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의학석사 학위논문

**The effect of calcium chloride for  
the reversal of neuromuscular  
blockade during recovery of general  
anesthesia**

**A randomized controlled study**

전신 마취 종료 시 염화칼슘의  
근이완 역전 회복 효과

무작위배정비교임상시험

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주 재 우

**A thesis of the Degree of Master of Medical Science**

**전신 마취 종료 시 염화칼슘의  
근이완 역전 회복 효과**

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**The effect of calcium chloride for  
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# ABSTRACT

**Introduction:** Ionized calcium plays an important role in neuromuscular transmission at both pre- and postsynaptic levels. The overall effect of ionized calcium at the neuromuscular junction is not yet evaluated in patients with nondepolarizing neuromuscular blockade. We hypothesized that administration of calcium chloride supplementary to acetylcholinesterase inhibitor could enhance the rate of neuromuscular recovery and reduce the incidence of residual neuromuscular blockade (RNMB) after surgery.

**Methods:** This single centre, randomized, controlled, double-blinded, parallel-group trial enrolled 58 patients scheduled for elective surgery lasting at least 60 minutes under general anesthesia. Patients were randomly allocated to receive 5 mg.kg<sup>-1</sup> of calcium chloride (calcium group, n = 26) or the same volume of normal saline (control group, n = 27) with 25 µg.kg<sup>-1</sup> of neostigmine and 15 µg.kg<sup>-1</sup> of atropine at the end of surgery. Neuromuscular function was monitored using acceleromyography with the TOF-Watch SX<sup>®</sup>. The primary endpoint was the time from neostigmine administration to recovery of a train-of-four ratio (TOFr) to 0.9. Secondary end points included TOFr after 5, 10, and 20 min after neostigmine administration, TOFr at the arrival of postanesthesia care unit (PACU), the incidence of RNMB.

**Results:** The time from neostigmine administration to recovery of TOFr to 0.9, was significantly faster in the calcium group than in the control group (5.0 [3.0-7.0] vs. 6.7 [5.7-10.0] min;  $P = 0.007$ ). TOFr 5 min after neostigmine administration was significantly higher in the calcium group than in the control group. (87 [74-100] vs. 68 [51-81] %;  $P = 0.002$ ) There were no differences between the two groups with respect to TOFr at PACU, TOFr after 10 and 20 min from neostigmine administration. The incidence of RNMB at 5 min following neostigmine administration was significantly lower in calcium group than in control group (13 [50%] vs. 22 [81.5%];  $P = 0.016$ ). All patients were extubated in the operating room. During PACU stay, all patients did not show any clinical sign of residual neuromuscular blockade or recurarization.

**Conclusion:** The use of calcium chloride at the reversal of nondepolarizing neuromuscular blockade enhances neuromuscular recovery at early recovery period. Further studies are required on the relationship between the calcium administration and clinical outcomes.

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**Keywords:** calcium chloride; residual neuromuscular block; postoperative complications; anesthesia recovery period

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# CONTENTS

<b>Abstract</b> .....	<b>i</b>
<b>Contents</b> .....	<b>iii</b>
<b>List of tables and figures</b> .....	<b>iv</b>
<b>Introduction</b> .....	<b>1</b>
<b>Methods</b> .....	<b>3</b>
<b>Study design and patient allocation</b> .....	<b>3</b>
<b>Study protocol</b> .....	<b>4</b>
<b>Data collection</b> .....	<b>6</b>
<b>Statistical analysis</b> .....	<b>6</b>
<b>Results</b> .....	<b>8</b>
<b>Discussion</b> .....	<b>13</b>
<b>Limitations</b> .....	<b>16</b>
<b>References</b> .....	<b>18</b>
<b>Abstract in Korean</b> .....	<b>23</b>

# LIST OF TABLES AND FIGURES

## Tables

Table 1 Baseline patient characteristics s .....	10
Table 2 Recovery of neuromuscular blockade after neostigmine administration.....	11

## Figures

Figure 1 Flow diagram of patient distribution .....	12
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# INTRODUCTION

During general anesthesia, sufficient muscle relaxation is usually required to ease endotracheal intubation and to secure adequate surgeon's view. However, incomplete reversal of neuromuscular blockade and residual post-operative paralysis are associated with the potentially negative outcome of patients. Residual neuromuscular blockade (RNMB) is a major risk factor in the development of postoperative pulmonary complications and increases postoperative morbidity and mortality [1-7].

