European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 2022; 26: 4289-4294

Effects of sugammadex and neostigmine on mucociliary clearance in general anesthesia

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Abstract. – OBJECTIVE: The aim of this study was to evaluate the effects of sugammadex and neostigmine used in general anesthesia on postoperative mucociliary clearance.

PATIENTS AND METHODS: This prospective, randomized and double-blind study was performed on 60 non-smokers with ASA I-III underwent inguinal hernia repair under general anesthesia. Mucociliary clearance was assessed by nasal saccharine transit time (STT). After the preoperative STT measurement, the patients were taken to the operating room, and divided into two equal groups as group 1 and 2 (n= 30 for each group). Midazolam, propofol, and rocuronium were used in all patients. Anesthesia was maintained by sevoflurane at a flow rate of 6 lt/min (50% O_2 - 50% N_2O) with a minimum alveolar concentration of 1.3-1.5. After the surgical procedure, atropine-neostigmine (20 mcg/kg - 50 mcg/kg) and sugammadex (2 mg/kg) were administered to group 1 and group 2, respectively, and then the patients were extubated. The postoperative STT was measured in postoperative period.

RESULTS: The mean age of the patients was 53 (±16) years, and 56 (93%) of them were male. There were no differences between the groups in terms of age, gender, height, weight, ASA score, and duration of anesthesia, duration of surgery, postoperative period, preoperative STT, and postoperative STT. However, when each group was evaluated separately, there was a statistically significant increase in the postoperative STT compared to the preoperative STT in both groups (p=0.005 for group 1, p<0.001 for group 2).

CONCLUSIONS: The effects of sugammadex and neostigmine used in general anesthesia on postoperative mucociliary clearance are similar, and postoperative mucociliary clearance is delayed.

Key Words:
Anesthesia, Neostigmine, Mucociliary clearance, Saccharin, Sugammadex.

Introduction

Mucociliary clearance is a non-specific defense mechanism of the respiratory tract against pathogens, such as particles, toxins, bacteria and viruses[1]. Suppression of mucociliary clearance due to general anesthesia and mechanical ventilation leads to secretion retention, atelectasis and an increased risk of pulmonary infection[2]. Digestion, urination, and mucociliary clearance are regulated by the muscarinic and nicotinic parasympathetic nervous systems. Mucociliary clearance is controlled by muscarinic 3 receptors[3-7] and delayed by atropine, antihistamines, morphine, cigarette smoke, temperature (<30°C, >40°C), dryness, tubocurarine, sevoflurane, isoflurane and desflurane, whereas acetylcholine, β_2 mimetics, aminophylline, ephedrine, epinephrine and prednisone accelerate it[2,7-10].

Acetylcholine (Ach) released from presynaptic nerve cells binds to cholinergic nicotinic receptors in postsynaptic muscle cells and contraction occurs in muscles (skeletal/smooth/cardiac). To facilitate endotracheal intubation and surgical procedure in general anesthesia, muscle relaxants (neuromuscular blocking agent, NMBA), such as vecuronium and rocuronium, are used. Reversing the effects of NMBA after the surgical procedure is indispensable for patient safety. Thus, neostigmine or sugammadex must be used in general anesthesia[11]. To prevent the cholinergic adverse effects caused by neostigmine, anticholinergic drugs – such as atropine – must be administered just before neostigmine.

Neostigmine, which is acetylcholinesterase inhibitor, accelerates mucociliary clearance by increasing the amount of ach, while atropine slows mucociliary clearance[12]. However, the net impact of simultaneous administration of the two drugs on mucociliary clearance is unknown. Sugammadex (Bridion, Patheon, Greenville, NC, USA) that encapsulate NMBA molecules in the plasma is a biologically inactive, non-muscarinic molecule[13]. Preferring sugammadex instead of neostigmine in general anesthesia reduces postoperative respiratory complications[14,15]. Besides, maintenance of mucociliary clearance contributes to reducing re-

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spiratory complications[2]. However, to our knowledge, there is no study in the literature that has investigated the effects of sugammadex on mucociliary clearance.

