

Retrospective Comparison of Age-Related Efficacy and Cost of Sugammadex and Neostigmine in Obese Female Patients Undergoing Elective Surgery

Elektif Cerrahi Uygulanan Obez Kadın Hastalarda Sugammadex ve Neostigminin Yaşa Bağlı Etkinlik ve Maliyetinin Retrospektif Olarak Karşılaştırılması

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ABSTRACT

Aim: The purpose of the study is to compare the clinical impact and cost of sugammadex and neostigmine in obese, young-elderly patients

Materials and Methods: In this study, the medical and anesthesia records of patients whose operation did not exceed 150 minutes and who used rocuronium as a muscle relaxant were evaluated retrospectively. Patients whose files were examined were divided into 4 groups according to age and drug given; Group YS: 2 mg/kg sugammadex between 20–60 years, Group ES: 2 mg/kg sugammadex between 60–80years, Group YN: 0.04 mg/kg neostigmin + 0.01 mg/kg atropine between 20–60 years, Group EN: 0.04 mg/kg neostigmin + 0.01 mg/kg atropine between 60–80 years. Time of TOF 25, 75, 90 recovery scores were recorded from the anesthesia records of the patients.

Results: Regarding the time to reach TOF 25,75,90, it was seen that the patients in Group YS and Group ES reached faster TOF values than Group YN and Group EN ($p<0,05$). Compared with neostigmine, patients who were given sugammadex in the same age group were found to have faster recovery time and statistically significant differences ($p<0,05$).

Conclusion: Sugammadex provides rapid and effective reversal of moderate neuromuscular block compared to neostigmine, with a very low incidence of side effects and faster recovery times.

Keywords: Neostigmine, Obesity, Sugammadex, TOF, Age

ÖZ

Amaç: Çalışmanın amacı, obez, genç-yaşlı hastalarda sugammadex ve neostigminin klinik etkisini ve maliyetini karşılaştırmaktır.

Gereç ve Yöntemler: Bu çalışmada, ameliyat süresi 150 dakikayı geçmeyen ve kas gevşetici olarak rokuronyum kullanılan hastaların tıbbi ve anestezi kayıtları retrospektif olarak değerlendirildi. Dosyaları incelenen hastalar yaş ve verilen ilaca göre 4 gruba ayrıldı; Grup YS: 20-60 yaş arası 2mg/kg sugammadexs, Grup ES: 60-80 yaş arası 2mg/kg sugammadexs, Grup YN: 20-60 yaş arası 0,04 mg/kg neostigmin + 0,01 mg/kg atropin, Grup EN: 60-80 yaş arası 0,04 mg/kg neostigmin + 0,01 mg/kg atropin. TOF 25,75,90 zamanı, derlenme skorları hastaların anestezi kayıtlarından kaydedildi

Bulgular: TOF 25,75,90'a ulaşma süreleri açısından Grup YS ve Grup ES'deki hastaların Grup YN ve Grup EN'ye göre daha hızlı TOF değerlerine ulaştığı görüldü. ($p<0,05$). Neostigmin ile karşılaştırıldığında, aynı yaş grubunda sugammadexs verilen hastaların daha hızlı iyileşme süresine sahip olduğu ve istatistiksel olarak anlamlı farklılıklar olduğu bulundu ($p<0,05$).

Sonuç: Sugammadexs, neostigmine göre orta dereceli nöromusküler bloğun hızlı ve etkili geri dönüşümünü sağlamakla birlikte, çok düşük yan etki insidansına ve daha hızlı iyileşme sürelerine sahiptir.

Anahtar kelimeler: Neostigmin, Obezite, Sugammadexs, TOF, Yaş

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Introduction

Neuromuscular blockers are agents frequently used during anesthesia to facilitate tracheal intubation, maintain mechanical ventilation, and make surgical operation conditions favorable. Reversal agents are used to reverse neuromuscular block and prevent postoperative residual curarization [1]

Postoperative residual decurarization due to neuromuscular blocker use is a problem of modern anesthesia. Neostigmine does not allow safe decurarization, especially when neuromuscular block monitoring cannot be performed [2]. Since these agents do not have full nicotinic selectivity, they also stimulate the muscarinic system and many serious undesirable effects may be encountered. To avoid these effects, decurarization is usually performed with the concomitant use of an anticholinergic agent (atropine, glycopyrrolate, etc.) [3].