Acetylcholinesterase inhibitors, such as neostigmine, have been widely used in clinical practice to reverse nondepolarizing neuromuscular blockade before the extubation of the trachea. They indirectly increase the acetylcholine concentration in the neuromuscular junction. Various factors, such as electrolyte imbalance, either potentiate or antagonize nondepolarizing neuromuscular blocking agents, which may result in a delayed recovery or an unexpected emergence during general anesthesia [8]. Therefore, the understanding of the physiology of potential variables that affects neuromuscular blockade is undoubtedly important for anesthesiologists.

Ionized calcium plays an important role in neuromuscular transmission, as it provokes the acetylcholine release from the motor nerve terminal and facilitates excitation-contraction coupling in muscle [9, 10]. However, ionized calcium also decreases the degree of depolarization at motor-end plate [11],



which makes the overall effect of ionized calcium at the neuromuscular junction unpredictable. Only a few reports have associated calcium with neuromuscular blockade [11, 12]. Furthermore, the effect of ionized calcium on nondepolarizing neuromuscular recovery induced by acetylcholinesterase inhibitor was not yet evaluated.

We tested the hypothesis that administration of calcium chloride supplementary to acetylcholinesterase inhibitor could enhance the rate of neuromuscular recovery and reduce the incidence of RNMB after surgery. The aim of this study was to compare the neuromuscular recovery time and the incidence of RNMB when neostigmine was administered with or without calcium chloride at the end of anesthesia.

# METHODS

## **Study design and patient allocation**

This single centre, randomized, controlled, double-blinded, parallel-group trial was approved by the institutional review board of Seoul National University Hospital (IRB No. 1402-111-560) in Seoul, Republic of Korea. This trial is registered at clinicalTrials.gov: NCT02213848. Between August 2014 and October 2014, ASA physical status I to III patients, aged 18 to 65 years, scheduled to undergo elective surgery with an expected duration of at least 60 minutes, under general anesthesia with endotracheal intubation, were studied. Written informed consent was obtained from all patients. Exclusion criteria included body mass index  $<18.5$  or  $>25.0$  kg/m<sup>2</sup>, suspected difficult airway, bronchial asthma, chronic obstructive pulmonary disease, neuromuscular disease, hepatic and renal diseases, drugs influencing the effect of neuromuscular blocking agents, allergy to the medication used in this trial, pregnancy, breast feeding state, history of malignant hyperthermia, contraindication to atropine or neostigmine, and hypercalcemia.

Patients were randomly allocated to the control group or the calcium group. Randomization was performed by using a computer-generated code with a block of 4 and the randomization table was stored by an independent investigator to ensure allocation concealment. Study medications were

prepared by an anesthesia nurse who was not involved in clinical practice. The attending anesthesiologists were blinded to study medications.

## **Study protocol**

On arrival in the operating room, electrocardiography, noninvasive arterial pressure, pulse oximetry, bispectral index were established. Anesthesia was induced and maintained with propofol and remifentanyl infusion through a target-controlled infusion device (Orchestra Base Primea, Fresenius Vial, Infusion Technology, Bad Homburg, Germany). The initial effect-site concentration of propofol was set by  $4 \text{ ug.ml}^{-1}$  for induction of anesthesia and was adjusted to achieve bispectral index 40-60. Remifentanyl was started to target the effect site concentration of  $4 \text{ ng.ml}^{-1}$  and was titrated according to the clinical decision. After the loss of consciousness, manual ventilation with mask was started, and neuromuscular monitoring was initiated.

