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# Reversal of Rocuronium Induced Neuromuscular Blockade in Lung Resection Surgery: A Comparison of Sugammadex and Neostigmine

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# *Akciğer Rezeksiyonu Cerrahisinde Rokuronyumun Nöromüsküler Blok Etkisinin Geri Döndürülmesi: Sugammadeks ve Neostigminin Karşılaştırılması*

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## ABSTRACT

***Introduction:*** *The aim of this study was to compare sugammadex and neostigmine in terms of reversing time, recovery time and extubation time in reversal of rocuronium-induced neuromuscular block in patients undergoing lung resection surgery.*
***Method:*** *A total of 60 patients under 75 years of age with an ASA status of II-III undergoing elective pulmonary resection (lobectomy, pneumectomy, wedge resection) who had adequate left ventricle function (EF >40%), normal renal, hepatic, and mental functions, were included in this study Patients were assigned into neostigmine (Group N, n=30) and sugammadex (Grup S, n=30) groups.*
***Results:*** *Time from starting of neuromuscular blockade reversing agent till reaching TOF>0.9 was significantly shorter in Group S (p=0.001). Similarly, extubation time and recovery time were significantly shorter in Group S (p=0.05; p=0.012, respectively). No statistically significant differences were observed between the two groups in terms of the operation time and duration of ICU stay. Postoperative complications were similar in both groups. Postoperative residual curarisation was not observed in both groups.*
***Conclusion:*** *In lung resection surgery, sugammadex appears to be a superior selective relaxant binding agent as compared to neostigmine in the reversal of rocuronium- induced neuromuscular block with earlier recovery and earlier achievement of TOF ratio of 0.9.*

***Keywords:*** *lung resection, one lung ventilation, sugammadex, neostigmine, rocuronium*

## ÖZ

***Amaç:*** *Bu çalışmanın amacı, tek akciğer ventilasyonu ile opere edilen hastalarda, rokuronyum ile oluşturulan nöromüsküler blokajın geri döndürülmesinde sugammadeks ve neostigminin geri döndürme süresi, derlenme süresi, ekstubasyon süresi açısından karşılaştırılmasıdır.*
***Yöntem:*** *Çalışmaya elektif lobektomi, pnömektomi veya wedge rezeksiyon planlanan ASA 2-3 grubu, 75 yaş altı, renal ve hepatik fonksiyon bozukluğu olmayan ve sol ventrikül ejeksiyon fraksiyonu %40'ın üzerinde olan toplam 60 hasta dâhil edildi. Hastalar Grup N (Neostigmine Grubu) ve Grup S (Sugammadeks Grubu) olmak üzere 2 gruba ayrıldı.*
***Bulgular:*** *Nöromüsküler blokajı geri döndürmek için uygulanan ajan sonrası TOF>0.9'a ulaşana kadar geçen süre Grup S'de anlamlı olarak daha kısa bulundu (p=0.001). Benzer şekilde ekstübasyon süresi ve derlenme süresi Grup S'de anlamlı olarak daha kısaydı (sırasıyla p=0.05; p=0.012). Ameliyat süreleri ve yoğun bakımda kalış süreleri açısından 2 grup arasında istatistiksel olarak anlamlı bir farklılık gözlenmedi. Postoperatif komplikasyonlar açısından her 2 grup arasında anlamlı farklılık bulunamadı. Hiçbir hastada postoperatif rekürarizasyon gözlenmedi.*
***Sonuç:*** *Çalışmamız, elektif akciğer rezeksiyonu ameliyatlarında nöromusküler bloke edici ajanın etkilerinin geri döndürülmesinde sugammadeksin neostigmine göre TOF oranının 0.9'a daha erken ulaşmasını sağlaması ve daha erken derlenmeye neden olması açısından daha üstün olduğunu göstermektedir.*

