

ORIGINAL ARTICLE

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The effect of gender on reversal of non-depolarizing block with Sugammadex**Alper Ozturk¹, Ozcan Piskin², Gamze Kucukosman², Bengu Gulhan Aydin², Dilek Okyay², Hilal Ayoglu²**¹*Ortakoy State Hospital, Clinic of Anesthesiology and Reanimation, Aksaray, Turkey*²*Bulent Ecevit University Medicine Faculty, Department of Anesthesiology and Reanimation, Zonguldak, Turkey*

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Abstract

Sugammadex is a rapid and selective aminosteroid agent that has entered use recently. We aimed to research the effect of gender on reversal of non-depolarizing block with sugammadex. We designed a prospective study. The research included a total of 100 cases who underwent rhinoplasty operation administered general anaesthesia. Cases were divided according to gender as male (Group M) and female (Group F). At the end of the operation for patients with TOF value 25%, patients were given 2 mg kg⁻¹ iv sugammadex. Duration from the rocuronium administration until the TOF value was zero (TOF0), the time from sugammadex administration until TOF reached from 25% to 90% was recorded (TOF25-90). The time from TOF90 to extubation was named the extubation duration. From the time the patients entered the PCU until Aldrete score was ≥ 9 was named the recovery duration and recorded. The time for the groups to TOF25-90 was 123.84 ± 38.03 s in Group M and 122.06 ± 30.461 s in Group F ($p > 0.05$). The extubation duration was 189.68 ± 41.37 s in Group M and 206.50 ± 45.99 in Group F ($p = 0.316$). The recovery time was 8.26 ± 14 min in Group M and 8.48 ± 14.23 min in Group F ($p = 0.328$). After the administration of sugammadex, there was no difference observed between the groups in terms of the TOF25-90 duration, recovery and extubation duration. As a result, conclusion was reached that gender did not affect rocuronium reversal with sugammadex.

Keywords: Sugammadex, gender, female, male, TOF**Introduction**

Muscle relaxant medications create sufficient muscle relaxation to both ease endotracheal intubation and provide comfortable working for the surgical team, and allow general anesthesia to be better tolerated by the patient [1].

To reverse the effect of muscle relaxant agents administered during anesthesia induction and/or maintenance, neostigmine and sugammadex are used [2]. Neostigmine inhibits the enzyme acetylcholinesterase causing an increase in the Ach amount in the synapse interval. This increase allows neuromuscular conduction and normal muscle functions to resume [3]. Currently for traditional decurarization cholinesterase inhibitor agents are used in combination with anti-muscarinic agents. Additionally cholinesterase inhibitors may be insufficient to reverse deep neuromuscular block and require time to show full effect [4].

Sugammadex is a rapid and selective aminosteroid agent that has entered use recently. Its effect is due to rocuronium and

vecuronium encapsulation and causes rapid recovery not linked to time of administration. Thus it provides muscle activity return in a short time [5].

In the literature due to gender differences, it has been shown that the pharmacokinetic and pharmacodynamic effects of anesthetic agents and neuromuscular blockers may change [6,7]. This research has focused on characteristics of anesthetic agents, such as being lipophilic or hydrophilic, and differences in metabolism and receptor levels between genders. However, we found no study researching the different effects of sugammadex depending on gender. As a result, we aimed to research the effect of gender on reversal of non-depolarizing block with sugammadex.

Material and Methods

This study was granted permission by × University, Medical Faculty, Health Application and Research Center Clinical Research Ethics Committee (15 / 03 / 2013, Decision No: 2013 / 11). Patient consent was obtained and the prospective study was completed from February - June 2014 in the Anesthesiology and Reanimation Department.

