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**REVERSAL OF VECURONIUM WITH NEOSTIGMINE :
A COMPARISON BETWEEN MALE AND FEMALE PATIENTS**

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Abstract : We investigated the differences between males and females in the reversal effect of neostigmine on neuromuscular blockade. Thirty male and 30 female patients undergoing elective general anesthesia were studied. Vecuronium was given in all patients anesthetized with nitrous oxide, oxygen, and sevoflurane. After the surgical procedure, when T1 (1st response in train-of-four (TOF))/control returned to 0.25, neostigmine 40 $\mu\text{g}/\text{kg}$ in combination with atropine 20 $\mu\text{g}/\text{kg}$ was given to antagonize residual neuromuscular blockade. Three, six, nine, 12, and 15 minutes after neostigmine reversal, T1/control or TOF ratio (T4/T1) did not significantly differ between the sexes. Also, 15 minutes after neostigmine administration, the number of patients in whom recovery from neuromuscular blockade was sufficient to guarantee good respiratory function, i.e., TOF ratio >0.74 , did not significantly differ between the sexes. In contrast, 15 minutes after neostigmine, the number of patients in whom recovery from neuromuscular blockade was adequate to ensure satisfactory recovery from neuromuscular blockade including the return of the faculty of sight, i.e., TOF ratio >0.9 , was significantly less in the males than in females (6 vs 14, $P=0.028$). In conclusion, 15 min after neostigmine, TOF ratio less often returns to a value of more than 0.9 in males than in females.

Key words : gender, vecuronium, neostigmine

INTRODUCTION

It has been shown that female patients are more sensitive to non-depolarizing neuromuscular blocking drugs than male patients¹⁻³⁾. Additionally, the duration of

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neuromuscular blockade caused by vecuronium or rocuronium was longer in women than in men^{1,2,4}). These findings are possibly related to the differences in body composition, distribution volume, and plasma protein concentration between the sexes⁵⁻⁷). Men have a greater percentage of muscle mass and lower percentage of fat than do women⁵). The volume of distribution is also greater in men⁶). The pharmacological effect of a drug is highly dependent on the degree of plasma protein binding. It was noted that the protein-bound fraction of vecuronium was 30%⁷), and that the concentration of plasma protein was lower in women than in men, which made women more sensitive to neuromuscular blocking drugs^{1,2}). As the percentage of muscle or fat, the distribution of volume, and the plasma protein concentration differ between men and women, the reversal effect of anticholinesterase on neuromuscular blockade may also differ between the sexes. However, no previous study has investigated the influences of gender on the anticholinesterase-induced reversal effect on neuromuscular blockade. The purpose of this study was to evaluate the difference in the reversal effect of neostigmine on vecuronium-induced neuromuscular blockade between males and females.

MATERIAL AND METHODS

The protocol of this study was approved by the local ethics committee. Written informed consent was obtained from each patient. Thirty adult male and 30 adult female patients, American Society of Anesthesiologists (ASA) physical status I-II, were allocated to the male group and female group, respectively. The patients were scheduled for elective surgery (simple or total mastectomy), orthopedic surgery (total knee replacement or total shoulder arthroplasty), ear nose and throat surgery (tympanoplasty), ophthalmologic surgery (segmental buckling or vitrectomy) lasting 2-4 hours, under general anesthesia. No patient had neuromuscular, hepatic, renal, metabolic, or cardiac disorders, or was receiving any drugs known to affect the action of neuromuscular blocking drugs.

Patients received diazepam 5-10 mg orally one hour before induction of anesthesia. After arriving at the operating room, in each patient, two stimulating electrodes were positioned over the ulnar nerve at the wrist. Also, two recording electrodes were placed over the adductor pollicis muscle. Anesthesia was induced with propofol 1.5 mg/kg and fentanyl 2 μ g/kg. After loss of the eyelid reflex, train-of-four (TOF) stimuli were delivered every 20 seconds using an electrical nerve stimulator of an anesthetic monitoring system (AS/3 Compact Monitor, Datex-Ohmeda Inc., Helsinki, Finland). Four single twitch stimuli consisting of 0.2 milliseconds duration square-waves were given at two Hz. The corresponding electromyographic amplitudes were quantified using the anesthetic monitoring system, and were displayed on the anesthetic monitoring system. The amplitudes of the electromyographic responses were recorded from the anesthetic monitoring system. In each patient, the monitoring system searched for the stimulus current

needed to achieve the maximal response of the adductor pollicis muscle automatically. The search began with 10 mA single twitch stimuli of 0.2 milliseconds-duration applied every one second, and the electromyographic response was measured. The stimulating current was increased in steps of 5 mA until the increase in current did not increase the electromyographic response. The stimulating current was then automatically increased by 15%, to produce a supramaximal stimulating current. If the supramaximal stimulating current was not found or the response was too weak to determine the current, the current was set at 70 mA. The supramaximal stimulating currents were compared between the two groups.

