

## Original Article

# Sugammadex Improves Neuromuscular Function in Patients Receiving Perioperative Steroids

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### ABSTRACT

**Context:** Sugammadex has steroid-encapsulating effect. **Aim:** This study was undertaken to assess whether the clinical efficacy of sugammadex was altered by the administration of steroids. **Setting and Design:** Sixty patients between 18 and 60 years of age with the American Society of Anesthesiologists I–IV and undergoing elective direct laryngoscopy/biopsy were included in this study. **Materials and Methods:** Patients were assigned to 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) monitoring. The preferred steroid and its dose, timing of steroid administration, and TOF value before and after sugammadex as well as the time to recovery (TOF of 0.9) were recorded. **Statistical Analysis Used:** SPSS software version 17.0 was used for statistical analysis. **Results:** There is no statistically significant difference between groups in terms of age, gender, preoperative medication use, and TOF ratio just before administering 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 before 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, steroids, sugammadex, train-of-four monitoring

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## INTRODUCTION

The effects of nondepolarizing neuromuscular blockers may either be terminated spontaneously or through the use of pharmacological agents.<sup>[1]</sup> 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.<sup>[2-5]</sup> 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, for example, toremifene and some

antibiotics. Concomitant use of sugammadex and oral contraceptives may lead to capture reactions and drug interactions. Similarly, missing the dose of floxacillin and progesterone prior to sugammadex use is recommended.<sup>[6]</sup> Experimental and clinical studies about relationship between sugammadex and steroid are in limited numbers. In an experimental study that studied

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the effects of sugammadex on progesterone levels in pregnant rats, they have found a nonsignificant decrease in progesterone in animals receiving sugammadex, with no effect on the clinical course of the pregnancy and with no increase in stillbirths and spontaneous abortions.<sup>[7]</sup> However, it has been demonstrated that sugammadex was not associated with adverse effects on steroid hormones.<sup>[8]</sup>

Irritation of the upper airway epithelium due to procedure-related manipulations during direct laryngoscopy may lead to the 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

This is a prospective observational study. After obtaining Local Ethics Committee approval and written informed consent, a total of sixty 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, obese patients, using drug interacting with neuromuscular blockers (e.g., magnesium, anticonvulsants, and 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 intraoperative 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 following routine induction (5 mg/kg sodium thiopental, 0.6 mg/kg of rocuronium

and maintenance (2% sevoflurane in 50% O<sub>2</sub> and remifentanyl infusion) of anesthesia. Before anesthesia induction, two electrodes were placed on the ulnar nerve trajectory to provide neuromuscular monitorization by train-of-four (TOF) device. The acceleration transducer was placed on the thumb, and the remaining four fingers were fixed on the arm board, thus allowing free movement of the thumb. The TOF device (TOF-Watch<sup>®</sup>S, Organon, Ireland) was set at 2 Hz and 0.2 ms with 10-s stimulation intervals. During recovery from anesthesia, the effect of rocuronium was reversed with sugammadex administered at a dose of 2 mg/kg. Sugammadex was injected at 10 min after steroid application.

Age, gender, preoperative medication use, and TOF ratio just before sugammadex were recorded for each patient, as well as the preferred steroid and its dose, time of administration, total TOF before sugammadex, and time to a TOF of 0.9.

Statistical analysis was done using IBM SPSS (Statistical Package for Social Sciences) software pack, version 20. After a variance analysis for the parametric data, mean  $\pm$  standard deviations were recorded. One-sample *t*-test was utilized to compare the groups. ASA risk status classes were evaluated using Chi-square test.  $P < 0.05$  was considered statistically significant.

## RESULTS

There is no statistically significant difference between groups in terms of age, gender, preoperative medication use, and TOF ratio just before sugammadex [Table 1].

The reached time of TOF ratio to 0.9 after sugammadex injection was significantly shorter in Group S ( $139.51 \pm 53.53$  s) as compared to Group C ( $184.68 \pm 55.14$  s) ( $P < 0.05$ ) [Table 2].

In Group C, twenty patients were given prednisolone (60–125 mg) whereas 10 were given dexamethasone (8 mg), with no difference between prednisolone or dexamethasone receivers in terms of the dose of sugammadex, TOF just before sugammadex injection, and the timing of steroid injection. However, the time to TOF 0.9 was significantly higher in prednisolone receivers ( $154.66 \pm 55.38$  s) as compared to those who received dexamethasone ( $107.70 \pm 32.82$  s) ( $P < 0.05$ ) [Table 2].

**Table 1: Demographic data of the patients**

|                | Age (year)        | Gender (male/female) | Using preoperative drug (n) | TOF count before sugammadex |
|----------------|-------------------|----------------------|-----------------------------|-----------------------------|
| Group C (n=30) | 55.62 $\pm$ 13.74 | 25/4                 | 3/30                        | 1.00 $\pm$ 1.36             |
| Group S (n=30) | 53.38 $\pm$ 13.57 | 28/2                 | 8/30                        | 1.19 $\pm$ 1.44             |
| Dexamethasone  | 47.00 $\pm$ 14.93 | 9/1                  | 3/30                        | 1.00 $\pm$ 0.94             |
| Prednisolone   | 56.42 $\pm$ 12.08 | 19/1                 | 5/30                        | 1.28 $\pm$ 1.64             |

TOF=Train of four

**Table 2: Time of train of four 0.9 of groups**

|                | Time of TOF 0.9 of groups (s) |
|----------------|-------------------------------|
| Group C (n=30) | 184.68±55.14                  |
| Group S (n=30) | 139.51±53.53                  |
| Dexamethasone  | 107.70±32.82                  |
| Prednisolone   | 154.66±55.38                  |

TOF=Train of four

## DISCUSSION

Postoperative residual curarization due to prolongation of the effect of nondepolarizing 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.

Sugammadex shows its effects through encapsulation of the steroidal neuromuscular blockers, its effects on the plasma levels of other molecules, hormones, or drugs with steroidal structure being a subject of research interest. Since endogenous steroids and steroidal drugs do not contain the quaternary ammonia ions in steroidal neuromuscular blockers (rocuronium and vecuronium), they have been reported to show a low affinity for sugammadex. Furthermore, another proposed mechanism for this low affinity involves the tight binding of steroidal hormones to specific protein transporters in plasma.<sup>[2]</sup>

Sugammadex possesses an extensive lipophilic inner cavity into which lipophilic groups have been incorporated to augment the electrostatic interaction with the positively charged nitrogen 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 the replacement of rocuronium with other steroidal molecules is unlikely due to the tight binding, resulting in the formation of a rocuronium–sugammadex complex.<sup>[9,10]</sup>

Zhang<sup>[11]</sup> in his 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 nonsteroidal compounds such as cortisone, atropine, and verapamil. He concluded

that the probability of the formation of complexes between sugammadex and these compounds is clinically insignificant, corresponding to a 120–700-fold lower capacity for complex formation as compared to rocuronium.

Although limited, the published data suggest that sugammadex may be involved in untoward interactions with steroids or steroidal molecules. In a prospective, double-blind, randomized, controlled study, dexamethasone's effects on the reversal time of sugammadex were evaluated in children undergoing tonsillectomy and adenoidectomy. It has been demonstrated that dexamethasone (0.5 mg/kg) did not affect the reversal time of sugammadex.<sup>[12]</sup> Another study has found that sugammadex was not associated with adverse effects on steroid hormones such as progesterone and cortisol while it might lead to a temporary increase in aldosterone and testosterone.<sup>[8]</sup>

## 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.

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## Conflicts of interest

There are no conflicts of interest.

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