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A Comparision of the Effect of Sugammadex on the Recovery Period and Postoperative Residual Block in Young Elderly and Middle-Aged Elderly Patients

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Background: The importance of the characteristics of anesthesia and postoperative residual curarization (PORC) in the elderly population should be a growing concern in this century.
Aims: To investigate the effect of sugammadex on the duration of the recovery from neuromuscular blocking agents and postoperative residual curarization in the young elderly and middle-aged elderly patients who underwent elective laparoscopic cholecystectomy, followed by a train of four (TOF) watch monitorization.
Study Design: Prospective clinical trial study.
Methods: Sixty patients over the age of 65 with American Society of Anesthesiologists I-III were divided into two groups according to their age (65-74 years old and ≥75 years old). Patients received sugammadex (2.0 mg/kg iv) at the reappearance of the second twitch of the TOF as an agent for reversal of neuromuscular blockage at the end of surgery. Patients were extubated at the time of TOF ≥0.9. The patients' TOF responses were evaluated with regards to PORC in at the 5th minute and were followed up for one hour in the recovery room. Reintubation was applied for those patients who developed PORC and had peripheric oxygen saturation <90% despite being given 6 L oxygen per min with a face mask.
Results: The onset time of neuromuscular blocking agent and time from T_2 to achieve TOF ratio 90% (the duration of sugammadex effect) or over were found to be longer in the middle-aged elderly group than in the young elderly group. A statistically significant relationship was found between age and the duration of TOF ratio to reach 0.9 in the same direction. The PORC incidence and rate of reintubation were found to be 1.7% in all patients.
Conclusion: In our opinion, it is necessary to remember that the duration of sugammadex effect on the recovery period is prolonged for patients who are aged ≥75 years compared to patients aged between 65-74 years. (ClinicalTrials.gov Identifier: ACTRN12615000758505)
Keywords: Elderly, postoperative residual curarization, reintubation, sugammadex

Young elderly people, middle-aged elderly people, and old elderly people have been classified, respectively, between 65-74 years of age, between 75-84 years of age, and over age 84 by gerontologists (1). A number of studies have indicated that the prevalance of postoperative residual curarization (PORC) increases with age (2,3).

The principle of train of four (TOF) Watch was to indicate a pattern of stimulation that did not require the comparison of evoked responses to a control response obtained before administration of a neuromuscular blocking agent (NMBA). As well as enabling the observer to compare T_1 (first twitch of the TOF) to T_0 (control), it also enables comparison of T_4 (fourth

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twitch of the TOF) to T_1. This is accepted as the TOF ratio. Throughout onset of non-depolarizing block, T_4 disappears at about 75% depression of T_1, T_3 at 80–85% depression of T_1, and T_2 at 90% depression. During recovery from non-depolarizing block: T_1 appears again, first followed by T_2, T_3, and finally T_4 (4). In order to rule out PORC, a TOF ratio of 0.9 or over is considered to be a gold standard (5,6).

The aim of the present study was to investigate the effect of sugammadex on the duration of recovery from NMBA and PORC in the young elderly and middle-aged elderly groups, followed by TOF-Watch monitorization.

MATERIALS AND METHODS

This prospective clinical trial was approved by local Ethics Committee (Bursa Şevket Yılmaz Training and Research Hospital Ethics Committee) and Australian New Zealand Clinical Trials (Registry Number: ACTRN12615000758505). Sixty patients over the age of 65, in whom laparoscopic cholecystectomy was planned and who are in American Society of Anesthesiologists (ASA) I-III group were included in the study after their informed consent was obtained. The patients were divided into two groups according to their age: the first were aged between 65-74 (young elderly, Group 1) and the second were aged ≥75 (middle-aged elderly, Group 2). Patients with renal and hepatic failure, musculoskeletal disease, family history of malignant hyperthermia, and body mass index over 30 were excluded from the study. It was also planned to exclude patients who undergo laparatomy after failed laparoscopic intervention, whose operation period is over two hours, and who are admitted after operation to intensive care unit in intubated manner (Figure 1). Patients who are not administered premedication were taken to operating room and heart rate (HR), peripheral oxygen saturation (SpO_2), mean arterial pressure (MAP) and body temperature were monitored.

