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The interaction of dexamethasone with sugammadex and rocuronium during general anesthesia in rhinoplasty surgeries

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ABSTRACT

Aims: Sugammadex is a cyclodextrin specifically designed to reverse the action of rocuronium through encapsulation. Theoretically, it is possible that sugammadex can encapsulate cortisone. There have been conflicting results regarding clinical dexamethasone-sugammadex interactions in patients under general anesthesia. The primary outcome of the present study is to investigate any possible alteration in the efficacy of sugammadex as a reversal of rocuronium due to dexamethasone injection in rhinoplasty surgery. The secondary outcome is evaluation of clinical observation sugammadex in these groups of patients.

Methods: Adult patients with the American Society of Anesthesiology (ASA) II risk class undergoing rhinoplasty were included. All patients received standard general anesthesia with neuromuscular blockade using rocuronium. Patients were allocated to either the dexamethasone group or control group. The anesthesiologist measured the time interval between sugammadex injection and the recording of the 90% train of four. Additionally, the duration required for extubation after sugammadex injection was recorded. Finally, the signs of residual respiratory insufficiency and muscle weakness were checked in the post-anesthesia care unit until the 2nd-hour post-surgery.

Results: Sixty-one patients were enrolled in the study. The dexamethasone group included 30, and the control group included 31 patients. The comparison of demographic and surgical characteristics of these two groups showed no statistical difference. The duration required for extubation was higher in dexmethasone group compared to control group (p=0.001). The total rocuronium administration dose was higher in dexmethasone group (p=0.01). The time required for the recovery of the head, upper, and lower extremity lifting was longer in the dexamethasone group (p=0.001, 0.003, and 0.047, respectively).

Conclusion: The present study demonstrated an interaction between sugammadex and dexamethasone, which affected the reversal of neuromuscular blockade during rhinoplasty surgeries.

Keywords: Dexamethasone, reversal time, rocuronium, sugammadex

INTRODUCTION

It is important to terminate the effects of neuromuscular blocker (NMB) drugs that provide muscle relaxation, which is one of the components of general anesthesia. Sugammadex is a cyclodextrin in a circular structure consisting of eight glucose molecules and gammacyclodextrin designed to encapsulate rocuronium for terminating the effects of non-depolarizing NMB drugs, especially those with steroid structure.[1] It antagonizes the effect of rocuronium, which is a nondepolarizing blocker, in a very short time, regardless of duration and dose, and completely eliminates undesirable results such as prolonged effect or residual block.[2-5]

Dexamethasone shares the same steroidal ring as rocuronium, leading to a possible encapsulation from sugammadex. If dexamethasone is encapsulated by sugammadex, less sugammadex will be available to reverse the rocuronium, resulting in a longer turnaround time. Dexamethasone is one of the most widely used corticosteroids for the treatment of many clinical conditions such as laryngeal, cerebral and surgical edema, as well as in combination with analgesics for multimodal analgesia and for the prevention of postoperative nausea and vomiting (PONV).[6-9]

Rhinoplasty is one of the most common cosmetic surgical procedures performed under general anesthesia.[10] Edema and ecchymosis may develop after rhinoplasty surgery. The edema and ecchymosis around the eyes and nose lead to anxiety for the patients and physicians. In addition, the presence of ecchymosis may prolong the duration of social isolation and the absence of work after surgery.

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It was reported that dexamethasone administration in rhinoplasty significantly decreased eyelid edema and ecchymosis.[11]

Additionally, as part of the multi-modal analgesia, dexamethasone is combined with non-steroidal anti-inflammatory agents to prevent PONV and laryngeal edema.

The relationship between dexamethasone and sugammadex has been investigated in vitro,[12] and in vivo,[13,14] but conflicting results have emerged. In vitro, dexamethasone dose-dependent inhibition of the reversal process of rocuronium by sugammadex was observed in functionally innervated human muscle cells,[12] whereas some studies showed no effect in real clinical conditions.[13-15]

The aim of this study was to investigate whether dexamethasone caused any changes in the efficacy of sugammadex as a reversal of rocuronium in patients undergoing rhinoplasty. The secondary outcome is to evaluate the results of clinical observations and to contribute to the literature.