Neuromuscular monitoring was performed continuously according to the international consensus guidelines, using acceleromyography (TOF-Watch SX<sup>®</sup>; Organon Ireland Ltd, a sub- sidiary of Merck and Co., Swords, Co., Dublin, Ireland) at the adductor pollicis muscle [13] . The acceleration transducer was placed on the volar side of the distal phalanx of the thumb. The forearm and fingers were cleaned and immobilized, and the electrodes were placed over the ulnar nerve on the volar side of the wrist.

Acceleromyography was calibrated using the automated calibration mode, and train-of-four (TOF) stimulation was continued until the signal was stabilized. After stabilization was completed, patients received rocuronium  $0.8 \text{ mg.kg}^{-1}$ , and TOF was monitored every 15 seconds. Endotracheal intubation was performed when a TOF count (TOFc) of 0 was achieved. Lungs were mechanically ventilated to maintain the end-tidal carbon dioxide concentration at 35-40 mmHg. TOF stimulation was continued every 15 seconds until the end of anesthesia. When TOFc was 2 or more,  $0.15 \text{ mg.kg}^{-1}$  of rocuronium was administered. Patients were warmed using water-circulating heating blanket to maintain core temperature over  $35.0^{\circ}\text{C}$  and skin temperature above  $32^{\circ}\text{C}$ .

At the end of surgery, neuromuscular blockade was recovered spontaneously until the fourth twitch of TOF (TOFc-4) returned. When TOFc-4 reappeared, patients received the neuromuscular reversal agents and the study medications. Patients received  $25 \text{ }\mu\text{g.kg}^{-1}$  of neostigmine and  $15 \text{ }\mu\text{g.kg}^{-1}$  of atropine for the reversal of neuromuscular blockade. For the study medication,  $5 \text{ mg.kg}^{-1}$  of calcium chloride was used in the calcium group, and the same volume of normal saline in the control group. Patients were extubated and moved to postanesthesia care unit (PACU) based on the clinical judgment of the attending anesthesiologist.

## **Data collection**

The primary endpoint was the time from neostigmine administration to recovery of TOF ratio (TOFr) to 0.9. Secondary endpoints included TOFr after 5, 10, and 20 min after neostigmine administration, TOFr at the arrival of PACU, and the incidence of RNMB at each time points. Residual neuromuscular blockade (RNMB) is defined as a train-of-four ratio(TOFr) of less than 0.9 with quantitative neuromuscular monitoring [14]

Patient's baseline characteristics and preoperative serum calcium concentration were recorded. During PACU stay, the presence of symptoms indicating of RNMB was assessed. Patients were asked by recovery staffs about the presence of general weakness, visual symptoms, difficulty swallowing [15-17]. To ensure blinding, the PACU staffs were blinded to the randomization schedule. The length of stay in PACU was also recorded.

## **Statistical analysis**

Sample size estimation was based on the recovery time of the neuromuscular block. A previous report showed that the usual recovery time in patients treated with neostigmine was  $500 \pm 200$  seconds (mean  $\pm$  SD)[18]. Assuming that calcium chloride supplementary to neostigmine decreases the recovery

timed to 300 s, a group size of 23 will be required to make a statistically significant difference using type I error of 0.05 and with the power of 0.9. Assuming a drop-out rate of 20%, 29 patients per group were required.

Results were analyzed using per-protocol approaches. Data were reported as counts and percentages for discrete variables, and median (interquartile range; IQR) for continuous variables. Continuous variables were analyzed by means of Mann-Whitney U test. Categorical variables were compared by using chi-square or Fisher's exact test. P value less than 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS 18.0 (SPSS Inc., Chicago, IL, USA)

## RESULTS

During the study, 58 patients were screened and recruited for the trial and randomized to either the control group (n = 29) or the calcium group (n = 29). Five patients were excluded from analysis after randomization because of consent withdrawal or protocol violations (Figure 1). Finally, 53 patients completed the study. Baseline characteristics were generally comparable between the two groups (Table 1). All the patients in both groups had normal calcium value on preoperative lab findings.

