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지도교수 오아영

이 논문을 의학석사 학위논문으로 제출함

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송인애의 의학석사 학위논문을 인준함

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Determination of the timing of reversal for the rapid recovery from cisatracurium

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Abstract

Determination of the timing of reversal for rapid recovery from cisatracurium

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Background: The maximal effect of neostigmine occurs within 10-20 min after intravenous administration, and adequate recovery from neuromuscular block within this period is recommended. We aimed to identify the appropriate time for neostigmine administration to achieve optimal recovery from a cisatracurium-induced neuromuscular block within this period.

Methods: In this prospective randomized controlled study, forty-eight adults undergoing surgery for chronic otitis media were analyzed. Anesthesia was induced and maintained with a targeted and controlled infusion of propofol and remifentanil. TOF-Watch SX® and conventional nerve stimulators were

applied to each arm. One arm was monitored for the evaluation of a tactile thumb response, and the other arm that was monitored to obtain train-of-four (TOF) ratios was shielded from the investigator whose data were collected using a laptop. Patients received 0.15 mg/kg of cisatracurium at induction and were randomized to receive neostigmine according to the following tactile responses: the appearance of a fourth TOF response (TOF4 group, n=16), absence of a fade to double burst stimulation (DBS) (DBSfade group, n=16), and absence of a fade to TOF stimulation (TOFfade group, n=16). The time from the administration of neostigmine to TOF ratios of 0.7, 0.8, and 0.9 were evaluated.

Results: The demographic data were not different among the groups. The times from the administration of neostigmine to TOF ratios of 0.9 were 12.6 ± 6.2, 10.1 ± 8.0, and 9.1 ± 6.8 min in theTOF4, DBSfade, and TOFfade groups, respectively. At 10 min after the administration of neostigmine, the percentage of patients with a TOF ratio greater than 0.9 were 50%, 63%, and 69% in the TOF4, DBSfade, and TOFfade groups, respectively. At 15 min after reversal, 81.3%, 87.5%, and 81.3% of the patients in the TOF4, DBSfade, and TOFfade groups, respectively, had TOF ratio values greater than 0.9 (no intergroup differences). The time from the injection of cisatracurium to the administration of neostigmine (69.3 ± 8.3 min) was significantly longer in the TOFfade group compared with the DBSfade and TOF4 groups (61.0 ± 8.3 and

61.0 ± 7.3; p=0.006).

Conclusion: We recommend administering neostigmine with the appearance of the fourth tactile response to TOF or the absence of a fade to DBS to recover from a cisatracurium-induced neuromuscular block to achieve a TOF ratio of 0.9 or more within a reasonable time.

Keywords: Cisatracurium, Neostigmine

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Introduction

A residual postoperative neuromuscular blockade in a postanesthesia care unit (PACU) is associated with a decreased ventilatory response to hypoxia, dysfunction of pharyngeal and upper esophageal muscles, an airway obstruction, and the aspiration of gastric contents [1-3].

A study by Debaene et al. [4] determined that residual neuromuscular blockage was common after a single injection of intermediate duration muscle relaxant, and no reversal was observed more than 2 h after the administration of a muscle relaxant.

With reversal agents, residual paralysis, which is defined as a train-of-four (TOF) ratio of less than 0.8, occurred in half of patients after anesthesia using intermediate-acting neuromuscular blocking agents [5]. Residual paralysis, which is defined as a TOF ratio of less than 0.7 in the PACU, occurred in patients who had received atracurium (4%) or vecuronium (8%) [6].

To evaluate optimal postoperative recovery from a neuromuscular block, good evidence-based practice recommends the objective monitoring of neuromuscular block quantities during peri-operative periods rather than clinical tests or qualitative assessments [7]. A TOF ratio, which is measured mechanically or by electromyography, that is greater than 0.9 is necessary to

avoid clinically significant residual paralysis. Visual disturbance, weak grip power, and disturbed swallowing reflex were observed in conjunction with TOF ratios of 0.9 or less [8]. However, in daily clinical practice, obtaining TOF ratios using these methods is not feasible.

Efforts have been made to determine the optimal time to achieve rapid and adequate recovery from neuromuscular block agents that are guided by simpler method, such as TOF counts. The recent guideline by Kopman et al. [9] suggested that a reversal agent be administered at the second twitch to TOF stimulation. Kirkegaard et al. [10] evaluated how long it would take to achieve a reversal from a cisatracurium-induced neuromuscular block when neostigmine was administered at the first, second, third, and fourth tactile TOF responses and failed to reveal recovery to a TOF ratio of 0.9 within a reasonable time. We aimed to determine the time at which to administer neostigmine to cause a rapid reversal of cisatracurium-induced neuromuscular block to a TOF ratio of 0.9 in a reasonable time.

Methods

After Institutional Review Board approval and informed consent, we studied 48 adult patients (American Society of Anesthesiologists physical status I, II) who were admitted for elective ear surgery. The exclusion criteria included the following: an age greater than 65 or less than 18 years; a history of neuromuscular disease, renal disease or elevated serum creatinine concentration; treatment with drugs known to interfere with neuromuscular function; or a body mass index greater than 30. The recruiting process is illustrated in the consort flow diagram (Figure 1).

Anesthesia

The patients were premedicated with 3 mg of intravenous midazolam 5 min before the induction of anesthesia. In the operating room, routine monitoring of blood pressure, electrocardiography, and pulse oximetry were initiated. Electrodes were placed on the forehead to monitor the bispectral index (BIS) (A-2000 BIS TM monitor, Aspect Medical Systems Inc., Natick, MA, USA).

