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### Evaluation of postoperative residual curarization: a prospective clinical study

#### Postoperatif rezidüel kürarizasyon değerlendirilmesi: prospektif bir klinik çalışma

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#### ABSTRACT

**Background:** Reversal of neuroblockade in general anesthesia is important to prevent possible complications. Currently, neostigmine and sugamedex are the agents of choice. The reversibility of blockade is evaluated by TOF (train-of-four) as well as clinical observation. Our goal is to research and evaluate both agents in terms of complications and residual blockade.

**Materials and Methods:** Our prospectively designed work included 100 cases operated under general anesthesia. demographic data, OF values, and complications were recorded.

**Results:** A total of 100 patients, 63 neostigmine and 37 sugamedex, were consisted of in the search. The mean age of the sufferers was 41.9±16.9 years. When age was compared between the groups, it was found that the neostigmine (N) group was younger (p=0.027). There was a likeness between the groups in terms of surgical time, BMI (body mass index), Spo2, heart rate, mean arterial pressure, and total rocuronium consumption. The TOF value of the group N was 1(0.87-1), while that of the group sugamedex (S) was 1(0.91-1) and was found to be significant (p=0.045). There was no difference in TOF between cases who received an additional dose of rocuronium and those who did not receive an additional dose of rocuronium.

**Conclusions:** As a result of the TOF values we obtained, we found that both agents were effective in removing the blockade, but the residual rate was statistically significantly lower in the sugamedex group, although not clinically significant. We did not encounter any complications in our study and we think that sugamedex is safer in terms of residual blockade.

**Keywords:** Residual neuromuscular blockade, such as Train-Of-Four (TOF) stimulators, neostigmine, sugamedex

#### ÖZET

**Amaç:** Genel anesteziye nöroblokajın geri döndürülmesi olası komplikasyonları önlemek açısından önemlidir. Şu anda neostigmin ve sugamedeks tercih edilen ajanlardır. Blokajın geri döndürülebilirliği klinik gözlemin yanı sıra TOF (train-of-four) ile de değerlendirilir. Amacımız her iki ajanı da komplikasyon ve rezidüel blokaj açısından araştırıp değerlendirmektir.

**Materyal ve Metot:** Prospektif olarak tasarladığımız çalışmamız genel anestezi altında ameliyat edilen 100 vakayı içeriyordu. Demografik veriler, OF değerleri ve komplikasyonlar kaydedildi.

**Bulgular:** Araştırmaya 63'ü neostigmin, 37'si sugamedeks olmak üzere toplam 100 hasta dahil edildi. Hastaların yaş ortalaması 41,9±16,9 yıldır. Gruplar arası yaş karşılaştırıldığında neostigmin (N) grubunun daha genç olduğu görüldü (p=0,027). Gruplar arasında cerrahi süre, BMI (body mass index), Spo2, kalp hızı, ortalama arter basıncı ve toplam rokuronyum tüketimi açısından benzerlik vardı. N grubunun TOF değeri 1(0,87-1), sugamedex (S) grubunun TOF değeri ise 1(0,91-1) olup anlamlı bulundu (p=0,045). Ek doz rokuronyum alan olgular ile ek doz rokuronyum almayan olgular arasında TOF açısından fark saptanmadı.

**Sonuç:** Elde ettiğimiz TOF değerleri sonucunda her iki ajanın da blokajın kaldırılmasında etkili olduğunu ancak rezidüel oranın sugamedeks grubunda klinik olarak anlamlı olmasa da istatistiksel olarak anlamlı derecede düşük olduğunu gördük. Çalışmamızda herhangi bir komplikasyonla karşılaşmadık ve rezidüel blokaj açısından sugamedex'in daha güvenli olduğunu düşünüyoruz.

**Anahtar Kelimeler:** Train-Of-Four (TOF) stimülatörleri, neostigmin, sugamedex, rezidüel nöromusküler blokaj

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## INTRODUCTION

One of the important elements in general anesthesia is neuromuscular blockade. Many agents such as pancuronium, vecuronium, cisatracurium, and rocuronium are used for the blockade. Rocuronium is at present used more commonly in anesthesia practice today due to its short startup time, and the shorter interval of effect. Therefore, we preferred rocuronium for neuromuscular blockade in our study.