The time from neostigmine administration to recovery of TOFr to 0.9, was significantly faster in the calcium group than those in the control group (5.0 [3.0-7.0] min vs. 6.7 [5.7-10.0] min;  $P = 0.007$ ) (Table 2). The time to extubation, time to end of anesthesia, and time to arrival at PACU were not significantly different between the two groups. TOFr 5 min after neostigmine administration was significantly higher in the calcium group than in the control group. (87 [74-100] % vs. 68 [51-81] %;  $P = 0.002$ ) There were no differences between the two groups with respect to TOFr at PACU, TOFr after 10 and 20 min from neostigmine administration

The incidence of RNMB at 5 min following neostigmine administration was significantly lower in calcium group than in control group (13 [50%] vs. 22 [81.5%];  $P=0.016$ ). RNMB at 10 and 20 min following neostigmine

administration was found in 1 (3.8%) vs. 6 (22.2%), 0 (0%) vs. 1 (3.7%) patients in calcium and control group, respectively.

All patients were extubated in the operating room. At the arrival of PACU, the number of patients with RNMB was 2 of 26 (7.4%) in the calcium group and 4 of 27 in the control group (15.4%) in the control group, but it was not statistically significant. During PACU stay, all patients did not show any clinical sign of residual neuromuscular blockade or recurarization.



**Table 1** Baseline patient characteristics

	<b>Calcium group (n = 26)</b>	<b>Control group (n = 27)</b>	<b>P Value</b>
<b>Age, yr</b>	55 (38-67)	55 (35-66)	0.676
<b>Male, n</b>	17 (65.4 %)	19 (70.4 %)	0.773
<b>Height, cm</b>	167 (159-171)	165 (163-172)	0.894
<b>Weight, kg</b>	65 (58-71)	64 (57-70)	0.908
<b>BMI (kg/m<sup>2</sup>)</b>	24.7 (20.8-26.4)	23.5 (21.3-24.9)	0.749
<b>Type of surgery, n (%)</b>			0.735
<b>Urology</b>	16 (61)	18 (67)	
<b>Plastic surgery</b>	9 (35)	8 (29)	
<b>Others</b>	1 (4)	1 (4)	
<b>Preoperative serum calcium concentration, mg/dL</b>	9.4 (9.2-9.5)	9.3 (9.1-9.6)	0.413
<b>Lowest core temperature, °C</b>	35.8 (35.4-36.0)	35.8 (35.4-36.0)	0.582
<b>Temperature at neostigmine administration, °C</b>	35.8 (35.6-36.0)	36.0 (35.6-36.2)	0.608
<b>Duration of surgery, min</b>	114 (83-145)	111 (82-143)	0.831
<b>Duration of anesthesia, min</b>	158 (134-187)	145 (125-190)	0.516

Data are presented as median (interquartile range), or number of patients (%).

BMI, body mass index; ASA, American Society of Anesthesiologists.