Anesthesia was administered by target-controlled infusions (TCI) using an Orchestra infusion pump system (Fresenius vial, Brezins, France) with propofol 4 μL/ml and remifentanil 3 ng/ml at the effect site.

Anesthesia was maintained with 50% medical air in oxygen using

remifentanil and propofol. Propofol effect-site target concentrations were adjusted to maintain the BIS between 40 and 50. Remifentanil effect-site target concentrations were controlled to maintain the mean blood pressure above 60 mmHg. Initially, the patients' lungs were ventilated using a bag and mask; tracheal intubation was performed approximately 10 min later after neuromuscular monitoring was established and 0.15 mg/kg of cisatracurium was administered. After tracheal intubation, mechanical ventilation was adjusted to maintain end-tidal carbon dioxide between 30 and 35 mmHg. Temperature was monitored continuously in the mid esophagus, and heating pads and warming air blankets were used to maintain a central temperature above 35 °C and the peripheral skin temperature on the adductor pollicis muscle above 32 °C

Neuromuscular Monitoring

Neuromuscular monitoring followed the Good Clinical Research Practice guidelines in pharmacodynamic studies of neuromuscular blocking agents [11]. After careful cleaning of the skin, two pediatric surface electrodes were placed on both arms over the ulnar nerve near the wrist at a distance of 3-6 cm. TOF-Watch SX® (Organon Ltd., Swords, Ireland) and conventional nerve stimulators were applied to each arm (figure 2). The arm was arranged for to

evaluate the tactile response of the thumb at random on the dominant or nondominant hand of the patient, and the other arm was used for obtaining TOF ratios and was shielded from the investigator; the data were automatically stored to a laptop using the TOF-Watch SX® monitor program (version 2.1). The hand and forearm that were used for recording the TOF ratios were firmly immobilized with tape, which left the thumb free without preload. The other hand was used for a tactile evaluation; the number of felt responses after TOF stimulations or DBS was counted, and the twitch response was defined as present if any response, regardless of strength, was felt during TOF stimulations or DBS. The number of tactile responses was counted during 25-s periods every 2 min. In all of the patients, evaluation of tactile responses was performed by the same anesthesiologist, who was well trained in the use of acceleromyography and was blinded to the acceleromyographic measurements on the contralateral hand. To decrease the stabilization period, a 50-Hz tetanic stimulation was applied for 5 s and followed after 1 min by TOF stimulation every 12 s. When the response to TOF was stable, calibration and supramaximal stimulation was ensured by the built-in calibration function (CAL 2) of the TOF-Watch SX® (figure 3). A stable baseline was documented at least 2-5 min (less than 5% variation in the first twitch [T1] and TOF) before the neuromuscular blocking agent was administered. All of the TOF ratio data were normalized.

Neuromuscular Block and Reversal

A neuromuscular block was induced with 0.15 mg/kg cisatracurium for less than 5 s. After this single dose of cisatracurium, the patients received 0.07 mg/kg neostigmine and 0.014 mg/kg glycopyrrolate at different levels of recovery. The patients were randomly assigned by computer-generated assignment to one of three groups; each group received the reversal drugs at the fourth (TOF4 group) tactile TOF response, absence of fade in response to DBS (DBSfade group) or TOF stimulations (TOFfade group).

The tactile duration of action was defined as time from the administration of cisatracurium to the reappearance of the first tactile TOF response. The duration of action calculated with TOF watch was defined as the time from the administration of cisatracurium to the reappearance of T1. The time from cisatracurium administration to the injection of neostigmine and to a TOF ratio of 0.9 was calculated.

Neuromuscular monitoring continued until the TOF ratio exceeded 0.9. Reversal times were defined as the time from the administration of neostigmine until the TOF ratio recovered to 0.7 (R0.7), 0.8 (R0.8), and 0.9 (R0.9). The final TOF ratios were normalized to the control TOF ratio. For example, a control TOF ratio of 90% would be changed to 81.8% (90/110) if the final TOF ratio was 110%.

Statistical Analysis

We studied 48 patients, with 16 patients per group. In the power analyses, the α error probability was set to 0.05, the β error probability was set to 0.20, and the effect size (1.05) was determined according to the mean (11.8, 7.54) and standard deviation (4.9, 2.9) of the time from the reversal to a TOF ratio of 0.7 when the reversal agents were administered at the first and second twitches to TOF from previous reports [10]. These power analyses indicated that 48 patients were required for the study. One-way analysis of variance and the Bonferroni *post hoc* test were used to test for differences between unpaired groups. The Wilcoxon signed rank test was used to compare the tactile duration of action and the duration of action calculated with TOF watch. A chi-squared test was used to test for differences between groups with regard to the proportion of patients reversed to TOF ratios of 0.70, 0.80, and 0.90 at 5, 10, 15, and 20 min, respectively, after neostigmine administration. $P < 0.05$ was considered statistically significant. All control TOF ratios were used after normalization with the final values.