In the intraoperative period, bronchial mucus transport velocity (BTV) or *in vitro* ciliary beat frequency (CBF) is used to measure mucociliary clearance, while *in vivo* nasal saccharin transport time (STT) test is used in the postoperative period[2,7,9,12,16]. Of these tests, the nasal STT test is a less invasive, cheaper and easier method.

This study aims at investigating the effects of sugammadex and neostigmine used in general anesthesia on postoperative mucociliary clearance using a nasal STT test.

Patients and Methods

This prospective, randomized and double-blind clinical trial was conducted in the Hitit University Erol Olçok Training and Research Hospital, Çorum, Turkey, between July 2020 and January 2022 after obtaining the written consent of the patients and approval of the Hitit University Faculty of Medicine Local Ethics Committee (Date:11/12/2019, Number:112). 60 non-smoker patients, aged between 18 and 80, who were scheduled for elective inguinal hernia surgery under general anesthesia, and were ASA I-III according to the American Society of Anesthesiologists (ASA) scoring system, were included in this study. Patients who were planned to receive elective inguinal hernia surgery, which was thought to have a minimal effect on mucociliary activity, were included in the study, since major abdominal surgeries and surgeries involving the respiratory tract were thought to disrupt mucociliary activity too much.

The study team was divided into two groups as general anesthesia team and nasal STT team. STT was applied to all patients by the same physician preoperatively and postoperatively. Patients were randomly assigned to one of two equal study groups, group 1 (neostigmine, n: 30) and group 2 (sugammadex, n: 30), by the anesthesia team, in order of arrival in the operating room.

The physician performed the STT test, the patient and the surgeon were blind. Pregnant women, patients had nose surgery, smokers, those with chronic lung, cardiac, renal, and hepatic diseases, those receiving atropine, corticosteroid, catecholamines, those with difficult in airway and obstructive sleep apnea, atopic or allergic patients, and patients with difficulty in cooperation were excluded from the study. Patients who had used any drugs (e.g., opioids, steroids and catecholamines), which could have effect on mucociliary clearance during the perioperative period, and who wanted to withdraw from this study at any stage were also excluded from the study. Age, sex, height, weight and ASA scores of the patients were recorded. The nasal STT test was performed in the preoperative room and the post-anesthetic care unit (PACU) under the same conditions (room temperature 23°C, relative humidity 60%). Saccharine Transition Time test: 1x1x1 mm saccharine (¼ tablet) was placed on the medial inferior concha of any nasal cavity of the patients while they were in the sitting position with their heads up. The time that the patient sensed the taste of sugar in the oropharynx was considered the STT value. If no sweet taste was experienced within 30 min, the test was stopped, and the patient was excluded from the evaluation. After the preoperative STT, the patients were taken to the operating room. Standard monitoring (ECG, non-invasive monitoring, SPO_2) and Train of Four (TOF) were performed on all patients. After administering 2 mg midazolam, 1-3 mg/kg propofol, and 0,6 mg/kg rocuronium to all patients, they were intubated orotracheally. For the maintenance of anesthesia, high-flow anesthesia was administered with sevoflurane at a fresh gas flow of 6 lt/min (50% O_2 - 50% N_2O) with a minimum alveolar concentration (MAC) value of 1.3-1.5. Tidal volume of 6-8 ml/kg and respiratory rate was adjusted to ensure a target end-tidal CO_2 value of 30-35 mm Hg. In the intraoperative period, 1 g paracetamol, 2 mg/kg tramadol, and 4 mg ondansetron were administered iv for postoperative analgesia, nausea, and vomiting. After the surgical procedure, atropine 20 mcg/kg and neostigmine 50 mcg/kg were administered to group 1, and 2 mg/kg sugammadex to group 2[17]. Patients with sufficient spontaneous respiratory effort (TOF>90%) were transferred to the PACU after extubating. Anesthesia and surgery duration were also recorded. The postoperative STT was measured at the earliest period when adequate cooperation was achieved with the patient in the PACU. The duration from extubation to STT was recorded as the postoperative period.

