

CLINICAL RESEARCH / KLİNİK ÇALIŞMA

THE EFFECT OF GENDER ON REVERSAL OF NONDEPOLARIZING BLOCK

NONDEPOLARİZAN BLOĞUN GERİ DÖNDÜRÜLMESİ ÜZERİNE CİNSİYETİN ETKİSİ

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SUMMARY

Introduction: We investigated the role of gender on the effect of neostigmine-antagonised nondepolarizing neuromuscular block.

Method: One hundred adult patients were enrolled in this study. The patients were divided into two groups as female group (n=50) and male group (n=50). Anesthesia induction was performed with propofol and fentanyl and maintained with desflurane inhalation to serve as a baseline, control TOF value (TOFc) was recorded and rocuronium 0.5 mg kg⁻¹ was injected thereafter. The duration of TOF value to reach zero (TOF-0) was recorded. Rocuronium injection was repeated in 1/4 of the initial dose when the TOF ratio recovered to 25% (TOF-25). Total rocuronium dose (TRmg), time interval between rocuronium administrations (TRt) and number of the total rocuronium administrations (TRs) were recorded. At the end of the operation, neostigmine and atropine were administered when TOF ratio reached to 25%, and the duration of the TOF ratio for rising from 25% to 90% (TOF25-90) was recorded. Protruding the tongue (TP) and to lift the head (HL) were also recorded after extubation.

Results: There were no differences between the demographic data and surgical duration of the groups. TOF-0 of the male group was longer than that of the female group (219.34 sec vs. 138.84 sec). In the male group TRt was shorter and TRs was higher (p<0.001). TOF25-90 of the male group was also found to be shorter than in the female group (p<0.05). Protruding the tongue and to lift the head were significantly lower in male patients.

Conclusion: Gender effects the antagonization speed of nondepolarizing neuromuscular block with neostigmine and nondepolarizing neuromuscular block recovers earlier in men than in woman.

KEY WORDS: Nondepolarizing block, Gender, Neuromuscular monitorization, Rocuronium, Neostigmine

ÖZET

Amaç: Cinsiyetin nondepolarizan bloğu geri döndürmek için verilen neostigminin etkisi üzerindeki rolünü araştırmayı amaçladık.

Yöntem: Genel anestezi uygulanacak 100 olgu çalışmaya dahil edildi. Kadın (n=50) ve erkek gruplarına (n=50) ayrılan olgulara propofol ve fentanyl ile anestezi induksiyonu yapıp desfluran inhalasyonu ile idame sağlandı. Kontrol TOF değeri kaydedilip 0.5 mg kg⁻¹ rocuronyum uygulandı. TOF değerinin sıfır (TOF-0) olmasına kadar geçen süre kaydedildi. TOF oranı %25 olduğunda, rocuronyum dozları ilk dozun 1/4'ü oranında tekrarlandı. Toplam rocuronyum miktarı (TRmg), tekrarlanma zamanı (TRt), rocuronyum tekrarlanma sayısı (TRs) kaydedildi. Neostigmin (40 mcg kg⁻¹) ve atropin (20 mcg kg⁻¹) verildikten sonra TOF değerinin %25'den %90 olmasına kadar geçen süre (TOF25-90) kaydedildi. Nöromusküler klinik değerlendirme amacıyla ekstübasyondan sonra baş kaldırma ve dil çıkarma testleri kaydedildi.

Bulgular: Gruplar arasında demografik özellikler ve cerrahi süreler açısından anlamlı farklılıklar yoktu. TOF-0 süresi erkek grubunda kadın grubuna göre uzun bulundu (219.34 sn'ye göre 138.84 sn). Erkek grubunda TRt daha kısa ve TRs daha fazlaydı (p<0.001). TOF25-90 erkek grubunda daha kısaydı (p<0.05). Baş kaldırma ve dil çıkarma testleri erkek grubunda anlam olarak kısaydı (p<0.05).

Sonuç: Neostigmin uygulandıktan sonra non depolarizan bloğun erkeklerde kadınlara göre daha erken geri döndüğü kanısına varıldı.