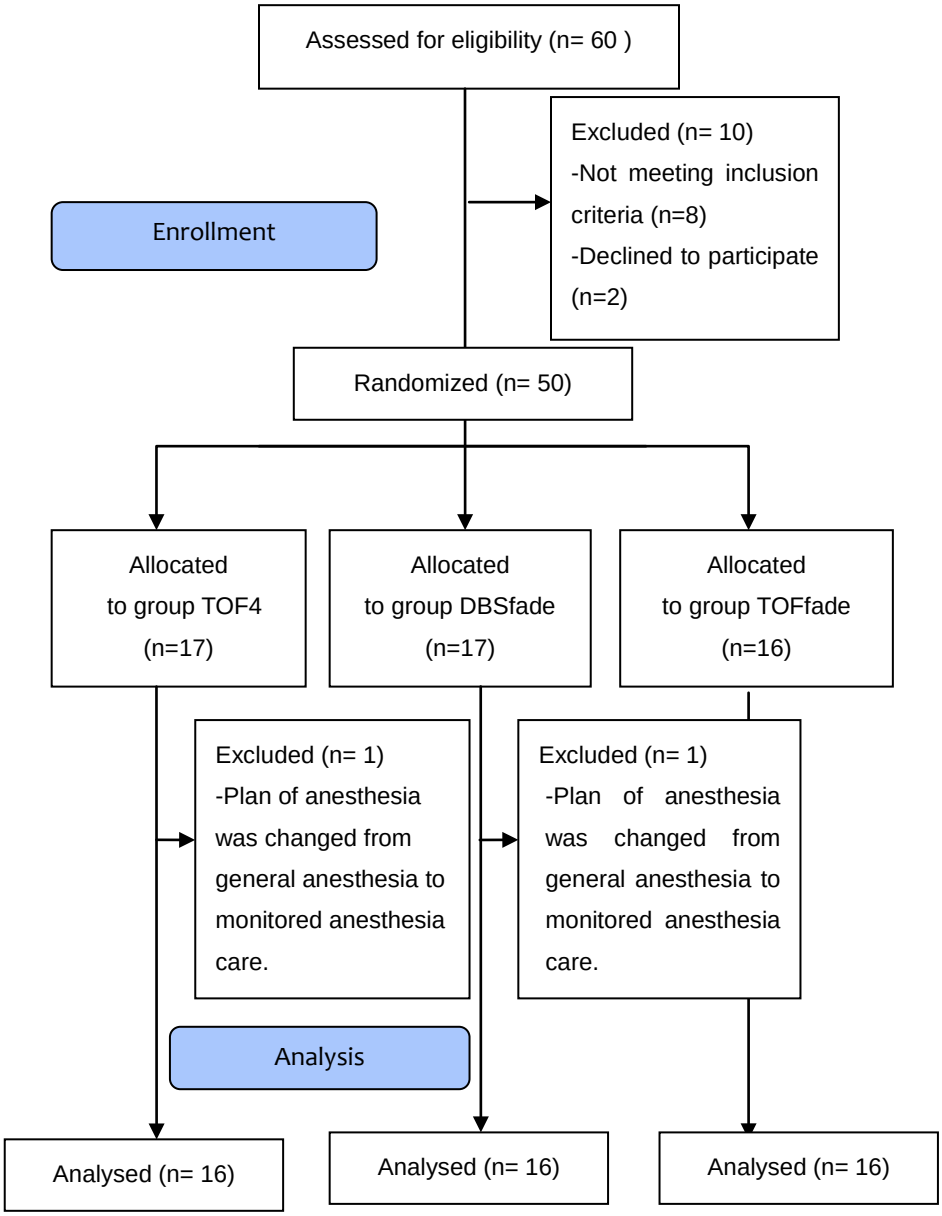


Figure 1. CONSORT Flow Diagram

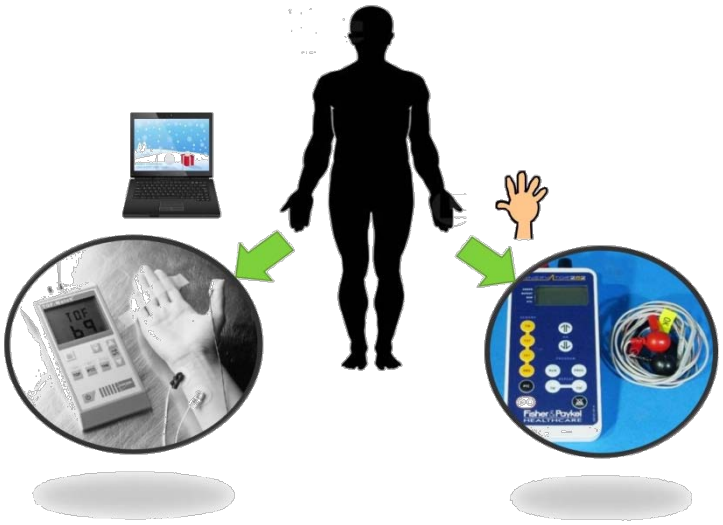


Figure 2. Schematic description of neuromuscular monitors

TOF-Watch SX® (Organon Ltd., Swords, Ireland) and conventional nerve stimulators were applied to each arm. The arm was arranged for evaluation of tactile response of thumb at random to dominant or nondominant hand of the patient and the other arm for obtaining TOF ratios was shielded not to be shown to an investigator and their data were collected in a laptop automatically using the TOF-Watch SX® monitor program (version 2.1). On the other hand used for tactile evaluation, the number of felt responses after TOF stimulations or DBS was counted and twitch response was defined as present if any response, regardless of strength, was felt during TOF stimulations or DBS.