Statistical Analysis

Before beginning this study, the number of samples for the groups was computed by power analysis (power=0.80). Power Analysis and Sample Size Software (PASS) package program (Version 11, trial version, NCSS, LLS, UT, USA) was used for power analysis. To calculate the estimated sample number to be used in this research, the hypotheses mean was 6 and 4, respectively, for the two groups, with an equal number of subjects in each group, while the standard deviation was 1.5, consistent with the literature. Alpha (α) was accepted as 0.05 (95% significance level). As a result of the power analysis, with an effect size of 0.373 and a power of 81% (0.81), the number of samples was 30 for each group and 60.

In this study, statistical analyses were conducted using the SPSS (Version 22.0, IBM Corp., Armonk, NY, USA) package software. Descriptive statistics were presented as mean±standard deviation for normally distributed continuous data, as median (min-max) for non-normally distributed continuous data and variables with ordinal data, and as numbers and percentages for categorical data. Normal distribution was analyzed by the Kolmogorov-Smirnov and Shapiro-Wilk tests. The homogeneity of variances was analyzed using Levene's test. For continuous variables, an independent sample *t*-test was used for normally distributed data comparing the mean of two independent samples, and the Mann-Whitney U test was used for data that did not show normal distribution. The Chi-square test was used for nominal variables. Comparisons between more than two groups were analyzed with analysis of variance (ANOVA) and Kruskal-Wallis' test for ordinal data (pain score). To determine which group caused the difference after the Kruskal-Wallis' test (post-hoc test), pairwise comparisons were made with the Mann-Whitney U test, considering the Bonferroni correction. The statistical significance level was considered to be $p < 0.05$.

Results

The mean age of all patients was 53±16 years (min-max: 21-80), and 56 (93%) of them were male. The mean ages of group 1 and 2 were 54±16 and 53±16 years, respectively. There were no differences between the groups in terms of gender and age (p=0.612 for gender and p=0.71 for age). The mean heights and weights were 169±7 and 170±7 centimeters and 75±10 and 77±11 kilograms in groups 1 and 2, respectively. There were no differences between the groups in terms of height and weight (p=0.794 for height, p=0.266 for weight). The mean postoperative period duration of all patients was 27 (17-46) minutes. The mean postoperative period durations of groups 1 and 2 were measured as 30 (18-44), 22 (17-46) minutes, respectively. There was no difference between the groups in terms of postoperative period (p=0.082). When the duration of anesthesia was evaluated, it was 60 (±15) for group 1, 65 (±23) for group 2, and 63 (±19) minutes for all patients. There was no difference between the groups in terms of duration of anesthesia (p=0.501). The mean surgical time of all patients was 46±19. It was 43±15 for group 1 and 49±22 minutes for group 2. There was no difference between the groups in terms of the duration of surgery (p=0.383). No difference was found between group 1 and group 2 in terms of ASA, preoperative STT and postoperative STT (Table I). However, when each group was evaluated separately, there was a statistically significant increase in the postoperative STT compared to the preoperative STT in both groups (p=0.005 for group 1, p<0.001 for group 2) (Figure 1).

Discussion

When PubMed database was searched in April 2022 regarding the effects of general anesthetic agents on mucociliary activity, no studies were found with sugammadex and neostigmine. A statistically significant decrease was observed in the postoperative mucociliary clearance rate in both groups; however, no significant difference was found between two groups in terms of preoperative STT and postoperative STT.