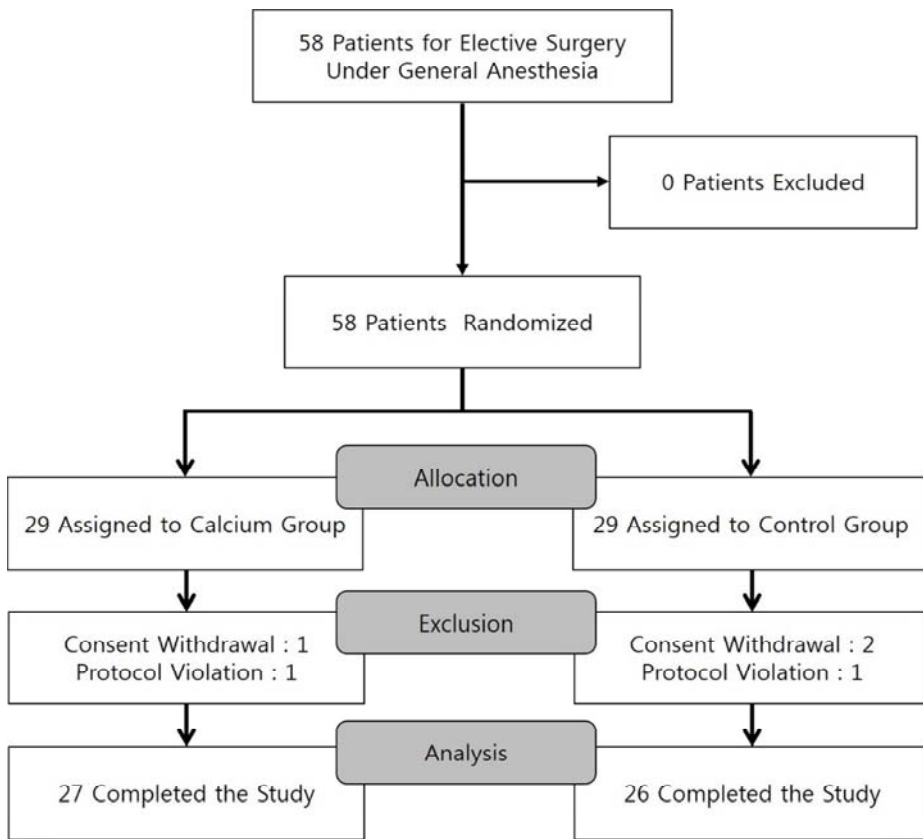
**Table 2** Recovery of neuromuscular blockade after neostigmine administration

	<b>Calcium group (n = 26)</b>	<b>Control group (n = 27)</b>	<b>P Value</b>
<b>Time from neostigmine administration to, min</b>			
<b>TOFr of 0.9</b>	5.0 (3.0-7.0)	6.7 (5.7-10.0)	0.007
<b>Extubation</b>	8.0 (7.0-11.0)	8.0 (6.0-13.0)	0.463
<b>End of anesthesia</b>	10.5 (8.8-14.0)	10.0 (8.0-16.0)	0.795
<b>PACU arrival</b>	12.0 (10.8-16.0)	12.0 (10.0-18.0)	0.830
<b>TOFr, %</b>			
<b>Neostigmine administration</b>	19 (9-27)	16 (12-30)	0.755
<b>5 min</b>	87 (74-100)	68 (51-81)	0.002
<b>10 min</b>	100 (100-100)	100 (90-100)	0.056
<b>20 min</b>	100 (100-100)	100 (100-100)	0.161
<b>at PACU arrival</b>	100 (100-100)	100 (100-100)	0.466
<b>Residual neuromuscular blockade after neostigmine administration</b>			
<b>5 min</b>	13 (50%)	22 (81.5%)	0.016
<b>10 min</b>	1 (3.8%)	6 (22.2%)	0.056
<b>20 min</b>	0 (0%)	1 (3.7%)	0.509
<b>at PACU arrival</b>	2 (7.4%)	4 (15.4%)	0.669
<b>PACU stay, min</b>	50 (46-62)	49 (45-60)	0.470

Data are presented as median (interquartile range), or number of patients (%).

TOFr, train of four ratio; PACU, postanesthesia care unit

**Figure 1** Flow diagram of patient distribution



## DISCUSSION

To our knowledge, this is the first randomized, controlled study to examine the effect of calcium chloride on the reversal of the nondepolarizing neuromuscular blockade induced by acetylcholinesterase inhibitor. In the calcium group, the time from neostigmine administration to recovery of TOFr to 0.9 was 25% shorter than that of the control group. We also found that the calcium chloride administration decreased the incidence of RNMB 5 min after neostigmine administration.

Although a few related studies were carried out, the overall effect of ionized calcium on the nondepolarizing neuromuscular blockade was in question for a long time. In a muscle-nerve model with guineapig, the increase in ionized calcium concentration decreased the sensitivity to tubocurarine and pancuronium [11]. A case report demonstrated that the duration of action of atracurium had been reduced in a patient with an increased serum calcium level secondary to hyperparathyroidism [12]. These studies imply that the higher serum calcium concentration is associated with the resistance to neuromuscular blockade. This is the first clinical study to confirm the antagonizing effect of ionized calcium on neuromuscular blockade, which well correlates with the previous studies.