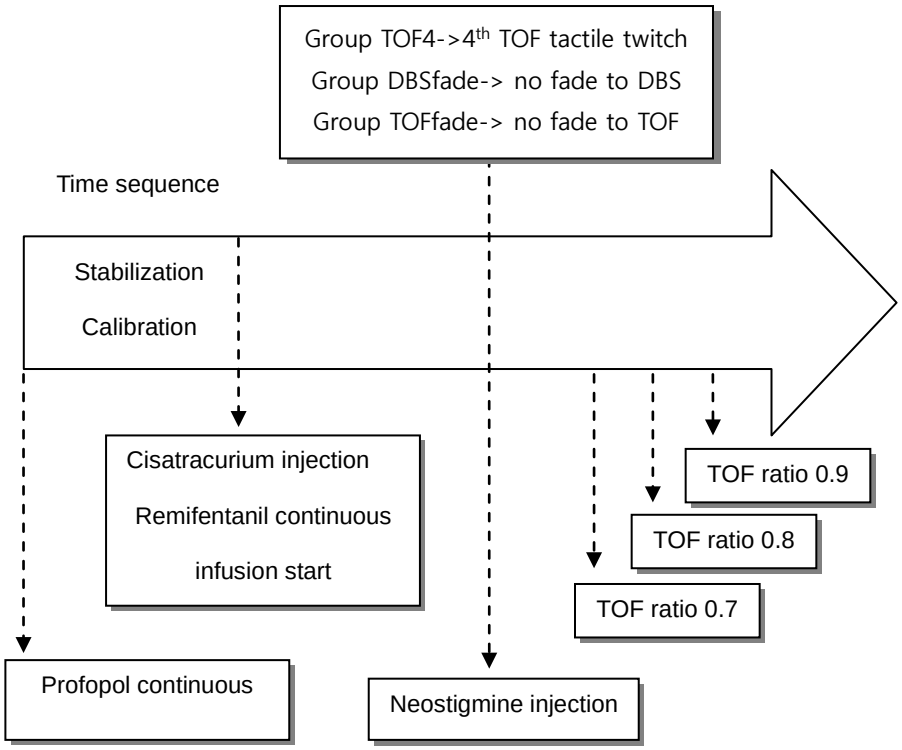


Figure 3. study protocol

When the response to TOF was stable, calibration and supramaximal stimulation was ensured by the built-in calibration function of the TOF-Watch SX®. After this single dose of cisatracurium, the patients received 0.07 mg/kg neostigmine and 0.014 mg/kg glycopyrrolate for reversal at the fourth (group TOF4) tactile TOF response, absence of fade in response to DBS (group DBSfade) or TOF stimulations (group TOFfade). And we recorded the time of TOF ratio of 0.7, 0.8, and 0.9.

Results

The three groups did not differ with respect to age, weight, body mass index or gender distribution (table 1). The duration of action measured by TOF monitoring (52 [34-68] min) was significantly longer compared with that measured tactically (45 [33-56] min).

The time from cisatracurium administration to the injection of neostigmine in the TOFfade group was longer than that of the other two groups (p=0.006) (figure 4), whereas there were no significant differences among these groups with respect to the time from the injection of cisatracurium to recovery to 0.9 of the TOF ratios (figure 5).

There was a significant difference between the groups with respect to R0.7 (p=0.026) (table 2). *Post hoc* testing indicated a significant difference between the TOF4 and TOFfade groups (p=0.028).

At 5 min after neostigmine administration, 31%, 25%, 0% of patients in the TOF4, DBSfade and TOFfade groups, respectively, had a TOF ratio that was less than 0.7 (p=0.043). In addition, 62% (n=10), 38% (n=6), 31% (n=5) of the patients in the TOF4, DBSfade and TOFfade groups, respectively had a TOF ratio less than 0.8, with no significant intergroup differences (figure 6A). Figure 6A also reveals that 94% (n=15), 69% (n=11), 63% (n=10) of patients in the TOF4, DBSfade and TOFfade groups, respectively had a TOF ratio less

than 0.9 (no significant intergroup differences).

At 10 min after administration of neostigmine, only one patient in the TOF4 group had a TOF ratio less than 0.7. Moreover, 13% (n=2), 19% (n=3), 0% (n=0) of patients in the TOF4, DBSfade and TOFfade groups, respectively had a TOF ratio less than 0.8 (no intergroup differences). Moreover, in figure 6B, 50% (n=8), 38% (n=6), 31% (n=5) of patients in the TOF4, DBSfade and TOFfade groups, respectively had a TOF ratio less than 0.9 (no intergroup differences) (figure 6B).

At 15 min after reversal of the neuromuscular block with neostigmine, there were no patients with a TOF ratio less than 0.7 in those groups. In figure 1C, 100% (n=16), 88% (n=14), 100% (n=16) of patients in the TOF4, DBSfade and TOFfade groups, respectively, had a TOF ratio greater than 0.8 (no intergroup differences). Moreover, 81% (n=13), 88% (n=14), 81% (n=13) of patients in the TOF4, DBSfade and TOFfade groups, respectively, had a TOF ratio greater than 0.9 (no intergroup differences) (figure 6C).

At 20 min after reversal via injection of neostigmine, there were no patients who had a TOF ratio less than 0.8, and 88% (n=14), 94% (n=15), 94% (n=15) of patients in the TOF4, DBSfade and TOFfade groups, respectively, had a TOF ratio greater than 0.9 (no intergroup differences). There was no difference between the control TOF ratios of patients at the absence of DBS fade compared with the control TOF ratio at the absence of TOF fade (0.38

±0.15 versus 0.29 ±0.07).