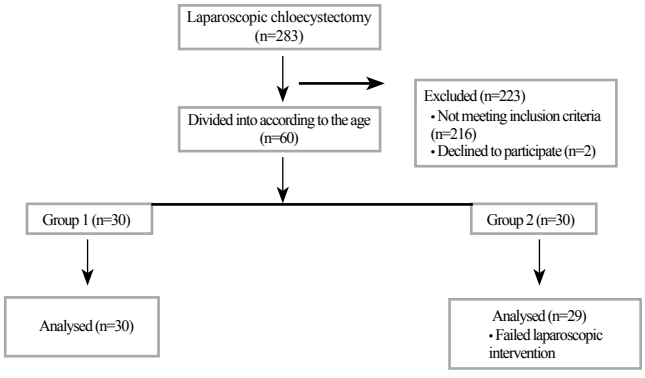

FIG. 1. Flow chart of patient enrolment and analysis

A train of four (TOF) Watch (TOF-Watch-SX Monitor, Organon Teknika; Oss, Netherlands) device was used to monitor nerve muscle transmission. Two surface electrodes were placed on the forearm ulnar nerve trace 2-3 cm apart, active and passive electrodes of the acceleromyograph and transducer was placed on the pulpa of the thumb. For sedoanalgesia, 0.03 mg/kg midazolam (Zolamid, Defarma; Ankara, Turkey) and 1 µg/kg fentanyl (Talinat, Vem; İstanbul, Turkey) iv was administered before calibration of the TOF-Watch device. Patients were preoxygenised for three minutes with 100% oxygen. TOF-Watch device was calibrated by supramaximal stimulation at 0.1 Hz frequency before induction. Propofol (Propofol, Fresenius-kabi; İstanbul, Turkey) 1.5 mg/kg, lidocaine (Jetmonal 2%, Adeka; İstanbul, Turkey) 1 mg/kg, fentanyl 1 µg/kg, and rocuronium (Esmeron, MSD; İstanbul, Turkey) 0.6 mg/kg iv were administered for anesthesia induction. Seventy mA supramaximal 4 TOF impulses were evaluated with 10 second intervals at 2 Hz frequency. When the TOF value was 0 (T_0), the patients were intubated. The duration of time from the administration of NMBA to the T_0 value was considered as the onset time of NMBA effect (I-T_0). Patients were ventilated with 50% O_2+50% N_2O and sevoflurane (E_TSEVO 1.5%) with 7 mL/kg tidal volume and 12 breath/min respiration rate. When the TOF response was ''2'' (T_2), if operation was continuing maintenance dose 0.15 mg/kg iv rocuronium was administered, and if operation was being terminated, then 2 mg/kg iv sugammadex (Bridion®, MSD, Istanbul, Turkey) was administered. The duration of the time until TOF responses reach from T_2 to $TOF_{0.9}$ (T_2-$TOF_{0.9}$) was recorded as the duration of sugammadex effect on recovery period and patients were extubated. HR, SpO_2, MAP values, skin temperature were recorded at the onset time, before induction and intubation time. E_TCO_2 and E_TSEVO measurements were recorded during the intraoperative period. Skin temperature was kept within the range of 36-36.9 °C. The duration of anesthesia, surgical time, the duration of NMBA effect (I-$TOF_{0.9}$), the time of last NMBA administration and total amount of NMBA was recorded. The patients' HR, SpO_2, and MAP (1st, 30th, and 60th min) were monitored for an hour in the recovery room. In terms of PORC, the TOF responses were evaluated at the 5th min. If TOF was <0.9, then postoperative residual curarization (PORC) was considered to be present and if TOF was ≥0.9, it was considered to be absent. Cases with TOF <0.9 or who have findings suggestive of PORC (dyspneia, SpO_2 <90, being unable to swallow secretions) underwent TOF monitorization for an hour. Patients whose SpO_2 value could not be kept over 90% despite the administration of 6 L/min oxygen were reintubated. Pain experienced by the patients in the early postoperative period was evaluated with Visual Analog Scale (VAS) (0: no pain to 10: unbearable pain). In patients with

a VAS score over 3, 1 mg/kg diclofenac sodium (Dikloron, Deva; İstanbul, Turkey) im was administered. Speech, swallowing, secretions, skin color, and the consciousness of the patient were observed. Complications and side effects such as nausea, vomiting, bronchospasm, apnea, hypoventilation, hyperventilation, allergy, reintubation, tachycardia, bradycardia, hypotension, analgesic, and antiemetic requirements were recorded. When the patients had nausea and vomiting, 4 mg ondansetron (Zofer, Adeka; İstanbul, Turkey) iv was given. The clinical condition of the patients was evaluated by Modified Aldrete Score (MAS) at their arrival in the recovery room and at the 30th and 60th min. If the score was 9 or over, then the patients were considered safe and they were sent to the clinic.