METHODS

The research protocol was approved by İstanbul Yeni Yüzyıl University Clinical Researches Ethics Committee (Date: 23.11.2016, Decision No:003). All study participants received detailed information about the study, and they all consented to enrollment in this study. All aspects of the study were conducted according to the Declaration of Helsinki.

The patients aged between 18 and 65 who were undergoing rhinoplasty at İstanbul Yeni Yüzyıl University Hospital Ear-Nose-Throat Surgery Clinic constituted the target population of this study. All patients had normal hematological and cardiopulmonary screening test results and gave written consent to participate in the study. Subsequently, we selected those with the American Society of Anesthesiology (ASA) scores I and II among these patients. Patients who went through a combined surgery, those with systemic arterial hypertension, anti-coagulative medication use, diabetes mellitus, neuromuscular disease, and a history of peptic ulcer treatment during the last five years were excluded. Additionally, patients who have been receiving corticosteroid treatment for other indications were excluded.

Standart anesthesia management was performed in all patients. However it was at the discretion of the anesthesiologist whether to use dexamethasone intraoperatively and this decision was not influenced or changed by the investigators. Thus the patients were allocated to either the dexamethasone group or control group per assigned anesthesiologist's decision.

Anesthesia Induction and Maintenance

All procedures were performed under general anesthesia. Standard anesthesia monitoring was established for every patient with non-invasive arterial blood pressure, electrocardiogram, pulse oximeter, and end-tidal capnography. In addition, a train-of-four (TOF)-Watch SX device (Organon Teknika BV, Boxtel, Netherlands) was used for neuromuscular conduction monitoring. The skin electrodes were placed over the ulnar nerve at the wrist of the arm.

Anesthesia was induced with 2 μg/kg fentanyl and 2mg/kg propofol. Rocuronium IV 0.6 mg/kg was administered, and the TOF value was allowed to reach 0 (TOF 0). After TOF 0, the patients were intubated. Subsequently, the peripheral nerve stimulator was switched to TOF mode (0.2 ms duration, 2Hz frequency) every 15 seconds. The number of thumb twitches recorded indicated the level of neuromuscular block. Patients were covered, and care was taken to stabilize the skin temperature of the thenar region at 32-34°C.

Anesthesia was maintained with 50% oxygen, 2% sevoflurane, and 0.25 μg/kg/min remifentanil IV infusion. During the surgery, when the TOF value was 25% (TOF25), one-fourth of the induction dose of rocuronium was repeated. At the end of the procedure, patients were left until TOF25 was reached. When TOF25 was reached, sugammadex [IV; 2 mg/kg (current body weight)] was administered. When the TOF values of all of the patients were 90% (TOF90), they were extubated. At the end of the surgery, all patients were administered 1 mg/kg tramadol IV combined with paracetamol 10mg/kg for postoperative pain management. Patients were transferred to the post-anesthesia care unit (PACU) and stayed there until a modified Aldrete score (MAS) of higher than 9 was reached.

Rhinoplasty Procedure

In all patients, a closed approach was used with an interseptocolumellar incision and resection of the depressor muscle of the nasal septum. A transcartilaginous bilateral incision of the alars 6 mm from the caudal margin of the lateral middle crura was performed. The cartilage was exposed for resection by dissection of the vestibular skin off the cartilage. Dieresis of the lower lateral cartilage with extension to the nasal dorsum was performed to expose the nasal structures. The perichondrium was opened by a single incision in the midline of the upper lateral cartilage, with the detachment of the perichondrium in continuity with the periosteum of the nasal bone. On the subperichondrial and subperiosteal plane under direct

sight, the osteocartilaginous hump was assessed. Bone resection was performed with a down-biting diamond rasp, and septal cartilage was resected with a scalpel blade. Resection of the caudal portion of the septum, a lateral osteotomy with low to low fracture, the closure of the mucosa with simple stitches of polyglactin 5.0, and application of a dressing with microporous tape were the final steps of the procedure.

Study Variables

The time between TOF25 and TOF90 was recorded in seconds (TOF25-90). Additionally, the time from the cessation of anesthetic gases until extubation, the time between the beginning of the surgical incision and the last skin suture (i.e. surgical duration) was also recorded. Also, upper and lower extremity and head lift times were included in the analysis.