Sugammadex is a fast-acting drug designed to surround rocuronium bromide [4]. Administration of sugammadex during rocuronium-induced neuromuscular block leads to rapid separation of free rocuronium molecules from plasma. A concentration gradient is formed as the remaining rocuronium molecules move from the neuromuscular junction to the plasma. Neuromuscular block ends rapidly with the diffusion of rocuronium molecules from the neuromuscular junction to the plasma [5].

As the obese and elderly population is increasing, the number of obese and elderly receiving general anesthesia is also growing. Anesthetic management is more difficult in obese and elderly patients. Geriatric patients are more sensitive to the depressant effect of the anesthetic drugs used and redistribution and elimination of the drugs used are slower [3]. Prolonged neuromuscular blockade is more frequently observed in obese patients because the distribution, metabolic half-life, and excretion of neuromuscular blockers change [6]. Most muscle relaxants are hydrophilic and their effects start early and last longer in obese patients [7]. The growth in the number of general anesthesia in elderly and obese patients leads to an increase in the number of perioperative complications, which in turn leads to an increase

in patient costs [8-9].

We aimed to compare the clinical efficacy and cost of sugammadex and neostigmine in obese-elderly and obese-young patients scheduled for elective surgery due to the increase in the obese and elderly population and the increase in healthcare costs.

Materials and Methods

In this study, after the approval of Suleyman Demirel University Clinical Research Ethics Committee (decision dated 27.07.2016 and numbered 134), the files of a total of 130 patients who underwent an elective operation in Suleyman Demirel University Faculty of Medicine, Obstetrics and General Surgery between January 1, 2016, and June 31, 2016, were retrospectively analyzed.

The data of American Society of Anesthesiologists (ASA) I-II, 20-80 years old, obese (BMI: 30-40) patients who underwent general anesthesia under elective conditions, whose operation time did not exceed 150 minutes, who used propofol, fentanyl, lidocaine, rocuronium as muscle relaxant in induction, desflurane, oxygen and nitrogen protoxide in maintenance and whose muscle relaxant effect was reversed with neostigmine or sugammadex were included in the study.

Exclusion criteria were determined; pregnant women, patients with liver failure, renal failure, morbid obesity, muscle disease, magnesium, calcium channel-blocking drugs, and those allergic to the drugs used were excluded from the study.

Information about the patients was collected by examining anesthesia forms, our hospital's data processing program, epicrises, and archive files. However, 20 patients were not included in the study because of missing data, 5 patients were pregnant and 5 patients had preoperative calcium channel blocker use in the evaluated files. The remaining 100 patients were divided into 4 groups according to their data and evaluated:

GROUPS:

GROUP Young-Sugammadex (YS): 2mg/kg sugammadex between 20-60 years of age

GROUP Young-Neostigmine (YN): 0.04 mg/kg

neostigmine + 0.01 mg/kg atropine between 20-60 years of age

GROUP Elderly-Sugammadex (ES): 2 mg/kg sugammadex between 60-80 years of age

GROUP Elderly-Neostigmine (EN): Patients aged 60-80 years who received 0.04 mg/kg neostigmine + 0.01 mg/kg atropine were divided into groups.

According to the data we obtained from the files, patients were evaluated in terms of demographic data (age, height (cm), weight (kg), Body Mass Index (BMI) (kg/m²), Corrected Body Weight (CBW) (kg), rocuronium dose (mg), surgical time (min), Train of four (TOF) values (TOF 25-75-90), recovery time (time from extubation to MAS 9), complications - side effects, cost (drug vial price per patient) and comparisons were made.