ANAHTAR KELİMELEER: Nondepolarizan blok, Cinsiyet, Nöromusküler monitörizasyon, Rocuronyum, Neostigmin

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INTRODUCTION

Muscle relaxants facilitate endotracheal intubation and surgical operations during general anesthesia, however postoperative residual curarization condition (PORC) due to inadequate antagonization of muscle relaxants can be observed postoperatively (1, 2). Respiratory failure caused by neuromuscular blokage was indicated as a frequently recorded factor increasing anesthetic morbidity (3). Routine monitoring of neuromuscular blockade and administration of anticholinesterase drugs when appropriate are suggested for prevention of PORC incidence (4, 5).

In recent years, it has been put forward that gender difference may affect pharmacokinetics and pharmacodynamics of anesthetic agents and neuromuscular blockers (6). Several studies examined the effects of gender on neuromuscular block related to rocuronium (7-10). However, we did not encounter any study on the role of gender difference on the reversal effect of neostigmine on rocuronium block.

We hypothesised that gender has an effect on the antagonization activity of neostigmine for rocuronium induced neuromuscular block. In order to test this hypothesis we have investigated the effect of gender on the antagonist action of neostigmine when used for rocuronium induced neuromuscular block.

MATERIALS AND METHODS

This randomized prospective study was carried out between 2011 and 2012 following the approval of Ethics Committee of Bulent Ecevit University (meeting no 2011/11, 17.03.2011).

The study included patients aged between 18-70 years and in ASA (American Society of Anesthesiologists) I-II physical status who were scheduled to have general anesthesia with neuromuscular blocking agent. The patients with egg and propofol allergy, BMI \geq 30 kg m⁻², having neurologic disorders and trauma history regarding the hand to be studied, drug utilization affecting neuromuscular blockade (anticonvulsant, aminoglycoside or polypeptide antibiotic etc.), renal, hepatic and metabolic dysfunction and difficult intubation possibility were excluded from the study. Moreover, pregnant patients and the patients whose Mallampati score \geq III were not included in the study.

After obtaining the written informed consent, 100 patients were included in the study. The female group of the study was named as Group F (n=50), and the male group was named as Group M (n=50). All patients were premedicated with midazolam of 0.07 mg kg⁻¹ (Dormicum®,

Roche, 5 mg mL⁻¹, France). Systolic and diastolic arterial blood pressures (SBP, DBP), heart rate (HR), peripheral oxygen saturation (SpO₂), adductor muscle and nasopharyngeal temperature of the patients were monitored and recorded throughout the operation. For neuromuscular conduction monitorization, TOF-WATCH® SX (Organon Teknika B V, Netherlands) device was utilized. After the skin preparation distal electrode (Neotrode® Neonatal ECG Electrode, USA) was placed on ulnar nerve trace which is 1 cm above the wrist joint. Proximal electrode was placed on the skin at 2-3 cm proximal to distal electrode. Through acceleration transducer was assembled to thumb and hand was fixed to operation table with a tape but thumb stayed free. Temperature probe was fixed to thenar part of the hand by a tape and all patients kepted warm for fixing the temperature of thenar part above 32 °C.

Before the induction, fluid replacement was initiated with 10 ml kg⁻¹ hr⁻¹ Ringer's solution. All intravenous fluids were kept within the room temperature. Anesthesia induction was carried out by 2 mg kg⁻¹ propofol (Propofol 1% Fresenius Kabi) and 1 µg kg⁻¹ fentanyl (Fentanyl citrate® 2ml 100⁻¹ µg). Anesthesia maintenance was provided with 6% desflurane inhalation. After loss of eyelash reflex, 3 control single twitch (0.1 Hz) stimulations were given with a peripheral nerve stimulator and response values were recorded. After that, rocuronium at a dose of 0.5 mg kg⁻¹ (Esmeron® 50 mg 5 mL⁻¹ N.V. Organon, Holland) was administered. The time span between rocuronium injection and TOF value reaching to zero (TOF 0) was defined as onset time and recorded. When TOF value became zero, the patients were intubated. Maintenance of anaesthesia in all cases was ensured through 50% O₂/N₂O and 6% desflurane. When TOF ratio reached to 25% (TOF 25) rocuronium during maintaince during maintaince anesthesia 1/4 the of the induction dose was repeated. At each repeat, TOF25 duration was recorded. Total rocuronium dose (TRmg), total number of rocuronium injections (TR_s) and, the first repeat time of rocuronium after induction (TR_i) were recorded. At the end of the operation when the TOF value reached to 25%, both groups were administered neostigmine (40 µg kg⁻¹) and atropine (0.02 µg kg⁻¹) intravenously. After application of neostigmine and atropine, the duration that elapsed between TOF 25 and TOF 90 was recorded as recovery time (TOF25-90). When TOF value reached to 90%, desflurane inhalation was terminated. When the patient was ready for extubation (respiratory frequency >8 min⁻¹, ETCO₂<50 mmHg, SpO₂>90%), the duration between TOF90 and extubation was recorded as extubation time