The research included a total of 100 cases, 50 male and 50 female, in American Society of Anesthesiologists (ASA) I and II,

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between 18 and 50 years and administered general anaesthesia. Cases were divided according to gender as male (Group M) and female (Group F). Patients with body mass index (BMI) > 30 kg .m⁻², allergies to eggs or the study medications, neurological disorder or previous trauma of the hand used for neuromuscular monitoring, using medications affecting neuromuscular blockage (anticonvulsants, aminoglycosides or polypeptide antibiotics, etc.), those postmenopausal, pregnant or breastfeeding, those with renal, hepatic or metabolic failure, patients with mallampati score III or above and those with possible difficult intubation were excluded from the study. During the study the demographic data of the patients [age, height, weight, BMI, general body weight (RBW), ideal body weight (IBW) and ASA classification] were recorded. The study calculated BMI using the formula weight (kg) [height (m)]⁻² while IBW was calculated as 22 × [height (m)]².

In both groups for premedication 30 min before the operation iv 0.03 mg / kg midazolam (Dormicum®, Roche, 5 mg mL⁻¹, Fonteney-sous-Bois, France) was administered. Patients taken to the operating room were given routine hemodynamic monitoring and TOF monitoring. During the operation the patients' systolic and diastolic blood pressure (SBP, DBP), heart rate (HR), peripheral oxygen saturation (SpO₂), adductor muscle temperature and nasal temperature were monitored. To monitor neuromuscular conduction, the TOF-WATCH® SX (Organon Teknika B V Nederland) device was used. Skin was cleaned with alcohol and cotton and after drying, a distal electrode (Neotrode ® Neonatal ECG Electrode, USA) was placed near the ulnar artery on the volar side of the wrist 1 cm from the wrist above the ulnar nerve. A proximal electrode was placed on the skin 2-3 cm proximal of the distal electrode. The acceleration transducer was mounted on the thumb and fixed to the operating table with plaster so the thumb was free. A temperature probe was placed on the tenar region of the hand, the patients were covered and care was taken that the temperature of the tenar region not drop below 32 °C.

The temperature of the operating room was set to 24 °C. A vein was opened and fluid replacement began (ringer lactate, 10 mL kg⁻¹ min⁻¹). All fluids administered to patients were given at room temperature. All patients were given preoxygenation with 100% oxygen. For induction, iv 2 mg kg⁻¹ propofol (Propofol® 1% Fresenius Kabi), 1 µg kg⁻¹ fentanyl (Fentanyl citrate® 2 ml / 100 mcg) and 1 mg / kg lidocaine (Aritmal %2 Osel İlaç Turkey) were administered. When eyelash reflexes were lost, calibration was completed using peripheral nerve stimulator. After waiting 1 min, 3 control single twitch (0.1 Hz) values were taken. Then 3 control TOF (train of four) values were taken. Later 0.6 mg/kg rocuronium (Esmeron® 50 mg / 5 ml N.V. Organon, Oss, Netherlands) was administered. The duration from the rocuronium administration until the TOF value was zero (TOF₀) was recorded. When the TOF value was zero (TOF₀) patients were intubated. All patients had anesthesia maintenance with 50 : 50% O₂ : N₂O and 1 MAC desflurane. During surgery when TOF ratio was 25% ¼ of the intubation dose of rocuronium was additionally administered and this duration was recorded as TOF₂₅. In all patients the repeated rocuronium number (RRn) and total rocuronium amount as milligrams (TRmg) were recorded. At the end of the surgical procedure the TOF value of the patients were recorded as TOF_{LAST}. The time from the beginning of surgical incision to the last suture was recorded as surgery duration. At the end of the surgical procedure if the TOF value

had not reached 25%, the TOF value was allowed to reach 25%. At the end of the surgical procedure for patients with TOF value 25%, patients were given 2 mg / kg iv sugammadex to reverse non-depolarizing block. The time from sugammadex administration until TOF reached from 25% to 90% was recorded (TOF₂₅₋₉₀). After the TOF value reached 90% desflurane administration was ended. The duration from anesthesia induction until TOF reached 90% was named the anesthesia duration and recorded. When the respiration frequency was > 8/min, EtCO₂ was < 50 mmHg, SpO₂ was > %90 and sufficient tidal volume was present, extubation was performed. The time from TOF₉₀ to extubation was named the extubation duration. After extubation patients with stabilized general situation were sent to the postoperative care unit (PCU). In the PCU, to monitor postoperative residual curarization (PORC) every 3 minutes for a total of 30 minutes the patients were asked to raise their heads and stick out their tongues. From the time the patients entered the PCU until Aldrete score was ≥ 9 was named the recovery duration and recorded. Patients monitored in PCU for at least 30 min, with no PORC observed and Aldrete score ≥ 9 were transferred to the ward. The primary outcome were the differences in duration of time to reach TOF₉₀, extubation time and the time to reach aldrete score ≥ 9 after extubation between the groups. Secorder outcome were measured time to reach TOF₀ and TOF₂₅ and TOF_{LAST}.