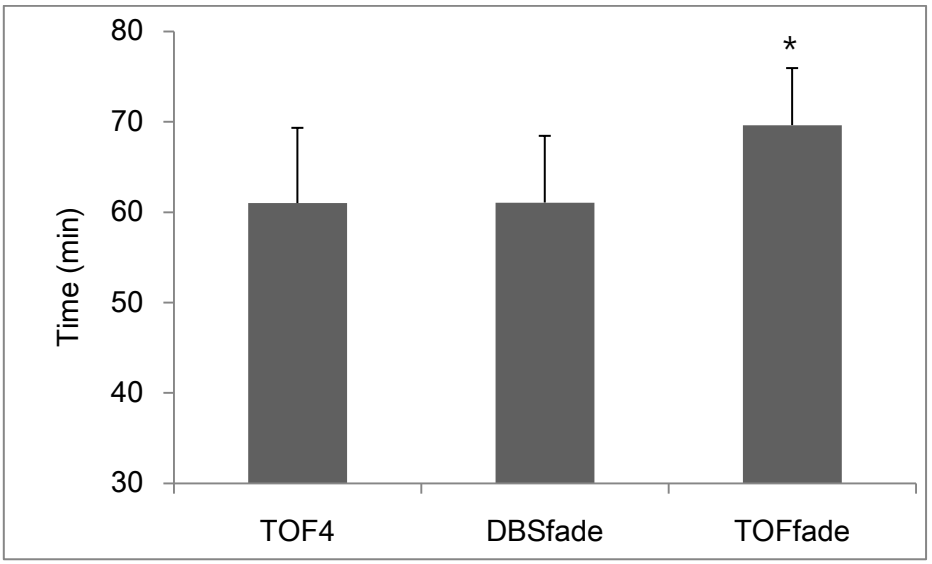


Figure 4. Time from administration of cisatracurium to injection of neostigmine

*P<0.05, There are significant differences of group TOFfade compared to group TOF4 and group DBSfade.

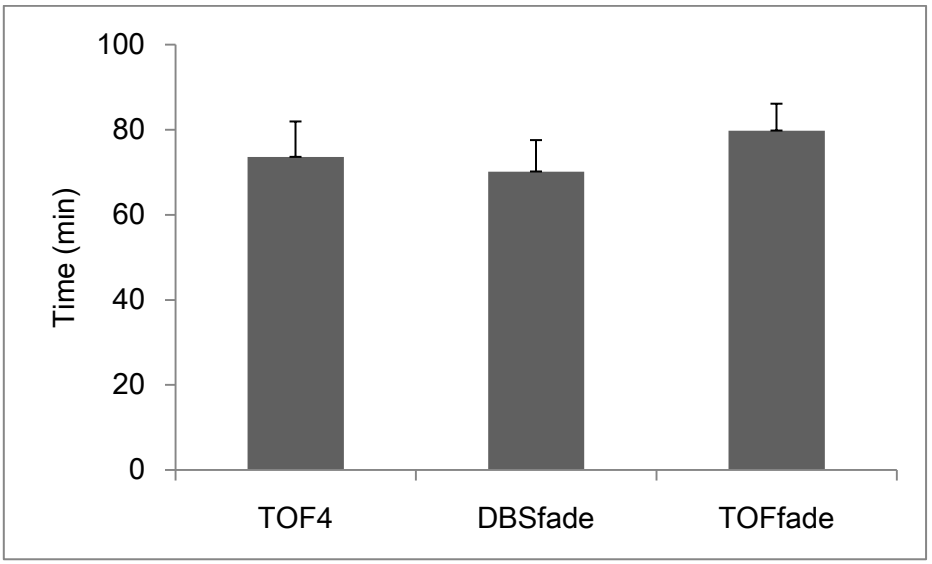


Figure 5. Time from administration of cisatracurium to recovery to TOF ratio of 0.9

No significant differences between groups.

Table 1. Demographic Data

Group	TOF4	DBSfade	TOFfade
Weight(kg)	64.1 ±10.3	63.0 ±10.2	60.0 ±8.9
Height(cm)	161.6 ±8.0	160.1± 9.2	164.0± 9.7
Body mass index(kg/m^2)	24.4± 3.0	24.4± 2.2	22.3 ±2.6
Age(yr)	47.1± 8.6	52.0± 8.2	44.8±9.5
Gender(M/F)	8/8	7/9	6/10

Data are mean ± SD or number of patients

Table 2. Time (min) from Neostigmine Administration to TOF Ratio 0.7, 0.8, and 0.9 respectively.

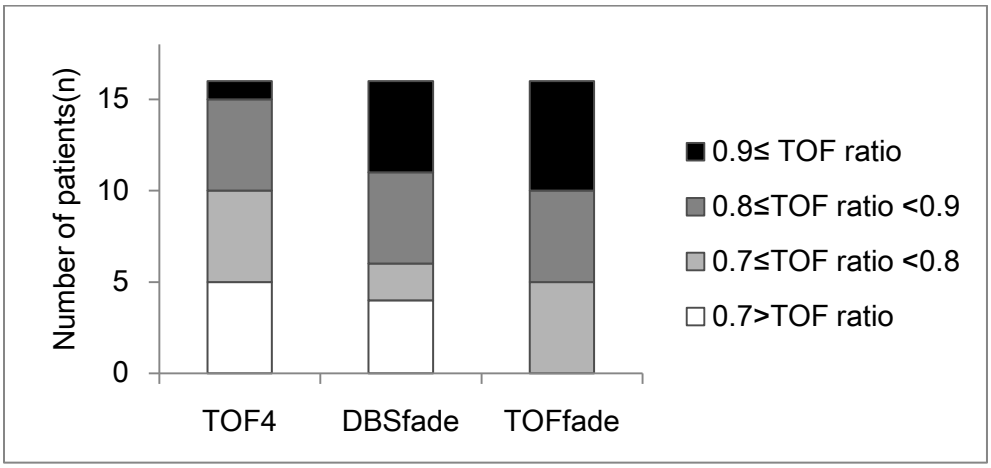
	Group TOF4 (N=16)	Group DBSfade (N=16)	Group TOFfade (N=16)
TOR 0.7	5.0 ± 2.2	4.4 ± 2.6	3.0 ± 1.2 *
TOR 0.8	7.3 ± 3.2	6.8 ± 5.0	4.4 ± 1.8
TOR 0.9	12.6 ± 6.2	10.1 ± 8.0	9.1 ± 6.8