Statistical evaluation

Statistical analysis of the study was carried out using Statistical Package 21.0 for Windows (SPSS Inc.; Armonk, NY, USA). Shapiro-Wilk test was used as normallity test. Continuous variables were compared using Mann-Whitney U test when the data were not normally distributed. Wilcoxon Signed rank test was used for dependent groups. Categorical variables were compared using Pearson's Chi-squared test and Fisher's exact test. Correlations between variables were tested using Spearman correlation coefficient. Results were given as median (min-max) values. The p value of <0.05 was considered statistically significant and the values were expressed as ''median-minimum-maximum'' or as a number. The power calculation for the present study was calculated according to the $T_{0.9}$ and an alpha level set at 0.05. The power was calculated as 0.64 according to recorded sample size.

RESULTS

Since laparoscopic surgery was terminated and laparotomy was initiated, one patient was excluded from the study and 59 patients were submitted to statistical evaluation. The demographic characteristics of the patients, duration of anesthesia, operation and the duration of NMBA effect (I-TOF$_{0.9}$) are shown in Table 1. It can be seen that there is no difference between the two groups (p>0.05). In the comparison of HR,

TABLE 1. Distribution of demographic characteristics, duration of anesthesia, operation, and duration of NMBA effect between the groups [number, median (minimum-maximum)]

Characteristics	Group 1 (n=30)	Group 2 (n=29)	p
Sex (M/F) (n)	6/24	7/22	0.945
Age (year)	67.9 (65-74)	78.1 (75-88)	0.818
ASA (I/II/III) (n)	5/20/5	4/20/5	
BMI (kg/m^2)	26.80 (21.5-30)	26.4 (21.5-30)	0.421
Duration of anesthesia (min)	64 (35-120)	60 (35-116)	0.964
Duration of operation (min)	42.5 (15-116)	40 (15-90)	0.903
I-TOF$_{0.9}$ (min)	42 (20-98)	40 (15-85)	0.089

M: male; F: female; ASA: American Society of Anesthesiologists; BMI: body mass index; NMBA: neuromuscular blocking agent; I-TOF$_{0.9}$: duration of NMBA effect

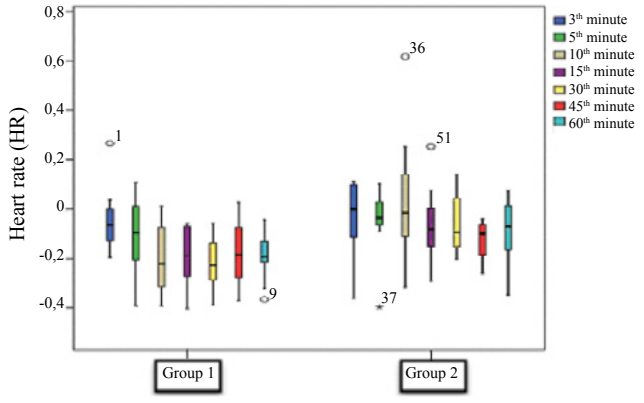

FIG. 2. A comparison of heart rate variability the between groups (3th, 5th, 10th, 15th, 30th, 45th, 60th min)

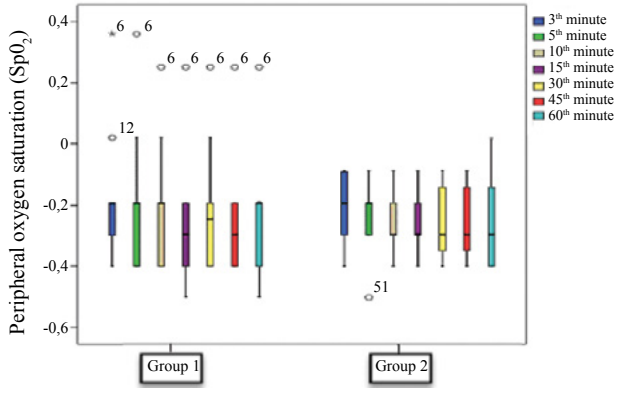

FIG. 3. Comparison of peripheral oxygen saturation between the groups (3th, 5th, 10th, 15th, 30th, 45th, 60th min)

