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ORIGINAL ARTICLE

Comparison of sugammadex and neostigmine–atropine on intraocular pressure and postoperative effects

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Abstract During surgery, changes in intraocular pressure (IOP) can be observed resulting from several factors, such as airway manipulations and drugs used. We aimed to investigate the effects of sugammadex and neostigmine on IOP, hemodynamic parameters, and complications after extubation. Our study comprised 60 patients, aged 18–65 years, with a risk status of the American Society of Anesthesiologists I–II who underwent arthroscopic surgery under general anesthesia. The patients were randomly assigned into two groups. At the end of the surgery, the neuromuscular block was reversed using neostigmine (50 μg/kg) plus atropine (15 μg/kg) in Group 1, and sugammadex (4 mg/kg) in Group 2. Neuromuscular blockade was monitored using acceleromyography and a train-of-four mode of stimulation. IOP was measured before induction and at 30 seconds, 2 minutes, and 10 minutes after extubation. A Tono-Pen XL applanation tonometer was used to measure IOP. This showed that elevation in IOP of patients reversed using sugammadex was similar to that recorded in patients reversed using neostigmine–atropine. When heart rate was compared, there was a significant difference between basal values and those obtained at 30 seconds and 10 minutes after extubation in the neostigmine–atropine group. Extubation time (time from withdrawal of anesthetic gas to extubation) was significantly shorter in the sugammadex group ($p = 0.003$) than in the neostigmine

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—atropine group. The postextubation IOP values of the sugammadex group were similar to the neostigmine—atropine group. Extubation time (time from withdrawal of anesthetic gas to extubation) was significantly shorter in the sugammadex group ($p = 0.003$) than in the neostigmine—atropine group.

Introduction

Several factors are involved in the pathogenesis of glaucoma, which is one of the leading causes of blindness worldwide. Among them, elevation in intraocular pressure (IOP) is the most definitive and confirmed cause [1]. IOP is influenced by many factors including genetics, age, refractive errors, and race [2]. Both surgical procedures and anesthesia can cause changes in IOP during surgery from such things as the patient's position, tourniquet use, airway manipulations (tracheal intubation, laryngeal mask insertion, etc.), and drugs used in anesthesia [3—5].

During general anesthesia, airway interventions can cause undesired elevations in IOP by increasing blood pressure and ocular blood flow [6]. Although it is known that tracheal intubation causes elevation in IOP, intubation is still used because it provides better airway management [7]. In addition, during tracheal intubation, IOP can increase because of factors such as the patient coughing or holding his or her breath [8]. Alteration in IOP during surgery is of particular importance in pediatric glaucoma cases or in cases involving penetrating intraocular injuries. In pediatric cases, there is a need for examination under anesthesia to perform IOP measurements; however, anesthetic agents can cause changes in IOP, making it difficult to obtain reliable results [9].

Acute elevation in IOP is a serious condition in cases with ocular perforation, and the stress response during tracheal intubation and extubation can cause such elevation, which is attributed to the sympathetic nervous system [7,10,11]. It has been suggested that adrenergic activation leads to increased central venous pressure and subsequent IOP elevation from the increased episcleral venous flow [12].

Both tracheal intubation and extubation cause activation of the sympathetic nervous system, which might lead to undesired effects, such as increased heart rate and arterial blood pressure in patients with hypertension, ischemic heart disease, and cerebrovascular disorders [13].

Sugammadex is now being used as an alternative to decurarization with acetylcholinesterase inhibitors. It is a selective relaxant that reverses the effects of the neuromuscular blockers rocuronium or vecuronium [14,15].

Postoperative residual block is associated with mortality, and it has been demonstrated that sugammadex decreases the incidence of residual block [16]. Sugammadex is a preferred agent in clinical practice because it provides for rapid recovery with no undesired adverse events. In this prospective randomized study, we aimed to investigate the effects of sugammadex and neostigmine on IOP, hemodynamic parameters, and complications after extubation.

Methods

The study was approved by the Institutional Ethics Committee of Mustafa Kemal University, Faculty of Medicine, Hatay, Turkey (Ethic Committee Approval Date: 04.10.2012; Approval Number: 08; Chairman: Selim Turhanoglu). The study has been registered in the Australian New Zealand Clinical Trials Registry at http://www.anzctr.org.au, registration number: ACTRN12614000651684.