Neostigmin, one of the cholinesterase inhibitors; has long been used to terminate neuromuscular blockade (NMB). Although most non-depolarizing anticoagulants are selectively effective, effects such as bradycardia, hypotension, nausea, and vomiting appear as disadvantages (Hristovska et al.,2017). Sugamedex specifically acts on short-acting agents such as rocuronium and vecuronium. Its most important advantage is that the blockade is effective in terminating even deep and moderate anesthesia levels. However, its disadvantages include cost, the risk of developing bronchospasm and serious bradycardia, and the lack of sufficient data on its use in newborns and babies under 2 years of age (Geldner et al.,2012). Sugammadex and neostigmine cause the removal of neuromuscular blockade with different mechanisms of action. Sugammadex reduces the amount of blocking agent by forming an inactive complex with vecuronium and rocuronium, while neostigmine eliminates the effect of the blockade by inhibiting the enzyme acetylcholine esterase

In addition to clinical observation of adequate spontaneous breathing and muscle strength, more measurement tools such as train-of-four (TOF) stimulators are used in the reversal of neuro blockade. The TOF device uses data obtained by sending four stimuli at 2 Hz frequency in 0.2 milliseconds at 8-10 second intervals. A ratio of >0.9 between the 4th stimulus (t4) and the 1st stimulus (t4/t1) on TOF indicates adequate reversal of muscle block.

Residual block can be defined as the inability to provide adequate muscle strength due to reasons such as inadequate use of anticholinergics or use of agents that prolong blockade, such as magnesium.

In this exploration, we targeted to evaluate the residual blockade during the postoperative recovery period in patients using neostigmine and sugammadex.

## MATERIALS AND METHODS

After the confirmation of the ethics committee, the prospective randomized resource was started according to the Helsinki declaration and consent flow chart. Randomization of the study was

performed by an uninvolved operating room staff using the closed envelope technique randomly, by dividing the patients into 2 groups: Neostigmine group (Group N) and Sugammadex group (Group S). The minimum sample size of our study was determined as 94 patients in total, with an alpha error of 0.05 and a beta error of 0.8. However, due to possible exclusion reasons, the study started with 120 patients between the ages of 18 and 70, with American Society of Anesthesiology (ASA) clinical classifications 1, 2, and 3, who were planned to operate under any general anesthesia. Informed consent was obtained from all patients and/or their legal guardians with a wet signature. Patients with neuronal conduction damage (diabetic neuropathy, demyelinating diseases, guilian barre, etc.), patients with advanced cardiac, hepatic, and renal diseases, pediatric and pregnant patients, patients with known deficiency of acetylcholine esterase. Some of the patients had to be excluded from the study due to the inability to obtain adequate respiratory and muscle strength, sugammadex administration after neostigmine, intubation, and transfer to the intensive care unit, and the study was continued with a total of 100 patients. All patients were evaluated preoperatively by an anesthesiologist.

Cases were taken to the operation room following an appropriate fasting period and standard monitoring was performed. Anesthesia induction was achieved with thiopental (5-7 mg kg<sup>-1</sup>) or propofol (2 mg kg<sup>-1</sup>) and fentanyl (2 µg kg<sup>-1</sup>) and 0.6 mg kg<sup>-1</sup> rocuronium bromide and orotracheal intubation was performed. Additional doses of rocuronium bromide were administered as 0.01 mg kg<sup>-1</sup>. At the end of the operation, the first group received sugammadex (2 mg kg<sup>-1</sup>) and the second group received atropine (0.01 mg kg<sup>-1</sup>) and neostigmine (0.03 mg kg<sup>-1</sup>) after antagonization with adequate respiration and muscle strength, and then were extubated and taken to the postoperative recovery room.

Measurements were made with TOF 5 minutes after the patients were taken to the postoperative recovery room. An acceleration transducer was placed on the thumb of the right hand and the motor response of the adductor pollicis muscle to the electrical stimulus given by 2 electrodes placed on the ulnar nerve of the forearm was recorded with a TOF device (Drager DeltaXL NMT). The measurement interval was set to 20 seconds and the pulse width to 200 microseconds. Age, BMI (body mass index), gender, comorbidities, pulse rate, and arterial and peripheral saturation of blood pressure were recorded. Patients who did not develop any complications and who had a modified Aldrete score of 9 and 10 were referred to the ward they came from.