*p<0.05, compared to group TOF4, numbers are mean ± standard deviation. TOF : train-of-four

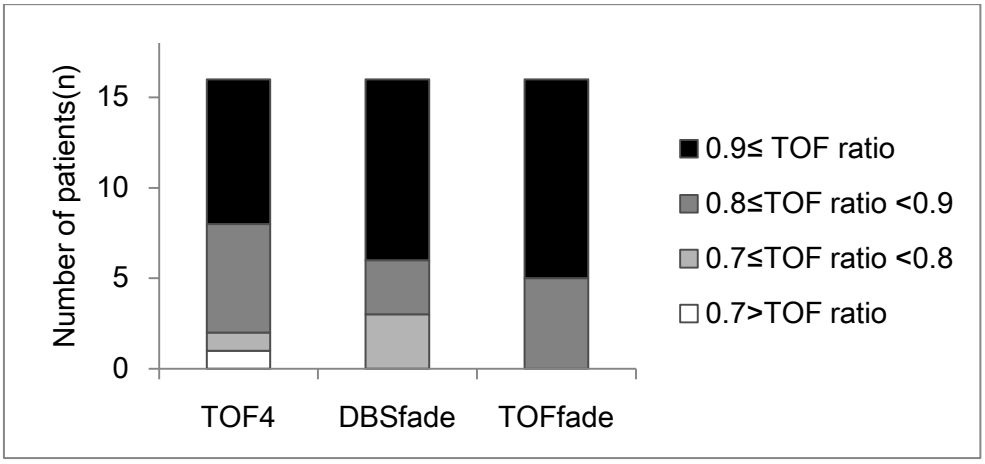
TOR : TOF ratio

Figure 6. Degree of antagonism at 5, 10, and 15 min after neostigmine administration.

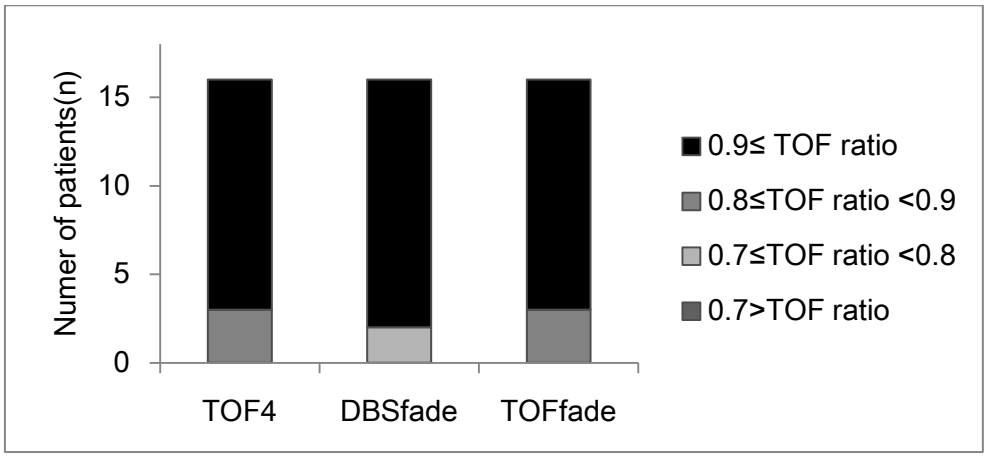
A. Degree of antagonism at 5 min after neostigmine administration.



B. Degree of antagonism at 10 min after neostigmine administration.



C. Degree of antagonism at 15 min after neostigmine administration.



Group TOF4 patients reversed at reappearance of the fourth tactile train-of-four (TOF) response, group DBSfade patients reversed at absence of fade to Double-burst-stimulation (DBS), group TOFfade patients reversed at absence of fade to TOF stimulations.

Discussion

A TOF ratio of 0.7 is considered to represent adequate recovery from a non-depolarizing neuromuscular blockade; however, a recent study by Murphy et al. [12] suggested that a TOF ratio of 0.7 is insufficient to prevent critical complications of residual paralysis in post-anesthesia care units. The hypoxic ventilatory response decreased at a TOF ratio of 0.7 in healthy volunteers without anesthesia [1]. Awake volunteers experienced upper airway obstruction at TOF ratios of 0.8 [13]. Moreover, with TOF ratios of less than 0.9, healthy volunteers experienced pharyngeal dysfunction with aspiration [14]. Therefore, TOF ratios of 0.9 were recommended for increasing safety in post-anesthesia care units. The results of our study revealed that the reversal of neuromuscular block caused by cisatracurium via the administration of neostigmine at the time of tactile fourth responses of TOF, absence of TOF or DBS fade can be reliable methods for achieving acceptable recovery (TOF ratio >0.9) within a reasonable time.

Kirkegaard et al. [10] demonstrated that the administration of neostigmine at the reappearance of tactile responses one to three to TOF stimulations could not ensure that reversal of neuromuscular block of cisatracurium achieved TOF ratios of 0.7 in 10 min. In contrast, our results indicated that all patients in TOFfade group achieved a TOF ratio of 0.7 within 5 min. At 10 min after the reversal of the neuromuscular blockade, 87.5% (n=14), 81.3%, (n=13), 100% (n=16) of patients in the TOF4,

DBSfade, and TOFfade groups, respectively, had a TOF ratio greater 0.8, whereas a TOF ratio greater than 0.9 was achieved in only 50%, 62.5%, and 68.7% of the TOF4, DBSfade, and TOFfade groups, respectively. At 15 min after the reversal, the majority (over 81%) of the patients in the three groups had a TOF ratio greater than 0.9.