Sacan et al[18] compared the effects of anticholinergic-cholinesterase inhibitor glycopyrrolate-neostigmine (14 mcg/kg-70 mcg/kg) and sugammadex (4 mg/kg) on postoperative dry mouth and found out that using glycopyrrolate-neostigmine caused more dry mouth than sugammadex. Moreover, Şahiner et al[19] revealed that using atropine-neostigmine (15 μg/kg-25 μg/kg) reduced catheter-related bladder discomfort more than sugammadex in the postoperative period. Those two studies show that the muscarinic effects of the anticholinergic-acetylcholinesterase inhibitor combination continue in the postoperative period but that sugammadex has no such effect. In this study, the effects of neostigmine and sugammadex on mucociliary clearance were similar. In addition, it was determined that neostigmine contributed more to the improvement of mucociliary clearance than sugammadex, although it was not statistically significant.

Two different studies conducted by Keller et al[2] and Ledowski et al[9] show that using sevoflurane or endotracheal intubation slows mucociliary clear-

Table I. Comparison of variables between Group 1 and Group 2.

Variables	All Patients (n=60)	Group 1, Neostigmin (n=30)	Group 2, Sugammadex (n=30)	p
Gender, M/F, n (%)	56 (93.3)/4 (6.7)	29 (96.7)/1 (3.3)	27 (90)/3 (10)	0.612
Age, years	53±16	54±16	53±16	0.710
Height, centimeter	170±7	169±7	170±7	0.794
Weight, kilograms	76±10	75±10	77±11	0.266
ASA score, n (%)				
I	22 (36.7)	10 (33.3)	12 (40)	0.321
II	31 (51.7)	18 (60)	13 (43.3)	
III	7 (11.7)	2 (6.7)	5 (16.7)	
Anesthesia Duration*	63±19	60±15	65±23	0.501
Surgery Duration*	46±19	43±15	49±22	0.383
Postoperative Period*	27 (17-46)	30 (18-44)	22 (17-46)	0,082
Preoperative STT *	10±4.5	10.8±5	9.2±3.3	0.169
Postoperative STT*	14.7±5.6	14.4±5	15±6.2	0.673

M: Male, F: Female, ASA: American Society of Anesthesiologists, STT: Saccharin Transport Time, *: Minutes.

ance in the intraoperative period. In those studies, the BTV test was used in the intraoperative period to measure mucociliary clearance. In our study, mucociliary clearance was evaluated by nasal STT, mean 27 minutes after the administration of sevoflurane was discontinued and the patients were extubated. The mucociliary clearance delaying effect of sevoflurane and endotracheal intubation continued not only in the intraoperative period, but also in the postoperative period in general anesthesia in which neostigmine and sugammadex were applied. In fact, sugammadex delayed mucociliary clearance slightly more than neostigmine. Since sugammadex does not have a protective effect on mucociliary clearance, other factors (such as effective coughing) may be effective in reducing postoperative respiratory complications.

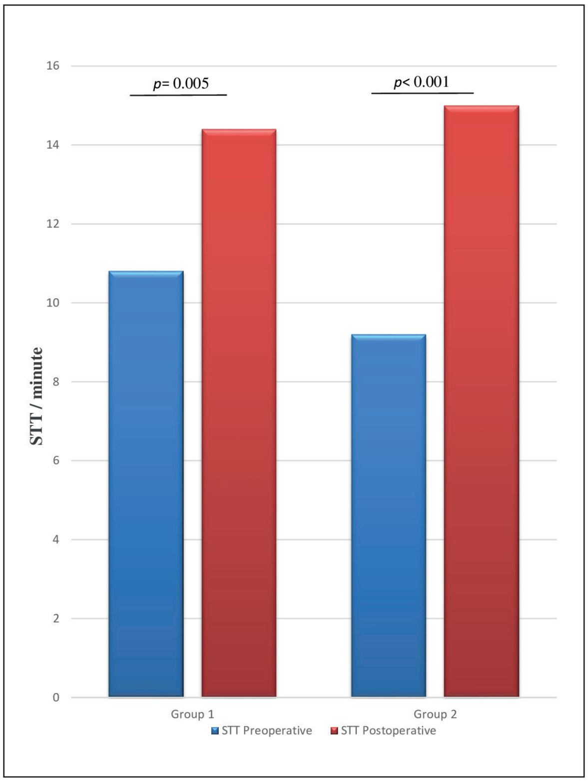

Figure 1. Group 1 and Group 2, Preoperative and Postoperative STT values. **STT:** Saccharin Transport Time.

