Sugammadex improves neuromuscular function with in patients receiving perioperative steroids

<table>
<thead>
<tr>
<th>Journal Name</th>
<th>Journal of the Pakistan Medical Association</th>
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</thead>
<tbody>
<tr>
<td>Manuscript ID</td>
<td>JPMA-2016-06-446</td>
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<tr>
<td>Manuscript Type</td>
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</tbody>
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1 **Reply to the reviewers’ comments**

<table>
<thead>
<tr>
<th>Reviewer Number</th>
<th>Original comments of the reviewer</th>
<th>Reply by the author(s)</th>
<th>Changes done on page number and line number</th>
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<tbody>
<tr>
<td>No</td>
<td>Statistically justify the sample size of just 30 subjects in each group.</td>
<td>We decided sample size according to G power electronic service. We added following part: “G Power 3.0.10 program was used for determining sample size. When they were accepted as effect size: 0.5, α error probability: 0.1 and power: 0.75 in this program’s t test family’s subtype (means: difference between two independent means (two groups)), sample size for each groups were found as 32. Therefore this study was included 60 patients.”</td>
<td>Page 6, line 5-9</td>
</tr>
<tr>
<td>No</td>
<td>Mention in what month and year this study was conducted.</td>
<td>We added this sentence: “this study was performed between February 2015 and January 2016.”</td>
<td>Page 5, line 4</td>
</tr>
<tr>
<td>No</td>
<td>Elaborate on your sampling methodology.</td>
<td>This part was added in methodology section. “In all patients, just before anesthesia induction, two electrodes were positioned on the left ulnar nerve trajectory by cleansing the forearm skin by alcohol for neuromuscular monitorization by TOF device. The acceleration transducer was positioned on the thumb, the others fingers were fixed on the arm board in order to allow movement of the thumb. In order to maintain a skin temperature above 33 C in the monitored arm, cotton pads were used. The TOF device (TOF-Watch®, Organon, Ireland) was set at 2 Hz and 0.2 ms with 10-</td>
<td>Page 5, line 20-27</td>
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sec stimulation intervals.”

<table>
<thead>
<tr>
<th>No</th>
<th>Why one-sample t-test was used to compare the two groups comparison.</th>
<th>When independent groups were compared inspect of parametric data, t test is preferred.</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>For figure 1, clearly mention under the table as to exactly what group C and S stands for.</td>
<td>Subtitle was added for Figure 1. “Group C: patients who did not received steroids; and Group S: patients who receive steroids.”</td>
<td>Page 11, line 2-3</td>
</tr>
<tr>
<td>No</td>
<td>Justify the wide age range of 18 – 60 years in this study.</td>
<td>We want to select adult patients when planning work. But, as you know, it is often a need for laryngoscopy in the geriatric population. Therefore, we did not want to included older patient, because change of their body composition and hormonal status may affect. However, the average age of the patients in both groups is 50-55 approximtely, as it may be followed as table 1.</td>
<td>-</td>
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“Sugammadex improves neuromuscular function with in patients receiving perioperative steroids”

Abstract

Objective: Based on the steroid encapsulating effect of sugammadex, this study was undertaken to assess whether the clinical efficacy of sugammadex was altered by the administration of steroids.

Methods: 60 patients between 18 and 60 years of age with ASA I-IV and undergoing elective direct laryngoscopy/biopsy were included in this study. Patients were assigned into two groups based on the intraoperative steroid use: those who received steroid (Group S), and who did not (Group C). After standard general anesthesia, patients were monitored with the train of four (TOF). The preferred steroid and its dose, timing of steroid administration, and TOF value before and after sugammadex as well as the reached time of TOF to 0.9 were recorded.

Results: There is no statistically difference between groups in terms of age, gender, preoperative medication use, and TOF ratio just before sugammadex. The reached time to TOF 0.9 after sugammadex administration was significantly shorter in Group S than Group C (p<0.05). A within group comparison in Group S showed no difference in TOF ratio immediately prior to sugammadex as well as the dose of sugammadex in those who received prednisolone, time to TOF 0.9 was higher in prednisolone receivers as compared to dexamethasone receivers (p<0.05).