The doses of the drugs used were calculated and administered according to the patient's corrected body weight (CBW).

CBW: ideal body weight (IBW)+0.4*(real body weight(RBW) - IBW), IBW: height (cm) - 105, BMI: weight/height (m²) was calculated according to the formulas.

Statistical Analysis

All data were analyzed with the statistical program SPSS 20.0 (Statistical Package for Social Sciences Inc; Chicago, IL, USA). Qualitative data were presented as numbers and percentages, and quantitative data were presented as mean and standard deviation. Kolmogorov-Smirnov test was used to analyze the distribution of the data. In this context, parametric tests were applied to normally distributed data, while nonparametric tests were applied to non-normally distributed data. The chi-square test was used to analyze qualitative data and the Mann-Whitney U test was used to analyze quantitative data. A two-way ANOVA test was used for intragroup comparisons. p< 0.05 was considered statistically significant.

Results

Demographic characteristics, CBW (kg), BMI (kg/m²), surgical time (min), and total rocuronium dose (mg) are shown in Table 1. There was no difference between the groups in terms of demographic

characteristics, CBW, total rocuronium dose, and duration of surgery, but there was a statistical difference in terms of age.

Table 1. Demographic characteristics, rocuronium dose, and duration of surgery according to groups

	Group YN (n:25)	Group YS (n:25)	Group EN (n:25)	Group ES (n:25)	*p
Age (years)	49.9 ±5.3	45.2 ±5.6	66.6 ±6.0	65.7±5.2	<0.001*
Height (cm)	157.4 ±3.8	157.6 ±4.1	158.0 ±5.1	157.6 ±3.9	0.965
Weight (kg)	83.6 ±7.7	82.4 ±6.6	81.3 ±9.8	79.9±5.4	0.359
BMI (kg/m ²)	33.3 ±2.0	33.2 ±2.4	32.7 ±2.8	32.4±2,1	0.464
CBW (kg)	65.0 ±5.0	65.4 ±4.0	64.4 ±6.0	64.0±3,6	0.740
Rocuronium Dose (mg)	54.88 ±10.2	55.2 ±8.9	52.6 ±7.7	57±7.2	0.652
Surgical time (min)	104.8 ±28.3	99.6 ±23.1	105.2 ±25.0	113.2 ±20.9	0.275

BMI: Body Mass Index, CBW: Corrected Body Weight, min:minutes
Data are shown as mean ±SD, Chi-square test used in the analysis of the variables, (p<0.05): Statistically significant

When TOF 25, 75, and 90 values were analyzed in patient groups aged 20-60 years, it was observed that sugammadex was more effective than neostigmine and there was a statistically significant difference (p<0.05) (Table 2). When TOF 25, 75, and 90 values were analyzed in the patient groups aged 60-80 years, it was observed that sugammadex was more effective than neostigmine and there was a statistically significant difference (Table 2).

Table 2. TOF 25, 75, and 90 values of sugammadex and neostigmine in patient groups aged 20-60 years and 60-80 years

	Group YN (n:25)	Group YS (n:25)	Group EN (n:25)	Group ES (n:25)	*p
TOF 25 (min)	6.64±1.8	1.52±0.7	7.08±1.1	1.72±0.7	<0.001*
TOF 75 (min)	9.68±2.0	2.72±0.8	10.48±1.4	2.96±0.7	<0.001*
TOF 90 (min)	11.24±2.4	3.04±0.7	12.16±1.6	3.80±0.7	<0.001*

TOF: Train of Four. Data are shown as mean ±SD, Chi-square test used in the analysis of the variables, (p<0.05): Statistically significant

When the recovery times were analyzed, it was observed that those who received sugammadex recovered faster than neostigmine in the patient groups aged 20-60 years (Group GN-Group GS) and it was found to be statistically significant (p<0.05) (Table 3). In patients aged 60-80 years (Group YN-Group YS), those who received sugammadex recovered faster than those who

received neostigmine, which was statistically significant ($p < 0.05$) (Table 3).