Data entry and analysis were made using IBM SPSS Statistics 22.0 software (IBM Corp., Armonk, NY, USA). Whether the variables were normally distributed was evaluated by Skewness-Kurtosis. When comparing two independent groups; a t-test for independent variables was used to analyze parametric data, the Mann-Whitney-U test was used to analyze nonparametric data, and the Chi-Square test was used to analyze categorical data.  $p < 0.05$ .

## RESULTS

A total of 100 patients, 63 neostigmine and 37 sugammadex, were consisted in the search. The mean age of the sufferers was  $41.9 \pm 16.9$  years. When age was compared between the groups, it was

found that the neostigmine group was younger ( $p = 0.027$ ). There was a likeness between the groups in terms of surgical time, BMI, Spo<sub>2</sub>, heart rate, mean arterial pressure, and total rocuronium consumption. There was a likeness between the groups in terms of smoking and gender. However, when compared in terms of ASA, it was found that group S included more ASA III patients and fewer ASA I patients ( $p = 0.012$ ). The TOF value of the group N was 1 (0.87-1), while that of the group S was 1 (0.91-1) and was found to be significant ( $p = 0.045$ ). There was no difference in TOF between cases who received an additional dose of rocuronium and those who did not receive an additional dose of rocuronium.

**Table 1.** Demographic data of patients.

	Neostigmine n=63	Sugammadex n=37	Total n=100	p Value
Age (years, Min-Max)	39 (18-67)	45 (18-78)	40 (18-78)	<b><i>0,041</i></b>
Gender (male, %)	22 (34,9)	13 (35,1)	35 (35,0)	0,983
BMI (kg/m <sup>2</sup> )	26,4 (20,2-36)	27,5 (18,4-42,9)	26,7 (18,4-42,9)	0,380
Cigarette (%)	15 (23,8)	9 (24,3)	24 (24,0)	0,380
ASA (%)	ASA I	6 (16,2)	29 (29,0)	<b><i>0,021</i></b>
	ASA II	23 (36,5)	66 (66,0)	
	ASA III	39 (61,9)	5 (5,0)	

Categorical data are given as number of cases (percentage). The chi-square test was used in comparison. Numerical data are given as median (minimum-maximum). Mann-Whitney test was used in comparison.  $P < 0.05$  was considered significant. Significant values are in bold and italics. BMI: Body Mass Index, ASA: American Society of Anesthesiology Score.

**Table 2.** Distribution of preoperative and postoperative characteristics according to groups.

	Neostigmine n=63	Sugammadex n=37	Total n=100	p Value
Hypnotic Agent (%)	Propofol	11 (29,7)	28 (28,0)	0,768
	Thiopental	46 (73,0)	72 (72,0)	
Additional Dose of Rocuronium (%)	25 (39,7)	18 (48,6)	43 (43,0)	0,382
SpO <sub>2</sub> ( min-max)	97 (91-100)	97 (91-100)	97 (91-100)	0,737
Heart Rate (min-max)	79 (53-108)	80 (61-121)	79,5 (53-121)	0,072
Mean Arterial Pressure (mmHg, Mean± SD)	97,0 ± 10,8	96,0 ± 10,8	96,2 (70,7-122)	0,630
Surgical Time (min, Min-max)	100 (45-360)	120 (45-185)	117,5 (45-360)	0,352
Total Rocuronium Dose (mg kg <sup>-1</sup> , Min-Max)	50 (40-90)	50 (30-80)	50 (30-90)	0,627
TOF Value	100 (87-100)	100 (91-100)	100 (87-100)	<b><i>0,045</i></b>

Categorical data are given as number of cases (percentage). The chi-square test was used in comparison. Mann-Whitney test was used in comparison. A t-test was used in the comparison.  $P < 0.05$  was considered significant. Significant values are in bold and italics. SD: standard deviation. TOF: tools such as train-of-four

**Table 3:** Comparison of TOF According to Whether An Additional Dose of Rocuronium Is Administered

	Additional dose of rocuronium		Total	p value
	Yes n:57	No n:43		
TOF Value (min-max)	100 (87-100)	100 (91-100)	100 (87-100)	0,246

TOF: tools such as train-of-four

## DISCUSSION

Neostigmine and sugamedex are frequently used agents in today's practice to relieve neuromuscular blockade. Our goal is to research and evaluate the residual blockade of these two agents during the postoperative recovery period. As a result of the TOF values we obtained, we saw that both agents were effective in removing the blockage, but the residue rate was lower in the group S.