The results were similar among three groups; however, it may be preferable to inject neostigmine at the fourth twitch to TOF stimulations or at the disappearance of fade to DBS because the time from the injection of cisatracurium to the injection of neostigmine in the TOFfade group was greater compared with that of the other two groups with respect to saving time.

If we regulated the level of neuromuscular block to be indicated by fourth tactile TOF responses or lack of fade to TOF stimulation or DBS up to the end of the surgery, the best strategy would be to reverse the neuromuscular block at the end of the surgery. However, anesthesiologists often encountered situations in which a high level of neuromuscular block remained when the surgery had already ended. The anesthesiologist is then faced with two choices: reverse with neostigmine first or wait for the neuromuscular block to spontaneously lower and then reverse with neostigmine. Bevan et al. [13] reported that earlier reversal induced recovery from a neuromuscular block with recuronium and vecuronium to a TOF ratio of 0.7 significantly faster; in contrast, earlier reversal had no effect on the time to achieve a TOF ratio of 0.9. Moreover, we found a similar result in that an early or late

injection of acetylcholinesterase inhibitors did not affect the time from injection of cisatracurium to recovery to a TOF ratio of 0.9 in the three groups. However, when there were only one to three twitches to TOF stimulations at the end of the operation, waiting until four TOF responses present or DBS disappears is a better strategy because it is a more predictable way to shorten the time from the administration of the reversal drug to recovery to a TOF ratio of 0.9.

Within a certain range, the effect of reversal depends on the dose. Anticholinesterase agents, including neostigmine, exhibit a ceiling effect [16]. In general, there was no additional benefit in administering doses exceeding 0.07 mg/kg of neostigmine; therefore, we chose that dose for our study.

Our study has limitations. There was a significant difference between the time from reversal with neostigmine to achieving TOF ratios of 0.7 in the TOFfade and TOF4 groups. However, there were no significant differences among the three groups with regard to the time from reversal to achieving TOF ratios of 0.8 and 0.9 or with regard to the number of patients achieving TOF ratios greater than 0.7, 0.8, and 0.9 at 5 min, 10 min, 15 min, and 20 min. These results may be attributed to the fact that the control TOF ratio in patients at the absence of the DBS fade is not different compared with the control TOF ratio at the absence of the TOF fade (0.38±0.16 versus 0.29±0.07). A previous study by Capron et al. [17] indicated that mechanomyographic TOF ratios of the thresholds of fade to DBS and TOF were 0.76±0.11 and 0.31± 0.15, respectively. The acceleromyographic TOF ratio of

threshold of fade to DBS in our study is smaller than values from previous reports. This difference was attributed to the subjectivity of DBS fade detection or to differences between the acceleromyographic and mechanomyographic data. In addition, small two twitches may have been caused by high resistance of the skin that was confused with a lack of fade to DBS.

The other limitation was the difference in the degree of antagonism at 10 min after a neostigmine injection between our study data with that from the study by Kirkegaard et al. [10]. Our data demonstrated that reversal at the fourth twitch to TOF stimulation was more efficient than that of Kirkegaard et al. [10]. One reason for this finding is that we used acceleromyographic TOF ratios instead of mechanomyographic TOF ratios. Mechanomyography has been considered the 'gold standard' for the quantification of neuromuscular block for many years [8]. However, the method is infrequently used, and mechanomyographic monitors are no longer manufactured. The acceleromyographic method has been compared with the mechanomyographic and electromyographic methods, and it is well documented that these methods cannot be used interchangeably [11, 18-20]. The acceleromyographic TOF ratio is often above 1.0 and slightly higher than the TOF ratio obtained with mechanomyography [18, 19]. Therefore, it has been suggested that the final TOF ratio should be normalized to the control TOF ratio to improve the accuracy of acceleromyography-derived recovery data [18, 20]. A previous study [18] reported that there were no significant differences between TOF ratios

obtained with mechanomyography and those obtained with acceleromyography after normalization. The times from reversal to achieving TOF ratios of 0.8 and 0.9 obtained with acceleromyography in our study were not significantly different from the data obtained before and after normalization, whereas the time from reversal to achieving a TOF ratio of 0.7 was significantly different ($p=0.01$). Another reason could be demographic differences; our patients were much thinner and healthier. In addition, we can consider racial differences.

In conclusion, it may be more preferable to administer neostigmine at the fourth tactile response to TOF or the disappearance of the fade to DBS to recover from a cisatracurium-induced neuromuscular block to achieve a TOF ratio of 0.9 or more within a reasonable time.

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요약 (국문초록)

배경 : Neostigmine의 최대 효과는 근이완제 역전 후 10-20분 후에 나타난다. 이 기간 안에 cisatracurium에 의한 적절한 근이완의 역전 수준까지 도달하기 위한 neostigmine의 투여 시점을 알아보고자 한다.