In the total intravenous anesthesia (TIVA) study, in which anesthesia was maintained with propofol, alfentanil, and vecuronium, mucociliary clearance was measured with intraoperative BTV, and a delay in mucociliary clearance was observed[20]. On the other hand, Ledowski et al[9] stated that intraoperative BTV and TIVA (Propofol-remifentanil, and rocuronium) did not significantly affect mucociliary clearance like sevoflurane-remifentanil anesthesia. These studies were performed intraoperatively, and neither neostigmine nor sugammadex were administered to patients during BTV measurement. Therefore, the effect of neostigmine or sugammadex in TIVA is difficult to predict. We did not use opioids in our study to avoid the possibility to affect mucociliary clearance. However, opioids used in these previous two studies may have affected mucociliary clearance. Therefore, it may be more accurate to investigate the effects of neostigmine or sugammadex on mucociliary clearance in opioid-free TIVA.

In another study[21] in which atropine-neostigmine was used and sugammadex was not used, mucociliary clearance was evaluated by nasal STT test. In this study, the effects of inhalation agents – sevoflurane, isoflurane, desflurane – on mucociliary clearance were investigated. In the study of Kesimci et al[21], which targeted 1 MAC Sevoflurane concentration, an increase in postoperative STT was observed. However, this increase was not statistically significant. In our study, the target MAC concentration was increased to 1.3-1.5 MAC. The significant increase in postoperative STT in both groups of our study may indicate that inhalation agent concentration directly affects mucociliary clearance. In addition, this increase was greater in the sugammadex group, which was not expected to have mucociliary clearance affected. This may be crucial in demonstrating the effect of sevoflurane concentration on mucociliary clearance.

It has been documented[16,22] that mucociliary clearance rate slows down in smokers and patients with Obstructive Sleep Apnea Syndrome (OSAS). Besides, using sugammadex instead of neostigmine in severe OSAS patients reduces postoperative respiratory complications[23]. Maintenance of mucociliary clearance is crucial in reducing postoperative complications. In normal healthy patients undergoing general anesthesia, sugammadex is expected to have no effect on mucociliary clearance. Therefore, the delaying effect of general anesthesia on mucociliary clearance in patients given sugammadex was clearly seen in our study. In patients with slow mucociliary clearance rate the effect of sugammadex on mucociliary clearance is unknown.

Limitation and Suggestions

The most important limitation of this study is the application of the standard anesthesia protocol (such as sevoflurane, endotracheal intubation, and high-flow anesthesia), which can affect the mucociliary activity.

Opioid free total intravenous anesthesia instead of sevoflurane, and laryngeal mask instead of endotracheal intubation may be more successful in demonstrating the effects of sugammadex and neostigmine on mucociliary clearance. In addition, the effects of sugammadex and neostigmine on mucociliary clearance should be investigated in patient groups with delayed mucociliary clearance.

Conclusions

In general anesthesia, the effects of sugammadex and neostigmine on postoperative mucociliary clearance are similar and postoperative mucociliary clearance is delayed. However, neostigmine is remarkably advantageous in terms of cost compared to sugammadex.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethical Approval

The approval of the Hitit University Faculty of Medicine Local Ethics Committee (Date: 11/12/2019, No.: 112). All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent

The study has been performed after obtaining the written consent of the patients.

Funding

There has not been any funding for this study.

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Authors' Contributions

The study was designed by MD. Assist. Prof. Serhat Ozciftci. Assist. Prof. Serhat Ozciftci collected and wrote the data of the cases and drafted the article.
Associate Prof. Dr. Yeliz Sahiner collected and wrote the data of the cases.
Statistics, supervision and translation of the article were made by Associate Prof. Dr. Ibrahim Tayfun Sahiner.

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