All patients gave written informed consent before participating. The study comprised 60 patients aged 18—65 years with American Society of Anesthesiologists I—II risk status who underwent arthroscopic surgery under general anesthesia. The patients were randomly assigned into two groups (neostigmin group, Group 1; and sugammadex group, Group 2) by computer-generated random numbers. Patients with hypertension or other chronic diseases, those who had previously undergone ocular surgery, and those with previous ocular diseases were excluded. In addition, patients allergic to tetracaine or other agents used in anesthesia were excluded.

Standard monitoring comprising electrocardiogram, noninvasive blood pressure measurements (systolic and diastolic blood pressures), heart rate, and peripheral arterial oxygen saturation was performed during surgery. In addition to standard monitoring, train-of-four (TOF-Watch SX; Organon Ireland Ltd., Dublin, Ireland) was used to monitor the level of neuromuscular blockade. After inserting an intravenous line, anesthesia was induced using propofol (2.5 mg/kg) and fentanyl (1.0 μg/kg), and after loss of eyelash reflex and calibration and stabilization of the TOF-Watch SX, rocuronium bromide (0.6 mg/kg) was administered in both groups. After administration of the appropriate bolus dose of rocuronium bromide, the patient was intubated as soon as the first response to the TOF stimulus (T1) decreased to below 10%. Anesthesia was maintained using desflurane 4—6% (3 L/min) in a 50:50% oxygen/air mixture. Hemodynamic parameters were recorded before and after induction and extubation. After the completion of surgery, when spontaneous recovery of neuromuscular blockade occurs with the appearance of T2, anesthesia was withdrawn and the neuromuscular block was reversed using a single intravenous dose of neostigmine (50 μg/kg) plus atropine (15 μg/kg) in Group 1, and a single intravenous dose of sugammadex (4.0 mg/kg) in Group 2. The primary efficacy endpoint for extubation was the time from sugammadex or neostigmine administration to recovery of the TOF ratio to 0.9. Operation time (time from skin incision to end of surgery) and adverse events (gagging, nausea, vomiting, breath holding, laryngospasm, and

tremors) were recorded. Modified Aldrete Recovery Score (MAS) was used as recovery criteria and the time to reach MAS > 8 was recorded. Hemodynamic parameters (heart rate, mean arterial pressure, peripheral arterial oxygen saturation) were measured before induction and at 30 seconds, 2 minutes, 10 minutes, and 30 minutes after extubation; IOPs were measured before induction and at 30 seconds, 2 minutes, and 10 minutes after extubation. Those with a baseline IOP of >30 mmHg were excluded. Tono-Pen XL applanation tonometer (Medtronic Solan, Jacksonville, FL, USA) was used to measure IOP. The tonometer was calibrated prior to each use. The IOP values of the patients were checked after application of one drop of sterile eye drop tetracaine 0.5% by an applanation tonometer.

Power analysis

Our primary hypothesis was that the used sugammadex resulted in a larger decrease in IOP after endotracheal intubation. Sample size estimation was based on the standard deviation of a similar study performed by Igboko et al. [17]. We used the IOP values after endotracheal tube extubation (17.1 ± 3.3 mmHg) determined by Igboko et al. [17]. To detect a 15% change in IOP, with an α error of 0.05, and a power of 90%, we calculated that the sample size should be at least 24 patients/group. Estimating an approximately 25% dropout rate, we included 30 patients in each group. The sample size estimation was performed using Power Calculator (Department of Statistics, University of California, Los Angeles; http://www.stat.ubc.ca/_rollin/stats/ssize).

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL, USA). Student *t* test was used to compare measurements between groups while a paired sample *t*-test was used for intragroup comparisons. Chi-square test was used to compare categorical variables. A *p* value <0.05 was considered statistically significant.

Results

No significant differences were detected between groups when demographic data and anesthesia time were compared (Table 1).