This represents that anesthesiologists may consider a decrease in the depth of non-depolarizing neuromuscular blockade as calcium chloride is

administered to patients during general anesthesia. Furthermore, in patients with shallow neuromuscular blockade, a recovery of spontaneous ventilation may be also possible after calcium administration. This may require administration of an additional neuromuscular blocking agent, but further evaluation is needed. In addition, in patients with delayed neuromuscular recovery, anesthesiologists may identify the presence of hypocalcemia to consider the injection of calcium chloride.

Ionized calcium hitherto has been believed to be an inappropriate drug to hasten the recovery of neuromuscular function. Despite this antagonizing effect of calcium was shown in the early recovery period, we were unable to show a significant improvement in clinical outcomes, including the incidence of RNMB at PACU arrival and the time from neostigmine administration to extubation. In the current study, the overall incidence of RNMB at PACU was 6 of 53 (11.3%). It corresponds well with previous studies that the incidence of RNMB at PACU arrival was 4.5-45.2% when intraoperative quantitative acceleromyographic monitoring was used [3, 5, 19, 20]. Although the time to recovery of TOFr to 0.9 was decreased, it did not result in early extubation or faster discharge from operating room or PACU. Considering that there are numerous factors affecting neuromuscular recovery, further evaluations are required. Furthermore, these results may be due to the small sample size. Sample size was calculated based on the primary outcome, which was the

recovery time from the reversal to TOFr to 0.9. To evaluate the clinical improvement, the primary outcome may be altered for the larger sample size.

A bolus of  $5 \text{ mg.kg}^{-1}$  of calcium chloride is recommended in acute symptomatic hypocalcemia in children, and also used widely in adult patients with acute hypocalcemia under anesthesia. Serum calcium concentration is maintained between  $8.5$  to  $10.5 \text{ mg.dL}^{-1}$  by homeostatic mechanisms and symptomatic hypercalcemia occurs at serum calcium concentration of  $15 \text{ mg.dL}^{-1}$ . Since administration of  $5 \text{ mg.kg}^{-1}$  of calcium chloride increases serum calcium concentration by  $0.7 \text{ mg.dL}^{-1}$  [21], it can be safely used in normocalcemic patients.

Sugammadex is a gamma-cyclodextrin drug that reverses nondepolarizing neuromuscular blockade. The introduction of sugammadex has made the reversal of neuromuscular blockade easier and safer, and with no regard to numerous factors that affect neuromuscular blockade and recovery. However, understanding of the physiology of neuromuscular blockade cannot be overlooked, since sugammadex is not always available. Sugammadex only binds to steroid neuromuscular blockers and does not reverse neuromuscular blockade by benzylisoquinolines. Economic and insurance aspects and the availability of use of sugammadex in the hospital can also be an issue.

## **Limitations**

There are limitations to the present investigation. First, since calcium chloride was administered at reappearance of TOFc of 4, efficacy of calcium chloride on neuromuscular recovery was assessed only in shallow neuromuscular block. Thus, further study is required in patients with moderate to deep neuromuscular block. Second, total and ionized serum concentration at the time of study drug administration was not assessed. Ionized calcium is biologically active form of calcium, and it consists of approximately 50% of serum total calcium. However, since the proportion of serum calcium bound to protein is affected by the albumin concentration and acid-base status [22, 23] and the estimation of the serum ionized calcium concentration is not precise [24], direct measure of ionized calcium is important. In addition, all the patients enrolled in this study showed normocalcemic on preoperative lab findings. Further studies are needed to examine the efficacy and safety of calcium chloride administration on the patients with hypocalcemia or hypercalcemia. Third, serum ionized magnesium concentration was not assessed. Magnesium is physiologic competitive antagonist of calcium, which can affect neuromuscular blockade and recovery [9]. Fourth, ionized calcium is well known to prevent the antibacterial effect of antibiotics [25]. In the current study, patients received 5 mg.kg<sup>-1</sup> of calcium chloride which is usual dose in anesthesia practice, and there was no sign suggesting any kind of infection during admission in all patients. If patients have a high risk of