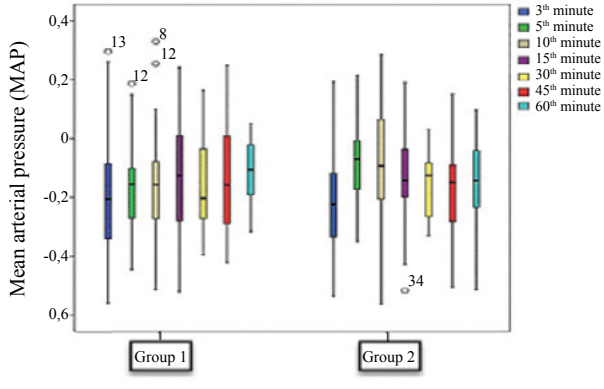

FIG. 4. Comparison of mean arterial pressure changes between the groups (3th, 5th, 10th, 15th, 30th, 45th, 60th min)

TABLE 2. Distribution of ETCO2 and ETSEVO values between the groups (mean±standard deviation)

Characteristics	Group 1 (n=30)	Group 2 (n=29)	p
Before intubation E_TCO_2	23.03±7.36	17.92±8.41	0.64
After intubation E_TCO_2	31.86±5.18	31.46±6.16	0.79
3th min			
E_TCO_2	31.44±5.00	33.14±4.65	0.19
E_TSEVO	1.28±0.42	1.06±0.60	0.12
5th min			
E_TCO_2	32.17±4.07	32.89±3.17	0.45
E_TSEVO	1.39±0.40	1.13±0.55	0.49
10th min			
E_TCO_2	34.03±3.73	34.03±3.31	0.99
E_TSEVO	1.43±0.40	1.28±0.63	0.29
15th min			
E_TCO_2	34.68±3.07	34.75±3.40	0.94
E_TSEVO	1.47±0.41	1.33±0.60	0.31
30th min			
E_TCO_2	35.51±2.78	35.26±3.99	0.79
E_TSEVO	1.16±0.68	1.21±0.65	0.78
45th min			
E_TCO_2	37.30±6.57	36.30±5.00	0.56
E_TSEVO	0.68±0.72	0.75±0.76	0.73
60th min			
E_TCO_2	35.23±5.35	34.81±4.44	0.83
E_TSEVO	0.21±0.54	0.94±0.74	0.38
Before extubation			
E_TCO_2	32.34±10.40	31.75±11.56	0.83
E_TSEVO	0.07±0.04	0.02±0.06	0.35

E_TCO_2: end tidal carbon dioxide; E_TSEVO: end tidal sevoflurane

SpO_2 MAP, E_TCO_2 and E_TSEVO values no significant difference was found between the groups in the operating room (p>0.05) (Figure 2-4, Table 2).

Total amount of NMBA was not found to be different between Group 1 (44.1 mg) and Group 2 (45.8 mg) (p>0.05). The maintenance dose of rocuronium was administered to two patients in Group 1 and to six patients in Group 2. However, there was no significant difference between groups in terms of the number of patients administered maintenance dose of rocuronium (p>0.05). The onset time of NMBA effect ($I\text{-}T_0$) was found to be longer in Group 2 (2.4 min) than in Group 1 (1.48 min) (p=0.009) (Table 3). The time of the last NMBA administration was similar between the two groups (p>0.05).

The duration of sugammadex effect on recovery period ($T_2\text{-}TOF_{0.9}$) was, respectively, 3.27 min and 5.5 min in patients in Group 1 and 2 (Table 3) (p<0.001). A moderately significant relationship was found between age and time to reach $TOF_{0.9}$ (r= 0.613). In Group 1, the duration of sugammadex effect on recovery period was 2.23 min earlier than in Group 2.

TABLE 3. Onset time of NMBA effect and the duration of sugammadex effect on recovery period between the groups [number, median (minimum-maximum)]

Characteristics	Group 1 (n=30)	Group 2 (n=29)	p
$I\text{-}T_0$ (min)	1.48 (1.07-6.16)	2.4 (1.36-6.58)	0.009*
$T_2\text{-}TOF_{0.9}$(min)	3.27 (1.41-5.37)	5.5 (2.47-9.54)	<0.001*

$I\text{-}T_0$: onset time of NMBA effect; $T_2\text{-}TOF_{0.9}$: duration of sugammadex effect on recovery period *p<0.05

TABLE 4. Compare of VAS and MAS values according to 30th and 60th minutes between the groups [number, median (minimum-maximum)]

Characteristics	Group 1 (n=30)	Group 2 (n=29)	p
VAS 30	0.0 (-7.0-0.0)	0.0 (-6.0-3.0)	0.902
VAS 60	0.0 (-7.0-0.0)	-1.0 (-8.0-3.0)	0.625
MAS 30	0.0 (0.0-2.0)	0.0 (-1.0-1.0)	0.387
MAS 60	0.0 (0.0-2.0)	0.0 (-1.0-1.0)	0.308