***Anahtar kelimeler:*** *akciğer rezeksiyonu, tek akciğer ventilasyonu, sugammadeks, neostigmin, rokuronyum*

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## INTRODUCTION

In patients undergoing lung resection surgery, postoperative complications such as respiratory failure, hypoxia, atelectasis, or metabolic disturbances are commonly observed following general anesthesia as a result of a number of factors such as the underlying disorder(s), and the site and extent of the lung resection [1]. In these patients, hypoxia, delayed extubation, or re-intubation may also occur due to postoperative residual curarization (PORC). The complications may also lead to prolongation of the intensive care unit (ICU) stay as well as increased treatment costs. Incomplete reversal of the effect of muscular relaxant may result in the failure to obtain full opening of the upper airways, aspiration, or impaired hypoxic respiratory stimulation through an effect on the peripheral chemoreceptors sensitive to hypoxia, even if a train-of-four (TOF) ratio greater than 0.7. In addition, even if a TOF ratio greater than 0.7 is accepted as the minimal threshold for extubation, more than half of the patients fail to achieve this degree of recovery [2]. Neostigmine inhibits the acetylcholinesterase enzyme in the neuromuscular junction, increases the amount of Ach in the junction, and allows the restoration of the agonist response against the competitive antagonist effect of the neuromuscular blocking agents. Especially in risk patients, when these drugs are given at the end of surgery, bronchoconstriction may developed or may be triggered by other factors such as tracheal tube, pain; which may cause postoperative pulmonary complications [3]. Sugammadex, a selective agent specifically developed for the amino-steroid neuromuscular blockers such as rocuronium and vecuronium, is used to reverse the neuromuscular block in patients undergoing anesthesia. Sugammadex is a modified gamma-cyclodextrin with a lipophilic nucleus and water soluble cyclic oligosaccharide structure. It is lead to allow the formation of a compound that on one hand allows the entrance of the steroid part of the neuromuscular blocking agent into the lipophilic nucleus while on the other hand does not permit its exit. Encapsulation acts as a synthetic receptor that allows separation of NMBA from the nicotinic Ach receptor. The complex formed this way results in quick decrease in the plasma free rocuronium concentrations [4,5].

The aim of the study reported in the present paper was to test the hypothesis that sugammadex improves neuromuscular blockade reversal in patients undergoing one lung ventilation compared with neostigmine. The primary endpoint of the study was the difference of the time from starting to till reaching TOF ratio>0.9. Secondary endpoints of the study were the recovery time, extubation time, duration of ICU stay and complications such as postoperative nausea and/or vomiting (PONV), sore throat, shivering, coughing, and hemodynamic changes.

## MATERIAL and METHODS

This study was carried out in accordance with the Declaration of Helsinki, approved by the Ethics Committee of the Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Istanbul, Turkey. Written informed consent was obtained from all patients. Patients who received general anesthesia for elective pulmonary resection (lobectomy, pneumectomy, wedge resection) were randomized by means of a computer-generated randomization order into two groups: Neostigmine Group (Group N) and Sugammadex Group (Group S). Patients with inadequate left ventricle function (EF <40%), abnormal renal or hepatic functions, presence of carotid lesions, abnormal mental functions, as well as body mass index of <18.5 or >25 kg/m$^2$ were excluded.

All patients were premedicated with intravenous midazolam 0.03 mg kg$^{-1}$. On arrival of the patient in the operating room, a peripheral venous catheter was established. Standard monitoring included invasive blood pressure (via 20G catheter in radial artery for continuous arterial pressure monitoring and blood gas sampling), 5-lead electrocardiography, and pulse oximetry. In all patients, general anesthesia