Statistical Analysis

We considered a 15% increase in the time from sugammadex administration to TOF 90 to be clinically relevant. A power calculation with a power of 0.80 at a=0.05 indicated a minimum 26 patients for each group. Because a dropout rate of%15-20 was expected a total of 62 patients with 31 patients in each group were included in the study.

Descriptive statistics of the categorical variables were given as numbers or percentages; continuous variables were provided as means±standard deviation (SD) or as medians (minimum-maximum). The Chi-square test was used to evaluate categorical variables. In addition, the paired t-test or Wilcoxon signed-rank test was used to compare the means/medians of variables as appropriate.

RESULTS

A total of 62 patients were enrolled in the study. One patient in dexamethasone group was excluded from the analyses due to surgical complication. Finally, data from the remaining 61 patients (30 patients in dexamethasone group and 31 patients in control group) were analyses for the study.

The mean age of the patients in the dexamethasone group was 31±10.07 and in the control group 30.77±6.63 years. There was no significant difference among the groups regarding patient age (p=0.510). The mean body mass index of the dexamethasone group was 23.48±2.55. and 22.93 ±2.74 in the control group (p=0.425). The ASA score comparison between the two groups revealed no significant difference. The duration of the surgical procedure was 156.77±23.72 minutes in the dexamethasone group and 156.67±30.23 minutes in the control group (p=0.988) (Table 1).

Table 1. Demographic data and duration of surgeries in the study groups (Values are presented as mean±SD or number with percentage)

	Dexamethasone group (n=31)	Control group (n=30)	p value
Age (years)	31.55±10.07	30.77±5.63	0.510
Height (cm)	171.94±6.55	172.53±7.27	0.737
Weight (kg)	69.68±10.37	68.47±10.35	0.650
BMI (kg/m²)	23.48±2.55	22.93±2.74	0.425
ASA I/II	26 (83.9%) / 5 (16.1%)	30 ((100%) / 0 (0%)	
Duration of surgery (min)	156.77±23.72	156.67±30.32	0.988

Intraoperative additional rocuronium requirement was 25.64±12.09 mg in the dexamethasone group and 14.19±12.46 mg in the control group. The required dose for rocuronium was significantly higher in the dexamethasone group compared to the control group (p=0.001). Time to TOF 90 after sugammadex administration was 111.27±33.02 seconds in the dexamethasone group and 87.90±14.01 seconds in the control group. The difference was statistically significant between the groups (p=0.001). Additionally, the extubation time was 152.57±57.48 seconds in the dexamethasone group and 102.58±30.22 seconds in the control group (p=0.001) (Table 2).

Table 2. Intraoperative measurements of additional rocuronium doses, times of TOF 0.9 and extubation. (Values are presented as mean±SD)

	Dexamethasone group (n=31)	Control group (n=30)	p value
Additional rocuronium (mg)	25.64±12.09	14.19±12.46	0.001
Time to TOF 0.9 (sec)	111.27±33.02	87.90±14.01	0.001
Time to extubation (sec)	152.57±57.48	102.58±30.22	0.001

The duration of the head-lifting, upper-extremity, and lower-extremity lifting were measured. The time required for head lifting was 168.33±63.77 in the dexamethasone group and 114.68±41.71 minutes in the control group (p=0.001). Similarly, the time required for the upper and lower extremity lifting was longer in the dexamethasone group (p=0.003 and p=0.047, respectively) (Table 3).

Table 3. Timing of clinical entities (head, upper and lower extremity lifting) (Values are presented as mean±SD)

	Dexamethasone group	Control group	p value
Head-lift (min)	168.33±63.77	114.68±41.71	0.001
Upper extremity -lift (min)	99.68±27.41	128.83±42.76	0.003
Lower extremity -Lift (min)	151.67±55.39	128.65±27.20	0.047

DISCUSSION

The present study demonstrated dexamethasone given intravenously at a dose of 10 mg after induction of general anesthesia in rhinoplasty surgery delayed the reversal of neuromuscular blockage with sugammadex. In this study, a single dose of dexamethasone after induction of general anesthesia received for prophylaxis against postoperative nausea, vomiting, and edema.