Once the supramaximal stimulating current had been established, the electromyographic amplitude of T1 was considered to be the control value. The control value was again determined 10 minutes after starting TOF stimuli, which were applied every 20 seconds, as was recommended previously⁸⁾. During the stabilization of neuromuscular monitoring, the patients' lungs were ventilated using a facemask with oxygen 6 L/minutes and sevoflurane 2% of inspired concentration. After recording the control value, vecuronium 0.1 mg/kg was administered intravenously to facilitate tracheal intubation.

After vecuronium, TOF stimuli were delivered every 20 seconds. In all patients, anesthesia was maintained with nitrous oxide 66% in oxygen and sevoflurane 1.7% of end-tidal concentration. When the depth of anesthesia was thought to be insufficient, a bolus dose of fentanyl 2 μ g/kg was administered. The lungs were ventilated to maintain normocapnia ($P_{ET}CO_2$ 32-38 mmHg). The end-tidal concentrations of anesthetic and $P_{ET}CO_2$ were measured continuously using a multiple gas monitor belonging to the anesthetic machine. During the surgical procedure, bolus doses of vecuronium 0.01-0.02 mg/kg were administered to maintain T1/control at less than 0.25. At the end of the surgical procedure, the administration of nitrous oxide and sevoflurane was stopped, and the lungs were ventilated with oxygen 6 L/min. When T1/control reached 0.25, a bolus dose of neostigmine 40 μ g/kg in combination with atropine 20 μ g/kg was administered. T1/control or TOF ratio measured three, six, nine, 12, and 15 minutes after the administration of neostigmine were compared between the two groups. Rectal temperature and surface skin temperature over the adductor pollicis muscle were monitored in each patient throughout the anesthetic management.

Patient characteristics, body mass index, supramaximal stimulating current, total dose of vecuronium, total dose of vecuronium/body weight, end-tidal concentration of sevoflurane at the time of neostigmine administration, and duration of surgery were compared between the two groups.

After tracheal extubation, we examined whether the patients were able to follow commands to open their eyes and squeeze the investigator's hand, and whether the patients showed clinical signs of impaired breathing, such as deficiencies in coordination, the use of auxiliary respiratory muscles, or signs of airway obstruction.

All results are expressed as number or mean \pm SD (range). Patient characteristics, body mass index, supramaximal stimulating current, total dose of vecuronium, total dose of vecuronium/body weight, end-tidal concentration of sevoflurane at the time of neostigmine administration, and duration of surgery were compared between the two groups using unpaired t-test. The comparison of T1/control or TOF ratio between the two groups at each time point was made using analysis of variance (ANOVA) followed by unpaired t-test with Bonferroni's adjustment. Fifteen minutes after neostigmine, the numbers of patients in whom TOF ratio was more than 0.74 or 0.9 were compared between the two groups using chi-square test. A P value < 0.05 was considered to be statistically significant. Statistical analyses were performed using a statistical package (SYSTAT 8.0, SPSS Inc., Chicago, U.S.A.) running on a personal computer.

RESULTS

As shown in Table 1, age, body mass index, end-tidal concentration of sevoflurane at the time of reversal, and duration of surgery did not significantly differ between the two groups. Total dose of vecuronium was significantly higher in the male group than in the female group; however, total dose of vecuronium/body weight did not significantly differ between the two groups. The end-tidal concentra-

Table 1. Patient characteristics, supramaximal stimulating current, total dose of vecuronium, total dose of vecuronium/body weight, end-tidal concentration of sevoflurane at the time of neostigmine administration, and duration of surgery in the two groups.

group	male ($n=30$)	female ($n=30$)	P
Age (years)	62 \pm 15	57 \pm 17	0.247
Height (cm)	164 \pm 8	153 \pm 7	< 0.001
Weight (kg)	62 \pm 13	53 \pm 7	0.001
Body mass index (kg/m ²)	23.2 \pm 4.2	22.5 \pm 3.10	0.490
Supramaximal stimulating current (mA)	45 \pm 10 (23-64)	33 \pm 8 (23-51)	< 0.001
Total dose of vecuronium (mg)	13.1 \pm 3.0	10.5 \pm 2.2	< 0.001
Total dose of vecuronium/body weight (mg/kg)	0.214 \pm 0.045	0.202 \pm 0.046	0.303
End-tidal concentration of sevoflurane (%) at the neostigmine administration	0.23 \pm 0.05	0.23 \pm 0.05	0.818
Duration of surgery (minutes)	183 \pm 31	169 \pm 30	0.081

Values are mean \pm SD (range). Age, body mass index, total dose of vecuronium/body weight, end-tidal concentration of sevoflurane at the neostigmine administration, and duration of surgery did not significantly differ between the two groups. Height, weight, supramaximal stimulating current and total dose of vecuronium in the male group were significantly higher than in the female group.