was induced with intravenous midazolam, 0.1 mg $kg^{-1}$, propofol, 2 mg $kg^{-1}$, fentanyl, 2 µg $kg^{-1}$. Neuromuscular blockade was monitored using TOF Watch SX® (Organon Ltd., Dublin, Ireland) acceleromyography, with skin electrodes located at the ulnar nerve trace to trigger stimulation of the adductor pollicis muscle. After calibration and stabilization of neuromuscular monitoring were performed in a standardized manner for each patient, rocuronium was administrated in a dose of 0.6 mg kg-1 and tracheal intubation was undertaken when twitch suppression was greater than 95%. All patients were intubated tracheally, with a 35F or 37F double lumen endotracheal tube (DLT) in females and a 37F or 39F DLT in males. Correct placement was determined using auscultation and fiberoptic bronchoscopy. Immediately after tracheal intubation, TOF ratio was checked; the post-tetanic count (PTC) was also checked when no TOF count was obtained. PTC was checked every 3 min to maintain a PTC count of 1 to 2. Bolus doses of 0.15 mg $kg^{-1}$ of rocuronium were used as appropriate to maintain PTC target. Anesthesia was maintained with 50% air and 5% to 6% desflurane in oxygen with positive-pressure ventilation in a circle system. End-tidal carbon dioxide was maintained between 30 and 35 mmHg. The depth of anesthesia was monitored using the bispectral index score (BIS) through standard electrodes (BIS-Sensor, Aspect Medical Systems, Norwood, MA, USA) on the forehead and, anesthetic dosage was adjusted to achieve a BIS value between 40 and 60 from the initiation of anesthesia to the end of surgery. Normothermia was preserved during the surgery. At the end of surgery, residual neuromuscular blockade was reversed with neostigmine at 0.05 mg $kg^{-1}$ combined with atropine 0.02 mg $kg^{-1}$ in the neostigmine group and with sugammadex 2 mg $kg^{-1}$ in the sugammadex group. An independent anesthesiologist prepared and coded the syringes containing the neuromuscular blockade reversal and gave to the anesthesiologists who were blinded to the administration of neuromuscular blockade reversal, responsible for data collection and in charge of TOF monitoring. At the end of the surgery, 0.9 desflurane administration was switched off in both groups and patients were extubated when TOF ratio reached 0.9.

Recovery time was defined as the time from the administration of neuromuscular blockade reversing agent to ability to hold the head or leg for 5 sec, hand gripping for 5 sec, presence of swallowing reflex, and the time to full recovery of consciousness. Extubation time was defined as the time from stoppage of anesthetic inhalation until the patient fulfilled criteria for safe extubation. PORC was defined either on the operating table or in the ICU as the patient's inability to lift and hold her/his head up for at least five seconds and/or inability to cough effectively or TOF<0.9 despite receiving a reversal agent. Duration of surgery, time from starting of neuromuscular blockade reversing agent till reaching TOF ratio > 0.9, recovery time, extubation time, duration of ICU stay and postoperative adverse events such as PONV, sore throat, shivering, coughing and bradycardia and PORC were also recorded.

All the patients were admitted to the intensive care unit (ICU) after surgery. Criteria for discharge from the ICU were that patients must be awake, cooperative, hemodynamically stable, have both an acceptable respiratory pattern and blood gas analysis (partial pressure of oxygen >70 mmHg and partial pressure of carbon dioxide <50 mmHg), and VAS score<5.

### Statistical analyses

Calculation of the sample size was based on the time from starting of sugammadex or neostigmine till reaching TOF ratio greater than 0.9. On the basis of previous studies, a calculated sample size of 23 patients per group was required to provide a statistical power of 0.90 and an alpha of 0.05 to demonstrate a 7 minute difference in the above time. Therefore, 30 patients per group were included to replace any dropouts. Statistical analysis was performed using the SPSS version 21 statistical software (SPSS Inc., Chicago, IL, USA). In addition to descrip-

tive statistics (mean, standard deviation), Kolmogorov-Smirnov test was used for the examination of the normal distribution of the data. Qualitative data were compared using chi-square test, while for quantitative data comparison Mann Whitney U test was used for the comparison of parameters between the groups. Within group comparisons for parameters was performed using Wilcoxon test. The results were assessed at a confidence interval of 95% with significance ($p<0.05$) and high significance ($p<0.01$) levels.

## RESULTS

A total of 90 patients were assessed for eligibility but a total of 30 patients were excluded. Twenty five patients did not meet the inclusion criteria and five patients refused to participate to study. Therefore, 60 patients enrolled in the study (Figure 1).

There was no difference in age, gender, height, weight, body mass index, and American Society of Anesthesiologists (ASA) physical status between the two groups (Table 1).