It is well known that sugammadex is a modified cyclodextrin that exerts its action as a neuromuscular block reversal agent through encapsulation of the steroidal neuromuscular blocking agent molecules thereby preventing their action at the neuromuscular junction.[16] However, this structure may interact with other similar molecules to rocuronium as well, such as hormonic contraceptives, fucidic acid, flucloxacillin, toremifene, or steroids, leading to decreased availability of sugammadex to act with rocuronium when these substances are also available in plasma.[17]

The result of this effect might theoretically be a clinical decrease in sugammadex's action and a delay in the reversal process.

The early report by Zhang[18] documented that sugammadex affinity to rocuronium is very much higher than that to corticosteroids, however different doses of the drugs have not been well identified as well as the duration of exposure. Additionally, Zwiers et al.[17] have investigated in detail those interactions, between sugammadex and 300 commonly used drugs, using a pharmacokinetic–pharmacodynamic model. The study demonstrated that flucloxacillin, fucidic acid, and toremifene had a potential of displacement, whereas specifically for dexamethasone, no such effect was proven.

On the other hand, an in vitro study by Rezonja et al.[12] in innervated human muscle cells, showed that there was a dose-dependent inhibition of sugammadex's action by dexamethasone. Therefore, studies in clinical conditions under general anesthesia were necessary. Three clinical trial results to date have failed to prove an interaction between dexamethasone and sugammadex.

Buonanno et al.[13] investigated the interaction of dexamethasone and sugammadex in a retrospective manner, by analyzing data from 45 patients who received general anesthesia with rocuronium. Patients were divided into three groups, who received dexamethasone 8 mg shortly after induction, dexamethasone 8 mg just before reversal, or ondasentron 8 mg (control group). No significant difference was observed between the three groups as for time to reversal of rocuronium using sugammadex, 2 mg/kg at the end of the operation, at reappearance of T2.

Batisti and et al.[19] studied 44 patients who had undergone cholecystectomy. Patients were divided into two groups, who received dexamethasone 5 mg shortly after induction, or 5 ml plasebo (control group). Similarly, Gulec et al.[14] studied the effect of intravenous dexamethasone (0.5 mg/kg) versus placebo, on sugammadex's action, in 60 children (aged 3-8 years) undergoing elective tonsillectomy and/or adenoidectomy, in a prospective, randomized manner.

No significant difference was also observed regarding the time required from administration of sugammadex until reversal of neuromuscular function to TOF 0.9 the two in both articles. However, there are studies in the literature that say the opposite. Salih et al.[???] In their study on 80 patients who had undergone strabismus surgery, they divided the patients into two groups and gave 0.25 $mg.kg^{-1}$ metoclopramide to one group and 0.5 $mg.kg^{-1}$ dexamethasone to the other group after induction. They concluded that the interaction of sugammadex and dexamethasone in children aged 1-6 years may prolong the recovery time of rocuronium after general anesthesia.

Articles in the literature have produced different results. However, in our study, Rezonja et al.[12] A similar result was obtained in the in vitro experimental model of. One issue to be investigated is the dose and timing of administration of dexamethasone. Because there is no reliable way in the literature to determine what dose of dexamethasone is needed to prevent reversal of sugammadex.

One interesting result from our study was that patients who received dexamethasone at induction of anesthesia, required more rocuronium to maintain their deep neuromuscular blockade, and this was statistically significant. The possible explanation might be that dexamethasone may act by facilitating the impulse generating end of the motor end plate and also may act at the presynaptic membrane stimulating the release of acetylcholine.[20] Our study has a number of limitations. Concentration measurements of dexamethasone in at the time of sugammadex administration was not measured.

CONCLUSION

We can conclude from the present study that the interaction between sugammadex and dexamethasone may prolong the duration of reversal of rocuronium after general anesthesia in the rinoplasty. Further randomized clinical trials are needed to investigate the effects of the timing and dose of corticosteroids administered and their interactions with sugammadex.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul Yeni Yüzyıl University Clinical Researches Ethics Committee (Date: 23.11.2016, Decision No:003).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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