≥90% during the recovery of muscle relaxation, glycopyrrolate 0.2 mg and pyridostigmine 10 mg were injected; however the TOF ratio was not measured in the post-anesthetic care unit. Therefore, the objective evaluation of residual muscle relaxation could not be performed and was alternatively evaluated using the reduction of O_2 saturation or respiratory distress expressed by the patient. Consequently, the discrepancy in residual muscle relaxation among the three groups was not verified. It is necessary to perform further studies comparing the effects of combined muscle relaxants injection according to liver function and residual muscle relaxation.

In conclusion, during laparoscopic cholecystectomy, the injection of the ED_{95} of rocuronium and cisatracurium can provide a more suitable muscle relaxation effect than the injection of intubating doses of rocuronium or cisatracurium alone.

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