postoperative infection, administration of calcium chloride may be decided considering risks and benefits. Fifth, in the current study, calcium chloride is used as an adjuvant to anticholinesterase. More research is needed on the effect of calcium chloride alone on nondepolarizing neuromuscular recovery. Finally, further evaluations on dose-response relationship for calcium are needed.

In conclusion, in patients undergoing general surgery under total intravenous anesthesia, the use of calcium chloride at the reversal of nondepolarizing neuromuscular blockade enhances neuromuscular recovery at early recovery period. Further studies are required on the relationship between calcium administration and clinical outcomes.



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# 국문 초록

**서론:** 이온화 칼슘은 신경근 전도 시에 시냅스 전과 후 모두에서 중요한 역할을 한다. 비탈분극성 근이완이 이루어지는 환자에서 이온화 칼슘이 신경 근육 접합부에 어떤 효과를 미치는지는 아직 밝혀지지 않았다. 본 연구진은 아세틸콜린에스테라아제 억제제에 염화칼슘의 추가 투여가 신경근 회복 속도를 향상시키고 수술 후 잔여 근이완의 빈도를 감소시킨다고 가정하였다.

**방법:** 본 연구는 단일 연구기관, 무작위 대조, 이중 맹검 연구로서 전신마취 하에 60 분 이상 지속되는정규 수술을 받는 58 명의 환자를 대상으로 하였다. 환자들은 무작위로 두 그룹으로 나뉘었고, 수술 종료 시 염화칼슘  $5 \text{ mg.kg}^{-1}$  (칼슘군,  $n = 26$ ) 또는 같은 부피의 식염수를 (대조군,  $n = 27$ ) neostigmine  $25 \mu\text{g.kg}^{-1}$ , atropine  $15 \mu\text{g.kg}^{-1}$  과 병용 정주하였다. 신경근 기능 평가는 TOF-Watch SX<sup>®</sup>를 이용한 acceleromyography 로 시행하였다. 주요 결과는 근이완 역전제 투여 후 train-of-four 비(TOFR) 0.9 도달하는데 걸리는 시간이었다. 이차 결과는 근이완 역전제 투여 5, 10, 20 분과 회복실 도착 시에 TOFR 및 잔여 근이완의 빈도를 보고자 하였다.

**결과:** Neostigmine 투여 후 TOFr 가 0.9 에 도달하는 데 걸리는 시간은 칼슘군이 대조군보다 유의하게 빨랐다. (5.0 [3.0–7.0] vs. 6.7 [5.7–10.0] min;  $P = 0.007$ ). Neostigmine 투여 5 분 후 TOFr 값은 칼슘 군이 대조군보다 유의하게 높았다 (87 [74–100] vs. 68 [51–81] %;  $P = 0.002$ ). 회복실 도착 시, Neostigmine 투여 10, 20 분 후 TOFr 값은 유의한 차이가 없었다. Neostigmine 투여 5 분 후 잔여 근이완의 빈도는 칼슘군에서 유의하게 낮았다 (13 [50.0%] vs. 22 [81.5%];  $P = 0.016$ ). 모든 환자는 수술실에서 기도 발관 하였다. 회복실 체류 중, 모든 환자에서 잔여 근이완을 시사하는 증상 혹은 소견이 발견되지 않았다.

**결론:** 비탈분극성 근이완 역전 시 염화칼슘의 사용은 조기 회복기의 근이완 회복을 촉진시켰다. 실제로 임상적인 호전을 보이기 위해 추가 연구가 필요할 것으로 생각된다.

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**주요어:** 염화칼슘, 잔여 근이완, 수술 후 합병증, 마취 회복 시기

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