When mean arterial pressure measurements were compared, there were significant differences between basal values and those obtained at 30 seconds, 10 minutes, and 30 minutes after extubation in the neostigmine—atropine group ($p = 0.013$; $p = 0.035$; and $p = 0.001$, respectively). In the sugammadex group, there were significant differences between basal values and those obtained at 30 seconds and 2 minutes after extubation ($p = 0.01$ and $p = 0.046$, respectively). No significant difference in mean arterial pressure was detected when groups were compared at all other time points ($p > 0.05$ for all; Figure 1).

When heart rate was compared, there was a significant difference between basal values and those obtained at 30 seconds and 10 minutes after extubation in the neostigmine—atropine group. In the sugammadex group, there was also a significant difference between basal values and those obtained at 30 seconds and 10 minutes after extubation. There was a significant difference in heart rate values obtained at 10 minutes after extubation compared with heart rate values at all other time points ($p < 0.01$; Figure 2).

When IOP values were compared, no significant differences were detected between groups ($p > 0.05$). In intragroup comparisons, IOP values measured before induction were lower than those obtained at all other time points in both groups (Figure 3), but a significant difference was detected only between IOP values measured before induction and those measured at 30 seconds after extubation ($p = 0.004$ and $p = 0.001$, respectively).

Extubation time (time from withdrawal of anesthetic gas to extubation) was significantly shorter in the sugammadex group ($p = 0.003$) than in the neostigmine—atropine group. The time to reach MAS > 8 was also shorter in the

Table 1 The demographic data of the groups.

	Sugammadex ($n = 30$)	Neostigmine—atropine ($n = 30$)	p^*
Age (y)	33.87 ± 13.85	33.60 ± 12.92	0.93
Sex (male/female)	20/10	19/11	0.78
Height (cm)	173.48 ± 8.4	172.93 ± 8.56	0.80
Weight (kg)	81.33 ± 12.05	76.07 ± 12.98	0.10
Body mass index (kg/m^2)	27.02 ± 4	26.3 ± 3.95	0.61
ASA (I/II)	12/18	16/14	0.30
Duration of anesthesia (min)	95.40 ± 37.56	80.93 ± 32.53	0.11

*$p < 0.05$ (significant).
ASA = American Society of Anesthesiologists.

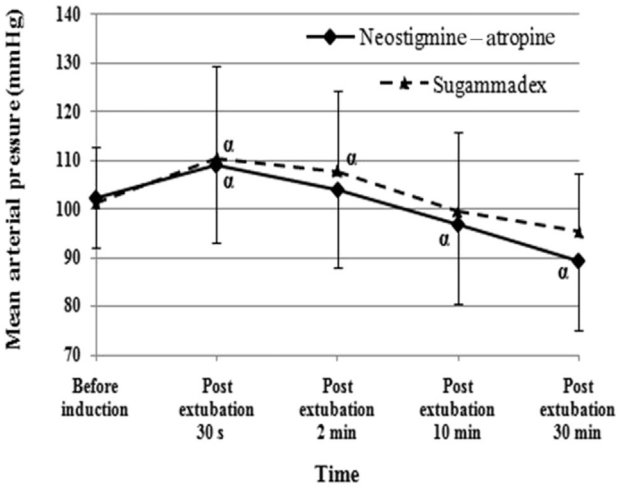

Figure 1. Mean arterial pressure at each time interval from baseline to 30 minutes after tracheal extubation. Bars represent standard deviation. $\alpha = p < 0.05$ compared with baseline value.

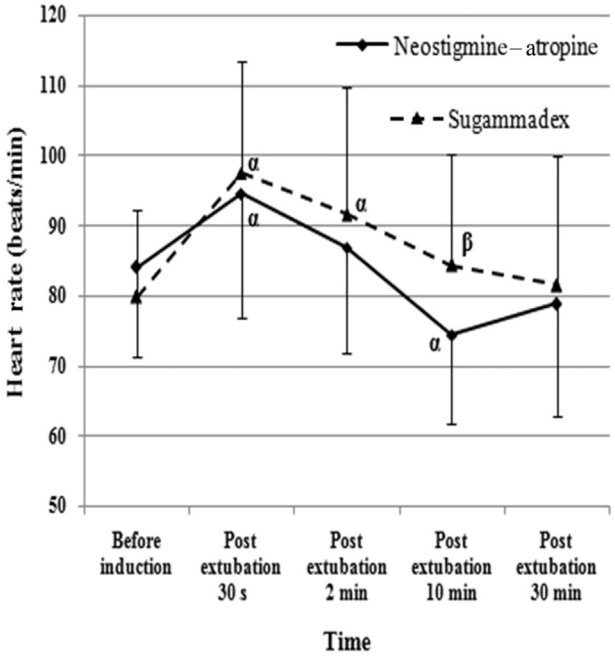

Figure 2. Heart rate at each time interval from baseline to 30 minutes after tracheal extubation. Bars represent standard deviation. $\alpha = p < 0.05$ compared with baseline value. $\beta = p < 0.05$ compared with the sugammadex group.