Conclusion: In patients receiving steroids, and particularly dexamethasone, an earlier reversal of neuromuscular block by sugammadex was found, in contrast with what one expect. Further studies are required to determine the cause of this effect which is probably due to a potential interaction between sugammadex and steroids.
**Keywords:** anesthesia, sugammadex, steroids, Train-of-four monitoring

### Introduction:

The effects of non-depolarizing neuromuscular blockers may either be terminated spontaneously or through the use of pharmacological agents.\(^1\)

Recently introduced sugammadex now represents an alternative to traditional decurarization provided by cholinesterase inhibitors. Sugammadex may abolish the effects of steroidal neuromuscular blockers through encapsulation. This unique mechanism of action allows quick reversal of neuromuscular block, even administered at intubation doses. Also, it is particularly effective in the quick restoration of spontaneous respiration through eliminating rocuronium induced muscular paralysis in patients who cannot be intubated and ventilated.\(^2\)\(^-\)\(^5\)

In patients undergoing procedures that pose a risk of airway obstruction, such as direct laryngoscopy, sugammadex should be the initial agent of choice since a quick reversal of the effect of rocuronium may be required. However, the product information for sugammadex refers to a potential reduction in its effects when it is used alongside with certain medications taken on the day of surgery, e.g. toremifene and some antibiotics. Concomitant use of sugammadex and oral contraceptives may lead to capture reactions and drug interactions. Similarly, missing the dose of fluoxacillin and progesterone prior to sugammadex use is recommended.\(^6\)

Irritation of the upper airway epithelium due to procedure-related manipulations during direct laryngoscopy may lead to development of edema formation. Intravenous steroids are commonly utilized to prevent adverse respiratory consequences after extubation in these patients. However, the effect of such routine steroid administration on the efficacy of sugammadex is currently unknown. Therefore, based on a presumptive encapsulation effect of sugammadex on steroid molecules, we compared the efficacy of sugammadex in patients who did or did not receive steroids.
**Materials and Methods:**

After obtainment of Local Ethics Committee approval and written informed consent, this study was performed between February 2015 and January 2016. A total of 60 patients with an American Society of Anesthesiologists (ASA) physical status risk class of I-IV and undergoing elective direct laryngoscopy were included in this study. Exclusion criteria included the presence of muscular disease, clinically significant neurological, psychiatric, hepatic, renal, cardiac, or endocrine conditions, diabetes mellitus, peripheral neuropathy, difficult cooperation, difficult intubation, current treatment with steroids or hormones, obesity use of agents interacting with neuromuscular blockers (e.g. magnesium, anticonvulsants, aminoglycosides), history of allergy to neuromuscular blocking agents, opioids, or other drugs, and alcohol and drug dependence.

Patients were divided into two groups based on the presence or absence of intra-operative steroid use: Group S (n=30), who received steroids; and Group C, (n=30), who did not receive steroids.

An intravenous access route was established in the right arm in all patients and following routine induction (5 mg/kg sodium thiopental, 0.6 mg/kg of rocuronium) and maintenance (2% sevoflurane in 50% O2 and remifentanil infusion) of anesthesia. In all patients, just before anesthesia induction, two electrodes were positioned on the left ulnar nerve trajectory by cleansing the forearm skin by alcohol for neuromuscular monitorization by TOF device. The acceleration transducer was positioned on the thumb, the others fingers were fixed on the arm board in order to allow movement of the thumb. In order to maintain a skin temperature above 33 C in the monitored arm, cotton pads were used. The TOF device (TOF-Watch®S, Organon, Ireland) was set at 2 Hz and 0.2 ms with 10-sec stimulation intervals. During recovery from anesthesia, the effect of rocuronium was reversed with sugammadex administered at a dose of 2 mg/kg.
Age, gender, preoperative medication use, and TOF ratio just prior to sugammadex were recorded for each patient, as well as the preferred steroid and its dose, time of administration, total TOF prior to sugammadex, and time to a TOF of 0.9.

G Power 3.0.10 program was used for determining sample size. When they were accepted as effect size: 0.5, α error probability: 0.1 and power: 0.75 in this program’s t test family’s subtype (means: difference between two independent means (two groups)), sample size for each groups were found as 32. Therefore this study was included 60 patients.

Statistical analysis were done using IBM SPSS (Statistical Package for Social Sciences) software pack, version 20. After a variance analysis for the parametric data, mean ± standard deviations were recorded. One sample t test was utilized to compare the groups. ASA risk status classes were evaluated using the chi-square test. A p value of less than 0.05 was considered significant.

Results:
There is no statistically difference between groups in terms of age, gender, preoperative medication use, and TOF ratio just prior to sugammadex (Table 1). The reached time of TOF ratio to 0.9 after sugammadex injection was significantly shorter in Group S (139.51 ± 53.53 sec) as compared to Group C (184.68 ± 55.14 sec) (p < 0.05) (Figure 1).