Statistical Analysis

Statistical analysis for the study was performed with SPSS 13.0 program. Categorical variables in the data set are given as frequency and percentage, measurement variables with continuous values are given as mean, standard deviation, median, minimum and maximum values. Normal distribution of measurement variables with continuous values was tested with the Shapiro Wilk test. For two-group comparison of normally distributed continuous variables the significance of means test was used; for variables without normal distribution 3-group comparisons were completed with the Kruskal Wallis test, and 2-group comparisons used the Mann Whitney U test. Differences between variables with measurements at different times were investigated with the Wilcoxon test for variables without normal distribution. Group comparisons of categorical variables were completed with the Pearson chi-square and Fisher exact chi-square tests. The relationship between measured variables was examined with correlation analysis. For all statistical analyses in the study, a p value of less than 0.05 was accepted as statistically significant.

Results

The demographic data of the patients are presented in Table 1. There was no difference between the groups in terms of age, RBW, BMI and ASA classification (p > 0.05), however there was a statistically significant difference in terms of height and IBW (p < 0.05). The mean height of patients in Group M was 172.98 ± 0.649 cm and in Group F was 162.24 ± 6.196 cm. The IBW of patients in Group M was 65.90 ± 4.9 kg while this was identified as 58.00 ± 4.4 kg in Group F.

There was no statistically significant difference between the groups in terms of surgical duration and duration of anesthesia (p > 0.05) (Table 1).

When the groups are compared in terms of TOF₀, TOF₂₅, TOF_{LAST}

and TOF₂₅₋₉₀ durations, there was no statistically significant difference found ($p > 0.05$) (Table 2).

The time for the groups to reach TOF of 0.9 (TOF₂₅₋₉₀) was 123.84 ± 38.03 s in Group M and 122.06 ± 30.461 s in Group F ($p > 0.05$). The extubation duration was 189.68 ± 41.37 s in Group M and 206.50 ± 45.99 in Group F ($p = 0.316$). The recovery time was 8.26

± 14 min in Group M and 8.48 ± 14.23 min in Group F ($p = 0.328$).

When the study groups are compared in terms of number of rocuronium repeated doses (RRn) and total rocuronium consumed (TRmg), there was no statistically significant difference found ($p > 0.05$) (Table 3).

Table 1. Distribution of sociodemographic factors and operative details via groups

	Grup M (n=50)	Grup F (n=50)	P
Age (year), SD	35.26 $\pm$ 13.5	38.10 $\pm$ 11.3	0.195
Height (cm), SD	172.98 $\pm$ 0.649	162.24 $\pm$ 6.196	0.001
RBW (kg), SD	69.36 $\pm$ 14.21	74.52 $\pm$ 13.118	0.062
IBW (kg), SD	65.90 $\pm$ 4.9	58.00 $\pm$ 4.4	0.001
BMI (kg m ⁻²), SD	24.84 $\pm$ 3.7	26.32 $\pm$ 4.3	0.094
Body Temperature (°C), SD	36.06 $\pm$ 0.3	36.12 $\pm$ 0.2	0.356
ASA I/II, n	19/31	25/25	0.227
Surgery time (min), SD	53.27 $\pm$ 25	47.73 $\pm$ 30.9	0.338
Anesthesia time (min), SD	61.25 $\pm$ 15	54.60 $\pm$ 17.9	0.250

F: Female; M: Male; BMI: Body Mass Index; ASA: American Society of Anesthesiologist score. RBW: Real body weight, IBW: Ideal body weight

Table 1. Time to recovery of TOF ratio to 0.9, extubation and recovery of Aldrete