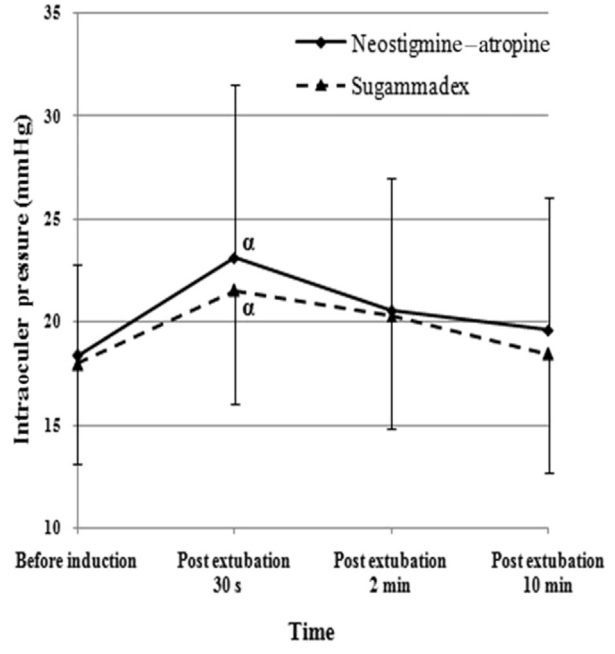

Figure 3. Intraocular pressure at each time interval from baseline to 30 minutes after extubation. Bars represent standard deviation. $\alpha = p < 0.05$ compared with baseline value.

sugammadex group, but the difference did not reach statistical significance (Table 2). When complications were assessed, it was found that nausea, vomiting, breath holding, and tremors were more common in the neostigmine–atropine group than in the sugammadex group, while laryngospasm and cough were equally common in both groups (Table 3).

Table 2 Comparison of the groups according to extubation time and recovery scores.

	Sugammadex ($n = 30$)	Neostigmine –atropine ($n = 30$)	p
MAS > 8	7.87 ± 3.34	8.43 ± 2.95	0.489
Extubation time (min)	3.03 ± 1.29	4.18 ± 1.49*	0.003

*$p < 0.05$ (significant).
MAS = Modified Aldrete Recovery Score.

Discussion

In this study, we observed that sugammadex used in the reversal of nondepolarizing neuromuscular blockage did not affect IOP such as neostigmine–atropine. Also, IOP values measured before induction were lower than those obtained at all other time points in the two groups.

There are several studies about the effects on IOP of interventions used during anesthesia. Anesthesia-related factors, such as premedication drugs, general anesthetics, and lung ventilation, are also known to affect IOP. Uncontrolled increase of IOP may lead to staining of the cornea with blood, obstruction of retinal arterioles, and optic atrophy.

In one such study, it was shown that tracheal intubation caused higher values in IOP when compared with Laringeal mask airway or I-gel [18,19]; however, to the best of our knowledge, there is no study comparing the effects of sugammadex and neostigmine on IOP. In this study, we observed that sugammadex used in reversal of nondepolarizing neuromuscular blockade did not affect IOP.

In a study by Madan et al. [8], the effects of tracheal intubation and extubation on IOP were investigated in both healthy children and those with glaucoma. Neostigmine (50 μg/kg) was used to reverse neuromuscular block in that study, and IOP values at 30 seconds and 2 minutes after extubation were found to be higher when compared with those obtained before intubation [8]. By contrast, our study was conducted on adult patients.

Table 3 Comparison of the groups according to the complications.