Time from starting of neuromuscular blockade reversing agent till reaching TOF>0.9 was significantly shorter in Group S (22±7.2 vs 6.1±4.1; $p=0.001$). Similarly, extubation time and recovery time were significantly shorter in Group S (26.2±8.3 vs 7.6±4.6; $p=0.05$, 29.1±7.4 vs 11.4±5.2; $p=0.012$, respectively). No statistically significant differences were observed between the two groups in terms of the operation time and duration of ICU stay ($p>0.05$). There were no significant differences in postoperative adverse events between the two groups. PORC was not observed in both groups. Complications such as pneumonia and atelectasia were similar in both groups ($p=0.545$) (Table 2).

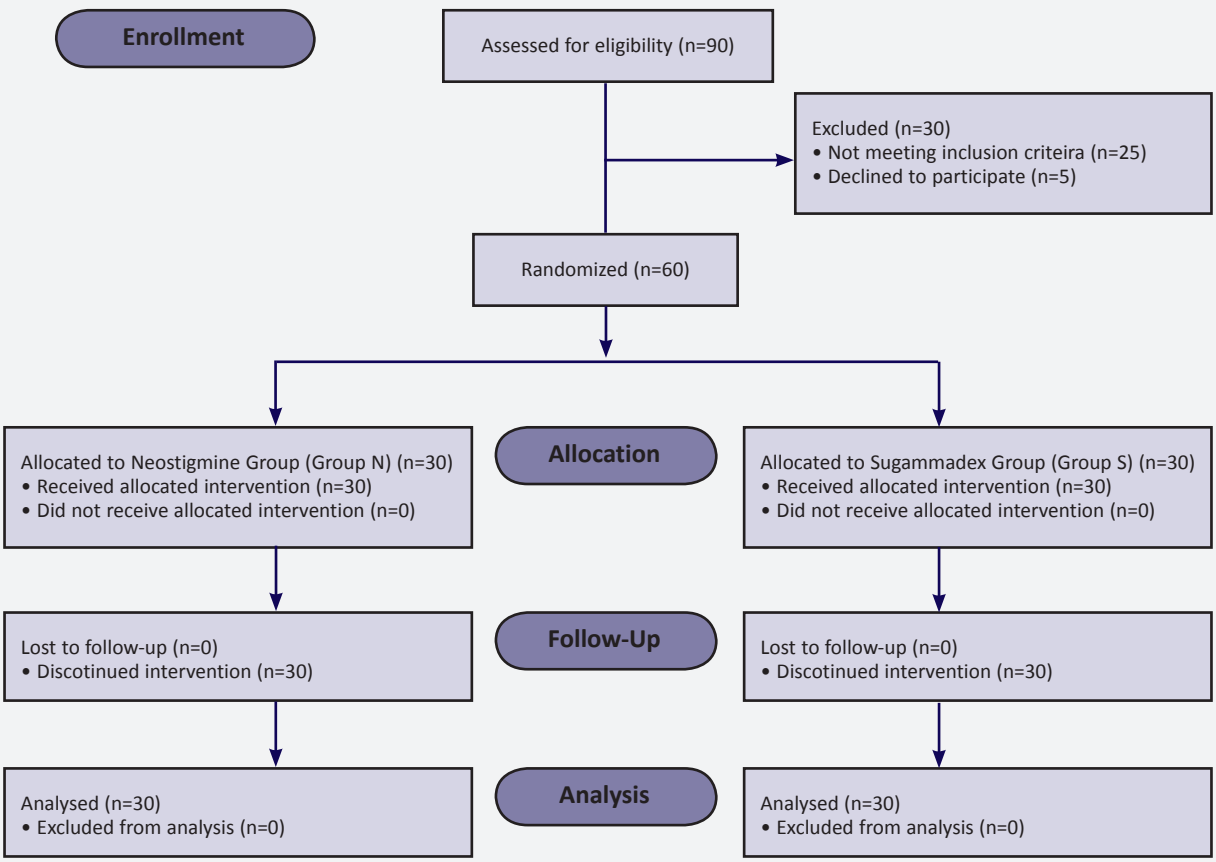


**Figure 1. Consort flow diagram.**

**Table 1. Patient characteristics (values are the mean±SD or the number and percentage).**

| | Group N (n=30) | Group S (n=30) | P value |
|---|---|---|---|
| Age, years | 52±9.6 | 51±10.2 | 0.676 |
| BMI, kg/m$^2$ | 23±3 | 23±4 | 0.893 |
| **Gender** | | | |
| Male, n (%) | 19 (63) | 20 (67) | 0.538 |
| Female, n (%) | 11 (37) | 10 (33) | 0.395 |
| **ASA status** | | | |
| II, n (%) | 15 (50) | 17 (57) | 0.634 |
| III, n (%) | 15 (50) | 13 (43) | 0.415 |
| **Type of surgery** | | | |
| Lobectomy, n (%) | 16 (53) | 14 (47) | 0.266 |
| Pneumonectomy, n (%) | 5 (17) | 6 (20) | 0.454 |
| Wedge resection, n (%) | 9 (30) | 10 (33) | 0.567 |

*BMI body mass index, ASA American Society of Anesthesiologists*

Heart rate was statistically higher and mean arterial pressure was statistically lower in Group N two min after administration of neuromuscular blockade reversing agent (p=0.033 and p=0.045, respectively). There were no significant differences between Group N and Group S in terms of HR and MAP after the last dose of rocuronium administered (Table 3).

**Table 3. Hemodynamic variables (values are the mean±SD).**

| | Group N (n=30) | Group S (n=30) | P value |
|---|---|---|---|
| **Heart rate, beats/min** | | | |
| After the last dose of rocuronium | 79±16 | 78±14 | 0.476 |
| 2 min after neostigmin or sugammadex administered | 87±16 | 76±16 | 0.033* |
| **Mean arterial pressure, mmHg** | | | |
| After the last dose of rocuronium | 86±13 | 90±7 | 0.289 |