Table 3. Recovery times of patients aged 20-60 years and 60-80 years who received sugammadex and neostigmine

	Group YN (n:25)	Group YS (n:25)	Group EN (n:25)	Group ES (n:25)	^a p
Recovery time (min)	13.16±7.6	7.92±4.4	14.4±6.7	9.08±3	<0.001*

Data are shown as mean ±SD, $p < 0.05$: Statistically significant, Chi-square test used in the analysis of the variables

When the complications and side effects between the groups were analyzed, no side effects and complications were observed in Group YS, nausea-vomiting was observed in one patient, and surgical incision site pain was observed in one patient in Group ES. In Group YN, salivation was observed in 6 patients, surgical incision site pain in 1 patient, and spasm in 1 patient. In group EN, increased salivation was observed in 5 patients, surgical incision site pain in 1 patient, nausea-vomiting in 2 patients, and bradycardia in 1 patient. When compared between groups, there was a significant difference in complications and side effects in neostigmine groups compared to sugammadex ($p = 0.032$).

When sugammadex and neostigmine were compared in terms of cost, it was observed that the price per patient of sugammadex (price per patient; 85 TRY) was higher than the other group (price per patient; 3.37 TRY) and there was a statistical significant difference ($p < 0.05$).

Discussion

Neuromuscular blocking agents (NMBA) are an important part of modern anesthesia. Muscle relaxants provide more favorable intubation conditions by suppressing voluntary and reflex muscle movements. In addition, adequate muscle relaxation is achieved for surgical intervention under less anesthetic agent requirement [10].

Sugammadex is a new-generation cyclodextrin derivative agent used in the reversal of the effect of steroidal NMBAs. It encapsulates lipophilic NMBAs with high affinity and forms encapsulation. Thus, the binding of steroidal NMBAs to the receptor is prevented [11]. Sugammadex can be administered at doses between 2 mg/kg and 16

mg/kg depending on the depth of neuromuscular blockade [12]. Sorgenfrei et al. examined the dose-response relationship of sugammadex in reversing neuromuscular block provided by rocuronium in their study, administered sugammadex at doses of 0.5, 1.0, 2.0, 3.0, and 4.0 mg/kg and found that sugammadex dose of 2 mg/kg and above was safe [13]. In our study, 2 mg/kg sugammadex was applied in moderate neuromuscular blocks (when TOF was 2) in parallel with the literature.

Neostigmine inhibits acetylcholinesterase at the nerve-muscle junction and increases acetylcholine levels and enables non-depolarizing muscle relaxant drugs to discharge acetylcholine receptors through competitive inhibition [3]. Choi et al. administered neostigmine at doses of 10 mcg/kg, 20 mcg/kg, and 40 mcg/kg in the superficial neuromuscular blockade and TOF values were examined. It was found that neostigmine administered at 40 mcg/kg reversed neuromuscular block effectively [14]. In our study, neostigmine was administered at a dose of 40 mcg/kg.

Obesity leads to changes in the pharmacodynamics of anesthetic drugs [7]. Van Lancker P. et al. compared the dose of sugammadex according to four different weights in morbidly obese patients (BMI>40) in the reversal of neuromuscular block provided by rocuronium. The time from TOF 2 to TOF 0.9 was IBW: 188 sec, IBW+IBW(20%): 154 sec, IBW+IBW(40%): 112 sec and RBW: 128 sec. In this study, sugammadex 2 mg/kg IBW+IBW (40%) was recommended as the optimal dose [15]. In our study, similar to this study, drugs were administered at the same dose according to CBW to reverse the neuromuscular block induced by rocuronium.