(E_i). After extubation, both groups had Neuromuscular Clinical Evaluation Test (NCET) in order to evaluate the antagonism of neuromuscular block. NCET involved asking the patients to protrude their tongues (TP) and to lift their heads (HL) within the 15 minutes after extubation. The times when the patients could carry out these instructions were also recorded.

Statistical Analysis

In statistical analysis of the data, SPSS 13.0 package program was used. Categorical variables were given together with frequency/percentage, mean measurement variables and standard deviation. Compatibility of measurement variables to normal distribution was tested by means of Shapiro Wilk test. For groups comparison Mann Whitney U test was used. The difference between the measurements of two variables without normal distribution in different periods was examined through Wilcoxon Test. In group comparisons of categorical variables, Pearson chi-square and Fisher chi square tests were used. Relationship between measurement variables was examined through correlation analysis.

Power analysis of the study was calculated by G-power 3.0.8 programme. The power of our study was determined as 0.841 (%84.1) when effect size and subject numbers in both groups were taken into consideration. In all statistical analysis of the study, the comparisons in

RESULTS

There was no statistically significant difference between groups in terms of surgical duration and demographical data (Table I).

There was no significant difference between female and male groups according to control values of single twitch (Stwitch_c) and train of four (TOF_c) values (Table II).

The TOF₀ value of the male group was longer than that of the female group, whereas TOF₂₅ value of male group was shorter ($p<0.05$) (Table III). Also rocuronium repetition time (TR_i) of the male group was shorter than that of the female group so that rocuronium doses were repeated more in the male ($p<0.05$) (Table III). There was no statistically significant difference between the groups in terms of TOF number (TOF_s), but in the male group, TOF₂₅₋₉₀ was shorter than that of the female group ($p<0.05$) (Table III). There was no difference between the extubation duration (E_i) and BMI values of the groups (Table III).

Postoperatively TP and HL times were shorter in the male group in comparison with the female group ($p<0.05$) (Table III). After extubation, 40% of the female patients were not able to protrude their tongues ($n=20$), whereas in male group, this percentage was 12% ($n=6$). At the same measurement time 66% of female patients ($n=33$) and 28% of male patients ($n=14$) could not lift their heads for 5 seconds (Table IV).

Table I. Comparison of demographical features and surgical duration of groups (Mean±SD)

	Group M (n=50)	Group F (n=50)	p
Age (year)	38.84±12.73	41.56±11.81	0.35
Length (cm)	175.52±6.24	163.72±5.13	0.27
Weight (kg)	77.68±9.72	67.90±10.20	0.43
BMI (kg m ⁻²)	24.68±2.87	24.86±3.52	0.64
Surgical duration (min)	53.30±50.45	47.70±54.11	0.33

Group F: Female Group; Group M: Male Group; BMI: Body Mass Index

Table II. Control values of Single Twitch (Stwitch_k) and Train of Four (TOF_k) of groups (Mean±SD)

	Group M	Group F	p
Stwitch _{k_1}	85.04±24.35	79.18±38.60	0.98
Stwitch _{k_2}	84.90±24.82	80.65±33.06	0.86
Stwitch _{k_3}	86.65±25.76	77.98±34.27	0.34
TOF _{k_1}	105.63±10.95	103.50±19.57	0.41
TOF _{k_2}	104.96±19.57	101.38±21.24	0.39
TOF _{k_3}	99.50±16.16	101.17±25.05	0.74

Group F: Female Group; Group M: Male Group; TOF: Train of Four; Stwitch: Single Twitch

which $p<0.05$ were accepted as statistically significant.