| 2 min after neostigmin or sugammadex administered | 95±12 | 102±9 | 0.045* |

**p<0.05*

## DISCUSSION

This randomized prospective study demonstrated that use of sugammadex statistically shortened the time from starting of neuromuscular blockade reversing agent till reaching TOF>0.9, recovery time and extubation time compared to the use of neostigmine.

**Table 2. Outcome variables (values are the mean ± SD or the number and percentage).**

| | Group N (n=30) | Group S (n=30) | P value |
|---|---|---|---|
| Time from starting of neuromuscular blockade reversing agent till reaching TOF>0.9, min | 22±7.2 | 6.1±4.1 | 0.001* |
| Duration of anesthesia, min | 207±36.9 | 221±40.1 | 0.199 |
| Duration of surgery, min | 184.8±44.9 | 202.2±38.8 | 0.249 |
| Extubation time, min | 26.2±8.3 | 7.6±4.6 | 0.005* |
| Recovery time, min | 29.1±7.4 | 11.4±5.2 | 0.012* |
| Duration of ICU stay, h | 14.4±5.1 | 16.2±3.9 | 0.432 |
| Rocuronium total dose, mg | 98.6±30.1 | 106.7±32.4 | 0.294 |
| **Postoperative adverse events** | | | |
| PONV | 3 (10) | 1 (3) | 0.714 |
| Sore throat | 1 (3) | 1 (3) | 1.000 |
| Shivering | 1 (3) | 1 (3) | 1.000 |
| Coughing | 2 (7) | 0 | 0.672 |
| Bradycardia | 1 (3) | 0 | 0.870 |
| **Complications** | | | |
| Pneumonia | 1 (3) | 1 (3) | 1.000 |
| Atelectasia | 2 (7) | 1 (3) | 0.545 |

*ICU intensive care unit, PONV postoperative nausea and/or vomiting,*

Incidence of postoperative pulmonary complications in lung resection surgery is greater than in other major procedures [6]. Therefore, reversal of neuromuscular block in lung resection surgery is very important due to avoid of postoperative pulmonary complications. Both neuromuscular monitoring and reversing of neuromuscular blockage are the most important issues of the management of neuromuscular blockade. Bailard et al reported that increased in quantitative measurement and reversal of neuromuscular block in the operating room was resulted the incidence of residual neuromuscular block defined as a TOF ratio less than 0.9 decreased from 62 to 3%. Murphy et al [7] reported that incomplete neuromuscular recovery was an important contributing factor in the development of adverse respiratory events after general anesthesia.