	Grup M (n=50)	Grup F (n=50)	P
TOF ₀ (s), SD	132.02 $\pm$ 27.158	125.80 $\pm$ 23.442	0.196
TOF ₂₅ (min), SD	50.66 $\pm$ 9.621	54.12 $\pm$ 11.0	0.623
TOF _{LAST} , SD	18.34 $\pm$ 6.49	20.62 $\pm$ 7.13	0.853
TOF ₂₅₋₉₀ (s), SD	123.84 $\pm$ 38.03	122.06 $\pm$ 30.461	0.519
Extubation time (s), SD	189.68 $\pm$ 41.37	206.50 $\pm$ 45.99	0.316
Recovery time (min), SD	8.26 $\pm$ 14	8.48 $\pm$ 14.23	0.328

TOF: Train of Four, TOF0: Time to 0% TOF, TOF25: Time to 25% TOF, TOFLAST: TOF at the end of surgery ratio %, TOF25-90: Time to 90% TOF

Table 3. Number of rocuronium administration and total amount of rocuronium

	Grup M (n=50)	Grup F (n=50)	P
RRn (n)	1.34 $\pm$ 0.62	1.28 $\pm$ 0.60	0.517
TRmg (mg)	54.62 $\pm$ 10.842	58.10 $\pm$ 9.972	0.615

RRn: Number of rocuronium administration, TRmg: Total amount of rocuronium

When patients are compared in terms of PORC incidence (raise head and stick out tongue every 3 minutes for 30 minutes) it was observed that all patients fulfilled the commands at each evaluation time. PORC was not observed in any patient.

There was no difference found between the groups in terms of systolic blood pressure, diastolic blood pressure and heart rate ($p > 0.05$).

Discussion

In our study researching the effect of gender on reversal of non-depolarizing block with sugammadex, we found that gender differences did not change the TOF₂₅₋₉₀, extubation and recovery duration.

As a result of pharmacokinetic and pharmacodynamic effects,

it is known that anesthetic agents may have different effective durations in women and men [6,8]. These differences may be due to pharmacodynamic differences such as differences in body fat and water composition, or to differences in metabolism [8].

The most important enzyme system providing metabolism of medication is the cytochrome P - 450 (CYP - 450) system [9]. Isoenzymes like CYP3A, CYP2D6, CYP1A2 and CYP2C9 are found within the CYP - 450 system. Studies have shown that different amounts of these isoenzymes are found in men and women [10]. Meibohm et al. [11] reported that this situation may cause different pharmacokinetic effects in men and women.

A literature scan shows there are many studies showing the effects of gender on anesthetic agents. Hoymork et al. [8] administered propofol infusion so BIS values remained between 40 and 60 in a total of 60 patients undergoing lower extremity operations and though the total amount of propofol consumed was the same in both genders, at the end of the operation the amount of propofol in plasma in women reduced more quickly and they reported that women woke earlier than men. Similarly a meta-analysis by Pleym et al. [6] reported that women were 30 - 40% less sensitive to propofol, and stated that this situation was due to increased volume of distribution of propofol in women due to high fat rates.

Studies showing the effect of gender on opioids used for general anesthesia have reported that men require a 25% higher dose of fentanyl and this situation may be due to pharmacokinetic differences linked to high drug excretion rates [12]. Similarly Pleym et al. [6] reported that to obtain the same pain score, men required 30 - 40% more morphine.

A study by Buchanan et al. [13] found that with the same anesthetic protocol for general anesthesia women recovered earlier than men; however women felt more pain in the recovery room and stayed there for longer. Whitley et al. [14] stated that this may be due to differences in the pharmacodynamics of women. Compared to men women have an excessive amount of estrogen. This hormone affects pain pathways and changes perception of pain. This situation may leave women more sensitive to opioid agents.

There are many studies on the effect of gender on muscle relaxing agents like atracurium, vecuronium and rocuronium. These studies have revealed that muscle relaxing agents have greater efficacy for women due to their hydrophilic structure [6,15].