Table III. Comparison of the groups in terms of TOF values, TRt, TRs, Et, TP and HL (mean± SD)

	Group M	Group F	p
TOF 0 (sec)	219.34 ± 89.82	138.84 ± 61.08	<0.001
TOF25 (min)	44.18 ± 11.72	61.73 ± 22.46	<0.001
TRt (min)	44.18 ± 11.72	61.73 ± 22.46	<0.001
TOF number (TOF _s)	20.24 ± 6.30	21.32 ± 6.39	0.464
TR _s	3.23 ± 0.93	2.68 ± 1.21	<0.001
TOF ₂₅₋₉₀ (sec)	215.56 ± 127.91	275.32 ± 148.55	0.02
E _t (sec)	151 ± 199.0 (min-max= 10-600)	126 ± 136.23 (min-max= 10-610)	0.465
TP (min)	3.36 ± 0.98	3.90 ± 1.71	0.004
HL (min)	4.20 ± 1.70	4.90 ± 2.15	0.005

Group F: Female Group; Group M: Male Group; TOF: Train of Four; TRt: The first rocuronium repetition time after induction; TRs: Repetition number of rocuronium; Et: Extubation duration; TP: Tongue protrusion; HL: Head lifting

Table IV. The results of neuromuscular clinical evaluation by time in groups (TP and HL)

	TP					HL				
Min	3	6	9	12	15	3	6	9	12	15
Group F (n=50)	30	48	50	50	50	17	43	50	50	50
Group M (n=50)	44*	50	50	50	50	36*	49*	49	50	50
P	0.001	0.247	1	1	1	<0.001	0.030	0.500	1	1

Group F: Female Group; Group M: Male Group; n: number of patients; TP: tongue protrusion; HL: head lifting; min: minute

*: p<0.05; Between Group F and Group M; Chi Square Test.

DISCUSSION

In this study, neostigmine is used to antagonize the neuromuscular block of rocuronium and it is found out that in the male group TOF0 duration was longer, rocuronium repetition duration and TOF25-90 were shorter and, postoperatively they could protrude their tongues and lift their heads earlier. Moreover, there was no significant correlation between BMI and TOF25-90.

There are evidences that pharmacokinetic and pharmacodynamic effects of anesthetics and neuromuscular blocking agents differ according to gender (11-14). In many studies about the effects of neuromuscular blocking agents on gender, it was indicated that female patients in general are 20-30 % more sensitive to the effects of neuromuscular blocking agents (11-14). The shorter onset time (TOF0) required for maximum muscle relaxation and longer recovery time for the reversal of the block supports this fact in females.

Adamus et al. (9) showed that after 0.6 mg kg⁻¹ of rocuronium, TOF0 was shorter (91.7±14.3 sec vs. 108.0±14.6 sec) and clinical duration (TOF25) was longer (43.3±7.8 min vs. 31.3±5.5 min.) in female group. However they found no difference between males and

females according to recovery index ((14.8±4 min vs. 14.7±5min). Mencke et al. (7) found out that after 0.45 mg kg⁻¹ rocuronium, TOF0 duration was shorter (168±65 sec vs. 211±56 sec) and TOF25 was longer in females and they observed that there was no difference in recovery index (9±4min vs. 9±3 min). In our study, after 0.5 mg kg⁻¹ i.v rocuronium we found out that TOF0 duration was shorter (138.84 sec vs. 219.34 sec) and TOF25 duration was longer in females (61.73 min. and 44.18 min) (p<0.05). These results are in accordance with the previous studies. However, we determined that TOF25-90 value of the females (275.2 sec.) was longer when compared to that of males (215.56 sec.) (p<0.05). Duration of neuromuscular block may change depending on inhalational anesthetic, ambient temperature and mean age of the patients (15, 16). The reasons of the differences between the results of our study and other studies may include different anesthesia methods, different doses of rocuronium used in induction, preferred intravenous or inhalational anesthetics, different ambient temperature and operation durations.