Complication	Sugammadex ($n = 30$)	Neostigmine –atropine ($n = 30$)	p*
Nausea and vomiting	6	8	0.754
Breath-hold	3	4	> 0.99
Laryngospasm	1	1	> 0.99
Shivering	4	8	0.333
Cough	5	5	> 0.99

*$p < 0.05$ (significant).

In our study, sugammadex and neostigmine—atropine caused similar changes in IOP. When IOP changes were assessed within the groups, a significant difference was observed between IOP values only at 30 seconds after extubation and those obtained before anesthesia induction, although there were elevations in IOP values after extubation in both groups. Based on our results, it can be suggested that reversal with sugammadex had no prominent negative effect on IOP. In a previous case, it was reported that IOP was maintained at <20 mmHg during extubation in a patient with a history of narrow-angle glaucoma who underwent surgery for a femoral neck fracture [20].

It is also known that neostigmine can cause bradycardia through direct activation of cholinergic receptors in the peripheral cardiac parasympathetic pathway, which can be prevented by atropine [21,22]. In our study, mean arterial pressure and heart rate were found to be higher in the sugammadex group compared with those in the neostigmine—atropine group despite the lack of a significant difference. In the neostigmine—atropine group, the heart rate was higher at 30 seconds and lower at 10 minutes after extubation when compared with baseline values; however, in the sugammadex group, the heart rate was higher at 30 seconds and 2 minutes after extubation when compared with baseline values. In addition, heart rate was lower at 10 minutes after extubation in the neostigmine—atropine group, while no significant difference in mean arterial pressure was detected between the groups. In a study by Jones et al. [23], it was reported that heart rate and mean arterial pressure were higher at 2minutes, 5 minutes, and 10 minutes after neostigmine administration but not after sugammadex administration when compared with baseline values. In a study by Lemmens et al. [24], it was shown that sugammadex had no significant effect on blood pressure, heart rate, ventilation, or thermoregulation. In another study, Koç et al. [25] compared neostigmine plus atropine with sugammadex and reported that there was no significant difference in systolic and diastolic arterial pressures or heart rate. The authors found that heart rate was significantly decreased at 6 minutes after neostigmine—atropine administration, but no such decrease was detected in the sugammadex group.

In studies on the pharmacokinetic properties of sugammadex, it was shown that sugammadex reverses the neuromuscular block induced by rocuronium and vecuronium in a rapid and effective manner. In dose-dependent studies, it was shown that sugammadex is also effective in reducing profound blockades [26—29]. The recommended dose of sugammadex is 2 mg/kg for a superficial block and 4 mg/kg for a profound block induced by neuromuscular blocking agents. Jones et al. [23] demonstrated that 4 mg/kg sugammadex reversed the neuromuscular relaxant effect of rocuronium more rapidly than neostigmine (70 μg/kg) plus glycopyrrolate (14 μg/kg). In a study on morbidly obese patients, Gaszysnki et al. [30] demonstrated that 2 mg/kg sugammadex provided more rapid reversal of neuromuscular functions than 50 μg/kg neostigmine and prevented residual curarization. In another study, it was shown that sugammadex markedly diminished extubation time when compared with neostigmine—atropine [26]. The results of our study agreed with those of previous studies in that extubation time was significantly shorter in the sugammadex group ($p = 0.003$) than in the neostigmine—atropine group. In addition, the time to reach MAS > 8 was shorter in the sugammadex group but the difference was not statistically significant.

In a study on 1444 patients by Ledowski et al. [31], it was reported that the incidence of postoperative nausea and vomiting was higher in patients who received neostigmine, and that sugammadex use might reduce the risk of pulmonary complications in elderly patients with a risk status of American Society of Anesthesiologists III—IV. In our study, there was no significant difference in complications between groups, but nausea, vomiting, breath holding, and tremors were more common in the neostigmine—atropine group, while laryngospasm and cough were equally common in both groups.

Not including the control group as well as the groups including the 2-mg/kg dose of sugammadex, has inevitably constricted the scope of the study. The effects of sugammadex on IOP may be examined in another study including these groups and a higher number of patients.

In conclusion, the postextubation IOP values of the sugammadex group were similar to the neostigmine—atropine group. Additionally, in agreement with previous studies, in our study extubation time was found to be shorter in the sugammadex group than in the neostigmine—atropine group. Further studies are needed that include more patients.

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