Traditionally, acetylcholinesterase inhibitors (e.g. neostigmine, piridostigmine, edrophonium) have been used for the reversal of the effect of neuromuscular blocking agents through inhibition of Ach breakdown in the neuromuscular junction [8,9]. However, several disadvantages associated with the use of these agents such as cholinergic side effects (bradycardia, bronchospasm, bronchial secretion, abdominal cramps) and, in certain situations inadequate reversal of the neuromuscular block, have limited their use. Sugammadex represents a novel approach for quick reversal of NMB. In patients undergoing surgery, sugammadex allows dose-dependent reversal of NMB due to rocuronium or vecuronium [10]. In comparative studies, sugammadex exhibited superiority over cholinesterase inhibitors in terms of the reversal of NMB at different time-points after rocuronium or vecuronium administration [11]. For instance, in routine reversal of deep NMB under sevoflurane anesthesia, the median time to TOF 0.9 recovery was 18-fold shorter with sugammadex than with neostigmine [9]. Sorgenfrei et al [12] examined the time from baseline to TOF ratio recovery for sugammadex and placebo at the time of re-emergence of T2. Accordingly, the time to TOF 0.9 was 21 minutes for placebo vs. 1.2 minutes for 3 mg $kg^{-1}$ of sugammadex and 1.1 minutes for 4 mg $kg^{-1}$ of sugammadex. Jones et al. [9] sugammadex and neostigmine were compared in their ability to reverse rocuronium or vecuronium induced NBT at 1-2 PTC. They reported that reversal of profound rocuronium-induced neuromuscular blockade was significantly faster with sugammadex versus with neostigmine. Choi et al [13] reported that sugammadex as the reversal agent significantly improved surgical conditions and reduced recovery time compared with neostigmine reversal. Similar to these reports, our patients who received neostigmine had a significantly prolonged time to TOF 0.9 as compared to those in sugammadex group.

In a study by Lemmens et al [14] sugammadex had no significant effects on blood pressure, heart rate, respiration, or thermoregulation. Kizilay et al [15] reported that sugammadex provided more hemodynamic stability compared to neostigmine-atropine combination in cardiac patients undergoing noncardiac surgery. In the current study, heart rate was statistically higher and mean arterial pressure was statistically lower two min after administration of sugammadex than neostigmine; which were consistent with previous studies.

Reversal of neuromuscular blockade by sugammadex is rapidly and achivement of deep breaths without residual muscle relaxation is more quickly [16]. These result in reduce the incidence of atelectasis and help to restore pulmonary function. Because the incidence of pulmonary complications is higher in lung resection surgery, sugammadex may be superior in terms of reducing these complications. However, in the current study, there are no differences in both groups in terms of postoperative pulmonary complications.

PORC following intraoperative neuromuscular blocking agent administration is common in the postoperative period, with rates ranging from 26% to 64% [17,18]. Errando et al [19] reported that 26.7% of patients had PORC after the use of a non-depolarising neuro-

muscular blocker. The fifth edition of the Association of Anesthetists of Great Britain and Ireland standards of monitoring was indicated that monitoring of neuromuscular blocking agents was mandatory [20]. Arbous et al [21] observed a significant decrease in PORC when monitoring muscle relaxation in the operating room and using reversal agents. Butterfly et al explained that the reason of lower incidence of PORC was the use of reversal of neuromuscular block [22]. PORC was not observed in any patients in the current study. The reason for this, consistent with the Butterfly et al, may be due to use of reversal of neuromuscular block. Another reason may be that the small sample size in the current study is insufficient to evaluate PORC.

In conclusion, although there was no difference in postoperative adverse events, sugammadex exhibited superiority over neostigmine in the reversal of rocuronium induced neuromuscular block as evidenced by earlier recovery and shorter time to TOF 0.9 in patients undergoing lung resection surgery. Further studies with higher sample sizes should be performed to support the conclusions of the current study.

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