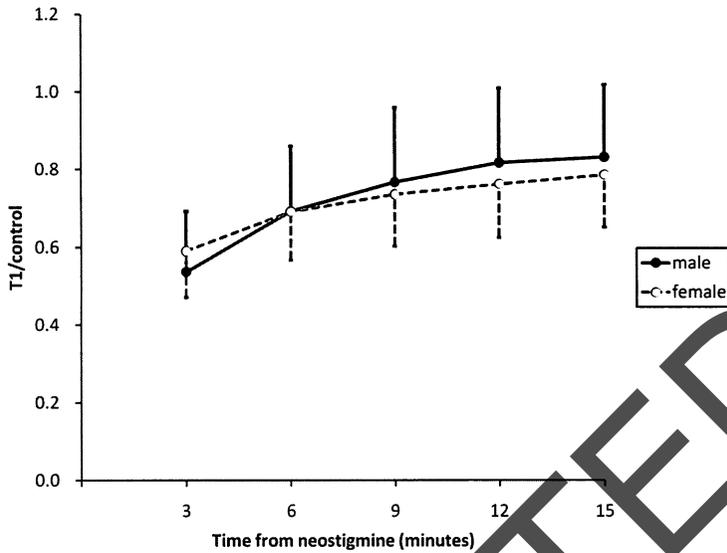


Fig.1. Recovery of T1/control after administration of neostigmine 40 $\mu\text{g}/\text{kg}$ in combination with atropine 20 $\mu\text{g}/\text{kg}$ in the male (●) and female (○) groups. Values are mean \pm SD. No significant difference was observed between the two groups.

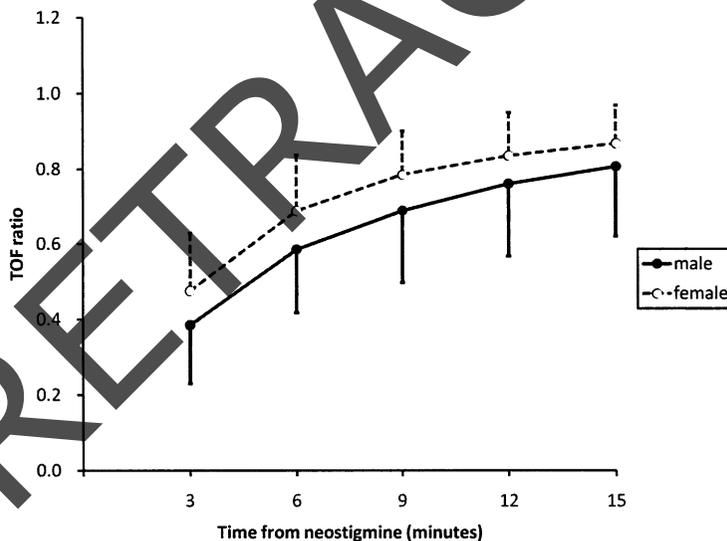


Fig.2. Recovery of TOF ratio after administration of neostigmine 40 $\mu\text{g}/\text{kg}$ in combination with atropine 20 $\mu\text{g}/\text{kg}$ in the male (●) and female (○) groups. Values are mean \pm SD. TOF=train-of-four. No significant difference was observed between the two groups.

tion of sevoflurane was less than 0.3% when neostigmine was given in all patients. In no patient did the rectal or surface temperature over the adductor pollicis decrease to less than 35.5 and 32.1°C, respectively. Height, weight, and supramax-

Table 2. Number of patients in whom recovery from neuromuscular blockade was sufficient to guarantee good respiratory function, i.e., TOF ratio > 0.74, and that in whom the faculty of sight was sufficient, i.e., TOF ratio > 0.9 in the two groups.

group	male (<i>n</i> =30)	female (<i>n</i> =30)	<i>P</i>
Number of patients in whom TOF ratio returned to a value of more than 0.74	22	27	0.095
Number of patients in whom TOF ratio returned to a value of more than 0.9	6	14	0.028

Values are number. TOF=train-of-four. Number of patients in whom TOF ratio was more than 0.74 did not significantly differ between the two groups, but that in whom TOF ratio was more than 0.9 was significantly less in the male group than in the female group.

imal stimulating current in the male group were significantly greater than in the female group.