In Group C, 20 patients were given prednisolone (60-125 mg) while 10 dexamethasone (8 mg), with no difference between prednisolone or dexamethasone receivers in terms of the dose of sugammadex, TOF just prior to sugammadex injection, and the timing of steroid injection. However, the time to TOF 0.9 was significantly higher in prednisolone receivers (154.66 ± 55.38 sec) as compared to those who received dexamethasone (107.70 ± 32.82 sec) (p<0.05) (Figure 2).
Discussion:
Postoperative residual curarization due to prolongation of the effect of non-depolarizing neuromuscular blocking agents remains a common and significant challenge in modern anesthesia that may pose significant risks for the patients’ safety. Recently introduced sugammadex with a modified gamma-cyclodextrin structure offers a viable alternative to the traditional decurarization by cholinesterase inhibitors in the context of the use of steroidal neuromuscular blocking agents.

As a matter of the fact that sugammadex exerts its effects through encapsulation of the steroidal neuromuscular blockers, its effects on the plasma levels of other molecules, hormones or drugs with steroidal structure has been a subject of research interest. Since endogenous steroids and steroidal drugs do not contain the quaternary ammonia ions in steroidal neuromuscular blockers (rocuronium, vecuronium), they have been reported to show a low affinity for sugammadex. Also, another proposed mechanism for this low affinity involves the tight binding of steroidal hormones to specific protein transporters in plasma. Sugammadex possesses an extensive lipophilic inner cavity into which lipophilic groups have been incorporated in order to augment the electrostatic interaction with the positively charged nitrogens of aminosteroidal molecules and to improve hydrophobicity. Mutual expulsion between the acidic functional groups maintains an open inner cavity of sugammadex. When the steroidal nucleus of rocuronium enters the cavity of sugammadex, the expulsion between the negatively charged carboxyl groups is interrupted, while the interaction between the positively charged nitrogen molecules of rocuronium and these carboxyl groups results in the formation of a tight bound. It has been shown that replacement of rocuronium with other steroidal molecules is unlikely due to the tight binding resulting in the formation of a rocuronium-sugammadex complex.7,8
Zhang et al. in their study testing the interaction between sugammadex and other molecules using isothermal titration microcalorimetry, investigated the likelihood of the formation of complexes between sugammadex and other steroidal and non-steroidal compounds such as cortisone, atropine, and verapamil. They concluded that the probability of the formation of complexes between sugammadex and these compounds is clinically insignificant, corresponding to a 120 to 700 fold lower capacity for complex formation as compared to rocuronium.

Although limited, the published data suggests that sugammadex may be involved in untoward interactions with steroids or steroidal molecules. But, we found that sugammadex was not associated with adverse effects on steroid hormones progesterone and cortisol, while it might lead to a temporary increase in aldosterone and testosterone in our previous study.

Conclusion:
However, contrary to what was expected, steroids administered at clinically relevant doses were associated with an increased effect of sugammadex, through yet unknown mechanism. Steroids, and particularly dexamethasone, resulted in earlier reversal of neuromuscular block by sugammadex. Further studies are warranted to elucidate this mechanism.

Disclaimer: It was presented as e-poster in Turkish Anestherdy and learnation congress 02 December 2015 antalyaiturkey.

Conflict of Interest: None

Funding Disclosure: None

References:


Figure legends

Figure 1: Time of TOF 0.9 of groups
Group C: patients who did not receive steroids; and Group S: patients who receive steroids.

Figure 2: Time of TOF 0.9 of Group S.
1 **Table 1: Demographic data of the patients**

<table>
<thead>
<tr>
<th></th>
<th>Age (year)</th>
<th>Gender (M/F)</th>
<th>Using preoperative drug (n)</th>
<th>TOF count before sugammadex</th>
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</thead>
<tbody>
<tr>
<td><strong>Group C (n=30)</strong></td>
<td>55.62 ± 13.74</td>
<td>25/4</td>
<td>3/30</td>
<td>1.00 ± 1.36</td>
</tr>
<tr>
<td><strong>Group S (n=30)</strong></td>
<td>53.38 ± 13.57</td>
<td>28/2</td>
<td>8/30</td>
<td>1.19 ± 1.44</td>
</tr>
<tr>
<td><strong>Dexamethasone</strong></td>
<td>47.00 ± 14.93</td>
<td>9/1</td>
<td>3/30</td>
<td>1.00 ± 0.94</td>
</tr>
<tr>
<td><strong>Prednisolone</strong></td>
<td>56.42 ± 12.08</td>
<td>19/1</td>
<td>5/30</td>
<td>1.28 ± 1.64</td>
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