VAS: Visual Analog Scale; MAS: Modified Aldrete Score

TABLE 5. Distribution of side effects and the need of analgesics/antiemetics between the groups (n)

Characteristics	Group 1 (n=30)	Group 2 (n=29)	p
Bradycardia	2	2	1.000
Arrhythmia	1	1	1.000
Bronchospasm	2	0	0.492
Nausea	1	1	1.000
Vomiting	1	0	1.000
Hypotension	0	0	-
Allergy	0	0	-
Analgesics	8	12	0.358
Antiemetics	1	1	1.000

Postoperative residual curarization was determined to have developed in one patient in Group 1 (3.3%) and reintubation was performed. The rate of the development of PORC and reintubation was found to be 1.7% and 1.7% in all patients. There was no significant difference between the groups with respect to the rate of PORC development and reintubation (p>0.05). In the comparison of HR, MAP changes and SpO_2, no significant difference was found between the groups in the recovery room (p>0.05). No significant difference was found between groups in a comparison of VAS and MAS scores in recovery room (Table 4) (p>0.05). The number of patients with side effects is demonstrated in Table 5 (p>0.05).

DISCUSSION

In the present study, age-related effects of sugammadex as a reversal agent on recovery time and PORC in the recovery

of neuromuscular block produced by rocuronium was investigated. It was established that the onset time of the NMBA effect ($I\text{-}T_0$) and the duration of sugammadex effect on recovery period ($T_2\text{-}TOF_{0.9}$) are more prolonged in patients who are ≥75 than between 65-74 year olds. No significant difference was found between groups with respect to the rates of PORC.

There are many publications reporting that the onset time of intermediate term NMBA's effect is prolonged in elderly patients (2,3,7). In the study of Matteo et al. (8), the time passing between the administration of rocuronium and the formation of neuromuscular block was found to be 4.1±1.5 min and 4.5±2.4 min in young (<60 age) and old (>70 age) patients, respectively. In elderly patients, in relation to decrease in total body fluid, muscular, hepatic, and renal blood flow along with the fall in cardiac output, the onset time of NMBA effect is delayed (9).

However there are very few studies investigating the effect of age on the efficay of sugammadex. In the study of Suzuki et al. (10), while post tetanic count (PTC) was 1-2, the reversal effect of sugammadex (4 mg/kg) on neuromuscular blocking was investigated on 30 female patients monitored with acceleromyography, and it was found that the duration of the effect of sugammadex was prolonged three fold in older patients (aged ≥70) compared to younger patients (aged 20-50). This was attributed to the delay in the duration of the effect of sugammadex owing to the decrease in cardiac output and muscular blood flow in the elderly. Decrease in blood flow was linked to reduction of vascular conduction associated with age and loss of muscular volume. Decreased blood flow leads to a slower increase of the plasma concentration of sugammadex and a decrease in the rate of free rocuronium molecules passing to plasma. Unlike this study, in our study sugammadex 2 mg/kg was used and the 65-74 age group was compared with patients ≥75 years of age. In the study of McDonagh et al. (11) 2 mg/kg sugammadex was applied to three groups, as follows: 18-64 years of age (adult), 65-74 years of age (elderly), and ≥75 years of age (old elderly). The geometric mean time (95% confidence interval) from sugammadex administration to recovery of the TOF ratio to 0.9 increased with age (adults 2.3 min and elderly, old elderly groups combined 2.9 min). Recovery of the TOF ratio to 0.9 was estimated to be 0.7 min slower in elderly and old elderly groups compared with adults ($p=0.022$). This was attributed to the slower distribution of sugammadex owing to the slower rate of dynamic circulation in elderly patients. It was stated that changes in the distribution and redistribution rates rocuronium, sugammadex and rocuronium-sugammadex complex may also play role in the alterations in muscular blood flow of elderly patients. In the present study, in the middle-aged elderly group, the duration of sugammadex effect on recovery period was prolonged by 2.23 min compared to the young elderly group. The study of McDonagh et al. (11) was phase 3a. Age related delay in the duration of sugammadex effect is related to many factors. In elderly patients, in addition to atherosclerotic changes, decrease in cardiac output, HR and muscular blood flow rate leads the onset of the effect of reversal agents, like other drugs, to be delayed (12). As a consequence of the decrease in regional blood flow, the duration of NMBA's and sugammadex effect is elongated (10,11). A slower increase in the plasma concentration of sugammadex gives rise to slower diffusion of rocuronium from neuromuscular junction. As rocuronium-sugammadex complexes are excreted by kidneys, the effect of rocuronium and sugammadex is prolonged due to decreased clearance (13,14).