Women show 20 - 30% greater sensitivity to the effects of muscle relaxants with aminosteroid structure compared to men [16]. The shorter time to reach maximum muscle relaxation (TOF_0) for women, and the longer time to reach TOF_{25} indicating the beginning of the reduction of the neuromuscular block effect and to reach TOF_{90} indicating the return of muscle power supports this idea [15,17].

When the body composition of men and women are compared, in terms of percent women have more fat and less water [18]. Lipophilic medications like opioids and benzodiazepines are observed to have higher volume of distribution in women compared to men when volume of distribution per kilogram body weight is compared. Contrarily hydrophilic medications like muscle relaxant agents have lower volume of distribution per kilogram in

women compared to men. As a result when the medication dose is regulated according to kilogram body weight, while women are reported to have low initial plasma concentration of lipophilic medications, they have high initial plasma concentrations of hydrophilic medications [19].

Xue et al. [15] in a study researching the effect of gender on rocuronium reported that women were more sensitive to rocuronium than men, and to obtain the same neuromuscular effect they required about 30% less rocuronium. The same study stated that in spite of administering equal doses of rocuronium at induction, the duration to reach TOF_{25} was longer for women.

Mencke et al. [7] researched the effect of gender on the pharmacodynamic effects of rocuronium and reported that, under general anesthesia administering 0.45 mg/kg rocuronium, for women the time to reach TOF_0 after induction was shorter (168 ± 65 s compared to 211 ± 56 s), while the time to reach TOF_{25} was longer (23 ± 5 min compared to 17 ± 5 min). The same study reported there was no difference in recovery times after operation between women and men (9 ± 4 min compared to 9 ± 3 min)

In a study of 848 patients using total intravenous anesthesia (TIVA), Adamus et al. [17] compared the TOF_0 , TOF_{25} and TOF_{25-75} duration after induction with 0.6 mg kg⁻¹ rocuronium. At the end of the study it was observed that the time to reach TOF_0 (91.7 ± 14.3 s compared to 108.0 ± 14.6 s) was shorter for women than for men, while the times to reach TOF_{25} (43.3 ± 7.8 min compared to 31.3 ± 5.5 min) and TOF_{25-75} (15.2 ± 5.1 min compared to 14.7 ± 4.0 min) were longer. They reported that women were more sensitive to muscle relaxant agents.

In our study of patients given general anesthesia, after administering equal doses according to kilogram of iv rocuronium (0.6 mg kg⁻¹) the durations to reach TOF_0 and TOF_{25} were compared for men and women. While the time to reach TOF_0 was 125.80 ± 23.442 for women, it was 132.02 ± 27.158 s for men. The duration to reach TOF_{25} was 54.12 ± 11.0 min for women and 50.66 ± 9.621 min for men. Though it appears numerically that women were more sensitive to rocuronium, statistically there was no significant difference found between men and women. It has been reported in studies that the effective duration of muscle relaxant agents used during operations may vary depending on the chosen inhalation anesthesia, temperature of the environment and the age of patients [3,20]. In our study there was no difference in the mean age of patients, the temperature of the environment was standardized and 1 MAC desflurane was administered as standard.

The continuing effects of muscle relaxant agents used during general anesthesia after the operation is named PORC [20]. Baillard et al. [21] defined PORC as TOF falling below 70% after extubation and reported the incidence of PORC in the recovery room was 42%. In spite of the use of neostigmine to reverse the effects of muscle relaxant agents, development of PORC may be observed. However, it is stated that after the use of sugammadex development of PORC is prevented [22,23].

In our study after the operation to monitor for PORC after extubation in place of TOF patients were asked to raise their heads and stick out their tongue every 3 minutes for a total of 15 minutes. At the end of the study the development of PORC was not observed

in any patient. This result is in accordance with the literature.

Sugammadex is a rapid and reliable reversal agent for neuromuscular block formed by rocuronium and vecuronium, which has entered anesthetic practice in recent years. Showing effect by encapsulating rocuronium and vecuronium, it causes rapid recovery independent of time of administration [24]. Depending on the intensity of muscle relaxation, 2-16 mg kg⁻¹ dose intervals are used [25].