Adamus et al. (10) conducted another study with rocuronium which showed that TOF0 was shortest in

young females (75 sec) and longest in elder males (135 sec) and TOF25 was shortest in young males (30 min) and longest in elder females (85 min). In the same study, TOF90 duration was shorter in young males when compared to young females (59 min vs. 76 min) and that in elder males it was shorter when compared to elder females (102 min vs. 128 min). This study points out that age has a significant effect on rocuronium block, especially in females.

In females, distribution volume of rocuronium is lower due to high fat rate, low muscle ratio and low body water percentage (11, 16). Moreover, in females total protein and albumine levels are low. These factors may cause an increase in plasma concentration of rocuronium. Rocuronium breakdown and elimination may differ according to gender. Liver microsomal enzymes activate differently according to gender, drugs metabolized in liver break down more expeditiously in males (17). In females, glomerular filtration and renal clearance are low (18). Thus, it is thought that rocuronium elimination is slow in females.

Tsai et al. (5) studied postoperative residual curarization (PORC) rates and they put forward that in females PORC rate (38%) was higher than that of males (22%). Debaene et al. (19), evaluated residual block without giving reversal agent in recovery room after various muscle relaxants in single intubation doses. They observed that PORC incidence in males and females were 60% and 36% respectively when assuming the paralysis threshold TOF rate as 0.90 (19). Moreover in the same study, lifting head test and tongue protrusion test failed in 51 (15%) and 35 (11%), respectively. Although TOF rate was higher than 0.90, 24 patients could not lift their heads and 16 patients failed tongue depressor test in the same study (19). In our study, while TOF rate is higher than 0.90, 26% of the patients extubated could not protrude the tongue and 47% could not lift their head before 6th minute, so our results have similarity with the results of this study.

In order to minimize the effects of PORC to shorten the time spent in the operating room and to minimize cost, it is especially suggested that an antagonist agent such as neostigmine should be used to eliminate the neuromuscular block at the end of the operation (20). Saitoh et al. (21) examined the effect of gender on reversal activity of neostigmine in vecuronium block. They found out that fifteen minutes after neostigmine, enough recovery was observed in both groups, but there

was a delay in progression of TOF rate higher than 90 % in male patients when compared with females. They related this result to the lower distribution volume, lower albumine level and lower body water percentage of females which may increase the plasma levels of neostigmine. In our study, with TP and HL tests we indicated that the males recovered earlier at 6th minute after extubation when compared with females. If we add the durations of TOF25-90 and Et to the six minute after extubation, we may consider that our TP and HL tests nearly took place in a time closer to measurement time of Saitoh et al. which was 15th minute after extubation (21). This means that our result is controversial with the finding of Saitoh et al. but there are studies supporting our findings (6, 22, 23). In our study, we did not want to continue monitoring TOF, as TOF stimulation would be painful in awake patients. Therefore, we do not have certain findings about the exceeding of TOF rate beyond 90%, which may be another limitation of our study.

In our study, TP and HL results made us consider that females recover later than males and different muscle groups display different levels of sensitivity to the effects rocuronium (8,13). In addition, the longer TOF25-90 duration after neostigmine in females may indicate that the reversal effect of neostigmine appear later in females. We may explain this situation with the higher sensitivity of females to the neuromuscular blocking agents and the difference in muscle masses of the genders (8, 9, 10).

Duration action of the neuromuscular blocking agents, preferred inhalational anesthetics, peroperative temperature, electrolyte and acid base changes and mean age of the patients affect peroperative curarization degree and postoperative recovery process (24). In our study we tried to standardize all these factors.

In conclusion, according to our results, females are more sensitive to neuromuscular blocking effect of rocuronium as the time to maximal block is shorter and recovery duration is longer in females. In addition, the reversal effect of neostigmine delays in females. Thus, during general anesthesia with neuromuscular blocking agents, we suggest that especially in female cases rocuronium dose should be decreased since they are more sensitive to the effects of neuromuscular blocking agents and neostigmine should be given earlier when compared to males since the effect of neostigmine delays also.

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