Three, six, nine, 12, and 15 minutes after neostigmine, T1/control or TOF ratio did not significantly differ between the two groups (Fig. 1 and 2).

Fifteen minutes after neostigmine, TOF ratios were 0.81 ± 0.12 (0.50–0.98) and 0.87 ± 0.10 (0.65–1.04) in the male and female groups, respectively, and all patients were awake and alert with stable vital signs. The trachea was extubated uneventfully. After tracheal extubation, all patients were able to follow commands to open their eyes and squeeze the investigator's hand. The patients were given oxygen 3–5 L/minute via a face mask, and SpO₂ was more than 98% in all patients. No patient showed clinical signs of impaired breathing nor had difficulty in breathing.

As shown in Table 2, 15 minutes after neostigmine, the number of patients in whom TOF ratio was more than 0.74 was not significantly different between the two groups. In contrast, the number of patients in whom TOF ratio was > 0.9 in the male group was significantly smaller than that in the female group.

DISCUSSION

This study shows that after administration of neostigmine the time course of recovery of T1/control or TOF ratio does not differ between males and females receiving vecuronium. However, 15 minutes after neostigmine, the reversal effect of neostigmine on vecuronium-induced neuromuscular blockade is more often insufficient in males than in females.

Sample sizes in this study were determined in view of the data in our previous study, which assessed train-of-four ratio (TOF ratio, T4/T1) 15 minutes after neostigmine⁹. In the previous study, mean TOF ratio was approximately 0.8, with a standard deviation of about 0.1. In the current study we would like to be able to detect a difference of 10% or more in mean TOF ratio between the two groups.

Statistical analyses were performed considering an α of 5% and a power of 90%. Based on this, 28 patients were required per group. These statistical analyses were in accordance with those in a previous report¹⁰. From this viewpoint, 30 men and 30 women were enrolled in this study.

It has been reported that females are more sensitive to vecuronium^{1,3} and rocuronium^{2,4} than males. Also, the duration of neuromuscular blockade caused by vecuronium or rocuronium was longer in women than in men^{1,2,4}. The exact reasons for the difference in the sensitivity to neuromuscular blocking drugs and in the duration of neuromuscular blockade between the sexes are still unclear. However, the most likely factors are thought to include differences in body composition, distribution volume, and plasma protein concentration⁵⁻⁷. Men have a greater percentage of muscle mass and lower percentage of fat than do women⁵. A larger dose of neuromuscular blocking drug is needed when there is less fat and more muscle⁶. Xue *et al.*¹ and Semple *et al.*³ reported that when compared with men, woman required 30% and 22% less vecuronium to achieve the same degree of neuromuscular blockade, respectively. It has also been shown that women are approximately 30% more sensitive to rocuronium compared with men². Additionally, the volume of distribution is less in women⁶. A lower dose of muscle relaxant is required to produce a comparable neuromuscular blockade when the volume of distribution is decreased². Moreover, the pharmacological effect of a drug is highly dependent on the degree of plasma protein binding. Duvaldestin *et al.*⁷ showed that the protein-bound fraction of vecuronium was 30% and vecuronium was mainly bound to albumin. It was demonstrated that the concentrations of total plasma protein and albumin in women decreased by 8% and 14%, respectively, when compared with those in men². The decreases in the concentrations of total plasma protein and albumin result in an increase in unbound drug in the body, which makes more drugs available to the tissue and receptor sites in women.

It was previously shown that 15 minutes after neostigmine which was given at a T1/control of 0.25, TOF ratio narrowly returned to a value of 0.9¹¹⁻¹³. TOF ratio of 0.74 indicates recovery of respiratory function, i.e., vital capacity exceeding 15 to 20 ml/kg, as well as ability to open the eyes widely, protrude the tongue, cough, and sustain head raising for at least 5 seconds¹⁴. TOF ratio of 0.9 is related to satisfactory recovery from neuromuscular blockade including the return of the faculty of sight¹⁵. According to these previous findings, in the present study, the numbers of patients in whom TOF ratio was more than 0.74 or 0.9 were also compared 15 minutes after administration of neostigmine between the two groups.