방법 : 전향적 무작위 배정 임상 연구로 계획하였고 만성중이염 치료를 위한 수술을 받는 48명의 성인을 대상으로 하였다. 전신마취는 propofol과 remifentanil로 전정맥마취를 목표농도조절주입펌프를 이용하여 시행하였고, TOF-Watch SX® 과 기존의 신경자극기를 각각 양팔에 부착하고 TOF-Watch SX® 를 부착한 팔은 관찰자가 볼 수 없도록 가리개가 장착한 상태로 기저 TOF 비가 12초 간격으로 컴퓨터 프로그램을 통해 자동적으로 수집하였고 다른 팔은 신경자극기로 train-of-four (TOF) 또는 double-burst-stimulation (DBS) 자극한 후에 촉진하였다. 0.15mg/kg 의 cisatracurium을 마취 유도시에 투여하였고 TOF 4 군은 TOF 자극시 4번째 자극에 대한 반응이 있을 경우, DBSfade 군은 DBS에 대한 자극의 fade가 사라진 순간, TOFfade 군은 TOF에 대한 자극의 fade가 사라진 순간에 neostigmine 0.07mg/kg를 투여하였다. Neostigmine 투여후부터 TOF 비가 0.7, 0.8, 그리고 0.9가 되는 시간을 각각 측정하였다.

결과: Neostigmine 투여후부터 TOF 비가 0.9가 되는 시간은 12.6 ± 6.2, 10.1 ± 8.0, 그리고 9.1 ± 6.8분 (TOF4군, DBSfade군, 그리고 TOFfade 군) 이었다. Neostigmine 투여후 10분에 TOF 비가 0.9이상이었던 환자는 50%, 63%, 그리고 69% 였고 근이완 역전제 투여 15분 후에는 81.3%, 87.5%, 그리고 81.3%였으며 각 군 간의 유의미한 통계학적인 차이는 없었다. Cisatracurium 투여 후 neostigmine 투여까지의 시간은 TOFfade군(69.3 ± 8.3 분)에서 TOF4군과 DBSfade군 (61.0 ± 8.3, 61.0 ± 7.3) 보다 유의미하게 길었다. (p=0.006).

결론: 결론적으로 적절한 시간 안에 TOF비 0.9이상 근이완을 역전하기 위해서는 TOF 자극시 4번 촉지될 때 또는 DBS시 fade가 사라진 순간 neostigmine을 투여하는 것을 추천한다.

주요어: Cisatracurium, Neostigmine

학번 : 2010-23691

감사의 글

논문을 마치고 나니 남들보다 다소 늦게 시작한 석사 과정 동안의 대학원 생활이 떠오릅니다. 대학원 생활 동안 많은 고민에 부딪혔고 지치기도 하였지만, 여러분의 도움 덕분에 이렇게 하나의 결실을 맺을 수 있었습니다.

초반에 많은 시행착오를 겪을 때마다 다시 연구에 매진할 수 있도록 이끌어주신 평생 은사 오아영 교수님께 진심으로 감사 드립니다. 교수님의 아낌 없는 지원과 소중한 가르침 덕분에 부족한 제가 본 연구의 초석을 다지고 어려움에 부딪힐 때마다 정진할 수 있는 기회를 얻을 수 있었습니다.

바쁘신 와중에도 저의 논문 심사를 맡아주시고, 저의 학문적인 깨우침 뿐 아니라 배움에 대해 노력하는 자세, 학자로서의 자세에 대해 모범을 보이시고 부족한 저를 한결 같이 소중하고 세심한 지도로 이끌어주시고 계시는 황정원 교수님께 깊은 감사의 말씀을 드립니다. 또한 바쁘신 가운데 저의 부족한 논문을 수정할 수 있도록 아낌 없는 조언을 해주시고 늘 수술장에서 훌륭한 수술자으로서 뵙고 있는 김정훈 교수님께도 깊은 감사의 말씀을 드립니다.

연구 기간 동안 늘 저의 연구에 관심을 가져주시고 이 논문이 나올

수 있도록 아낌 없이 지원해 주셨으며 평소 걸출한 연구와 교육열, 진료 다방면에서 모범을 보여주시며 몸소 지도해주신 도상환 과장님께도 감사의 마음을 전하고 싶습니다. 석사 과정 동안에 물심양면 지원해 주시고 저의 잘못을 지적해주시어 더 나은 인간으로 성장하는데 밑거름이 되도록 해 주셨으며 늘 대학원 학생들이 정진할 수 있도록 격려해주시는 김진희 교수님께도 감사의 마음을 전하고 싶습니다.

제가 연구와 진료를 병행하면서 어려움을 겪을 때 상담해 주시고 힘이 되어 주신 전영태 교수님, 대학원 생활 동안 통증 분야에 대한 가르침을 주신 이평복 교수님, 수혈 분야에 대해 가르침을 주시고 바쁘신 와중에 학생 지도와 연구에서 늘 성실하고 세심한 모습으로 모범이 되어 주신 한성희 교수님, 중환자실에서의 진료와 연구에 아낌없는 지원을 해주시는 박상헌 교수님, 통계를 비롯하여 많은 가르침을 주시며 저희 집안 통증 주치의인 남상건 교수님, 저의 연구에 관심을 가져주시고 제가 활발히 연구할 수 있도록 늘 배려해주시며 병원 생활 전반에 걸쳐 챙겨주시고 도움을 주신 유정희 교수님께도 감사의 마음을 전합니다. 이 자리를 빌어 펠로우 때부터 연구 및 진료 전반에서 많은 도움을 주셨으며 고락을 함께 했던 현재는 미국에서 연수 중인 나효석 교수님께도 감사 드립니다. 또한 연구원으로서 늘 동생같이 챙겨주고 힘이 되어준 이윤서

연구원에게도 감사 드립니다.

석사 과정 동안 늘 심적으로 물적으로 지원을 아끼지 않으며 같이 기뻐해주신 양가 부모님, 시할머님과 아가씨에게도 감사 드리며, 마지막으로 같이 박사과정을 마무리하면서 스트레스도 많고 힘들었을 텐데 늘 곁에서 묵묵히 정성 어린 지원을 아끼지 않으며 사랑해 준 남편에게 감사를 드립니다.