Neuromuscular blockade in general anesthesia facilitates intubation, reduces possible complications such as vocal cord damage, and allows the surgeon to work more comfortably during the operation (Keating et al., 2016) We used rocuronium in our study because it has a short onset of action and a short-medium duration of action. Although it has a short half-life, agents such as neostigmine and sugammadex are used at the end of the operation to ensure native breathing, obtain sufficient muscle strength, and prevent residual blockade. Residual blockade, which is the main subject of our study, is especially important due to pulmonary complications (pneumonia, prolonged intubation, etc.) (Li et al., 2021). Age, metabolic rate, magnesium use (Mg), neuromuscular diseases (myesenta graves, etc.), as well as diseases such as preeclampsia, are some of the reasons that increase residual blockade. In the articles published by Gupta and colleagues, they showed that magnesium sulfate not only prolongs the duration of action of muscle relaxants but also has an effect as a muscle relaxant (due to being a calcium antagonist) (Gupta et al., 2006). However, in our study, patients with a history of Mg use were not included in the work for standardization of the work.

Neostigmine, a cholinesterase inhibitor, reverses nerve blockade by preventing the metabolism of acetylcholine (Ach) at the neuromuscular junction. However, sugamedex forms a complex with the blocking agent, providing a specific and more rapid reversal of blockade. Reversal of blockade can be measured with devices such as TOF stimulator, and Double burst stimulation (DBS). Since we have a TOF stimulator in our hospital, we performed our measurements with it. A TOF value  $>0.9$  indicates an adequate muscle strength. Geldner et al. published their study with 140 patients and found a faster recovery with sugamadexin compared to neostigmine, and reported a lower incidence of side effects compared to neostigmine. Fortier et al. found that the residual rate (TOF $<0.9$ ) of neostigmine was 9.4% in their prospective multicenter study of 302 patients in Canada (Fortier et al., 2015). In a meta-analysis published in 2016, Carron et al. reported that sugamedex had less residual blockade than neostigmine and was safer than neostigmine (Carron et al., 2016). In their retrospective study of 10491 patients, Li et al.

reported that patients on neostigmine (5.9%) and sugamedex (4.2%) were similar in terms of pulmonary complications (Li et al., 2021) Jones et al. compared 4 mg/kg sugamedex with neostigmine and reported that sugamedex resulted in a faster reversal (Jones et al., 2008). However, we think that the dose of sugamedex in these studies is a dose open to discussion. Because the same effect is obtained with 2 mg/kg in the studies in the literature. As a matter of fact, Pongrácz et al. used different doses of sugamedex (0.5 mg/kg, 1 mg/kg, 2 mg/kg) and reported that 0.5 mg/kg sugamedex provided adequate return in approximately  $8.5\pm 3.5$  minutes, although the duration of action was later (Pongrácz et al., 2013) In the data we obtained in our study, although not clinically significant, statistically, the analysis of TOF values showed that residual blockade was less in the sugamedex group.

Although its safe use in adults has been shown more widely in studies, the use of sugamedex in pediatric patients can be considered its most important limitation. Studies on this subject are more limited and insufficient. Sari et al., in their study in pediatric groups, stated that sugamedex did not show a significant incidence of side effects (Sari et al., 2013). What Duran et al. did in pediatric patients who underwent bronchoscopy in 2021; In their study, they stated that bronchospasm developed in 6 patients, hypoxia developed in 5 patients, and larangospasm developed in 2 patients, and that sugamedex and neostigmine were similar in terms of complications and that sugamedex provided a faster recovery (Duran et al., 2022). It is a clear fact that studies on larger patient groups are needed on this subject.

In our study, there was no difference between the groups in terms of duration of surgery, BMI spo<sub>2</sub> heart rate, mean arterial pressure, total rocuronium consumption, smoking, although this may be due to the lower incidence of side effects of sugamedex. However, we think that the incidence of side effects is lower with sugammadex.

Since our study was a single-center study, the data are limited. In addition, there were no data on the duration of effect since our study was looked at postoperatively in the recovery room.

## CONCLUSION

As a result of the TOF values we obtained, we found that both agents were effective in removing the blockade, but the residual rate was statistically significantly lower in the sugamedex group, although not clinically significant. We did not encounter any complications in our study and we think that sugamedex is safer in terms of residual blockade. Sugamedex group included more elderly

and ASA 3 patients. From this point of view, we think that it is a preference due to the lower incidence of side effects.

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