The effect of inhalation anesthesia on peripheral tissue perfusion may contribute to age related changes in the effect of sugammadex (15). In our study, considering that different inhalation anesthetics may have different neuromuscular blocking effects, sevoflurane was used in all patients for standardization. Given that the duration of exposure to sevoflurane is similar in both groups, it is our belief that TOF measurements are not influenced by inhalation anesthesia.

The diagnosis of PORC is made based upon the monitorization of neuromuscular transmission and the evaluation of clinical symptoms and findings. Many studies have observed that monitorization of neuromuscular transmission decreases the frequency of PORC (16,17). It is recommended that monitorization of neuromuscular transmission be performed primarily in elderly patients, in dysfunction of the kidney and liver, in patients with cardiovascular disease and asthma, in diseases involving neuromusculoskeletal system, in those who are morbidly obese, and in long lasting surgical interventions. In addition, in order to determine whether the respiratory events occurring in early stage of recovery emanates from NMBA or other anesthetic agents (opioid, benzodiazepin, volatile anesthetics), it is beneficial to monitor neurmuscular transmission. In the present study, neuromuscular transmission was monitored in the elderly population at high risk of PORC and a cut off value of TOF 0.9 was accepted in the determination of PORC. In the study of Hayes et al. (7), the incidence of PORC was higher in patients over the age of 65 than those under the age of 65 (respectively, 65%, and 47%). They attributed this to slower recovery of NMBA effects and a slower rate of reversal of neuromuscular transmission block in old patients compared to young patients. The incidence of PORC has been reported to vary between 53% to 93% in long acting NMBA's and between 3.5% and 95% in intermediate acting NMBA's (18,19). In the study of Murphy et al. (20), in which rocuronium was used and neostigmine was administred as reversal agent, a TOF ratio of <0.9 was accepted for PORC definition and the

incidence of PORC was found to be 30%. In the present study, in which sugammadex was used as a reversal agent, the rate of PORC was found to be 1.7%. In the observational study of Takagi et al. (21), it was found that after neostigmine and sugammadex were administered, the incidence of PORC was, respectively, 23.9% and 4.3%. It was stated that sugammadex significantly decreased the rate of PORC and that PORC can be prevented at a rate of 80% with sugammadex.

Sugammadex makes a rapid, efficient, and reliable reversal state (22). As the recovery period is prolonged, the unsafe period after extubation is also prolonged (23). Duveldestin et al. (24) found that a sugammadex dose of ≥4 mg/kg enabled a more rapid recovery. In a case report by Eleveld et al. (25) of a 48 year old female patient who was undergoing general anesthesia, it was reported that 42 min after NMBA administration, while PTC was 1-2, following the administration of 0.5 mg/kg sugammadex, the patient had a TOF ratio of 0.9 and was completely awake, the TOF response temporarily regressed to the first twitch response. This was attributed to the inadequate dose of sugammadex, one patient was also diagnosed with PORC with superficialization of respiration in the recovery room, who suffered impairment in consciousness, a fall of SpO_2 to 82% and 5th min TOF ratio of 0.76.

The limitation observed in this study is the absence of dosage investigation for faster recovery from neuromuscular transmission blockage in elderly patients. Further studies are required to determine the effective dosage of sugammadex in elderly patients, especially over the age of 74. A further limitation was the small number of patients. Hence, further studies are required with a greater number of elderly patients.

In conclusion, it is necessary to remember that the duration of sugammadex effect on the recovery period is prolonged for patients who are aged ≥75 years compared to patients aged between 65-74 years.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Bursa Şevket Yılmaz Training and Research Hospital.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed. Externally peer-reviewed

Author contributions: Concept - E.Y., C.Y., D.K.; Design - E.Y., C.Y., D.K., H.B.; Supervision - E.Y., C.Y., D.K., H.B.; Resource - E.Y., S.B., Y.A., H.E.S.; Materials - E.Y., C.Y., D.K.; Data Collection and/or Processing - E.Y.; Analysis and/or Interpretation - E.Y., C.Y., D.K., H.B.; Literature Search - E.Y., S.B., Y.A., H.E.S.; Writing - E.Y., C.Y., D.K., H.B.; Critical Reviews - H.B.

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