Pişkin et al. [26] in a study, administered 2 mg kg⁻¹ sugammadex and 50 µg kg⁻¹ neostigmine + 20 µg kg⁻¹ atropine for decurarization when TOF was reach 25% in patients given rocuronium for muscle relaxation. The time for TOF to reach 90% was 2.19 min in the sugammadex group, while it was 6.47 min in the neostigmine group. In our study at the end of the operation when the TOF rate was 25% both men and women were administered iv 2 mg kg⁻¹ sugammadex. In accordance with the literature the duration to reach TOF 90% was measured as 122.06 ± 30.46 s in women and 123.84 ± 38.03 in men. In our study when TOF reached 90% inhalation agents were discontinued. When extubation criteria were met the patients were extubated. In women the extubation duration was measured as 206.50 ± 45.99 s, while this value was 189.68 ± 41.37 s for men. However, there was no statistical difference found between the duration to reach TOF 90% and extubation duration in men and women. Though there are studies in the literature showing female patients wake earlier, it is known that patients may be affected by many pharmacokinetic and pharmacodynamic factors during the operation. Research on the use of muscle relaxant agents according to BMI have shown that muscle relaxant administration for obese patients may be more appropriate according to IBW, as in situations where muscle relaxants are given according to RBW the duration of neuromuscular block effect may lengthen [27]. In our study medication doses were given according to RBW. However, there was a statistical difference between women and men in terms of IBW ($p < 0.05$). In women IBW was measured as 58.00 ± 4.4 kg, while for men this was 65.90 ± 4.9 kg. Contrary to the literature information, we believe the reason for no difference in waking duration for male and female genders is due to our medication administration calculated according to RBW. It is known that especially in obese patients, lipophilic medications have different volume of distribution in the body fat and fluid compartments [18]. This situation has brought administration of anesthetic agents for use in obese patients according to IBW to the agenda. In a study by Sanfilippo et al. [30] where doses of sugammadex were set according to IBW and RBW, they stated that there was no difference between the two doses in terms of the recovery time and PORC. Considering sugammadex is a very expensive agent and dosing according to IBW is more effective, unnecessary administration will be avoided.

A study by Buchanan et al. [13] assessed the duration from extubation after the operation to patients responding to commands as the recovery criteria and reported this duration was 8.3 ± 11.8 min for men and 6.8 ± 7.3 for women. In our study the recovery duration was measured as 8.26 ± 14 min for men and 8.48 ± 14.23 min for women.

Body temperature is one of the most important factors affecting the return of neuromuscular functions after administration of muscle relaxant agents. Bilgin et al. [29] researched incidence of residual

neuromuscular block with rocuronium under different hypothermic cardiopulmonary bypass conditions in a study. They found that in cardiac operations with long duration and hypothermia below 30 °C, spontaneous recovery time and postoperative residual neuromuscular block increased obviously and that as hypothermia deepened, the amount of muscle relaxant required reduced. As a result of this effect, in our study peripheral body temperature was measured with a probe on the thumb, while central body temperature was monitored with a nasal probe. During the operation patients were warmed so that both peripheral and nasal temperatures were kept above 32 °C.

After rocuronium administration at induction, the duration to TOF₀ and TOF₂₅ and TOF_{LAST} values were similar for both genders. After the administration of sugammadex, there was no difference observed between the groups in terms of the TOF₂₅₋₉₀ duration, recovery and extubation duration. As a result, the conclusion was reached that gender did not affect rocuronium reversal with sugammadex according to RBW.

Though the prospectus information for sugammadex reports no difference in pharmacokinetic characteristics between men and women, it is known that gender may change these characteristics as it affects the pharmacokinetic and pharmacodynamic characteristics of anesthetic and muscle relaxant agents.

Due to the project budget of our study, the plasma concentrations of sugammadex were not measured in the genders. This is the most significant limitation of the study. However, the lack of a study showing the effect of gender on sugammadex in the literature is the most important feature of this study.

Conclusion

In conclusion this study observed that sugammadex administered had similar effects in both genders. The conclusion was reached that advanced studies comparing different sugammadex doses may be beneficial to research the effect of gender on sugammadex.

Competing interests

The authors declare that they have no competing interest.

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