In this study, there was no difference on the dose of vecuronium and neostigmine per body weight between the two groups. T1/control or TOF ratio did not significantly differ between males and females 3, 6, 9, 12, and 15 minutes after neostigmine. Also, 15 minutes after neostigmine, the number of patients in whom TOF ratio was more than 0.74 did not significantly differ between males and females. However, 15 minutes after neostigmine, the number of patients in whom TOF ratio

was more than 0.9 was significantly smaller in males than in females. Therefore, the reversal effect of neostigmine on vecuronium-induced neuromuscular blockade in men is considered to be inferior to that in women.

Pleym *et al.*¹⁶⁾ have described that the water content is smaller in females than in males. They also postulated that the volume of distribution for water-soluble drug such as neuromuscular relaxant might be lower in females than in males, and that the initial concentration of water-soluble drugs will be higher in females. This idea is thought to support the previous finding that the females are more sensitive to neuromuscular blocking agents. On the other hand, neostigmine has also been reported to be water-soluble^{17,18)}. Consequently, the females would be more sensitive to neostigmine, too. For these reasons, recovery of neuromuscular blockade would have been more sufficient in females than in males.

It has been recommended that anticholinesterase be given when T1/control returns to 0.25¹⁹⁻²¹⁾. Furthermore, it was demonstrated that if neostigmine 40 $\mu\text{g}/\text{kg}$ was given at a T1/control of 0.25, TOF ratio just barely returned to a value of 0.9, 15 minutes after neostigmine¹¹⁻¹³⁾. In addition, the antagonizing effect of neostigmine 40 $\mu\text{g}/\text{kg}$ on neuromuscular blockade was more effective than the dose of 20 or 80 $\mu\text{g}/\text{kg}$ ¹¹⁾. Based on these findings, in this study, neostigmine 40 $\mu\text{g}/\text{kg}$ was administered when T1/control returned to 0.25, and the monitoring of neuromuscular blockade was continued for 15 minutes after neostigmine.

In the present study, 15 minutes after neostigmine, TOF ratios ranged from 0.50 to 0.98 and from 0.65 to 1.04 in the male and female groups, respectively. Thus, the lowest TOF ratio measured 15 minutes after neostigmine was 0.50. A TOF ratio of 0.50, of course, indicates insufficient recovery from neuromuscular blockade. However, all patients were able to follow commands to open their eyes and squeeze the investigator's hand after tracheal extubation. Additionally, no patient showed clinical signs of impaired breathing nor had difficulty in breathing. Pedersen *et al.*²²⁾ reported that a hand grip could be maintained in some postoperative patients with TOF ratios as low as 0.25-0.4. Bissinger *et al.*²³⁾ also noted that no patient with TOF ratios of 0.37-1.00 showed clinical signs of impaired breathing. These findings may support the present results that a patient with a TOF ratio of 0.50 did not complain of loss of strength. Nevertheless, Kopman *et al.*¹⁵⁾ investigated the relationship between TOF ratio and clinical symptoms in awake healthy volunteers, and postulated that at TOF ratios < 0.75, all volunteers were uncomfortable. In their study, most volunteers reported that speaking required great effort and that swallowing was becoming difficult. In addition, most volunteers found it impossible to sip water through a straw because they could not maintain a tight seal with their lips. Eriksson *et al.*²⁴⁾ demonstrated that TOF ratios < 0.90 were associated with functional impairment of the muscles of the pharynx and upper esophagus and therefore a potentially decreased ability to protect the airway against regurgitation and aspiration. With regard to these findings, TOF ratios should be more than 0.90 in patients after extubation.

The administration of sevoflurane was stopped in this study before the neostigmine injection. It has been reported that antagonism of vecuronium-induced neuromuscular blockade by neostigmine is impaired during administration of sevoflurane or isoflurane, and that even if the administration of inhalation anesthetic is stopped at the time of reversal, the impairment is not eliminated²⁵. Then if sevoflurane was not used, the reversal effect of neostigmine might be further improved.

The present study showed that the supramaximal stimulating current was higher in men than in women. As the skin thickness increases, the supramaximal stimulating current for the monitoring of neuromuscular blockade becomes high²⁶. It was noted that skin thickness was greater in men than in women²⁷. With regard to this, it is not surprising that the supramaximal stimulating current is higher in men than in women.

In conclusion, when neostigmine 40 $\mu\text{g}/\text{kg}$ in combination with atropine 20 $\mu\text{g}/\text{kg}$ is given when T1/control returns to a value of 0.25, the time course of recovery of T1/control or TOF ratio does not differ between males and females receiving vecuronium. However, 15 minutes after neostigmine, TOF ratio less frequently returns to a value of more than 0.9 in males than in females.

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