When we look at the studies comparing the efficacy of sugammadex and neostigmine, Woo et al. showed that sugammadex at a dose of 2 mg/kg administered when TOF ratio reached 2 provided TOF 0.9 after an average of 1.8 minutes, whereas the average time to reach TOF 0.9 with neostigmine administered when TOF was 2 was found to be 14.8 minutes in their study on a total of 128 patients [16]. In a review by Chambers et al., the clinical effect of sugammadex was evaluated and a total of 2132 abstracts and 265 publications

were reviewed. In shallow blocks, mean TOF values of 1.3-1.7 min for sugammadex, 21-86 min for placebo, 17.6 min for neostigmine, and 0.9 TOF values were found. In deep blocks, TOF 0.9 values of 2.7 min for sugammadex, >90 min for placebo, and 49 min for neostigmine were found [17]. Unal et al. compared the efficacy, cost, and respiratory complications of sugammadex and neostigmine in patients with obstructive apnea syndrome. In the times to reach TOF 0.9, sugammadex was found to be 2 minutes and neostigmine 8 minutes [18]. In our study, the time to reach TOF 0.9 was found to be 3.04 min for sugammadex in young patients and 3.8 min in elderly patients, while neostigmine was found to be 11.24 min in young patients and 12.16 min in elderly patients and a statistically significant difference was found ($p<0.001$).

Ach esterase inhibitors affect muscarinic receptors as well as nicotinic receptors and related side effects occur (bradycardia, hypotension, bronchoconstriction, hypersalivation, nausea, and vomiting) [19]. Sugammadex, on the other hand, affects NMBA via encapsulation, and muscarinic side effects are not observed since there is no interaction at the receptor level [20]. Diego et al. investigated postoperative visual analog score and nausea and vomiting in 88 morbidly obese patients who underwent bariatric surgery. The patients were divided into two groups neostigmine and sugammadex. In the post-anesthetic care unit (PACU), the visual analog score and nausea and vomiting values of the group given sugammadex were found to be lower at 30 and 60 minutes [21]. Similar to the results of the previous studies, side effects were observed less in the patient groups receiving sugammadex in our study.

Residual curarization is the presence of still blocked nicotinic receptors in the postoperative patient [22]. Although the effect of NMBAs is carefully monitored and reversed in the operating room, residual effects may occur in the early period. Esteves et al. found that 26% of patients admitted to PACU had a TOF value below 0.9 [23]. It has been reported that residual curarization is higher in elderly patients and therefore, it is recommended that neuromuscular junction conduction monitoring should be performed in the recovery room until the postoperative TOF ratio is 0.9 and above to prevent residual curarization,

especially in elderly patients [24]. Considering these studies, the gold standard TOF response that provides neuromuscular recovery has been accepted as 0.9.

Looking at the studies in which postoperative recovery scores were evaluated, Pişkin et al. compared the postoperative recovery times of sugammadex and neostigmine in their study and found that the MAS ≥ 9 score of sugammadex and neostigmine was 8.26 min and 16.93 min, respectively, and a statistically significant difference was found [25]. When MAS in our study was analyzed, a statistically significant difference was found between the sugammadex and neostigmine groups ($p<0.001$).

In terms of cost, in the study conducted by Unal et al., the efficacy and cost of sugammadex and neostigmine were compared in patients with obstructive apnea syndrome, and although the vial price of sugammadex was higher in terms of cost, sugammadex was found to be more advantageous than neostigmine in terms of complications and total cost [17]. In terms of cost, sugammadex was found to be more expensive than neostigmine in terms of drug price in our study and a statistically significant difference was found ($p<0.001$). However, a complete cost analysis could not be performed because the effect of the time spent in the operating room and PACU on the price, the prices of operating room doctors, technicians, and personnel were not taken into account, and the prices of the patient's side effects and complication-related conditions could not be calculated.

Our study has some limitations. The first of these is that our study was retrospective. In addition, difficulties in accessing archival documents, insufficient epicrises, and deficiencies in anamnesis forms caused difficulties. Another limitation is that TOF values were not analyzed in PACU, and the lack of detailed cost analysis constitutes another limitation of the study.

Conclusion

Despite its higher cost compared to neostigmine in young and elderly obese patients, sugammadex was found to be effective in terms of rapid and effective reversal from moderate neuromuscular

block, very low incidence of side effects, and reduced recovery time.

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